The effect of Patient Pathway for colorectal cancer on treatment costs in Norway

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Acknowledgement

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List of abbreviations

AJCC - American Joint Committee on Cancer

CRC – Colorectal cancer

CT - Computed tomographic

FFS – Fee-for-service

GP – General Practitioner

HELFO – Norwegian Health Economics Administration

HNPCC - Hereditary nonpolyposis colorectal cancer

ICD - International Classification of Diseases

iFOBT - Immunological fecal occult blood testing

MDT – Multidisciplinary team meetings

MRI - Magnetic resonance imaging

NCR – National cancer register

NoMA - Norwegian Medicines Agency

NORCCAP - Norwegian Colorectal cancer Prevention

NPR – National patient register

NSP - National Screening Program

OOP – Out-of-pocket payment

PP – Patient Pathway

RHA - Regional Health Authorities

RHA – Regional Health Authority

TME - Total mesorectal excision

TNM - Tumor-Node-Metastasis

UICC - Union for International Cancer Control

WHO - World Health Organization

Abstract

Background: In 2015 Norway introduced a Patient Pathway for colorectal cancer. The program was aimed to standardize colorectal cancer treatment process, reduce heterogeneity in treatment approaches between Regional Health Trusts and solve the problem of unnecessary delays in waiting times for diagnostic and treatment. Patient Pathways are likely to impact costs of colorectal cancer treatment and therefore budget planning and decision-making process.

Objective: The main objective of this master thesis was to estimate the impact of implementing the cancer Patient Pathway on colorectal cancer treatment costs, in order to support decisions on budget allocation and health care expenditure.

Methods: Data from the Cancer Registry of Norway and the Norwegian Patient Register from 2012 until 2017 were used to statistically test for significant differences between patients that were not included in the Patient Pathway (reference period from 2012 until 2014), and patients that were included (in 2016-2017, after the implementation). Costs were estimated and adjusted for the 2016 consumer price index based on the DRG system with two intervals: two-months after diagnosis, and one-year cost after diagnosis. Log-linear regression analysis was then performed with the transformation of the dependent variable (cost). Regressions were also run for separate cancer stages to observe the effect depending on disease severity. The linktest was applied to check that the model is properly specified and the Breusch-Pagan test was ran to check for heteroscedasticity. Different scenarios using stage-specific costs were considered, together with the propensity score matching to compare costs.

Results: The main finding is that the introduction of the Patient Pathway for colorectal cancer led to an increase in treatment cost for both colon and rectal cancer in 2016 in comparison to baseline period 2012-2014. As per regression outputs, two-month treatment costs for rectal cancer increased by 41.2% in comparison to the baseline period (2012-2014), while for colon cancer it increased by 33.6%. The biggest increase in one-year treatment cost in 2016 was observed for colon cancer - 46.5%, while for rectal it was 32%, both compared to the baseline period. According to per stage analysis of two-month cost, rectal cancer is more expensive to treat in the second stage (50.3% for patients included in the Pathway) and for colon cancer, during the first stage (52.3%), both with significant p-values (<0.001). While for one-year, the costs are more similar for all stages. Rectal cancer is more expensive for the second and fourth stages (29.2% and 23.6%, respectively) also for patients included in the pathway. Colon cancer has a similar pattern, costing more for the first and fourth stages (48.2% and 53.1%).

The findings are supported by propensity score matching results, for one-year cost both for colon and rectal cancer, which identified positive treatment effects. Although the results of matching for two-month cost are a bit controversial, especially for rectal cancer. Overall costs increased due to the Patient Pathways for several reasons, such as decreased waiting time and standardized treatment process. We also observed that some patient groups were given preference for being included into the Patient Pathway program, which could make the results biased.

Conclusion: There is a considerable cost increase after the implementation of the Patient Pathway program. The cost effect was already seen in 2015 (year of implementation). The increase for the two-month period was higher than the cost increase for one-year. Registry data plays an important role in providing knowledge on costs to support optimal resource allocation and budget planning. However, in a priority setting, both costs and effects should be calculated to ensure optimal resource allocation. Therefore, additional research should account for the health outcomes of the introduction of Patient Pathway, as a consequence of more standardized pathways. If accounting only for the costs, the results and the evidence might be biased for decision-makers.

1. Introduction

On a global scale, cancer is the leading cause of death, accounting roughly for 10 million deaths in 2020. Death from colorectal cancer (CRC) corresponds to 1.93 million cases, being the third most common type of new cases in the world. [1] The incidence of cancers is expected to increase due to increased life expectancy, new detection methods, and screening aimed at prevention and early diagnosis. As the number of cancer increases, colorectal cancer cases also increase, together with substantial costs of treatment.

Previous research has identified the urgent need to develop tools to inform and support cancer care delivery and manage resource utilization in a better way. Improve clinical pathways might be a way to utilize medical expertise while optimizing cancer care delivery [2].

Despite the pessimistic incidence scenario, between 30 to 50% of cancers can be prevented by avoiding risk factors and implementing prevention strategies. The economic burden of the disease can be scaled down through early detection and improved treatment pathways. Overall, many cancer patients can have a higher chance of survival if diagnosed early and treated appropriately [3]. However, cancer Patient Pathways can have different effects, both positive and negative. This thesis will investigate the effect of Patient Pathways for colorectal cancer on treatment costs in Norway.

The number of colorectal cancer cases increases with an aging population, together with the fact that every year new costly drugs are launched on the market, therefore it is expected a substantial increase in the cost of colorectal cancer treatment. Thus, for healthcare providers to be able to make decisions regarding reimbursement, it is important to consider the cost-effectiveness of preventive and treatment alternatives in order to optimize resource allocation [4]. For this reason, investigation of costs becomes actual both from a societal and healthcare perspective.

In this thesis we touched the topic which was not previously explored. The focus of previous research on Patient Pathways was to measure effect in waiting time and quality of services. The main objective of this master thesis is to investigate whether the introduction of a Patient Pathway for colorectal cancer led to a treatment cost increase for colon and rectal Cancer in the period 2015 to 2017. Direct healthcare costs were adjusted for cancer stage, age groups, gender and diagnosis year in order to investigate the impact of Patient Pathway on costs of colorectal cancer in Norway.

In Chapter 2 we started explaining how the Norwegian healthcare system and cancer strategy will be explored to set the backdrop for cancer Patient Pathways, introduced in 2015. We will also discuss how the compulsory financing system works among primary and specialist health care.

Chapter 3 will provide an introduction to colorectal cancer in Norway, the risk factors, epidemiology, and staging system for further use when working with dataset. Information on the clinical management and treatment guidelines, highlighting the current practice in Norway, is essential for making assumptions and interpreting research results. In addition, the total costs of colorectal cancer from different perspectives will be discussed.

In chapter 4 we set the background for the introduction of the Patient Pathway program and what the program represents through diagnostic and treatment processes. This in a key chapter to set the important background for our master thesis. We will also discuss which assumptions the Patient Pathway Program has on costs.

Chapter 5 will contribute to a better overview of the dataset from the Norwegian Patient Register and the Cancer Registry of Norway used in the current research and methods of cost calculations used in the analysis. An explanation of the variables used in the main analysis will be given, as well as the patient population characteristics. Throughout this chapter, there will be given brief explanations of the theoretical framework to support the analysis with a focus on the statistical methods used to explore the relationship between costs. In addition, methods for exploring the causality will be discussed, such as propensity score matching.

In Chapter 6 we will present the results of one-year year and two-month treatment cost analysis and its dynamics before and after Patient Pathway introduction. Both results of mean costs analysis and log-linear regression analysis will be provided and then further discussed on chapter 5. The results for the propensity score matching were also presented, identifying treatment effects for both one-year and two-month costs.

To support the results obtained via regressions we used propensity score matching identifying treatment effect for both one-year and two-month costs.

In chapter 7 the main findings from the analysis will be interpreted, discussed, and compared to similar research on the Patient Pathways. Confounders and arguments for cost increases and decreases will be presented. The strengths and the limitations are also addressed.

In the end, chapter 8 will summarize the main findings of the study. The conclusion will also recommend the need for future research and possible gaps and areas of interest for further

analysis. The thesis' contribution to the important discussion about introducing Patient Pathways will also be highlighted.

2. The Norwegian health care system

In Norway, access to health care is considered a basic social right. Citizens who are legally residing in the country are entitled to publicly fund healthcare services [5]. Ensuring universal and equitable access to the system is an important health policy embedded in the Municipal Health and Care Act of 2011 and the Patients' Rights Act of 1999 [5].

The government is responsible for providing care to the population, in accordance with the fundamental concept of equal and universal access, decentralization, and free choice of provider. [6] Norway's organization of health services is semi-decentralized. The regulation and supervision of the health care activities are the responsibility of the national authorities, while most provision tasks were transferred from the central to the county and municipal administrative levels [6].

Primary health and social care are under the responsibility of the municipalities, with the Ministry of health playing an indirect role through legislation and funding mechanisms. In specialized care, the government acts with a direct role through ownership of hospitals and its provision of directives to the boards of Regional Health Authorities (RHA) [6]. At the same time, operative tasks are delegated to various subordinate agencies, such as the Directorate of Health and the Norwegian Medicines Agency (NoMA). In addition, about fifteen compulsory national health registers collect various types of health data, e.g., the cancer registry [5, 6].

Usually, the first contact that a patient has during a medical emergency is through the primary health care service and the General Practitioner (GP). In Norway, the GP will work as a gatekeeper for secondary health care services. Patients will need a referral to assess specialized hospitals if in need of special treatment or in case of cancer [5]. All citizens residing in Norway will be entitled to a GP through the national scheme, although the arrangement is voluntary, almost 99.6% of the population are registered through the GP scheme. In general, the GP has the main responsibility of the patients' overall health, treatment and diagnosis. [6]

After assessing the health care system through primary care, some patients might be referred to secondary health services. It is within the secondary health care services that Norway can ensure the provision of specialized diagnostic services, treatment, and follow-up for each patient [5].

All patients can then choose which hospital they would like to be treated since regardless of the geographical location, the tendency is that Norwegian hospitals become more and more specialized [6].

There are four different regional health authorities (RHA) in Norway, which are responsible for the supervision of specialist inpatient somatic and psychiatric care. The RHAs are constituted of forty-seven regional facilities with specialized health services. Usually, medical services with high complexity are provided in university hospitals each of the 4 regions has at least one university hospital located in a large city [5]. Therefore, highly specialized care is concentrated in urban areas and most of the people living in rural areas have to travel long distances to access certain types of care [5].

When connecting the Norwegian health care system with cancer care and its national cancer strategy, it is relevant to mention the gradual development of palliative care in the country [5]. In general, palliative care services are offered at all levels of care. For instance, if the patient decides to stay at home to receive treatment, it will be provided by the GPs within the municipal home care services [5]. While, if the patient needs to be treated in a hospital, all main facilities have multidisciplinary palliative care teams providing ambulatory services. Specialist palliative care for patients with complex needs is centered in inpatient units in larger hospitals [5].

2.1. Healthcare financing in Norway

The quality and effectiveness of the Norwegian Health care system is among one of the best in Europe [7]. However, it comes at a cost, and according to the WHO, in 2017 Norway had the highest share of public spending on health in the European region [10]. The compulsory financing system itself accounted for more than 85% of the current health expenditure [7, 10].

The system was established on the principles of universal access, decentralization, and offering a free choice of provider [8]. The way to finance the system is through taxes, income-related employee/employer contributions, and out-of-pocket payments (OOP).

The health care coverage in Norway includes a vast range of services with a cost-sharing burden for the residents. In fact, the share of OOP spending is among the lowest in the European Union, approximately 15% in 2017, especially for the fact that cost-sharing ceilings are applied to services and medications [7].

The major source of revenue for the health care system is general taxation (accounting for 74%), together with public funds (approximately 11%) and OOP payments. In general, most of the national taxes are used to provide secondary care and part of primary care, while municipal taxes provide almost all the funds for primary care [8].

Although the health care policy is controlled in a centralized way, the provision of health care is decentralized. The municipalities are responsible for organizing and financing primary health and social care according to the local demand. While specialized care has direct control from the central Government, especially for the managerial and financial side of the hospital sector [7]. In general, the Norwegian health system is not centralized, but there are some attempts to improve the coordination between specialized and primary care [8].

2.1.1. Primary health care

The municipalities are responsible for the primary care of the population in order to solve health problems that do not require hospitalization. The first medical contact a patient has is through a General Practitioner (GP), and it is usually with the primary health care service. If for instance, colorectal cancer patient needs to be referred to a specialized hospital or specialized care, the person will need the GPs referral to move forward with the treatment [9]. As a result of Patient Pathway introduction it was set a low threshold to be referred to specialized care.

There are three sources to finance the primary care services provided by the GPs:

- Through municipalities and the capitation system.
- Out-of-pocket payments.
- The Health Economics Administration (HELFO) through fee-for-service (FFS).

While the capitation system accounts for 30% of the GPs' income, the 70% remaining are paid by OOP and FFS. There is also the case when the GPs earn salaries and are employed by the municipalities and for those cases, this happens through subsidies from HELFO. [8]

2.1.2. Specialist health care

The secondary health care service provides specialized diagnostic, treatment, and follow-up for the patients referred from the primary care services. Different types of cancer and diseases, in

general, have arisen, forcing hospitals to become more specialized. The patients, for instance, can choose the hospital they would like to be treated, disregarding the geographical location.

In Norway, there are four Regional Health Authorities (RHA), responsible for specialist inpatient somatic and psychiatric care. Annually, each RHA receives an annual budget from the Ministry of Health and it is up to each region to decide how to distribute the money among the regional facilities [8].

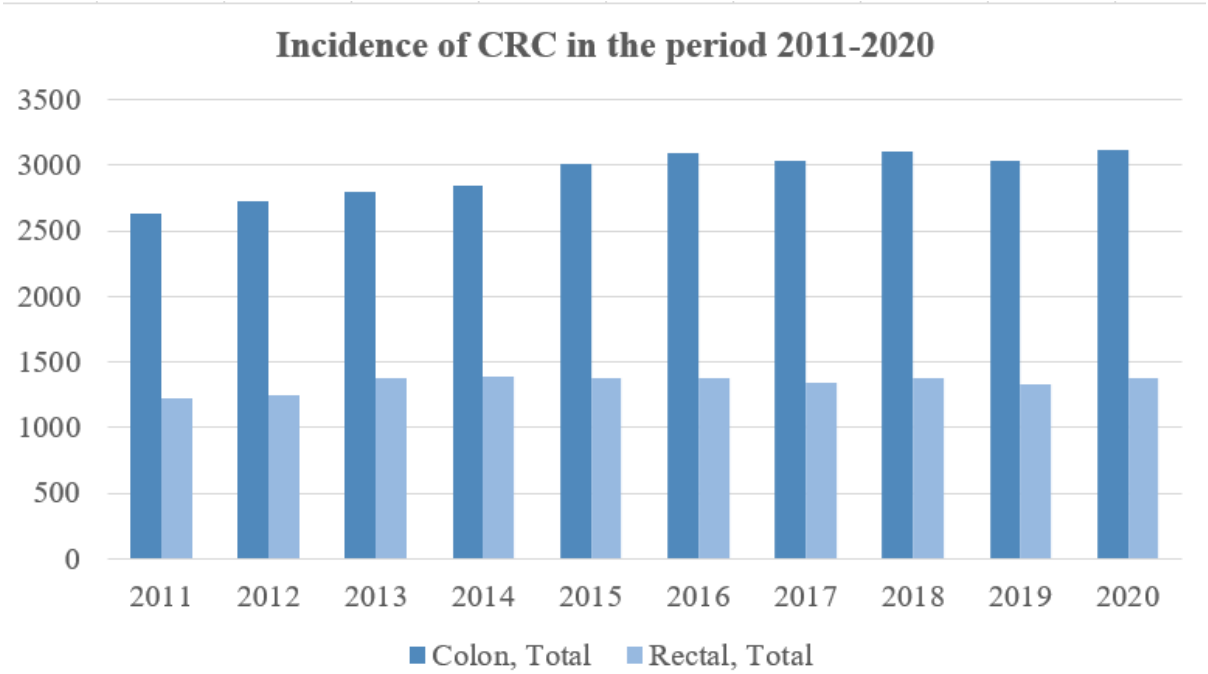
The payment scheme is based on a mixed financing system with block grants and activity-based funding via diagnosis-related groups (DRGs), complemented by quality-based. Besides the money from the RHAs, regional hospitals also get transfers from OOP payments for outpatient care.

3. Colorectal cancer in Norway

Colorectal cancer [CRC] is the second most common cancer diagnosis in Norway, after prostate cancer among men, and breast cancer among women [11]. Individuals diagnosed with colorectal cancer are assigned ICD-10 code defining main diagnosis. It ranges from ICD-18 - Malignant neoplasm of the colon; C19 - Malignant neoplasm of the recto sigmoid junction; until C20 - Malignant neoplasm of the rectum. All cases for patients with C18 code are considered as colon cancer, while C19 and C20 are rectal cancer patients.

As of December 31, 2020, the prevalence of colorectal cancer in Norway was 38 048 individuals, out of them 24 768 were diagnosed with colon cancer and 13 280 with rectal cancer. The incidence level in 2020 was the following: 3 121 individuals diagnosed with colon cancer (ICD-18) and 1 373 individuals with rectal cancer (ICD-19 and ICD-20) [11]. The dynamic of new diagnosed colorectal cancer cases in the period 2011-2020 is presented in the Figure 1. The disease caused 1 542 deaths in 2020. [11].

Figure 1: *Incidence of Colorectal cancer in the period 2011-2020*



Note. From "Incidence of CRC in the period 2011-2020" by Cancer Registry of Norway. Cancer in Norway 2020 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway, 2021.

According to the forecasts, the number of cases of colorectal cancer in Norway will increase and in 2032–36, it is assumed that there will be more than 6,700 new cases per year [12]. The changes occur mainly due to aging in the population. As per recent updates from Statistics Norway the proportion of persons 70 years or older will change from 12%, in 2020, to 21% in 2050 [13]. This can entail the increase incidence of colorectal cancer and result in rising costs for treating colorectal cancer.

3.1. Etiology

Colorectal cancer originates from epithelial cells in the mucosa and starts as a growth on the inner lining of the colon or rectum. This growth forms benign clumps of cells – the so-called polyps. Over time, polyps can turn into colon cancers. The chance that a polyp turns into cancer depends on the type of polyp, its size and number of polyps. [14, 15, 16]

Adenomatous polyps, sessile serrated polyps and traditional serrated adenomas are called pre-cancerous conditions as they tend to turn into cancer.

Approximately 95% of colorectal cancer are adenocarcinomas. The rest 5% is represented by less common tumor types - lymphomas, sarcomas, carcinoid tumors and gastrointestinal stromal tumors. They normally start spreading in hormone-producing cells, immune cells, or underlying connective tissues. [15, 16]

As a cancerous tumor grows into blood- or lymph vessels, it can be to other parts of the body forming metastasis [16].

Most cases of colorectal cancer occur sporadically, while approximately 5% of cases may be associated with hereditary predisposition. The following hereditary forms of colorectal cancer are caused by genetic mutations and likely to start at a young age:

- Lynch syndrome, HNPCC (hereditary nonpolyposis colorectal cancer) making up 2-4% among colorectal cancer patients. The lifetime risk of developing cancer in a person with Lynch syndrome is 60-80%.
- Familial adenomatous polyposis is detected in approximately 1% of patients with colorectal cancer. In 100% of cases, this condition is resulted in the development of colorectal cancer by the age of 30.
- Attenuated familial adenomatous polyposis and MAP (MUTYH Associated Polyposis) occur in rare but more severe hereditary forms [15, 16].

3.2. Risk factors

The risk factors associated with the incidence of colorectal cancer can be categorized into two groups:

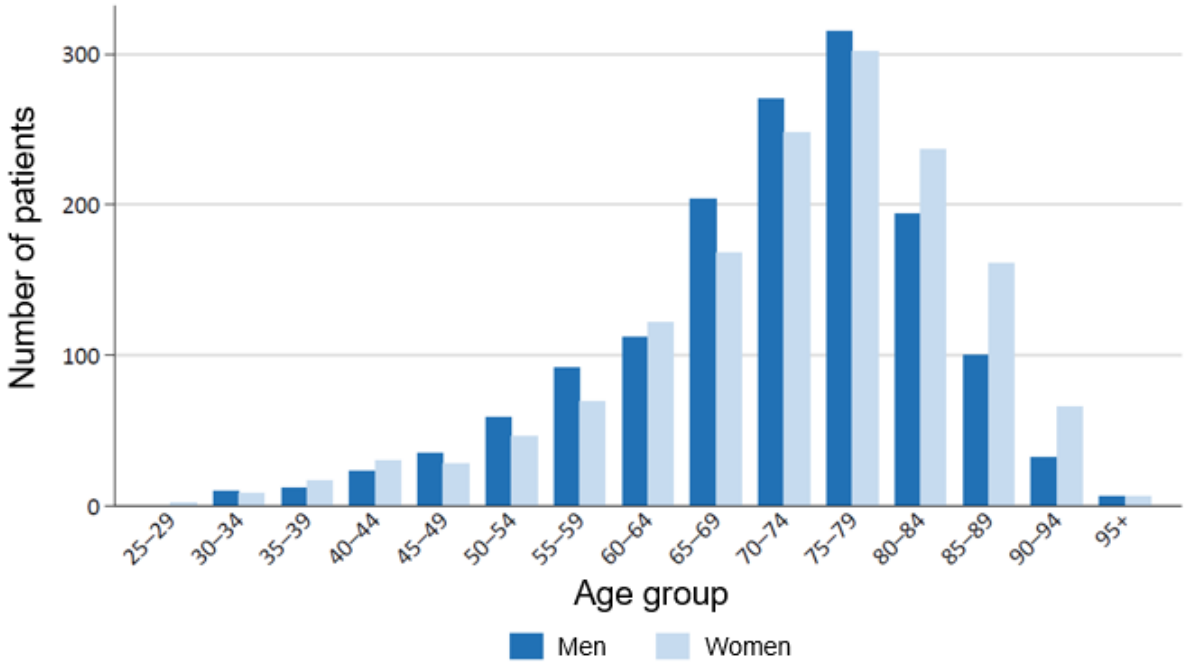
- Non-modifiable, which an individual cannot control.
- Environmental and lifestyle risk factors. [17]

Non-modifiable risk factors

Age

The likelihood of being diagnosed with colorectal cancer increases after the age of 50. The vast majority of diagnosed with colorectal cancer in 2020 in Norway belong to the age group of 60–80 years [74.8% of men and 71.3% of women]. The median age at diagnosis is 73 years for men and 75 years for women. The distribution of age and gender at diagnosis with colorectal cancer in Norway is shown in Figure 2. [18]

Figure 2: *Number of patients diagnosed with colorectal cancer in 2020 in Norway*



Note: From Cancer Registry of Norway. National quality register for colon and rectal cancer, Annual Report 2020. The Norwegian Cancer Registry, 2021

Adenomatous Polyps in the bowel

The precursor lesions of colorectal cancer as 95% of cases develop from these adenomas [17]. Risk increases with the number of polyps and their growth.

Family History and inherited genetic risk

About 20% of all patients with colorectal cancer may have familial colorectal cancer, meaning that other family members have been affected by this disease. The risk, in this case, is moderately increased and the reasons for this are not clear. Most likely, it can be explained by shared environmental factors and inherited genes [17, 22]. Hereditary forms of colorectal cancer caused by genetic mutations are high-risk factors.

Previous cancer and medical conditions.

Individuals who had colorectal cancer in the past have an increased risk of recurrence [19]. The 5-year recurrence rate among stage I patients is 5%, in stage II patients - 12%, in stage III patients is 33% [21]. Other cancer types, especially breast, ovary and uterine are also risk factors. This might be caused by an adverse event from undergone treatment, radiation

exposure, or genetic changes [19]. Medical conditions like type 2 diabetes, gallstones and acromegaly increase the risk of getting colorectal cancer [19, 20].

Inflammatory Bowel Diseases

Ulcerative colitis and Crohn's disease are examples of diseases which cause inflammation in the bowel. The relative risk of colorectal cancer in patients with the above-mentioned diseases is approximately between 4- to 20-times [17, 19]. There is some evidence that the risk of colorectal cancer is higher in people who have Helicobacter pylori infection, which causes stomach ulcers. [19]

Environmental and lifestyle risk factors

Diet

Diet is one of the key risk factors influencing colorectal cancer incidence. Changes in food habits might reduce up to 70% of this cancer burden [17]. Diet low in fiber and high in animal protein, red or processed meats and saturated fat causes colorectal cancer. As per the latest report on diet in Norway prepared by the Norwegian Institute of Public Health, intake of whole grains, vegetables, fruits and fish is too low, while the intake of foods high in saturated fat, salt and sugar is too high [23].

Obesity

Overweighted or obese individuals will have more estrogens circulating and fewer insulin sensibility, and those two factors are believed to influence cancer risk, particularly when associated with excess of abdominal adiposity [17]. The risk is not only associated with higher energy intakes, but also with the metabolic efficiency. According to different studies, individuals who are able to use their energy more efficiently may be at lower risk of colorectal cancer. In addition to this, in Norway, approximately 25% of middle-aged men and 20% of middle-aged women have obesity with a body mass index over 30 kg / m^2 [24].

Physical activity

Lack of physical activity is interrelated with obesity factor and considered to cause about a fourth to a third of colorectal cancers. The evidence of decreasing risk with regular physical activity is stronger for colonic than for rectal cancer [17]. Moderate physical activity raises the body's metabolic efficiency and capacity while reducing blood pressure and insulin resistance. However, among the adult Norwegian population, about 30 percent follow the WHO recommendations for physical activity [25].

Smoking and alcohol consumption

Evidence shows that 12% of colorectal cancer deaths are caused by smoking. Both alcohol and tobacco are cancerogenic and increase cancer growth in the colon and rectum [17]. In the adult population in Norway, about 30% use tobacco with the largest share of snus [26]. Alcohol consumption by men is almost double as high as by women which can partly explain the higher prevalence of cancer among men.

Non-modifiable factors are closely connected to the environment, reflecting cultural and social lifestyles. Thus, environmental factors are considered to be primary risk factors for colorectal cancer [17].

Most of the risk factors listed above contributes to the increasing comorbidity among patients with colorectal cancer. Different studies indicate that comorbidity in patients with colorectal cancer is common and it has increased extensively during the last years. [27, 28, 29]

Comorbidity or multimorbidity diseases are defined as a life-shortening disease, often-chronic conditions existing in at least one, two, or more organ systems [multimorbidity]. It is a long-term health condition or disorder that occurs in the presence of primary diseases, such as colorectal cancer or any other type of cancer. [27] Comorbidity represents a challenge when treating patients with colorectal cancer, given that half of the patients are aged older than 70 years; therefore, the diagnosis of colorectal cancer is often related to the presence of other chronic conditions. [27, 28]

According to different research, there are three types of most prevalent comorbidities for colorectal cancer, such as hypertension (25.9% of the cases), diabetes (17.3%), and gastric disease (11.4%). [28] For patients under 50 years, the most common comorbidities are anemia (9.1%) and diabetes (7.4%), while in patients older than 79 years, hypertension (32.7%) is the most prevalent comorbidity condition. [28]

Comorbidity has an important impact on the management and prognosis of colorectal cancer patients. Patient Pathways and cancer guidelines need to consider outstanding comorbidities, in order to benefit the prognosis of the most disadvantaged patients who carry the greater burden of the comorbidity. Understanding the patterns of cancer comorbidity may help further research into the influence of specific comorbidities on costs of cancer treatment and in short-term mortality.[28]

3.3. Staging

Based on the diagnosis, colorectal cancer can be categorized according to severity, which is strongly correlated with prognoses. This process is called staging. The stage at diagnosis is the determinant of colorectal treatment outcomes [30]. Discovering cancer at an early stage often allows for more treatment options [30]. A staging system is used not only to determine treatment but also to measure the progression of cancer and quantify statistically the chances of survival [30]. Doctors often assign the stage of cancer by combining the Tumor-Node-Metastasis (TNM) Classification of Malignant Tumors (TNM). The American Joint Committee on Cancer (AJCC) has created the TNM system, which is the most often used for colorectal cancer cases. It means the extent (size) of the tumor (T) and if it has spread to lymph nodes (N) besides the presence of metastasis (M) [33]. The letters TNM are followed by numbers that provide more details about each of the factors. A higher number means that the cancer is more advanced. The staging system is summarized in Table 1.

Table 1: *The TNM Classification of Malignant Tumors*

Tumor (T)	**T0/Tis**	**T1**	**T2**	**T3**	**T4**
The extent (size) of the primary tumor	T0: No primary T1: In situ cancer	Spread into nearby structures within a < 3cm	Between 3 - 5cm	7cm	The tumor has > 7cm
Nodes (N)	**N0**	**N1**	**N2**	**N3**	
Degree of spread to nearby lymph nodes	Nearby lymph nodes do not contain cancer	Metastasis in 1–3 regional lymph nodes	Metastasis in four or more regional lymph	Metastasis in several regional lymph nodes	
Metastasis (M)	**M0**	**M1**			
The spread (metastasis) to distant sites	No distant metastasis	Metastasis to distant organs (beyond regional lymph nodes)			

Note. Adapted from Tumor-Node-Metastasis [TNM] from Edge, S. B., & American Joint Committee on Cancer [Eds.]. [2010]. *AJCC cancer staging manual* [7th ed]. Springer.

Once the values for T, N, and M have been determined, they are combined with a specialized staging system; considering the national guidelines for colorectal cancer in Norway, the Union for International Cancer Control (UICC) staging system was preferred over the Duke´s classification. However, the TNM system is mostly used by physicians to record the anatomical grade of the tumor and is often condensed into categories such as group or stage. The UICC classification is adopted with the intention of calculating the extent of spread of the tumor [31].

The combination and interaction of the TNM staging system and the UICC stages, compared to the CRN parameters of diagnostic are summarized in Table 2.

Table 2: *The combination and interaction of TNM staging system with the UICC classification system and the CRN parameters.*

UICC Stages	Parameters	pTNM
Stage 0	In situ, not malignant tumor	Tis, T0N0
Stage I	Cancer, no metastases	T1T0, T2T0
Stage II	Cancer, regional lymph node metastases	T3N0, T4N0
Stage III	Cancer, local infiltration of skin or surrounding tissue without distant metastases (with or without regional lymph node metastases)	T1N1, T2M1, T1N2, T2N2, T3N1, T4N1, T3N2,T4N2,
Stage IV	Cancer, distant metastases	M1
Unknown	Cancer, unknown stage	In case of missing information about TNM

Note. Adapted from the Cancer Registry of Norway, 2015 [34]

Besides the type of cancer a person has, the stage of the cancer is one of the most important factors when doctors try to determine a patient's prognosis. These staging groups are used on a global scale, including clinicians in Norway.

3.4. Screening program for colorectal cancer in Norway, results of pilot project

The purpose of screening for colorectal cancer is to reduce the incidence and mortality from colorectal cancer via detecting it in early stages or averting precursors to cancer [35].

In 1999, the NORCCAP (Norwegian colorectal cancer Prevention) project started as a pilot on a possible national screening program [36]. Screening examinations were carried out for 3 years (1999-2001) in Oslo and Telemark. In total, 20 572 individuals aged 50-64 comprised the screening group, 10 283 randomized to receive a flexible sigmoidoscopy and 10 289 to receive a combination of once-only flexible sigmoidoscopy and immunological fecal occult blood testing (iFOBT). The study also considered a control group, comprised of 78 220 individuals [36].

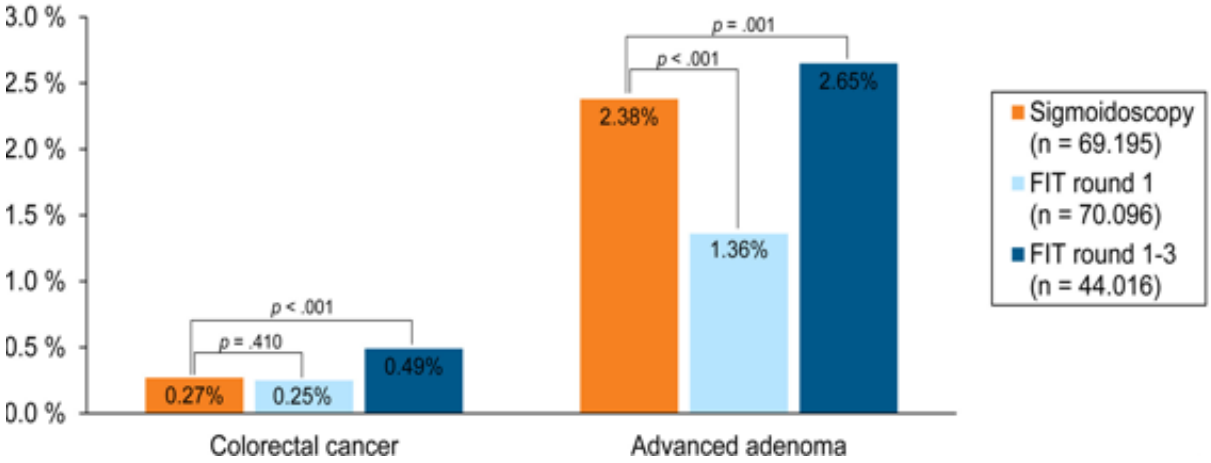
Blood samples were also taken and the participants were followed over time. The results have been published in more than 64 articles and it has been of great importance to routine clinical activity and the study is still ongoing [36]. In one of the studies published [37], after a median of 11 years, 71 participants died of colorectal cancer in the screening group against 330 in the control group (31,4 vs 43,1 deaths per 100 000 individuals [37]. Colorectal cancer was diagnosed in 253 participants in the screening group vs 1086 in the control group (112 vs 141

cases per 100 000 individuals). The incidence was reduced in all the age groups. In the end, there was no difference between flexible sigmoidoscopy only vs the flexible sigmoidoscopy and IFOBT screening groups [37]. The study concluded that once-only flexible sigmoidoscopy screening or flexible sigmoidoscopy and iFOBT reduced colorectal cancer incidence and mortality on a population level compared with no screening.

In addition to NORCAAP, in 2017, the Norwegian Directorate of Health delivered a proposal for a National Screening Program (NSP) for colorectal cancer to the Ministry of Health and Care Services. The proposal was grounded by research, health economic analyzes, ethical assessments and experiences obtained via pilot screening program in Health South-East [35].

The pilot screening program started in 2012 and recruited 140 000 patients of both living in Southeast Norway. It was designed as a blind two-armed study, registered at clinicaltrials.gov (NCT01538550). Participants were randomly assigned to one of the diagnostic methods: FIT (fecal immunochemical test) checks or flexible sigmoidoscopy [38]. So far, more than 500 people have been diagnosed with colorectal cancer. Almost 400 of discovered cancer cases were at early stages with high survival prognoses. In addition, 4000 advanced polyps, often leading to colorectal cancer, were removed through the pilot project. The pilot discovered that repeated FIT checks gave better results than one-time sigmoidoscopy or one-time FIT check [39, 40]. The results of a pilot project are presented in Figure 3.

Figure 3: *Colorectal cancer and advanced adenoma detection rates among invited individuals in the sigmoidoscopy arm, FIT round 1, FIT round 1-3.*



Note: From Randel, Schult, A. L., Botteri, E., Hoff, G., Bretthauer, M., Ursin, G., Natvig, E., Berstad, P., Jørgensen, A., Sandvei, P. K., Olsen, M. E., Frigstad, S. O., Darre-Næss, O., Norvard, E. R., Bolstad, N., Kørner, H., Wibe, A., Wensaas, K.-A., de Lange, T., & Holme, Øyvind. [2021]. Colorectal cancer Screening With Repeated Fecal Immunochemical Test Versus Sigmoidoscopy: Baseline Results From a Randomized Trial. Gastroenterology [New York, N.Y. 1943], 160[4].

From 2022, the Cancer Registry will gradually introduce a national screening program for colorectal cancer. The whole population over 55 years will be included in the program and offered a FIT check every other year for 10 years. The option of colonoscopy will be offered later after building up capacity. It is estimated to take around 4 years before RHFs are ready to offer screening to the whole Norwegian population turning 55 years [38].

National Screening Program can be considered as an element of the pathway that starts at the early stage of the patient journey and improves overall results. In this thesis, the effect of screening is not considered due to the fact that the analyzed data is for the period before the conducted screening. The pilot screening project may have had some implications on the cost before 2015, but it is considered to be minor. Even though screening programs are not the major concern of our thesis, it plays an important role in the national cancer strategy and it will be briefly addressed in the treatment guidelines.

3.5. Treatment Guidelines

The National guidelines assure that the public service in cancer care is of good quality and equally distributed throughout the country. It was established to make correct prioritizations, provide a coherent treatment pathway, and standardize the provision of services. The guidelines represent an expression of the best practices and formalization of different professional groups' recommendations. [41]

The Norwegian Health Directorate is responsible for writing and revising the national guidelines for different types of cancer, including the diagnostic, treatment, and follow-up. It is continuously revised to make sure it can reflect the best practices. [41]

Diagnostics

Symptoms and diagnosis of colorectal cancer depend partly on tumor location. Bleeding is very common in tumors of the rectum and sigmoid. While anemia is more common in tumors from proximal to the colon. However, these symptoms also occur in several other diseases of the digestive tract, and therefore both laboratory and clinical examinations are required for diagnosis confirmation. Both for colon and rectal cancer Fecal Occult Blood Test is used for diagnosis. Laboratory tests are normally performed within primary health care. Clinical examinations are different for colon and rectal cancers and performed in the secondary healthcare system [41].

Rectal cancer.

The primary diagnosis is usually made by rectoscope with a biopsy. Sometimes imaging methods such as the CT / MRI (magnetic resonance imaging) pelvis are used.

For the patients which are not supposed to have surgery, it is important to obtain a histological test, in case it is relevant for oncological treatment.

Colon cancer.

The primary method of diagnostic of colon cancer is colonoscopy with further biopsy. In case of incomplete colonoscopy, CT (Computed tomographic) colonography is indicated as a complementary method, it can detect lesions ≥ 10mm.

Primary treatment

The current treatment options for colorectal cancer consist of surgery and neo- /or adjuvant therapy. Adjuvant therapy is a treatment given after the main treatment (surgery) to reduce the chance of recurrence. It includes chemotherapy, radiotherapy and immune therapy. Possible treatment alternatives will rely on the stage and location in the colon or rectum, as well as other factors such as overall health condition [41, 42].

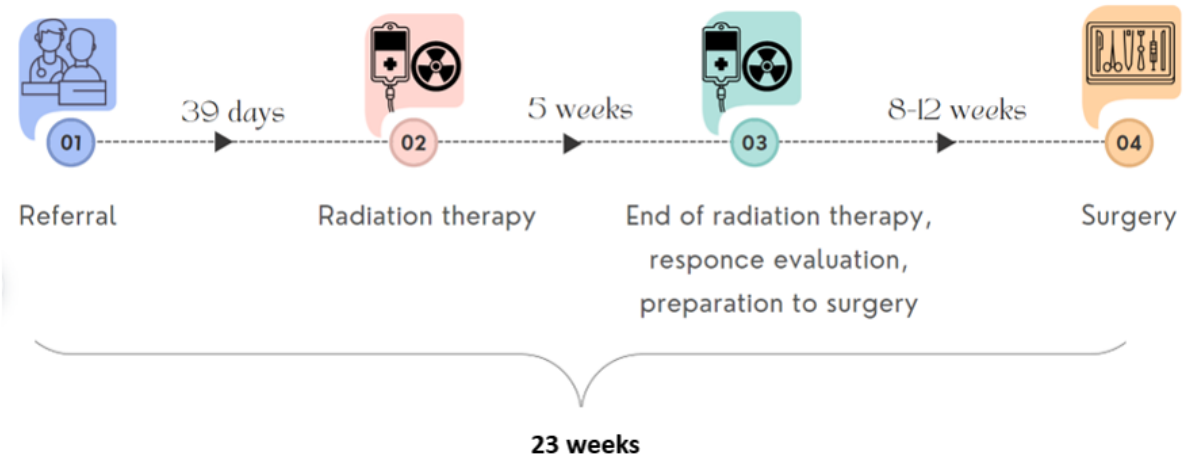
Rectal cancer without metastases

The choice of surgical method is based on tumor size, localization, and comorbidity. All patients with rectal cancer should be evaluated whether the purpose of surgery is radical or palliative. In some cases, the disease has progressed so far that palliative resection is not appropriate. Total mesorectal excision (TME) is a common procedure that involves the removal of the primary tumor along with its lymphatic pathways. T1 tumors that do not have high-risk pathological properties can be resected endoscopically. In the case of large tumors or suspected malignancy endoscopic submucosal resection is a preferred alternative. Low anterior resection (LAR), proctectomy and abdominoperineal resection (APR) is a variant for larger tumors.

Patients with suspicion of lymph node metastases are offered preoperative neoadjuvant therapy. Radiation therapy for rectal cancer is targeted to reduce the risk of recurrence, reduce the size of the tumor, and preferably avoid downstaging. Chemotherapy is given concomitantly with radiation therapy for better effect. As per the National Quality Register for Colorectal cancer the proportion of patients, receiving radiation therapy is 30% - 40% [41].

Evaluation of the response of neoadjuvant radiotherapy is done with an MRI of the pelvis, CT of the thorax or abdomen, and rectoscope 6–8 weeks after the end of treatment. In case of tumor progression, the patient is urgently operated on. In case of response to radiation therapy, surgery is performed from 8–12 weeks after completion of radiation therapy. The clinical pathway of patients with rectal cancer without metastases with treatment lead times is represented in the Figure 4.

Figure 4: *Patient Pathway and duration of treatment cycle of patients with rectal cancer without metastases.*



Treatment option for rectal cancer patient is defined by the diagnosed stage, age, general health condition and risk group. In Table 3 we presented treatment alternatives for the patients with different rectal cancer stages. Clinical pathway of patients with 0 and I stages is rather short as it does not imply neoadjuvant or adjuvant therapy.

Table 3: *Treatment pathway of patients with rectal cancer per different cancer stages*

Stage	Neo-adjuvant therapy	Surgical procedures	Adjuvant therapy
0	-	Turmor removal via rectoscopy; TME	
I	-	Turmor removal via rectoscopy; TME	
II	Radiation therapy or combination therapy	TME, LAR, APR or proctectomy	Chemotherapy; Radiation therapy
III	Combination therapy	TME, LAR, APR or proctectomy	Combination therapy
IV	Combination therapy	TME, LAR, APR or proctectomy	Chemotherapy, radiation therapy, immunotherapy

Standard *neo-adjuvant therapy* regimen for patients with T4 tumors is 2 Gy x 25 with the total duration of 5 weeks. Patients with resectable and low-risk tumors can be treated to a greater extent with 5 Gy x 5 lasting 1 week. For patients older than 75 years with reduced functional level, poor general condition and / or severe comorbidity regimen of 5 Gy x 5 with 1 week duration is often an alternative.

Adjuvant radiotherapy 2Gy x 25 combined with chemotherapy can be assessed by microscopic or macroscopic non-radical resection. Chemotherapy may be an alternative to radiotherapy for patients with high risk of local recurrence, especially for T4 turmors or other risk factors. Patients operated after neoadjuvant radiochemotherapy are not offered adjuvant chemotherapy as standard treatment but can be assessed individually based on risk factors.

Colon cancer without metastases

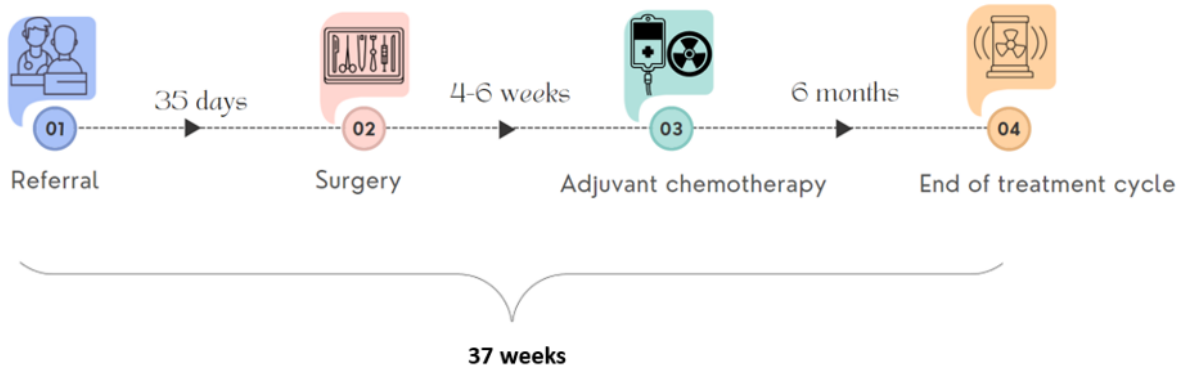
In some cases, at an early-stage polyp can be removed via colonoscopy, then surgery is not needed. Partial colectomy (resection of intestinal segment invaded by tumor) is the standard treatment of patients with colon cancer at I, II, and III stages. At later stages when the cancer is spread to nearby lymph nodes, the affected lymph nodes should be removed during the surgery. In stage IV, when metastasis is spread to other organs and distant lymph nodes surgery is considered only in rare cases for life-prolonging purposes.

A carcinoembryonic antigen (CEA) should be done after surgery to check carcinoembryonic antigen levels. This is a protein and antigen that is formed from the colon mucosa and where the concentration in the blood often increases with colon cancer. CEA is normally used to monitor the progression of the disease.

Adjuvant chemotherapy is the standard treatment for the stages of progression. The purpose of adjuvant chemotherapy is to eliminate microscopic tumors and possible recurrence. It should start within 4-6 weeks after surgery and last from 3 to 6 months depending on different factors and the patient's condition. For stage IV, chemotherapy is the main treatment, but radiation therapy can also be used for relieving symptoms. Immunotherapy may be offered after chemotherapy as an option.

Based on the treatment guidelines and lead times from the Patient Pathway we have outlined standard clinical pathway of patient diagnosed with colon cancer without metastases. This pathway covers patients receiving both surgical and adjuvant therapy and presented on the Figure 5.

Figure 5: *Patient Pathway and duration of treatment cycle of patients with colon cancer with metastases.*



Treatment offer varies and depends on the cancer stage and other factors like age, risk group and comorbidities. In Table 4 presented treatment alternatives for the patients with different colon cancer stages. As seen clinical pathway of patients with earlier stages is shorter than for patients with stages of progress due to the lack of adjuvant therapy.

Table 4: *Treatment pathway of patients with colon cancer per different cancer stages*

Stage	Surgical procedures	Adjuvant therapy
0	Polyp/turmor removal via colonoscopy; Colectomy	-
I	Polyp/turmor removal via colonoscopy; Colectomy	-
II	Colectomy	Chemotherapy
III	Colectomy; Surgery for nearby lymph nodes removal	Chemotherapy; Combination therapy
IV	No curative surgery, only life-prolonging/palliative	Chemotherapy, radiation therapy, immunotherapy *

** For stage IV the chemotherapy, radiation therapy, immunotherapy is main treatment*

Adjuvant chemotherapy regimen and duration for II and III stages patients is defined by patient's age and risk group. Alternatives for each stage and age group are presented on the Table 5.

Table 5: *Adjuvant chemotherapy regimens according to age- and risk group*

		Age group				
		Below 70		70 - 75		>75
Stage	**Risk status**	**Low-risk**	**High-risk**	**Low-risk**	**High-risk**	
II	**Treatment**	NOT OFFERED	CAPOX/ FOLFOX or Capecitabine	NOT OFFERED	CAPOX/ FOLFOX or Capecitabine	FLv* or capecitabine based on functional level and comorbidities
	Duration	-	*3-6 months*	-	*6 months*	*6 months*
III	**Treatment**	CAPOX/ FOLFOX	CAPOX/ FOLFOX	FLv* or capecitabin		FLv* or capecitabine based on functional level and comorbidities
	Duration	*3 months*	*6 months*	*6 months*		*6 months*

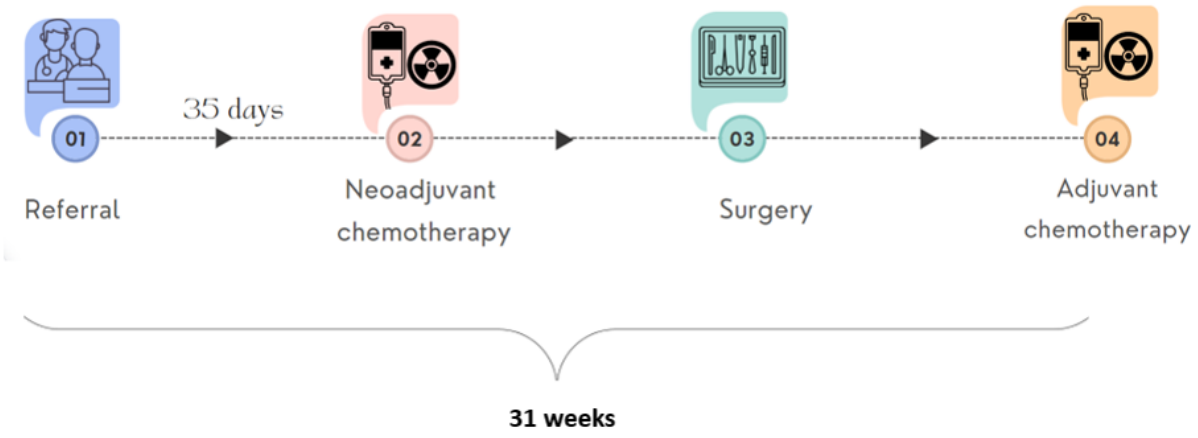
**FLV - combination regimen consisting of 5-fluorouracil and calcium folinate*

Patients over 75 years are carefully evaluated and trade-off between risk and benefit is taken into consideration. All in all they have less chances to get adjuvant therapy than younger patients due to poor health conditions and comorbidities.

Colon and rectal cancer with metastases

The treatment pathway of patients of both cancer types with metastases in organs usually starts with chemotherapy before the surgery and ends with 6-month adjuvant chemotherapy after it. The clinical pathway of such patients is presented in the Figure 6.

Figure 6: *Patient Pathway and duration of treatment cycle of patients with Colorectal cancer with distant metastases.*



Follow-up

Patients after curative resections of colon and rectal cancers should be monitored 1 month after treatment and followed up on an individual basis in case of adverse events and functional

disorders associated with cancer treatment. The new national follow-up program after curative treatment for colorectal cancer is based on the following premises:

1. screening for resectable metastases in the liver and lungs for the first 3 years when the risk is highest
2. focus on treatment-related negative impacts on quality of life and function:
    a. bowel / neo-rectum function
    b. the function of pelvic organs
    c. other radiation effects (microfractures of the pelvis, neuropathy)
    d. effects related to adjuvant chemotherapy
    e. general symptoms such as fatigue
3. the possibility of contact with the health service between the intervals of ailments related to cancer treatment
4. The control procedure supposes that a complete assessment of the remaining colon and rectum is made in connection with the primary cancer treatment.

Screening for resectable metastases in the liver and lungs after 1, 2, and 3 years should be offered to patients with curative resections of colorectal cancer of stages II and III in case the health state allows relevant oncological and surgical treatment. After the age of 80 routine follow-up is not offered. A follow-up plan is stipulated by the national guidelines and is presented in Table 6:

Table 6: *Follow-up recommendation plan of patient with rectal and colon cancer undergone where curative resection or oncological treatment.*

RECTAL CANCER									
Month after surgery	1	3 - 6	6	12	18	24	30	36	60
CEA (carcinoembryonic antigen)	✓		✓	✓	✓	✓	✓	✓	✓
Oncologist		✓							
CT lung / liver / abdomen / pelvis				✓		✓		✓	
Colonoscopy									✓

COLON CANCER									
Month after surgery	1	3 - 6	6	12	18	24	30	36	60
CEA (carcinoembryonic antigen)	✓		✓	✓	✓	✓	✓	✓	✓
Surgeon		✓							
CT lung / liver / abdomen / pelvis				✓		✓		✓	
Colonoscopy									✓

Recurrence

The follow-up plan described in the previous chapter is aimed to detect recurrences that can significantly reduce the length of life. The median survival of untreated patients with recurrences is 15 months. Patients with local recurrence are treated with the same methods as patients with primarily diagnosed colorectal cancer. Local recurrence in colon without proven inoperable metastases is normally assessed for surgery, often after adjuvant therapy.

Patients with local recurrent rectal tumor without detected metastases are treated with surgery. Reoperation in recurrence has poor oncological results with a high recurrence rate and reduced survival. The results of recurrent surgery are significantly better neoadjuvant treatment precedes surgery.

In some cases, re-radiation therapy may offered to patients who have previously received neoadjuvant or adjuvant radiation therapy. It is often used hyper-fraction technique offering 1.2 Gy twice a day till total dose of 40.8 Gy, or 1.5 Gy twice a day for a total dose of 40-45 Gy, combined with capecitabine. In case of palliative intention, it may be relevant to use radiation once per day without simultaneous chemotherapy. Treated with chemoradiotherapy and surgery survive 5-year in 20–35% of cases.

Palliative treatment

The aim of palliative treatment is to achieve the best possible quality of life and prolongation of life for patients with incurable diseases minimizing the possible risk of adverse events. There can be offered the following methods of palliative treatment of colorectal cancer: palliative surgery, endoscopy with stenting, Interventional radiology, and palliative radiation therapy for locally advanced tumors.

In general, the implementation of treatment guidelines can be costly and time-consuming. However, it can increase the efficiency of the treatment pathway, standardizing the process and therefore, optimizing resource and cost use.

3.6. Total cost of colorectal cancer, economic disease burden

In population and public health, it is recognized two approaches of measuring the burden of a disease. The most common approach has been labeled “biomedical.” It considers the impact of disease and disability on bodies from onset through the whole disease flow and measured in health-adjusted life years. The biomedical approach of disease burden focuses on the sick

individual and ignores the burden for the nearest circles society. The other approach is called the economic or cost-of-illness approach. It focuses on the financial costs of illnesses for individuals, households, healthcare systems, and societies [43, 44].

The economic burden of a disease includes several cost elements:

- Direct health care costs that are attributable to patient care - hospital beds, cancer drugs, medical personnel and equipment, etc.
- Informal care costs: these imply hours of unpaid care spent by family, creating an opportunity cost of their time.
- Intangible costs - the value of lost life years and lost quality of life due to premature death or reduction in patient's life quality.
- Indirect cost - production losses due to mortality and morbidity [45, 46].

Increasing incidence of colorectal cancer and advances in therapeutic innovation have contributed to increase all categories of the above-mentioned costs [44].

There have been conducted two pan-European studies aiming to quantify colorectal cancer disease burden and taking into consideration societal perspective:

- A population-based cost-of-illness study calculating the economic burden of colorectal cancer in 33 European countries based on 2015 activity and costing data [44].
- A prevalence-based cost-of-illness study estimating the cost of 6 major cancer types of a digestive system based on 2018 data. The research is commissioned by Digestive Cancers Europe and delivered by the Swedish Institute of Health Economics [45].

These two studies represent the most comprehensive analysis to date of the economic burden of colorectal cancer and digestive cancers in Europe. However, the researchers consider that the data should be interpreted with caution [45].

According to the first research, the economic burden of colorectal cancer across Europe in 2015 was €19.1 billion. Direct health care made up 39.4% of the total economic burden, while the rest 60.6% attributed to non-healthcare cost [44].

The economic burden for Norway was estimated as €474 million, broken down into €21.5 million (4.5% of the total economic burden) of health-care costs, and non-healthcare costs of €452.7mi (95.5% of the total economic burden). Such a high ratio of non-healthcare costs can be partly explained by the fact that Norway is a high-income country and productivity losses

due to disease are considerable. According to Norwegian health economists', research aiming to calculate the societal cost for all cancer types in Norway, direct health care costs make up 9% of the total disease burden. Compiled results of the study are represented in Table 7.

Table 7: *Costs (× €1000) of colorectal cancer in Norway and proportion of health-care costs, 2015.*

Health-care costs						**Productivity costs**		**Informal care costs € (%)**	**Total non-health-care expenditure costs, € (%)**	**Total costs, €**
Primary care costs, € (%)	Outpatient care costs, € (%)	Emergency care costs, € (%)	Hospital care costs, € (%)	Systemic anti-cancer therapy costs, € (%)	Total health-care expenditure costs, € (%)	Mortality costs, € (%)	Morbidity costs, € (%)			
1 419 (6.6%)	4 964 (23.1%)	242 (1.1%)	10 744 (50.1%)	4 088 (19.1%)	21 456 (4.5%)	36 526 (7.7%)	395 589 (83.4%)	20 540 (4.3%)	452 655 (95.5%)	474 110

Note: From Henderson, French, D., Maughan, T., Adams, R., Allemani, C., Minicozzi, P., Coleman, M. P., McFerran, E., Sullivan, R., & Lawler, M. (2021). The economic burden of colorectal cancer across Europe: a population-based cost-of-illness study. *The Lancet. Gastroenterology & Hepatology*, *6*(9), 709–722. https://doi.org/10.1016/S2468-1253(21)00147-3

As per the research conducted on digestive system cancer types, the economic burden for them jointly amounted to €39 billion in Europe in 2018. Colorectal cancer caused the highest cost and amounts to €19 billion. Total costs of colorectal cancer in Norway are represented in Table 8. Research partly used data from the report "Cancer in Norway: Cost for patients, health services and society" conducted by Oslo Economics in 2016 based on the data for 2014.

Table 8: *Total cost of colorectal cancer, in million €, 2014.*

	Direct costs		**Informal care costs**	**Indirect costs**		**Total costs**
Cancer type	Health expenditure	Cancer drugs		Mortality	Morbidity	
Colon cancer	146.3	13.9	35.9	60.5	41.5	284.3
Rectal cancer	72.4	6.5	16.9	29.0	26.3	144.6

Note: From Hofmarcher T, Lindgren P. The Cost of Cancers of the Digestive System in Europe. IHE Report 2020:6. IHE: Lund, Sweden.

Regarding cost per patient, Joranger et.al. [47] modeled and validated the cancer costs for patients diagnosed with colorectal cancer from the age of 70 until death or up to 100 years. The focus was on the health care payer perspective and the costs included in-hospital treatment, radiation and chemotherapies, treatment of recurrence and complications, besides follow-ups

and visits to a general practitioner [47]. The study is from 2015 and it analyzed stage-specific costs of colorectal cancer. The authors included the analysis of the cost and clinical pathway for colorectal cancer from an observational study at the largest university hospital in Norway with 2 049 patients. It combined parameters from different sources compiling a model-based estimate for analysis of costs and survival. The model estimated a cost range from € 23 386 for stage I to € 61 396 for stage IV. Stage III costs were € 49 894 and for stage II patients, € 33 501. [47]

Previous literature on stage specific costs, such as the 2017 Spanish study retrospectively collected demographic data, clinical data and resource use of a sample of 529 patients. The estimated total cost per patient was € 8644 for stage I, € 12 675 for stage II, € 13 034 for stage III, and € 24 509 for stage IV. [45] The conclusion was that hospitalization is the main cost component. In addition, the total annual cost for colorectal cancer extrapolated to the whole Spanish health system was € 623.9 million [45].

In 2008, a French study used data from the population-based registry to estimate the direct costs of medical care for 384 colorectal cancer diagnosed patients in 2004 [46]. The authors defined the cost of management as the sum of all health expenditures over the twelve months following the date of diagnosis. The mean cost for first-year management was € 24 966. In addition, the costs from stage I to stage IV increased from € 17 596 up to € 35 059. Hospitalization accounted for the greatest economic burden (55, 2%), followed by medical purchases (24, 4%) and outpatient care (17, 8%), among others. Therefore, the results from the French study indicated that total costs depend mainly on the stage at diagnosis. [46] The cost of treatment can be lower at early stages, however, the correlation between cost of resources employed in patient care and management remains unclear [44].

In our thesis, we will consider the health care perspective and explore health care costs, though we consider that such measures as the introduction of the Patient Pathway will influence informal and indirect costs.

3.7. Factors influencing costs

The diagnosis and treatment of cancer can be costly [48]. Normally, patients will have unplanned expenses related to their care [49]. The costs of cancer treatment will vary significantly from patient to patient and depending on the type of cancer. However, there are different factors that contribute to an individual overall cost of their health care. [48]

The insurance status or the type of insurance coverage someone has, for example, is one of the most important factors determining the final cost for patients [48, 49]. It can be a monthly amount paid (premium insurance), deductible (the patient pays out of pocket first), co-payment (a flat fee per procedure), or as it is in Norway, out-of-pocket cap (limiting a patient payment each year before costs starts being covered) [48]. Another important factor is the so-called balance billing. It happens when a person encounters unanticipated costs, for example, consulting with a provider that was not included in the insurance network or when the plan does not reimburse the full amount billed. Therefore, the patient has to pay the difference.

Other factors are considered when discussing the Norwegian health care system. The treatment plan (types of treatment), for instance, if the patient undergoes surgery, chemotherapy, or radiation, combined with the duration and the number of surgeries or drugs, causes costs to vary substantially. [48] The stage at which a patient is diagnosed is another important factor, given the fact that it determines the treatment plan and potential outcomes [48, 49]. The geographical location, the age of the patient along with the treatment setting, and gender.

The geographic location should be considered as an important factor for costs, especially in Norway, given its many rural and remote areas. Even though the number of GPs is well distributed in the country, specialists are concentrated in the capital or urban areas, which means that the costs will vary based on how far the patient lives from the city center. Normally, areas with high costs of living tend to have higher treatment costs. [48]

Another relevant factor is the treatment setting. Treatment fees can be based depending on whether care will be delivered at a clinic, a hospital, or at the GP's office. Sometimes patient may choose where they would like to receive the treatment, but other times they are not in a position to make the decision and this might incur additional costs. [48]

The age at which the patient is diagnosed with cancer can be considered another factor to influences the cost. However, the age factor is closely related to the stage group of the patient. Studies suggest that patients in the age group of 65 years and with stage IV tumors increase the

average length of hospital stay and average costs [50, 51]. Other studies are more in line with the results of the thesis, proving that resource utilization (costs and days) will increase with more advanced disease and younger age [52].

The factor gender was also included in the regression analysis of this thesis, given that gender is not only important for costs but also for assessing equity of care [53]. Bugge et al. (2021), tested the costs of cancer for phase-and gender-specific in Norway and the conclusion was that males may have higher treatment costs than females for the majority of cancer types, including colorectal cancer [54]. Even though the difference is slightly small, previous studies also find differences in costs between genders [55].

3.8. National cancer strategy in Norway

The National cancer strategy in Norway is harmonized with Europe's Beating Cancer Plan and its flagship initiatives focusing on prevention, early detection and equal patient access [56].

The first national cancer plan in Norway was issued in 1999 and aimed to reduce the number of new cancer cases through a long-term strategy for prevention and improving the offer within diagnostics and treatment. Later, there was elaborated several consecutive national cancer strategies defining activities for preventative work, screening programs, diagnostics, treatment and rehabilitation. Special attention was paid to the development and maintenance of cancer registers and research activities.

The current national cancer strategy "Leve med kreft" (2018–2022) defines the following national objectives:

- Building up patient-oriented cancer care.
- Norway to become a pioneering country for well-organized Patient Pathways.
- Norway to become a pioneer in cancer prevention.
- Improved survival.
- The best possible quality of life for cancer patients and relatives [57].

The second goal of the national cancer strategy – "Norway to become a pioneering country for well-organized Patient Pathways" is directly connected to the topic of this master thesis. Standardized Patient Pathway for colorectal cancer helps to improve the quality of colorectal

cancer care and create predictability for the patients. Apart from qualitative implications, it may entail cost consequences, which is the topic of the current research.

The national cancer strategy is also focused on reduction of adverse events and so-called "postponed effect", caused by cancer treatments and giving negative impacts on patients. It is aimed to map possible "postponed effects" and reduce their incidence [58].

Cancer strategy in Norway is supported by two mutually reinforcing principles:

- Patient inset in focus and actively participates in the decisions on the treatment.
- Improvement of treatment quality and providing comprehensive and well-coordinated health care. [57]

In the framework of national cancer strategy, there were elaborated 24 national action plans for various cancer types including guidelines for diagnostics, treatment and follow-up. The action plan for colorectal cancer was updated in January 2021 and contains the latest treatment recommendations.

National health authorities have also published a row of guiding documents that are supposed to strengthen the preventive efforts and are closely connected to colorectal cancer prevention. Among these are the National Action Plan for a better diet (2017–2021), National strategy against tobacco (2013–2016), A future without tobacco (2012), and the strategy to reduce radon exposure (2009). [58]

4. Patient Pathway for colorectal cancer

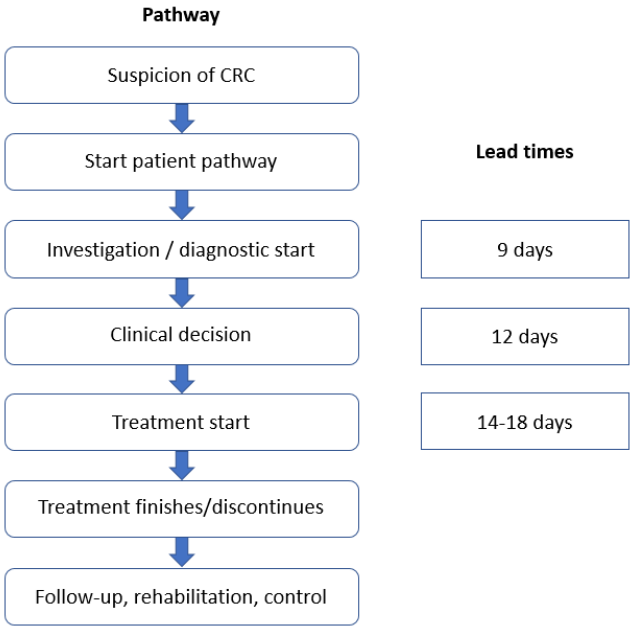
The main problem in the organization of colorectal cancer diagnostic and treatment in Norway was the inefficiency of the process. This was first of all caused by the considerable amount of stakeholders involved in the diagnostic and treatment cycle, besides the lack of coordination between them. The other problem was variation in the service offerings, lack of colorectal cancer treatment standards, and detailed guidelines. Due to the absence of coordination of the diagnostic process and therefore long waiting time, a higher amount of cases were identified in later stages and therefore worsened outcomes [59].

To respond to these problems, the Patient Pathway for colorectal cancer was introduced on the 1st of January 2015. The Patient Pathway for colorectal cancer is one of the 28 national standardized cancer pathways. It is based on the National action program and guidelines for

diagnosis, treatment and follow-up of colorectal cancer [60]. Norway built its Patient Pathway on the Danish experience, where the first Patient Pathway was introduced in 2008.

The Patient Pathway represents a standardized route the patient follows through the diagnostic and treatment process. The pathway starts from the referral of a patient with a grounded suspicion of cancer for examination within specialist health care [61]. The flow chart for Patient Pathway is represented in Figure 7.

Figure 7: *Patient Pathway for colorectal cancer – flowchart.*



Note: From Helsedirektoratet. Pakkeforløp for Tykk- og endetarmskreft. https://www.helsedirektoratet.no/pakkeforlop/tykk-og-endetarmskreft/introduksjon-til-pakkeforlop-for-tykk-og-endetarmskreft visited on 10th, January 2022.

The Patient Pathway describes the organization of diagnostic and treatment, the interaction between patient and health care stakeholders, defines responsibilities and lead times for diagnostic and treatment.

The purpose of the Patient Pathway for Cancer is to ensure that patients experience a well-organized, comprehensive, and predictable treatment course without unnecessarily non-medically justified delays in assessment, diagnostics, treatment and rehabilitation. [59].

The main instruments of the implemented Patient Pathway for colorectal cancer aiming to solve the above-mentioned problems are diagnosis and treatment lead-times, multidisciplinary teams meetings and pathway coordinator.

Diagnosis and treatment lead times

The pathway lead times is a stipulated maximum time (in calendar days) the different phases in the process should take. Lead time for colorectal cancer pathway is represented in Appendix 10.2 Table A 1. The Norwegian government set a targeted to complete 70% of all pathways within these lead times. The Regional Health Trusts ensure that the lead times are followed. Data on the actual lead times is reported and can be tracked.

Multidisciplinary teams meetings

Multidisciplinary teams (MDT) meeting for thorough interdisciplinary investigations and making decisions on patients' treatment. Weekly MDT meetings are attended by a wide range of health care specialists and used for discussions of patients' disease path, treatment alternatives and making decisions. This measure ensures proper follow-up of each patient and aimed to improve quality.

Pathway coordinators

Pathway coordinator is a main contact person the patients and main source of information on Patient Pathway. The coordinator is in charge of appointments, logistics and continuity of the package process. [59, 60, 61]

In addition to above mentioned instruments, Patient Pathway set a low threshold to be referred to specialist health care for diagnostic. All patients over 40 years having at least one of three symptoms: unexplained bleeding from the intestine, change of stool for over four weeks and discovered tumor or polyp can be referred to the Patient Pathway. Thus, there is increased chances to diagnose cancer earlier.

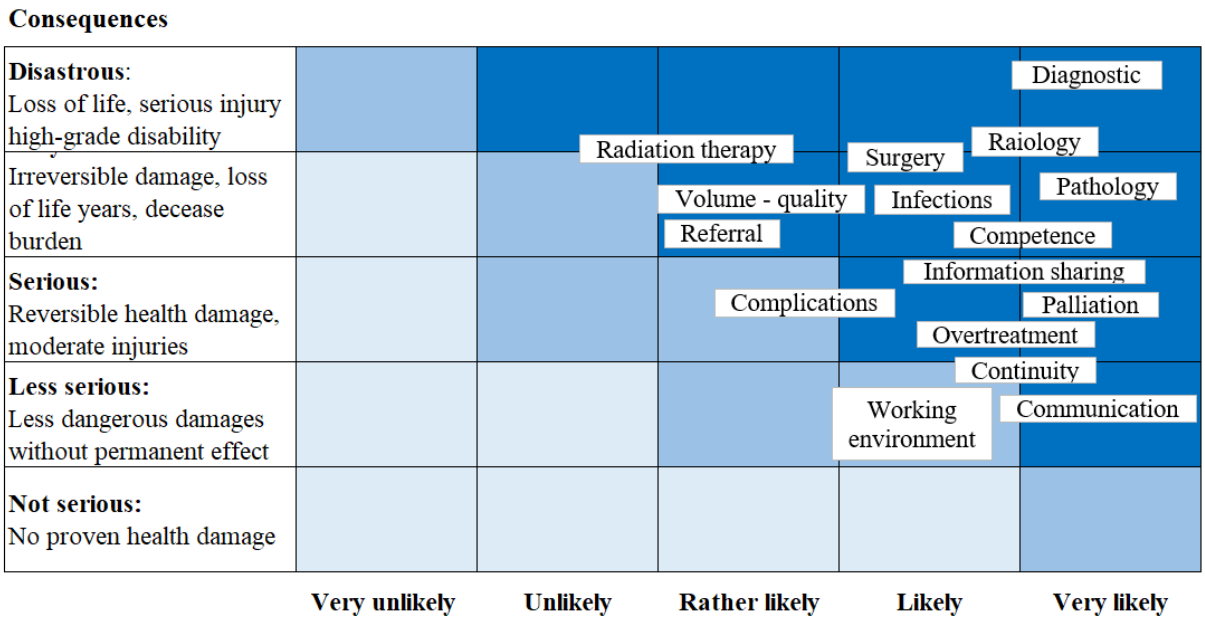
As per the statistics from National Patient Register (NPR) published on the Norwegian Directorate of Health, 73% of patients, included in the colorectal cancer Patient Pathway were diagnosed and treated within the stipulated lead times in the period 01.01.15 – 01.12.2021 [62].

In this master thesis, we aimed to check which implications Patient Pathway had on costs. This problem should be considered from two perspective: short-term and long-term.

4.1. Background for Patient Pathway for colorectal cancer

The purpose of the Patient Pathway is to provide for patients to experience a well-organized and predictable process without unnecessary delays in diagnostics and treatment. Time to diagnosis and treatment is defined by capacity and effectiveness of organization. In 2010, the Norwegian Board of Health Supervision conducted risk analysis of cancer treatment on the national level in order to identify the risk areas and bottlenecks in the treatment of cancer. The risk analyses revealed that the most important problems were associated with late diagnosis, information flow between different stakeholders and lack of continuity in patient care. The research was conducted with the help of literature search and review of multiple data sources as audit reports, media cases, official statistics, adverse events database maintained by the Norwegian Medicines Agency and interviews with health care professionals. As a result of the work, it was identified 16 most important problem areas in cancer treatment in Norway, summarized in the Appendix 10.2 Table A 3. They were further set-up in a risk matrix according to Figure 8, defining severity level of consequences. The most important risk factor was delays in diagnostics and unnecessary non-medical delay, which is considered to have disastrous consequences and lead to loss of life or serious injuries [63].

Figure 8: *Norwegian cancer treatment risk matrix. Relationships between 16 most important problems*

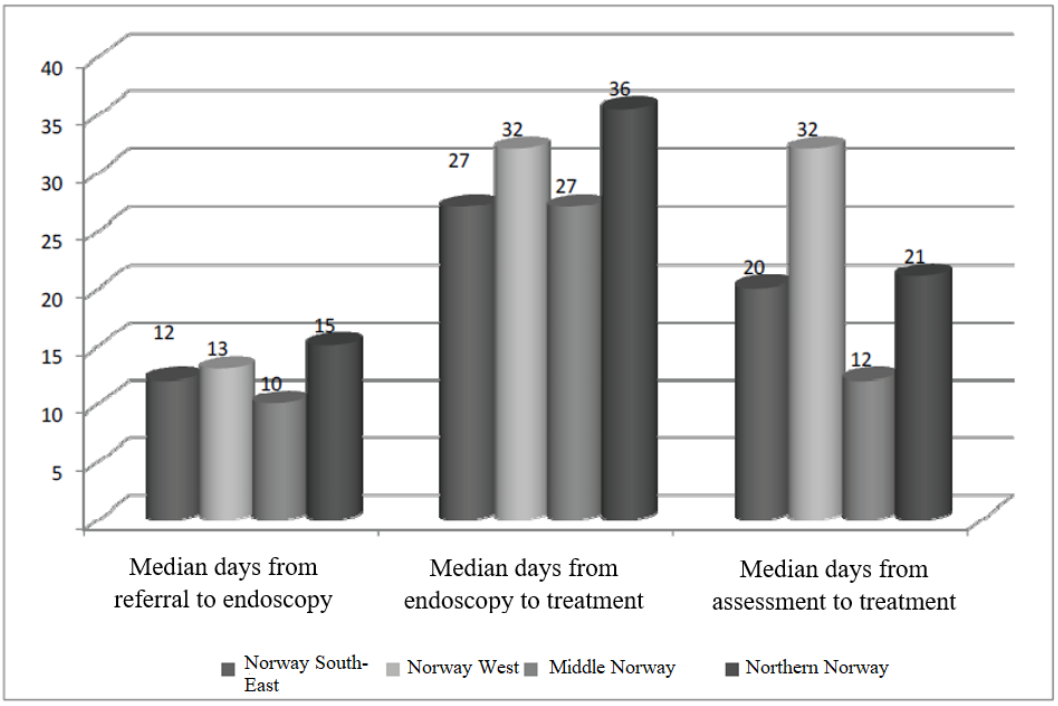


Note. Adapted from Rapport fra Helsetilsynet 4/2010 «Risikobildet av norsk kreftbehandling», 2010. Available on:

https://www.helsetilsynet.no/globalassets/opplastinger/Publikasjoner/rapporter2010/helsetilsynetrapport4_2010.pdf/

At the same time SINTEF (Applied research, technology and innovations) conducted research on waiting time for patients with breast or colorectal cancer based on patient unique episode data. It covered both diagnostic and treatment procedures. As a results of the research it was discovered big regional differences in waiting times from diagnosis till further treatment. Median waiting time for different procedures are presented on the Figure 9. Central Norway is the region with the shortest waiting time, while patients from the West have the longest [64]. Research revealed the problem of inequality of access to diagnostic and treatment services for breast cancer and colorectal cancer patients.

Figure 9: *Median waiting time from referral date to endoscopy, from date of endoscopy to first treatment and from assessment to treatment.*



Note: Adapted from Kalseth B. (2016). Beskrivelse av venteforløp for pasienter med brystkreft eller kreft i tykktarm og endetarm basert på pasiententydige episodedata. (Report No. SINTEF A19098). SINTEF Teknologi og samfunn

According to Director of Medical Strategy and Development for Northern Norway Regional Health Authority share of patients with Colorectal cancer treated within 20 days is 61,3% for Norway [65].

According to National treatment guidelines for colorectal cancer chemotherapy should be started within 4-6 weeks after the surgery. Olsen et al. (2016) conducted research based on

dataset for 2008 - 2013 to investigate whether the guidelines were followed. The analysis showed for 49% of patients receiving chemotherapy did not start within the 6 weeks deadline [66].In addition, there have been observed significant differences between hospital – for instance at St. Olavs Hospital share of patients started chemotherapy after 6 weeks deadline was 27%, while at Sykehuset Telemark this share was 67% [66].

As described above, the problem of delays in waiting times and inequality of access to cancer treatment was common for different types of cancer and therefore required joint measures at national level. Patient Pathway was elaborated with intention to solve these problems and making patients' pathway predictable.

4.2. Assumptions on Patient Pathway implications on cost

In this master thesis study, we aimed to evaluate the effect of implementation of Patient Pathway introduction on costs per patient. The effect can be considered both from short-term and long-term perspective.

A set of measures of Patient Pathway is aimed to reduce waiting time and ensure equitable patient access to cancer treatment. Reduction of waiting time is expected to result in more treatment activities provided to the patient at the same period of time and earlier access to treatments. For instance, adjuvant therapy can be started within 4-6 weeks after the surgery as required by guidelines, which was not the case before Patient Pathway introduction [63]. Treatment started later has less effect and contributes to adverse events [64], which results in additional costs.

A low threshold for referral leads to a higher number of cases for further investigation and inclusion into PP. This can argument for both mean treatment cost increase and mean cost decrease. From the one side this measure helps patients with earlier cancer stages and less evident symptoms to be referred to specialist care. Patients with early cancer stages require less advanced treatment and fewer treatment activities as mentioned in chapter 3.5. Such patients will contribute to reduction of mean cost. From the other side Patient Pathway is aimed to provide equitable access to cancer treatment for all type of patients. This implies no differentiation based on age, gender, comorbidities, other patient characteristics and geographical location. This approach eliminates access deny for patients at high risk. Inclusion of more high-risk patients into Patient Pathway arguments for cost increase. Equitable access

might also eliminate the amount of acute surgeries. About 15–25% of all patients with colon cancer are admitted acutely. Mortality among these patients is around 10–25% [64]. A significant proportion of acute patients are of older age and have comorbidities. Part of these cases can be avoided due to access to Patient Pathway and early treatment. In-time treatment of both patients with less severe and more severe cancer stages and comorbidities impacts survival. From one side it will positively influence mortality level and more patients have chance to recover. From the other side, patients with later cancer stages will live longer and require more maintaining treatment or palliative care throughout the life, which will drive cost increase.

From the above-mentioned argumentation, it is not evident which effect Patient Pathway could have on costs in a short-term perspective. Some arguments drive for higher costs and some in the direction of lower costs. Final results are largely defined by patient-mix and size of different age- and risk groups. In a long-term perspective the effect can be less predictable.

5. Data and methods

To estimate the impact of the cancer Patient Pathway on cost data from two linked registers were used: The Cancer Registry of Norway (CRN) and The Norwegian Patient Register (NPR). The following sections will provide a description of the datasets, variables used in the analysis and statistical analysis.

5.1. Ethical considerations

Data approval was necessary from the Cancer Registry of Norway (CRN) and The Norwegian Patient Register (NPR) in order to conduct the analysis using their respective dataset. The data was accessed through a platform called TSD and it had anonymous patient IDs and no other registry linked. Given that the data consists of health registry data (Helseregisterloven § 29), a notification was necessary from the Regional Committee for medical and health research (REK). Approval from REK was received on the 12th of November. The approvals were attached to the Appendix 10.1 of our master thesis.

5.2. The Cancer Registry of Norway

We used data from the Cancer Registry of Norway (CRN) and the Norwegian Patient registry (NPR). The study sample was defined by CRN. The data included all individuals diagnosed with colorectal cancer (CRC) in the period from 2012 until 2017, except 2015, and are divided in the ICD-10 codes as the main diagnosis. Ranging from ICD-18 until C20. All cases for patients with ICD-10 C18 are considered as colon cancer, while C19 and C20 are rectal cancer. The CRN dataset provides timeliness data of high quality and comparability with estimated completeness of 98.8% for all cancer sites [67]. The CRN uses the personal identification number (PID number) assigned to every Norwegian citizen to update the registry every month to ensure the integrity of new cancer cases. Whenever a patient is diagnosed with cancer, clinics, treatment centers with radiation therapy, and pathological reports (biopsy, surgery, autopsy, and cytology), are the sources used to report the cancer status to the CRN. [68, 69].

In order to estimate an interaction between costs and survival, data from the CRN were collected for colorectal cancer. In the first section, it will be described the CRN dataset used in the analysis together with assumptions made for the collected variables.

Other than the colon and rectal variables, the patient ID (numerical), date of diagnosis (interval), age (numerical), and the TNM variables (categorical) will be included. The complete explanation of the type of variable used and the criteria are presented in Appendix 10.2 Table A 2. The original dataset from the CRN before merging of the data contained 26 095 records.

5.3. The Norwegian Patient Register

The Norwegian Patient Register (NPR) is one of Norway's central health registries and is run by the Norwegian Directorate of Health [70].

NPR contains information on all persons who have received treatment at specialist health care and all persons on the waiting list for treatment. Among the data which NPR collects is the information on a stay at health institutions, diagnoses, and all health-related procedures that are performed on the patients. Information on both inpatient and outpatient services, besides daycare are also collected from the Norwegian Patient Register. Reporting to the NPR is mandatory, therefore the data is complete. [70, 71]

Since 2007, the Norwegian Parliament decided to amend the Health Register Act to establish a personally identifiable, encrypted NPR [70]. This provided opportunities for following the course of treatment over years and across hospitals, as well as linking data from the patient register with data from other registers. In the current Master thesis, we merged the dataset from NPR and NCR, which let us conduct a more precise analysis using variables from both data sources.

Dataset from NPR contains information on activities for all individuals with colorectal cancer diagnosis in the period 2012-2017. The list of activities for these individuals was not limited to cancer-related treatment. For higher precision of the analysis, the treatment activities not related to colorectal cancer were excluded. The list of excluded procedures is presented in Appendix 10.2 Table A 5. The initial dataset from NPR before dropping irrelevant activities contained 768 848 records.

The variables used in the analysis included gender (categorical), year of procedure (numerical), the DRG code (categorical), the main diagnostic group (hdg), a patient's death year (numerical), etc. For a complete explanation of the variables from NPR used in the analysis, check Appendix 10.2 Table A 4.

5.3.1. Patient population

Ensuring data quality

For the variables of interest presented in the previous table, a few steps were taken to guarantee accuracy and quality for coding the data. Both the CRN and the NPR have a patient identification number (ID number) containing 5 digits and they will match in both registries. Besides the matching PIDs, the NPR data have an enter date no earlier than 31 days before the diagnosis date, in other words, the NPR records the data starting from a month before the diagnosis date. Therefore, the data was checked by PID records, in order to identify whether patients were missing or had multiple records. In order to avoid those problems, the CRN and NPR data files were merged and it accounted for the PIDs only once.

Preparation

To ensure that the accounted cases would be related to colorectal cancer, it was necessary to drop some variables. ICD-10 codes are the main diagnosis; considering the range from C18 to C21. However, C21 refers to the malignant neoplasm of the anus and anal canal, which goes

beyond the range of colorectal cancer. So, we dropped all cases classified as ICD-10 C21 from the dataset.

Besides C21, a filter was created for age groups. Most patients with colorectal cancer in Norway belong to the age group of 60–80 years, therefore after tabulating the age frequency on Stata, patients under 40 years old did not have a significant frequency (below 0.48%), representing a total of 3,495 individuals. Thus, all patients under 40 years old were dropped from the analysis, and eight age groups were then created.

The year of diagnosis and treatment was also a relevant variable. Given the fact that the present work will compare the results before and after the Patient Pathway program, which started on first of January 2015, the analysis should include two years earlier and two years after. Therefore, patients treated or diagnosed before 2012 will not be considered. However, data from 2017 is not available in the registries. Thus, the period of consideration will include the range from 2012 until 2016, given the fact that 2015 is lacking data because it was the year of the implementation of the program.

To ensure patient anonymity, the variables for date of diagnosis and date of death were given in month or year format, not including the specific date. This however created a survival time of zero for those patients who died within the month they received the diagnosis. Therefore, to guarantee that survival time for these patients would be included in the analysis a date variable was included.

The last step for preparation was regarding the main diagnostic group (HDG) combined with the DRG code. According to the CRN, every patient is assigned to a diagnostic group, ranging from one until 23, plus 30, 40 and 99. In order to keep individuals related to colorectal cancer, some groups were dropped. All DRG codes included in HDGs 22 and 30 were removed, as well as some specific DRG codes in the 1, 2, 3, 4, 5, 8, 9, 14 and 19 main diagnostic groups.

The complete explanation of dropped variables according to the specific HDG are presented in Appendix 10.2 Table A 5.

Staging procedure

The National program with guidelines for diagnosis, treatment, and follow-up of cancer of the colon and rectum combined with the CRN utilizes a condensed staging system for colorectal cancer [72, 73]. Given the fact that our master thesis is based on the guidelines and the CRN, the analysis shall be performed within the parameters expressed by Table 2 on chapter 3.3.

Stages ranging from 0 to IV, besides the unknown stage. Further analysis and the incidence rates by stage for colorectal cancer were also identified through the coding system.

Following variables from the CRN were used for assigning the relevant stages.

Table 9: *CRN variables used for defining cancer stage*

Variable in CRN	Assigned TNM	UICC Stages
T0Colon T0Rectum	T0	Stage 0
T1Colon T1Rectum	T1	Stage I
T2Colon T2Rectum	T2	
T3Colon T3Rectum	T3	Stage II
T4aRectum T4bRectum T4Colon	T4	
N1aRectum N1bRectum N1Colon N1cRectum	N1	Stage III
N2Colon N2Rectum	N2	
Levermet_fjern Hjernemet_fjern Lungemet_fjern Peritoneummet_fjern Skjelettmet_fjern Fjernelkmet_fjern Annetfjernmet_fjern	M1	Stage IV
Missing information	Missing information	Unknown

Population characteristics

Selected patient characteristics for patients diagnosed with colon cancer are presented in Table 10. There was a total of 16 344 patients diagnosed with colon cancer between 2012 and 2017. Two main categories were selected to present the characteristics; age and stage. Females represent a bigger amount of the population when considering colon cancer, with stage III as

the most common stage and the age group of 90 and over as the most frequent ones. While for males, stage IV is the most common one, with the age group of 60-69 as the most frequent.

Table 10: *Patient characteristics. Patients diagnosed with colon cancer from 2012 until 2017 by age and stage.*

COLON CANCER						
	Males		Females		Total	
	N	%	N	%	N	%
Age						
40-49	283	*4 %*	305	*4 %*	588	*4 %*
50-59	824	*11 %*	798	*9 %*	1622	*10 %*
60-69	2099	*27 %*	1822	*21 %*	3921	*24 %*
70-75	1374	*18 %*	1370	*16 %*	2744	*17 %*
75-80	1261	*16 %*	1399	*16 %*	2660	*16 %*
80-85	1127	*14 %*	1404	*17 %*	2531	*15 %*
85-90	643	*8 %*	965	*11 %*	1608	*10 %*
90 and over	233	*3 %*	437	*5 %*	670	*4 %*
TOTAL	**7 844**	***100 %***	**8 500**	***100 %***	**16 344**	***100 %***
Stage UICC						
0	2689	*34 %*	2980	*35 %*	5669	*35 %*
I	914	*12 %*	969	*11 %*	1883	*12 %*
II	1257	*16 %*	1385	*16 %*	2642	*16 %*
III	554	*7 %*	660	*8 %*	1214	*7 %*
IV	891	*11 %*	826	*10 %*	1717	*11 %*
Unknown	1539	*20 %*	1680	*20 %*	3219	*20 %*
TOTAL	**7844**	***100 %***	**8500**	***100 %***	**16 344**	***100 %***

In addition to colon cancer, selected patient characteristics for patients diagnosed with rectal cancer are presented in Table 11. There was a total of 7 632 patients diagnosed with rectal cancer between 2012 and 2017. The same main categories were selected to present the characteristics, age and stage. In rectal cancer, males represent the bigger proportion of patients, in stage IV and group of 60-69 as the most frequent categories. While for females, the unknown stage is the most common one, in the age group of 90 and over.

Table 11: *Patient characteristics. Patients diagnosed with rectal cancer from 2012 until 2017 by age and stage.*

RECTAL CANCER						
	Males		Females		Total	
	N	%	N	%	N	%
Age						
40-49	227	*5 %*	188	*6 %*	415	*5 %*
50-59	680	*15 %*	466	*15 %*	1146	*15 %*
60-69	1462	*32 %*	839	*27 %*	2301	*30 %*
70-75	743	*16 %*	470	*15 %*	1213	*16 %*
75-80	643	*14 %*	395	*13 %*	1038	*14 %*
80-85	463	*10 %*	350	*11 %*	813	*11 %*
85-90	240	*5 %*	254	*8 %*	494	*6 %*
90 and over	72	*2 %*	140	*5 %*	212	*3 %*
TOTAL	**4 530**	***100 %***	**3 102**	***100 %***	**7 632**	***100 %***
Stage UICC						
0	476	*11 %*	349	*11 %*	825	*11 %*
I	773	*17 %*	557	*18 %*	1330	*17 %*
II	1274	*28 %*	861	*28 %*	2135	*28 %*
III	509	*11 %*	338	*11 %*	847	*11 %*
IV	712	*16 %*	417	*13 %*	1129	*15 %*
Unknown	786	*17 %*	580	*19 %*	1366	*18 %*
TOTAL	**4 530**	***100 %***	**3 102**	***100 %***	**7 632**	***100 %***

For current research change in patient-mix can be essential since age and cancer stage defines treatment pathway and therefore may directly impact cost and research outcome. As per data in Table 12 number of patients diagnosed with II stage of rectal cancer after Patient Pathway introduction decreased, while number of patients diagnosed with III stage of rectal cancer increased. For colon cancer number of patients of both II and III stages increased through the whole analyzed period.

Table 12: *Proportions of patients with different cancer stages diagnosed with rectal and colon cancer in the period 2012-2017*

RECTAL CANCER												
UICC	**2012**		**2013**		**2014**		**2015**		**2016**		**2017**	
Stage	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
0	149	*12 %*	171	*13 %*	178	*14 %*	124	*10 %*	110	*9 %*	90	*7 %*
1	207	*17 %*	237	*18 %*	240	*18 %*	232	*18 %*	206	*16 %*	207	*17 %*
2	463	*39 %*	462	*35 %*	417	*32 %*	287	*22 %*	273	*21 %*	232	*19 %*
3	23	*2 %*	52	*4 %*	81	*6 %*	173	*13 %*	250	*20 %*	268	*22 %*
4	212	*18 %*	221	*17 %*	220	*17 %*	199	*16 %*	162	*13 %*	114	*9 %*
Unkhown	144	*12 %*	166	*13 %*	170	*13 %*	267	*21 %*	280	*22 %*	316	*26 %*
Total	1198		1309		1306		1282		1281		1227	

COLON CANCER												
UICC Stage	**2012**		**2013**		**2014**		**2015**		**2016**		**2017**	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
0	1292	*50 %*	1316	*51 %*	1316	*50 %*	764	*28 %*	507	*18 %*	462	*17 %*
1	235	*9 %*	244	*9 %*	221	*8 %*	369	*13 %*	414	*14 %*	397	*15 %*
2	434	*17 %*	373	*14 %*	378	*14 %*	441	*16 %*	522	*18 %*	489	*18 %*
3	19	*1 %*	55	*2 %*	65	*2 %*	224	*8 %*	432	*15 %*	417	*16 %*
4	334	*13 %*	326	*13 %*	314	*12 %*	323	*12 %*	252	*9 %*	162	*6 %*
Unkhown	272	*11 %*	278	*11 %*	364	*14 %*	626	*23 %*	738	*26 %*	750	*28 %*
Total	2586		2592		2658		2747		2865		2677	

For both cancer types we observe increase of number of patients with unknown cancer stage.

Analysis of age groups dynamics reveals that both for rectal and colon cancer amount of patients below 75 year increased after Patient Pathway implementation. Share of patient above 75 years does not exceed 35% for rectal cancer and 45% for colon cancer meaning that patients diagnosed with rectal cancer are younger.

Table 13: *Proportions of patients belonging to different age groups diagnosed with rectal and colon cancer in the period 2012-2017*

RECTAL CANCER												
	Diagnosis year											
Age group	2012		2013		2014		2015		2016		2017	
	N	%	N	%	N	%	N	%	N	%	N	%
40-49	55	*5 %*	79	*6 %*	62	*5 %*	72	*6 %*	75	*6 %*	71	*6 %*
50-59	167	*14 %*	182	*14 %*	208	*16 %*	194	*15 %*	202	*16 %*	192	*16 %*
60-69	356	*30 %*	411	*31 %*	400	*31 %*	393	*31 %*	383	*30 %*	355	*29 %*
70-75	173	*14 %*	207	*16 %*	197	*15 %*	185	*14 %*	203	*16 %*	247	*20 %*
75-80	177	*15 %*	162	*12 %*	172	*13 %*	187	*15 %*	173	*13 %*	166	*13 %*
80-85	143	*12 %*	157	*12 %*	145	*11 %*	126	*10 %*	137	*11 %*	105	*9 %*
85-90	97	*8 %*	73	*6 %*	82	*6 %*	95	*7 %*	87	*7 %*	60	*5 %*
>90	31	*3 %*	40	*3 %*	42	*3 %*	32	*2 %*	27	*2 %*	38	*3 %*
Total	1 199	*100 %*	1 311	*100 %*	1 308	*100 %*	1 284	*100 %*	1 287	*100 %*	1 234	*100 %*

COLON CANCER												
	Diagnosis year											
Age group	2012		2013		2014		2015		2016		2017	
	N	%	N	%	N	%	N	%	N	%	N	%
40-49	82	*3 %*	90	*4 %*	106	*4 %*	97	*3 %*	109	*4 %*	103	*4 %*
50-59	274	*11 %*	287	*12 %*	260	*10 %*	245	*9 %*	294	*10 %*	260	*10 %*
60-69	665	*26 %*	618	*26 %*	654	*24 %*	682	*24 %*	690	*24 %*	609	*22 %*
70-75	391	*15 %*	190	*8 %*	425	*16 %*	503	*18 %*	517	*18 %*	510	*19 %*
75-80	426	*16 %*	411	*17 %*	414	*15 %*	467	*17 %*	481	*17 %*	458	*17 %*
80-85	418	*16 %*	442	*18 %*	437	*16 %*	426	*15 %*	406	*14 %*	399	*15 %*
85-90	238	*9 %*	255	*11 %*	270	*10 %*	265	*9 %*	292	*10 %*	279	*10 %*
>90	99	*4 %*	110	*5 %*	105	*4 %*	112	*4 %*	119	*4 %*	114	*4 %*
Total	2 593	*100 %*	2 403	*100 %*	2 671	*100 %*	2 797	*100 %*	2 908	*100 %*	2 732	*100 %*

Patient Pathway

The period of 2012-2014 was considered as a reference, providing the data before the Patient Pathway implementation in 2015. The data for 2015 can be considered as a transition period since the registration of Patient Pathway in NPR started only in 2016. Therefore, data for 2016 and 2017 was used to evaluate the Patient Pathway effect on cost.

The challenge we faced is that for the same patient was provided different information on patient's inclusion into the pathway. The same patient was both indicated as included and not included in the Patient Pathway when looking at different treatment activities this patient received. This might be partly caused by the fact that some procedures were not related to colorectal cancer and the information on patient's inclusion into the pathway was not available and therefore not registered. We assumed that if at least one treatment record contained the information that the patient was included in the Patient Pathway, then this patient was assigned the status as "included into Patient Pathway". All patients diagnosed with colorectal cancer in the period 2012-2014 were considered as "not included". For all individuals diagnosed in 2015 the information on inclusion into pathway was considered as "missing".

There were a total 23 976 patients diagnosed with colorectal cancer between 2012 and 2017 and included in the analysis. 2 450 patients with colon cancer and 1 429 patients with rectal cancer were included in the Patient Pathway in 2016 and 2017. Table 14 provides summarized information on the number of patients included in the Patient Pathway in the different years of the analyzed period.

Table 14: *Amount of patients diagnosed with rectal and colon cancer in the period 2012-2017 and included (Yes) or not included (No) in the Patient Pathway for colorectal cancer.*

	COLON CANCER						RECTAL CANCER					
	Missing data*	%	Yes	%	No	%	Missing data*	%	Yes	%	No	%
Year of diagnosis												
2012					2 602	100 %					1205	100 %
2013					2 615	100 %					1312	100 %
2014					2 677	100 %					1308	100 %
2015	2804	100 %					1285	100 %				
2016			1260	43 %	1 654	57 %			735	57 %	553	43 %
2017			1190	44 %	1 542	56 %			694	56 %	540	44 %
Total	2804		2450		11090		1285		1429		4918	

** registration of variable "patient pathway" in Cancer Register started in 2016*

Table 15 provides information on the patient mix - proportions of patients of different gender, age groups and cancer stage before Patient Pathway implementation and after. The period after

includes three groups: included into Patient Pathway, not included and data for 2015 when status of inclusion into pathway is unknown.

It is observed that higher proportion of patients belonging to younger age groups was included into Patient Pathway in comparison to baseline years. At the same time, it is identified that proportion of older patients is higher among patients not included into Patient Pathway. These findings are relevant both for rectal and colon cancer. Share of patients with more severe colon and rectal cancer stages (III and IV) was higher among patients included into Patient Pathway. After Patient Pathway introduction proportion of patients with unknown cancer stage increased.

Gender distribution was more or less stable for rectal cancer. For colon cancer men had higher chance of not being included into Patient Pathway.

Table 15: *Patient mix before and after Patient Pathway introduction.*

RECTAL CANCER								
	Before PP (n= 3818)		**Included (n= 1429)**		**Not included (n=1092)**		Missing info (n=1284)	
Gender								
Male	59 %		61 %		61 %		58 %	
Female	41 %		39 %		39 %		42 %	
Age								
40-49	5 %	79 %	6 %	85 %	5 %	78 %	6 %	
50-59	15 %		16 %		15 %		15 %	
60-69	31 %		31 %		27 %		31 %	
70-75	15 %		18 %		18 %		14 %	
75-80	13 %		13 %		13 %		15 %	
80-85	12 %		9 %		11 %		10 %	
85-90	7 %		5 %		7 %		7 %	
>90	3 %		2 %		3 %		2 %	
UICC stage								
zero	13 %		8 %		8 %		10 %	
I	18 %		14 %		19 %		18 %	
II	35 %		21 %		19 %		22 %	
III	4 %	21 %	22 %	34 %	19 %	28 %	13 %	
IV	17 %		12 %		10 %		15 %	
Inknown	13 %		23 %		24 %		21 %	

COLON CANCER								
	Before PP (n= 7867)		**Included (n= 2448)**		**Not included (n=3192)**		Missing info (n=2797)	
Gender								
Male	48 %		49 %		47 %		48 %	
Female	52 %		51 %		53 %		52 %	
Age								
40-49	4 %	70 %	3 %	74 %	4 %	69 %	3 %	
50-59	10 %		10 %		10 %		9 %	
60-69	25 %		25 %		22 %		24 %	
70-75	15 %		19 %		17 %		18 %	
75-80	16 %		17 %		16 %		17 %	
80-85	16 %		15 %		14 %		15 %	
85-90	10 %		8 %		11 %		9 %	
>90	4 %		3 %		5 %		4 %	
UICC stage								
zero	50 %		15 %		19 %		28 %	
I	9 %		14 %		15 %		13 %	
II	15 %		19 %		18 %		16 %	
III	2 %	14 %	18 %	25 %	13 %	21 %	8 %	
IV	12 %		8 %		7 %		12 %	
Inknown	12 %		27 %		27 %		23 %	

5.4. Cost

Costs were estimated based on the DRG-weights system. Diagnosis-Related Groups are a way of relating the type of patient treated to the costs incurred in the hospital [74]. The main goal of the DRG system is to classify patients and pool them according to their consumption of hospital resources in an attempt to better control increasing costs [74]. The expenses are then distributed among patient groups according to distribution formulas, resulting in one cost per patient in each patient group (DRG-cost). In addition to this, DRGs must be compared, and then a relative cost is calculated, namely the cost-weight. When the cost-weight is equal to one, it is defined as the average patient, and then for all patients, the relative use of resources is compared with this average cost. Therefore, patients are placed in a DRG group and the system will estimate the mean cost of treatment for each group of patients based on the average patient [74, 75]. Every year the DRG system is updated in Norway with new diagnoses and new procedure codes. When new methods are introduced or when treatment practices are changed, there is also a need for change in the grouping rules in the DRG system [75].

The calculation follows a method of multiplication of the DRG weight and its corresponding annual DRG unit-price. Table 16 summarizes the unit cost from 2012 until 2017.

Table 16: *DRG-Unit price in NOK.*

Year	2012	2013	2014	2015	2016	2017
DRG-Unit price in NOK	38 209	39 447	40 772	41 462	42 163	42 753

Note: Adapted from Helsedirektorat. Innsatsstyrt finansiering og DRG-systemet (n.d). Retrieved March 25, 2022, from https://www.helsedirektoratet.no/tema/finansiering/innsatsstyrt-finansiering-og-drg-systemet

The calculations performed on DRG used the annual unit price for somatic services multiplied by the DRG weight, for example, treatment done in 2012:

$$= 38\,209 \times DRGweight$$

Most frequently used DRG's are represented in the Table 17. Divided by non-surgical procedures, such as outpatient consultations, chemotherapy, as well as radiation therapy; surgical procedures, such as surgery and resections; and diagnostic procedures such as colonoscopy. In the last column, it is calculated the average number of procedures that a patient undergoes among the above-mentioned categories. If we consider the total amount of rectal

patients as 7 632 and colon patients as 16 344, we can divide N by the sample size and then get this average number of procedures per patient.

Table 17: *Most frequently DRGs used in rectal cancer treatment.*

RECTAL CANCER				
DRG	**Non-surgical procedures**	**N**	**%**	**Visits per rectal patient**
906A	Outpatient consultation with a tumor in the digestive tract	52 935	38 %	7
851F	Outpatient external radiation therapy for cancer of the digestive organs	34 638	25 %	5
856F	Outpatient drug treatment of cancer of the digestive organs	31 069	23 %	4
906O	Outpatient consultation regarding other digestive diseases	19 045	14 %	2
TOTAL		**137 687**	**100 %**	**7 632**
DRG	**Surgical procedures**	**N**	**%**	**Visits per rectal patient**
172	Malignant diseases of the digestive organs with comorbidity or complications	4 861	44 %	1
146	Resection procedure on the rectum with comorbidity or complications	4 456	41 %	1
148	Major surgeries on the small intestine and colon with comorbidity or complications	1 632	15 %	0,21
TOTAL		**10 949**	100 %	**7 632**
DRG	**Diagnostic procedures**	**N**	**%**	**Visits per rectal patient**
710O	Colonoscopy	5 953	100 %	0,8
TOTAL		**5 953**	100 %	**7 632**

Table 18: *Most frequently DRGs used in colon cancer treatment.*

COLON CANCER				
DRG	**Non-surgical procedures**	N	%	**Visits per colon patient**
856F	Outpatient drug treatment of cancer of the digestive organs	73 771	38 %	5
906A	Outpatient consultation with a tumor in the digestive tract	68 195	35 %	4
923O	Outpatient clinic for factors that are important for the health condition/contact with the health service	29 359	15 %	2
410A	Chemotherapy without acute leukemia as co-diagnosis, unspecified	22 222	11 %	1
TOTAL		**193 547**	100 %	**16 344**
DRG	**Surgical procedures**	N	%	**Visits per colon patient**
148	Major surgeries on small intestine and colon with comorbidity or complications	10 836	37 %	0,7
317O	Dialysis treatment, day medical treatment	9 536	32 %	0,6
172	Malignant diseases of the digestive organs with comorbidity or complications	9 005	31 %	0,6
TOTAL		**29 377**	100 %	**16 344**
DRG	**Diagnostic procedures**	**N**	**%**	**Visits per colon patient**
710O	Colonoscopy	12 018	100 %	0,7
TOTAL		**12 018**	100 %	**16 344**

Further, the cost for each patient was defined as a sum of all colorectal cancer-related treatment at the hospital.

Costs per each patient were defined for the following time intervals: two-months after diagnosis, and one year cost after diagnosis. These time intervals were selected based on assumptions and were aimed to check Patient Pathways' influence on cost.

Assumptions on cost

Two-months costs after diagnosis was selected based on the lead times stipulated in the Patient Pathway for colorectal cancer:

- From referral to surgery or neo-adjuvant chemotherapy – 35 days;
- From referral neo-adjuvant radiation therapy – 39 days.

This interval will give an indication of whether Patient Pathway influenced both waiting time and costs.

Checking costs only for the first month would not be ideal as a patient can be diagnosed in the second half of the month and then most expensive treatment procedure – surgery will not be included. Therefore, analysis based on the cost for two first months after diagnosis would give more precisions in answering the question of the master thesis.

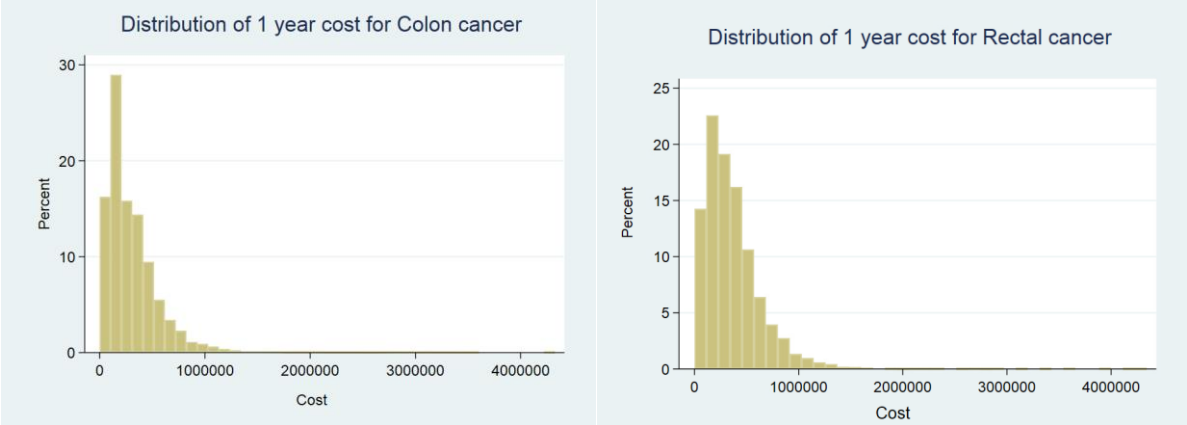
One-year treatment cost is selected to cover the whole treatment cycle, which ensures more precise analysis. Based on the treatment guidelines we have defined the duration of the treatment cycle for three categories of patients represented in the background section, chapter 3.5. The treatment pathways are generalized but give the overall impression about treatment duration. Based on this info and taking into consideration possible postpones we have decided to select the cost for the first year after diagnosis as essential for observing the potential effect of the Patient Pathway on cost.

Visual inspections of cost

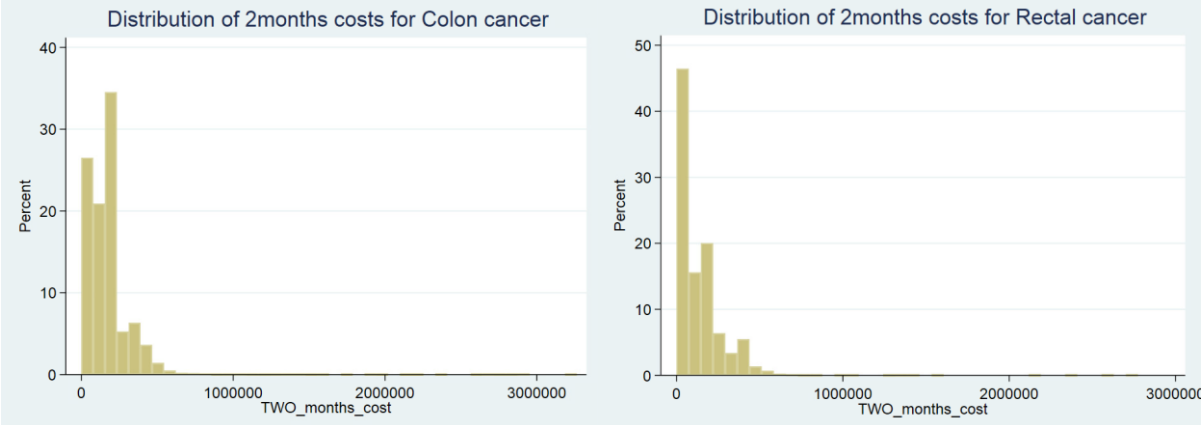
Visual inspection of histograms confirmed positive-skew distribution of treatment costs both for rectal and colon cancers. The histograms for one-year cost and two-month costs are presented on Figure 10.

Figure 10: *One-year and two-months cost distribution for rectal and colon cancer*

one-year costs



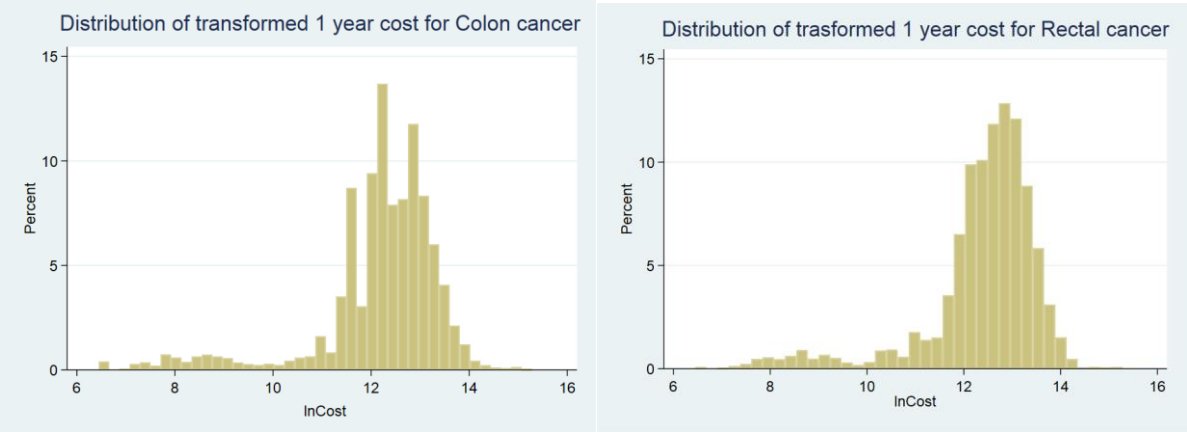
two-months costs



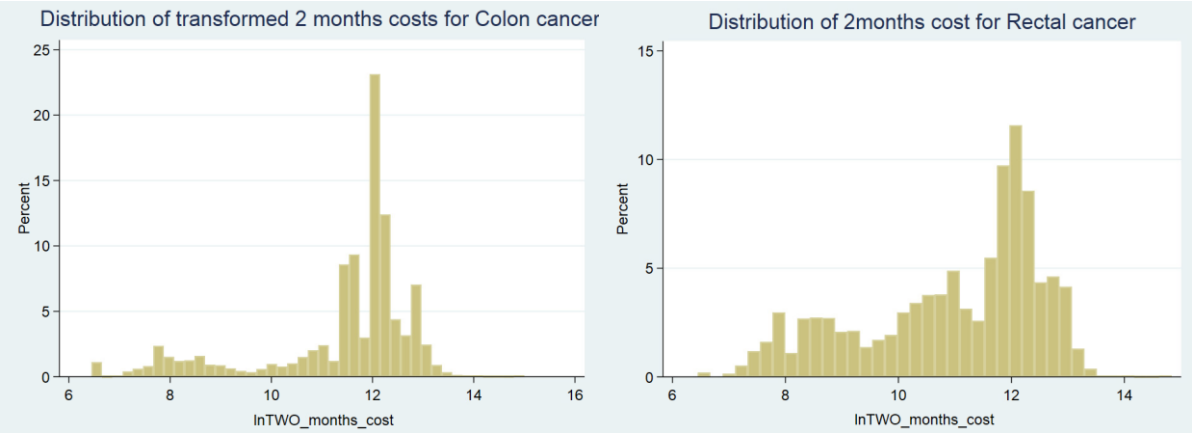
To solve the problem of skewed costs we used natural log-transformation and generated new variables for one-year cost and two-month costs. The distribution of transformed variables for one-year cost and two-month costs became close to normal and is represented in Figure 11.

Figure 11: *One-year and two-months log-transformed cost distribution for rectal and colon cancer*

Transformed one-year costs



Transformed two-month costs



5.5. Statistical analysis

In this chapter we will describe the different types of analysis we apply to evaluate differences in treatment costs for rectal and colon cancer and the impact of Patient Pathway program. First, we will present the methods for differences in crude estimates of costs; second, regression analysis to evaluate the effect of Patient Pathway on treatment costs, and lastly propensity score matching to estimate the effect of Patient Pathway on costs.

The distribution of healthcare costs is generally right skewed with a long tail and can include a substantial proportion of observations with zero costs [77]. In order to assess the difference in the samples before and after the Patient Pathway, we need to quantify the mean cost and effect between the two groups and determine whether these differences are likely to be due to chance.

There are different alternatives to compare costs using nonparametric tests, for example, Mann–Whitney U (or Wilcoxon rank-sum) test, the Kolmogorov–Smirnov test, and the Kruskal–Wallis test. However, when we address non-normal cost distribution, some analysts have transformed costs in an attempt to make the distribution of the resulting variable more normal [77]. It is important to note that when transforming the costs, we need to estimate and draw inferences about the transformed scale, e.g., the logarithmic, square root, or reciprocal transformation [77, 78].

5.5.1. Regression analysis

To estimate the effect of the Patient Pathway on treatment cost for rectal and colon cancer, we applied a multivariate regression to include several covariates to account for factors like risk (age and stage). Given that cost is a continuous variable with a skewed distribution, we applied a log-linear regression model with the transformation of the dependent variable (cost of rectal and colon cancer treatment).

When using regression analysis, the main goal is to model the effect of a set of explanatory variables $x1, \ldots, xk$ on a variable *y*, the variable of primary interest. In this thesis, y is cost. The y variable is called the response or dependent variable and the x's are called covariates or independent variables [78].

5.5.2. Log-linear regression

The logarithmic transformation is the regular way of handling non-linear relationships between the dependent and the independent variables. A log-linear model is a regression approach where the natural log of the dependent variable is used in the regression and it is useful in the transformation of skewed variables into close to normal variables. It can also be applied to overcome problems of heteroscedasticity [77].

In the analysis of this thesis, the cost of treatment (rectal and colon cancer) for individual *i* is defined as *Yi*.

To capture the effect of Patient Pathway on costs we applied several log-linear regressions; two time periods for costs (two months and one year); according to cancer type – rectal and colon cancer, and according to UICC stage.

The log-linear regression function can be expressed as:

$$Log(Yi) = \alpha + \beta_{PP1} X_{PP1} + \beta_{PP2} X_{PP2} + \beta_{PP3} X_{PP3} + \beta_{Gi} X_{Gi} + \beta_{A50} X_{A50} + \beta_{A60} X_{A60} + \beta_{A70} X_{A70} + \beta_{A80} X_{A80} + \beta_{A90} X_{A90} + \beta_{D} X_{D} + \beta_{S1} X_{S1} + \beta_{S2} X_{S2} + \beta_{S3} X_{S3} + \beta_{S4} X_{S4} + \beta_{Su} X_{Su} + \beta_{Ye1} X_{Ye1} + \beta_{Ye2} X_{Ye2} + \varepsilon_i$$

Where Yi is treatment costs, α is the constant term, β_{PP1}, β_{PP2}, β_{PP3}, β_G, β_A, β_D, β_s, β_{Ye} are parameters to be estimated by the regression, and ε_i is the random term defined by $N\sim(0, \sigma^2)$. The covariates are defined as:

- PP_s is the dummy variable representing the Patient Pathway program, where s=0, 1, 2, 3. The reference group, PP_0, is representing those treated in the period before the introduction of Patient Pathway (2012 to 2014), while PP_1 is a dummy for patients included in the Patient Pathway program in 2016, PP_2 is the dummy for patients not included in the program in 2016 and PP_3 the dummy for the introduction year, 2015, where inclusion in the Patient Pathway was not registered in the data.
- G_r is the dummy for the gender. The reference category is male and G_1 is female.
- A_q is the dummy category for the age groups (q=40-49, 50-59, 60-69, 70-79, 80-89 and above 90). The reference is the patients in the age group 40 until 49 years, A_{50} the age group from 50 until 59, A_{60} the age group from 60 until 69, A_{70} the age group from 70 until 79, A_{80} the age group from 80 until 89, and A_{90} for the age group older than 90 years.
- S_v is the dummy for the UICC stages (v = 0, 1, 2, 3, 4, u). The reference category, S_0 is the zero stage. S_1 is the dummy for stage 1, S_2 is the dummy for stage 2, S_3 is the dummy for stage 3, S_4 is the dummy for stage 4, and S_u is the dummy for the unknown stage.
- Ye_i is the dummy for the year of diagnosis. The reference group is 2012. Ye_1 is the dummy for 2013 and Ye_2 is the dummy for 2014.
- D is the dummy for dead.

In a multivariable analysis, some complications can arise including heteroscedasticity among the independent variables, causing problems in retransformation. Furthermore, subgroup-specific retransformation may not necessarily be unbiased when the analysis includes multiple variables [77].

To identify the effect of Patient Pathway on costs, we conducted two steps: first we evaluated the estimated coefficient β_{PP1} , second, we evaluated whether , $\beta_{\mathrm{PP}\ 1}$ was significantly different than β_{PP2} . In multiple regression analysis, we want to test the hypothesis made for the coefficients. The F-test has the purpose of testing if there are any significant differences between two regression coefficients. In this thesis, we tested for the Patient Pathway dummies (β_{PP1} and β_{PP2}). So, we want to test the hypothesis:

$$H_0: \beta_{\mathrm{PP1}} = \beta_{\mathrm{PP2}}$$

$$H_1: \beta_{\mathrm{PP1}} \neq \beta_{\mathrm{PP2}}$$

That is the two slope coefficients β_{PP1} and β_{PP2} are equal. We did the test to see whether the Patient Pathway program influences cost and whether this is significantly different. After testing, we could prove that the differences are significant and it makes sense to have the dummies for the Patient Pathway program. The p-value is <0.05, which means that we accept the null hypothesis and we can prove that there is no bias and we can proceed to matching.

The results for the F test will be further discussed in the chapter 6.

5.5.3. Tests

The Linktest command on Stata is used to detect misspecification. The idea is that if the model is properly specified, we will not find any additional predictors that are statistically significant. After running the command on Stata, we checked the predicted value (_hat) and the linear predicted value squared (_hatsq) as the predictors to rebuild the model. The _hat should be a statistically significant predictor, while the _hatsq should not have much predictive power except by chance [79].

We also checked the R-squared to see the percentage of the cost variable variation that is explained by the linear model. From the regressions, we observed a low R-squared for both one-year and two-months cost. The R-squared was between 7% and 14% for our model. However, we have to bear in mind that the R-squared does not indicate whether our regression

model is adequate. We can have a low R-squared value for a good model, or a high R-squared value for a model that does not fit the data [79].

After the linktest and the R-squared check, we need to test whether the residuals are distributed with equal variance at each level of the predictor variable (homoscedasticity). When this assumption is infringed, we say that heteroscedasticity is present in the residuals [79]. It is important to use significance tests in the model to make inferences about the costs, and testing for heteroscedasticity is one way to make sure our inferences are not baseless. After running the log-linear regression, we did the estat hettest, which is the default test for heteroscedasticity. The estat test generated a p-value of 0.000 for rectal and for colon cancer (one-year and two-month outputs). These outputs are smaller than our chosen significance value of 0.05, and it indicates a statistically significant Chi-square test. Therefore, our results indicate the presence of heteroscedasticity on cost.

5.5.4. Matching – Propensity score matching

There are different ways of identifying causal effects. The best way for parametric estimations is regression, while for non-parametric methods, matching is more suited. Matching is a method where we can partition the sample into subpopulations with similar values of confounding variables and compare patients within the subpopulations [80, 81].

The objective of matching is to create covariate balance for the distributions of the confounding covariates. In other words, matching is to take observations that were treated (D = 1), observe the coefficient (x) and then select non-treated observations with similar (or identical) values of x [80]. In our master thesis, we decided to use one of the most common forms of matching: propensity score matching (PSM) [80].

There are multiple confounding variables and matching the whole sample might be an impossible task, especially due to the lack of data. PSM is a solution as we construct a scaled conditional probability of receiving the treatment assignment given the vector of covariates [80]. The propensity score will provide a good counterfactual for valid causal inference using the observational data. In our dataset, the controlled subjects are the dummy variable “1” for those individuals in 2016, while the treated subject is the dummy “0”, for those patients before the Patient Pathway. Therefore, we did PSM for matching one-year cost and two-month cost.

The PSM Matching was based on cases diagnosed in 2012-2014 and 2016. We conducted three matching procedures for each caner type with different categories of treated and untreated.

First matching: Patients diagnosed with cancer in 2012-2014 were considered as untreated group. Patients included into Patient Pathway in 2016 were considered as treated group. Number of patients in each group per cancer type is represented in the Table 19.

Table 19: *Number of patients with diagnosed rectal and colon cancer in treated (included into Patient Pathway) and untreated (baseline years) groups*

RECTAL CANCER	Number of patients	% from Total
Untreated (*Baseline period 2012-14*)	3818	84 %
Treated (*Included into PP*)	735	16 %

COLON CANCER	Number of patients	% from Total
Untreated (*Baseline period 2012-14*)	7 867	86 %
Treated (*Included into PP*)	1 258	14 %

Patient mix for both matched groups is presented in the Table 20. We see that matching samples are more or less balanced though proportions of patients with more severe cancer and patients of younger age is higher for treated groups both for rectal and colon cancer. But size of sample is essential for obtaining proper matching results.

Table 20: *Patient mix in untreated (baseline years) and treated (included into Patient Pathway) groups*

RECTAL CANCER	Before PP (n= 3818)		Included (n= 735)	
Gender				
Male	59 %		63 %	
Female	41 %		37 %	
Age				
40-49	5 %		7 %	
50-59	15 %		16 %	
60-69	31 %	79 %	33 %	84 %
70-75	15 %		17 %	
75-80	13 %		13 %	
80-85	12 %		9 %	
85-90	7 %		5 %	
>90	3 %		1 %	
UICC stage				
zero	13 %		9 %	
I	18 %		14 %	
II	35 %		22 %	
III	4 %	21 %	21 %	34 %
IV	17 %		14 %	
Inknown	13 %		20 %	

COLON CANCER	Before PP (n= 7867)		Included (n= 1258)	
Gender				
Male	48 %		48 %	
Female	52 %		52 %	
Age				
40-49	4 %		3 %	
50-59	10 %		10 %	
60-69	25 %	70 %	25 %	73 %
70-75	15 %		18 %	
75-80	16 %		17 %	
80-85	16 %		15 %	
85-90	10 %		10 %	
>90	4 %		2 %	
UICC stage				
zero	50 %		15 %	
I	9 %		14 %	
II	15 %		19 %	
III	2 %	14 %	18 %	26 %
IV	12 %		9 %	
Inknown	12 %		25 %	

Second matching: Patients diagnosed with cancer in 2012-2014 were considered as untreated group. Patients NOT included into Patient Pathway in 2016 were considered as treated group. By this we checked whether there have been changes in cost versus baseline period also for patients not included into Patient Pathway. This was made to validate the results of the first

matching and check whether there have been other effects impacting costs apart from inclusion into Patient Pathway. Number of patients in each group per cancer type is represented in the Table 21.

Table 21: *Number of patients with diagnosed rectal and colon cancer in treated (not included into Patient Pathway) and untreated (baseline years) groups*

RECTAL CANCER	Number of patients	% from Total
Untreated (*Baseline period 2012-14*)	3818	87 %
Treated (*Not included into PP*)	552	12 %

COLON CANCER	Number of patients	% from Total
Untreated (*Baseline period 2012-14*)	7 867	86 %
Treated (*Not included into PP*)	1 650	14 %

Patient mix for both matched groups is presented in the Table 22. As in previous matching the samples are balanced with higher prevalence of patients with more severe cancer in treated groups. For colon cancer age groups for treated and untreated are very alike, while for rectal cancer share of patients of younger groups is higher in the untreated group. Sample size is big enough for obtaining reliable matching results.

Table 22: *Patient mix in untreated (baseline years) and treated (NOT included into Patient Pathway) groups*

RECTAL CANCER	Before PP (n= 3818)		NOT included (n= 552)	
Gender				
Male	59 %		60 %	
Female	41 %		40 %	
Age				
40-49	5 %		5 %	
50-59	15 %		16 %	
60-69	31 %	79 %	26 %	76 %
70-75	15 %		15 %	
75-80	13 %		14 %	
80-85	12 %		13 %	
85-90	7 %		9 %	
>90	3 %		3 %	
UICC stage				
zero	13 %		9 %	
I	18 %		18 %	
II	35 %		20 %	
III	4 %	21 %	18 %	25 %
IV	17 %		12 %	
Inknown	13 %		24 %	

COLON CANCER	Before PP (n= 7867)		NOT included (n= 1650)	
Gender				
Male	48 %		47 %	
Female	52 %		53 %	
Age				
40-49	4 %		5 %	
50-59	10 %		10 %	
60-69	25 %	70 %	23 %	71 %
70-75	15 %		18 %	
75-80	16 %		16 %	
80-85	16 %		13 %	
85-90	10 %		10 %	
>90	4 %		5 %	
UICC stage				
zero	50 %		19 %	
I	9 %		15 %	
II	15 %		18 %	
III	2 %	14 %	13 %	22 %
IV	12 %		9 %	
Inknown	12 %		26 %	

Third matching: Patient NOT included into Patient Pathway in 2016 were considered as untreated group, patients included into Patient Pathway in 2016 was considered as treated group. This was also made to validate the results and to see whether any difference between these two groups is observed. Both groups are from the same year, but there exists the problem

of selection bias. The number of patients in each group per cancer type is represented in the Table 23.

Table 23: *Number of patients with diagnosed rectal and colon cancer in treated (not included into Patient Pathway) and untreated (included into Patient Pathway) groups*

RECTAL CANCER	Number of patients	% from Total
Untreated (*Not included into PP*)	552	43 %
Treated (*Included into PP*)	735	57 %

COLON CANCER	Number of patients	% from Total
Untreated (*Not included into PP*)	1 650	57 %
Treated (*Included into PP*)	1 258	43 %

Patient mix for both matched groups are presented in the Table 24. From the table we observe that for colon cancer prevalence of patients at younger age and patients with later cancer stages is considerably higher in treated group. For rectal cancer we do not see that effect, the groups are more balanced. We believe that sample size is still enough for getting appropriate matching results.

Table 24: *Patient mix in untreated (NOT included into Patient Pathway) and treated (included into Patient Pathway) groups*

RECTAL CANCER	NOT included (n= 552)		Included (n= 735)	
Gender				
Male	60 %		63 %	
Female	40 %		37 %	
Age				
40-49	5 %		7 %	
50-59	16 %		16 %	
60-69	26 %	76 %	33 %	84 %
70-75	15 %		17 %	
75-80	14 %		13 %	
80-85	13 %		9 %	
85-90	9 %		5 %	
>90	3 %		1 %	
UICC stage				
zero	9 %		9 %	
I	18 %		14 %	
II	20 %		22 %	
III	18 %	25 %	21 %	34 %
IV	12 %		14 %	
Inknown	24 %		20 %	

COLON CANCER	NOT included (n= 1650)		Included (n= 1258)	
Gender				
Male	47 %		48 %	
Female	53 %		52 %	
Age				
40-49	5 %		3 %	
50-59	10 %		10 %	
60-69	23 %	71 %	25 %	73 %
70-75	18 %		18 %	
75-80	16 %		17 %	
80-85	13 %		15 %	
85-90	10 %		10 %	
>90	5 %		2 %	
UICC stage				
zero	19 %		15 %	
I	15 %		14 %	
II	18 %		19 %	
III	13 %	22 %	18 %	26 %
IV	9 %		9 %	
Inknown	26 %		25 %	

Treatment dependent variable was defined as inclusion/not inclusion into Patient Pathway. To match patients on treated and untreated groups we choose the same variables as in case with the regressions: gender, age group, death status and stage. It should be highlighted that matching was done on the aggregated level and not for the stages due to relatively low number of patients

for each cancer stage. For example, for rectal cancer we only have 735 patients included into pathway. Therefore, we should bear in mind that if we split those 735 according to each stage, from zero to IV, the sample size for each stage would be very small. The small sample sizes can lead to poor matching and unstable estimations of the treatment effect. Studies on propensity score matching suggest that the efficacy with sample sizes smaller than 500 is limited [82]. Other researchers suggest that sample sizes smaller than 300 may be too small for matching when prediction of group assignment is high [83]. Therefore, for those reasons, matching for each stage will not provide enough observations to obtain valid results.

6. Results

The following part contains findings obtained via data analysis with the use of statistical methods described in the chapter 5.

6.1. Two-months cost

The mean two-months cost for treatment of rectal and colon cancer in the period 2012-2016 are presented in Table 25. We adjusted costs using the consumer price index and took prices for 2016 as a basis. Costs of treating colon cancer are higher than rectal cancer both before and after Patient Pathway introduction. For both rectal and colon cancer two-month mean costs increased in 2015, when the Patient Pathway was introduced. Even though rectal cancer had a higher increase in percentage, colon cancer had the higher cost in real numbers as we can see in table 25. While in 2016, both rectal and colon cancer it became cheaper to treat, having a reduction of -3% and -1% in costs, respectively, when compared to the year of introduction of Patient Pathway.

Table 25: *Mean cost for two-months treatment of colon and rectal cancer in the period of 2012-2016*

RECTAL CANCER			COLON CANCER		
Year	**Mean cost, adjusted for consumer price index for 2016**	**Change vs previous year, %**	**Year**	**Mean cost, adjusted for consumer price index for 2016**	**Change vs previous year, %**
2012	121 710	n/a	2012	160 955	n/a
2013	122 463	1 %	2013	168 633	5 %
2014	134 885	10 %	2014	166 990	-1 %
2015	**151 391**	**12 %**	**2015**	**180 737**	**8 %**
2016	147 198	-3 %	2016	178 432	-1 %

6.1.1. Loglinear regression

Rectal

Loglinear regression output is presented in table 26. From Table 26 we see that the two-month cost among rectal cancer patients included in Patient Pathway in 2016 increased by 41.2% (0.3455 and p<0.000) compared to rectal cancer patients treated before the introduction (2012-2014). For patients not included in the pathway program in 2016, the cost increased by 40% (0.3366 and p<0.000). The costs also increased for patients treated in 2015 by almost 60% (0.4698 and p < 0.000). As the coefficient for Patient Pathway includes both the impact of changes in treatment over year and the introduction of Patient Pathway, to conclude on the effect of Patient Pathway on costs, we tested whether the differences in costs among individuals included in the Patient Pathway, were significantly different from those not included in 2016. F-test results for rectal cancer shows that p>0.05 and this means we reject null hypothesis and cost difference between included into Patient Pathway and not included is not significant. The results can be biased. Other covariates included in the regression were gender, age, cancer stages, and death status. For the stages, the reference group is the zero stage and it is noticed that the II stage has the biggest effect on costs, followed by stage IV. Stage II costs 49% (0.3985 and p<0.001) more than stage zero. Results for all stages, except the unknown are significantly higher at a p-value<0.001. The effect of age on costs were only significant for the two oldest age groups (85-89 years and 90 years and above). Compared to patients between 40-49 years, patients 90 years and older, had 70% (-0.355 and p=0.012) lower costs.

When considering gender, treating women is 75% (0.5601 and p=0.132) more expensive than treatment men, but the result is not significant.

Table 26: *Loglinear regression output for two-months cost of rectal cancer*

RECTAL CANCER			
Two-months cost	**Coef. (b)**	**Std. Err.**	**P>|t|**
Patient pathway (reference - before patient pathway introduction)			
Included	0.3455	0.7271	0.000
Not included	0.3366	0.0758	0.000
Introduction year (2(	0.4698	0.0644	0.000
Gender			
Women	0.5601	0.3714	0.132
Age group (reference - 40-49)			
50-59	-0.1825	0.0905	0.044
60-69	-0.0232	0.0843	0.782
70-75	-0.0237	0.0900	0.793
75-80	0.0626	0.0922	0.497
80-85	-0.0151	0.0966	0.876
85-90	-0.2507	0.1079	0.020
>90	-0.3505	0.1392	0.012
Death status			
Dead	-0.1639	0.0415	0.000
UICC Stage (reference - zero stage)			
1	0.2033	0.7142	0.004
2	0.3985	0.6568	0.000
3	0.2579	0.0800	0.001
4	0.3236	0.0742	0.000
Unknown	-0.0642	0.0714	0.369
Year of diagnosis (reference - 2012)			
2013	-0.0050	0.0632	0.937
2014	0.2398	0.0634	0.000
Const.	10.6818	0.1080	0.000

Linktest showed that the model is properly specified with a _hatsq of 0.842, although Breusch-Pagan test revealed the presence of heteroscedasticity. While the explanatory power is very little (about 3%), meaning that the model explains only 3% of the variation in two-month treatment cost.

We have also compared the impact of inclusion of patients into the Patient Pathway for different cancer stages (from 0 to the fourth stage). No trend or pattern were founded for these regressions. Significant results were found for the second stage, with a representative cost increase for those patients not included into the Patient Pathway (0.717 and $p<0.000$). Stage IV seems to be another costly stage, however, only the cots increased for the introduction year (0.546 and $p<0.000$) has a significant p-value. The results are only significant for patients within the second stage and for fourth stage, but only during the introduction year of the program. For patients in other stages, the cost increase is not significant (p-value>0.05). F-test conducted for each stage and identified that in none of stages the difference in cost between patients included into Patient Pathway and not included was significant. The output of the analysis per stages is presented in the Table 27.

Table 27: *Loglinear regression output for two-months treatment cost of rectal cancer for different stages*

RECTAL CANCER						
	Cancer Stage	**Zero Stage**	**I Stage**	**II Stage**	**III Stage**	**IV Stage**
Patient pathway (reference - before patient pathway						
	Coef. (b)	**0.488**	**-0.023**	**0.503**	**-0.050**	**0.578**
Included	*Std. Err.*	*0.269*	*0.192*	*0.133*	*0.299*	*0.188*
	P>|t|	*0.070*	*0.905*	*0.000*	*0.866*	*0.759*
	Coef. (b)	**0.577**	**-0.280**	**0.717**	**-0.033**	**0.337**
Not included	*Std. Err.*	*0.272*	*0.192*	*0.142*	*0.304*	*0.205*
	P>|t|	*0.035*	*0.146*	*0.000*	*0.915*	*0.101*
	Coef. (b)	**0.374**	**0.352**	**0.658**	**0.116**	**0.546**
Introduction year	*Std. Err.*	*0.218*	*0.167*	*0.111*	*0.301*	*0.145*
	P>|t|	*0.086*	*0.035*	*0.000*	*0.701*	*0.000*
Gender						
	Coef. (b)	**-0.194**	**-0.759**	**0.026**	**0.108**	**0.009**
Women	*Std. Err.*	*0.129*	*0.098*	*0.065*	*0.096*	*0.089*
	P>|t|	*0.133*	*0.438*	*0.688*	*0.262*	*0.921*
Age group (reference - 40-49)						
	Coef. (b)	**-0.114**	**-0.371**	**-0.246**	**-0.281**	**-0.074**
50 - 59	*Std. Err.*	*0.322*	*0.266*	*0.164*	*0.197*	*0.183*
	P>|t|	*0.723*	*0.164*	*0.134*	*0.154*	*0.687*
	Coef. (b)	**0.394**	**-0.157**	**-0.176**	**-0.112**	**0.037**
60 - 69	*Std. Err.*	*0.299*	*0.249*	*0.150*	*0.182*	*0.171*
	P>|t|	*0.187*	*0.528*	*0.241*	*0.537*	*0.831*
	Coef. (b)	**0.113**	**-0.149**	**-0.090**	**-0.505**	**0.131**
70 - 75	*Std. Err.*	*0.317*	*0.260*	*0.160*	*0.207*	*0.186*
	P>|t|	*0.721*	*0.565*	*0.573*	*0.015*	*0.481*
	Coef. (b)	**0.442**	**0.090**	**-0.044**	**-0.135**	**0.044**
75 - 80	*Std. Err.*	*0.313*	*0.267*	*0.163*	*0.217*	*0.202*
	P>|t|	*0.158*	*0.737*	*0.789*	*0.535*	*0.827*
	Coef. (b)	**0.212**	**-0.194**	**-0.136**	**-0.005**	**0.093**
80 - 85	*Std. Err.*	*0.326*	*0.277*	*0.167*	*0.236*	*0.233*
	P>|t|	*0.516*	*0.485*	*0.413*	*0.983*	*0.691*
	Coef. (b)	**0.076**	**-0.463**	**-0.340**	**-0.262**	**0.045**
85 - 90	*Std. Err.*	*0.354*	*0.314*	*0.184*	*0.283*	*0.300*
	P>|t|	*0.830*	*0.141*	*0.065*	*0.354*	*0.880*
	Coef. (b)	**-0.235**	**0.108**	**-0.226**	**-0.621**	**0.265**
> 90	*Std. Err.*	*0.362*	*0.418*	*0.261*	*0.393*	*1.030*
	P>|t|	*0.515*	*0.796*	*0.385*	*0.115*	*0.797*

Colon cancer

Loglinear regression output is presented in Table 28. From the Table we see that the two-month cost among colon cancer patients included in Patient Pathway in 2016 increased by 33.6% (0.0362 and p=0.367) compared to rectal cancer patients treated before the introduction (2012-2014). For patients not included in the pathway program in 2016, the cost increased by 13.7% (-0.1225 and p<0.001). The costs also increased for patients treated in 2015 by almost 29% (0.2316 and p < 0.000). We have also tested whether the difference in costs among individuals included in the Patient Pathway, were significantly different from those not included in 2016, and got confirmed that the results are not biased (p<0.001).

Analyzing the covariate age group, we observe that patients belonging to group 75 until the group of 90 years, have a significative p-value (<0.00). For colon cancer, all age groups are cheaper when compared to the reference group (40-49 years). In comparison to the rectal cancer, colon cancer have more significative p-values, not only for age groups, but for death status, stage III and IV, besides the stage unknown.

In addition, when considering gender, treating women is cheaper in 7% (-0.082 and p < 0.000).

Table 28: *Loglinear regression output for two-months cost of colon cancer*

COLON CANCER			
Two-months cost	**Coef. (b)**	**Std. Err.**	**P>|t|**
Patient pathway (reference - before patient pathway introduction)			
Included	0.0362	0.0401	0.367
Not included	-0.1225	0.0378	0.001
Introduction year (2015)	0.2316	0.0339	0.000
Gender			
Women	-0.0802	0.0192	0.000
Age group (reference - 40-49)			
50-59	-0.0753	0.0587	0.199
60-69	-0.0575	0.0540	0.287
70-75	-0.0943	0.0555	0.089
75-80	-0.2492	0.0557	0.000
80-85	-0.4302	0.0562	0.000
85-90	-0.6008	0.0594	0.000
>90	-0.8557	0.0702	0.000
Death status			
Dead	-0.3307	0.0209	0.000
UICC Stage (reference - zero stage)			
1	-0.0485	0.0330	0.141
2	0.0833	0.0291	0.004
3	0.1653	0.0406	0.000
4	0.2928	0.0343	0.000
Unknown	-0.2895	0.0286	0.000
Year of diagnosis (reference - 2012)			
2013	0.0505	0.0337	0.134
2014	0.1183	0.0335	0.000
Const.	12.5442	0.0587	0.000

Regarding the linktest, the model is also properly specified with a _hatsq of 0.706, although Breusch-Pagan test revealed the presence of heteroscedasticity. In addition to the linktst, the explanatory power is higher than for rectal cancer, but still low (7.3%). The trends are not the same when comparing the stages, in the case of colon cancer, stage IV is the most significant one. While for rectal cancer, the second stage was the most expensive one.

In addition, when comparing the impact of inclusion of patients into the Patient Pathway for different cancer stages, no trend or pattern were observed for these regressions. Significant results were found for the first stage, with a representative cost amount for those patients included into the Patient Pathway (0.523 and $p < 0.000$). Stage III seems to be another costly stage, however, none of the results had a significant p-value of less than 0.000. Only a few covariates used in the regression are significant.

F-test conducted for different stages identified that for all stages excepting zero stage the results can be biased due to the fact that differences in costs among individuals included in the patients pathway are significantly different from those not included.

Regression output for analysis per cancer stages is presented in the Table 29.

Table 29: *Loglinear regression output for two-months treatment cost of colon cancer for different stages*

COLON CANCER						
	Cancer Stage	**Zero Stage**	**I Stage**	**II Stage**	**III Stage**	**IV Stage**
Patient pathway (reference - before patient pathway						
	Coef. (b)	**0.197**	**0.523**	**0.204**	**0.692**	**0.366**
Included	*Std. Err.*	*0.103*	*0.141*	*0.110*	*0.300*	*0.170*
	P>|t|	*0.056*	*0.000*	*0.065*	*0.021*	*0.032*
	Coef. (b)	**-0.080**	**0.499**	**0.170**	**0.582**	**0.165**
Not included	*Std. Err.*	*0.091*	*0.133*	*0.106*	*0.300*	*0.163*
	P>|t|	*0.379*	*0.000*	*0.111*	*0.052*	*0.312*
	Coef. (b)	**0.255**	**0.465**	**0.255**	**0.782**	**0.265**
Introduction year	*Std. Err.*	*0.069*	*0.126*	*0.099*	*0.302*	*0.120*
	P>|t|	*0.000*	*0.000*	*0.010*	*0.010*	*0.028*
Gender						
	Coef. (b)	**-0.056**	**0.087**	**-0.151**	**-0.065**	**-0.022**
Women	*Std. Err.*	*0.040*	*0.698*	*0.057*	*0.075*	*0.074*
	P>|t|	*0.165*	*0.215*	*0.008*	*0.384*	*0.765*
Age group (reference - 40-49)						
	Coef. (b)	**0.048**	**0.146**	**-0.048**	**-0.244**	**-0.205**
50 - 59	*Std. Err.*	*0.134*	*0.241*	*0.181*	*0.208*	*0.179*
	P>|t|	*0.718*	*0.544*	*0.789*	*0.241*	*0.252*
	Coef. (b)	**0.122**	**0.211**	**0.089**	**-0.187**	**0.069**
60 - 69	*Std. Err.*	*0.124*	*0.219*	*0.164*	*0.193*	*0.167*
	P>|t|	*0.327*	*0.335*	*0.588*	*0.334*	*0.678*
	Coef. (b)	**0.201**	**0.488**	**0.061**	**-0.215**	**0.095**
70 - 75	*Std. Err.*	*0.127*	*0.221*	*0.168*	*0.200*	*0.177*
	P>|t|	*0.114*	*0.027*	*0.715*	*0.281*	*0.593*
	Coef. (b)	**0.202**	**0.459**	**0.096**	**-0.143**	**0.101**
75 - 80	*Std. Err.*	*0.128*	*0.221*	*0.169*	*0.199*	*0.180*
	P>|t|	*0.113*	*0.038*	*0.568*	*0.474*	*0.578*
	Coef. (b)	**0.182**	**0.502**	**0.050**	**-0.405**	**0.057**
80 - 85	*Std. Err.*	*0.128*	*0.225*	*0.170*	*0.205*	*0.188*
	P>|t|	*0.156*	*0.026*	*0.770*	*0.048*	*0.762*
	Coef. (b)	**0.200**	**0.273**	**0.026**	**-0.278**	**-0.056**
85 - 90	*Std. Err.*	*0.134*	*0.230*	*0.179*	*0.220*	*0.239*
	P>|t|	*0.137*	*0.236*	*0.884*	*0.207*	*0.816*
	Coef. (b)	**-0.191**	**0.281**	**-0.081**	**-0.920**	**0.194**
> 90	*Std. Err.*	*0.152*	*0.278*	*0.204*	*0.266*	*0.463*
	P>|t|	*0.211*	*0.312*	*0.691*	*0.001*	*0.675*

6.2. One-year cost

As stated for two-months costs, we have also adjusted the numbers for one-year according to the consumer price index for 2016 (basis year). Mean costs for one-year treatment of rectal and colon cancer in the period of 2012 until 2016 are presented in Table 30. Costs of treating rectal cancer are higher than colon cancer both before and after Patient Pathway introduction, which differs from the costs for two-months. For both rectal and colon cancer one-year mean costs increased in 2015 when the Patient Pathway was introduced. A higher increase has occurred for colon cancer.

Table 30: *Mean cost for one-year treatment of colon and rectal cancer in the period 2012-2016*

RECTAL CANCER			COLON CANCER		
Year	**Mean cost, adjusted for consumer price index for 2016**	**Change vs previous year, %**	**Year**	**Mean cost, adjusted for consumer price index for 2016**	**Change vs previous year, %**
2012	376 013	n/a	2012	327 331	n/a
2013	398 715	6 %	2013	323 995	-1 %
2014	395 752	-1 %	2014	325 263	0 %
2015	**409 313**	**3 %**	**2015**	**345 778**	**6 %**
2016	403 254	-1 %	2016	338 009	-2 %

Analysis of mean costs per stage were performed for one-year costs and it revealed that the biggest increase in mean costs for treating rectal cancer in 2015 occurred due to rectal cancer at earlier stages. For colon cancer, the situation is different and the increase in meant costs is mostly caused by the III and the IV stages. No other pattern is observed via analysis per stage. The result of the analysis is presented in Table 31.

Table 31: *Mean cost for one-year treatment of colon and rectal cancer per stages*

RECTAL CANCER												
Year	**Stage 0**		**Stage I**		**Stage II**		**Stage III**		**Stage IV**		**Unknown**	
	mean cost	vs prev. year	mean cost	vs prev. year	mean cost	vs prev. year	mean cost	vs prev. year	mean cost	vs prev. year	mean cost	vs prev. year
2012	301 108	n/a	299 022	n/a	397 353	n/a	406 340	n/a	500 976	n/a	305 885	n/a
2013	294 665	-2 %	312 341	4 %	455 424	15 %	419 374	3 %	507 305	1 %	318 979	4 %
2014	290 356	-1 %	286 610	-8 %	413 099	-9 %	443 036	6 %	582 032	15 %	351 347	10 %
2015	**388 204**	**34 %**	**341 933**	**19 %**	**447 947**	**8 %**	**503 341**	**14 %**	**517 655**	**-11 %**	**295 084**	**-16 %**
2016	302 548	-22 %	319 475	-7 %	430 400	-4 %	461 199	-8 %	584 009	13 %	332 823	13 %

COLON CANCER												
Year	**Stage 0**		**Stage I**		**Stage II**		**Stage III**		**Stage IV**		**Unknown**	
	mean cost	vs prev. year	mean cost	vs prev. year	mean cost	vs prev. year	mean cost	vs prev. year	mean cost	vs prev. year	mean cost	vs prev. year
2012	312 024	n/a	248 690	n/a	351 526	n/a	398 696	n/a	422 422	n/a	315 617	n/a
2013	299 913	-4 %	296 495	19 %	341 015	-3 %	329 592	-17 %	449 675	6 %	290 011	-8 %
2014	306 534	2 %	278 732	-6 %	346 173	2 %	360 734	9 %	440 907	-2 %	292 469	1 %
2015	**316 721**	**3 %**	**286 222**	**3 %**	**353 530**	**2 %**	**397 190**	**10 %**	**468 108**	**6 %**	**321 489**	**10 %**
2016	310 236	-2 %	272 356	-5 %	353 656	0 %	380 355	-4 %	506 155	8 %	295 923	-8 %

6.2.1. Loglinear regression

Rectal cancer

Loglinear regression output is presented in Table 32. From the Table we see that one-year treatment cost among rectal cancer patients included in Patient Pathway increased by 32% (0.2843 and $p<0.001$) in comparison to rectal cancer patients treated before Patient Pathway introduction. For patients not included into Patient Pathway the cost increase of 5.8% is not significant (0.0565 and $p>0.05$). Cost also increased by 10.6% (0.1012 and $p<0.05$) in 2015 – the year of Patient Pathway introduction.

F-test result confirmed that the difference in cost between patients included into Patient Pathway and not included is significant.

Linktest showed that the model is properly specified, although the Breusch-Pagan test point out on the presence of heteroscedasticity.

The explanatory power of the regression, R-squared is 0.1459, meaning that the model explains 14% of the variation in one-year treatment cost.

The same covariates as in regressions for two-months cost (gender, age, cancer stages, and death status) are used in the regression for one-year costs. It is observed that disease severity and higher stages make a considerable impact on cost increases – for instance, for stage III costs are double as high as for zero stage (0.0565 and $p<0.001$). In contrast, the one-year cost for patients in older age groups decreases. The results are significant for age groups including patients over 80 years with $p<0.05$. Results for age-group 70-75 can be also considered as significant as p-value is at the border-level with $p=0.051$. Treating men with rectal cancer is 13% more expensive (-0.1392 and $p<0.001$) than treating women during the first year after diagnosis, in contrast to results for two-months cost

Table 32: *Loglinear regression output for 1year cost of treating rectal cancer*

RECTAL CANCER			
One-year cost	**Coef. (b)**	**Std. Err.**	**P>|t|**
Patient pathway (reference - before patient pathway introduction)			
Included	0.2843	0.0491	0.000
Not included	0.0565	0.0534	0.290
Introduction year (20	0.1012	0.0416	0.015
Gender			
Women	-0.1391	0.0261	0.000
Age group (reference - 40-49)			
50-59	-0.1134	0.0641	0.077
60-69	-0.0489	0.0597	0.413
70-75	-0.1250	0.0642	0.051
75-80	-0.1643	0.0653	0.012
80-85	-0.3231	0.0679	0.000
85-90	-0.6083	0.0752	0.000
>90	-1.0341	0.0973	0.000
Death status			
Dead	-0.1938	0.0287	0.000
UICC Stage (reference - zero stage)			
1	0.2995	0.0488	0.000
2	0.6719	0.0444	0.000
3	0.7418	0.0580	0.000
4	0.8497	0.0502	0.000
Unknown	0.0643	0.0495	0.194
Year of diagnosis (reference - 2012)			
2013	0.0763	0.0406	0.071
2014	0.0618	0.0408	0.129
Const.	12.2720	0.0748	0.000

We have also compared the impact of inclusion in the Patient Pathway on costs for the different cancer stages. One-year cost increase for the patients included in the pathway program is only significant for the patients with II stage – 34% increase (0.292 and $p<0.001$) and IV stage – 26.6% increase (0.236 and $p<0.05$). For patients with III stage cost increase with 27% (0.244 and $p>0.05$) is not significant. There are sporadic cost changes, and no clear trend between cancer stage and cost change can be found. For patient not included into Patient Pathway cost increases almost for all stages excepting 0 stage, the biggest increase is observed for stage IV – 17.7% (0.163 and $p>0.05$), none of these results are significant. At the introduction year (2015) cost increase is less in comparison to 2016. The results are significant for II stage – 19.8% increase (0.181 and $p <0.05$) and IV stage – 15.5% increase (0.144 and $p<0.05$).

Cost for treating women is less than treating men at all stages, excepting III stage where treating women is 3.9% expensive (0.038 and $p>0.05$).

Cost decrease for patients as the age increase for all cancer stages starting from 70 years, but for earlier stages results are less significant than for later stages.

F-test result shows that difference in costs between patients included into the pathway and not included are significant only for II stage. Results for other stages are biased.

The output of the analysis per stage is presented in Table 33.

Table 33: *Loglinear regression output for one-year treatment cost of rectal cancer for different stages*

RECTAL CANCER						
	Cancer Stage	**Zero Stage**	**I Stage**	**II Stage**	**III Stage**	**IV Stage**
Patient pathway (reference - before patient pathway introduction)						
Included	**Coef. (b)**	**0.226**	**0.206**	**0.292**	**0.244**	**0.236**
	Std. Err.	*0.222*	*0.120*	*0.071*	*0.168*	*0.085*
	P>|t|	*0.307*	*0.086*	*0.000*	*0.146*	*0.005*
Not included	**Coef. (b)**	**-0.047**	**0.087**	**0.073**	**0.070**	**0.163**
	Std. Err.	*0.245*	*0.120*	*0.081*	*0.174*	*0.100*
	P>|t|	*0.848*	*0.469*	*0.372*	*0.689*	*0.103*
Introduction year	**Coef. (b)**	**0.080**	**-0.015**	**0.181**	**0.244**	**0.144**
	Std. Err.	*0.178*	*0.095*	*0.058*	*0.166*	*0.069*
	P>|t|	*0.652*	*0.872*	*0.002*	*0.143*	*0.037*
Gender						
Women	**Coef. (b)**	**-0.215**	**-0.171**	**-0.102**	**0.038**	**-0.072**
	Std. Err.	*0.111*	*0.060*	*0.036*	*0.065*	*0.045*
	P>|t|	*0.053*	*0.005*	*0.005*	*0.553*	*0.106*
Age group (reference - 40-49)						
50 - 59	**Coef. (b)**	**-0.424**	**0.180**	**-0.208**	**0.042**	**-0.052**
	Std. Err.	*0.278*	*0.167*	*0.091*	*0.129*	*0.093*
	P>|t|	*0.128*	*0.283*	*0.023*	*0.745*	*0.574*
60 - 69	**Coef. (b)**	**0.067**	**-0.060**	**-0.210**	**0.058**	**-0.089**
	Std. Err.	*0.260*	*0.156*	*0.083*	*0.121*	*0.087*
	P>|t|	*0.798*	*0.701*	*0.012*	*0.628*	*0.305*
70 - 75	**Coef. (b)**	**-0.117**	**-0.171**	**-0.162**	**-0.103**	**-0.155**
	Std. Err.	*0.276*	*0.164*	*0.090*	*0.142*	*0.095*
	P>|t|	*0.672*	*0.299*	*0.071*	*0.470*	*0.101*
75 - 80	**Coef. (b)**	**-0.080**	**0.043**	**-0.354**	**-0.155**	**-0.339**
	Std. Err.	*0.272*	*0.168*	*0.906*	*0.144*	*0.102*
	P>|t|	*0.769*	*0.801*	*0.000*	*0.283*	*0.001*
80 - 85	**Coef. (b)**	**-0.330**	**-0.139**	**-0.496**	**-0.357**	**-0.592**
	Std. Err.	*0.283*	*0.174*	*0.093*	*0.155*	*0.116*
	P>|t|	*0.245*	*0.423*	*0.000*	*0.021*	*0.000*
85 - 90	**Coef. (b)**	**-0.519**	**-0.444**	**-0.833**	**-0.505**	**-0.762**
	Std. Err.	*0.306*	*0.195*	*0.101*	*0.174*	*0.147*
	P>|t|	*0.090*	*0.023*	*0.000*	*0.004*	*0.000*
> 90	**Coef. (b)**	**-1.052**	**-0.771**	**-1.034**	**-1.157**	**-1.120**
	Std. Err.	*0.315*	*0.251*	*0.146*	*0.246*	*0.493*
	P>|t|	*0.001*	*0.002*	*0.000*	*0.000*	*0.023*

Colon cancer

Loglinear regression output is presented in Table 34. The impact of Patient Pathway introduction on one-year treatment cost for colon cancer is considerably higher than for rectal cancer. One-month cost among colon cancer patients included into Patient Pathway increased in 2016 by 47.3% (0.3874 and $p<0.001$) in comparison to 2012-2014. Cost increase after Patient Pathway introduction is also observed for patients not included in the Patient Pathway and

makes up 22.8% (0.2054 and p-value<0.001). The cost also increased to patients treated 2015 by 27.1% (0.2397 and p<0.001).

As in the case of rectal cancer, the model is properly specified, but heteroscedasticity takes place. The explanatory power of the regression for colon cancer is lower than for rectal cancer, R-squared is 0.077 meaning that the model explains 7.7% of the variation in one-year treatment cost.

The same covariates were used as in the case of rectal cancer and the trends are alike. One-year cost increases with disease progression, but the increase from one stage to the next is not as drastic as in the case of rectal cancer. The impact from all the covariates used in the regressions is significant except the one for age groups under 70 years.

F-test result showed that difference in cost between included into Patient Pathway and not included is significant with p<0.001.

Table 34: *Loglinear regression output for one-year cost of treating colon cancer*

COLON CANCER			
One-year cost	**Coef. (b)**	**Std. Err.**	**P>|t|**
Patient pathway (reference - before patient pathway introduction)			
Included	0.3874	0.0421	0.000
Not included	0.2054	0.0384	0.000
Introduction year (2(	0.2397	0.0328	0.000
Gender			
Women	-0.3659	0.0219	0.000
Age group (reference - 40-49)			
50-59	0.0378	0.0621	0.543
60-69	0.0372	0.0572	0.515
70-75	-0.0329	0.0590	0.557
75-80	-0.1532	0.0592	0.010
80-85	-0.3772	0.0596	0.000
85-90	-0.5554	0.0633	0.000
>90	-0.7911	0.0747	0.000
Death status			
Dead	-0.3659	0.0219	0.000
UICC Stage (reference - zero stage)			
1	-0.0884	0.0350	0.012
2	0.0790	0.0304	0.009
3	0.1823	0.0467	0.000
4	0.2796	0.0349	0.000
Unknown	-0.2993	0.0305	0.000
Year of diagnosis (reference - 2012)			
2013	0.0535	0.0325	0.100
2014	0.1231	0.0324	0.000
Const.	12.4870	0.0614	0.000

Regression output for analysis per cancer stage is presented in Table 35.

In contrast to rectal cancer, a one-year cost increase for colon cancer after Patient Pathway introduction is relevant both for earlier stages and later ones. However, as well as for rectal cancer the increase of 46.5% (0.382 and $p > 0.05$) for patients with III stage of colon cancer is not significant. The highest cost increase is observed for I - 62% (0.482 and $p<0.001$) and IV stages –70% (0.531 and $p<0.001$).

For patient not included into Patient Pathway cost increases is more or less at the same range for all cancer stages - from 26.7% (0.237 with $p<0.05$) for II stage to 35.2% (0.302 with $p<0.05$) for I stage, but for I and III stages results are not significant with $p<0.05$. In 2015 cost increase is less than for patients included into Patient Pathway in 2016 and varies from 22% for zero stage (0.2 and $p<0.001$) to 43% for I stage (0.357<0.001). The results are significant for all stages excepting III.

Cost for treating women is less then treating men at all stages, and the results are significant excepting III and IV stages.

Correlation between age and cost is best observed for patients with stage IV cancer: the older age leads to less costs, but the results are significant for age groups above 75 years. No similar patterns for other stages are observed, but the common trend is that for patients over 75 years cost decreases.

F-test per each stages showed that differences in cost for patients included into Patient Pathway and not included is significant for zero and IV stage.

Table 35: *Loglinear regression output for one-year treatment cost of colon cancer for different stages*

COLON CANCER						
	Cancer Stage	**Zero Stage**	**I Stage**	**II Stage**	**III Stage**	**IV Stage**
Patient pathway (reference - before patient pathway introduction)						
Included	**Coef. (b)**	**0.341**	**0.482**	**0.352**	**0.382**	**0.531**
	Std. Err.	*0.089*	*0.113*	*0.093*	*0.217*	*0.112*
	P>|t|	*0.000*	*0.000*	*0.000*	*0.079*	*0.000*
Not included	**Coef. (b)**	**0.112**	**0.302**	**0.237**	**0.297**	**0.273**
	Std. Err.	*0.072*	*0.102*	*0.088*	*0.217*	*0.102*
	P>|t|	*0.122*	*0.003*	*0.007*	*0.171*	*0.007*
Introduction year	**Coef. (b)**	**0.200**	**0.357**	**0.215**	**0.287**	**0.243**
	Std. Err.	*0.053*	*0.094*	*0.078*	*0.217*	*0.079*
	P>|t|	*0.000*	*0.000*	*0.006*	*0.185*	*0.002*
Gender						
Women	**Coef. (b)**	**-0.065**	**-0.285**	**-0.180**	**-0.069**	**0.006**
	Std. Err.	*0.032*	*0.068*	*0.050*	*0.065*	*0.051*
	P>|t|	*0.042*	*0.000*	*0.000*	*0.292*	*0.913*
Age group (reference - 40-49)						
50 - 59	**Coef. (b)**	**0.108**	**0.159**	**0.032**	**-0.024**	**-0.144**
	Std. Err.	*0.108*	*0.197*	*0.164*	*0.193*	*0.123*
	P>|t|	*0.316*	*0.422*	*0.847*	*0.902*	*0.241*
60 - 69	**Coef. (b)**	**0.046**	**0.160**	**-0.015**	**0.018**	**-0.141**
	Std. Err.	*0.100*	*0.179*	*0.151*	*0.179*	*0.113*
	P>|t|	*0.646*	*0.371*	*0.920*	*0.919*	*0.214*
70 - 75	**Coef. (b)**	**0.016**	**0.332**	**-0.259**	**-0.028**	**-0.189**
	Std. Err.	*0.103*	*0.182*	*0.155*	*0.187*	*0.121*
	P>|t|	*0.879*	*0.068*	*0.095*	*0.882*	*0.120*
75 - 80	**Coef. (b)**	**-0.088**	**0.253**	**-0.280**	**-0.195**	**-0.460**
	Std. Err.	*0.103*	*0.182*	*0.156*	*0.187*	*0.123*
	P>|t|	*0.390*	*0.163*	*0.072*	*0.297*	*0.000*
80 - 85	**Coef. (b)**	**-0.278**	**0.087**	**-0.541**	**-0.528**	**-0.879**
	Std. Err.	*0.103*	*0.185*	*0.155*	*0.190*	*0.127*
	P>|t|	*0.007*	*0.640*	*0.001*	*0.005*	*0.000*
85 - 90	**Coef. (b)**	**-0.444**	**-0.067**	**-0.744**	**-0.663**	**-0.941**
	Std. Err.	*0.108*	*0.190*	*0.163*	*0.203*	*0.163*
	P>|t|	*0.000*	*0.724*	*0.000*	*0.001*	*0.000*
> 90	**Coef. (b)**	**-0.744**	**-0.241**	**-0.793**	**-1.539**	**-1.649**
	Std. Err.	*0.121*	*0.227*	*0.186*	*0.242*	*0.298*
	P>|t|	*0.000*	*0.288*	*0.000*	*0.000*	*0.000*

6.3. PSM Matching

Results for treated group – patients included into Patient Pathway, untreated group – patients before Patient Pathway introduction.

From matching results, we conclude that two-months cost of patient diagnosed with rectal cancer in 2016 and included into Patient Pathway are higher than two-months costs of patient with the alike characteristics diagnosed with cancer before Patient Pathway introduction. The increase is equal to 31 454.31 NOK. Average effect for rectal cancer is higher than for colon the increase for colon cancer is equal to 27 042.25 NOK. Matching output is represented on the Table 36.

Table 36: *Results of Matching for two-months cost for patients diagnosed with rectal and colon cancer. Treated group – patients included into PP, untreated – baseline.*

RECTAL CANCER			
Two-months cost	**Coef**	**St. Err.**	**P > z**
Average treatment effect for patients inclued into patient pathway vs baseline period	31 454.31	8 252.01	0.000

COLON CANCER			
Two-months cost	**Coef**	**St. Err.**	**P > z**
Average treatment effect for patients inclued into patient pathway vs baseline period	27 042,25	6 109,52	0.000

Matching outcome for one-year cost showed that the average treatment effect from including patients into a Patient Pathway for rectal and colon cancer are rather alike, but the standard error for rectal cancer is higher than for colon.

Inclusion of a person diagnosed with rectal cancer into the Patient Pathway resulted in 68 982.42 NOK increase in one-year treatment cost in comparison to one-year treatment cost for the person with similar characteristics diagnosed with cancer in 2012-2014. The increase for the patient diagnosed with colon cancer and included into the Patient Pathway in 2016 versus patients diagnosed before Patient Pathway implementation is 68 954.23 NOK. The matching output is represented in Table 37.

Table 37: *Results of Matching for one-year cost for patients diagnosed with rectal and colon cancer. Treated group – patients included into PP, untreated – baseline.*

RECTAL CANCER			
One-year cost	**Coef**	**St. Err.**	**P > z**
Average treatment effect for patients inclued into patient pathway vs baseline period	68 982.42	14 627.98	0.000

COLON CANCER			
One-year cost	**Coef**	**St. Err.**	**P > z**
Average treatment effect for patients inclued into patient pathway vs baseline period	68 954.23	10 473.66	0.000

Results for treated group – patients NOT included into Patient Pathway, untreated group – patients before Patient Pathway introduction

Matching results for two-month costs are controversy to the matching results described above.

We also observe a treatment effect for two-month costs for patient not included into Patient Pathway in comparison to patient with the same characteristics in the baseline period. This effect is higher than in previous matching.

Thus, two-months cost of patient not included into Patient Pathway exceeds two-months costs for patient with the alike characteristics in the baseline period with 47 958.92 NOK, while the effect for previous matching made for included into Patient Pathway was 31 454.31 NOK. For patients diagnosed with colon cancer the increase is 34 167.86 NOK, while the effect for previous matching made for included into Patient Pathway was 27 042.25 NOK. Matching output is represented on the Table 38.

Table 38: *Results of Matching for two-months cost for patients diagnosed with rectal and colon cancer. Treated group – patients NOT included into PP, untreated – baseline.*

RECTAL CANCER			
Two-months cost	**Coef**	**St. Err.**	**P > z**
Average treatment effect for patients not included into pathway in comparison to baseline period	47 958.92	8 910.87	0.000

COLON CANCER			
Two-months cost	**Coef**	**St. Err.**	**P > z**
Average treatment effect for patients not included into pathway in comparison to baseline period	34 167.86	10 441.14	0.001

One-year treatment cost of a person diagnosed with rectal cancer in 2016 and not included into the Patient Pathway was 38 617.54NOK higher in comparison to one-year treatment cost for the person with similar characteristics diagnosed with cancer in 2012-2014. The increase for the patient diagnosed with colon cancer and not included into the Patient Pathway in 2016 versus patients diagnosed in the baseline period is 50 348.86NOK. The effect related to patients pathway for colon cancer patients is less than for rectal. Matching results for one-year treatment cost are in line with the results obtained in the previous matching where we defined a treated group as patients included into Patient Pathway. The matching output is represented in Table 39.

Table 39: *Results of Matching for one-year cost for patients diagnosed with rectal and colon cancer. Treated group – patients NOT included into PP, untreated – baseline.*

RECTAL CANCER			
One-year cost	**Coef**	**St. Err.**	**P > z**
Average treatment effect for patients not included into pathway in comparison to baseline period	38 617.54	14 448.5	0.008

COLON CANCER			
One-year cost	**Coef**	**St. Err.**	**P > z**
Average treatment effect for patients not included into pathway in comparison to baseline period	50 348.86	12 299.33	0.000

Results for treated group – patients included into Patient Pathway, untreated group – patients NOT included into pathway introduction

The results of matching for two-months costs are not significant with p-value >0.05.

The average treatment effect on two-months cost for rectal and colon cancer are different. Average effect for rectal cancer is negative meaning that two-months cost of treated patient is lower with 12 491.59 NOK than two-months cost of untreated patient with the same characteristics. For colon cancer the treatment effect is positive. Matching output is represented in the Table 40.

Table 40: *Results of Matching for two-months cost for patients diagnosed with rectal and colon cancer. Treated group – patients included into PP, untreated – baseline.*

RECTAL CANCER			
Two-months cost	**Coef**	**St. Err.**	**P > z**
Average treatment effect for patients inclued into patient pathway vs not included	-12 491.59	8 706.13	0.151

COLON CANCER			
Two-months cost	**Coef**	**St. Err.**	**P > z**
Average treatment effect for patients inclued into patient pathway vs not included	1 563.05	6 542.40	0.811

Treatment effect on one-year cost from inclusion of a person diagnosed with rectal cancer into the Patient Pathway is 28 784.96 NOK in comparison to a person with similar characteristics but not included into Patient Pathway. The result is not significant with $p<0.05$. The increase for the patient diagnosed with colon cancer is less and equal to 20 480.48, in this case the result is significant. The matching output is represented in Table 41.

Table 41: *Results of Matching for one-year cost for patients diagnosed with rectal and colon cancer. Treated group – patients included into PP, untreated – baseline.*

RECTAL CANCER			
One-year cost	**Coef**	**St. Err.**	**P > z**
Average treatment effect for patients inclued into patient pathway vs not included	28 784.96	16 132.03	0.074

COLON CANCER			
One-year cost	**Coef**	**St. Err.**	**P > z**
Average treatment effect for patients inclued into patient pathway vs not included	20 480.48	10 261.78	0.046

7. Discussion

In this study we aimed to investigate what impact Patient Pathway introduction had on colorectal cancer treatment cost in a short-term perspective. Preliminary we found both arguments for cost increase and factors driving in the direction of lower costs. As a result of the research, we conclude that one-year and two-months treatment cost increased both for patients with rectal and colon cancer. Cost increase is observed also for the patients not included into

Patient Pathway, which makes interpretation of the results more complex and requires consideration of other confounding factors.

7.1. Main findings

The central finding in this study is that the introduction of a Patient Pathway for colorectal cancer led to an increase in treatment cost for colon and rectal cancer after Patient Pathway introduction. This can be considered as a positive effect and valid both for one-year and two-months treatment costs. Regression analysis outputs showed that two-month treatment costs for rectal cancer increased by 41.2% in comparison to the baseline period (2012-2014), while for colon cancer it increased by 33.6%. The biggest increase in one-year treatment cost in 2016 was observed for colon cancer (46.5%), while for rectal it was 32%, both compared to the baseline period. The results are significant ($p < 0.000$), except for two-months costs for colon cancer ($p=0.367$). The findings are supported by propensity score matching, which identified positive treatment effects for patient included into Patient Pathway. Matching results for patients not included into Patient Pathway are controversial showing that two-months cost increase is higher for patient not included into Patient Pathway than two-months cost increase for patients included into pathway. This might be partly explained by patient mix included into matching groups. Thus, share of younger patients and patients with more cancer stages is higher in the group not included into Patient Pathway. These groups are allowed to have more intensive treatment and have less contraindications for surgery within first two months.

The cost increase for the two-months period is higher than the cost increase for one-year. This can be explained by the fact that health care professionals are following lead times stipulated in the Patient Pathway. This leads to providing many treatment activities during the first two-months. Moreover, patients are supposed to get surgery no later than 35 days after referral, except for patients assigned for neo-adjuvant therapies. DRG weight for surgery is considerably higher than for other treatment activities, therefore the increase for two-months costs are higher than the increase for one-year cost. According to the report on Patient Pathways implementation conducted by Melby et al. [84] in different wards exists internal priorities among patients: those with the most severe condition are prioritized over the ones with a less serious condition. It can be assumed that patients with more severe cancer stages and expensive therapies are treated first and increase costs. Although this observation contradicts with the Patient Pathway goal and equal access to treatment, it effects the outcome.

Analysis by stage for rectal cancer showed that two-months treatment cost of patients included into the pathway considerably varies from stage to stage. The regression result is significant only for II stage where proportion of patients before Patient Pathway (35%) and included into Patient Pathway (22%) is considerable for providing statistical power. F-test revealed existing bias of results, there might be some exogenous factors influencing the outcome which we did not take into consideration.

Increase in one-year treatment cost for patients with rectal cancer included into the pathway is highest for patients with II, III and IV stages. This can be explained by treatment guidelines assuming that patients with later rectal cancer stages receive radiation and combination therapy which drives costs. F-test confirmed that the results are unbiased.

Per stage analysis for colon cancer point out on highest increase of both two-month and one-year treatment cost for patients with I stage. Treatment guidelines assume only surgery for this patient group. There might have been some other factors driving total costs for these patients in 2016 like comorbidities. Significant two-months cost increase for patients with III cancer stage is explained by patient mix. Share of patients with III stage colon cancer included into Patient Pathway (18%) is considerably higher than share of patient with the same stage in a baseline period (2%). As mentioned previously patients with more severe conditions were prioritized despite of equality principles of Patient Pathway program, this can be the other explanation for cost increase for patients with III stage of colon cancer. For one-year treatment cost, higher increase is observed for the patients with IV cancer stage included into Patient Pathway. This might be explained both by long chemotherapy and palliative therapy regimen and possible comorbidities. F-test for both one-year and two-months costs confirmed that the results are unbiased.

As per the other assumption, inclusion in Patient Pathway, better coordination of the diagnostic process should contribute to more cases detected at early stages and therefore less expensive treatment. This assumption argues for partly cost decrease. In a reality, there was no discovered pattern of patients with less severe cases after 2014. Changes in the number of patients per stage throughout the analyzed period are sporadic. Therefore, cost decreasing hypothesis can't be confirmed. It is observed a clear tendency of an increasing number of patients with stage III and several patients with missing data on cancer stage in the period 2015 to 2017. This might be explained by an increased focus on the patient and willingness to provide a more precise diagnosis which might require further investigation and lead to missing information on the stage. The other explanation is given by Melby et al. [84] via interview of healthcare personnel,

it was revealed that the coding and registering process was perceived as a time-consuming activity that was downgraded. This happened especially at the beginning of Patient Pathway implementation.

The other assumption was that a lower threshold to be referred and included in the Patient Pathway could contribute to an increased number of patients for investigation and more activities as well as more diagnosed cases, which would drive the costs up. But via analysis, we have not observed that number of patients diagnosed with colorectal cancer considerably increased. This might be partly explained by Melby et al [84]. Whether patients should be included in the Patient Pathway or not is finally decided at the hospital level. There have been regular cases when patients referred to the Patient Pathway by GP were taken out as hospital personnel disagreed that they met the requirements for a pathway. Population characteristics, such as age and gender, are one of the key factors influencing costs.

In a study conducted by Olsen et al [85], the likelihood of not being included in the Patient Pathway for colorectal cancer increased if the patient was older than 90 years. On one side older patients tend to have more comorbidities and therefore would contribute to costs increase. On the other side according to treatment guidelines treatments are not provided or limited for the patients of older age groups. For example, patients over 75 years should be considered individually for adjuvant therapy and whether it should last 3 or 6 months. As seen from regression outputs treating patients belonging to older age groups is less expensive. The fact that younger patients are included in the Patient Pathway drives cost increases.

The other outcome of Olsen et al paper [85] points out that males with rectal cancer had a higher likelihood of being included in the Patient Pathway. In our MT we have found out that treating men with rectal cancer is more expensive than treating women. This can explain the increased cost driven by men.

The results of our analysis are in line with the conclusion of Olsen et al [85] and confirms that patients diagnosed with regional stage have more chances to be included into Patient Pathway than patients with a localized tumor. Patients with a metastatic tumor have less chances to be included into the Patient Pathway. We observed that the share of patients with regional tumors is higher than with localized. This also can explain the cost increase trend.

According to Melby et al [84] to follow defined lead times hospitals conducted several examinations in parallel instead of waiting for the first test results and then proceeding with the next one. For example, at the diagnostic stage patient is first examined with a CT, but instead

of waiting for the CT result, the patient is immediately referred to PET to ensure that patient is diagnosed within a stipulated period. This leads to extra resource use and shift costs.

All these improvements were possible due to resource reorganization letting remove the bottlenecks at the hospital level. For example, assessments of referrals for further investigation were done regularly while before pathway implementation it was once a week. The use of health care personnel with highly required expertise was minimized in other activities than pathways.

Melby et al. [84] mentioned the changes in terms of radiation therapy which were introduced just before the Patient Pathway introduction - in the period 2013–2014. Guidelines for adjuvant radiotherapy for breast cancer changed. In the new guidelines, the recommended fractions were reduced from 25 to 15, and therapy duration decreased from 5 to 3 weeks. This contributed to increased capacity in radiation departments and had a spillover effect on other cancer types including colorectal cancer. Thus, waiting times and cost for radiotherapy for colorectal cancer decreased starting from 2014 due to other reasons than Patient Pathway introduction.

The other possible factor for cost increase is patient mix, i.e., proportion of high- and low-risk patients and the prevalence of patients of certain age groups. Treatment guidelines for colorectal cancer delimit patients of high risk and low risk as well as patients below 75 years and above 75 years. These groups of patients are offered different clinical paths and times of treatment. Older and high-risk patients are offered less intensive treatment to avoid a potential adverse event or in some cases are offered only palliative care. We do not know whether there was any significant change in the proportion of high-risk versus low-risk patients after Patient Pathway implementation as this information is not available, therefore conclusion on this part can't be made. As per age groups mix – we have observed increase in the number of patients below 75 years and a slight decrease in the number of patients in the age group above 80 years. This might give effect on treatment cost due to the fact that neoadjuvant and adjuvant therapy is less preferred for older groups.

Other possible confounders to mention are the appearance of more advanced diagnostic equipment and pharmaceuticals. Advanced types of diagnostic equipment provide more precise diagnostic in a shorter time. New drugs might either have less or milder adverse events or better treatment effects, but more severe adverse events. These confounders are not explored but can hypothetically influence treatment costs.

Before the implementation of Patient Pathways, there was identified a considerable difference in service offerings due to a lack of detailed guidelines and standards. Diagnostic and treatment

procedures practiced within different Regional Health Trusts varied a lot. Such differentiation had a negative impact both on treatment cost and waiting times. Introduced Patient Pathway standardized clinical paths and defined which services should be provided at each cancer stage through treatment guidelines. Standardization is a tool that is aimed to increase efficiency, improve quality, and optimize costs.

One of the central roles in Patient Pathways belongs to pathway coordinators, who ensure efficient utilization of capacity and resources and optimal logistics. This has a positive effect on hospital budgets. At the implementation stages hospitals set up meeting points where they got together and talked about organization and logistics. In this way, the Patient Pathway process strengthened networks across hospitals and contributed to the optimized use of resources and unnecessary decrease in waiting times [84].

We have not found any similar research comparing costs before Patient Pathway implementation and after, which could validate our results. But there was conducted research by Nilson et al [86], which aimed to investigate the dynamic of waiting times for 5 cancer types including colorectal cancer in the period 2007-1016. This paper can be partly used to validate our results since our assumption on cost increase was linked to waiting times.

The study identified consistently decreasing waiting times in the period 2007-2016, but no significant change after Patient Pathway implementation. Changes occurred mainly due to a reduction in median waiting times for radiotherapy while waiting times for surgery remained approximately the same. One of the reasons mentioned previously implies a spillover effect from changed treatment guidelines for breast cancer. The other argument provided in the paper is a "waiting time guarantee" announced by the Norwegian government in June 2011. It was set a target to treat 80% of patients within 20 days from diagnosis [85]. In colorectal cancer treatment guidelines this lead time is defined as 14 days from diagnostic to surgery or chemotherapy or 18 days to radiation therapy. It is stated that improvement already started when the politicians brought up the problem of waiting time.

Our research does not cover the period before 2012, but following the logic provided, we can guess that cost increases were detected already before Patient Pathway introduction.

7.2. Crowding out effects

One of the negative sides of Patient Pathways is the crowding out effects. All the improvements described in the previous chapters were possible due to resource reorganization. Patient pathways became a new priority category after the implementation and use of health care personnel with highly required expertise was minimized in other activities than pathways. However, the prioritization of patients included in the Patient Pathway goes at the expense of other patients. The so-called crowding-out effect is when patients with a higher priority are provided treatment or palliative care before patients with lower priority [87].

Interviews of hospital employees provided by Melby et al [84] revealed that patients with recurrence and other patient groups with unpleasant but harmless conditions were given lower priority.

Although the criteria for inclusion in the Patient Pathway are clear, there is a proportion of patients who turn out not to have cancer. When a high proportion of patients without the cancer diagnosis among the Patient Pathway is noted, it indicates the presence of a wide funnel for inclusion. Wide funnels in Patient Pathways may also result in higher proportions of cancer patients included in Patient Pathways and therefore fewer cancer patients diagnosed and treated outside Patient Pathway [3]. The highest proportions of Patient Pathway patients without the cancer diagnosis were found in pathways for colorectal cancer (65% and 69% for males and females) [85].

According to research conducted in Sweden [87, 88] the crowding-out effect was strong and unintended and resulted in longer waiting times for other patients and patient groups in need of the same health care resources. Therefore, the negative side of having Patient Pathways for cancer is that some patients with serious diseases may not fall under the pathway and will consequently be displaced in favor of the pathway patients.

7.3. Strengths and Limitations

The strength of this research is that it is based on real patient-level data from two linked Norwegian registers and covers 3 years before Patient Pathway implementation and 1 year after. The data is complete and the problem of selection bias is eliminated or minimized.

Nevertheless, like in any research, there exist limitations related both to data, assumptions, and interpretation of outcomes. Therefore, results should be considered cautiously.

Data

Conclusions for one-year cost are done for two first years of Patient Pathway introduction, for one of which (2015) information on inclusion into Patient Pathway is missing. So, the analysis for one-year cost is done based only on data for 2016. At the beginning of Patient Pathway's introduction, there might have been start-up problems that caused biased outcomes. There was previously mentioned the problem of data registration and correct Patient Pathway coding. Due to lack of time data input was downgraded and we observed missing information on the Patient Pathway inclusion. Thus, according to official statistics published by the Norwegian Directorate of Health [58] total number of patients who went through the Patient Pathway in 2016 was 3488 while according to our data number of patients diagnosed with colorectal cancer in 2016 and included in the pathway was 1995 (1260 patients with colon cancer and 735 patients with rectal). Even though part of the patients can be transferred from 2015 the difference is significant.

Another problem with the data set is related to information on staging. Almost 20% of the analyzed dataset does not have a record of TNM status and metastases which can make results biased. In addition, we cannot exclude human errors and the fact that some of the information of TNM was inaccurately inputted. This problem is relevant both for the periods before and after the Patient Pathway introduction.

The process of preparing data, merging it and making it appropriate for the analysis could have potentially resulted in some errors, but we hope these errors are minor.

Another type of data that would be useful to have for the analysis, but which is currently missing in CRN, is whether a patient is considered a low-risk or high-risk.

All the above-mentioned decreases precision level or indicates that the results do not represent the real situation. In addition, analysis based on the first three years after the Patient Pathway introduction gives an impression only of a short-term effect. Further research on the data for the following periods is needed in order to observe the implications of the Patient Pathway on costs in the long perspective.

Methods and Outcomes

Even though multiple regression let us observe the interconnection between cost and inclusion into Patient Pathway there are some problems with the obtained outcomes. First of all, explanatory power both for one-year cost and two-months costs is very low. The possible solution here could be to include more explanatory covariates. For example, we haven't considered regional specific, though inclusion counties might lift statistical power. But even when R-squared is low, low p-values still indicate a real relationship between the predictors and the response variable. The other problem of the model is the fact of heteroscedasticity detected in all run regressions, therefore the analysis results may be invalid. We checked if excluding some covariates from regressions would solve the problem, but it did not. So, the model is at least not over specified. As offered above there might be a solution to include more variables as the model is possibly underspecified. Heteroscedasticity may be either a problem of the regression model or a problem of the dataset. Models involving a wide range of values, as in the case of costs, are more subject to heteroscedasticity. We tried using the GLM model and tested for different specifications, but finding appropriate specifications and link was problematic.

There is also a part of uncertainty regarding the decision on which treatment activities to exclude from the analysis. NPR includes information on all the treatment activities, while some of them can be not cancer related. It is complicated to define whether the treatment is caused by adverse events after cancer therapy and therefore should be included in the cancer treatment cost, or it could be some treatment that patient had before cancer was diagnosed. Therefore, we do not exclude that information on treatment cost is biased.

And lastly, the regional specific is not considered in this master thesis, while it makes it relevant to explore it in further research at least at the level of Regional Health Trusts. There are at least two reasons for this: unequal access to medical services and different patient mix.

Despite the above-mentioned limitations, this master thesis explores an actual topic that was not previously brought up. It also forms a basis for further research on Patient Pathway implications on cost, especially considering the long-term perspective.

8. Conclusion

The main objective of this master thesis was to investigate the impact of the Patient Pathway Program on colorectal cancer treatment costs in Norway from a short-term perspective. We found results leading both to higher and lower costs, but in general, it was more costly to treat patients after the implementation of the Program. We also have to consider that with the new Patient Pathway, the treatment became more efficient in terms of more treatment within a specific time window.

There are considerable differences between the two types of cancer. Two-month treatment costs for rectal cancer increased by 41.2% in comparison to the baseline period (2012-2014), while for colon cancer it increased by 33.6%. The biggest increase in one-year treatment cost in 2016 was observed for colon cancer - 46.5%, while for rectal it was 32%, both compared to the baseline period. The increase can be explained by the shorter clinical pathway in the new program, where colon cancer patients are supposed to get surgery no later than 35 days after referral, while a substantial proportion of rectal patients starts with radiation therapy. Through model adjudication, the log-linear regression was the best regression to perform the analyses. Covariates that could impact costs such as gender, age groups, cancer stages, and death status were included. Although the explanatory power of the regressions was around 14%, the results proved to be significant, with a p-value lower than 0,000, except for 2 months costs for colon cancer (p=0.367). Linktests showed that the model is properly specified, although the Breusch-Pagan test revealed the presence of heteroscedasticity. The findings are supported by propensity score matching results which identified positive treatment effects.

Even though the effect explored in this master thesis is considered short-term (2 years covered), the results showed that the costs increased due to decreased waiting time, due to more services provided per defined period and change in patient mix. The data registries played an important role in the analyses. Through the use of registries, we are able to support decisions on budgets and planning in the health service, besides informing decision-makers on resource use and treatment practice.

We expect that this thesis can serve as a starting point for future research and provides valuable insight on cost impact after the implementation of colorectal cancer Patient Pathways, which may guide the government's actions and future study within the field of resource utilization especially considering the long-term perspective. Additional research should focus on survival

analysis together with cost analyses, besides the consideration of the regional differences within Norway to account for socioeconomic variables and in a long-term perspective.

9. References

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10. Appendices

10.1. Data Approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst A	Tove Irene Klokk	22845522	12.11.2021	23531

Eline Aas

Prosjektsøknad: Kostnader ved kreft: fokus på colorectal cancer
Søknadsnummer: 2013/2090
Forskningsansvarlig institusjon: Universitetet i Oslo

Prosjektsøknad: Endring godkjennes

Søkers beskrivelse

Målet med denne studien er å kartlegge ressursbruk i helsesektoren for pasienter med kreft, med et spesielt fokus på pasienter med colorectal cancer. Vi vil følge pasienter med colorectal cancer sitt forløp fra diagnose til død. I tillegg skal vi sammenligne kostnaden ved å dø av kreft med å dø av andre årsaker. I alle analysene vil vi evaluere hvordan kostnadene fordeler seg mellom de ulike nivåene i helsesektoren ved å benytte data fra nasjonale register: Norsk pasientregister, KUHR, IPLOS, GERICA og Reseptregisteret. Det eksisterer i dag restriksjoner på mulighetene til å bruke data fra IPLOS-registeret (som beskriver behov og bruk av pleie-og omsorgstjenester). Dette prosjektet løser problemene ved å koble Oslo Kommunes Gerica-register med de andre registrene. Gerica-registeret inneholder liknende variabler som IPLOS, men er ikke begrenset mht kobling med andre registre.

Vi viser til søknad om prosjektendring mottatt 04.11.2021 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet i Regional komité for medisinsk og helsefaglig forskningsetikk (REK) på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

REKs vurdering

Det søkes om å inkludere to nye medarbeidere i prosjektet:

- Anna Evjen, Universitetet i Oslo.
- Helena Menezes Domingues, Universitetet i Oslo.

Det søkes videre om å utvide prosjektperioden med ny prosjektslutt 31.12.2030. Dette begrunnes med at man skal rekruttere en PhD-student som skal bruke data fra prosjektet, og det må sikres at man har tid for videre analyser og publisering.

Sekretariatet har vurdert endringene og har ingen innvendinger mot at disse gjennomføres.

REK sør-øst A
Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon:22 84 55 11 | **E-post**:rek-sorost@medisin.uio.no
Web:https://rekportalen.no

Vedtak

Komiteen godkjenner med hjemmel i helseforskningsloven § 11 annet ledd at prosjektet videreføres i samsvar med det som fremgår av søknaden om prosjektendring under forutsetning av at ovennevnte vilkår oppfylles, og i samsvar med de bestemmelser som følger av helseforskningsloven med forskrifter.

Prosjektet er godkjent frem til sluttdato 31.12.2030. Etter prosjektslutt skal opplysningene oppbevares i fem år for dokumentasjonshensyn. Enhver tilgang til prosjektdataene skal da være knyttet til behovet for etterkontroll. Prosjektdata skal således ikke være tilgjengelig for prosjektet. Prosjektleder og forskningsansvarlig institusjon er ansvarlig for at opplysningene oppbevares indirekte personidentifiserbart i denne perioden, dvs. atskilt i en nøkkel- og en datafil. Etter disse fem årene skal data slettes eller anonymiseres. Vi gjør oppmerksom på at anonymisering kan være mer omfattende enn å kun slette koblingsnøkkelen, jf. Datatilsynets veileder om anonymiserings-teknikker.

Vi gjør samtidig oppmerksom på at det også må foreligge et behandlingsgrunnlag etter personvernforordningen. Dette må forankres i egen institusjon.

Sluttmelding
Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest 6 måneder etter sluttdato 31.12.2030, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Jacob C. Hølen
Sekretariatsleder
REK sør-øst

Tove Irene Klokk
Seniorrådgiver
REK sør-øst

#23531 Kostnader ved kreft: fokus på colorectal cancer

Application Info

Søknadsid:	23531
Utlysning:	Prosjektsøknad
Søker:	Eline Aas
Prosjektleder:	Eline Aas

MEDISINSK OG HELSEFAGLIG FORSKNINGSPROSJEKT

1 GENERELLE OPPLYSNINGER

1.1 Utsatt offentlighet

1.2 Tidsramme for prosjektet

1.2.1 Prosjektstart	01.01.2014
1.2.2 Prosjektslutt - tidspunkt hvor du planlegger at publisering av resultater i prosjektet skal være overstått.	31.12.2030

1.3 Prosjekttittel

1.3.1 Norsk tittel	Kostnader ved kreft: fokus på colorectal cancer

1.4 Prosjektleder

Registrerte opplysninger om prosjektleder

ID	10446
Fornavn	Eline
Etternavn	Aas
Telefon	22845036
Mobiltelefon	41141924
Oppnådd akademisk grad	ph.d/Dr. grad

Klinisk kompetanse

Ingen

Stilling	Førsteamanuensis

1.5 Forskningsansvarlig institusjon

1.6 Samarbeidende institusjoner

1.7 Prosjektmedarbeidere

Navn	Terje P Hagen
Stilling	Avdelingsleder
Prosjektrolle	Prosjektmedarbeider

Navn	Tor Iversen
Stilling	Professor
Prosjektrolle	Prosjektmedarbeider

Prosjektrolle	Medarbeider

Navn	Anna Evjen
Akademisk grad	Bachelorgrad
Stilling	Masterstudent
Institusjon	Universitetet i Oslo
Prosjektrolle	Prosjektmedarbeider

Navn	Helena Menezes Domingues
Akademisk grad	Bachelorgrad
Stilling	Masterstudent
Institusjon	Universitetet i Oslo
Prosjektrolle	Prosjektmedarbeider

1.8 Initiativtaker

1.9 Utdanningsprosjekt

1.10 Utprøving av utstyr

1.10.1 Omhandler prosjektet klinisk utprøving av medisinsk eller annet utstyr?

Nei

1.11 Samarbeid med utlandet

1.11.1 Har prosjektet noen form for samarbeid med utlandet?

Nei

1.12 Andre prosjekter med betydning for vurderingen

1.12.1 Har REK behandlet framleggingsvurdering, annet prosjekt eller generell biobank som kan være relevant for vurderingen av dette prosjektet?

Ja

1.12.1.1 Hvilke?

Prosjektnummer	Prosjektnavn	Relevans
	Terje P Hagen: Comparative effectiveness analyses of coordinated care initiatives in three Nordic countries.	

2 PROSJEKTOPPLYSNINGER OG METODE

Oppsummering av forskningsprosjektet

2.1 Prosjektbeskrivelse

Målet med denne studien er å kartlegge ressursbruk i helsesektoren for pasienter med kreft, med et spesielt fokus på pasienter med colorectal cancer. Vi vil følge pasienter med colorectal cancer sitt forløp fra diagnose til død. I tillegg skal vi sammenligne kostnaden ved å dø av kreft med å dø av andre årsaker. I alle analysene vil vi evaluere hvordan kostnadene fordeler seg mellom de ulike nivåene i helsesektoren ved å benytte data fra nasjonale register: Norsk pasientregister, KUHR, IPLOS, GERICA og Reseptregisteret. Det eksisterer i dag restriksjoner på mulighetene til å bruke data fra IPLOS-registeret (som beskriver behov og bruk av pleie-og omsorgstjenester). Dette prosjektet løser problemene ved å koble Oslo Kommunes Gerica-register med de andre registrene. Gerica-registeret inneholder liknende variabler som IPLOS, men er ikke begrenset mht kobling med andre registre.

Studiemetode/-design

3 FORSKNINGSDATA

Innsamling av data

Tidligere registrerte opplysninger

3.2 Skal det forskes på tidligere registrerte opplysninger?

Ja

3.2.2 Skal det hentes opplysninger fra sentrale helseregistre?

Ja

3.2.2.1 Opplysninger fra Sentrale helseregistre

Register	Hvilke opplysninger skal hentes, oppgi kategorier av variabler og anslag på antall
Norsk pasientregister (NPR)	Fødselsnummer (11-sifer) Alder Innleggelsestidspunkt Planlagt/akutt innleggelse DRG (vekt) DRG (korrigert vekt) DRG (type) Type spes.tjeneste Diagnose Dødelighet Medisinske og kirurgiske prosedyrer Se vedlagte variabelliste
Legemiddelregisteret (tidligere Resept-reg.)	Variabler som beskriver dato for kjøp av medikamenter, samt medikamenttype (ATC-koder) Se vedlagt variabelliste.
Dødsårsaksregisteret	Fødselsnummer (11-siffer) Tidspunkt for død (dato) Dødsårsak (ICD10) Dødssted (hjem, institusjon) Dødskommune/bydel.
Kreftregisteret	Fødselsnummer (11-sifer) Kjønn Alder (diagnosetidspunkt) Diagnosedato Fylke Lokalisjon (Lok_Icd7 - informasjon om svulstens utgangspunkt) Basis (basis for diagnose – angir metode som ligger til grunn for diagnose) Metastase (metastase-koder). Angir metastase og lokalisjoner. Rectumcancerregisteret (et register under kreftregisteret) Screeningstatus Alvorlighetsgrad (DUKE stadium)

3.2.3 Skal det hentes opplysninger fra nasjonale kvalitetsregistre?

Nei

3.2.4 Skal det hentes opplysninger fra befolkningsbasert(e) helseundersøkelse(r)?

Nei

3.2.5 Skal det hentes opplysninger fra regionalt eller lokalt helseregister?

Ja

3.2.5.1 Opplysninger fra regionalt eller lokalt helseregister

Register	Hvilke opplysninger skal hentes, oppgi kategorier av variabler og anslag på antall
Oslo Kommunes Gerica-register	Se vedlagt variabelliste

3.2.6 Skal det hentes opplysninger fra annet behandlingsrettet register?

Nei

3.2.7 Skal det hentes opplysninger fra andre norske registre?

Ja

3.2.7.1 Skal du hente opplysninger fra:

- Statistisk sentralbyrå
  FD-trygd, informasjon om utdanning, inntekt, sivil status, arbeidsstatus, kommune/bydel, kjønn

3.2.10 Skal det hentes opplysninger fra pasientjournal?

Nei

3.2.11 Skal det foretas sammenstilling av opplysninger om enkeltpersoner fra ulike registre?

Ja

3.2.11.1 Beskriv hvordan data skal kobles sammen

Data fra NPR, KUHR, Gerica, Reseptregisteret, Folkeregisteret, FD-trygd, Dødsårsaksregisteret og Kreftregisteret kobles på grunnlag av personnummer. Formålet med koblingen er å studere pasientforløp og ressursbruk for pasienter med colorecal cancer. Vi vil også evaluere om sosioøkonomi er en avgjørende faktor for ulike pasientforløp. I tillegg vil vi se på hvordan dødsårsak påvirker ressursbruken i helsesektoren.

Humant biologisk materiale

3.4 Skal det forskes på humant biologisk materiale?

Nei

Stråling

3.5 Ioniserende stråling

Nei

Begrunnelsen for valg av data og metode i prosjektet

3.6 Redegjør for den faglige og vitenskapelige begrunnelsen for valg av data og metode

Ved å kople data fra tilgjengelige databaser hvor pasientene kan identifiseres på individnivå, kan vi se på den totale ressursbruken i helsesektoren over en lang periode for alle pasienter som er diagnostisert med og behandlet for colorectal cancer.
Ved å bruke databaser kan vi se på ressursbruken for alle pasienter med colorecal cancer uten å ekskludere noen subgrupper (for eksempel pasienter med komorbiditet som ofte blir ekskludert fra klinisk kontrollerte studier, og som gir et feil bilde av kostnaden for hele pasientgruppene). Vi kan i registerstudier heller se på de kausale mekanismene bak pasienters bruk av helsetjenester, for eksempel hvordan alder og kjønn påvirker bruk av helsetjenester. Kreftbehandling blir mer og mer individualisert – gjennom en registerstudie er det stor sannsynlighet for at vi kan identifisere "vanlige" pasientforløp på grunn av det store antallet av pasienter vi forventer å få informasjon om.
Norsk pasientregister (NPR), KUHR, GERICA og Reseptregisteret vil gi data om bruk av helsetjenester i alle nivå av sektoren. Kreftregisteret og Dødsårsaksregisteret vil bli brukt for å plukke ut vår studiepopulasjon, som skal inkludere alle pasienter diagnostisert med colorectal cancer, og alle personer som dør og deres dødsårsak i løpet av ett år (det siste året som er tilgjengelig når data skal kobles). Kreftregisteret gir data om diagnosetidspunkt, type kreft, typologi osv. Dødsårsaksregisteret gir informasjon om dødsårsak og tidspunkt for død. FD-trygd gir data om sosioøkonomiske variabler. Nasjonalt register for tykk- og endetarmskreft gir oss data om screeningstatus (hvordan kreften er oppdaget) og alvorlighetsgrad (DUKE stadium).

4 STUDIEPOPULASJON OG SAMTYKKE

Studiepopulasjon (forskningsdeltakere/utvalg)

4.1 Hvem skal inkluderes i studien?

- Pasienter/klienter
  Søknaden omfatter fire separate prosjekt – hvor vi i alle prosjektene skal bruke de samme registrene for å se på totale utgifter i helsesektoren (NPR, KUHR, GERICA, Reseptregisteret) men hvor studiepopulasjonen vil endres. Under er studiepopulasjonen i de fire prosjektene beskrevet separat. 1) For å evaluere kostnaden for pasienter det første året etter diagnostisering tar vi utgangspunkt i diagnoseinformasjon fra Kreftregisteret og plukke ut alle pasienter som

Samtykke

4.6.2 Vil det bli innhentet samtykke for voksne?

Nei

4.7 Er samtykke allerede innhentet?

Nei

4.8 Søkes det om fritak fra kravet om å innhente samtykke?

Ja

4.8.2 For hvilke opplysninger søkes det om fritak fra kravet om å innhente samtykke?

Registerdata

5 INFORMASJONSSIKKERHET, DATAFLYT OG DELTAKERNES RETTIGHETER

Behandling av personopplysningene i prosjektperioden

5.1 Behandles det personidentifiserbare opplysninger direkte identifiserbare med 11-sifret personnummer eller navn, adresse og/eller fødselsdato i hele prosjektperioden?

Nei

5.2 Behandles data indirekte identifiserbare ved bruk av koblingsnøkkel?

Ja

5.2.1 Beskriv hvordan koblingsnøkkel vil bli oppbevart og hvem som vil ha tilgang

Statistisk sentralbyrå eller Helsedirektoratet

5.3 Kan personidentifiserbare opplysninger være systematisk reidentifiserbare ved kombinasjon av variabler?

Nei

Ivaretakelse av deltakernes rettigheter i prosjektperioden

Håndtering av data/materiale ved prosjektslutt

Datadeling

5.16 Planlegges det noen form for datadeling etter prosjektslutt?

Ja

5.14.1 Beskriv

Vi ønsker primært å beholde materialet i avidentifiserbar form, men kan også leve med at det anonymiseres.
Ved krav om sletting vil det også bli etterkommet.

6 AVVEINING AV NYTTE OG RISIKO

Angi forutsigbar nytte eller fordeler nå eller i fremtiden

Angi mulig risiko/ulempe nå eller i fremtiden

6.4 For den enkelte deltaker/pasient

Vi ser ingen

Tiltak for å redusere eller begrense risiko og ulempe

6.7 Redegjør for tiltak

Ikke relevant

Forsvarlighet

6.8 Gi en samlet vurdering av prosjektets forsvarlighet for å begrunne at nytten står i et rimelig forhold til den risiko/ulempe som pasienter/deltakere utsettes for

Ettersom vi benytter registerdata foreligger ingen risiko for personene som omfattes av analysene.

7 FORSIKRING, FINANSIERING OG PUBLISERING

Forsikring for forskningsdeltakere

Interesser

7.2 Finansieringskilder

Søknad om finansiering av prosjektet er sendt til Helse Sør-Øst og Norges Forskningsråd.

7.3 Godtgjørelse til institusjon

Ingen

7.4 Honorar til prosjektleder/-medarbeidere

Ingen

7.5 Eventuelle interessekonflikter for prosjektleder/-medarbeidere

Ingen

Publisering

7.6 Er det restriksjoner med hensyn til offentliggjøring og publisering av resultatene fra prosjektet?

Nei

7.7 Redegjør for hvordan resultatene skal gjøres offentlig tilgjengelig

Publikasjoner i fagfellevurderte tidsskrifter basert på et høyverdig datamateriale. Det vil bli skrevet akademiske rapporter i skriftserie ved Institutt for helse og samfunn (UiO) og nasjonale og internasjonale akademiske tidsskrifter.
Universitetet i Oslo har fire studieprogram hvor informasjon fra prosjektet vil bli formidlet i tillegg til nasjonale og internasjonale konferanser.

Kompensasjon til deltakere

7.8 Planlegges det å gi kompensasjon til pasienter/deltakere?

Ja

7.8.1 Beskriv

Ingen

8 VEDLEGG

8.1 CV for prosjektleder/ansvarshavende	0 vedlegg
8.2 Forskningsprotokoll	0 vedlegg
8.11 Andre nødvendige vedlegg	0 vedlegg

9 ANSVARSERKLÆRING

10.2. Data and materials

Table A 1: Lead times in Patient Pathway for colorectal cancer

From received referral till first meeting for diagnostic		9 calendar days
From first diagnostic meeting till diagnosis is set and treatment plan is defined		12 calendar days
From end of diagnostic till start of treatment	Surgery	14 calendar days
From end of diagnostic till start of treatment	Medical treatment	14 calendar days
From end of diagnostic till start of treatment	Radiation therapy	18 calendar days
From receiving referral to treatment start	Surgery	35 calendar days
From receiving referral to treatment start	Medical treatment	35 calendar days
From receiving referral to treatment start	Radiation therapy	39 calendar days

Table A 2: *Variables from the Cancer registry of Norway used in the analysis*

Variable		Type of variable
Patient ID		Numerical
Date of diagnosis		Interval
ICD10		Categorical
Age		Numerical
TNM	Tis until T4 (11 Variables)	Categorical
	N1 until N2 (6 Variables)	Categorical
	M (7 Variables)	Categorical

Table A 3: *The risk overview of the Norwegian cancer treatment – 16 most important problem areas*

Problem areas	**Description**
Diagnosis	Delays in diagnostics on various levels and waiting time for test results
Radiology	Problems related to radiological service (waiting time, quality and coordination between institutions, both public and private)
Pathology	Incorrect diagnostics or poorly performed diagnostics
Infections	Failure in infection prevention and treatment of infection
Competence	Weaknesses in knowledge transfer, recruitment and further training of health personnel
Information sharing	Failure in information flow and coordination between actors. Missing a portal with valid treatment recommendations and action programs
Palliative services	Failure of palliative care, especially for patients at the end of life
Overtreatment	The limits of treatment are stretched in severe cancer. Difficult conversations are postponed or moved unnecessarily between treatment levels
Surgery	Failures in surgical treatment initial treatment, complications)
Volume and quality	Too few patients are treated in some health trusts. This can lead to poor quality and treatment results
Referral	Referrals are delayed or missing. Failing receipt and follow-up of test results
Complications	Missing overview and monitoring of serious complications at national level
Communication	Poor information and involvement of patients and their relatives
Radiation therapy	Late complications of radiation therapy can be overlooked, follow-up after radiation therapy should be risk-based
Continuity	Lack of treatment continuity, too many actors involved and poor coordination between them
Working environment	Personnel is burn out. Unsatisfactory working environment that can weaken patient services

Table A 4: *Variables from the National Patient Register used in the analysis*

Variable	Description	Type of variable
lopenr	Patient unique number (the same as variable pid in NCR)	Numerical
aar	Year of procedure	Numerical
kjonn	Patients gender	Categorical
innDato	Date of procedure start	Interval
pakkeforlop	Inclusion in patient pathway (Yes, No, Missing data)	Categorical
drg	DRG-code	Categorical
korrvekt	DRG weight	Numerical
hdg	Main diagnosis group	Categorical
dod aar	Yeas of patient's death	Numerical

Table A 5: *CRN parameters of main diagnostic group (HDG) combined with DRGs*

DRG codes	Drg names	HDG codes	Hdg names
DD01	Other day treatment	1	Diseases of the nervous system
570O	Insertion or replacement of neurological stimulation equipment, day surgery treatment	1	Diseases of the nervous system
901C	Outpatient consultation regarding disease of the peripheral nerves	1	Diseases of the nervous system
801W	Outpatient treatment of conditions of the nervous system with local injection of botulinum toxin	1	Diseases of the nervous system
801T	Adjustment of implanted infusion equipment or shunt	1	Diseases of the nervous system
801H	Outpatient treatment of neurological disorders with infusion of special drugs	1	Diseases of the nervous system
801U	Neuropsychological examination	1	Diseases of the nervous system
902O	Outpatient consultation regarding other eye diseases	2	Eye diseases
802U	Outpatient treatment for AMD and macular edema with local drug injection or photodynamic method	2	Eye diseases
DD02	Other day treatment	2	Eye diseases
802P	Other outpatient examination and treatment of eye conditions with specified measures	2	Eye diseases
903C	Outpatient consultation regarding sleep apnea	3	Ear, nose and throat diseases
803U	Hearing examinations and hearing improvement measures	3	Ear, nose and throat diseases
187O	Other outpatient dentistry	3	Ear, nose and throat diseases
803R	Diagnostic intervention in sleep apnea	3	Ear, nose and throat diseases
DD03	Other day treatment	3	Ear, nose and throat diseases
803T	Dental implant treatment	3	Ear, nose and throat diseases
803V	Minor procedure related to teeth and gums	3	Ear, nose and throat diseases
187A	Tooth extraction and restoration	3	Ear, nose and throat diseases
804P	Local interventions in the thorax	4	Diseases of the respiratory system
DD04	Other day treatment	4	Diseases of the respiratory system
905O	Outpatient consultation regarding other circulatory diseases	5	Diseases of the circulatory system
116O	Implantation or replacement of pacemaker, day surgery treatment	5	Diseases of the circulatory system
805S	Physiological heart examination	5	Diseases of the circulatory system
905A	Pole consultation regarding atrial fibrillation and other arrhythmias or conduction disturbances	5	Diseases of the circulatory system
905C	Pole consultation regarding angina pectoris and ischemic heart disease, excluding AMI	5	Diseases of the circulatory system
115B	Implantation or replacement of pacemaker	5	Diseases of the circulatory system
DD05	Other day treatment	5	Diseases of the circulatory system
805P	Electroconversion of cardiac arrhythmia	5	Diseases of the circulatory system
107A	Coronary bypass without cardiac catheterization or complex concomitant procedures u / bk	5	Diseases of the circulatory system
107C	Coronary bypass with complex concomitant procedures or m / bk	5	Diseases of the circulatory system
DD08	Other day treatment	8	Diseases of the musc. system and connective tissue
242E/F	Osteoarthritis u, w / bk	8	Diseases of the musc. system and connective tissue
232O	Arthroscopy, day surgery treatment	8	Diseases of the musc. system and connective tissue
232O	Arthroscopy, day surgery treatment	8	Diseases of the musc. system and connective tissue
471N	Bilateral or multiple major joint prosthetic surgeries in extremities	8	Diseases of the musc. system and connective tissue
908O	Outpatient consultation regarding other diseases of the musculoskeletal system	8	Diseases of the musc. system and connective tissue
209D	Insertion or replacement of hip prostheses, or insertion or printing of prosthesis in the knee or ankle.	8	Diseases of the musc. system and connective tissue
908A	Pole injury due to fracture, dislocation or soft tissue injury in arms, legs or pelvis	8	Diseases of the musc. system and connective tissue
908E	Outpatient consultation regarding tendinitis and bursitis	8	Diseases of the musc. system and connective tissue
980H	EH-related musculoskeletal conditions without accommodation	8	Diseases of the musc. system and connective tissue
908D	Outpatient consultation regarding systemic connective tissue diseases	8	Diseases of the musc. system and connective tissue
808Y	Orthopedic bandaging	8	Diseases of the musc. system and connective tissue
908F	Outpatient consultation regarding disorders and injuries in the back and neck	8	Diseases of the musc. system and connective tissue
908E	Outpatient consultation regarding tendinitis and bursitis	8	Diseases of the musc. system and connective tissue
908B	Outpatient consultation regarding osteoarthritis	8	Diseases of the musc. system and connective tissue
214C	Operations on the column excl. spondylodesis m / bk	8	Diseases of the musc. system and connective tissue
908R	Orthopedic diagnostic ultrasound	8	Diseases of the musc. system and connective tissue

909A	Outpatient consultation regarding minor skin injuries	9	Diseases of the skin and subcutaneous tissue
909B	Outpatient consultation regarding chronic wounds	9	Diseases of the skin and subcutaneous tissue
909E	Outpatient consultation regarding eczema and dermatitis	9	Diseases of the skin and subcutaneous tissue
909D	Outpatient consultation regarding psoriasis and other papulosquamous disorders	9	Diseases of the skin and subcutaneous tissue
814S	Medication termination of pregnancy	14	Diseases during pregnancy and childbirth
914P	Obstetric diagnostic measures, including screening of pregnant women	14	Diseases during pregnancy and childbirth
914O	Outpatient consultation regarding pregnancy, childbirth and childbirth	14	Diseases during pregnancy and childbirth
914Q	Fetal diagnostic examinations	14	Diseases during pregnancy and childbirth
381O	Abortion, day surgery treatment	14	Diseases during pregnancy and childbirth
814P	Other health care in connection with miscarriage and complications after abortion	14	Diseases during pregnancy and childbirth
378N	Operations in extrauterine pregnancy	14	Diseases during pregnancy and childbirth
436A/B	Other mental disorders due to abuse w, u/ bk	19	Mental disorders and substance abuse
426C	Other disorders of mood <60 years	19	Mental disorders and substance abuse
426D	Other disorders of mood> 59 years	19	Mental disorders and substance abuse
426B	Bipolar disorder> 59 years	19	Mental disorders and substance abuse
426A	Bipolar disorder <60 years	19	Mental disorders and substance abuse
	All DRGs codes related to group 22	22	Burns
	All DRGs codes related to group 30	30	Diseases of the breast