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Emergency Presentation of Colon Cancer

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EMERGENCY PRESENTATION OF COLON CANCER

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If you want the rainbow, you gotta put up with the rain

- Dolly Parton

To my family, with love

ABSTRACT

Colon cancer is the second most common form of non-skin cancer in Sweden for men and women respectively. Up to one fourth of all colon cancer cases are reported to present as emergencies, which is associated with a higher postoperative mortality and a lower 5 year survival, and affects the total survival in the colon cancer group. The overall aim of this thesis was to explore factors associated with emergency presentation of colon cancer.

In a population-based record study (n=604) including all patients from the GDH in Eskilstuna, 1996-2005 it was found that the rate of emergency cases using a strict definition was 17% . These patients had more late-stage cancers and were most frequent during summer (36%), (the corresponding number for elective cases was 16%, 7.8; p<0.049) (I).
 An even larger population-based record study (n=853) was also performed including four different counties in the Uppsala-Örebro region, 2006-2008. The symptom profile differed according to mode of presentation and 54% in the subacute (reported as emergencies, but operated after >3 days from admittance) group had reported ≥2 symptoms associated to colon cancer the last 12 months prior to surgery, and 44% had already undergone a recent examination of the large bowel. Postoperative and 90-days mortality were lower in the acute group (8% and 15%) but more pronounced in the subacute group (15% and 28%). Five-year survival was 40% in the acute group and the corresponding number in the subacute group was 28% (II).

The association between socioeconomic factors (SES) and mode of presentation was investigated in a register study including all patients with colon cancer in the Stockholm and Uppsala-Örebro regions 1997-2006 (n=12 293). Emergency presentation of colon cancer was most common in patients above the age of 80 (27.8%), stage IV (34.6%) and among patients with the lowest income (Q1) (27.7%). In a multiple regression model, OR for emergency presentation was 1.24 (95% CI 1.04-1.49) for unmarried and 1.22 (95% CI 1.03-1.45) for low income patients (III).

Within the context of this thesis a pilot study concerning gene expression was also performed in which differences between emergency and elective colon cancer was found.

Keywords: colon cancer, emergency, risk factors, stage, survival, incidence, management, symptoms, socioeconomic status

LIST OF PUBLICATIONS

This thesis is based on the following papers, referred to in the text with Roman numerals.

I.   H. Gunnarsson, T. Holm, A. Ekholm, LI. Olsson. **"Emergency presentation of colon cancer is most frequent during summer".** Colorectal disease. 2010 mar; **13**: 663-668.

II.   H. Gunnarsson, K. Jennische, S. Forssell, J. Granström, P. Jestin, A. Ekholm, LI. Olsson. **"Heterogeneity of Colon Cancer Patients Reported as Emergencies".** Submitted.

III.   H.Gunnarsson, A. Ekholm, LI. Olsson. **"Emergency presentation and socioeconomic status in colon cancer".** Eur J Surg Oncology 2013 Apr; 1-6.

CONTENTS

LIST OF ABBREVIATIONS

APC   Adenomatous Polyposis Coli
C   Clinical
CC   colon cancer
CI   Confidence interval
CIMP   Island methylator Phenotype pathway
CIN   Chromosomal Instability
CRP   C Reactive Protein
CT   Computer Tomography
DNA   Deoxyribo Nucleic Acid
ECC   Emergency colon cancer
EGFR   Endothelial Growth Factor Receptor
FAP   Familial Adenomatosis Polyposis
GDH   General District Hospital
GP   General Practitioner
GSK   Glycogen Synthase Kinase
HNPCC   Hereditary Non Polyposis Colon Cancer
HPS   Hyperplastic Polyposis Syndrome
IL   Interleukin

LEF   Lymphoid Enhancer Factor

LISA   Longitudinal Integrated Database on Labour Market Research
Mb   Morbus
MSI   Micro Satellite Instability
NS   not significant
NSAID   Non-Steroid Anti-Inflammatory Drug
OR   Odds Ratio
P   Pathological
PCR   Polymerase Chain Reaction
PPV   Positive Predictive Value
Q   Quartile
RNA   Ribonucleic Acid
ROC   Regional Oncologic Centre

SEMS   Self-Expanding Metallic Stent
TCF   Transcription Factor
TNM   Tumor Node Metastasis
WBC   White Blood Cell count
Wnt   Wingless/integration
Vs   Versus

1 INTRODUCTION

1.1 COLON CANCER

1.1.1 Descriptive Epidemiology

Colorectal cancer is the third most common cancer in men, the second most common in women, and the fourth most common lethal malignancy globally (1). In Europe, colorectal cancer is the second and third most common malignancy in women and men respectively, while the second most cancer-related cause of death overall, constituting about 14 % of all cancers (1). The numbers have stabilized or decreased, particularly in younger age groups (2), and the greatest increase in incidence of colon cancer is currently observed in Asia and in Eastern Europe (2). In Sweden, there are about 4,000 new cases per year (3, 4), of which 90% occur after the age of 50 (5) and with an equal distribution across the sexes (3).

1.1.2 Risk Factors

Family History

Apart from age, heredity is the strongest risk factor for colon cancer. It is estimated that about 5-10% of all patients have a family history of the disease (6), including Hereditary Non-Polyposis Colorectal Cancer (HNPCC/Lynch syndrome) and Familial Adenomatosis Polyposis (FAP). Other rare genetic diseases associated with an increased risk of colon cancer are Gardner syndrome, Juvenile and Peutz-Jeghers polyposis, and Hyperplastic Polyposis Syndrome (HPS).

Inflammatory Bowel Disease

Patients with inflammatory bowel disease, ulcerative colitis, and Mb Crohn are at an increased risk of colon cancer. However, corticosteroids, 5-aminosalicylic acids (5-ASAs) and immunomodulators, as well as more modern drugs such as biological therapy in the form of antibodies, have improved the treatment of IBD and decreased the risk of colon cancer (7). Endoscopic surveillance and colectomy as prophylactic management moderate this risk (8).

Lifestyle Factors

Diet and nutrition is estimated to be the cause of 30-50% of all colon cancer worldwide (9), and is the greatest exogenous factor in the etiology of colon cancer (2).
Red or processed meat, obesity and an excessive calorie intake (both from fat and carbohydrates), as well as high levels of alcohol consumption and tobacco use are associated with colon cancer (10). A low grade of physical activity is also associated with an increased risk for colon cancer (11). Protection from colon cancer is provided by a variety of vegetables, fruits, dairy and egg products, as well as unabsorbable fibers (12). In addition, fish oil and phytochemicals are anti-inflammatory and inhibit colon cancer development (13), as does vitamin D (14). Folate intake also seems to reduce the incidence of colon cancer (15).

1.1.3 Carcinogenesis and Molecular Biology

The molecular biology of colon cancer is thoroughly studied, and has been found to be both heterogeneous and complex, with many different genes involved in various steps (16). The transformative development from a benign polyp into a malignant tumor, the adenoma-carcinoma sequence, was first described in 1990 (17), and has been linked to the accumulation of mutations.
One of the most studied genes is the tumor suppressor gene Adenomatous Polyposis Coli (APC), which is hypothesized to be the gate-keeper for further malignant transformation, but a number of other tumor suppressor genes and oncogenes contribute to the complexity of the tumorigenesis (18, 19).

Three distinct molecular mechanisms of genetic instability resulting in genetic aberrations have been identified; Chromosomal Instability (CIN), which stands for chromosomal gain or loss and is present in more than 2/3 of colon cancer tumors, Micro Satellite Instability (MSI/MIN), which is more common in right-sided tumors, and CpG Island Methylator Phenotype (CIMP), which results in an altered gene expression (epigenetic changes) without altering the DNA sequence (20, 21).

Recent advances in genetics and cellular biology have made it possible to translate detailed genetic information into pathways that fulfill distinct cellular functions. Two important pathways identified in colon cancer tumorigenesis are the Wnt-/beta-catenin and EGFR-Kras pathways (22-25). Both of these regulate cell growth and differentiation, and the Wnt pathway is also involved in regulation of apoptosis. The APC gene is part of the Wnt signaling pathway in sporadic colon cancer. About 80% of the APC is mutated, while the corresponding number in beta-catenin is 10% in sporadic colon cancer (24).

Differences in gene expression profiling, validated by immunohistochemical analysis, have been found between primary and metastatic colon cancer, and the proliferation rate of the liver metastases of colon cancer has been found to be reduced compared to that of primary tumors (26).

1.1.4 Symptoms and Investigation

Colon cancer presents with a wide range of symptoms, including altered bowel habits, diarrhea, constipation, weight loss, abdominal pain, and fatigue, the latter associated with occult bleeding and anemia. Right-sided colon cancer is more often associated with anemia, while left-sided tumors are more often associated with visible blood in stools and changes in bowel habits (27). First symptoms may be vague or diffuse.
In all, most of these symptoms have a low predictive value for colon cancer. For instance, only 1% of all patients that contact a doctor for abdominal pain have a colorectal malignancy (28). Bleeding and weight loss are estimated to have the highest association with colon cancer (29, 30). Abdominal pain has been associated with late-stage colon cancer (31). In general, iron-deficiency anemia has been considered a marker for colorectal cancer, but it is also associated with the longest delay in diagnosis

in primary care, as well as the worst prognosis (32). The absolute number of symptoms has been suggested as a risk assessment tool for suspected colon cancer (33). Two or several symptoms or repeated attendances with the same symptom should alert the physicians of the need for investigation (29).

The high sensitivity of colonoscopy has made it the golden standard of investigation for patients with symptoms possibly caused by colon cancer. The rate of missed colon cancers was between 2-6% in a Canadian register study (34), depending on the location of the tumor. Other advantages are the opportunity afforded for biopsies and the fact that patients are not exposed to radiation. If a colonoscopy is incomplete, or contraindicated for some reason, a CT colonography is performed (33). A population-based Dutch study including more than 1,800 patients determined that the sensitivity of CT colonography is above 94% (35).

1.1.5 Stage

Nowadays, the TNM (Tumor, Node, Metastasis) system is widely used. Clinical (c)TNM is the basis for treatment, and pathological (p)TNM is the basis for prognosis. According to the latest and 7th edition of TNM, **T** indicates the extent of spread through the layers that form the wall of the colon and rectum. The tumor growth in these layers given in order from the innermost to the outermost, are: growth into the mucosa (Tis), growth into the submucosa (T1), growth into the muscularis propria (T2), growth into the subserosa (T3), growth through the serosa (T4a) and the most advanced stage, direct growth to other organs (T4b). **N** indicates whether or not the cancer has spread to nearby lymph nodes and, if so, how many lymph nodes are involved, from 0->7 (N0-N2b). **M** indicates whether or not the cancer has spread to other organs (M0-M1b) (36). Acurate nodal staging is of crucial importance in determining treatment and prognosis (37). The number of evaluated lymph nodes is also considered a quality measure of colon cancer surgery and pathology (38), and the required minimum number of them in the specimen is twelve (39). This minimum is met to 85% in all operations in recent years in Sweden (40). Based on the TNM system the cancer is classified as stage I (T1-T2, N0, M0), stage II (T3-T4, N0, M0), stage III (any T, N1-2, M0) and stage IV (any T, any N, M1).
In Sweden stage II is most prevalent (30%), followed by stage III (26%) and stage IV (20%) cancers (40, 41).
Different symptoms have also been associated with different TNM stages; visible blood in stools is more often associated with a lower TNM stage, whereas abdominal pain is more common in patients with cancers with a higher TNM stage (27, 31).

1.1.6 Treatment

Primary treatment for colon cancer involves curative resection (R0) of the affected part of the bowel with central ligation of supplying arteries and draining of veins and lymph vessels, as well as mesenteric resection and a primary anastomosis. Traditionally the operation was often done by "blunt" dissection. However the CME (complete

mesocolic excision) technique, which emphasizes an extensive mesenteric resection along the embryologic planes, has been more frequently used and is analogous to TME, which is now a fully accepted method for rectal cancer surgery worldwide (42). There are basically three types of operations for elective colon cancer; right-sided hemicolectomy, left-sided hemicolectomy and sigmoidectomy. Laparoscopic surgery improves short term outcome has no negative impact on long term outcome (43), but is only used in about 10% of colon cancer operations in Sweden, although this number increases every year (40). However, this is a low figure internationally, and in Denmark, for instance, more than 60% of all colon cancer surgery is done laparoscopically (44).

Adjuvant chemotherapy in colon cancer is based on 5-fluorouracil in combination with Levamisol or folic acid. It is offered during 6 months postoperatively to patients with stage III tumors, patients with stage II tumors with vascular and perineural growth, and a biological age of less than 75 years. The 5-year disease-free survival has increased from 55% to 67%, and overall survival has increased from 64% to 71% (45).

Surgical treatment for generalized colon cancer, mainly to the liver and lungs, has become standard treatment during recent years, and is an established practice for selected patients. If the intention is curative, preoperative chemotherapy during 6-8 weeks is given followed by metastasectomy or resection of the primary tumor in a two-step procedure or sometimes synchronously. Five-year survival after resection with a curative intent is 48% with hepatic metastases present and 32% for pulmonary metastases, but only 31% when both are present (46).

About 8% of colon cancer patients have synchronous or metachronous peritoneal carcinomatosis (47), and, whenever possible, treatment involves cytoreductive peritonectomy and intraperitoneal chemotherapy (HIPEC). When left untreated, the prognosis for peritoneal carcinomatosis is poor, with a median survival of seven months (48).

Chemotherapy based on oxaliplatin and irinotecan is used in palliative cases, increasing the median survival by up to 20 months (41).
This also involves monoclonal antibody drugs such as anti-EGFR (panitumumab, cetuximab) and anti-VEGF (bevacizumab), the former provided wild type KRAS (49), which occurs in 30%-50% of colorectal cancer cases.

1.1.7 Postoperative Mortality and Prognosis

During the last years in Sweden, thirty-day postoperative mortality rate in elective patients is about 2%, and increases with age so that for patients older than 80 years the rate is 4,5% (40).

Surgery alone cures approximately 50% of the patients (50). Overall, survival in colon cancer has increased, and is now approximately 55%, due to the use of adjuvant chemotherapy, resection of the primary tumor and metastasectomy (51). The long term survival proportion is given for each stage in Figure 1.

4

Even in the most advanced stage, primary resection is associated with an increased survival (52).
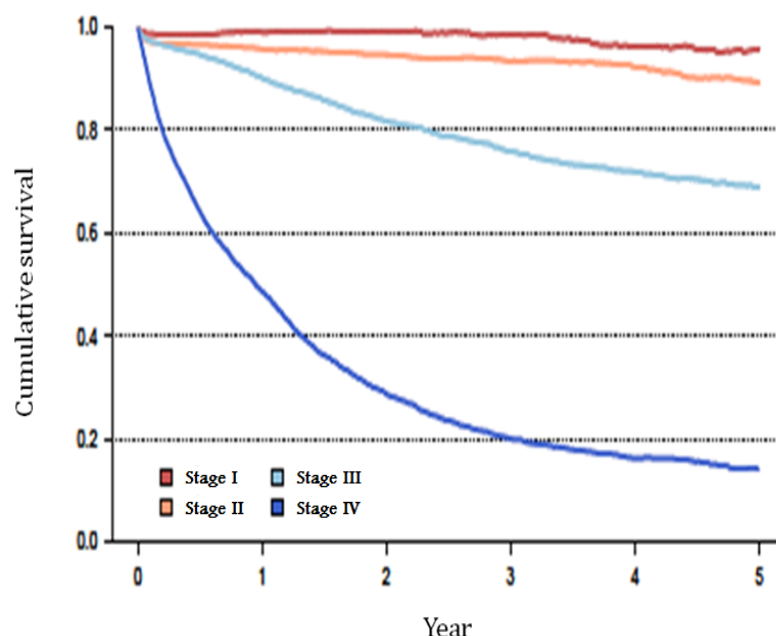

Figure 1: Relative survival according to cancer stage (53). (Published with the permission of the Swedish colon cancer registry).

1.1.8 Prevention

For primary prevention, NSAID and aspirin in certain doses have been demonstrated to give protection from sporadic colon cancers (54, 55) and adenomas (56), but this is not yet in clinical use. Life style factors such as diet, physical activity, and alcohol and tobacco use are also important for preventing colon cancer (10).

The standard strategy for secondary prevention or screening for colon cancer is initial testing by means of fecal occult blood test (FOBT; guaiac-based or immunochemical) and endoscopy (sigmoidoscopy/ colonoscopy). A meta-analysis including four population-based randomized controlled trials found FOBT screening to reduce mortality of colorectal cancer by one sixth among individuals who participated in at least one round-up (57).

Flexible sigmoidoscopy inserted up to colon descendens or the splenic flexure, with 60% of all colorectal neoplasms within reach, is another option for screening. As adenomatous polyps are the precursor of colorectal cancer, removing them will prevent colorectal cancer (58). Once-only sigmoidoscopy between ages 55 and 64 years was found to reduce the incidence of distal colorectal cancers by half (59).

1.1.9 Socioeconomic Factors

The incidence of colon cancer has been found to be associated with socioeconomic factors (60, 61), albeit in contradictory ways. Some studies have shown an association between higher social class and increased incidence of colon cancer (62, 63) while others, predominantly in the USA and Canada, found higher social status to be negatively correlated with colon cancer (64-66). Low income patients are more likely to recur than average or high income patients (67).
Stage at diagnosis in colon cancer was not associated with socioeconomic factors in colon cancer, as opposed to rectal cancer, in a Danish study (68).

Survival also seems to be consistently less favorable for patients with lower socioeconomic status (64, 69). One explanation for this is diagnostic delay, which has been shown to be longer in this group (70). Adjuvant treatment is also less often offered to patients with low socioeconomic status (69).

The lower participation in screening programs associated with SES, particularly in men, unmarried, and divorced patients, may to some extent explain the higher incidence and mortality (71).

1.2 EMERGENCY PRESENTATION OF COLON CANCER

1.2.1 Descriptive Epidemiology

The rate of colon cancer presenting as emergencies varies widely in the literature, from 8% to 34% (72-75). One explanatory factor for this is the variation in the definition of emergency colon cancer (Appendix). A distinction between emergency/urgent and scheduled/elective colon cancer has been proposed (76, 77). One classification defines emergency as surgery within one hour, while an urgent operation is within 24 hours, a scheduled operation within three weeks and an elective when convenient for patient and surgeon (78). Other terms used for `emergency´ are `obstructive/perforated´(41), `acute´ (79), `complicated´ (67, 74), `advanced´ (80), `strictured´ (80), and `contracted´ (81) colon cancer.

In an Italian cohort study comparing two different time periods (1975-1984 vs. 1995-2004), and in a Norwegian study comparing three different time periods (between1980 and 2004) the total colon cancer incidence increased, but the rate of emergency cases declined over the years (74, 82). On the other hand, in a Canadian register study comparing 1996-1998 to 1999-2001 the rate of emergency colon cancer did not drop (83).

1.2.2 Factors Associated with Emergency Presentation

Previously recognized risk factors in emergency colon cancer are shown in Table III. A few American studies have recognized ethnicity as a risk factor predisposing African Americans and Hispanic women for an acute course (84-86). A couple of American studies demonstrate that emergency presentation is associated with comorbidity, both

when expressed as a high ASA grade (87) and as a Deyo score (a scoring system including 22 different diseases) (83). In a British study conducted between 1982 – 1992, the latter has also been shown in the elective group when specifying national diseases such as diabetes, coronary artery and cerebrovascular diseases, as well as neurological deficits and pulmonary diseases (88). Furthermore, it has been found that emergency patients are more likely to lack a GP (83, 89).

Reference(s)	Identified factor
Raine(90), Wong(91), McArdle(75), Rabeneck(83)	High age
Wong(91)	Low age
Bass(92), Chiarugi(93), Jestin(72)	Advanced stage
Raine(90), Rabeneck(83), McArdle(75)	Female sex
Raine(90), Diggs(94)	Access to health care service
Bowman(84), Ahuja(85), Irby(86)	Ethnicity
Raine(90)	Low income
Scott(89)	Civil status (widows)
Rabeneck(83)	Comorbidity
Yoo(95)	Smoking, corticosteroids
Scott(89), Rabeneck(83)	Lack of GP

Table I. Factors associated with emergency presentation of colon cancer in previous studies.

1.2.3 Pathogenesis

Emergency colon cancer has been studied as a separate entity to a very limited extent. However, inflammatory response has been shown to differ in the sense that emergency patients have higher levels of IL-1β, IL-6 and CRP (96, 97), as well as an increase in WBC and hypoalbuminemia preoperatively (98). In a Japanese study, 166 colorectal cancers were classified macroscopically as either stricture or nonstricture type. Strictured tumors, 47 /166 (28%) were more often associated with an abundance of fibrosis, and had a higher recurrence rate and a significantly shorter time to recurrence (80). Another Japanese study found "Contracted" tumors to have higher grade of lymphatic and venous permeation, as well as lymph node metastasis, due to a high interaction between the tumor and the extracellular matrix (ECM) that is probably induced by cancer cells (81). A recent Swedish study found that colon cancer presenting as emergency cases had a more aggressive histopathologic profile, with more multiple tumors, more perineural and vascular infiltration, and more mucinous tumors with signet-ring cells than elective cases (99). Two studies report right-sided tumors to be more common in the emergency group (83, 95), another found this more common in left-sided tumors (72), and a fourth study found no difference (92).

1.2.4 Symptoms and Investigation

The predominant state of an emergency course is obstruction (100, 101), which represents 80-90% of all acute colon cancers. In early stages, this is characterized by intermittent abdominal pain and constipation, but when left unrecognized will eventually lead to a distended abdomen and, in cases of complete obstruction, no passage of flatus or stool. In case of an incompetent ileocaecal valve, vomiting occur, as well as less distension of the bowel.

Perforation constitutes about 10-20% (40, 74, 91) of all emergencies, either at the site of the tumor or proximal to the tumor, typically in the caecum, which is most distended according to the law of LaPlace. Perforation will cause peritonitis with movement-related abdominal pain, nausea, and vomiting. Bleeding from the tumor is another possible acute state of colon cancer, although an infrequent one (102). In a Swedish population-based study (2007-2011), only 4% of the emergency patients were operated upon due to bleeding (40).

Patients with emergency colon cancer present with abdominal pain more often, while electives have rectal bleeding more often (77, 89, 103). Symptom duration is estimated to be shorter for emergency patients (approximately 3 months) (31, 104, 105). In a Norwegian study, the average symptom duration was as brief as 3 days for emergency patients defined as "patients with acute symptoms hospitalized without scheduled investigations or treatment" (101).

Patients presenting with suspected emergency colon cancer are investigated by abdominal computer tomography (CT), with or without a barium enema. Rectoscopy is mandatory to exclude a distal (rectal) cause for obstruction.

1.2.5 Stage

The stage distribution in emergency colon cancer is more advanced compared to elective cases (72, 91, 106), and about 85% are in stage III or IV in emergency colon cancer (102). Moreover, the prevalence of synchronous distant metastases is 27% in emergency patients, compared to 15% in electives (107).
The number of lymph nodes removed during emergency surgery has not been shown to be lower than for elective colon cancer patients (102, 108).

1.2.6 Treatment

Colon cancer surgery in the emergency state is associated with a number of difficulties. It is more technically challenging, it requires access to high or subspecialized competence at short notice at all times and the patients are less well prepared, both physiologically and mentally (108).

Right-sided hemicolectomy with primary anastomosis is the resection of choice in low risk patients with proximal tumors. If there is a risk of anastomotic leakage, ileostomy is recommended. Subtotal or total colectomy should be performed when tumors are located in transversal or in the proximal left colon and causing a distended right colon

(109). In left-sided tumors there are several options (105). Sigmoidal tumors used to be treated with segmental resection and colostomy, but this has more and more increasingly often been replaced by resection with primary anastomosis in low risk patients (48).

Primary or staged resection is dependent on the condition of the patient and the spread of the disease. If the patient suffers from high ASA grade, staged resection is preferred, with Hartman´s procedure with primary resection and sigmoidal stoma being the most common (110). An up-and-coming alternative strategy is to initially treat the emergency state by a diverting stoma to unload the bowel and then optimize the patient and resect the tumor under stable conditions. Laparoscopy can be used in the emergency setting if obstruction is present (111). Approximately one third of all patients with obstruction do not receive an R0 operation due to distant metastases or locoregional tumor infiltration (41).

Colonic stenting as a bridge to surgery in colon cancer causing obstruction is possible but no consensus concerning this treatment has been reached so far (112). It may represent a safe and effective procedure as a bridge to surgery when the required skills are available (113), as long as no perforation is present. Stent is also plausible in palliative patients who cannot go through surgery (52). There are three main complications related to stent; migration which occurs in more than one fifth of the patients, obstruction which occurs in less than one fifth of the patients, and perforation which occurs in about one tenth of the patients (41).

Adjuvant chemotherapy is recommended in stage III, for both emergency and elective patients. In addition, adjuvant chemotherapy is also recommended to risk groups with stage II tumors, as for emergency colon cancer patients (73, 108).

1.2.7 Postoperative Mortality and Prognosis

Postoperative mortality (30 days) in all emergency colon cancer patients in Sweden 2007-2011 was 9,5%, but >16% in patients older than 80 years (40). In a study from Denmark, postoperative mortality was 22%, mostly due to medical complications such as infection, thromboembolism, renal failure, and heart-failure (87). A British study on colon cancer reported that the risk of 30-day postoperative mortality is increased during duty hours; it is doubled if the surgery is performed between 17.00-24.00 (OR=1.99) and almost tripled (OR=2.92) if the patient is operated upon between 24.00-08.00 (114). The differences are possibly associated with the competence of the surgeon. Colorectal surgeon specialists decreased the odds ratio for a lethal postoperative outcome in a Norwegian study conducted over 25 years (82), and this was also observed in a British study comparing unsupervised trainees to consultant surgeons (115).

The overall 5-year survival rate for colon cancer presenting as emergency is below 30% (75, 77, 116-118), and stage-specific 5-year survival is also lower in emergency than in electively presenting colon cancer (73, 98, 119).

A lower rate of curative (R0) operations (72, 75, 91, 97), older patients and a more advanced stage distribution (92, 93, 120) are possible explanations. Other possible explanations include an increased proportion of occult metastases, predominantly in the liver, and an excess production of cytokines precipitating cardiovascular events (75). However, survival in the emergency group has increased over the years (1975-84 vs. 1995-2004 in an Italian study (74), 1980-89 vs. 1990-99 vs. 2000-2004 in a Norwegian study (82), and between 1991 and -94 in a British study (106). This is most likely due to an increased curative intent (74) and an increased attendance of colorectal specialists during surgery (82). In Italy, long-term survival in elective patients has increased by 22% since 1975, while the corresponding number in emergency patients is only 6% (74).

The recurrence rate is higher in emergency patients compared to elective patients, probably due to a lower rate of curative resections. In a Swedish study from 2005, the resection rate was 69% in the emergency and 84% in the elective cases (72). However, this has increased, and another Swedish study from 2013 found it to be 81% in the emergency and 92% in the elective group (40). The recurrence is predominated by distant metastases (120).

1.2.8 Prevention

Screening programs using FOBT have been associated with a reduction of emergency presentation (121, 122); by as much as 47% in a British study (123). Fast-track flexible sigmoidoscopy service for symptomatic patients has also been shown to reduce the rate of emergency cases from 36% to 26% (124).

Access to health care services has also been recognized as an important factor for prevention of emergency presentation (89). A Canadian study found that the likelihood of an emergency presentation was reduced in areas with better access to colonoscopy (83).

1.2.9 Socioeconomic Factors

The association between socioeconomic status and mode of presentation of colon cancer has, to some extent, been investigated previously. Patients with lower incomes or who reside in deprived areas were more likely to present as emergencies according to Canadian and British studies (83, 90). An ecological study from the UK reported the risk of an emergency presentation to be more than twice as high for patients from deprived areas (125), but another British study including over 2,000 patients found no variation in the frequency of emergency presentation of colon cancer between deprived and affluent patients (126). A recent study from Sweden included emergency presentation and educational level, and a trend but no significant association was found among patients below the age of 75 (69). Furthermore, widowed colon cancer patients were found to present as emergencies more often in a British study from the 1980´s (89).

2 OBJECTIVES

The overall aim of this thesis was to investigate possible explanatory factors associated with emergency presentation of colon cancer.

The specific objectives of the different studies were to:

I.   Investigate the frequency of emergency colon cancer and search for associated clinical factors.
II.   Characterize the population of colon cancer patients reported as emergencies.
III. Estimate the association between mode of presentation and socioeconomic factors.

3 MATERIAL AND METHODS

3.1 PAPER I

Material
All colon cancer patients treated at the department of surgery at the General District hospital in Eskilstuna 1996 - 2005 (n = 604) were eligible. Patients admitted through the emergency room, operated on within three days of admission, and with an emergency condition (obstruction, perforation or bleeding) confirmed at surgery were classified as colon cancer emergencies (ECCs).

Method
The frequency of emergency presentation using the study definition and the one used at ROC (the Regional Oncologic Centre) was compared in terms of patient numbers. All clinical records were scrutinized, and information on tumor characteristics, comorbidity and social aspects were collected. Data from the ROC was also retrieved, including surgical variables such as blood loss and surgical competence. Survival was analyzed using Kaplan-Meier estimates and log-rank test. The effect of several risk factors on survival was analyzed by means of Cox regression.

3.2 PAPER II

Material
All cases of colon cancer reported as emergencies to the ROC from Dalarna, Sörmland, Uppsala, and Värmland counties were included, along with randomly selected elective colon cancer controls (1:2) 2006-2008 (n=853).

 Method
Primary care and surgical records from all patients were scrutinized for symptoms associated with colon cancer, investigation, referral and date of surgery related to date of admittance. Stage and survival were retrieved from the ROC register. The chi-square, Student's *t* and Mann-Whitney tests were used to test any differences between groups. Postoperative mortality and long-term survival was analyzed using Kaplan-Meier estimates, and the log rank test was used for comparison. A multivariate Cox regression model, adjusting for age, sex and stage, was employed, and 5-year hazard ratios (HRs) were calculated.

3.3 PAPER III

Material
All patients with colon cancer reported to the Regional Oncological Centers in the Uppsala-Örebro and Stockholm regions 1997-2006 (n=12,293) were included, accounting for more than 40% of the Swedish population.

Method

Information on civil status, education, income, place of birth, and children for the year before diagnosis, available from Statistics Sweden, was linked to the quality registry and analyzed by means of logistic regression.

4 RESULTS

4.1 PAPER I

Using the study definition the rate of ECC was 97/585 (17%), while it was 27% in the register from the Regional Oncologic Centre (ROC). ECC patients were older (median 77 vs. 74, p = 0.02), had more stage III and IV cancers (65 vs. 47 %; χ^2= 9.4, p<0.001), and had fewer cancers located in the caecum (20 vs. 33 %, χ^2= 4.3 p = 0.04).
ECC was most frequent from June to August (36%) whereas elective cases were evenly distributed throughout the year (χ^2= 7.8; p = 0.05). Five year survival was 18% in ECC and 38% in the elective group (p<0.001). Hazard ratio for death within five years among emergency patients, 30-day mortality excluded, and adjusted for age, stage, and sex was 2.25 (95% CI 1.42 - 3.55).

4.2 PAPER II

Among patients reported as colon cancer emergencies to the ROC (n=263), 158 (60%) were operated within three days and categorized as acute, whereas 105 (40%) had surgery more than three days after admittance. This group was categorized as subacute cases. In this group, 52/105 (50%) were stage IV, compared to 36/158 (23%) in the acute and 83/577 (15%) in the elective group (X^2=82.44; p<0.001). In the subacute group, there were more females, 64/105 (61%) compared to the acute71/158 (45%) and elective 277/577 (48%) groups (X^2=7.0; p=0.03).
Fort four per cent (46/105) had already had a recent examination of the large bowel, and more than half, 51/94 (54%), had reported two or more symptoms associated with colon cancer to primary care during the last 12 months prior to surgery.

	Elective	Acute	Subacute	X^2; p-value
30-day mortality	1.9	8.2	15.2	14.6; p<0.001
90-day mortality	4.3	14.9	35.6	98.5; p<0.001
Survival at 5 years	57.8%	40.1%	28.3%	151.8; p<0.001
HR	1.00 (ref)	1.88 (1.46-2.44)	2.29 (1.71-3.08)	

Table II. Postoperative mortality and outcome at five years according to mode of presentation.

4.3 PAPER III

The overall frequency of emergency cases was 23%. Over one third, 1011/2856 (35%), of the emergency group were above the age of 80, and 874/2856 (31%) were between 70 and 79 years old. In a univariate analysis old, unmarried, widowed, low educated, low income and childless patients operated in a GDH were significantly associated with an emergency presentation. No significant difference in sex, region or period was found.

The odds ratio (OR) for emergency presentation in low income patients (Q1) was 1.30 (95% CI 1.00-1.52). This was most pronounced in men, OR 1.46 (95% CI 1.15-1.85), for patients <70 years, OR 1.42 (95% CI 1.08-1.88), and for patients >80 years, OR 1.50 (95% CI 1.08-2.10). For unmarried patients, OR was 1.23 (95% CI 1.03-1.46), increasing to 1.48 (95% CI 1.02-2.14) among patients above the age of 80. In the youngest age group, low education was also associated with an emergency presentation (OR 1.25; 95% CI 1.02-1.52).

5 DISCUSSION

This thesis explores emergency presentation of colon cancer as a specific entity, from different perspectives. The causes, or ultimate etiology, behind emergency presentation are not well known, and many factors seem plausible.

Patient-related factors

No association between sex and mode of presentation was found in these studies; men and women faced an equal risk (study I, II and III). Some previous studies have found a higher risk for females, although not adjusted for the higher life expectancy in women compared to men (75, 83, 91, 102), as the incidence of colon cancer is associated with age (50). Emergency patients were older than their elective counterparts (study I, II, III), and this is in accordance with previous studies. In study II (and with a tendency in study III) a J-shaped curve was shown, illustrating that patients younger than 59 years and older than 85 years were at greater risk of an acute course, and this was also found in an Australian study (91).

Unmarried patients and patients with low income were more likely to present as emergencies than other colon cancer patients, even in contemporary Sweden. Previous studies in the field have pointed out deprivation (83, 90, 125) and civil status (widows) (89) as inflicting factors. The mediating factors between a lower socioeconomic status and emergency presentation are not well explored. Are patients with certain socioeconomic background more reluctant to seek health care, do they interpret possible colon cancer symptoms differently, is their access to health care less good, or are their symptoms neglected to a larger extent when in contact with health care? Are there predisposing lifestyle factors, such as smoking, which increases the risk of an acute course (95), or diet or physical activity, which have still not been studied in terms of mode of presentation? It has been shown that the interaction between patient and doctor differs depending on the socioeconomic status of the patient (127), which potentially affects further management. Unmarried colon and breast cancer patients have a longer delay for referral and diagnosis compared to others (70). This could be of crucial importance in a colon cancer that is close to complete obstruction. Possibly, a colon cancer can advance and later obstruct in these circumstances.

American studies have identified African Americans to be at an increased risk of an acute course (84, 86), independent of socioeconomic status (85). Due to the low numbers and the heterogeneity of immigrants among colon cancer patients' ethnicity was not included as a covariate in study III.

Comorbidity has been found to be more common among emergency colon cancer patients (83, 87, 120, 128). On the other hand, another study has seen higher comorbidity in electives (88).This is in contrast to our findings that comorbidity did not differ between the groups (II).

One difficulty in comparing comorbidity is the multitude of measurements of comorbidity used in various studies, e.g. Charlson/Deyo-score for specific diseases from ICD-10, or functional status (ASA-stage).

Health care related factors

Primary care and symptoms
Emergency and elective colon cancer patient were found to present with different profiles of symptoms less than 12 months prior to surgery (study II). Rectal bleeding was reported for about 21% of the electives, compared to 5% and 10% in the acute and subacute groups respectively, and this is probably the symptom easiest to initiate an investigation upon. Some 35% in the elective group had abdominal pain, compared to 45-44% in the acute and subacute group respectively. Had all patients with at least 2 symptoms associated with colon cancer been managed promptly, this would include 54% of both all elective and subacute cases, as well as 46% of all acute cases of colon cancer. Acute and subacute patients are associated with abdominal pain (II), as found previously with an odds ratio of 2.3 for an emergency course (103).
The subacute patients also reported anemia/fatigue which also was documented for more than half of the electives (II). This has also been reported in a British study in 50% of the colon cancer patients (30).

Both abdominal pain and anemia/fatigue are diffuse symptoms with low PPV:s, and as mentioned above, only 1% of the patients in primary care with colorectal symptoms have a cancer (103). The number of different symptoms related to colon cancer is most likely also a factor for the selection for further investigation, but this was not the case in study II, in which one-third of the subacute patients had ≥3 symptoms, which constitutes a failure for the health care services. More than 45% of the acute patients reported abdominal pain in study II. Being alert to a deeper characterization of the quality of abdominal pain may prevent an acute course.

More than 80% of patients, regardless mode of presentation, had been in contact with primary care during 12 months preceding surgery (II), which indicates that primary care may be important for avoiding emergency presentation of colon cancer. Patients lacking a GP are at an increased risk for emergency presentation of colon cancer (83, 89).

It has also been shown that an increased primary care physician supply is negatively correlated with colorectal incidence (129), especially in late-stage colorectal cancers (130).

In both the acute and subacute group of colon cancer patients (reported as emergencies) more than every fourth or every third (27% and 39%, respectively) had already been referred for elective colon examinations (colonoscopy, CT colon) (II). This indicates that delay after investigation may also be important in preventing a final presentation of colon cancer as emergencies.

Lower access to health care services both geographically (90) and economically (in terms of health care insurances) (94) has been shown to increase the emergency rate. This might indicate that delay contributes to an emergency presentation. Findings of a seasonal variation (study I) may represent the same reduced access to health care, due to summer vacations.

A British study has shown that patients who take their symptoms less seriously are more than 3 times more likely to have colorectal cancer compared to patients seeking health care service for any colon cancer symptom (131).
The shorter symptom duration in the emergency group (101, 119) would make it difficult to suspect, and thus detect, a tumor, but even so, >73% and 82% of the emergency and subacute patients respectively had reported some colon cancer-related symptom (II).
Two studies, one Swedish and one Canadian, have found that access to colonoscopy, which may prevent acute states, is better outside main cities (Toronto and Uppsala respectively) (69, 132).

Prevention

This thesis has identified some avenues for further study of possible prevention opportunities for emergency presentation of colon cancer. This includes identifying risk groups (unmarried, elderly or low income patients), prompt investigation of all patients with at least two symptoms associated with colon cancer, and avoiding delay from investigation during the surgery and summer periods.

Every year, there are 4000 cases of colon cancer in Sweden, of which 17% are emergencies according to study I. This gives a prevention potential of 680 emergency patients/year and almost 13 cases/week (680/52=13) nationally. Emergency patients stay at the hospital for an average 18 days postoperatively, compared to 10 days in the elective group (72). In addition to this, emergency patients often suffer more from complications (87) which in turn increase the costs of reoperations, radiological examinations and laboratory tests. For every colon cancer patient presenting as an emergency, faced with acute surgery, a compulsory pair of questions for health care ought to be: could this have been prevented?

Stage and age are important factors for survival in colon cancer, but so is mode of presentation (133).
Most importantly though, thirty-day mortality is higher in the emergency group, at 11% compared to 5% in the elective group (study I). Preventing emergency presentation

represents an opportunity to reduce mortality related to colon cancer. Reduced long term survival may be an effect of an inherent aggressiveness in the emergency tumors.

6 CONCLUSIONS

I. Ambiguities in the definition of emergency presentation weaken informative comparisons of the rate of colon cancer patients presenting as emergencies between populations and time periods. Seasonal factors may affect an acute course.

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II. Patients reported as colon cancer emergencies are a heterogeneous group. Patients classified as emergencies but operated upon after three days have a worse stage distribution and outcome. The absolute number of different symptoms may be used to prevent emergency presentation.

III. Emergency presentation of colon cancer is associated with marital status and low income and it is essential to take this into account in efforts aimed at reducing the rate of emergency cases.

Overall conclusions

Emergency presentation of colon cancer is multifactorial. In every study included in the thesis, distinct differences related to mode of presentation have appeared.

The rate of emergency cases may potentially be looked upon as a quality measure of the health care system, including general awareness, information to patients/ public, accessibility, selection for further investigation, and waiting time for surgery.

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7 FUTURE PERSPECTIVES

There are several areas for further research into mode of presentation in colon cancer;

The tendency is that obstructed patients are not operated upon until they are medically optimized and a colorectal team is available to treat the patient. It would be interesting to analyze postoperative mortality and long term survival for patients treated in these circumstances, and compare the outcome with patients who have been operated upon during duty hours and not by a specific team.

Furthermore, as part of a prevention strategy against emergency presentation it would be valuable to initiate a prospective study to analyze the management of colon cancer with an emergency presentation and the delay from diagnosis to surgery for emergency patients. Another important measure for preventing emergency cases is to ensure that vulnerable groups participate in population-based screening programs.

However, another aspect of mode of presentation of colon cancer is the possible involvement of inherent, truly biological differences. Within the framework of this thesis, a pilot study has therefore been performed with the stated objective of comparing gene expression in surgical cases of emergency and elective presentation of colon cancer.

All patients included in Paper I were eligible for this pilot study. Three emergency and three elective patients were randomly selected for microarray analysis, and another seven patients from each group were randomly selected to validate the results.

Formalin fixed, paraffin embedded (FFPE) cancer samples were analyzed by microarray analysis (Affymetrix) for gene expression profiling. All the up- or down-regulated gene expressions that differed more than two-fold between the groups were analyzed using Ingenuity Pathway software, and finally verified by qPCR for gene expression and Western Blot for protein expression and phosphorylation pattern.

Of 30 000 genes analyzed, it was found that 1047 were significantly up-regulated and 814 down-regulated in emergency compared to elective cases. The differences were mainly found in two signaling pathways; EGFR and Wnt signaling. Both pathways regulate cell growth and differentiation, but in particular, the Wnt pathway also regulates proliferation and apoptosis. Three important intracellular proteins in the Wnt pathway (GSK3β, LEF-1 and TCF) were up-regulated in the emergency tumors. The gene expression of Wnt signaling was validated by qPCR. Furthermore, the EGFR/STAT1-mediated signaling pathway was also up- regulated and phosphorylated in emergency colon cancer, while the EGFR/MEKK/JNK pathway was up-regulated and JNK1 were highly phosphorylated in elective patients.

The finding of a difference in gene expression between emergency and elective colon cancer, related to growth and proliferation, supports the hypothesis of emergency colon cancer as inherently more aggressive. This is further underpinned by the more

advanced stage (study I, II and III) that has also been shown in previous studies (72, 99) and the shorter symptom duration (101). In a recent Swedish article, emergency tumors had a more advanced morphology (99) which also was shown in Study I. Grade of differentiation did not differ, however (91, 99).

This pilot study may be the starting point for larger studies in the future, where gene expressions are compared in relation to mode of presentation. It also raises questions about adjuvant chemotherapy and different responses to that in terms of gene expression.

Future research could also study if epigenetic alterations are the initiating events resulting in an acute course or if epigenetic alterations are secondary to mode of presentation.

8 SUMMARY IN SWEDISH

Tjocktarmscancer är den tredje vanligaste cancersjukdomen i Sverige, liksom i resten av västvärlden. Det är också den cancerform som tar flest liv efter lungcancer. Den vanligaste formen av akut koloncancer är tumörorsakad ileus (tarmvred) vilket drabbar ca 800/år, men även perforation(hål på tarmen) eller blödning från tumören förekommer som orsaker till ett akut insjuknande. Dödligheten i samband med operation, och på flera års sikt i den akuta gruppen är påtagligt högre än för patienter som inte opereras akut, det vill säga elektiva patienter. Det är oklart varför akuta patienter har så pass mycket sämre prognos. Det är ofullständigt studerat varför cirka 25 % av alla patienter med koloncancer har ett akut förlopp.

Den här avhandlingen bygger på tre delstudier och undersöker dels faktorer associerade till ett akut insjuknande, dels faktorer som kan påverka överlevnaden samt möjligheten att förebygga ett akut insjuknande.

I Studie I, som inkluderade samtliga koloncancerpatienter på Mälarsjukhuset, Eskilstuna (n=604) mellan 1996-2005, var syftet att utifrån en strikt definition kvantifiera de akuta patienterna, analysera överlevnaden och söka riskfaktorer. Patienterna identifierades med hjälp av ett register från Regionalt Onkologiskt Centrum (ROC) och en journalgenomgång genomfördes för att sedermera analyseras statistiskt. Studien fann att de akuta patienterna, som utgjorde 17 %, i högre utsträckning opererades under sommarmånaderna, samt att patienter som debuterade akut hade mer än dubbelt så stor risk att dö inom 5 år från operationen jämfört med deras elektiva motsvarigheter.

I Studie II genomfördes åter en större journalgenomgång med patienter från fyra olika landsting i Uppsala-Örebroregionen 2006-2008, (n=854) med hjälp av registret i ROC. Syftet var att kartlägga i vilken utsträckning akuta och elektiva koloncancerpatienter haft kontakt med primärvården och i så fall om det varit möjligt att förhindra ett akut förfarande. Patientmaterialet indelades i tre grupper utifrån hur de klassificerats som akuta, subakuta och elektiva. Många patienter från alla tre grupper hade haft kontakt med primärvården, och det framgick också att de flesta hade påbörjat en utredning. En liten andel av patienterna insjuknade akut i väntan på utredning, men en fjärdedel av de akuta patienterna insjuknade i väntan på operation. De elektiva patienterna uppgav fler symtom som var koloncancerrelaterade. Överlevnadsanalyser visade att de subakuta patienterna hade sämst prognos, både på kort och på lång sikt.

Studie III var en registerstudie med patienter från Uppsala-Örebro samt Stockholmsregionen, 1997-2006 (n=12 293). Data inhämtades från Statistiska Centralbyrån med syfte att undersöka huruvida socioekonomiska faktorer påverkar risken att insjukna akut. Patienter med låg inkomst, låg utbildning samt patienter i singelhushåll löpte större risk för ett akut insjuknande.

Det gjordes även en pilotstudie på DNA-nivå i syfte att jämföra genuttryck i akuta och elektiva tumörer. För detta användes en i sammanhanget väl etablerad teknik kallad

microarray. Resultatet av genuttrycket skiljde sig tumörtyperna emellan, vilket möjligen talar för att den akuta formen av koloncancer är en mer aggressiv cancersjukdom jämfört med koloncancer som opereras elektivt. Den här studien får dock fungera som utgångspunkt för större studier i framtiden.

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11 APPENDIX

Reference and country	Period	Total nr.	Emergency cases	Rate emergency (%)	Definition by	Postop (%)	5-y survival (%)
(100); Spain	2005	936	107	11	Surgery	15	---
(87); Denmark	2001-2005	15,752	2,157	14	Registry	22	---
(92); Ireland	2000-2006	278	91	33	Presentation		---
(123); UK	1999-2004	1,236	290	23	Presentation/Surgery	13	---
(83); Canada	1999-2001	21,908	3,959	51	Registry		0.87 (OR)
(95); USA	1997-2002	185	35	19	Surgery	17	40
(72); Sweden	1997-2001	3,259	806	25	Surgery	10	---
(91); Australia	1997-2001	1,270	209	16	Surgery	16	---
(4); Sweden	1996-2000	2,775	590	21	Surgery	11	1.68 (HR)
(120); Spain	1996-1998	266	59	22	Presentation + 24-h Surgery	15	61 (3yrs)
(83); Canada	1996-1998	19,448	3,780	49	Registry		1(OR)
(74); Italy	1995-2004	472	42	9	24-h surgery	5	41
(88); USA	1995-2004	184	29	16	Surgery	34	---
(101); Norway	1993-2007	1,129	279	25	Presentation/Surgery	10	---
(106); UK	1991-1994	3,200	986	31	Presentation	8	39
(116); UK	1988-1993	1,024	75	7	24-h surgery	4	29
(89); UK	1982-1992	905	272	30	Presentation	19	29
(121); UK	1981-1995	1,782	468	26	Presentation	10	---
(77); UK	1981-1991	735	63	9	24-h surgery	16	19
(74); Italy	1975-1984	513	81	16	24-h surgery	14	19
(104); UK	1972-1982	1,033	523	51	Presentation	25	---

Table III. Rate of emergency presentation of colon cancer found 1972-2005.

I

Emergency presentation of colon cancer is most frequent during summer

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Abstract

Aim The frequency of emergency colon cancer (ECC) was determined using a reproducible definition of 'emergency' to analyse the impact of mode of presentation on long-term prognosis and to search for risk factors for an emergency presentation.

Method All patients with colon cancer treated at one Swedish GDH between 1996 and 2005 ($N = 604$) were eligible. Patients admitted through the emergency room, operated on within three days and with an emergency condition confirmed at surgery were classified as ECC. Survival was analysed by Kaplan–Meier estimates and risk of death by Cox regression.

Results The rate of ECC was 97/585 (17%). Patients with ECC were older (median 77 vs 74, $P = 0.02$), they had more stage III and IV cancers (65% vs 47%; $\chi^2 = 9.4$,

$P < 0.001$) and had a cancer located in the caecum less often (20% vs 33%, $\chi^2 = 4.3$ $P = 0.04$). ECC were most frequent between June and August (36%), whereas elective cases were evenly distributed throughout the year ($\chi^2 = 7.8$; $P = 0.049$), Crude 5-year survival was 18% in ECC and 38% in the elective group ($P < 0.001$). The hazard ratio for death within five years in ECC, with 30-day mortality excluded and adjusted for age and sex was 2.25 (95% CI; 1.42–3.55).

Conclusion Emergency presentation of colon cancer is an independent and adverse risk factor for long-term survival. The causes of a seasonal variation need to be clarified.

Keywords Colon cancer, emergency, stage, population-based, survival, risk factors

Introduction

In Sweden, colon cancer is the second most common type of cancer in both sexes, constituting about 7% of all cancers [1]. The reported rate of colon cancer presenting as an emergency varies between 9% and 33% [2–4]. The prognosis of emergency colon cancer (ECC) is known to be worse [5], since the disease is more advanced at presentation, but stage-specific survival is also lower in ECC compared with electively presenting colon cancer [2,6]. The duration of symptoms in ECC is shorter [7] and ECC seems to represent a more aggressive subset of colon cancer.

Previous research on ECC has mainly focused on surgical management [8,9], and aetiological factors causing the emergency course have not been thoroughly

explored. It is known that the rate of emergency cases decreases when a screening programme is operating [10]. Lower socio-economic class has been associated with ECC [5,8,11–13] and the accessibility to healthcare services has been recognized as another important factor [12]. The role of psychological factors such as denial of symptoms or the ability to recognize and interpret incipient symptoms of bowel obstruction, is little investigated. Intrinsic, genetic factors causing variations in biological aggressiveness, immunological responses or comorbidity are other possible explanations that may contribute to an emergency presentation.

Discrepancies and ambiguities in the definition of 'emergency' makes it difficult to compare the results between different studies of ECC. The aims of this study were to determine the frequency of colon cancer with an emergency presentation in a population-based setting using an explicit definition, to analyse survival on the basis of this definition and to identify possible risk factors for an emergency presentation of colon cancer.

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Method

The Regional Oncological Centre Registry

In Sweden, in addition to a nationwide compulsory cancer registry, detailed information concerning all cases of colon cancer is reported to six Regional Oncological Centres (ROC). This includes information on patient characteristics, tumour location, tumour stage, surgical treatment and complications, postoperative morbidity and mortality, tumour histopathology, information on oncological treatments, and follow-up data on recurrence and survival. All surgeons treating patients with colon cancer are obliged to report these data, including details on the nature of the operation performed. In the report, 'emergency operation' is defined as 'the operation has been performed acutely/ subacutely for medical reasons'. This classification thus depends on the judgment of the individual surgeon.

Study population and study definition of emergency

All patients admitted with colon cancer to the Department of Surgery at the General District Hospital of Eskilstuna, which serves approximately 180 000 inhabitants, between the years of 1996 and 2005, were identified by record diagnosis (N = 604). All clinical records were retrieved and patients were categorized as either emergency or elective. This was done without knowledge of the classification reported to the ROC. For the purpose of this study, three criteria were required for the definition of an emergency presentation: Admission through the emergency room, laparotomy within 72 hours of admission and an acute condition such as obstruction, perforation or bleeding because of colon cancer confirmed at surgery.

Information on the mode of presentation, subtype of emergency condition (obstruction, perforation, bleeding), age and sex of the patient and date of surgery was retrieved from the records. In addition, surgical details such as operation time, bleeding volume, competence level of the surgeon and the pathological report were retrieved from the ROC registry.

During the study period, 513 patients were reported to the Regional Oncology Centre in Uppsala. The reason for the difference in number, compared with primary data from the Department of Surgery in Eskilstuna, is that the registry was not fully initiated until 1997 and the coverage rate has not been complete.

Nested case–control study

Ninety-seven patients were identified as having an emergency presentation. An almost equal number (n = 98) of patients were randomly chosen from the elective group as controls. Localization of the tumour, morphology, grade of differentiation and number of lymph nodes reported by the pathologist were all recorded. Information on comorbidity (hypertension, cardiovascular diseases, lung diseases, diabetes, other malignancies, neurological diseases, renal diseases, psychiatric drugs), marital status and place of residence (urban *vs* nonurban) was also retrieved.

Statistics

Student's *t*-test, the chi-square test and Mann–Whitney *U* test were used to analyse differences between the groups. Survival was calculated from the date of surgery until death or the end of follow-up (29th October 2008). Survival data were analysed by Kaplan–Meier estimates and the log rank test was used for group comparisons. Multivariate analysis was performed using Cox's proportional hazard regression and hazard ratios (HRs) for 5-year survival, and 95% confidence interval (95% CI) adjusted for age, sex and stage were estimated. The effect of an increased early postoperative mortality in emergency cases was avoided, since the first thirty postoperative days were excluded. All analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA). *P*-values were two-sided.

Results

Frequency

Five of the 604 patients identified with colon cancer were not operated on and medical records of 14 patients were missing. Thus, 585 patients were included in the study (Fig. 1). The number of cases of colon cancer presenting as an emergency according to the definition used for the study was 97/585 (17%). Of these 97 patients, three had been classified as elective cases in the quality registry (ROC). In contrast, the operating surgeons had reported 137/513 (27%) to be emergency cases to the ROC. Obstruction was found in 87/97 (90%) of the emergency patients, 10 had a perforation; seven within the tumour and three proximal to the tumour. There was no emergency operation because of bleeding.

Age, sex and seasonal distribution

Patients presenting with ECC were older (median 77 years) than the elective group (median 74 years) but had a similar sex ratio (Table 1). The frequency of ECC doubled during the summer period of June to August (36%) compared with December to February (17%), in contrast with elective colon cancer surgery that was fairly
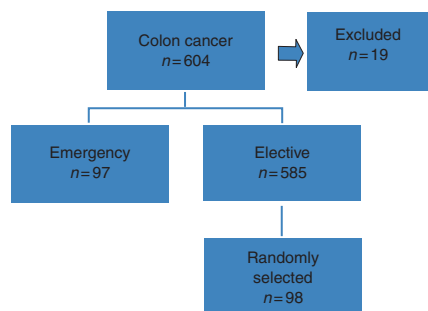
Figure 1 Flow chart for the study population.

Figure 2 Kaplan–Meier survival curves for patients with emergency ($n = 97$) and elective presentation of colon cancer ($n = 98$).

Table 1 Baseline characteristics for patients with colon cancer by mode of presentation, Eskilstuna GDH, 1996–2005 ($n = 585$).

	Emergency $n = 97$	Elective $n = 488$	P
Age mean	75	72	0.04
Median [range]	77 [40–93]	74 [32–99]	0.02
Sex M:F	48:49	246:242	
Seasonal variation	$n = 97$	$n = 482$	
December–February	16 (17)	115 (24)	0.05*
March–May	22 (23)	140 (29)	
June–August	35 (36)	115 (24)	
September–November	24 (25)	112 (23)	
Stage	$n = 87$	$n = 403$	
I	0	56 (14)	< 0.001*
II	30 (34)	156 (39)	
III	36 (41)	115 (28)	
IV	21 (24)	76 (19)	
Surgeon's competence	$n = 89$	$n = 409$	
Trainee	11 (12)	32 (8)	0.04*
General specialist	31 (35)	113 (28)	
Colorectal specialist	47 (53)	264 (65)	
Blood loss (ml)	$n = 85$	$n = 404$	
Median (range)	300 [0–3700]	200 [0–2500]	< 0.001

*Chi-square test. Percentages in brackets.

evenly distributed throughout the year ($\chi^2 = 7.8$; $P = 0.049$) (Table 1).

Stage distribution and surgery

In ECC, there was no stage I cancer and two-thirds of all patients already had either lymph node or distant metastases at presentation, (65% *vs* 47%, $\chi^2 = 9.4$, $P < 0.001$) (Table 1). An accredited colorectal surgeon operated on 53% of the emergency cases and on 65% of the elective patients ($\chi^2 = 4.3$; $P = 0.04$).

Prognosis

The 30-day mortality rate for emergency cases was 10/95 (11%), compared with 26/480 (5%) in the elective group ($P = 0.07$). Two-year survival was 42% in the emergency and 65% in the elective group ($P = 0.03$); five-year survival was 18 and 38% ($P \leq 0.001$). Respective median survivals were 524 days (17 months) and 1955 days (65 months) ($P \leq 0.001$) (Fig. 2).

Nested case–control study

Cancer of the ascending and sigmoid colon was more common and those of the caecum less common in the emergency group (20% *vs* 33%; $\chi^2 = 4.3$ $P = 0.04$) (Table 2).

Involvement of more than two-thirds of the circumference was more common in emergency cases (73% *vs* 51%; $\chi^2 = 11.5$; $P = 0.009$). There were no statistically significant differences in the number of examined lymph nodes, comorbidity or frequency of single households between the groups.

Cox regression

Patients from the nested case–control study were included in a multivariate regression model where survival was adjusted for age and sex in addition to mode of presentation. The first 30 postoperative days were

Table 2 Clinical variables of emergency presentation of colon cancer (*n* = 97) and elective colon cancer controls (*n* = 98), Eskilstuna GDH 1996–2005.

	Emergency *n* = 97	Elective *n* = 98	*P*
Age years mean	75	71	0.03
Median [range]	77 [40–93]	73 [45–97]	0.02
Sex M:F	48:49	47:51	0.9
Localization	*n* = 90	*n* = 89	
Caecum	18 (20)	30 (33)	0.04*
Ascending	17 (19)	11 (13)	
Transverse	5 (6)	4 (5)	
Descending	8 (9)	7 (8)	
Sigmoid	42 (47)	39 (41)	
Morphology	*n* = 83	*n* = 67	
Circumferential	20 (24)	14 (21)	0.009*
> 2/3 of the circ	41 (49)	20 (30)	
> 1/2 of the circ	20 (24)	24 (36)	
< 1/2 of the circ	2 (2)	9 (13)	
Lymph nodes	*n* = 75	*n* = 93	
Mean	6.7	7.6	0.5*
Median [range]	6 [0–19]	6 [0–29]	
Differentiation	*n* = 88	*n* = 88	
Low	19 (20)	12 (12)	0.4*
Medium	65 (67)	72 (74)	
High	4 (4)	4 (4)	
Comorbidity	*n* = 87	*n* = 87	
Hypertension	25 (29)	36 (41)	0.1*
Living conditions	*n* = 84	*n* = 87	
Own household	79 (94)	85 (98)	0.3*
Other	5 (6)	2 (2)	
Marital status	*n* = 52	*n* = 46	
Single household	20 (38)	13 (28)	0.4*
Cohabiting	32 (62)	33 (72)	
Place of residence	*n* = 89	*n* = 88	
Urban	41 (46)	44 (50)	0.6*
Nonurban	48 (54)	44 (50)	

*Chi-square test. Percentages in brackets.

Table 3 Hazard ratios (HR) for relation between age, sex, stage and mode of presentation and overall death within 5 years among patients with colon cancer, Eskilstuna GDH, 1996–2005 (*n* = 195).

	HR	95% CI	*P*
Age	1.05	1.03–1.08	< 0.001
Sex			
Women	1.00		
Men	1.52	0.98–2.36	0.06
Stage			
I	1.00		
II	1.76	0.23–13.51	0.59
III	2.02	0.26–15.47	0.50
IV	8.13	1.07–62.02	0.04
Mode of presentation			
Elective	1.00		
Emergency	2.25	1.42–3.55	< 0.001

were involved in the development towards an emergency presentation of colon cancer.

The population-based approach of this study is an obvious strength. All but a very small number of the eligible patients were included in the first review of records, and we believe our finding of a rate of 17% ECC using the study definition is valid. Within the same population, a rate of 27% emergency cases were reported based on the judgment of individual surgeons when submitting their returns to the Regional database. The definition they used is obviously more inclusive and could possibly be taken to mean 'nonelective'. A distinction between emergency/urgent and scheduled/elective surgery has been proposed [14]. Another classification defines emergency as surgery within one hour while an urgent operation is within 24 hours, a scheduled operation within three weeks and an elective when convenient for patient and surgeon [15]. In our opinion, these categories are not optimal for reflecting the clinical course of bowel obstruction. For this group of patients, a 24-hour limit is too narrow for diagnosis, preparation, and in many cases waiting for access to the operation theatre. Comparison of the data presented in this study with other studies is difficult owing to lack of standardisation of the definition of ECC [2,10]. The rate of ECC may be declining, with a rate as low as 9% being reported using the definition of surgery within 24 hours because of obstruction, perforation or bleeding [4]. A recent study from Ireland has, however, reported a rate of 33% of ECC defined as admission to hospital through the emergency department [16].

Patients classified as elective using the study definition but reported as emergency cases to the ROC registry had a survival rate closer to the patients with ECC than to the

excluded to avoid confounding by early deaths because of emergency surgery. Given these prerequisites, the hazard ratio for death within five years in the emergency group was 2.25 (95% CI 1.42–3.55; *P* < 0.001) (Table 3).

Discussion

Every sixth patient with colon cancer presented as an emergency in this population-based study. The risk of death within five years was double that for elective treatment, 30-day mortality excluded, suggesting that ECC represents a biologically more aggressive subtype of colon cancer. ECC had different anatomical and temporal distributions during the year, conferring bowel width at the location of a colon tumour, and healthcare logistics

elective group. The main reason for not being included in the emergency group was surgery being delayed until the third day after admission. This indicates that colonic obstruction is a continuum and that our own or any other definition of the condition is arbitrary. Obstruction was the most common diagnosis followed by perforation. Bleeding was not seen in any of the cases included in the study, which previously has been reported [17] probably because of the low number of emergency cases in the study.

Determining the rate of ECC is also of value from the perspective of increasing screening efforts for colorectal cancer. A reduced rate of ECC (from 28% to 24%) was reported in a screening project using faecal occult blood testing [10]. In a more recent study reporting patients treated from 1999 to 2004, the fall in ECC was dramatic from 29% to 16% [18]. Furthermore, a fast-track flexible sigmoidoscopy service for symptomatic patients reduced the rate of ECC from 36% to 26% [19].

The seasonal variation in emergency presentation found in this study is of unknown origin. Climate is a possible explanation, but there is at present no logical hypothesis concerning factors such as higher temperature and longer days on tumour development. Perhaps the holiday period might lead the patient or general practitioner to delay referral with a consequently increased number of emergency admissions. In a British study, 63% of patients with ECC reported suggestive symptoms to their GP at least 30 days before surgery [20]. Further studies in this field and ways to identify and prevent an emergency presentation are needed.

The competence of surgeons in the emergency group was somewhat lower compared to surgeons in the elective patients in this study. Patients with ECC also had a greater blood loss, indicating that emergency operations are technically more difficult, especially for surgeons with less experience. However, half of the patients with ECC in this study were operated on by a specialist surgeon. The literature on the impact of the experience of a surgeon on colon cancer outcome varies, ranging from evidence of a higher mortality for nonspecialist surgeons [21] to no difference [22]. A difference in the experience of surgeons between ECC and elective colon cancer may, however, have contributed to the differences in survival rates found in this study, but this factor is unlikely to explain this fully.

Several studies have reported on the short-term increased risk of death after ECC surgery [22–24]. In a recent Danish study, the 30-day mortality rate was 22% in patients having emergency surgery [17]. ECC presents with a more advanced pathological stage, as seen in the present population. Even after excluding 30-day mortality, there was a twofold risk of death

within five years when adjusting for, age, sex and stage. This is similar to a previous finding of an increased risk of death of 1.8 in emergency *vs* elective patients with colon cancer [25].

With regard to the nested case–control part of this study, it is important to stress that it was initiated to generate hypotheses on the possible reasons for an emergency presentation, and we acknowledge that it is too underpowered to give definite answers. However, the finding of a differing anatomical distribution in emergency and elective colon cancer is of interest. It is logical that intestinal diameter is one of the factors that determines the mode of presentation for colon cancer. The greater prevalence of hypertension in elective cases might raise the suspicion of colon cancer in patients having regular blood pressure checks by the GP may perhaps prevent some colonic cancers developing into an emergency presentation. A satisfactory doctor–patient relationship is clearly important in this respect. The observation that patients with emergency presentation more commonly live in single households is interesting and suggests a future area for research.

This study has demonstrated the multifactorial aetiology of ECC, and future research will need to take the various factors into account. A clear and reproducible definition of ECC needs to be generally adopted to allow comparisons between studies. The seasonal variation needs to be further elucidated.

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II

Heterogeneity of Colon Cancer Patients Reported as Emergencies

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Abstract

Background

Up to one-fourth of all colon cancer patients are reported as emergencies, and the aim of the study was to scrutinize mode of presentation in this group.

Material and method

All reported cases of emergency (n=263) and randomly selected elective controls (1:2) of colon cancer in four Swedish counties 2006-08 were eligible (n=854). Symptoms and aspects of management retrieved from surgery and primary care records; outcomes were compared using Kaplan-Meier estimates and Cox regression.

Results

Among patients reported as emergencies, 158/263 (60%) were operated within three (acute) and 105 (40%) after more than three days (subacute). In the latter group, 20/94 (21%) had reported two, and 31/94 (33%) three or more symptoms associated with colon cancer to primary care during the last 12 months prior to surgery, 46/105 (44%) had already had an examination of the large bowel, and 52/105 (50%) were stage IV, as opposed to 36/158 (23%) in the acute and 83/577 (15%) in the elective group (p<0.001).

Thirty- and 90-day mortality was 15.2% and 35.6% in the subacute, 8.2% and 14.9% in the acute (p=0.001) and 1.9% and 4.3% in the elective group (p<0.001); 5-year survival 28.3%, 40.1% and 57.8% respectively (p<0.001). HR, adjusted for age, sex and stage, was 1.88 (1.5-2.4) for the acute and 2.29 (95% CI 1.7-3.1) for the subacute group.

Conclusion

Colon cancer patients reported as emergencies but operated upon more than three days after admittance had the worst outcome. Efforts to decrease the interval between admission and

surgery is one important aspect but a wider attention must also be paid to this group of patients.

 Introduction

Colon cancer is the third most common malignancy in Sweden, as it is in the entire western world (1). The frequency of emergency presentation of colon cancer has varied widely within the range of 8-34% (2-6). In most recent investigations, though, the rate is estimated to be 20-25% (4, 7-9). Postoperative mortality rates range from 8-22%, which is considerably higher than for elective colon cancer surgery (10, 11). Long-term survival (5-years) is also lower in the emergency group, at about 40%, to be compared to 60% in the non-emergency group (12, 13). The conversion of emergency colon cancer into elective cases could therefore, in theory, contribute to a lowering of the overall mortality of colon cancer, in addition to reducing the workload of emergency surgical services.

The introduction of a screening program for colorectal cancer is associated with a reduction of colon cancer with an emergency presentation (14, 15), but the opportunities for preventing emergency presentation among symptomatic patients are less well studied. Nevertheless, more than half, 39/62 (63%) of British patients had reported symptoms associated with colorectal cancer to their GP´s at some time between two years and thirty days before their emergency presentation (16). Another British study demonstrated that emergency colon cancer patients are less likely to have seen their GP on a regular basis (17). A large study from Ontario, Canada involving more than 40,000 patients with colorectal cancer found the lack of a regular source of primary care to be an independent risk factor for emergency presentation with obstruction or perforation (18). Any association between health care services and emergency presentation of colon cancer is therefore deserving of further investigation. The

aim of this study was to scrutinize mode of presentation of colon cancer in a population-based setting and, secondarily, to examine the relation of mortality to mode of presentation.

Method

The Regional Oncological Centre Registry

It is mandatory for all cases of colon cancer in Sweden to be reported to a quality registry, which is initially managed at six Regional Oncological Centres (ROCs). In this study, the quality registry at the ROC in the Uppsala-Örebro region was used. The registry includes detailed information concerning patient characteristics, treatment including date of surgery, stage, and survival. Each reported patient has to be classified as either an elective or an emergency case. An "emergency patient" is defined as a patient for whom "the operation has been performed ***acutely or subacutely*** for medical reasons". This classification is thus contingent upon the judgment of each individual surgeon reporting on the patient. The very broad definition of emergency presentation used by the registry makes any comparison between hospitals and counties even more uncertain. "Emergency presentation" was therefore operationalized using three study-specific criteria; 1) admittance through the emergency room, 2) surgery within 3 days from admittance, and 3) obstruction, perforation or bleeding confirmed during the operation. The three day-limit was arbitrary, but considering the time required for diagnosis, resuscitating before surgery, and possible difficulties in getting access to the operation theatre for patients with incomplete obstruction or an incompetent ileocaecal valve, it was not considered unreasonable based on current clinical practices. Patients fulfilling the three criteria are referred to as "acute" in the following sections and those not

fulfilling the criteria but still reported to the registry as emergency cases are referred to as "subacute".

Four counties (Dalecarlia, Sörmland, Uppsala and Värmland) within the Uppsala-Örebro region in central Sweden, with different demographic profiles and geographic conditions, were chosen. Uppsala, being the fourth largest city in Sweden and a center of higher education, is characterized by a younger population (mean age 40 years) compared to Dalecarlia, Värmland and Sörmland (mean ages 43, 43,and 42) (19). Uppsala and Sörmland are more densely populated (39 and 44 inhabitants/km^2) compared to Dalecarlia and Värmland (10 and 16 inhab/km^2 respectively) (19). The counties also vary considerably in terms of physician density, with 478 physicians/10^5 inhabitants in Uppsala county, compared to 287, 303 and 325 in the counties of Värmland, Sörmland and Dalecarlia respectively as of 2007 (20).

During the years 2006-08, 1430 patients were reported to the ROC registry as operated for colon cancer in the four counties (350 in Dalecarlia, 313 in Sörmland, 347 in Uppsala, and 420 in Värmland). All cases reported as emergencies to the registry (n=263), as well as twice that number of randomly selected controls, with a margin of at least 10% to cover missing records, were requested from the ROC registry (n=591). The case-control 1:2 ratio was chosen to increase the power of the study.

The size of the population in 2007 (21) was used to estimate the incidence of emergency colon cancer in each county. The total number of patients with colon cancer, including operated as well as non-operated cases reported to the ROC registry, was used for comparison between counties.

Surgical and Primary Care Records

Surgical records for all patients were scrutinized (HG, KJ, SF, JG) to determine mode of presentation according to the study definition. Information on the first investigation (endoscopy, radiology) and referring units was also extracted from the surgical records.

For almost all patients, primary care records were available in the same electronic database as the surgical records from each of the four counties. A few patients had been in contact with private primary care physicians, and copies of those records were asked for separately.

Records from all primary care visits during the last 12 months prior to surgery were thus also scrutinized. All visits to the GP during this period were noted, regardless of the purpose of the visit. A checklist of symptoms associated with colon cancer (abdominal pain, anemia/fatigue, constipation, diarrhea, bleeding, and weight loss) was used, and all records documenting any of these symptoms were registered for study purposes. Any chronic diseases were also noted at this point.

Study Population

In total, 854 colon cancer patients were eligible. Mode of presentation could not be determined for three patients, due to missing information in the surgical records. Primary care records were missing for another four in the ROC emergency group, and one patient was not operated. Among patients classified as elective cases in the ROC registry, 8/591 (1.3%) fulfilled the study criteria for acute emergency presentation, and were thus included in this group. Primary care records were missing for five patients reported as elective cases to the ROC, and one patient was not operated. The final number of patients in the study was thus 840 (Figure 1).

Statistics

In a previous study, a seasonal variation of emergency presentation was observed. With the assumption of an equal distribution of emergency cases throughout the year, 80% power and a 1:2 ratio case-control, it was estimated that 200 emergency patients would be needed to detect a seasonal variation in this study as well. Based on a previous study from the region, we estimated there would be 18 cases with an acute presentation per county and year reported to the registry (4) and that a period of three years would be sufficient.

The chi-square, Student's t and Mann-Whitney tests were used to test any differences between the groups. Survival was calculated from the date of surgery until death or the end of follow-up (28th June 2012). Postoperative 30- and 90-day mortality and 5-year survival were analyzed with Kaplan-Meier estimates, and the log rank test was used for comparison. A multivariate Cox regression model, adjusting for age, sex and stage, was employed, and hazard ratios (HRs), including a 95% confidence interval (CI), were calculated to estimate the risk of death within five years in relation to the mode of presentation. The first 30 postoperative days were excluded from this last analysis.

All p-values reported were two-sided and all analyses were performed using SPSS® version 19.0 (SPSS, Chicago, Illinois, USA).

Results

Mode of presentation

Among patients reported as emergency cases to the ROC registry, 158/263 (60.0%) fulfilled the study criteria for acute presentation of colon cancer (Figure 1), whereas 105 (40.0%) did not fulfill the criteria and were classified as subacute cases. The most common reasons were not being operated within the time limit of three days from admittance (95/105; 90.5 %),

and/or not being admitted through the ER (33/105; 31.4 %). Eight patients had been reported as elective cases to the ROC, but fulfilled the study criteria for acute presentation, whereas 577 remained as elective cases.

The proportion of all cases of colon cancer reported as emergencies using the ROC definition varied, from 16.9% in Sörmland to 20.0% in Värmland, and under the study criteria the fraction of acute colon cancer varied from 8.6% in Uppsala to 12.8% in Dalecarlia (Table I). The fraction of patients reported as emergencies and also fulfilling the study criteria for acute colon cancer also varied somewhat between the counties – from Dalecarlia (45/64; 70%), to Sörmland (33/53; 62%), Värmland (50/84; 59%), and Uppsala (30/61; 49%) (X^2=5.8; p=0.1). The estimated incidence of emergency presentation of colon cancer as reported to the ROC registry varied from 6.4 to 10.2 /10^5 inhabitants in the counties of Sörmland and Värmland respectively, and under the study criteria it varied from 3.1 to 6.1 /10^5 in Uppsala and Värmland county.

Clinical Characteristics and Management

One fifth of all patients in both the acute and subacute groups (according to study criteria) were aged 85 and over (19.0% and 21.0% respectively), compared to 13.0% in the elective group (X^2=13.3; p= 0.35) (Table II). The lowest proportion of acute and subacute surgery was found in the age group of 65-69 years.

Male patients presented more often as acute cases according to the study criteria (54.8%) whereas subacute surgery was more common in women (61.0%) (X^2=7.0; p=0.03) (Table III). Stage was more advanced in the acute group compared to the elective cases, but even more so in the subacute group, with half of all patients (52/105, 49.5%) having a generalized disease at surgery (X^2=82.4; p<0.001).

Most patients had been in contact with primary care at some time during the 12 months preceding surgery, but to a somewhat lesser extent (82.3%) in the acute group (X^2=4.9; p=0.08). No more than 347/577 (60.5%) of the elective group had undergone a colonoscopy as their first diagnostic investigation. In the acute and subacute group, 43/158 (27.2%) and 46/105 (39.1%), respectively, had already had either a colonoscopy or a radiological examination of the colon performed as a first examination during the last year prior to surgery.

In the acute group, almost 60% of patients went directly to the emergency department without referral, whereas in the subacute group this was the case for 40% of patients (X^2=159.1; p< 0.001).

Symptoms Recorded in Primary Care

Symptoms recorded up to 12 months before presentation differed significantly between the three modes of presentation based on study criteria (Table IV). Rectal bleeding and anaemia/fatigue was significantly less common prior to an acute presentation, while constipation and weight loss was more common in the sub acute group.

A larger proportion of patients in the acute and subacute group had no symptoms associated with colon cancer recorded in primary care compared to the elective group (26.2% and 18.1% vs. 12.4%; p=0.004) (Table IV). However, two or more symptoms associated with colon cancer were recorded in primary care up to 12 months before surgery for 59/130 (45.4%) patients in the acute group, and 51/94 (54.3%) in the subacute group.

Outcome

The 30-day mortality rates for patients in the acute, subacute and elective groups (as defined by the study criteria) were 8.2%, 15.2%, and 1.9% respectively (X^2=14.6, p=0.001). The

corresponding numbers for 90-day mortality were 14.9%, 35.6%, and 4.3% (X^2= 98.5, p<0.001). Five-year survival rates in these groups were 40.1%, 28.3%, and 57.8% respectively (X^2= 151.8; p=<0.001) (Figure 2).

In a multivariate Cox regression model (first 30 days excluded), HR was 1.88 (95% CI 1.46-2.44) for acutely operated patients, and 2.29 (1.71-3.08) for the subacute group (Table V).

Discussion

This study has identified a group of colon cancer patients reported as emergencies but operated upon three days or more after admittance. These patients had a more disadvantaged stage distribution and a doubled postoperative mortality compared to those operated upon within three days. The heterogeneity thus found among patients reported as emergencies highlights the importance of clear and unambiguous definitions of "emergency presentation" for future comparative studies of colon cancer populations.

A retrospective design was adopted, i.e. the quality of data could be no better than what was originally documented in the records. In each of the four counties involved, one single physician scrutinized the records, and although it was done according to common instructions, the work was nevertheless carried out independently. We have not been able to find any other study that uses the same time interval of three days from admittance to surgery among colon cancer patients reported as emergencies to identify or separate those operated acutely from those operated with some delay, and this is obviously a limitation of the study. In general, definitions of emergency presentation of colon cancer are found to vary widely, which explains the great disparity, from 9% (surgery within 24 h) (3) to 51% (no definition given)

(5). Again, this underlines the potential utility of a clear-cut taxonomy for reporting presentation of colon cancer.

This study did not assess every patient with colon cancer during 2006-2008 in the four counties included. A few patients with an acute presentation may be found among those patients categorized as electives in the quality registry, and these were not randomly selected as controls in our study. However, out of the 591 patients with elective colon cancer selected from the ROC quality registry, we only found 8 (1.3%) patients to fit our study criteria, and these patients were categorized as acute colon cancer. Hence, the estimated proportion and incidence of acute colon cancer might be slightly low, but the important point is the considerable variation between closely located counties rather than the absolute figures.

The large differences observed in the incidence of acute colon cancer (according to study criteria) may to some extent be caused by differing age distributions in the populations of the various counties, as a larger proportion of acute colon cancer was found in the oldest age group. This may in turn be explained by a reported decrease in the overall incidence of colon cancer for patients aged 85 and over (22), whereas those developing emergency states, such as obstruction, can be expected to present to health care to a larger extent than elderly patients with colon cancers that remain undiagnosed. A somewhat larger proportion of younger patients (-59 years) was also found in the acute and subacute compared to the elective group, and such a J-shaped curve has been reported previously (12).

These variations also point to opportunities for prevention, in identifying crucial factors associated with a lower frequency of emergency presentation. One example of this is a study from Ontario, where the likelihood of emergency presentation of colon cancer was found to be lower outside Toronto, because access to colonoscopy resources was better in rural areas (18).

One important finding is the unacceptably high 30- and 90-day postoperative mortality of 15% and 35% among patients with obstructing colon cancer reported as emergencies but operated with a subacute approach. We have not been able to find any similarly defined group in the literature to evaluate these figures, and the abundance of different definitions of emergency presentation of colon cancer may be one reason for this. The more disadvantaged stage distribution is an obvious contributing factor to the higher 30- and 90-day mortality in the subacute group, but cardiovascular/respiratory comorbidity or diabetes did not differ significantly between the acute, subacute and elective groups. Our study was not designed to answer the question of why some patients were operated with a delay of more than three days, but this is an urgent task for a prospective study. The degree of obstruction as well as the time span until operation after admittance is not known in this group.

An initiative on Timing of Acute Care Surgery classification (TACS) was published earlier this year (23), high-lighting the lack of evidence on proper timing of emergency surgery. The authors suggest definitions of Time To Surgery (TTS), Ideal Time To Surgery (iTTS) and Actual Time To Surgery (aTTS), and even a ratio aTTS/iTTS to be used for quality assessment. Further studies on appropriate timing of emergency surgeries were requested, and we suggest colon obstruction to be included in this work.

The distribution of symptoms among acute, subacute and elective cases of colon cancer was found to differ already at the consultation in primary care. One important aspect to keep in mind is that many symptoms associated with colon cancer have low predictive values. For instance, only 1 % of all patients with abdominal pain are estimated to have a colorectal cancer (24). Australian researchers even found that colorectal cancer is associated with rectal bleeding and weight loss only, and not with any other large bowel symptoms (e.g. change in bowel habits, constipation, diarrhea, or abdominal pain) (25). We have not been able to

classify the severity of the symptoms documented. However, the development of algorithms for symptoms associated to colorectal cancer has also included the absolute number of symptoms as an important factor (26). In both the acute and subacute group, a fairly large proportion of patients had reported two or more *different* symptoms, and yet ended up as being operated for colon cancer acutely or subacutely. Paying more attention to the actual number of different symptoms may represent a simple but very useful way of improving alertness to colorectal cancer in everyday clinical work, and may potentially increase the fraction of patients undergoing scheduled or elective operations.

On the other hand, in the acute and subacute group, 27% and 44% of patients, respectively, had already been referred for "elective" examinations, such as colonoscopy and colon CT. For the population investigated in this study we therefore suggest first reviewing the management and time frames from bowel examination until surgery.

Finally, one interesting similarity was observed between the acute and subacute group, which they did not share with the elective group. When adjusting for differences in age, sex and stage, they both had an approximately doubled risk of death within 5 years, in accordance with what has been reported previously for the acute group (4). Obstruction as such seems to be associated with a worse prognosis.

In conclusion, our study found that 40 % of colon cancer patients reported as emergencies were operated more than three days after admittance. Several reasons are plausible – decision-making being postponed due to delays in diagnosing obstruction of the colon or the obstruction being found to be incomplete, the need for resuscitation, or difficulties in getting access to the operation theatre. Notably, 30-day mortality was twice as high among patients operated upon three days after admittance compared to for those operated within three days (15% vs 8%), which makes Time To Surgery in colon cancer obstruction an important field

for research and quality improvement efforts. In addition, cases designated as subacute in this

study represent a vulnerable subgroup of colon cancer patients that must be further explored.

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Table I. Frequency and incidence of emergency presentation of colon cancer as reported to the Regional Oncology Cancer Centre and according to study criteria in four Swedish counties, 2006-08.

Values in parentheses are percentages of the total number of cases of colon cancer in each county.

		Cases reported		Incidence ** / 10^5	
County *Population 2007*	All colon cancer 2006-08	Emergencies reported to the registry	Acute according to study criteria*	Emergencies reported to the registry	Acute according to study criteria
Dalecarlia *275,618*	350	65(18.6)	45 (12.8)	7.7	5.4
Sörmland *265,190*	313	53(16.9)	33 (10.5)	6.4	4.1
Uppsala *323,270*	347	61(17.6)	30 (8.6)	7.4	3.1
Värmland *273,826*	420	84(20.0)	50 (11.9)	10.2	6.1
Total *1,137904*	1430	**263 (18.4)**	**158 (11.0)**	7.7	4.6

*Admittance through the emergency room, surgery within 3 days and obstruction, perforation or bleeding confirmed at surgery

**Crude annual incidence per 100,000 inhabitants (not age-standardised)

Table II. Mode of presentation of colon cancer according to study criteria by age groups (n=840). Values in parentheses are percentages.

Age	Acute	Subacute	Elective
-59 yrs	22 (13.9)	13 (12.4)	61 (10.6)
60-64	16 (10.1)	12 (11.4)	59 (10.2)
65-69	15 (9.5)	10 (9.5)	76 (13.2)
70-74	21 (13.3)	17 (16.2)	103 (17.9)
75-79	28 (17.7)	14 (13.3)	117 (20.3)
80-84	26 (16.5)	17 (16.2)	86 (14.9)
85- yrs	30 (19.0)	22 (21.0)	75 (13.0)
Total	158 (100.0)	105 (100.0)	577(100.0)

Table III. Clinical characteristics of colon cancer by mode of presentation using study criteria (n=840). Values in parentheses are percentages.

	Acute n=158	Subacute n=105	Elective n=577	p-value
Age median	76 (54)	75 (61)	74 (71)	0.35
Sex				
Male	86 (54.8)	41 (39.0)	298 (51.8)	0.03
Female	71 (45.2)	64 (61.0)	277 (48.2)	
Comorbidity				
Cardiovascular diseases	70 (48.3)	48 (47.1)	300 (55.4)	0.34
Diabetes	16 (11.1)	14 (14.1)	97 (17.9)	0.12
Respiratory diseases	17 (11.9)	11 (11.3)	46 (8.6)	0.39
Stage (pTNM)				<0.001
I	7(4.5)	2 (1.9)	75 (12.8)	
II	55 (35.5)	22 (21.2)	236 (41.4)	
III	52 (33.5)	25 (23.9)	169 (29.6)	
IV	36 (23.3)	52 (49.7)	83 (14.6)	
Missing	5(3.2)	3 (2.9)	9 (1.6)	
Any consultation in primary care ≤12 months prior to surgery	130 (82.3)	94 (89.5)	508 (88.0)	0.08
First diagnostic examination (from any dept)				
Colonoscopy	15 (9.6)	28 (27.5)	347 (60.5)	<0.001
Radiology colon [1]	28 (17.8)	18 (17.6)	126 (22.0)	
Radiology other [2]	98 (62.4)	50 (49.9)	85 (14.8)	
Perop	16 (10.2)	6 (5.9)	14 (2.4)	
Missing	1(0.6)	3 (2.9)	5(3.2)	
Referral				
Primary care	39 (24.8)	29 (28.4)	276 (48.3)	<0.001
Internal medicine	8 (5.1)	16 (15.7)	150 (26.2)	
Other	17 (10.8)	15 (14.7)	67 (11.7)	
No referral	93 (59.2)	42 (41.2)	79 (13.8)	
Missing	1(0.6)	3 (2.9)	5(3.2)	

[1] Colon CT, single and double contrast barium enema

[2] Abdominal CT, abdominal plain film

Table IV. Symptoms and number of symptoms associated with colon cancer recorded in primary care ≤12 months prior to surgery by mode of presentation using study criteria (n=732).

Symptoms	Acute n=130 (%)	Subacute n=94 (%)	Elective n=508 (%)	p-value
Rectal bleeding	6 (4.6)	11 (10.5)	107 (21.1)	<0.001
Constipation	40 (25.3)	28 (29.8)	98 (19.3)	0.01
Abdominal pain	59 (45.4)	41 (43.6)	179 (35.2)	0.05
Loss of weight	16 (12.3)	24 (25.5)	86 (16.9)	0.03
Anaemia/Fatigue	37 (28.5)	42 (44.7)	281 (55.3)	<0.001
Diarrea	22 (16.9)	28 (29.8)	123 (24.2)	0.07
Number of different symptoms				0.004
0	34 (26.2)	17 (18.1)	63 (12.4)	
1	37 (28.5)	26 (27.7)	166 (32.7)	
2	31 (23.7)	20 (21.3)	144 (28.3)	
≥3	28 (21.6)	31 (33.0)	135 (26.6)	

Table V. Estimated 5-year hazard ratios (HR) by mode of presentation in colon cancer using study criteria, in four Swedish counties 2006-08 (n= 794).

	HR	95% CI	p-value
Age			
-69 (Ref)	1.00		
70-79	1.69	1.28-2.23	<0.001
80-	2.52	1.94-3.29	<0.001
Sex			
Men (Ref)	1.00		
Women	0.98	0.79-1.22	0.86
Stage			
I (Ref)	1.00		
II	2.37	1.19-4.71	0.01
III	4.57	2.31-9.02	<0.001
IV	13.3	6.70-26.40	<0.001
Mode of presentation			
Elective (Ref)	1.00		
Subacute	2.29	1.71-3.08	<0.001
Acute	1.88	1.46-2.44	<0.001

Figure 1. Study population of colon cancer reclassified according to study criteria (SC) of emergency (n=840).
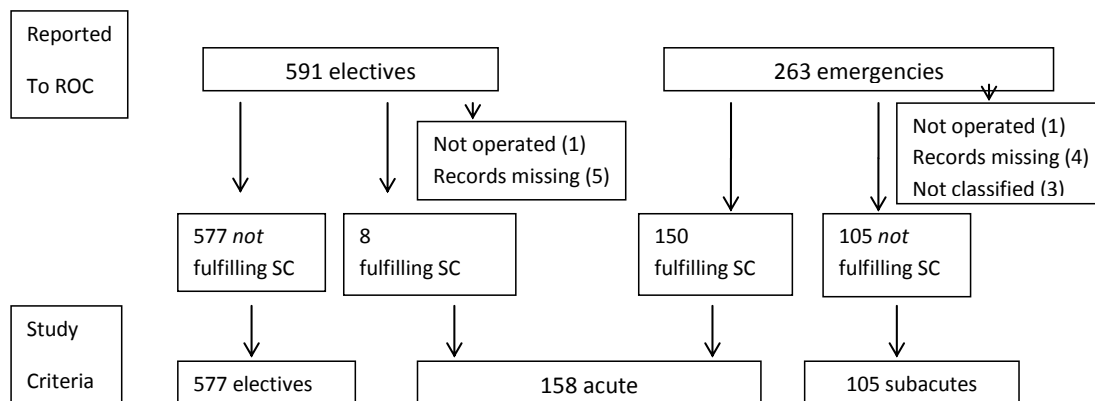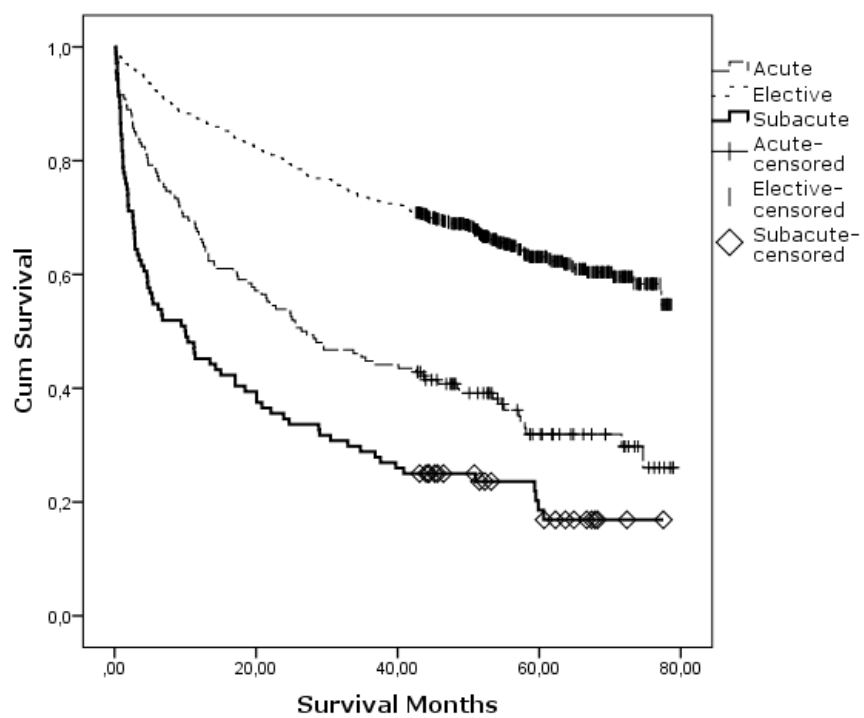
Figure 2. Kaplan-Meier survival curves for patients with elective (n=577), subacute (n=105) and acute (n=158) presentation.

III

Emergency presentation and socioeconomic status in colon cancer

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Abstract

Background: Emergency presentation affects up to every fourth patient with colon cancer, and is associated with worse outcomes. The aim of this study was to investigate any association between socioeconomic status (SES) and mode of presentation in colon cancer.

Materials and methods: Individually attained data on civil status, education and income were linked to quality registries for colon cancer in two large Swedish regions 1997–2006 ($n = 12\ 293$) and analyzed by logistic regression, adjusting for age, sex, stage, region and socioeconomic variables.

Results: The frequency of emergency presentation was 23%; 27.8% among patients above the age of 80, and 20.0% among patients aged 70–79 ($p < 0.001$). There was no difference between men and women (22.6% vs. 23.8%; $p = 0.1$). Among patients with stage IV colon cancer, 34.6% presented as emergencies.

Odds ratio for an emergency presentation in unmarried patients was 1.24 (96% CI 1.04–1.48), and for unmarried patients above the age of 80, OR was 1.45 (95% CI 0.98–2.13).

Among patients below the age of 70 with compulsory education only, OR was 1.22 (95% CI 0.98–1.48). For patients within the lowest income quartile (Q1), OR was 1.24 (95% CI 1.04–1.49). This was most pronounced in men (OR 1.34; 95% CI 1.40–1.72), in patients below the age of 70 (OR 1.36; 95% CI 1.02–1.82), and above the age of 80 (OR 1.41; 95% CI 1.00–1.98).

Conclusion: Emergency presentation of colon cancer is consistently associated with socioeconomic factors, and this must be considered in efforts aimed at reducing the overall frequency of emergency cases.

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Keywords: Colon cancer; Emergency; Civil status; Education; Income

Introduction

Colon cancer is the third most common form of malignancy in both men and women worldwide, with an estimated 1.2 million cases annually, as well as the fourth most common cause of cancer-related death.[1] About 20–25% of all colon cancer is estimated to present as a surgical emergency.[2] Such cases being associated with a considerably higher postoperative mortality of 8.2–22.1%,[3–7] and a 5-year survival rate of around 40%, as opposed to that of elective patients, which is over 60%.[8,9] Risk factors for emergency presentation of colon cancer are not well understood, but the combined effect of it being a relatively common and severe condition, makes it an urgent field to explore.

The association between socioeconomic status (SES) and mode of presentation of colon cancer has, to some extent, been investigated previously. Patients that had lower incomes or lived in deprived areas were more likely to present as emergencies according to a Canadian and a British study.[10,11] Another British study reported the risk of an emergency presentation to be more than twice as high for patients from deprived areas[12] but yet another British study has found no variation in the frequency of emergency presentation of colon cancer between deprived and affluent patients.[13] A recent study from Sweden focused on emergency presentation and educational level, and a trend but no significant association was found among patients below the age of 75.[14] One study from the 1980's in the UK found widowed patients to present as emergencies more often.[15]

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In all, we hypothesized that several aspects of patients' socioeconomic position are of importance for mode of presentation in colon cancer, and set out to explore the association to civil status, education and income, in a population-based setting.

Materials and methods

Regional clinical quality registries on colon cancer

All cases of colon cancer reported to the Regional Oncology Centre (ROC) in the Uppsala-Örebro and Stockholm regions during 1997−2006 were included. These two regions were chosen as the Uppsala-Örebro region contains both rural and more densely populated areas, while the Stockholm region represents the population and health care of a larger city. The ROC registries in the two regions cover almost 100% of all colon cancer patients since 1997 and 1996, respectively.[16] These quality registries provide information on mode of presentation, likewise surgical and pathological aspects including stage, and type of hospital.

The Uppsala-Örebro registry offers information on mode of presentation by defining emergency cases as operations "performed acutely/subacutely for medical reasons". In the Stockholm region each surgeon independently classifies the operation as an emergency or non-emergency, and specific reasons for the classification are not included in the registry.

Socioeconomic variables from Statistics Sweden

Statistics Sweden is the governmental agency responsible for reporting national official statistics and has well elaborated registries including several socioeconomic variables. The registries are based on the compulsory personal ten-digit identity number, which is used for almost all administrative purposes in Sweden. In this study, the Total Population Register was used for information on civil status, number of children, and place of birth. Information on patients' highest attained levels of education and annual income was obtained from a continuously updated longitudinal integrated database on labour market research (LISA). Data on education was not available for patients >79 years, as for elderly citizens this information is mainly based on self-reports whereas for younger generations there is direct input from educational institutions. Information on income was received from the national tax office. All socioeconomic variables were retrieved for the year preceding the patient's diagnosis.

Civil status was categorized as *married, unmarried, divorced* or *widowed*. Educational levels were categorized as *compulsory, further* or *university education*. Income comprised family income, and included the total income of a household, presumably in order to give a more accurate measure of the total economic situation of a patient

than one based only on individual income. Income was adjusted for inflation using the price basic amount index and then categorized into *quartiles (Q1-Q4)*. The variable child/ren was dichotomized into *yes* or *no*. Place of birth was categorized into *Sweden, the Nordic countries, the Rest of Europe* and *the Rest of the world* (except Europe). Hospitals were denoted as *university, general district* and *district hospitals*, depending on where the operation had taken place.

Patients

In total, 13 004 patients were reported as being afflicted with colon cancer to the two ROC quality registries between 1997 and 2006; 6691 (54%) in the Uppsala-Örebro region, and 5694 (46%) in the Stockholm region. Some 583 (4.5%) patients were not operated on and could thus not be classified as emergency cases or not, and they were excluded. Another 92 were excluded because they did not live within the regions in question, but were, for various reasons, operated on within one of the two regions. Information on mode of presentation was missing for 36 patients and the resulting total number of patients included was 12 293.

Statistics

Initially, chi-square tests were performed to compare the proportions of patients with emergency and elective presentations within the various groups defined by each variable. If a significant difference ($p < 0.05$) was obtained, the variable was included in a multiple logistic regression analysis. However, no information was available on the pattern of referrals due to the emergency condition itself. Any difference associated with the frequency of emergency presentation by type of hospital would be difficult to interpret, and this variable was therefore not included in the multivariate analyses.

Separate models were performed for men and women, as well as for three different age groups (<70, 70−79 and ≥80 years). Time periods (1997−2001 vs. 2002−2006), and regions (Uppsala-Örebro vs. Stockholm) were also compared. The results were expressed as an odds ratio with a 95% confidence interval. *P*-values were two-sided. All analyses were performed using SPSS® version 19.0 (SPSS, Chicago, Illinois, USA).

Results

Basic characteristics

Overall, 23.2% of all colon cancer patients presented as an emergency (Table 1). About half of the patients had a localized (stage I and II) tumor and just above half of all patients were married when diagnosed with colon cancer. Educational data was missing for every fourth patient,

Table 1
Basic characteristics of colon cancer patients 1997–2006 (*n* = 12 293).
Values in parentheses are percentages.

	(%)
Mode of presentation	
Emergency	2856 (23.2)
Elective	9437 (76.8)
Age	
−69	4416 (35.9)
70−79	4248 (34.6)
80−	3629 (29.5)
Sex	
Men	5987 (48.7)
Women	6306 (51.3)
Stage	
I	1411 (11.5)
II	4670 (38.0)
III	3567 (29.0)
IV	2428 (19.8)
Missing	217 (1.8)
Region	
Uppsala-Örebro	6653 (54.1)
Stockholm	5640 (45.9)
Missing	217 (1.8)
Civil status	
Married	6349 (51.6)
Unmarried	1180 (9.6)
Divorced	1704 (13.9)
Widow/widower	3037 (24.7)
Missing	23 (0.2)
Education	
Compulsory school	4268 (34.7)
Further	3370 (27.4)
University	1781 (14.5)
Missing	2874 (23.4)
Income	
Q1	3042 (24.7)
Q2	3067 (24.9)
Q3	3100 (25.2)
Q4	3061 (25.0)
Missing	23 (0.2)
Children	
Yes	10 083 (82.0)
No	2210 (18.0)
Place of birth	
Sweden	10 820 (88.0)
Nordic countries	707 (5.8)
Europe except Nordic c:s	504 (4.1)
World except Europe	262 (2.1)
Missing	0
Type of hospital	
University	2733 (22.2)
General District	6086 (49.5)
District	2469 (21.9)
Missing	1005 (8.2)

Table 2
Mode of presentation of colon cancer in relation to basic characteristics
(*n* = 12 293). Values in parentheses are row percentages.

	Emergency *n* = 2856 (%)	Elective *n* = 9437 (%)	*p*-Value
Age			<0.001
−69	971 (22.0)	3445 (78.0)	
70−79	874 (20.0)	3374 (80.0)	
80−	1011 (27.8)	2618 (72.2)	
Sex			0.125
Men	1354 (22.6)	4634 (77.4)	
Women	1502 (23.8)	4803 (76.2)	
Stage			<0.001
I	84 (6.0)	1327 (94.0)	
II	934 (20.0)	3736 (80.0)	
III	951 (26.7)	2616 (73.3)	
IV	839 (34.6)	1589 (65.4)	
Region			0.052
Uppsala-Örebro	1597 (23.9)	5094 (76.1)	
Stockholm-Gotland	1275 (22.4)	4419 (77.6)	
Period			0.519
1997−2001	1377 (23.5)	4485 (76.5)	
2002−2006	1479 (23.0)	4952 (77.0)	
Civil status			<0.001
Married	1353 (21.3)	4996 (78.7)	
Unmarried	311 (26.4)	869 (73.6)	
Divorced	379 (22.2)	1325 (77.8)	
Widow/Widower	807 (26.6)	2230 (73.4)	
Education			0.018
Compulsory school	969 (22.7)	3299 (77.3)	
Further	715 (21.2)	2655 (78.8)	
University	347 (19.5)	1434 (80.5)	
Income			<0.001
Q1	842 (27.7)	2200 (72.3)	
Q2	739 (24.1)	2328 (75.9)	
Q3	646 (20.8)	2454 (79.2)	
Q4	623 (20.4)	2438 (79.6)	
Children			0.021
Yes	2301 (22.8)	7782 (77.2)	
No	555 (25.1)	1655 (74.9)	
Type of hospital			0.004
University	688 (25.2)	2045 (74.8)	
General District	1580 (26.0)	4506 (74.0)	
District	557 (22.6)	1912 (77.4)	

and every other patient was treated at a General District hospital.

Univariate analyses

Patients aged 80 years and above had a higher occurrence of emergency presentation than patients aged 70−79 years (χ^2 = 126.7, $p < 0.001$) (Table 2). Among colon cancer patients presenting as emergencies, more than every third patient (1011/2856; 35%) was thus above the age of 80. There was no significant difference in the frequency of emergency presentation between men and women ($p < 0.1$). More than one third of stage IV patients presented as emergencies (χ^2 = 467.3, $p < 0.001$). The frequency of emergency colon cancer was somewhat higher in the Uppsala-Örebro than in the Stockholm region ($p = 0.05$). A higher proportion of patients with emergency presentation were unmarried and widowed (χ^2 = 39.5, $p < 0.001$). The frequency of emergency presentation among patients with compulsory school as final education was 22.7%, to be compared to 19.5% among university educated patients (χ^2 = 8.08, $p < 0.02$). Among patients in the lowest income quartile (Q1), 27.7% presented as emergencies compared with 20.4% in Q4, (χ^2 = 59.21, $p < 0.001$).

Multivariate analyses

In the adjusted model, OR for emergency presentation in unmarried patients was 1.24 (95% CI 1.04–1.49) (Table 3). For patients with income Q1, OR was 1.22 (95% CI 1.03–1.45). For all practical purposes, the results remained the same when one covariate (income or civil status) was removed (*further data not shown*). Having children was not associated with emergency presentation in the multivariate analyses.

The association between income Q1 and mode of presentation was more pronounced in men, OR 1.34 (95% CI 1.04–1.72), compared to OR 1.15 (95% CI 0.91–1.48) in women (Table 4).

Patients with the lowest income (Q1) had the highest likelihood of an emergency presentation through all age groups (Table 5). For Q1 patients below the age of 70 OR was 1.36 (1.01–1.82) and for those above the age of 80 OR was 1.41 (95% CI 1.00–1.98). The likelihood of an emergency presentation in colon cancer increased with age among unmarried patients, to 1.45 (95% CI 0.98–2.13) among those above the age of 80.

Separate models were used for comparing two sub periods (1997–2001 and 2002–2006), and for comparing the two regions, but no new information was gained (*further data not shown*).

Potential prevention of emergency presentation by age

If the frequency of emergency presentation of colon cancer were the same in all patients with colon cancer as for the group aged 70–79 years, i.e. 20%, this would have

Table 3
Estimated odds ratio from a multiple regression model to predict emergency presentation of colon cancer (n = 12 053).

	OR	CI 95%
Age	1.01	1.01–1.02
Stage		
I	1.00 (ref)	
II	3.89	3.08–4.90
III	5.84	4.63–7.38
IV	8.60	6.79–10.90
Region		
Stockholm	1.00 (ref)	
Uppsala-Örebro	1.05	0.96–1.15
Civil status		
Married	1.00 (ref)	
Unmarried	1.24	1.04–1.49
Divorced	0.97	0.83–1.13
Widow/Widower	1.01	0.96–1.25
Income		
Q4	1.00 (ref)	
Q1	1.22	1.03–1.45
Q2	1.08	0.94–1.25
Q3	0.95	0.83–1.08
Children		
Yes	1.00 (ref)	
No	1.02	0.90–1.15

Table 4
Estimated odds ratio from a multiple regression model to predict emergency presentation of colon cancer for men (n = 5852) and women (n = 6201).

	Men	95% CI	Women	95% CI
Age	1.01	1.01–1.02	1.01	1.00–1.02
Stage				
I	1.00 (ref)		1.00 (ref)	
II	4.72	3.28–6.81	3.34	2.47–4.52
III	6.60	4.57–9.53	5.37	3.97–7.27
IV	9.30	6.42–13.48	8.28	6.08–11.27
Region				
Stockholm	1.00 (ref)		1.00 (ref)	
Uppsala-Örebro	1.10	0.97–1.28	1.01	0.89–1.14
Civil status				
Married	1.00 (ref)		1.00 (ref)	
Unmarried	1.24	0.96–1.61	1.25	0.97–1.63
Divorced	0.91	0.73–1.14	1.00	0.81–1.25
Widow/Widower	1.15	0.93–1.41	1.11	0.92–1.33
Income				
Q4	1.00 (ref)		1.00 (ref)	
Q1	1.34	1.04–1.72	1.15	0.91–1.48
Q2	1.15	0.95–1.39	1.01	0.81–1.25
Q3	0.96	0.75–1.14	0.92	0.75–1.13
Children				
Yes	1.00 (ref)		1.00 (ref)	
No	0.91	0.75–1.10	1.12	0.94–1.33

resulted in a reduction from the actual number of 2856 (23%) to a hypothetical number of 2459 (20%) patients. This difference, 397 patients, equals 397/2856 (14%) of all emergency cases of colon cancer.

Discussion

This study has revealed a consistent association between mode of presentation and socioeconomic status in colon cancer patients. Unmarried and low income patients have been identified as risk groups but also colon cancer patients over the age of 80.

Strengths and weaknesses

A population-based approach, based on quality registries with a near complete coverage was used for this study and this provides a basis for well generalizable results in our opinion. Individually obtained data was used for assessing the socioeconomic position of patients and, in addition, three different measures of socioeconomic position were used, which is of importance. Civil status, education and income are known to be associated, but they do not completely overlap.[17] In the search for risk groups for emergency presentation of colon cancer, it was therefore important to include several aspects of patients' socioeconomic position. It is also noteworthy that no screening program for colorectal cancer was in use in the two regions during the period of the study. This is important, as screening reduces the number of emergency presentation

Table 5
Estimated odds ratio from a multiple regression model to predict emergency presentation of colon cancer in three age categories; −69 years ($n = 4296$), 70−79 ($n = 3903$), 80− ($n = 3550$).

	−69 yrs		70−79 yrs		80 yrs−	
	OR	95% CI	OR	95% CI	OR	95% CI
Stage						
I	1.00(ref) (ref)		1.00(ref)		1.00 (ref)	
II	4.91	3.08−7.84	4.83	3.06−7.63	2.83	2.01−4.00
III	7.82	4.91−12.44	7.54	4.77−11.93	3.85	2.71−5.46
IV	9.78	6.13−15.60	12.13	7.63−19.28	6.19	4.31−8.89
Region						
Stockholm	1.00(ref)		1.00(ref)		1.00(ref)	
Uppsala-Örebro	1.09	0.93−1.26	1.06	0.90−1.25	0.98	0.84−1.14
Civil status						
Married	1.00(ref)		1.00(ref)		1.00(ref)	
Unmarried	1.07	0.84−1.37	1.18	0.80−1.75	1.45	0.98−2.13
Divorced	0.87	0.69−1.10	0.98	0.73−1.31	1.03	0.75−1.43
Widow/Widower	1.00	0.72−1.38	0.96	0.75−1.24	1.24	1.00−1.53
Education						
University	1.00(ref)		1.00(ref)		Na	
Compulsory	1.20	0.98−1.48	1.09	0.84−1.40	Na	
Further	1.15	0.94−1.40	0.98	0.75−1.28	Na	
Income						
Q4	1.00(ref)		1.00(ref)		1.00(ref)	
Q1	1.36	1.02−1.82	1.19	0.85−1.67	1.41	1.00−1.98
Q2	1.16	0.92−1.47	1.15	0.88−1.51	1.24	0.90−1.70
Q3	0.95	0.78−1.15	0.93	0.72−1.19	1.30	0.94−1.41
Children						
Yes	1.00		1.00		1.00	
No	0.90	0.72−1.14	1.04	0.82−1.33	1.15	0.93−1.41

of colon cancer,[18] and participation in screening programs is associated with a more privileged socioeconomic position.[19]

One weakness of the study is the definition of "emergency presentation" which was slightly different in the two regions. The overall frequency and the adjusted odds ratio were somewhat higher in the Uppsala-Örebro region than they were in Stockholm, and we do not know to what extent this represents a "true" difference. Another weakness is the official categorization of civil status at Statistics Sweden, which could fail to accurately reflect the actual situation for some people. Most obvious is the omission of "cohabiting without marriage" as an option in the official statistics, but other sources of misclassification are also possible. However, for the generations included in the study, we expect the official categorization of civil status to offer a useful approximation. Finally, information on educational level was missing for patients above the age of 80.

Factors associated with emergency presentation

Several of our findings are in concordance with previous reports. One study from the UK in 1982−1992 reported elderly widowed patients to be at an increased risk of emergency presentation,[15] and our findings support the previously demonstrated association between income and emergency presentation.[10,12]

What, then, is the actual mechanism that causes unmarried and low-income patients to present as emergency cases more often than other patients with colon cancer? There is no reason to expect an altered biology in these groups. Different associations have been observed to an emergency presentation. Access to health care services has been identified as an important factor.[20] Uninsured patients in the USA are reported to be at greater risk for an acute course.[20] If patients lack a regular source of primary care, the risk of an acute course is increased.[10,15] Patients from less privileged social groups have a longer delay for referral and diagnosis than others.[21] Even though symptom duration in emergency colon cancer is known to be shorter,[22] diagnostic delay may be an important etiological factor. Receipt of colorectal investigation was associated with socioeconomic background in Canada.[23] The interaction between doctors and patients may differ due to the social background of patients,[24] which may in turn affect further management. Apparently, various explanations are at hand. Possibly there are also other causes for an acute course which has not been thoroughly studied like reluctance to seek health care services but also the organizations of different health care systems.

The frequency of emergency presentation was highest among patients over 80 and under 70 years of age, a pattern that has been previously demonstrated.[9] We found no association between mode of presentation and sex, even though

previous studies have reported a female predominance in colon cancer with an acute course.[9−11,25] Ethnicity is reported as a risk factor for an emergency presentation in the USA,[26] but due to the heterogeneity among patients born outside Sweden in this material, we refrained from further analyses.

Future studies

Reducing emergency presentation is of interest to health care services globally. In this study, hypothetically, every seventh patient with an emergency presentation would have been avoidable if there had been no variation by age, i.e. there had been no increased risk for emergency presentation among elderly patients with colon cancer. As a potential way to reduce the burden of emergency colon cancer, diagnostic work up for elderly patients with possible colon cancer ought to be scrutinized.

Conflict of interest statement

The authors declare no conflict of interest.

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