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Factors Influencing Selection of Treatment for Colorectal Cancer Patients

NINA CAVALLI-BJÖRKMAN



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Abstract

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In Sweden and elsewhere there is evidence of poorer cancer survival for patients of low socioeconomic status (SES), and in some settings differences in treatment by SES have been shown.

The aim of this thesis was to explore factors which influence cancer treatment decisions, such as knowledge reaped from clinical trials, patient-related factors, and physician-related factors. In a register study of colorectal cancer, all stages, patients were stratified for SES-factors. Differences were seen with regards to clinical investigation, surgical and oncological treatment and survival, with the highly educated group being favored. Survival was better for highly educated patients in stages I, II and III but not in stage IV.

In a Scandinavian cohort of newly metastasized colorectal cancer patients, recruitment to clinical trials was studied. Patients entering clinical trials had better performance status and fewer cancer symptoms than those who were treated with chemotherapy outside of a clinical trial. Median survival was 21.3 months for trial-patients and 15.2 months for those treated with chemotherapy outside a trial. Those not treated with chemotherapy had a median survival of just 2.1 months. Patients in clinical trials are highly selected and conclusions drawn from studies cannot be applied to all patients.

In the same cohort, treatment and survival were stratified for education, smoking and indicators of social structure. Highly educated patients did not have a survival advantage. Patients who lived alone were offered less combination chemotherapy and surgery of metastases than other patients and had 4 months shorter survival than those who lived with a spouse or child. In a fourth study, 20 Swedish gastrointestinal oncologists were interviewed on which factors they considered when deciding on oncological treatment. Oncologists feared chemotherapy complications due to lack of social support, and ordered less combination chemotherapy for patients living alone. Highly educated patients were seen as well-read and demanding, and giving in to these patients' requests for treatment was regarded as a way of pleasing patients and relatives and of avoiding conflict.

Keywords: colorectal cancer, socioeconomic status, clinical trials, family support, living alone, patient-physician interaction

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List of publications

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

- I. **Cavalli-Björkman N, Lambe M, Eaker S, Sandin F, Glimelius B.** "Differences according to educational level in the management and survival of colorectal cancer in Sweden". *Eur J Cancer*. 2011 Jun;47(9):1398-406.
- II. **Sorbye H, Pfeiffer P, Cavalli-Björkman N, Qvortrup C, Holsen MH, Wentzel-Larsen T, Glimelius B.** "Clinical trial enrolment, patient characteristics, and survival differences in prospectively registered metastatic colorectal cancer patients". *Cancer*. 2009 Oct 15;115(20):4679-87.
- III. **Cavalli-Björkman N, Qvortrup C, Sebjørnsen S, Pfeiffer P, Wentzel-Larsen T, Glimelius B, Sorbye H.** "Lower treatment intensity and poorer survival in metastatic colorectal cancer patients who live alone". *Accepted for publication, Br J Cancer*.
- IV. **Cavalli-Björkman N, Glimelius B, Strang P.** "Equal cancer treatment regardless of education and family support? A qualitative study on oncologists' decision-making". Submitted for publication.

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Abbreviations

AJCC	American Joint Committee on Cancer
ALAT	alanine aminotransferase
ALP	alkaline phosphatase
APR	abdomino-perineal resection
AR	anterior resection
BM	bone metastasis
BSC	best supportive care
CI	confidence interval
CRC	colorectal cancer
CT	computer tomography
EGF	epidermal growth factor
FDG	F-18-fluorodeoxyglucose
5-FU	5-fluorouracil
HR	hazard ratio
K-RAS	Kirsten rat sarcoma viral oncogene homologue
LDH	lactate dehydrogenase
LISA	longitudinal integrated database on labour market research
LM	liver metastasis
mCRC	metastatic colorectal cancer
MDT	multidisciplinary team conference
NCI	National Cancer Institute
NRN	national registration number
NS	not significant
OR	odds ratio
PET	positron emission tomography
PS	performance status
QoL	quality of life
SCB	Statistical Central Bureau
SES	socioeconomic status
TNM	tumour-node-metastasis
UNL	upper normal limit
VEGF	vascular endothelial growth factor
WBC	white blood cell count
WHO	World Health Organization

Introduction

Medical decision-making is a complex process which involves considering medical, social and financial circumstances before recommending treatment to patients. In my clinical practice I spend much time teaching medical students, and it is evident to me that making these decisions requires that which Swedish doctors call “klinisk blick”, which roughly translates as a “clinical eye” for the patient’s circumstances. When decisions are made purely based on the medical information available to us, it may be ill-suited to the patient’s life-conditions. This often becomes evident when a clinical recommendation is formed within a multidisciplinary team conference (MDT), where cases are presented but patients themselves do not participate. The extension of the MDT is the consultation where patient and doctor later meet, and sometimes recommendations have to be revised when patients present with social, financial or geographical challenges, or with previously unknown co-morbidity, which makes the intended treatment impossible.

In this thesis my aim has been to explore different aspects of the choices that physicians make. Today we rely heavily on results from clinical trials to guide us when it comes to offering the treatment that will be best for our patients. We also work under national and regional guidelines, which state that all patients have the right to receive the best possible care and that it should be equal and fair. Above all this is the Hippocratic Oath, our ethics, the reason we once chose to study medicine. Nonetheless, reports keep coming which show that there *are* differences in medical treatment and outcome between people in our society. In this thesis, I myself contribute two such studies. It is demoralizing to think that the medical profession supports differential treatment of people and of the utmost importance to explore *why*. My modest contribution towards further knowledge in this area is hopefully just the beginning.

Background

Treatment and survival gradients

In the past decades, medical developments have improved the outlook for patients with colorectal cancer (CRC). Improvements have been made with regards to diagnostic procedures, radiotherapy (RT), surgical excision, adjuvant and palliative chemotherapy (1-4). In very recent years, targeted drugs have been added to the list of possible treatments for these patients (5).

Developments have benefited patients with limited disease, where a larger fraction is now cured, and those with advanced disease, where more intensive palliative treatments have prolonged survival. One group of patients previously considered incurable; those with limited liver- or lung metastases, can now be offered curative surgery or RT. A fraction of these patients will live to be long-term survivors, or even be completely cured of their cancers.

There is evidence from a number of clinical studies that life for the patient with metastatic CRC (mCRC) can now be prolonged to a median overall survival of over 20 months (6-8), given that the most modern treatment can be used. This is compared to 5-6 months if the patient receives best supportive care (BSC) only (2). For oncologists, these figures are dramatic. But are they real? Are the individuals behind these figures representative of the average mCRC patient? The clinical impression of many oncologists is that some patients do go on to be long-term-survivors, but a large number do not survive for more than a few months after the diagnosis of mCRC.

The dramatic development of this field comes at increased cost, which also raises the question of which treatments are available for which patients. In some areas of the world there are vast differences between what treatments can be afforded by, and offered to, patients (9). Social and economical inequality can lead to very large discrepancies in treatment in countries where the public health care sector is sparsely financed (10). Patients will then rely on private health care options which offer state-of-the-art cancer care, if they can afford it. From many countries there have been reports of large differences in cancer care due to patients' socioeconomic status (SES) (11, 12). Studies have shown differences in disease stage at diagnosis, with less privileged patients presenting with more advanced disease, as well as differences in diagnostic procedures, treatment and, ultimately, survival (13-15). "Lead times"; meaning the time between different health care interventions or possibly more aptly described as "waiting time" for patients have

been reported to be longer for poorer patients than for those more well off (16). In rural areas, where geographical distance to health care facilities may be larger, and educational level lower, patients may also have difficulty accessing health care (17-19).

Disturbingly, there have been reports of differences even in countries with a strong public health care sector (20, 21). In the Nordic countries public health care is tax financed and available to all patients regardless of social standing. Private health care options in the cancer field are few or non-existent. There are regional guidelines which regulate what treatment should be given, and many physicians believe that treatment is equal and fair for these reasons. Still, a number of reports have shown differences in treatment with regards to SES in Scandinavia (22, 23) as in other countries with similar systems (24-26). The reasons for these differences are not known, but of utmost importance to explore further. Colorectal cancer (CRC)

CRC is the third most common malignancy worldwide, with higher prevalence in developed than in developing countries. In Sweden roughly 3900 new cases of colon cancer and almost 2000 new cases of rectal cancer were diagnosed in 2009. When adjusted for population growth and increased life expectancy, incidence has risen slightly over time.

In Sweden, the relative 5-year-survival reported for colon cancer was 56% for men and 61% for women in 2008. Corresponding figures for rectal cancer were 58% for men and 63% for women (27). In recent years survival has improved especially for rectal cancer patients due to intense efforts by the medical profession to raise treatment standards (4, 28-30). As with most malignancies, the key to cure is early diagnosis and treatment. Surgical removal of the tumour is indisputably the most important part of the treatment, although addition of adjuvant chemotherapy has improved survival rates in more recent years.

Rectal cancer is defined as an adenocarcinoma in the distal part of the large intestine, situated a maximum of 15 centimetres above the anal verge. A colon cancer is defined as an adenocarcinoma situated in the large intestine anywhere between the valvula Bauhini and the rectum.

Patients with symptoms from the large intestine should be examined in such a way that cancer can be excluded. This means clinical examination, rectoscopy and tests for occult bleeding by F-haemoglobin x 3. The colon must thereafter be examined by either colonoscopy or virtual colonoscopy. Barium enema is used more and more seldom. Colonoscopy is superior to barium enema as it enables direct inspection of the bowel lumen, and because biopsies may be taken if tumours or polyps are found(31). There is evidence that the sensitivity is higher for virtual colonoscopy, done through advanced 3-D-reconstruction of computer tomography (CT), than for barium enema (32).

Tumours and polyps should whenever possible be biopsied for pathological analysis. The overwhelming majority of cancers in the colon and rectum are adenocarcinomas, but carcinoid tumours, melanomas and squamous epithelial cancers do occur, as do a variety of benign or pre-malignant lesions, the latter especially in the form of polyps.

Stage refers to the extent of the primary tumour and the spread within the body. In order to correctly stage the disease, CT or ultrasound of the liver and abdomen are done for all patients, and for rectal cancers magnetic resonance imaging (MRI) of the pelvis is included. Positron emission tomography (PET) has emerged as an interesting addition to the investigations done to map possible spreading of the cancer. Using F-18-fluorodeoxyglucose (FDG), glucose uptake in tissue can be measured. Since tumour tissue is hyper-metabolic, uptake in tumours is often higher than in surrounding tissue. FDG-PET is not routinely available for all patients yet and currently used in cases where distant spread is suspected but unconfirmed by standard radiological investigations, or when spread must be excluded before curative therapy is initiated.

The staging system most frequently used is that of the American Joint Committee on Cancer (AJCC). The studies in this thesis were done during a time frame when the TNM (tumour-node-metastasis) 5 was used. The current version is TNM 7, introduced in 2010.

Surgical treatment

Surgical resection of a CRC is the most important part of cancer treatment. Choice of surgical method is dependent on a number of factors: tumour localization, patients' age and general condition, concurrent diseases and patient preference.

CRCs can be situated anywhere between the caecum and the distal part of the rectum. For tumours situated in the caecum, colon ascendens and first third or two thirds of the transverse colon, right-sided or extended right-sided hemicolectomy are the methods of choice. For tumours in the distal third of the transverse colon and the colon descendens, left-sided hemicolectomy is opted for. Sigmoid tumours are excised with a sigmoid resection and very distal tumours, in the recto-sigmoid area can be excised by sigmoid resection combined with a high anterior resection (AR). AR refers to a removal of parts of the rectum including the mesorectum, after which the left colon is anastomosed to the remaining part of the rectum.

When patients have multiple tumours in different parts of the colon and rectum, colectomy is an option. This method involves resecting the entire colon including ten centimetres of the distal ileum. If the rectum is involved, it too is removed. The remaining ileum is anastomosed either to the remaining rectum or to the anus. In the latter case a pelvic reservoir is created using

parts of the small bowel so that the patients' chances of postoperative continence increase.

Rectal cancer surgery is difficult and there is wide acceptance for the belief that it should be centralized and performed by a limited number of surgeons who have had special training for it (33). There are three methods in use, namely 1) AR with anastomosis, 2) Hartmann's procedure and 3) abdomino-perineal resection (APR). AR is the method of choice for tumours in the upper and middle parts of the rectum. If the tumour is situated so that sufficient surgical margin can be achieved distally (i.e. healthy intestine of sufficient length can be removed below the tumour), AR is performed. The proximal sigmoid segment is then anastomosed with the remaining part of the rectum, enabling the patient to stay continent. Results with regards to post-operative bowel problems vary and generally the anastomosis should not be too close to the anus if the patient is to have acceptable bowel function. If the anastomosis is low, an AR syndrome with urgency is often seen, at least during the first year. Different surgical methods, such as creating a pouch, can alleviate the problems. If the tumour is situated close to the anus, rectal amputation is opted for. Rectal amputation involves complete resection of the rectum, the anal canal and the sphincters as well as a permanent sigmoideostomy. The perineum is closed by suturing. Hartmann's operation is a procedure where the tumour is removed and the proximal part of the colon is led through the abdominal wall as a colostomy. The remaining rectum is thereafter sealed off. Hartmann's method is an option for patients with rectal cancers but who cannot be offered AR because of poor sphincter function, or for elderly patients who cannot tolerate extensive surgery in the form of an APR (34).

A large fraction of patients (20-25%) with colon cancer has emergency surgery due to bowel obstruction or perforation. This type of emergency procedure is associated with higher postoperative morbidity and mortality, as well as being a risk factor for recurrence of cancer after surgery (35). For these patients overall complication rate is higher because of stress on the bowel by obstruction. Some patients have bowel distension proximally of the tumour, with poor circulation of the bowel wall. Spontaneous perforation of the bowel with subsequent leakage of contents into the abdominal cavity increases risk of infection and other postoperative complications. When surgery is done in the above situations the overall conditions will dictate the surgical approach. Bowel with poor circulation will have to be removed and often a stoma, which relieves pressure on the intestinal wall, is opted for. If primary anastomosis of intestinal segments is possible, it is done, with or without an ileostomy to facilitate healing of the anastomosis. If primary anastomosis is not deemed possible, a colostomy is opted for. Hartmann's operation is an option for patients having emergency surgery and whose general condition is poor, but it is by many considered a "last resort" rather than an optimal surgical approach.

Oncological treatment

RT is an option for some rectal cancer patients, either preoperatively when intent is curative or when patients with advanced disease are distressed by symptoms from the primary tumour. Different RT regimens have been under study and there is now agreement that preoperative RT is superior to post-operative. The purpose of RT in this setting is to reduce risk of local recurrence, and it is given to patients with tumours classified as “bad” or “ugly”, i.e. with a significant risk of relapse at the primary site. On-going trials are currently investigating which regime, if any, is superior. In Sweden the Stockholm III-trial is running, in which most patients considered for preoperative RT are randomized between a 5x5Gy-regimen and a longer 2x25Gy-regimen (36). After the 5x5Gy-regimen, surgery is performed either immediately or with delay. Several centres combine RT with chemotherapy for patients with both “bad” and “ugly” tumours. In Sweden only those considered “ugly” and in need of maximum neo-adjuvant treatment for downstaging or downsizing purposes receive radiochemotherapy (37).

Chemotherapy long consisted of different variations of administration of 5-fluorouracil (5-FU). Since the 1960's and up until the launch of irinotecan in the year 2000, 5-FU was the only drug with significant anti-cancer-activity for CRC-patients. Worldwide there is still disagreement as to which is the superior schedule of administration of 5-FU, with bolus injections and different varieties of continuous infusions being used. With the approval of irinotecan and oxaliplatin in 2000 and 2004, respectively, new possibilities emerged and survival for metastatic patients was prolonged. Adjuvant administration of 5-FU, alone or with oxaliplatin has improved cure rate for patients with stage III disease (38), and is now considered gold standard. Targeted drugs are recent additions to the therapeutic range, with bevacizumab, cetuximab and panitumumab being the three presently in use (39). All are monoclonal antibodies; bevacizumab targets the Vascular Endothelial Growth Factor (VEGF-) receptor while cetuximab and panitumumab target the Epidermal Growth Factor (EGF-) receptor. The latter two were used in all patients until, in 2007, evidence emerged that they were only effective in the subgroup of patients with non-mutated (or wild-type) K-RAS (Kirsten rat sarcoma viral oncogene homologue). Since then, testing for this mutation is routine in clinical practice and cetuximab and panitumumab are not an option for all patients (40).

The intent of oncologic treatment can be:

Neo-adjuvant – given before a surgical or radiotherapeutic treatment and aiming to reduce risk of relapse.

Conversion – given to patients with a primarily inextirpable cancer where oncologic treatment, if successful, may render the tumour resectable.

Adjuvant – given after surgery to those patients with tumour characteristics that put them at a high risk of relapse. Generally this is taken to apply to patients estimated to have a 30% risk of disease recurrence or higher. Adjuvant oncologic treatment can reduce this risk substantially and in absolute terms more so for patients with higher risk than for those with lower risk.

Palliative – aiming to reduce tumour symptoms, improve quality of life (QoL) and, if possible, prolong survival.

Palliative treatments and supportive care

RT is a good option for patients with distressing local symptoms, either from the primary tumour or from metastases (41). For instance, patients with rectal cancer where the tumour has not been removed can be treated with a palliative 5x5Gy setup to reduce pain, bleeding and stenosis (42). RT is also widely used for metastases to the skin, lymph nodes and in any region where they give rise to local symptoms. RT is considered gold standard for treatment of painful bone metastases and is also used to consolidate orthopaedic stabilisation of pathological bone fractures.

Palliative chemotherapy for mCRC long consisted of only one regimen: 5-FU. Today we aim to treat all patients with at least the three types of classic chemotherapeutic agents with activity in CRC (5-FU, irinotecan and oxaliplatin) (7) before we discontinue treatment and offer the patient supportive care. Some patients are also offered antibody treatment but discussion is ongoing with regards to which patients benefit most from this treatment (39), and cost has to be taken into consideration especially with targeted therapies (43).

Supportive care used to envelop the use of cortisone, analgesics and other drugs to offer symptom control to patients in whom anti-cancer treatment was no longer possible. The term now has a broader meaning and includes supportive interventions during all stages of the disease, such as anti-emetics during chemotherapy and counselling during rehabilitation after treatment. Interesting data from an American group has shown that in lung cancer patients, survival can be improved with early access to good palliative care, even though no anti-cancer treatment is given (44). This has led to a renewed interest in areas of cancer care which are not directed specifically towards anti-tumour activity. Many research groups now study the effects of lifestyle, physical activity, emotional support and symptom control in improving QoL and survival in cancer patients.

Socioeconomic Status (SES)

SES is defined by a combination of factors including income, level of education and occupation. For research purposes, parameters of SES which have been studied include individual income, average income in area of habitation, educational level, house or car ownership and ethnic background. Strictly not SES-factors, but studied in the same context are parameters indicative of family structure and social support such as marriage/cohabitation, number of children, number of close friends and congregation membership.

A large number of studies linked to SES have been done with regards to race. In North America in particular, many groups have studied if cancer care varies for patients of different racial origin (45-48). This area is complex since incidence of some cancers is higher in blacks than in whites and there is also some evidence of different biological profiles of the respective diseases by race (10, 49). Many authors have concluded through multivariate analyses that when adjusting for race and SES, SES seems to be a stronger determinant of cancer prognosis than race, although the two are closely interconnected and likely to confound each other (50-52). In this thesis, race as an indicator of SES is not explored further except when discussing how identification between patient and doctor can influence clinical decision-making.

SES and cancer care worldwide

A number of reports have shown a relationship between SES and cancer treatment and survival in countries on all continents (12, 48, 53, 54). It is an undisputed fact that individuals with low SES have poorer cancer survival than those with high SES (20, 26, 55). This has been attributed to many factors: co-morbidity, higher incidence of smoking in communities with low SES, possible substance abuse, poorer diet, lower educational level which may hinder access to health care (16) as well as difficulty affording cancer treatment. Health care seeking patterns vary by social standing which in turn might influence treatment and survival (56). SES is also known to affect participation in cancer-screening programs, with low-SES-communities participating to a lesser extent than those of high SES (57). Postoperative complications have been reported to be higher in lower socioeconomic groups (58), which may be due to a higher incidence of co-morbidity or to the fact that low-SES-patients tend to present with more advanced disease.

SES and cancer care in the Scandinavian countries

The Scandinavian countries all have public health care systems which are tax-financed and available to all citizens regardless of their financial situation. In Sweden, regional cancer centres provide and update treatment guide-

lines, so that treatment should be equal between geographic regions and, ultimately, between individual patients. Similar organizations are present in the other Scandinavian countries. It has been believed that the differences seen in other parts of the world do not exist in Scandinavia. Recent Swedish studies within the fields of breast, lung, prostate and colorectal cancer unfortunately indicate differences due to SES similar to those observed in other countries (59-63).

In Scandinavia, a parameter which has been favoured in research regarding SES is maximum attained level of education. Partly due to a long socialist tradition, income gaps are not as pronounced in Scandinavia as in many other developed countries. Education level can be easily measured and reflects SES from youth and onwards. A disadvantage with this parameter is that it is dependent on the availability of higher education. Many people who are now elderly have had more difficulty accessing university education than young Scandinavians do today.

Aims

- I To explore the possible relationship of SES to diagnostic procedures, treatment of CRC and survival using two Swedish quality registers (paper I)
- II To study the characteristics of mCRC-patients that are enrolled in clinical trials and to study if and how trial patients differ from non-trial patients with regards to clinical characteristics, treatment and survival (paper II)
- III To investigate the possible relationship of SES to treatment and survival in a cohort of consecutive mCRC patients from three Nordic countries (paper III)
- IV To study oncologists' own reasons for selecting treatment for cancer patients, by interview and subsequent qualitative content analysis (paper IV)

Patients and methods

Paper I

Clinical Quality Registers

Regional Clinical Quality Registers have been set up in Sweden to monitor the quality of management of cancer patients. Most of these registers have good coverage (the registers used in paper I having 98% and 100% completeness, respectively). The Quality Registers are checked for completeness through matching with the Swedish Cancer Register. They are neither uniform in the type of data recorded, nor in the time span that they cover. For instance, the registers used in paper II contained information on diagnostic procedures in CRC in one region but not in the other.

Other registers

The LISA database (longitudinal integrated database on labour market research) contains all individuals over the age of 16 registered as residents of Sweden. It is continuously updated and includes information on occupation, highest attained education, annual income, sick leave, welfare dependency (where applicable) and employment status.

Linkage between databases is facilitated by the ten-digit national registration number, which all Swedish citizens have since birth or since immigrating.

In paper I, cross-linkage of two Regional Clinical Quality Registers of CRC with the LISA database generated information on diagnostic procedures, treatment and survival with respect to SES in a region where the population is almost 4 million. Registers from two health-care regions (Uppsala-Örebro and Stockholm-Gotland) were used. All registered rectal cancer patients from the years 1995-2006 and all colon cancer patients from the years 1997-2006 in the above regions constituted the study cohort. Educational level was chosen as the strongest SES-parameter both due to its strength as an indicator of SES in Sweden and to its completeness in the registers. Other parameters such as income, employment status, marital status and economic index were tested but judged inferior to educational level due to higher percentage of missing data. Patients were divided into

low, middle or high educational level (9 years of school or less, high school, and university or the equivalent).

Paper II and III

A Scandinavian cohort of patients who were diagnosed with mCRC was set up for research purposes in October 2003. The aim was to obtain an unselected population of mCRC-patients at three university hospitals which were the only cancer-treating facilities in their respective regions, i.e. which received all referrals. Odense University Hospital lies on the island and county of Funen in Denmark, with a population of 475,000. Haukeland University Hospital in Bergen lies in the county of Hordaland, Norway, with a population of 450,000. Uppsala University Hospital lies in the county of Uppsala, with a population of 280,000. All mCRC patients referred for oncologic treatment in these three hospitals between October 1, 2003 and August 1, 2006, were prospectively registered. Patient history, clinical characteristics and all treatment given were recorded prospectively. Missing data was at a later date retrieved from the patients' charts.

Sevenhundred and sixty patients were registered. Clinical characteristics, background data, treatment given and reasons for treating were registered. No patients were lost to follow-up.

In paper II, the focus was on clinical trial recruitment and reasons for entering or not entering a cohort patient into a trial were studied.

For paper III, data on possible antibody treatment and secondary curative surgery was added to the database by retrieving this information from the patients' files. This study was done at a later date than that presented in paper II and the Swedish cohort was checked against the Clinical Quality Registers to identify missing individuals, which resulted in a further 28 patients being added. These patients had either been referred directly to palliative care at diagnosis, or had been referred to the Uppsala department of oncology without being registered in the cohort. The vast majority of these patients had very advanced cancers and never received anti-tumoural treatment. In Denmark, 7 patients were found to have been misregistered and were excluded from the cohort. In Denmark and Norway, checking for missing patients through matching with the cancer registers was not possible. SES variables (marital status, having children, educational level, smoking and living alone) were tested against treatment factors. Patients were divided into two educational groups: university and non-university. Married patients were stratified by sex as a previous study had indicated interactions between educational level and marital status, which in turn influenced survival (64). Correction for possible confounding effects of age and co-morbidity was done.

Paper IV

Swedish clinical oncologists working with gastrointestinal cancer, including CRC, were identified in the register of the national society for gastrointestinal oncology. In total, 22 informants were sent information on the study and 18 expressed interest in participating. Informants were selected through maximum-variation sampling with regards to sex, age, place of work (university hospital or rural hospital) and years of experience as specialist of oncology. When 18 oncologists had been recruited for the study a further two were contacted and asked to participate. These two were chosen as they both worked in a rural setting and one was young whilst the other was approaching retirement. The original 18 plus the latter two constituted a population with good spread in the areas described above, and was judged to be sufficient to reach data saturation.

The interviews were conducted by the first author in the informants' places of work, taped and later transcribed in verbatim mode. Most interviews took between 25 and 45 minutes and transcribed ranged from 1858 to 4739 words. Questions were open ended and the interviewer did not follow a fixed list of questions, but aimed to let the informants talk freely on given topics. The main subject was factors which may influence clinical decision-making other than pure disease-related factors, such as the role of relatives, the patients' social network, age, language barriers and the oncologists' working conditions. The oncologists were also asked about the possible role of the educational level of the patient and of identification with the patients or the patients' relatives.

Qualitative content analysis

The interviews were analysed using inductive qualitative content analysis (65, 66). Qualitative methodology is favoured when there is limited knowledge of the subject to be studied. It differs from quantitative research in many ways, beginning with the selection of informants. In quantitative research, random selection of study material is important to ensure that results can later be applied on the population from which the study sample was taken (generalizability). Random sampling and randomization between study arms are also ways to control bias (67). In qualitative research informants are chosen with the intent of gaining a rich material which can lead to a deeper understanding of the areas of study (68). In maximum-variation sampling, used in paper IV, informants are purposely selected to represent a heterogeneous group so that many different themes may appear during the interviews.

Content analysis refers to the processing of the transcribed interview material. In inductive content analysis, researchers rely on inductive reasoning in which meaning units, codes and themes are extracted from the material

through repeated examination and comparisons of data. “Inductive” methodology is explained by Kirsterud as “bottom-up” whilst deductive is “top-bottom” (69). By this she means that deductive methodology uses knowledge from a general level to make assumptions of one specific case. Inductive, on the other hand, is the opposite: using knowledge gained from a few cases to increase understanding of the group as a whole.

In paper IV, the analysis was done by the first and last author using the following steps: (A) the transcribed interviews were read through to obtain an overall impression (naive reading). (B) the material was re-read carefully to identify significant meaning units. (C) the meaning units were condensed and abstracted to codes. (D) the codes were then compared and sorted into categories and themes. (E) the categories and themes were compared to the entire interview, to make sure that the interpretation was consistent and coherent with the text as a whole, and that the meaning had not been transformed in the process of the analysis. (F) the categories and themes were compared to avoid overlapping, and content descriptions were developed. (G) quotations were used to exemplify the findings.

Statistical analyses

All statistical tests were two-sided, using the 5% significance level.

In paper I, differences between the three educational levels were tested using the chi-square test and the Kruskal-Wallis test. Overall survival was calculated using the Kaplan-Meier method and Cox proportional hazard models were used to assess survival differences between educational groups. Relative survival was calculated using tables for expected survival in the general population (70). Excess mortality was modelled in a Poisson regression model.

In paper II, two-group comparisons were done using exact chi-square tests for dichotomous or nominal, exact Mann-Whitney U tests for ordinal and Student t-tests for continuous variables. Survival analyses used the Kaplan-Meier method with log-rank tests for univariate and Cox regression for multivariate analyses.

In paper III, logistic regression for dichotomous and ordinal outcomes was used. Two group comparisons were performed using exact chi-square tests for dichotomous or nominal; exact Mann-Whitney tests for ordinal and Student t-tests for continuous variables. Overall survival analyses for all patients were done using the Kaplan-Meier method with log-rank test for univariate and Cox regression for multivariate analyses. A separate Cox regression analysis was done to deduce possible confounding effects of high age and co-morbidity on survival in patients living alone.

Results

Paper I

All patients contained in the registers for colon cancer and rectal cancer were included in the study group. Patients who were 75 years or older at diagnosis were excluded since information on educational level and occupation was less complete in this age group. Individuals born outside of Sweden were excluded as they constituted a very heterogeneous group and because many patients were lost to follow-up. One colon cancer patient was lost to follow-up. This way 5715 colon cancer patients and 3899 rectal cancer patients remained in the cohort.

By educational level, there was no clear difference in tumour stage at presentation for colon cancer patients. Rectal cancer patients of higher educational level more often had early-stage disease. Of note was that the patients of middle and high educational level were on average 5 years younger at diagnosis than the patients with low educational level. Since this could in itself affect the results, statistical adjustment for age was done and this did not alter the results. Diagnostic procedures differed between patients of higher and lower education. Patients with university education had significantly more often preoperative CT or MRI than others. For colon cancer patients this difference was also seen with preoperative colonoscopy, which was more often done in patients of higher education while it was more common that patients from the low education group instead had colon x-ray (barium enema).

Elective surgery was slightly more common in the highly educated group, and postoperative complications were less frequent for them. Adjuvant chemotherapy, considered state-of-the-art for stage III colon cancer, was more frequently offered to patients of high educational level. Preoperative RT for rectal cancer was less often given to patients of low educational level. There was no clear difference in surgical technique by educational level for colon cancer patients, but in rectal cancer AR was more common for highly educated patients. Surgery resulting in colostomy was done in 35.5% of patients with lower education but only in 26.9% ($p=0.005$) of those with higher education.

Survival was better in highly educated groups in both colon and rectal cancer in stages I-III but not in stage IV. Better survival was shown in divorced or married patients compared to widowed or single patients (data not

shown). With regards to employment status the best survival was observed in those who were employed or students, compared to those who were unemployed or had disability pension, although these latter groups were small. In an attempt to explain survival differences between educational groups, correction for sex, age, elective/emergency surgery, type of hospital and preoperative RT was done but the observed gradients were unaffected by this.

Paper II

Prospectively, 764 patients were registered. Four were excluded due to either misregistration or other malignancy than CRC at autopsy. Palliative chemotherapy was given to 464 patients, of which 36%, or 169 patients, were included in a clinical trial. The most common reasons for not entering a clinical trial was poor performance status (PS), prior adjuvant chemotherapy and co-morbidity. Few patients failed to enter a trial because they were not considered for it by the oncologist.

The patients that entered a clinical trial differed from those who were treated with chemotherapy outside of a trial in that they had better PS, less pain, anorexia and weight loss. Trial patients were also younger than those treated outside of a trial. In general, patients offered combination chemotherapy were often 75 years of age or younger. Only 13% of those aged 80 or over were treated with chemotherapy.

BSC only was given to 32% of all patients in the cohort. Reasons for not offering chemotherapy to this group were poor PS, high age, co-morbidity and that the patient declined offered treatment.

Median survival was longest for patients treated within a clinical trial (21.3 months), followed by those treated with chemotherapy outside of a trial (15.2 months). For those patients only receiving BSC, median survival was only 2.8 months, and even shorter; 2.1 months, for those with poor PS having only BSC.

For all 760 patients in the cohort, median survival was 10.7 months.

Paper III

In this population-based material, more than half of the patients had significant co-morbid conditions and 38% had PS 2 or worse.

Patients who lived alone more often presented with synchronous metastases than patients who lived with someone (OR 2.17, 95% CI 1.32-3.55) and were less often treated with combination chemotherapy and surgery of metastases. Patients with university education more often had surgery of metastases than patients with non-university education (OR 2.22, 95% CI 1.10 –

4.49), but no other differences in treatment due to educational level were seen. Smokers had significantly poorer PS than non-smokers but no differences in treatment were observed for them or for married men/married women or between patients with or without children. All data was adjusted for age and co-morbidity.

Patients who lived alone had statistically significantly shorter median survival than those who lived with someone (7.7 months vs. 11.7 months, $p < 0.001$), as did patients with co-morbidity (8.0 months vs. 12.5 months, $p = 0.01$). No significant differences in survival were seen with regards to smoking status, having children or education level. No differences in survival were observed between married women and married men.

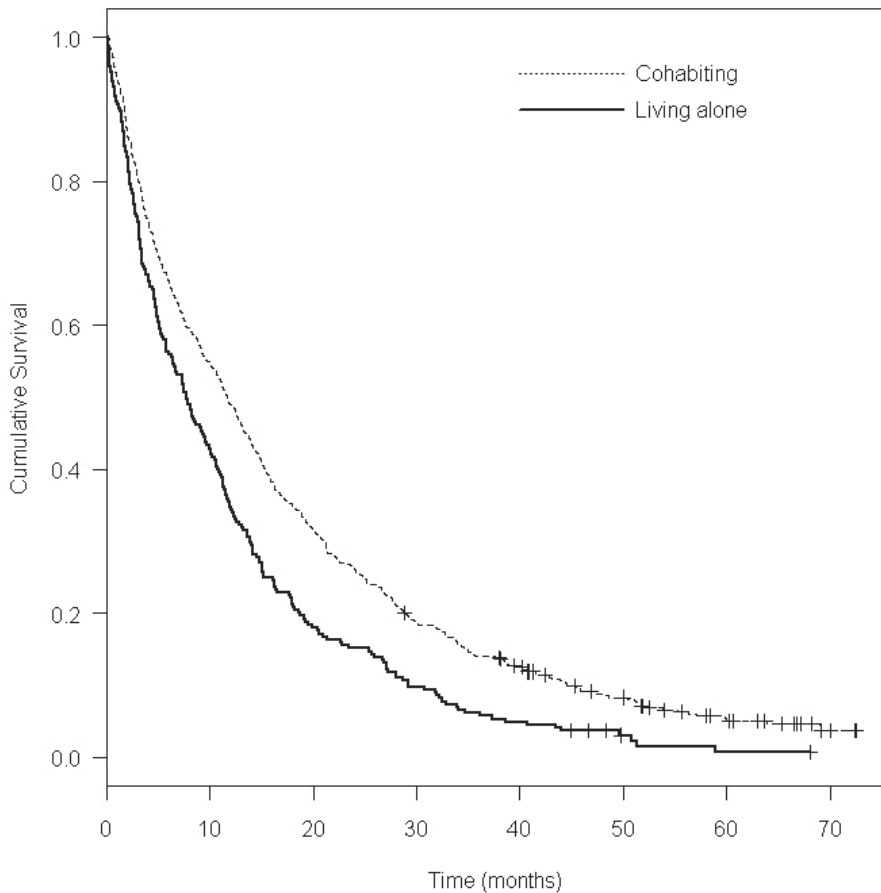


Figure 1: Kaplan Meier of survival for patients living alone vs. for those who live with someone

Paper IV

Twenty clinical oncologists were recruited for the study and interviewed in their own respective places of work. After transcribing and analysing the interviews, the first and third author agreed on a number of themes which appeared during the work process.

Patients living alone were seen by the oncologists as a vulnerable group. Communication with these patients was regarded as more difficult and doctors were not always sure that the patients understood important instructions regarding cancer treatment. As a group, they were seen as less keen to have cancer treatment and by some doctors also as having lower QoL and less to live for than those patients who had a partner. Unaccompanied patients could sometimes be seen as having poorer PS simply due to their lack of a partner.

When patients lived alone, it made oncologists worry about side-effects, and of patients' ability to handle them. Many consciously chose less toxic treatment for individuals without family support and expressed fear of harming patients who were left on their own to deal with adverse effects of treatment. It was suggested that these patients should be referred to a palliative outpatient unit or district nurse to compensate for frail social network. Dedicating extra time to explaining cancer treatments to patients who live alone was also discussed as a possible way of compensating for their perceived communication difficulties.

The role of relatives was discussed, and oncologists felt that some relatives do influence which treatment the patient asks for and also which treatment the doctor chooses. The oncologists felt that the role of relatives had been strengthened in later years and that they were more involved in patient treatment than before. The upside of this is obvious; intensified support for the patient as well as reassurance for the doctor, who is able to prescribe potentially toxic treatment when a good social network exists. The downsides which doctors described were demands on their time, which they felt were difficult to meet, as well as a feeling of being constantly questioned, of no longer being considered an authority.

Oncologists were very aware of the educational level of the patients. Highly educated patients were seen as well-read and communicative, often equipped with many questions. Patients with lower education were described as compliant, less communicative and often satisfied with the treatment they received. The concept of trust was discussed by some doctors, who felt that highly educated patients had less trust in their physician and in the health-care system as a whole than did patients with lower education.

Many oncologists expressed distress over previous reports that SES-factors affect cancer treatment in Sweden. While many said that this was unfair and in contradiction to their own ethical standards, they also agreed that highly educated patients tend to get more treatment simply because they demand it. A widespread feeling was that doctors are poorly equipped to

handle demands from patients, that it is distressing when patients are dissatisfied with their physician and that it is better to give in to demands to avoid confrontation. Sometimes these demands were subconscious – one oncologist said that just knowing the patient's occupation from the referral documentation gave preconceived ideas of what treatment demands to expect in the upcoming consultation.

With regards to the entity of patients who are very eager to receive oncological treatment, even when it is not expected to be beneficial, doctors described this patient category as difficult to handle. These patients were seen as panicking in the face of life-threatening disease and not receptive to arguments normally used in patient discussions. Again, some oncologists felt it was best to give in and let the patients have the treatment they requested, while others thought this unethical. One positive aspect of treating these patients was that they were extremely motivated and rarely felt that side-effects were a problem. Oncologists felt safe treating patients who were well informed and who had expressed willingness to tolerate adverse effects.

Discussion

Clinical decision-making is complex. Doctors consider tumour factors, clinical guidelines, recent results from clinical trials as well as a number of patient factors before recommending treatment to their patients. Knowing the patients' life-circumstances, appraising their personality and judging their ability to cope with treatment are all part of this process. It has been shown that physicians adhere to clinical guidelines to varying degrees, which indicates that a multitude of other factors must be considered in the decision-making process (71, 72). Ubel et al. have shown in an experimental setting that physicians are likely to choose more potent treatment for themselves than they recommend to their patients (73), which may indicate that to recommend toxic treatment to a patient one must know that person well and be able to appraise which resources are available in the home environment should complications arise.

A major factor for physicians to consider is co-morbidity. Co-morbidity is known to be up to 50% more prevalent in populations with low SES than in those with high SES (74), and it is therefore seen as a confounder in SES-studies and often used as a likely explanation when survival gradients are found (75, 76). Environmental factors such as lower standard of living, higher incidence of smoking/substance abuse as well as dietary differences have been suggested as alternative explanations (77). Having other severe disease in addition to cancer is known to decrease both overall and cancer-specific survival (78). Specifically, postoperative morbidity and mortality increases for patients with concurrent diseases (79), but it also influences long-term survival. Frederiksen has suggested after a register study that co-morbidity and, to a lesser extent, lifestyle, can account for the entire differences in survival by SES seen in CRC (80). Since information on co-morbidity was not available in the Clinical Quality Registers used in paper I, it could not be used in the statistical analyses, which is this study's main weakness. However, while relevant co-morbidity should disqualify patients from adjuvant chemotherapy it would not influence the decision to treat with RT, as this can be given even to those with substantial co-morbidity and poor PS. In paper I the percentage of preoperatively irradiated patients is larger in the highly educated group, even though stage I tumours and high tumours (> 10 cm from the anal verge) were more common. This latter fact should have led to less irradiation in this group instead of more. There is no simple explanation for the fact that patients with low SES in our cohort re-

ceive less RT than patients with high SES, although this finding has been reported by other researchers (22).

With regards to diagnostic procedures, colonoscopy was significantly more common in patients of high educational level. This has also been shown in an American study on screening practices, where doctors favoured colonoscopies for patients of higher education and faecal occult blood test for others (54). In an attempt to see if our finding could be explained by availability of colonoscopy at the hospital closest to the patient, we scrutinized all hospitals within the studied region. As highly educated patients tend to prefer urban areas, we expected to find records of more colonoscopies at university hospitals, but this was not the case. In fact, the hospital where the largest numbers of colonoscopies were done in relation to colon x-ray was a small hospital in a very rural setting where few highly educated persons live. The largest hospital in the area; a university hospital, had one of the lowest percentages of colonoscopies of all hospitals in the region.

In two European studies it has been shown that surgery resulting in a permanent colostomy is more often done in patients with low SES (55, 81). When operating on rectal cancer patients, surgeons strive to restore continence by anastomosing the sigmoid to the distal part of the rectum. If the tumour is too “low”, i.e. situated in close proximity to the anus, this is often not possible. In our material, low tumours were less common in highly educated patients, and AR more common. While it is tempting to explain the higher number of colostomies in the low education group by the tumour’s distance from the anus, it is unlikely that this is the only explanation. Two hundred and nineteen patients with low tumours in the highly educated group had only 160 (73%) colostomies, while 513 patients with low tumours in the low education group resulted in 433 (84%) colostomies. The percentage difference indicates that even when tumours were low, surgeons more frequently attempted an AR in the highly educated group.

In paper II, characteristics of trial patients are studied and compared to those patients who are not entered into clinical trials. The percentage of patients accrued to a trial was 36% of those offered chemotherapy, which by international standards is a high rate. While it is important to contribute to development by clinical research, it is also vital that the findings are applicable to the patient population. Bias with regards to patient selection could be due to physician’s choice, failed eligibility criteria, patient declining trial enrolment or logistic factors at the medical facility hindering clinical trial enrolment. In paper II physician selection seemed to be a minor factor, which is supported in paper III where no differences in SES were seen between patients accrued to trials. Instead, the main reason for not participating in a trial was failed eligibility criteria: poor PS, co-morbidity and having had prior adjuvant chemotherapy. Interestingly, although many of these patients were judged “too sick” to be treated within the confines of a clinical protocol, the majority of them (185 patients) went on to be treated with combina-

tion chemotherapy outside of a trial, and another 110 of the patients were treated with 5-FU.

One conclusion in paper II is that if strict inclusion criteria for clinical trials are used, results not applicable to the general patient population will be produced. There is also a risk that the general impression of cancer treatment, and prognosis, is impacted by trial results. Survival for the trial patients in paper II was a median 21.3 months, which is excellent. However, this was only true for a minority, or 159 out of 760 patients in the cohort. For the 244 patients not receiving chemotherapy, median survival was a meagre 2.4 months. When including all patients in the cohort median survival was 10.7 months – a far stretch from the two years people have now come to expect after recent treatment developments.

In paper III, the same cohort as in paper II is used to study possible differences in treatment and survival by SES. An advantage in this, smaller, patient material compared to the register cohort in paper I, is that information on co-morbidity is available. The prevalence of co-morbidity in this population-based cohort is almost identical with that of an Italian study (82). Other figures seem low by international standards – treatment by secondary curative surgery, for instance. The explanation lies in the consecutively recruited, population-based cohort. When patients of all ages, PS and co-morbidity are included, as opposed to the selection of the young and healthy for clinical trials, it is reflected in treatment and survival statistics.

When adjusting for co-morbidity, educational level, marriage, smoking, and having children had no effect on treatment, clinical trial accrual and survival (with the exception of a higher number of highly educated patients having secondary surgery than those of lower education). However, all patients in paper III had stage IV-disease, and in paper I survival gradients were seen in all stages *except* stage IV. Data on oncological treatment for stage IV was not available in the registers and thus not covered in paper I, which makes comparison difficult. The interesting findings in paper III concerned patients who lived alone.

Social support and the effect of social network on cancer survival have been studied previously (83-86). Having active friendships, engaging in social activities and having a partner can improve cancer survival (87-91). In paper III, patients living alone were less often treated with combination chemotherapy and surgery of metastases. Their PS was not significantly poorer than that of other patients but they more often presented with synchronous metastases.

Survival of patients living alone was significantly shorter than for those living with someone. This is in line with previous findings (92, 93), but it is remarkable. If PS is not poorer than for other patients, then lower treatment intensity probably contributes to shorter survival in this group. Reports which focus on the category of patients who live alone are scarce. In an American study on survival of head-neck cancer patients, men without a

partner were found to be at a striking disadvantage, even after controlling for disease variables (94). For Non-Hodgkin Lymphoma, patients who live alone present more often with advanced disease (95), as do lung cancer patients (96). The results in these studies are in line with our findings in paper III.

While co-morbidity certainly is an important factor when trying to account for differences in cancer treatment and survival of different SES, there seem to be other explanations. Doctors are known to, consciously or subconsciously, take note of patients' SES during consultations (97). In American settings where uninsured patients must pay for their treatment, several studies have shown that clinical management varies by patients' SES (9, 98, 99). In a free-for-all system, such as in the Nordic countries, differential treatment is more difficult to explain.

Doctors have been shown to be influenced by patients' physical appearance, race, occupation and financial circumstances (100, 101). A number of groups have studied concordance in patient-doctor relationships and found that patients benefit when they perceive their doctor as similar to them – by race or ethnic origin, educational level or religious inclination (102, 103). The doctors, in turn, are more communicative and volunteer more information in concordant relationships to patients than in discordant ones (104). A problem in this equation is that the doctor will always be of a high educational level, and concordance by education is thus impossible to achieve in most doctor-patient relationships. Patients of lower educational level have been shown to have difficulty navigating the health system and of understanding medical information (105, 106). There is agreement that patients with lower SES should be provided with *more* time and *more* support from the health care system to compensate for their perceived disadvantage (107, 108). Instead, studies show that doctors volunteer less information and spend less time on consultations with patients of low SES (109).

Doctors are known to adapt their communication styles and clinical behaviour when seeing highly educated patients (110, 111). Siminoff et al. showed that doctors spend longer time talking to highly educated patients, while Shin concludes in a Korean study that patients with higher education are dissatisfied with consultation times, which they feel are still too short (109, 112). The Swedish oncologists describe highly educated patients as communicative, questioning, well-read and with high expectations and demands. Patients with lower education, on the other hand, were described as more silent, compliant and trustful. The doctors in paper IV say they are devoting their time to highly educated patients with many questions and high demands, whilst the group with poorer survival demands less attention from their doctor. Raising the awareness of these patterns is important in the quest towards equal treatment between patients. The differences in diagnostic intensity, treatment and survival can partly be explained by subconscious tailoring of care by SES. Doctors struggle to meet requests by demanding pa-

tients (113), which may result in over-treatment, whilst reducing expectations and treatment intensity for low SES-patients and for those who live alone. This latter phenomenon is probably believed to be in patients' best interest, but it is misdirected. A more constructive approach would be to increase support and consultation times for vulnerable patients to ensure that they can receive the same treatment as those of higher SES.

Summary and general conclusions

1. There are gradients in diagnostic activity, treatment and survival by educational level in a large Swedish population of CRC patients.
2. Patients entering clinical trials constitute a subgroup with good PS, little co-morbidity and few cancer symptoms. In other words, they are the “healthiest” minority and cannot be said to be representative of the average cancer patient. This is due to the firm inclusion/exclusion criteria in clinical trials, but should be kept in mind before trying to apply results from clinical trials in daily clinical practice.
3. In a cohort of mCRC-patients, differences in treatment by educational level cannot be seen after correction for co-morbidity, with the exception of more surgery of metastases for highly educated patients. It is possible that co-morbidity is of such clinical importance that it can explain treatment and survival differences seen between groups of high and low SES. However, it should be noted that these results are from a population of stage IV-patients, who in paper I had no differences in survival by educational level and no data on given treatment was available for analysis.
4. mCRC-patients who live alone receive less intensive treatment and have poorer survival than patients who live with someone.
5. Oncologists express caution when treating patients who live alone as they fear adverse treatment effects may be difficult to handle without social support.
6. Oncologists consider factors such as patients’ or relatives’ demands, patients’ educational level and social network when deciding on suitable cancer treatment.

Summary in Swedish

Faktorer som påverkar val av behandling vid kolorektalcancer

När läkare fattar beslut om vilken behandling de ska rekommendera cancerpatienter väger de in en lång rad faktorer. Viktigast är naturligtvis uppgifter om cancersjukdomen – vilken typ av cancer, vilken utbredning i kroppen, vilka behandlingsmöjligheter står till buds? Dagens onkologer är beroende av den kunskap som fås genom ny forskning för att kunna erbjuda sina patienter det senaste och bästa i cancerbehandling. Regionala och nationella behandlingsrekommendationer uppdateras kontinuerligt med målet att alla patienter i Sverige skall ha tillgång till behandling enligt vetenskap och beprövad erfarenhet, samt att behandlingen ska vara likvärdig. Detta senare krav är särskilt viktigt då det finns en rad rapporter, från Sverige och från andra länder, som tyder på att personer med olika social bakgrund inte har samma prognos. Patienter med hög socioekonomisk status (SES) har i allmänhet bättre prognos och längre överlevnad i cancer än patienter med låg SES.

Det finns rapporter som påvisar skillnader inte bara i prognos utan även i sjukvårdens handläggning och i vilken behandling patienterna erbjuds. Att sådana skillnader finns i USA, där man har tillgång till bättre sjukvård om man kan betala för den, är inte förvånande. Mer oroväckande är att man har kunnat påvisa behandlingsskillnader i länder som Canada, Nederländerna och Australien, där sjukvårdssystemen liknar det svenska. Under senare år har man även i Sverige och övriga nordiska länder kunnat påvisa skillnader i behandling av olika cancertyper beroende på SES. Vad detta beror på är inte känt.

I arbete I görs en genomgång av ett stort antal patienter som behandlats i Mellansverige för tjock- och ändtarmscancer under åren 1995-2006. De register som förs över dessa cancertyper är mycket kompletta och uppdateras regelbundet mot cancerregistret så att inga patienter skall missas. Genom länkning av tumörregistren mot LISA-databasen, som innehåller uppgifter om yrke, utbildningsnivå, inkomst osv hos personer i Sverige, kunde patienterna i registret delas in i olika socioekonomiska nivåer. Man såg därmed att patienter med låg utbildningsnivå (grundskola) utreddes med äldre och mindre sofistikerade metoder än patienter med hög utbildningsnivå (universitet eller motsvarande). Koloskopi var vanligare hos högt utbildade medan

lågutbildade oftare genomgick kolonröntgen. När det gällde operation fick lågutbildade oftare en kvarvarande stomi efter operationen än högutbildade fick. Den onkologiska behandlingen (strålbehandling före operation och cytostatika efter operation) gavs oftare till hög- än till lågutbildade patienter. Överlevnaden skilde sig åt i stadium I, II och III men inte i stadium IV, vilket innebär att högutbildade genomgående hade längre överlevnad än lågutbildade utom då canceren var spridd redan vid diagnos.

I arbete II studerades vilka patienter som inkluderas i kliniska studier. Att de är representativa för den genomsnittlige cancerpatienten är viktigt för tolkningen av forskningsresultat. Under 33 månader samlade tre skandinaviska sjukhus in samtliga patienter som kom med nydiagnosticerad spridd tjocktarms- eller ändtarmscancer. 760 patienter registrerades varav 296 var från Bergens universitetssjukhus i Norge, 330 från Odense universitetssjukhus i Danmark och 134 från Uppsala Akademiska Sjukhus. Patienterna skilde sig åt mycket vad gäller allmäntillstånd. Vissa var mycket pigga och tenderade att rekryteras till kliniska studier medan andra var svårt sjuka och remitterades direkt till en Hospiceavdelning eller annan form av palliativ vård. De patienter som kom att ingå i kliniska studier uppfyllde de krav som de flesta forskningsprotokoll idag har; de hade gott allmäntillstånd, få cancersymptom, nära normala laboratorieprover. Av totalt 760 patienter kunde 169 ingå i kliniska studier och de patienterna levde med onkologisk behandling i median 21,3 månader. De patienter som inte ingick i en klinisk studie men som ändå kunde få onkologisk behandling hade en medianöverlevnad på 15,2 månader medan de som inte fick någon onkologisk behandling levde endast 2,8 månader i median. Den största patientgruppen; 244 patienter, var den som inte kunde få någon onkologisk behandling och som därmed hade mycket kort överlevnad. Studie II illustrerar onkologers kliniska dilemma; den kunskap vi får ur kliniska forskningsprojekt är endast giltig för den lilla subgruppen av våra piggaste patienter, men kunskapen gäller inte vår största patientgrupp. Ytterligare en viktig slutsats med studie II är att man kritiskt bör ifrågasätta den utbredda föreställningen att medianöverlevnaden vid spridd kolorektalcancer nu är över 20 månader. Det budskapet kommer starkt från olika forskargrupperns rapporter, som även patienter läser, men gäller alltså i vår studie enbart en minoritet av patienterna.

I arbete III uppdaterades patientgruppen från arbete II genom matchning mot det regionala cancerregistret i Uppsala-Örebro. Uppsalapatienterna kom därför att bli något fler medan man i Odense strök 7 patienter ur den danska gruppen som felregistrerats. Därmed var patientantalet i arbete III 781. Vi använde uppgifter om utbildningsnivå, civilstånd, rökning, om patienterna hade barn eller levde ensamma för att analysera behandling och överlevnad i förhållande till socioekonomi. I detta arbete hade vi tillgång till uppgifter om komorbiditet; eventuella andra svåra sjukdomar som patienterna hade. Detta är viktigt eftersom andra sjukdomar kan spela stor roll för vilken cancerbehandling som ska ges – t.ex. kan man inte ge viss cytostatika vid svår hjärt-

sjukdom. Uppgift om patienternas komorbiditet användes för att korrigera de data vi fick i analyserna.

I arbete III kan vi inte se några skillnader i behandling mellan rökare och icke-rökare, gifta män och gifta kvinnor eller mellan patienter med och utan barn. Högutbildade patienter fick oftare operera bort metastaser än andra patienter men hade i övrigt inga behandlingsfördelar. Den grupp som föll ut i analyserna var ensamboende patienter, som signifikant mer sällan fick kombinationscytostatika och kirurgi av metastaser. De ensamboende hade också oftare än andra patienter metastaser redan då sjukdomen upptäcktes. De enda två faktorer som signifikant påverkade överlevnaden var komorbiditet och att leva ensam. Ensamboende patienter levde i median 4 månader kortare än patienter som bodde med en partner eller ett barn.

Det är en viktig iakttagelse i arbete III att vi inte kan se behandlingsskillnader när vi har möjlighet att korrigera för komorbiditet. I arbete I saknades uppgifter om komorbiditet och det är möjligt att en del av de skillnader som iaktogs där skulle ha minskat eller försvunnit om man haft möjlighet att korrigera för andra svåra sjukdomar patienterna hade. Att ensamboende patienter får mindre omfattande behandling och därtill dör snabbare än patienter som bor med någon är dock ett nytt fynd, som hittills bara beskrivits i ett fåtal studier.

Arbete IV utgörs av en intervjustudie med svenska onkologer som arbetar med kolorektal cancer. Tjugo onkologer intervjuades på sina respektive arbetsplatser angående faktorer som de väger in i behandlingsbeslut. Intervjuerna skrevs ut och analyserades med kvalitativ metodik.

Onkologerna ansåg att patienters anhöriga har inflytande över val av behandling, både genom påverkan på patienten och på läkaren. Anhöriga beskrevs som mer delaktiga i cancerbehandling nu än tidigare, vilket var en fördel för patienterna som fick gott stöd under sjukdomens olika faser. Patienter som saknade socialt nätverk sågs av onkologerna som en utsatt grupp och att patienten var ensam angavs som ett skäl att erbjuda mindre kraftfull behandling. Onkologerna motiverade detta med omsorg om patienten och rädsla att en ensam patient inte skall kunna hantera svåra behandlingsbiverkningar på egen hand.

Högutbildade patienter sågs som pålästa och pådrivande. Konsultationer med högutbildade patienter kunde vara krävande på grund av stora mängder frågor som patienter och anhöriga ställde och man beskrev att dessa patienter ofta hade specifika önskemål eller krav rörande behandling. Lågutbildade patienter sågs som mindre kommunikativa och beskrevs ha mer tillit, både till läkaren och till sjukvården som helhet. Patienter som själva var drivande och krävde att få vissa behandlingar tenderade att få dem, enligt onkologerna. Att ordinera behandling till en patient som kräver det motiverades med att konflikter bör undvikas med svårt sjuka patienter och att det är viktigt att patienten blir nöjd.

Arbete IV visar att det finns både medvetna och undermedvetna motiv som påverkar onkologens val av behandling. Antaganden gjordes ibland om patienter baserade t.ex. på utbildningsnivå där behandlingen delvis kunde bli en annan därför att man trodde att patienten förväntade sig det. Ett mycket viktigt fynd i arbete IV är att den relativa underbehandling som görs av ensamboende patienter kan förklaras av att onkologer inte vågar utsätta dessa patienter för potentiellt livshotande biverkningar. Interaktion mellan läkare och patient samt att onkologer tar hänsyn till sociala och ekonomiska faktorer kan bidra till att förklara de behandlingsskillnader som setts i arbete I och III.

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