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Chapter 1

General introduction and outline of this thesis

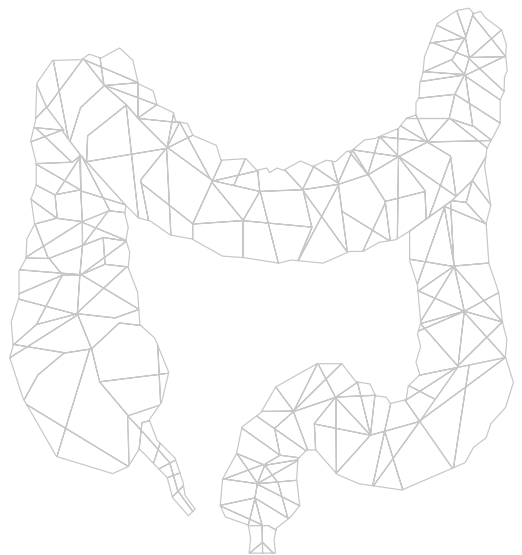
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Improving the outcome of colorectal cancer: the European
Registration of Cancer Care (EURECCA) project

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GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

Colorectal cancer is one of the most common cancers in Europe and the incidence is still growing. It is the third most common diagnosed cancer in males, and the second in females. Besides, it is the second most important cause of cancer death in Europe.¹ The incidence rates vary across Europe, with higher rates in developed countries, as compared to developing countries.² These geographic differences appear to be attributable to the differences in dietary and environmental exposures. In the Netherlands the incidence is high as compared to other European countries with an incidence of over 57 per 100 000 per year (European Standardized Rate).

Age is a major risk factor for colorectal cancer. The highest incidence is between 70 and 79 years of age, which makes it a disease of the elderly patient (see figure 1). Together with the fact that our population is ageing it is anticipated that the number of elderly patients with colorectal cancer will grow during the coming years.³

Approximately two thirds of the colorectal cancer incidence occurs in the colon, and about one third occurs in the rectosigmoid and rectum. Stage of disease is based on the growth of the tumour into the wall of the intestine, tumour growth in lymph nodes, and tumour growth into other organs.⁴ About 25% of the patients will present with lymph node metastases without distant metastases at time of diagnosis, these patients are diagnosed as stage III colorectal

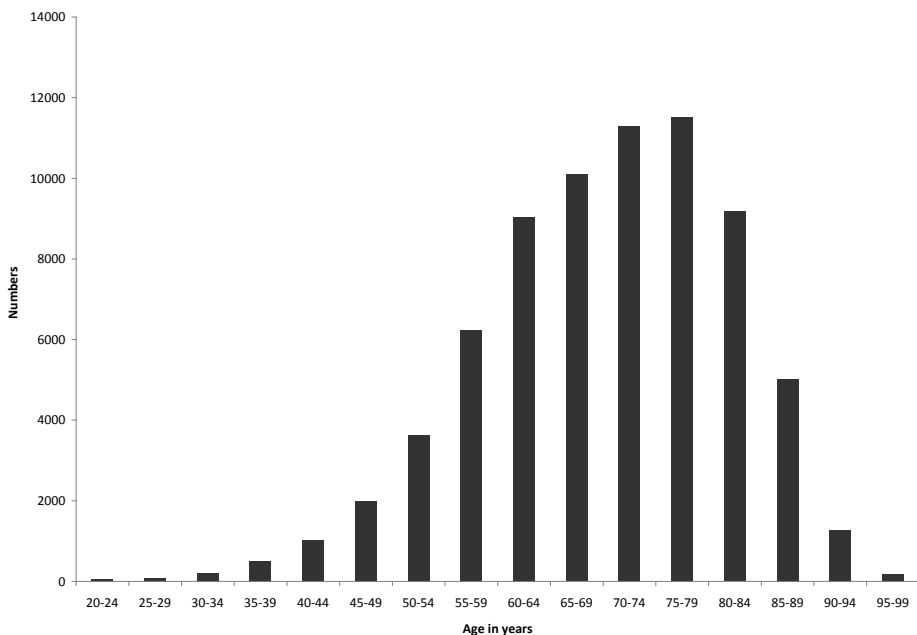


Figure 1: Crude number of new cases per 5-year age group from 2005 until 2010

cancer. Furthermore, approximately 20 to 25% of the patients with colorectal cancer will have distant metastases at time of diagnosis, most often in the liver and/or lungs, also called stage IV colorectal cancer. Patients without distant and lymph node metastases have stage I or stage II disease, depending on the growth of the tumour in the wall of the intestine and surrounding structures.

Over the past decades survival has improved as a result of several changes in the therapy of colorectal cancer. The EUROCARE working group has shown improvement in survival of colorectal cancer patients in Europe, Survival substantially increased over time in all European regions. In general, increases were more pronounced in younger than in older patients, for earlier than for more advanced cancer stages and for

rectum than for colon cancer.⁵ With all the multidisciplinary approaches to treat colorectal cancer, it has to be emphasized that surgery remains the mainstay of curative colorectal cancer. To improve the overall outcome of colorectal cancer, one can focus on improvement of treatment or enhancement of quality of care; both parts will be discussed in this thesis.

PART I COLORECTAL CANCER; TREATMENT AND SURVIVAL

Since colon and rectal cancer are treated as different entities, they will be discussed separately in this thesis. In the treatment of early colon cancer, the first step is the surgical removal of the tumour and loco regional lymph nodes. Nowadays the classical abdominal resection is increasingly replaced by laparoscopic surgery. Besides, for early stages of colon cancer advanced endoscopic techniques such as endoscopic mucosal resection, endoscopic submucosal dissection, or even endoscopic mucosal ablation are described as less invasive experimental alternatives of colectomy.⁶⁻⁸ Additionally, advances have been made in perioperative care with the implementation of fast track programmes for colorectal surgery.^{9,10}

In the beginning of the 1990's Moertel et al showed in a randomised clinical trial that stage III patients treated with adjuvant chemotherapy have a significant decrease in recurrence and an improvement in survival.¹¹ Since then, the use of adjuvant chemotherapy has been incorporated in guidelines. Since the mid 2000's the use of adjuvant chemotherapy for high risk stage II patients has been implemented in the Dutch guidelines.¹² High risk stage II patients are defined as patients with a T4 tumour, poor differentiation, perforation or obstruction at time of diagnosis, less than 10 lymph nodes examined, and/or angio-invasion. The time trends in the use and costs of adjuvant chemotherapy, and survival for stage III colon cancer patients in the Netherlands from 1990-2008 are shown in *Chapter 2*. Factors associated with omitting adjuvant chemotherapy in these patients are described in *Chapter 3*.

The improvement in survival over time is accompanied by changes in treatment, although in subgroups, such as elderly patients and patients with comorbidities, these changes in treatment have occurred in a lesser extent.¹³ *Chapter 4* consists of a retrospective study comparing

the survival improvement of younger, middle-aged, and elderly over time. In general, survival of elderly colorectal cancer patients is worse as compared to younger patients. *Chapter 5* shows the importance of the first postoperative year on the survival differences between older and younger colorectal cancer patients.

As in colon cancer, surgical removal of the tumour is the main curative treatment for rectal cancer patients. Phil Quirke in 1986 identified that there was a high positive predictive value of the circumferential resection margin involvement for the subsequent development of locally recurrent cancer and poor survival.¹⁴ Conventional resection consisted of blunt dissection, which failed to clear the pelvis of mesorectal disease and resulted in an increased risk of positive lateral margins.¹⁵ Consequently, the total mesorectal excision (TME) technique, which is defined by embryological planes, and with a sharp dissection, has been introduced.¹⁶ Since introducing the TME technique, the local recurrences have decreased from 15-50% to below 10%.¹⁷⁻²¹

The preferred type of resection depends on the anatomical location of the tumour, all using TME resection. Tumours located in the lower rectum, near the anal sphincter, should undergo an abdominal perineal resection (APR) in most cases, resulting in a permanent colostomy. For tumours in the middle or upper part of the rectum, a low anterior resection (LAR) is indicated. With this surgical method the anal sphincter remain will be preserved.

In the Swedish Rectal Cancer trial patients included from 1987 until 1990 had a significant lower local recurrence rate when treated with preoperative, short course, 5 x 5 Gy radiotherapy (27% in surgery only compared with 11% for patients treated with preoperative radiotherapy followed by immediate surgery).²² In the 1990's the Dutch Colorectal Cancer Group designed a trial using standardised TME surgery; the Dutch TME trial.²³ After the Swedish Rectal Cancer trial had demonstrated the beneficial effect of radiotherapy, the remaining question was whether radiotherapy was still beneficial in combination with standardised, good, TME surgery.^{22,24} The results of the Dutch TME trial demonstrated improved local control, with an even lower local recurrence rate for patients treated with preoperative radiotherapy. For patients with a negative resection margin, the effect of radiotherapy was irrespective of the distance from the anal verge and led to an improved cancer-specific survival, which was nullified by an increase in other causes of death, resulting in an equal overall survival. Nevertheless, preoperative short term radiotherapy significantly improved ten year survival in patients with a negative circumferential margin and TNM stage III.²⁵ Since the introduction of preoperative radiotherapy, the interval between short course radiotherapy has been discussed as this could result in differences in outcome. *Chapter 6* addresses the impact of the interval between preoperative short course radiotherapy and surgery on outcome of rectal cancer patients in two time periods.

Besides radiotherapy, also chemoradiation (45-50 Gy of radiotherapy combined with chemotherapy) is often used as preoperative treatment for locally advanced rectal cancer patients. In contrast to short course radiotherapy followed by immediate surgery, chemoradiation

followed by surgery in six to eight weeks does induce downstaging.^{26,27} For locally advanced rectal cancer and patients with more than four lymph nodes expected to be positive the Dutch guidelines recommends chemoradiation.¹²

Since the use of adjuvant chemotherapy in stage III colon cancer patients is recommended, the National Institute of Health (NIH) recommend that adjuvant chemotherapy should be used in rectal cancer patients as well, based upon the results of a few small trials in the USA.²⁸⁻³⁰ These conclusions have been criticised since the trials are well underpowered, patients were included before the TME technique was introduced, and radiotherapy, if given, was delivered postoperatively. Nowadays, preoperative radiotherapy or preoperative chemoradiation, depending on the mesorectal fascia involvement, is considered to be the gold standard.³¹ Although the effect of adjuvant chemotherapy could be similar in rectal as in colon cancer, there is little direct evidence to support this since the introduction of preoperative treatment. A recent Cochrane review has shown that rectal cancer patient treated without preoperative treatment do benefit from adjuvant chemotherapy, while for rectal cancer patients treated with preoperative treatment, this remains unknown.³²

PART II INTERNATIONAL COMPARISONS IN COLORECTAL CANCER TREATMENT AND SURVIVAL

Quality of health care has a high priority on the political agenda of most European countries. Surgical quality assurance program, also called surgical audit, is a quality instrument that collects detailed clinical data from different health care providers, which can be adjusted for baseline risk and subsequently fed back to individual hospitals or surgeons. Major improvements have been achieved with national audits.³³⁻³⁵ However, although all the national audits achieved excellent results, differences in treatment and outcome remain between European countries.³⁶ This suggests that further improvement is possible. To reduce the differences between the countries by identifying and spreading 'best practice', the European CanCer Organisation (ECCO) initiated an international, multidisciplinary, outcome-based quality improvement program: European Registration of Cancer Care (EURECCA). The goal is to create a multidisciplinary European registration structure for patient, tumour, and treatment characteristics linked to outcome registration.³⁷ The EURECCA project makes use of existing national audit registrations and started with colorectal cancer, at this moment European audit projects of other solid tumour types, such as breast cancer, gastric cancer, oesophageal cancer, and pancreatic cancer, are developed. *Chapter 7* describes the 'core dataset' (variables that are included by at least 8 of the 9 audit registries) of EURECCA colorectal. The cumulative experience of EURECCA's participants could be used to identify a 'core dataset' that covers all important aspects needed for high quality auditing and at the same time lacking needless data items that only consumes administrative effort. After defining the 'core dataset', the next

step is to compare treatment and survival between countries. The first EURECCA analyses are described in *Chapter 8*, which is a comparison of the use of preoperative treatment for rectal cancer patients between Norway, Sweden, Denmark, Belgium and the Netherlands. Currently, randomised controlled trials (RCT's), systematic reviews, and meta-analyses are seen as the highest level of evidence. Unfortunately, randomised controlled trials are costly, time consuming, subgroups may be underrepresented in trials, and certain research questions remain unanswered by randomised clinical trials. A relatively new analysis in medicine is an instrumental variable analysis. In randomised controlled trials the type of treatment is assigned randomly, which makes sure that both treatment groups are comparable. Therefore, the results of both treatment arms can be compared in a randomised controlled trial. Since in observational studies the type of treatment is not randomly assigned to the patients, but probably based on patients' characteristics, treatment results cannot be compared without confounding by indication in most cases. An instrumental variable is a factor which is not related to both patients' characteristics and prognosis, and therefore can function as a pseudo randomisation.^{38,39} The prognosis of different treatment strategies can then be compared. In *Chapter 9* a new preoperative treatment for rectal cancer used in a specialised clinic in Canada has been compared with standard of care in a specialised clinic in the Netherlands. This study should be hypothesis generating to lead to a randomised controlled trial comparing the treatment strategies.

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