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Variation in diagnosis, treatment and outcome in colon and rectal cancer

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Summary

In the Netherlands, colorectal cancer is a major health problem. It is the third most common cancer among males and the second most common cancer among females. In 2008, more than 12,000 patients were diagnosed with colorectal cancer and almost 5,000 patients died of the disease. Survival of both patients with colon cancer and patients with rectal cancer has increased over time, among others due to changes in treatment. Further improvement of outcome could be achieved by optimizing the care. In the Netherlands, evidence-based multidisciplinary guidelines for the diagnosis and treatment of colorectal cancer patients provide recommendations about optimal care. Adherence to these guidelines should, therefore, be high. Several factors may lead to variation between regions and hospitals in guidelines adherence. The aim of this thesis was to identify factors which influence quality of care and outcome of patients with colorectal cancer by exploring the variations in diagnosis, treatment and outcome among patients with colon and rectal cancer in the Netherlands. Data from the population-based Netherlands Cancer Registry were used for the analyses.

In **chapter 2** trends in treatment and survival of colorectal cancer patients were reported and locoregional recurrences among patients with colon cancer were analysed. **Chapter 2.1** describes the changes in treatment and outcome of patients with rectal cancer in the Netherlands in the period 1989-2006. Similar to the shift from postoperative to preoperative radiotherapy in the guidelines, we observed an increase in the proportion of patients with stages II and III disease receiving preoperative radiotherapy and a decrease in the proportion of patients receiving postoperative radiotherapy. Neoadjuvant chemoradiation was introduced in the Netherlands in 2005, although few patients with stage II and III disease already received this therapy in the period 1994-1998. The proportion of patients treated with neoadjuvant chemoradiation gradually increased over time. Both the use of adjuvant chemotherapy for patients with stage III disease and the administration of chemotherapy for patients with stage IV disease increased, especially among younger patients. Five-year relative survival rates increased from 53% in the period 1989-1993 to 60% in the period 2004-2006 among males and from 53% to 59% among females. Survival improvement was most pronounced in patients with stage III disease. Changes in treatment strategies have played an important role in the improved survival.

Chapter 2.2 gives an overview of trends in the treatment and outcome of patients with colon cancer in the Netherlands during the period 1989-2006. A marked increase in the administration of adjuvant chemotherapy among patients with stage III disease and to a lesser extent among patients with stage II disease, especially among younger patients,

was observed. The use of chemotherapy among patients with stage IV disease also increased. Five-year relative survival rates increased from 52% in the period 1989-1993 to 58% in the period 2004-2006 among males and from 55% to 58% among females. Survival improvement was most pronounced among patients with stage III disease. This survival improvement might be due to the increased administration of adjuvant chemotherapy.

Due to the changes in treatment in rectal cancer, there is an increased interest for locoregional recurrences in rectal cancer. Despite comparable locoregional recurrence rates in colon cancer, only a few studies on locoregional recurrences among patients with colon cancer have been published. Therefore, **chapter 2.3** aimed to describe the incidence of locoregional recurrences in a large cohort of patients with colon cancer, to identify prognostic factors and to define risk groups for locoregional recurrences. The five-year locoregional recurrence rate was 6.4% among colon cancer patients diagnosed in the period 2000-2003. The risk of developing a locoregional recurrence was highest at 0.5 to 1 year after surgery. Prognostic factors were left-sided tumours, T3-T4 tumours, positive lymph nodes and not receiving adjuvant chemotherapy. Based on these prognostic factors a Locoregional Recurrence Risk Score (LRRS) was calculated and four risk groups were defined. Five-year locoregional recurrence rate was 2.5% for the group with the lowest risk and 25.1% for the group with the highest risk.

Choice of treatment and accurate estimation of prognosis is determined by adequate staging. Therefore, a sufficient number of lymph nodes has to be evaluated. There is no widely accepted standard of the number of lymph nodes that should be evaluated. The guidelines of the International Union Against Cancer advise the evaluation of at least 12 lymph nodes, whereas the Dutch guidelines for colon and rectal cancer recommend a minimum of 10 evaluated lymph nodes. In **chapter 3** the quality of the lymph node evaluation among patient with rectal and colon cancer diagnosed in the period 2000-2006 was analysed. The median number of evaluated lymph nodes was 7 among rectal cancer patients (**chapter 3.1**) and 8 among colon cancer patients (**chapter 3.2**). Although an improvement in the number of evaluated lymph nodes was demonstrated over time, both studies demonstrated that in the total study period an adequate lymph node evaluation was performed in less than 50% of the patients. As a consequence, positive lymph nodes might be missed, since the proportion of patients with positive lymph nodes increased with increasing number of evaluated lymph nodes. The number of evaluated lymph nodes was affected by gender, age, depth of invasion, nodal involvement, tumour localisation and type of resection. Rectal cancer patients who received preoperative radiotherapy were less likely to have an adequate lymph node evaluation.

For both rectal and colon cancer, we found that patients whose lymph nodes were evaluated in an academic pathology laboratory were more likely to have an adequate lymph node evaluation. Large variations between individual pathology laboratories were revealed, with a median number of evaluated lymph nodes ranging from 4 to 15 lymph nodes between pathology laboratories in colon cancer and from 4 to 11 lymph nodes in rectal cancer. After adjustment for the variation on the pathology laboratory level, variation on the hospital level remained both among patients with colon cancer and among patients with rectal cancer, suggesting that both surgeons and pathologists play a role in an adequate lymph node evaluation.

The risk of death increased with decreasing number of evaluated lymph nodes, both among patients with positive as well as with negative lymph nodes. In both groups, patients with less than 10 evaluated lymph nodes had a significant higher risk of death compared to patients with 10-12 evaluated lymph nodes. Furthermore, the role of the lymph node ratio (the number of positive lymph nodes divided by the total number of evaluated lymph nodes) in survival was investigated in both studies. The risk of death increased with increasing lymph node ratio and it was demonstrated that the lymph node ratio was an important prognostic factor for colon and rectal cancer patients with stage III disease.

The studies in **chapter 4** describe the variation in adherence to the guidelines and outcome by regions and characteristics of individual hospitals in the period 2001-2006 in the Netherlands. In **chapter 4.1**, guidelines adherence was determined for preoperative radiotherapy and chemoradiation among rectal cancer patients. Large variation between individual hospitals in the use of preoperative radiotherapy was revealed. The proportion of patients who received preoperative radiotherapy ranged from 100% to less than 50% per hospital. Males, younger patients, tumours with a deeper invasion and with nodal involvement were more likely to receive preoperative radiotherapy. Patients diagnosed in teaching or university hospitals had a lower chance and patients diagnosed in high-volume hospitals had a higher probability of receiving preoperative radiotherapy. There was variation between CCC-regions in the use of preoperative radiotherapy and in the administration of chemoradiation. Postoperative mortality was lower among females, younger patients, patients who underwent an abdominoperineal resection and patients diagnosed in a high-volume hospital. Overall, there were no differences between hospital type and volume in survival. Patients with T1 rectal tumours diagnosed in high-volume hospitals had a better survival than patients diagnosed in low-volume hospitals.

Chapter 4.2 analysed guidelines adherence for lymph node evaluation and adjuvant chemotherapy for colon cancer patients. Large variations between individual hospitals in

adequate lymph node evaluation was demonstrated, with the proportion of patients of whom 10 or more lymph nodes were evaluated ranging from 70% to less than 20% per hospital. Colon cancer patients diagnosed in university hospitals had a higher chance compared to patients diagnosed in non-teaching hospitals and patients diagnosed in high-volume hospitals had a lower chance of having 10 or more lymph nodes evaluated compared to patients diagnosed in low-volume hospitals. Furthermore, large differences were found in the administration of adjuvant chemotherapy. The proportion of patients with stage III disease who received adjuvant chemotherapy varied from less than 50% to more than 90% between individual hospitals. Males, younger patients and patients diagnosed in more recent years were more likely to receive adjuvant chemotherapy. The chance of receiving adjuvant chemotherapy was lower among colon cancer patients diagnosed in teaching hospitals and university hospitals. Patients diagnosed in university hospitals and high-volume hospitals had a better survival than patients diagnosed in non-teaching hospitals and low-volume hospitals, respectively.

In conclusion, for improvement of quality of care and outcome, focussing on only one factor is insufficient. Considerable variation in guidelines adherence among patients with colon and rectal cancer in the Netherlands exists. Major differences were noted between hospitals and pathology laboratories in the accuracy of lymph node staging and between hospitals and CCC-regions in applied treatment strategies. To optimize quality of care, proper comparison between hospitals and probably outcome, more attention should be paid in reducing variation in staging and treatment. Part of the observed variation is associated with type and volume of hospitals and pathology laboratories. However, the large differences between individual institutions suggested that these characteristics do not account for all variation. To obtain targets for improvements, further research is required to identify other factors causing the variation between individual hospitals, e.g. by monitoring the whole care process. This may provide medical specialists regular feedback about their performances and will probably give more insight into aspects that could be improved.