Summary

Colorectal cancer is the second leading cause of cancer related death behind lung cancer. Large improvements have been made in the treatment of colon cancer in the past twenty years with more effective but also more radical treatments becoming available. With the increasing life expectancy in the Western world, colon cancer is increasingly becoming a disease of the elderly with over 50% of the diagnoses occurring in patients over 70 years of age.
This thesis describes a cohort of patients diagnosed with colorectal cancer between 2002 and 2008 in the Zaans Medisch Centum, a teaching hospital in the vicinity of Amsterdam.

The first part of the thesis deals with patient related factors that influence prognosis and choice of treatment. The population included in randomised controlled trials investigating current treatment modalities does not correspond with the one seen in daily practice. The observational studies and sub-analyses of patients over 70 included in these RCT's do show a positive effect of surgery and adjuvant chemotherapy on survival. However, whether this means that those who choose conservative management are being under-treated remains the subject of further study.

Chapter one tries to quantify the influence of age and comorbidity on the outcomes of colorectal cancer. This retrospective cohort study shows that age and comorbidity influence survival despite the diagnosis of colon cancer. Furthermore, the percentage of patients dying from tumour related causes remains constant with increasing age/comorbidity while the number of patients dying from competing causes increases. This supports a choice for less intensive treatment for elderly frail patients as their expected survival benefit is reduced due to a reduced life expectancy.

Chapters two and three examine two subgroups of patients, the oldest of old, and the patients dying within 30 days of surgery. Increasing age and the extent of disease were primarily associated with perioperative mortality with almost half of the fatalities occurring after a palliative resection. Most frequent causes of death were abdominal sepsis and cardiovascular events. Of the octo- and nonagenarians 43% was still alive 5 years after the diagnosis. Of the patients dying within 5 years 32% died from non-tumour related causes, 22% due to complications of tumour treatment, and 46% as a result of the colorectal cancer. Clinicians should carefully weigh individual risk and benefit of treatment in frail elderly patients.

The second part of the thesis describes tumour and treatment related factors that are associated with risk of recurrence in the curative treatment of colorectal cancer.
Chapter four describes the association between dose reduction of adjuvant chemotherapy and risk of recurrence in patients with colon cancer. We found that a dose reduction of 5FU and oxaliplatin was associated with reduced recurrence free survival. Interestingly, reduction of just the oxaliplatin was not. Our study also adds to previous evidence that patients with high-risk stage 2 colon cancer should also be considered for adjuvant therapy.
Chapter five zooms in on the clinical importance of venous invasion in lymph node negative colon cancer and the risk of recurrence using a caldesmon stain to improve sensitivity for venous invasion. Our study strengthens previous evidence that venous invasion is an additional risk factor for recurrence comparable to the more accepted T4 stage of the tumour.
Chapters six and seven deal with neoadjuvant treatment for rectal cancer. Chapter six describes the outcomes of neoadjuvant radiotherapy. Survival was comparable in patients undergoing radiotherapy with a short or a long waiting period as well as patients not undergoing any neoadjuvant therapy. Patients not receiving radiotherapy had a lower disease stage, thus the hypothesis is that their expected survival benefit was offset by radiotherapy in the other groups. Interestingly, radiotherapy with a longer waiting period suggested a trend towards a lower disease stage in the resection specimen.

Chapter seven deals with the accuracy of MR in staging of rectal cancer. Patients undergoing surgery for rectal cancer with a pre-operative staging MR were included. We found a lower accuracy of the staging MRI for T-stage when compared to the resection specimen than reported in previous literature (61% vs. 75%). Thus, the accuracy of MR leaves much to be desired. Clinicians should be vigilant for undertreatment based on the assurances of a low TN-stage on the MR. Radiotherapy led to significant down staging in the majority of patients. However, still 13% of patients showed a higher disease stage in the resection specimen.

In conclusion, this thesis is a major argument to include more patients over 70 years of age in prospective treatment trials for colorectal cancer. The elderly frail patient takes up an increasing part of daily practice with a lack of prospective randomised research in this population. A less intensive treatment of this patient group can be considered based on increased risk of death from competing causes. However, overall survival of octogenarians undergoing curative surgery is reasonable, thus refraining from surgery should not be considered in general. Adjuvant chemotherapy can be omitted more easily as this deals with secondary prevention. Still, of the octo- and nonagenarians in our cohort, 22% of 5-year mortality can be lead back to a complication of tumour treatment. Staging of colorectal cancer and determining the appropriate treatment remains difficult despite major advances in imaging and risk stratification. High risk stage 2 colon cancer comes with recurrence risks similar to stage 3 disease and provides an indication for adjuvant chemotherapy. Especially the role of venous invasion as a risk of recurrence might be essential, sensitivity for this finding can be increased by using an elastic stain (which highlights the smooth muscle cells in the vascular wall). Neoadjuvant treatment regimens and staging through MRI remain subjects of debate. Clinicians should be aware of the limited accuracy of staging through MR. More sophisticated MR equipment may alleviate this problem in the future.