Improving colorectal cancer care: treatment and outcomes of patients with colorectal cancer

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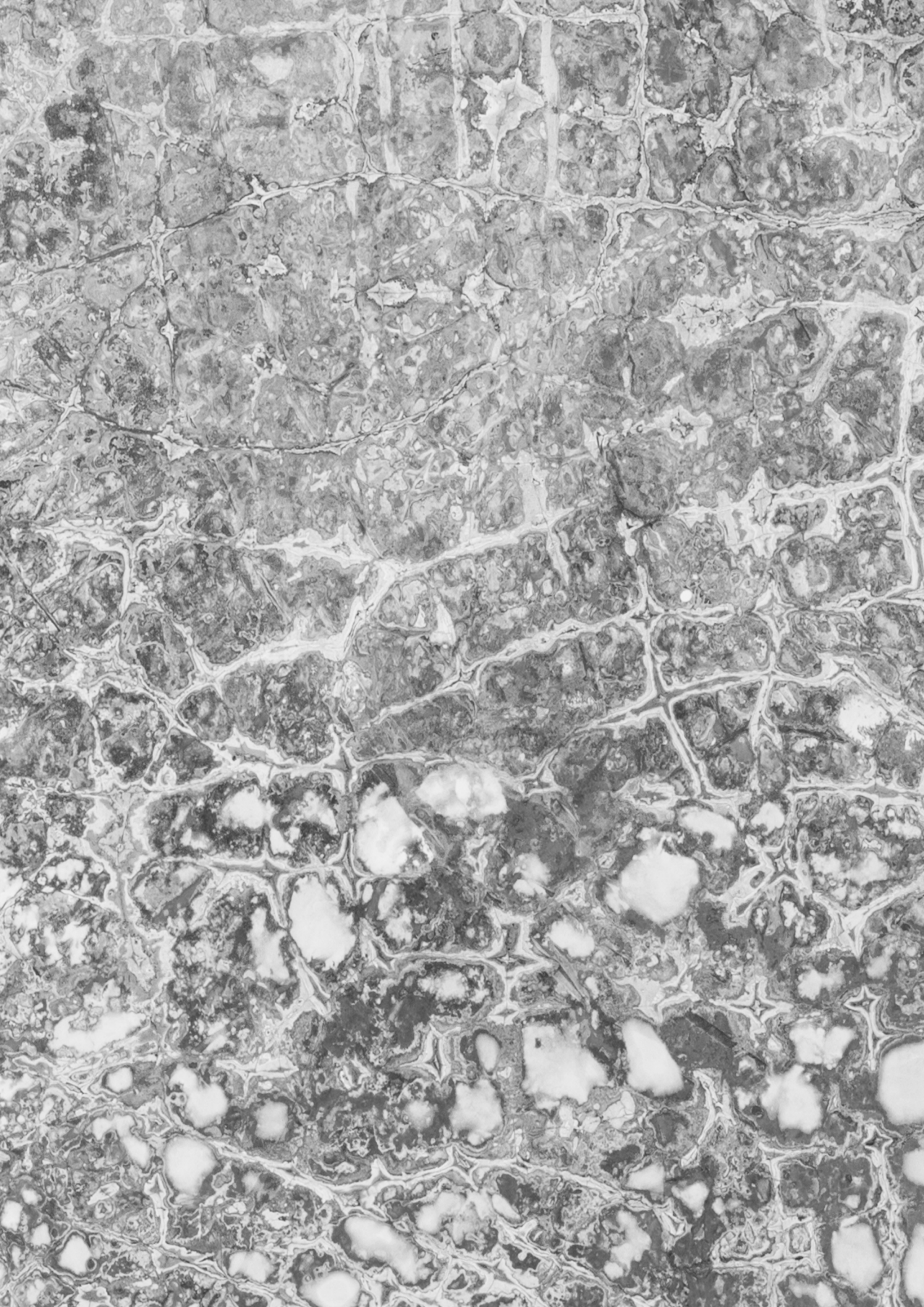

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Summary, general discussion and future perspectives

SUMMARY

PART I: EVALUATING TREATMENT OF PATIENTS WITH STAGE I-III COLORECTAL CANCER

In **Chapter 2**, the most frequent complications after surgery for stage I-III colon cancer were identified, and we assessed the association between these complications and survival and recurrences. Thirty-day mortality after surgery for colon or rectal cancer underestimates one-year mortality, with stage III disease, comorbidity, and postoperative surgical complications as risk factors for excess mortality in the first year after surgery for colon cancer.[1,2]

Patients who suffered from complications had decreased one-year and five-year survival, whereas an increasing number of complications had no additional impact. Anastomotic leakage, excessive blood loss, (abdominal) sepsis, delirium, and the occurrence of an abscess were associated with long-term survival, and/or recurrences. These findings underline the prolonged impact of complications on survival and recurrences, not only one year after surgery, but also on long-term outcomes.

Chapter 3 shows a decrease in thirty-day and one-year mortality over time in patients ≥75 years with stage I-III colon cancer, though the absolute decrease was small. Especially in older patients, 30-day and one-year mortality are still high for both colon and rectal cancer. This implies that the focus should be on the first postoperative year in older patients with colorectal cancer to further improve outcomes.

Chapter 4 described the outcomes of the PROCTOR-SCRIPT trial, investigating the effectiveness of adjuvant chemotherapy compared with observation after (chemo) radiotherapy and total mesorectal excision (TME) among patients with (y)pTNM stage II or III rectal cancer. Adjuvant chemotherapy might prevent the occurrence of distant metastases, though the use of adjuvant chemotherapy for patients with rectal cancer treated with preoperative (chemo)radiotherapy is extensively debated.[3] After a median follow-up of five years, we could not demonstrate a significant benefit of adjuvant chemotherapy with fluoropyrimidine monotherapy in terms of overall survival, disease-free survival, and recurrences. However, the intended inclusion was not reached due to poor patient accrual. The lack of statistical power may have prevented the detection of statistically significant differences in outcomes between observation and adjuvant chemotherapy.

Though four out of five European randomised controlled trials comparing adjuvant chemotherapy with observation after preoperative (chemo)radiotherapy and surgery in

patients with rectal cancer showed no benefit of adjuvant chemotherapy, and one trial with the majority of patients not having preoperative treatment showing a borderline significant improvement in overall survival only, none of these trials have individually ended the discussion about the role of adjuvant chemotherapy.[4-8] Therefore, in **Chapter 5**, we investigated the effectiveness of fluorouracil-based adjuvant chemotherapy after preoperative (chemo)radiotherapy and TME in a meta-analysis including individual patient data from four of the above mentioned trials. In patients with (y)pTNM stage II or III rectal cancer, who had a R0 resection after low anterior resection or abdominoperineal resection, and a tumour located within 15 cm of the anal verge, fluorouracil-based adjuvant chemotherapy did not improve overall survival, disease-free survival, and distant recurrences compared with observation. However, subgroup analyses suggest that patients with a tumour between 10 cm and 15 cm from the anal verge might benefit from adjuvant chemotherapy in terms of disease-free survival and distant recurrences.

PART II: INTERNATIONAL COMPARISONS ON TREATMENT AND OUTCOMES OF PATIENTS WITH COLORECTAL CANCER

In the second part of this thesis we compared patterns of care and survival outcomes of patients with colorectal cancer in Europe using data from countries participating in the EURECCA project.

In **Chapter 6**, we reported on quality assurance in the management of colorectal cancer and elaborated on the aims of the EURECCA project. There is considerable variation in survival outcomes between European countries.[9] Quality assurance can be defined as all those planned and systematic actions necessary to achieve minimal requirements of good cancer care. Quality assurance in the management of colorectal cancer could eventually lead to improved cancer care and less variation. The European Registration of Cancer Care, EURECCA, has been initiated to reduce differences between European countries, and collects patient and treatment data of national audit registries or national cancer registries to be analysed in order to identify where further improvement is needed.

Chapter 7 provided more insight into the use of adjuvant chemotherapy and into relative survival outcomes among patients with stage II colon cancer. Population-based national cohort data from the Netherlands, Denmark, Sweden, England, Ireland, and Belgium were obtained, as well as single-centre data from Lithuania. An interesting finding was a large variation in the proportion of patients with stage II colon cancer receiving adjuvant chemotherapy, though we observed no clear linear pattern between adjuvant chemotherapy and adjusted relative survival. Sweden and Belgium both had a better adjusted relative survival compared with the Netherlands. Although we found no clear linear pattern between adjuvant chemotherapy and relative survival, differences in the

proportion of adjuvant treatment might still partly, but not solely, contribute to these differences in survival.

In **Chapter 8**, we evaluated preoperative and postoperative treatment strategies and relative survival of patients with stage I-III rectal cancer. Neighbouring countries were compared, and showed more preoperative radiotherapy and less preoperative chemoradiation in the Netherlands compared with Belgium, in Sweden compared with Denmark, and in England compared with Ireland. Adjuvant chemotherapy was more often given in Belgium compared with the Netherlands, in Denmark compared with Sweden, and in England compared with Ireland. We observed no differences in relative survival between neighbouring countries. The variation in treatment strategies reflects the differences in national guidelines and underlines the lack of international consensus on optimal treatment strategies for stage I-III rectal cancer.

Chapter 9 described treatment strategies and overall survival of patients with incurable metastatic colorectal cancer. Treatment strategies varied between the Netherlands and Norway, with especially more surgery and less radiotherapy in Norway. Adjusted overall survival was better in Norway for all patients and for patients <75 years, but survival was worse for patients ≥75 years. Differences in treatment strategies probably contribute to differences in survival outcomes, while the effect of specific treatments may differ between younger and older patients.

Future perspectives

In the era of multidisciplinary management and shared-decision making, analyses from a unified European population-based dataset, of course combined with results from trials as well as the search for additional biomarkers will be the challenge for the future to better select subgroups of patients for treatment. More importantly, intensified neoadjuvant (chemo)radiotherapy addresses the need to monitor patients carefully with intense radiological follow-up to only intervene in case of tumour recurrence. In some patients, this can even avoid surgery in case of long-lasting complete response.

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GENERAL DISCUSSION

Survival of patients with colorectal cancer improved markedly over the past decades, as a result of advances in screening, staging procedures, treatment, and surveillance.[1-5] However, still about 20% of patients with colorectal cancer develop metachronous metastases and 20% of all patients with colorectal cancer have metastatic disease at diagnosis.[6,7] Several treatment modalities, such as total mesorectal excision (TME) and preoperative (chemo)radiotherapy for rectal cancer, as well as adjuvant chemotherapy for stage III colon cancer, have been studied extensively and showed to improve cancer-related outcomes.[3,4,8-10] On the contrary, the effectiveness of other treatment modalities including adjuvant chemotherapy for rectal cancer and for stage II colon cancer, and surgery of the primary tumour in incurable metastatic colorectal cancer are still subject of debate.[11-13] Moreover, there is considerable short-term and long-term morbidity after (chemo)radiotherapy or surgery which should be taken into account. Further defining optimal treatment strategies is therefore of great importance. This thesis focused on improving evidence for treatment modalities that are currently subject of debate for patients with colorectal cancer. This was done using data from randomised controlled trials as well as cancer registry data.

Part I of this thesis focused on treatment, its complications, and outcomes of patients with stage I-III colorectal cancer by using trial data as well as cancer registry data.

In part II, patterns of care and survival across European countries were evaluated for patients with stage II colon cancer, stage I-III rectal cancer, and incurable metastatic colorectal cancer by analysing data from national cancer registries.

PART I: EVALUATING TREATMENT OF PATIENTS WITH STAGE I-III COLORECTAL CANCER

Perioperative care

Thirty-day mortality is widely accepted as a benchmark measure of outcome to determine risks and benefits of surgical procedures. However, thirty-day mortality underestimates the risk of dying in the first postoperative year after curative surgery for stage I-III colorectal cancer with excess mortality in the first year up to 30%. Comorbidity, stage III tumours, emergency surgery, and postoperative surgical complications have been identified as risk factors for excess mortality in the first year.[14] Moreover, a previous study suggested that major postoperative complications have a negative impact on long-term survival as well.[15] Interestingly, age-related differences in colorectal cancer survival are mainly due to differences in mortality in the first postoperative year; patients ≥75 years who survived the first year had the same cancer-related survival compared to younger patients.[16]

As complications are shown to be a risk factor for one-year excess mortality, we identified the most frequent complications after surgery for stage I-III colon cancer and we studied the association between complications and short-term survival, long-term survival, and recurrences in **Chapter 2**. We found that over 40% of patients had one or more complications. Complications were associated with decreased short-term overall survival and long-term overall survival, even under the condition of surviving the first postoperative year. An increasing number of complications had no additional impact on survival. Ileus, anastomotic leakage, pneumonia, excessive blood loss, electrolyte disorders, cardiac arrhythmia, delirium, abscess, urinary tract infection, and (abdominal) sepsis were the most frequent complications. Moreover, anastomotic leakage, electrolyte disorders, and abscess were risk factors for recurrence within five years after surgery. From this study, it can be concluded that complications not only have an effect on short-term survival, but also on long-term overall survival. Some specific complications are also associated with recurrences, though the exact mechanism has not been elucidated. Focusing on reducing complication rates could eventually lead to better outcomes.

Monitoring time trends in cancer care could be helpful in cancer control. For example, it could give insight in the relation between cancer mortality and changes in exposure to risk factors, or to changes in cancer care. In **Chapter 3**, we assessed time trends in 30-day and one-year mortality in patients with stage I-III colorectal cancer. It was found that that there was a 25% relative decrease in 30-day and 19% relative decrease in one-year mortality in patients ≥75 years with stage I-III colon cancer, while the absolute decrease was 2.1% and 3.5% in 30-day and one year mortality respectively. For younger patients, we observed low 30-day and one-year mortality rates, implying that a further reduction in mortality would be difficult to achieve. However, 30-day and one-year mortality rates are still high for older patients with stage I-III colorectal cancer. Focusing on older patients with colorectal cancer in order to select the right patients for the right treatment could further improve outcomes of colorectal cancer care.

Adjuvant chemotherapy for patients with rectal cancer

Adjuvant chemotherapy aims to prevent the occurrence of distant metastases by eliminating circulating tumour cells and micrometastases. The use of adjuvant chemotherapy after preoperative (chemo)radiotherapy and TME for patients with rectal cancer has been extensively debated as a result of inconclusive evidence. This is also shown in large differences in various treatment guidelines. The Dutch guideline for example, states that there is no indication for adjuvant chemotherapy for patients with rectal cancer.[17] On the contrary, the US NCCN guideline recommends adjuvant chemotherapy for all patients with stage II or III rectal cancer after preoperative chemoradiotherapy and surgery, although it is recognised that conclusive data are lacking.[18]

Advice to give adjuvant chemotherapy to patients with stage II or III rectal cancer was based for a long time on extrapolation of results from randomised clinical trials on adjuvant chemotherapy for colon cancer, as well as on studies showing a benefit of adjuvant 5-fluorouracil (FU) based chemotherapy after radical surgery for rectal cancer before the era of standardised TME and without the use of preoperative (chemo) radiotherapy.[10,19]

In **Chapter 4**, we reported the results of the PROCTOR-SCRIPT study, a randomised controlled phase III trial. In this trial, patients aged ≥18 years with a rectal adenocarcinoma, who had preoperative (chemo)radiotherapy and TME, (y)pTNM stage II or III, and R0 (PROCTOR and SCRIPT) or R1 (SCRIPT) resection, were randomised between observation and adjuvant chemotherapy with 5-FU/LV (PROCTOR) or capecitabine (SCRIPT). After almost thirteen years, the trial was closed due to poor patient accrual without reaching the intended inclusion of 840 patients. In total, 470 patients were included, of whom 439 were eligible for analyses. After a median follow-up of five years, we could not demonstrate a significant benefit in overall survival, disease-free survival, and recurrences for adjuvant chemotherapy, though the lack of statistical power may have prevented detection of small differences.

Three other trials, the I-CNR-RT trial, the EORTC 22921 trial, and the CHRONICLE trial also compared adjuvant chemotherapy with observation after preoperative (chemo) radiotherapy and surgery. These studies all did not demonstrate a benefit of adjuvant chemotherapy.[20-22] On the contrary, the QUASAR trial found a small benefit in survival and recurrence for patients with rectal cancer, but only 21% of these patients had preoperative radiotherapy.[23]

To get more information about the role of adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer, we did a meta-analysis of individual patient data. The results were described in **Chapter 5**. Data from the PROCTOR-SCRIPT trial, the I-CNR-RT trial, the EORTC 22921 trial, and the CHRONICLE trial could be obtained. Patients with (y)pTNM stage II or III disease, who had a R0 resection after a low anterior resection or abdominoperineal resection, and a tumour located no more than 15cm from the anal verge, were included. Our findings showed no benefit of adjuvant chemotherapy on overall survival, disease-free survival, and distant recurrences. Although there are several limitations of the individual studies in our meta-analysis, including poor compliance to adjuvant chemotherapy, two studies without sufficient power, and a long accrual period with changes in practice over time as for example TME and type of chemotherapy, we think this meta-analysis provides the best available evidence comparing adjuvant chemotherapy with observation after preoperative (chemo)radiotherapy for patients with rectal cancer and it is unlikely

that there will be new trials investigating this subject. Therefore, we think there is no evidence for the use of adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery.

A uniform definition of the rectum is important for optimal treatment of upper rectal tumours and distal sigmoid tumours. However, different definitions to distinguish the rectum from the sigmoid have been used in studies and guidelines. The most reported pragmatic definition of the rectum is a tumour ≤15cm from the anal verge, though the most reported ideal definition of the rectum on imaging is the sigmoid take-off.[24] In the meta-analysis in **Chapter 5**, we did a subgroup analysis comparing the effect of adjuvant chemotherapy stratified by distance of the tumour from the anal verge. We found that tumours located 10-15cm from the anal verge had a benefit with adjuvant chemotherapy regarding disease-free survival and distant recurrences. Because we detected no significant interaction between distance from the anal verge and treatment group, these results are not definitive. Nevertheless, these results raise the question if tumours located 10-15cm from the anal verge should be considered as colon tumours, though further research is warranted for definitive conclusions.

Compliance to adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery is suboptimal. In the EORTC 22921 trial 43% completed all cycles of chemotherapy, while this was 48% in the CHRONICLE trial, and 55% of patients in the I-CNR-RT trial received three to six courses of chemotherapy.[20-22] In the PROCTOR-SCRIPT trial presented in **Chapter 4**, compliance to adjuvant chemotherapy was 73.6%, which may be higher compared to the EORTC 22921 trial and I-CNR-RT trial because patients were randomised postoperatively. Compliance may be higher than in the CHRONICLE trial because in the PROCTOR-SCRIPT trial 5-FU monotherapy was used, while combination chemotherapy was used in the CHRONICLE trial.

In conclusion, based on the results reported in this thesis, there is no evidence to support the use of adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery in patients with stage II or III rectal cancer. It is suggested that patients with a tumour located 10-15cm from the anal verge might benefit from adjuvant chemotherapy, though these results are not definitive.

PART II: INTERNATIONAL COMPARISONS ON TREATMENT AND OUTCOMES OF PATIENTS WITH COLORECTAL CANCER

Population-based observational studies

Evidence-based medicine is the use of best available research to guide clinical decision making in patients and is intended to complement clinical judgment in individual patients.

Randomised clinical trials are considered to be the gold standard to evaluate the effect of cancer treatment. However, in general, trials have strict inclusion and exclusion criteria and are therefore limited in predicting real-world outcomes.[25] On the contrary, evaluating treatment effectiveness in observational studies is disputable. Observed outcomes may be the result of differences among patients being given either one or the other treatment. Moreover, there could be residual confounding despite attempts to adjust for identified differences between two treatment groups.[26]

There are several situations in which randomised clinical trials are not feasible, and attempts have been made in order to use observational data to evaluate treatment effectiveness. A tool that can be used to estimate treatment effects and to reduce residual confounding in comparative effectiveness research is instrumental variable analysis, where an instrumental variable is defined as a factor that is related to treatment, but neither directly nor indirectly related to the study outcome.[27,28]

In **Chapter 6**, we elaborated on the EURECCA (European Registration of Cancer Care) project, which is a quality assurance programme that aims to create a multidisciplinary European registration structure for patient, tumour, and treatment characteristics in relation to outcomes in order to improve the quality of cancer care and to reduce variation in outcomes. Quality assurance programmes aim to optimise the quality of care by determining standards and assuring that these standards are met. Although several aspects of cancer treatment have been studied extensively and shown to improve outcomes, there is still considerable variation in outcomes between European countries that cannot be easily explained.[1]

To get insight into treatment strategies and outcomes between European countries for patients with stage II colon cancer, stage I-III rectal cancer, and incurable stage IV colorectal cancer (**Chapter 7, 8, 9**), we collected data of national, population-based cancer registries of countries willing to participate in the EURECCA project. Currently, over twenty European countries have a national cancer registry with coverage of the entire population. Other European countries have no complete coverage, or lack the existence of a national cancer registry. In total, cancer registries in Europe cover about 60% of the European population, though coverage increases over time.[29]

Several common variables were collected from the national cancer registries, which resulted in valuable insights into treatment strategies and outcomes. However, there are also challenges left when it comes to data comparison between European countries. As a result of privacy legislation, it is impossible for some countries to establish a national cancer registry, or it is not allowed to share data to participate in a European project as EURECCA. Moreover, not all national cancer registries collect the same data variables

and do not collect data in the same manner. Differences in access to health care and differences in health care systems imply difficulties in data comparison.

Adjuvant chemotherapy for patients with stage II colon cancer

As already described in the introduction of this thesis, there is ongoing debate about the benefit of adjuvant chemotherapy for patients with stage II colon cancer since previous studies did not demonstrate an improvement in overall survival, but only a better disease-free survival.[12] Clinicopathologic features that are associated with a worse prognosis in patients with stage II colon cancer include a pT4 stage, a poorly differentiated tumour, lymphovascular or perineural invasion, bowel obstruction or perforation, inadequate lymph node sampling (<12), and a high preoperative carcinoembryonic antigen.[30] In Europe, it is advised to consider adjuvant chemotherapy in patients who present with at least one of the high-risk features.[31]

Within the EURECCA project, we were able to obtain data from seven European countries to compare the use of adjuvant chemotherapy and to compare relative survival. The results of this international comparison are shown in **Chapter 7**. Common data variables included information on gender, age, year of incidence, TNM stage, tumour grade, and the use of adjuvant chemotherapy. Information on pathological TNM substage IIA or IIB was not available in England. Moreover, information on tumour grade was not available in Denmark and unknown in 3.5% - 12.0% in the other countries.

In this study, we observed large differences in the use of adjuvant chemotherapy between European countries. The proportion of all patients with stage II colon cancer receiving adjuvant chemotherapy ranged from 7.1% in the Netherlands to 29.0% in Belgium, while this ranged from 4.7% in the Netherlands to 25.1% in patients with stage IIA colon cancer, and from 22.4% to 49.4% in patients with stage IIB colon cancer. Although there was large variation in the proportion of patients receiving adjuvant chemotherapy between European countries, we found no clear linear pattern between the proportion of adjuvant chemotherapy and adjusted relative survival. However, a better adjusted relative survival was observed for Sweden and Belgium compared with the Netherlands, and also patients from Ireland had a better adjusted relative survival compared with the Netherlands in patients with stage IIA disease.

It is an interesting finding that the proportion of adjuvant chemotherapy differs largely between European countries, with the biggest difference between the Netherlands and Belgium. Although several high-risk features were identified to be associated with a worse prognosis and adjuvant chemotherapy is given to high-risk groups only, there is no international consensus on the exact definition of high-risk stage II colon cancer. For example, in the MOSAIC study, high-risk stage II colon cancer was defined

as the presence of at least one of the following criteria: pT4 stage, perforation, or less than 10 lymph nodes examined.[32] It would have been of value to have information on other high-risk features except tumour substage to unravel the differences in the use of adjuvant chemotherapy between European countries. Moreover, patients with stage II colon cancer with tumour microsatellite-instability do not benefit from adjuvant chemotherapy.[33] However, information on microsatellite status is not available either. Patient characteristics as for example comorbidity and physical functioning would also give insight in why differences in the use of adjuvant chemotherapy exist.

Standard adjuvant chemotherapy for patients with colon cancer consists of fluoropyrimidine (oral capecitabine or infusion of 5-FU/LV) combined with oxaliplatin. When there is a contraindication for oxaliplatin, fluoropyrimidine monotherapy could be considered.[34-36] Interestingly, the long-term results of the MOSAIC study showed only a small non-significant improvement of 3.7% in overall survival and a non-significant improvement of 5.7% in disease-free survival for combination chemotherapy compared with fluoropyrimidine monotherapy in patients with high-risk stage II colon cancer.[32] Furthermore, optimal duration of adjuvant chemotherapy for high-risk stage II colon cancer is not completely clear, although three months of adjuvant chemotherapy seems to be non-inferior to six months of adjuvant chemotherapy.[37] To identify subgroups of patients who may benefit from adjuvant chemotherapy and to identify best practices with population-based data, it would be very relevant for national cancer registries to collect more detailed data items on patient characteristics such as comorbidity, on tumour characteristics, and on treatment and its toxicity and compliance.

Our international comparison on adjuvant chemotherapy and relative survival in patients with stage II colon cancer shows large variation in the use of adjuvant chemotherapy between European countries, though no clear relation between the proportion of adjuvant chemotherapy and relative survival was demonstrated. This supports the idea that there is no indication for routine administration of adjuvant chemotherapy in patients with stage II colon cancer. Further defining selection criteria for adjuvant chemotherapy could eventually result in optimal treatment for subgroups of patients with stage II colon cancer. Registering detailed information in national cancer registries on patient and tumour characteristics as well as on treatment would be helpful to get insight which patient subgroups may benefit from adjuvant chemotherapy.

Treatment strategies for patients with stage I-III rectal cancer

Guidelines regarding preoperative and postoperative treatment strategies for patients with stage I-III rectal cancer differ between countries. It is evident that preoperative radiotherapy followed by total mesorectal excision is effective in reducing the probability of local recurrences and there is a benefit in cancer-specific survival compared with total

mesorectal excision only.[4] Moreover, for locally advanced rectal cancer, preoperative chemoradiotherapy is thought to be necessary to achieve a tumour-free circumferential resection margin, and a complete pathological response (pCR) could be achieved in almost 30% of patients with cT2 cancers and in over 15% of cT3 cancers.[38] However, the benefits of preoperative (chemo)radiotherapy should be carefully weighed against the morbidity associated with it, as for example faecal incontinence, bladder dysfunction, and sexual dysfunction.[39,40] It is therefore challenging to avoid undertreatment as well as overtreatment for patients with rectal cancer. As already discussed before, adjuvant chemotherapy after preoperative (chemo)radiotherapy and total mesorectal excision is subject of debate and large differences in European guidelines exist regarding the recommendation of adjuvant chemotherapy.

In **Chapter 8**, we did a EURECCA international comparison of oncologic treatment strategies and relative survival of patients with (y)pTNM stage I-III rectal cancer. Population-based national cohort data from seven European countries and single-centre data from one European country were obtained. Large differences in preoperative and postoperative treatment strategies for patients with stage I-III rectal cancer were observed between neighbouring European countries. More preoperative radiotherapy and less preoperative chemoradiotherapy was given in the Netherlands compared with Belgium, in Sweden compared with Denmark, and in England compared with Ireland. Single-centre data from Lithuania showed that over eighty percent of patients had no preoperative treatment. Patients from Belgium compared with the Netherlands, from Denmark compared with Sweden, and from England compared with Ireland more often received adjuvant chemotherapy. In Spain, over half of the patients had preoperative chemoradiotherapy and about sixty percent had adjuvant chemotherapy. Comparing the Netherlands and Belgium for example, adjuvant chemotherapy was given in 9.6% of patients in the Netherlands while this was 39.1% in Belgium where adjuvant chemotherapy is advised in patients without preoperative (chemo)radiotherapy and advised to be considered in patients with stage II or III disease after preoperative (chemo) radiotherapy. Besides the fact that there is large variation in adjuvant chemotherapy between these neighbouring countries, it is an interesting finding that still almost ten percent of patients in the Netherlands were not treated according to guideline recommendations.

Although we observed large differences in preoperative and postoperative treatment strategies, we found no differences in relative survival between neighbouring countries. Information on clinical TNM stage would have been very useful in this study. Unfortunately this was not available or missing in a large amount of patients. As a result, analyses could not be performed by substage, because differences in preoperative treatment would have resulted in incomparable data when analysing (y)pTNM substages separately.

Moreover, there might be unknown differences in data registration, there still could be residual confounding although we adjusted the analyses for potential confounders, and data on treatment was recorded as unknown in England if a patient had surgery and no record of receiving preoperative or postoperative treatment. Other details on treatment and for example comorbidity were not available.

This study gives insight in the enormous variation in preoperative and postoperative oncologic treatment strategies. However, we found no clear relation between preoperative and postoperative treatment strategies and adjusted relative survival.

Treatment strategies for patients with incurable metastatic colorectal cancer

Over the past years, survival of patients with incurable metastatic colorectal cancer improved significantly with fluoropyrimidine-based chemotherapy with oxaliplatin or irinotecan often combined with bevacizumab, or EGFR inhibitors (cetuximab or panitumumab).[41-46] Moreover, there is no doubt that obstruction, perforation, or severe bleeding of the primary tumour requires emergency surgery. However, there is ongoing debate about the potential benefit of surgery of the primary tumour in patients with incurable metastatic colorectal cancer with an asymptomatic primary tumour.[47] Several trials have failed to reach a sufficient number of patients and closed prematurely, while results from other trials are still awaited.[48-52] Meanwhile, attempts have been made to study the effect of surgery of the primary tumour in patients with asymptomatic metastatic colorectal cancer with observational data. Retrospective studies demonstrated a benefit of resection of the primary tumour, but these studies are at high risk of confounding by indication as surgery of the primary tumour was not randomised. Patients who did not have surgery of the primary tumour had more extensive metastatic disease, poorer performance status, more comorbidity, and higher alkaline phosphatase and carcinoembryonic antigen (CEA) levels.[53] It is likely that these patients had a worse prognosis on beforehand. For this reason, we need to be cautious to conclude from these data that surgery of the primary tumour results in better survival of patients with incurable metastatic colorectal cancer.

Because it is difficult to directly compare surgery of the primary tumour and survival using retrospective data, we compared treatment strategies and overall survival of patients with incurable metastatic colorectal cancer on country level in **Chapter 9**. We also assessed the effect of different treatment strategies on mortality within the first year using country as an instrumental variable to mimic randomisation. For this EURECCA international comparison, we collected national, population-based data from the Netherlands and Norway. Our results demonstrate that patients from Norway underwent surgery of the primary tumour more often than patients from the Netherlands. Moreover, it may be that patients from the Netherlands received more

chemotherapy than patients from Norway, especially in older patients. However, data on chemotherapy are not complete in the Norwegian Colorectal Cancer Registry and these results should therefore be interpreted with caution. Radiotherapy of the primary tumour in patients with rectal cancer was given less frequent in Norway compared with the Netherlands. Overall, there were no differences observed in crude overall survival between the Netherlands and Norway for patients with incurable metastatic colorectal cancer, though a small survival benefit was observed for Norway compared with the Netherlands after adjustment for potential confounders. Also patients <75 years from Norway had a slightly better crude and adjusted overall survival than patients from the Netherland. On the contrary, patients ≥75 years from Norway had a worse crude and adjusted overall survival compared with the Netherlands. Using instrumental variable analysis, no benefit in one-year mortality was found for a treatment strategy with a higher proportion of surgery of the primary tumour.

Unfortunately, data on chemotherapy was not complete in the Norwegian Colorectal Cancer Registry. Also no information is available in both cancer registries on for example emergency surgery, symptoms of the primary tumour, chemotherapy regimen, toxicity, chemotherapy compliance, comorbidity, and ASA classification. Moreover, especially in this patient group with palliative care, it would be of relevance to have information on quality of life and patient preferences. Still there could be residual confounding as a result of the retrospective design of the study.

From this study, it can be concluded that although there is considerable variation in treatment strategy with especially more surgery and less radiotherapy in Norway compared with the Netherlands, there are only very small differences in overall survival between these two countries and the clinical relevance of the small survival differences could be questioned. Furthermore, different treatment strategies had no effect on one-year mortality using instrumental variable analysis. Comparing treatment strategies and survival on country level prevents the problem of confounding by indication as happened in retrospective studies directly comparing surgery of the primary tumour with observation in patients with asymptomatic incurable metastatic colorectal. Small survival differences between the Netherlands and Norway that we observed may be partly the result of differences in treatment strategies, but there may be other factors as well that impact on survival. Although we can conclude from this study that there are large differences in treatment strategy and only very small differences in overall survival, we cannot define which patient subgroups to select for various treatment options, in particular who will or will not benefit from surgery of the primary tumour. This still remains subject of debate, although the current evidence does not support routine surgery of the primary tumour in patients with asymptomatic incurable metastatic colorectal cancer.

FUTURE PERSPECTIVES

A paradigm shift is occurring in gastrointestinal cancer care from a one-size-fits-all therapy based on TNM stage to that of individually tailored therapy. Furthermore, in gastrointestinal cancer care including rectal cancer care, there is an important shift towards intensified neoadjuvant therapy in order to improve outcomes and even omission of surgery seems to be possible in a selected group of patients.

Given the high rate of complications after surgery for non-metastasised colorectal cancer and its negative impact on short-term and long-term outcomes, a prehabilitation and rehabilitation programme may contribute to reduce complications in older patients who are fit enough for surgery.[54] Although we observed high 30-day and one-year mortality rates especially among patients ≥75 years, a more recent study showed that the difference between older and younger patients in terms of one-year relative postoperative survival became smaller.[55] Geriatric consultation can contribute in final multidisciplinary treatment decision-making. Moreover, strict protocolised Enhanced Recovery After Surgery care improvement processes, resulting in shorter length of hospital stay and less complications, could very well have contributed in reducing the gap in outcomes between older and younger patients.

We found no evidence for the routine use of adjuvant chemotherapy after preoperative (chemo)radiotherapy and total mesorectal excision for patients with rectal cancer. Older research comparing preoperative versus postoperative chemoradiotherapy demonstrated that preoperative treatment leads to better adherence to chemotherapy and less toxicity.[56] A shift towards intensified neoadjuvant therapy for locally advanced rectal cancer is going on. In the meantime, the results of the RAPIDO trial show a lower disease-related treatment failure, as a result of less distant metastases, in patients with high-risk locally advanced rectal cancer after preoperative short-course radiotherapy, followed by chemotherapy and total mesorectal excision compared with conventional chemoradiotherapy.[57] Moreover, since neoadjuvant chemoradiotherapy can result in a complete clinical response, this can result in less extensive surgery, and even in a "watch-and-wait" strategy to spare patients from surgical treatment has been approached in a selected group of patients.[58,59]

An initiative such as EURECCA creates a platform to reflect on cancer care and improve cancer outcomes. Population-based database analyses can result in evidence-based and tailor-made treatment. As shown in this thesis, comparing data from cancer registries gives valuable insight in treatment strategies and outcomes between European countries. However, a core unified dataset in Europe, ideally prospectively collected, including detailed data on patient characteristics such as comorbidity and functional status, on

tumour characteristics, on treatment and its related toxicity and complications, and on outcomes including oncologic outcomes as well as quality of life, would be essential to further use epidemiological data to optimise and improve colorectal cancer care.

In the era of multidisciplinary management and shared-decision making, analyses from a unified European population-based dataset, of course combined with results from trials as well as the search for additional biomarkers will be the challenge for the future to better select subgroups of patients for treatment. More importantly, intensified neoadjuvant (chemo)radiotherapy addresses the need to monitor patients carefully with intense radiological follow-up to only intervene in case of tumour recurrence. In some patients, this can even avoid surgery in case of long-lasting complete response.

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