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

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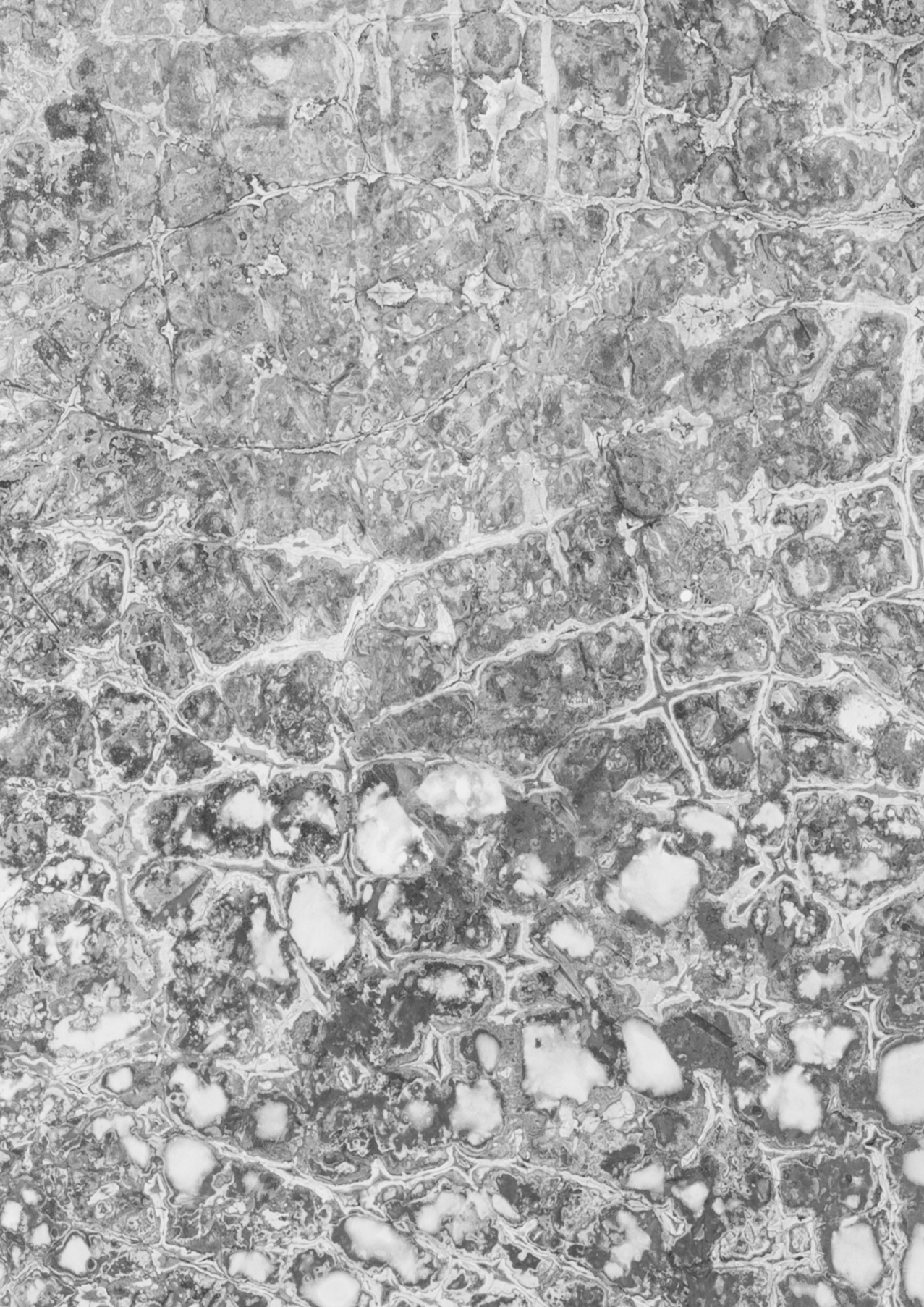

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Treatment strategies and overall survival for incurable metastatic colorectal cancer - a EURECCA international comparison including 21,196 patients from the Netherlands and Norway

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ABSTRACT

Background

The potential benefit of surgery of the primary tumour in patients with asymptomatic metastatic colorectal cancer is debated. This EURECCA international comparison analyses treatment strategies and overall survival in the Netherlands and Norway in patients with incurable metastatic colorectal cancer.

Methods

National cohorts (2007 – 2013) from the Netherlands and Norway including all patients with synchronous metastatic colorectal cancer were compared on treatment strategy and overall survival. Using country as an instrumental variable, we assessed the effect of different treatment strategies on mortality in the first year.

Results

Of 21,196 patients (16,144 Dutch and 5,052 Norwegian), 38.6% Dutch and 51.5% ($p<0.001$) Norwegian patients underwent resection of the primary tumour. In the Netherlands, 58.2% received chemotherapy compared with 21.4% in Norway. Radiotherapy was given in 9.5% of Dutch patients and 7.2% of Norwegian patients. Using the Netherlands as reference, the adjusted HR for overall survival was 0.96 (95% CI 0.93 – 0.99; $p=0.024$). Instrumental variable analysis showed an adjusted OR of 1.00 (95% CI 0.99 – 1.02; $p=0.741$).

Conclusions

Treatment strategies varied significantly between the Netherlands and Norway, with more surgery and less radiotherapy in Norway. Adjusted overall survival was better in Norway for all patients and patients <75 years, but not for patients ≥75 years. Instrumental variable analysis showed no benefit in one-year mortality for a treatment strategy with a higher proportion of surgery and a lower proportion of radiotherapy. Our findings emphasise the need for further research to select patients with incurable metastatic colorectal cancer for different treatment options.

INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, with 1.4 million new cases and 694,000 cancer deaths estimated to have occurred in 2012.[1] Approximately 20% of all patients with colorectal cancer have distant metastases at diagnosis.[2] Although a selected group of patients with metastatic colorectal cancer can be treated with curative intent, treatment options are limited to palliative therapy for the majority of patients.[3] Survival of patients with incurable metastatic colorectal cancer has improved significantly over the past years with advances in systemic therapy.[4] Median overall survival is approximately five to six months with symptom-directed palliative care alone, while survival increases to 11 to 12 months with fluoropyrimidine monotherapy, and to about two years with fluoropyrimidine-based combination chemotherapy with oxaliplatin or irinotecan often combined with bevacizumab, or EGFR inhibitors (cetuximab or panitumumab).[5-10]

Surgical resection of the primary tumour in patients with incurable metastatic colorectal cancer is indicated in case of obstruction, perforation, or severe bleeding. On the contrary, the potential benefit of surgery of the primary tumour in patients with asymptomatic disease is extensively debated.[11,12]

Randomised controlled trials (RCTs) are considered to be the gold standard to evaluate treatment effectiveness. However, no results are yet available from RCTs comparing surgery versus no surgery of the primary tumour in asymptomatic patients with unresectable metastatic colorectal cancer, and well-designed trials have been unable to recruit patients by various reasons including for example a smaller patient population than anticipated and the perception of the doctor about the best treatment strategy.[13] Moreover, results from retrospective studies are at high risk of confounding by indication and should therefore be interpreted with caution.

As an alternative, instrumental variable analysis can be used, which is a promising tool to estimate treatment effects and to reduce residual confounding in comparative effectiveness research.[14,15] An instrumental variable is defined as a factor that is related to treatment, but neither directly nor indirectly related to the study outcome.[14]

The aim of the present EURECCA international comparison is to compare treatment strategies and to compare overall survival between the Netherlands and Norway in patients with incurable metastatic colorectal cancer, and to define optimal treatment strategies using country as an instrumental variable.

METHODS

Patients

National datasets with (almost) 100% coverage of incident cases from the Netherlands Cancer Registry (NL), and the Cancer Registry of Norway (NO) including detailed data from the Norwegian Colorectal Cancer Registry were included.[16,17] We selected all patients diagnosed with synchronous metastatic colorectal cancer between 2007 and 2013. To define patients with incurable metastatic disease, we excluded patients who underwent surgery of metastasis. Patients without surgery of metastatic disease or with unknown data on surgery of metastatic disease were included.

We collected information on age, gender, primary tumour localisation (colon or rectum), year of diagnosis, clinical T-stage, clinical N-stage, localisation of metastases, treatment, and vital status at date of last follow-up. Clinical T-stage was classified as T0-2, T3, T4, or unknown. Clinical N-stage was classified as N0, N+, or unknown. Localisation of metastases was defined as liver only, lung only, other but one localisation, ≥2 localisations, or unknown. Information on treatment consisted of surgery of the primary tumour, radiotherapy of the primary tumour, and chemotherapy, all defined as no, yes, or unknown.

While data on surgery and radiotherapy are of very good quality in the Norwegian Colorectal Cancer Registry, data on chemotherapy are not complete, and must be interpreted with caution.

Statistical analyses

Median follow-up was calculated according to the reverse Kaplan-Meier technique.[18] Analyses were performed for all patients, as well as stratified by localisation of the primary tumour (colon, rectum), and age (<75 years, ≥75 years).

We performed a chi-square test to compare the proportion of surgery of the primary tumour, chemotherapy, and radiotherapy of the primary tumour between the Netherlands and Norway. Overall survival was defined as time from diagnosis to death of any cause or to end of follow-up (censored). To compare overall survival between the Netherlands and Norway, we used Kaplan-Meier curves. Crude and adjusted Cox proportional hazards models were performed to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) to study the association between country and overall survival with the Netherlands as a reference category. We adjusted for the following potential confounders: age, gender, localisation of the primary tumour, and year of diagnosis. Median survival was calculated according to the Kaplan-Meier method and compared by the Log-rank test. A Kaplan–Meier curve was constructed to compare overall survival between the Netherlands and Norway.

Using country as an instrumental variable (pseudo-randomisation), we assessed the effect of different treatment strategies on mortality (yes/no) within the first year using the instrumental variable estimation procedure (ivregress) in Stata adjusted for age, gender, localisation of the primary tumour, and year of diagnosis.

As a sensitivity analysis, survival analyses were performed excluding patients with unknown data on surgery of metastatic disease.

A p-value of <0.05 was considered as statistically significant. Analyses were performed with IBM SPSS Statistics 23.0 and STATA SE 12.0.

RESULTS

A total of 21,196 patients were included; 16,144 from the Netherlands, and 5,052 from Norway. Data on surgery of metastatic disease were unknown for 803 (3.8%) of these patients. Patient and tumour characteristics are shown in Table 1. Median follow-up of surviving patients was 4.3 years (IQR 2.7 – 6.1 years).

Table 1. Patient and tumour characteristics

	The Netherlands (*n*=16,144)	**Norway** (*n*=5,052)
Age (years)	70 (14-102)	72 (19-104)
Gender		
Male	9,111 (56.4)	2,671 (52.9)
Female	7,033 (43.6)	2,381 (47.1)
Localisation primary tumour		
Colon	12,007 (74.4)	3,898 (77.2)
Rectum	4,137 (25.6)	1,154 (22.8)
Year of diagnosis		
2007	2,143 (13.3)	690 (13.7)
2008	2,217 (13.7)	731 (14.5)
2009	2,221 (13.8)	727 (14.4)
2010	2,386 (14.8)	743 (14.7)
2011	2,372 (14.7)	721 (14.3)
2012	2,355 (14.6)	750 (14.8)
2013	2,450 (15.2)	690 (13.7)
Clinical T-stage		
T0-2*	556 (3.4)	262 (5.2)
T3	3,552 (22.0)	881 (17.4)
T4	3,550 (22.0)	641 (12.7)
Unknown	8,486 (52.6)	3,268 (64.7)
Clinical N-stage		
N0	2,918 (18.1)	245 (4.8)
N+	7,337 (45.4)	1,021 (20.2)
Unknown	5,889 (36.5)	3,786 (74.9)
Metastases		
Liver only	6,608 (40.9)	772 (15.3)
Lung only	753 (4.7)	156 (3.1)
Other, but one localisation	2,283 (14.1)	872 (17.3)
≥2 localisations	6,353 (39.4)	362 (7.2)
Unknown	147 (0.9)	2,890 (57.2)

Data are presented as median (minimum-maximum) or as *n* (%)

* Including one patient with T in situ

All patients

Figure 1 depicts the various treatment strategies in the Netherlands and Norway. In the Netherlands, a lower percentage of patients underwent surgery of the primary tumour compared with Norway (38.6% *vs.* 51.5%; p<0.001). Moreover, 58.2% of Dutch patients received chemotherapy. In Norway, 21.4% of patients received chemotherapy and data on chemotherapy was unknown in 41.2% of patients (p<0.001). Of all patients, 9.5% received radiotherapy of the primary tumour in the Netherlands compared with 7.2% of patients from Norway.

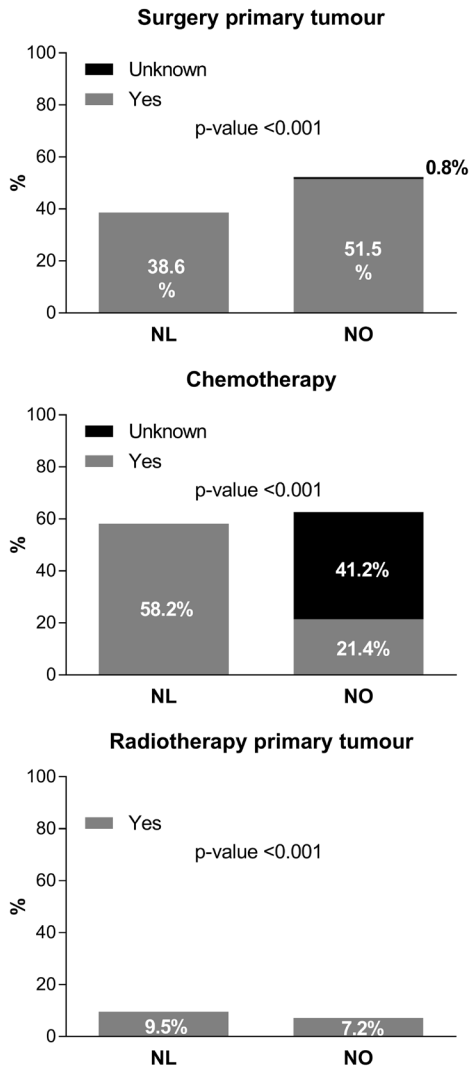
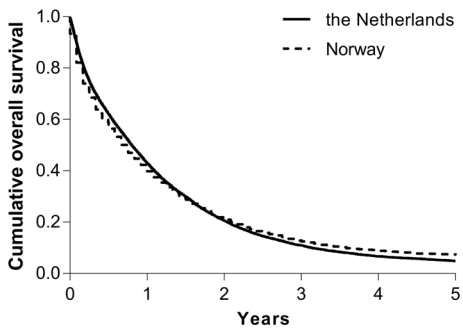


Figure 1. Treatment strategy

Median overall survival was 9.6 months in the Netherlands and 9.0 months in Norway. No difference in crude overall survival was found between the two countries (HR 0.99, 95% CI 0.96 – 1.03; p=0.731; Figure 2). After adjustment for potential confounders, the HR was 0.96 (95% CI 0.0.93 – 0.99; p=0.024) for Norway compared with the Netherlands.



Number at risk						
The Netherlands	16,144	6,923	2,809	1,242	589	307
Norway	5,052	2,021	905	444	245	139

Figure 2. Overall survival

Colon cancer

Figure 3 shows the treatment strategy in the Netherlands and Norway for patients with colon cancer. In the Netherlands, 44.9% of patients with colon cancer underwent surgery of the primary tumour compared with 55.6% in Norway (p<0.001). Chemotherapy was administered in 56.5% of Dutch patients. In Norway, 18.5% of patients received chemotherapy and data on chemotherapy was unknown in 40.4% of patients (p<0.001). Median overall survival for patients with colon cancer was 8.8 months in the Netherlands and 8.0 months in Norway (HR 1.00, 95% CI 0.96 – 1.04; p=0.958; Figure 4). After adjustment for potential confounders, the HR was 0.97 (95% CI 0.93 – 1.01; p=0.095).

Rectal cancer

Figure 3 shows treatment strategies for patients with rectal cancer. A lower percentage of patients in the Netherlands underwent surgery of the primary tumour compared with Norway (20.1% *vs.* 37.4%; p<0.001). Chemotherapy was given in 63.2% of Dutch patients. In Norway, 31.2% of patients had chemotherapy, while data on chemotherapy was unknown in 44.2% of patients (p<0.001). In the Netherlands, 37.1% of patients had radiotherapy of the primary tumour. In Norway, 31.5% of patients had radiotherapy of the primary tumour (p<0.001).

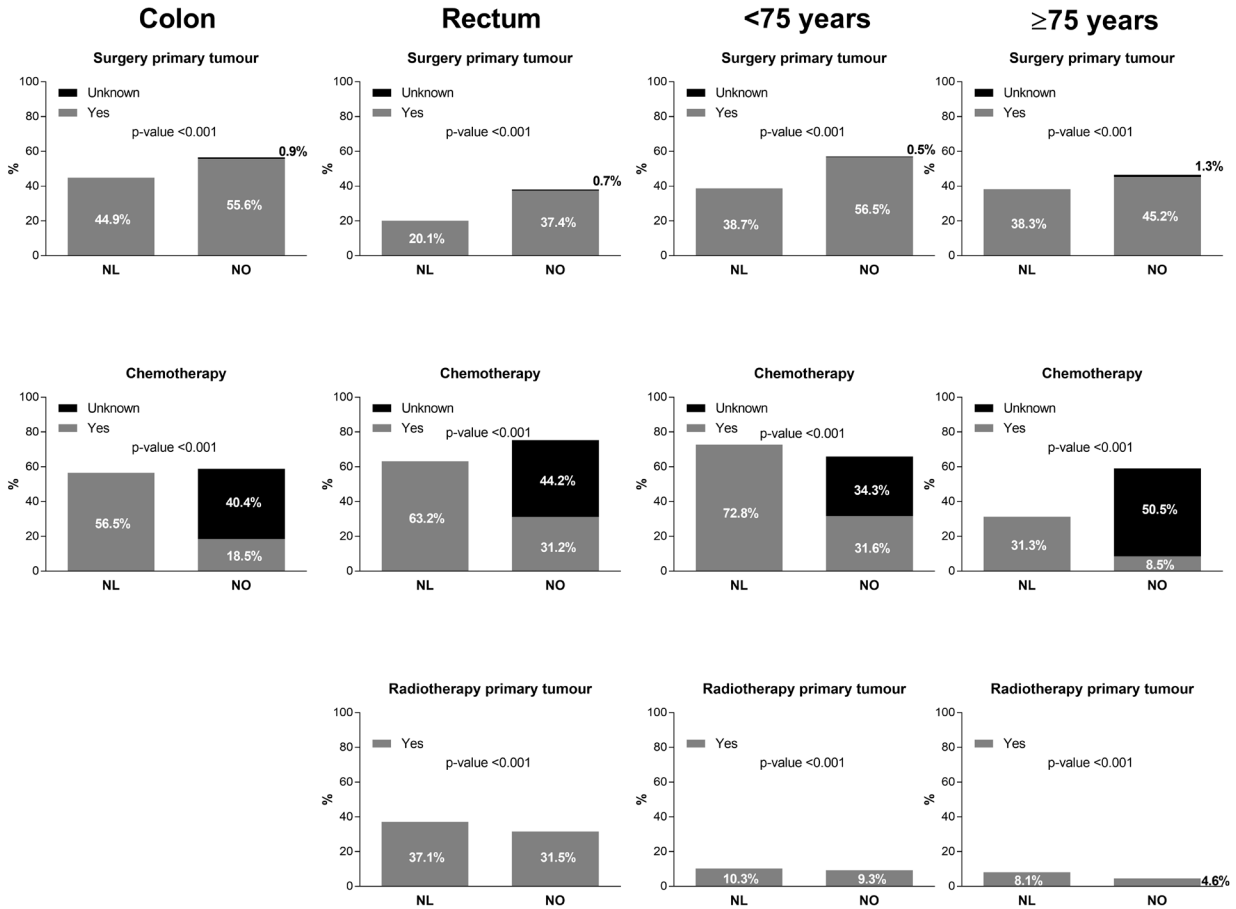


Figure 3. Treatment strategy for patients with colon and rectal cancer

Median overall survival for patients with rectal cancer was 12.0 months in the Netherlands as well as in Norway (HR 0.96, 95% CI 0.89 – 1.03; p=0.248; Figure 4). After adjustment for potential confounders, the HR was 0.95 (95% CI 0.88 – 1.02; p=0.122).

Patients <75 years

In the Netherlands, 38.7% of patients <75 years with colorectal cancer underwent surgery of the primary tumour compared with 56.5% of patients from Norway (p<0.001). Moreover, 72.8% of Dutch patients had chemotherapy. In Norway, 31.6% of patients received chemotherapy, while data on chemotherapy was unknown in 34.3% of patients (p<0.001). Radiotherapy of the primary tumour was given in 10.3% of Dutch patients and 9.3% of Norwegian patients (p<0.001; Figure 3).

Median overall survival for patients <75 years was 11.9 months in the Netherlands and 13.0 months in Norway (HR 0.89, 95% CI 0.85 – 0.93; p<0.001; Figure 4). After adjustment for potential confounders, the HR was 0.89 (95% CI 0.85 – 0.93; p<0.001).

Patients ≥75 years

In the Netherlands, 38.3% of patients ≥75 years with colorectal cancer underwent surgery of the primary tumour compared with 45.2% in Norway (p<0.001). Of all Dutch patients, 31.3% received chemotherapy. Of all Norwegian patients, 8.5% received chemotherapy and data on chemotherapy was unknown in 50.5% of patients. Radiotherapy of the primary tumour was given in 8.1% of Dutch patients and in 4.6% of Norwegian patients (Figure 3).

Median overall survival for patients ≥75 years was 6.1 months in the Netherlands and 4.9 months in Norway (HR 1.08, 95% CI 1.02 – 1.13; p=0.004; Figure 4). After adjustment for potential confounders, the HR was 1.07 (95% CI 1.01– 1.12; p=0.014).

Sensitivity analysis

When excluding patients with unknown data on surgery of metastatic disease, median overall survival was 9.6 months in the Netherlands and 10.0 months in Norway (HR 0.91, 95% CI 0.88 – 0.94; p<0.001). After adjustment for potential confounders, the HR was 0.89 (95% CI 0.86 – 0.92; p<0.001).

Instrumental variable analysis

Using instrumental variable analysis, no difference was observed between the treatment strategy in Norway compared with the treatment strategy in the Netherlands on mortality within the first year (OR of 1.00, 95% CI 0.99 – 1.02; p=0.741).

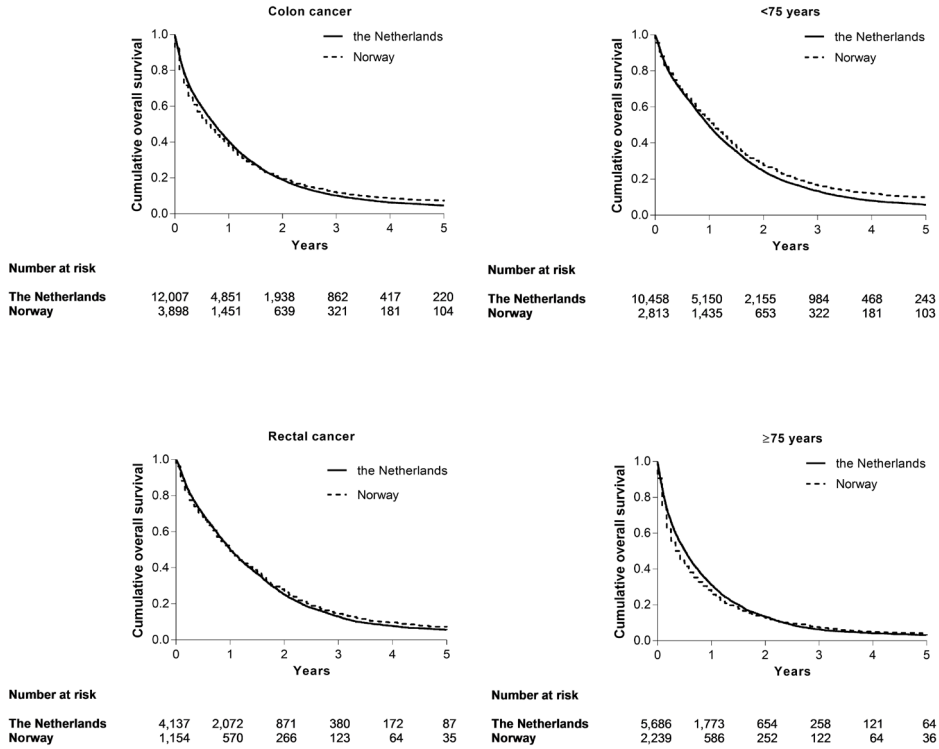


Figure 4. Overall survival by localisation (colon, rectum) and age (<75 years, ≥75 years)

DISCUSSION

This study shows remarkable variation in treatment strategies between the Netherlands and Norway for patients with incurable metastatic colorectal cancer. In Norway, more patients underwent surgery of the primary tumour compared with the Netherlands. Moreover, Dutch patients possibly received more chemotherapy, particularly in the group of patients ≥75 years; however, data on chemotherapy was unknown for about forty percent of Norwegian patients. The proportion of patients with rectal cancer receiving radiotherapy of the primary tumour was lower in Norway compared with the Netherlands.

We observed no differences in crude overall survival between the Netherlands and Norway. However, after adjustment for potential confounders, our study showed a small survival benefit in Norwegian patients, also for patients <75 years. On the contrary, patients from Norway aged ≥75 years had a worse crude and adjusted survival. Moreover,

when stratified by tumour localisation (colon or rectum), no significant difference in survival was observed, although the effect is in the same direction as for all patients. 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.

Resection of the primary tumour in asymptomatic patients with unresectable metastatic colorectal cancer has traditionally been performed to prevent subsequent complications including obstruction, perforation, or severe bleeding. A lower postoperative mortality rate was reported for elective colorectal cancer surgery than for emergency surgery in patients with metastatic disease[19], which is one of the main arguments in favour of initial resection of the primary tumour in asymptomatic patients with incurable metastatic colorectal cancer. On the contrary, the incidence of developing symptoms or tumour complications leading to emergency surgery of the primary tumour is 9-29% according to previous studies[20-22], so a considerable number of patients, in particular octo- and nonagenarians, may be spared from surgery-related morbidity or mortality by adhering to a conservative treatment policy.[23] Also, palliative radiotherapy of the rectal tumour may provide effective symptom palliation and reduce the need for surgery of the primary tumour.[24,25]

Over the last two decades, survival of patients with metastatic colorectal cancer improved greatly. Several factors may have contributed to better clinical outcomes, including improvements in the efficacy of systemic treatment, an increase in the number of patients that can be treated curatively, changes in follow-up and earlier detection of metastatic disease.[3]

Also with the advances in chemotherapeutic regimens, there is a trend toward a non-surgical management, although only 58.2% of Dutch patients received chemotherapy. Possible explanations for this could be frailty, patients' preferences, or clinical condition. A retrospective cohort study using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results colorectal cancer registry demonstrated that the annual rate of surgery of the primary tumour decreased from 74.5% to 57.4% between 1988 and 2010.[26] Still, for asymptomatic patients with incurable metastatic disease, the benefit of primary tumour resection is uncertain.

In a meta-analysis of Clancy *et al.* including 21 retrospective studies examining the effect of primary tumour resection in patients with unresectable metastatic disease, resection of the primary tumour was associated with better overall survival compared with chemotherapy alone.[27] All included studies were at high risk of confounding by indication since surgery of the primary tumour was not randomised. For example, this meta-analysis showed that patients who underwent surgery of the primary tumour were likely

to have less extent of metastatic disease and could therefore have a better prognosis on forehand compared with patients who did not undergo surgery of the primary tumour. Additionally, patients in the non-surgery group had poorer performance status, more comorbidity, higher alkaline phosphatase and carcinoembryonic antigen (CEA) levels, and different sites of the primary tumour. Moreover, resection did not significantly reduce the risk of complications of the primary tumour.[28]

More recent studies using comparative effectiveness research including instrumental variable analysis also show varying results. For example, a study by Alawadi *et al.* showed that resection of the primary tumour was not associated with improved overall survival.[29] On the contrary, several other studies found a benefit for patients with incurable stage IV colorectal cancer who underwent surgery of the primary tumour.[30-32]

There are some ongoing randomised trials, as for example the CAIRO 4 study, investigating the (long-term) effects of primary tumour resection in unresectable stage IV colorectal cancer.[33-35] However, these results are still awaited. Some of these trials also included quality of life as a secondary outcome measure, which may be of additional value in the decision-making process.

Interestingly, we observed a survival benefit in Norwegian patients aged <75 years, while a worse survival was observed in Norwegian patients aged ≥75 years. This might at least partly be explained by differences in the frequency of surgery of the primary tumour between the Netherlands and Norway. In both age groups, surgery of the primary tumour is more often performed in Norway. A previous study by Dekker *et al.* showed that decreased survival in the elderly is mainly due to differences in early survival in patients who had surgery for stage I-III colorectal cancer.[36] These results are in line with a recent study by Mehta *et al.* evaluating the comparative effectiveness of initial chemotherapy versus resection of the primary tumour in older patients with metastatic colorectal cancer. It was found that chemotherapy as initial treatment resulted in similar or better two-year survival.[37] Postoperative complications are a plausible reason for early mortality. Thus, it might be that younger patients may benefit from surgery due to less postoperative mortality, while older patients die more often as a result of postoperative complications.

A lower percentage of patients with the primary tumour located in the rectum underwent primary tumour resection compared with patients with the primary tumour in the colon, which is as expected because surgery for rectal cancer is technically more difficult than surgery for colon cancer, more proximal tumours have an increased risk of bowel obstruction, and resection of the primary tumour in rectal cancer is associated with higher postoperative morbidity and negative side effects. Moreover, palliative

radiotherapy is a highly effective treatment option for local control of rectal cancer, but not for colon cancer. We observed no differences in survival between the Netherlands and Norway.

This study has some limitations. There might be unknown differences in data registration between the two countries and differences in data completeness of other treatment modalities than surgery exist. Although we adjusted the analyses for potential confounders, residual confounding by unmeasured factors cannot be excluded due to the retrospective design of the study. For example, it is unknown what role differences in health-care systems, or differences in screening or diagnostic procedures between the two countries play. Some variables are not complete in the registries, as for example chemotherapy. Ideally we would have adjusted the analyses for location and number of metastases as well. However, there was missing data for a considerable part, and this variable introduced interaction. This should be studied in future studies with a bigger dataset by stratifying on this variable. Moreover, we had no detailed information on primary tumour symptoms, emergency surgery, type or dose of chemotherapy, toxicity, chemotherapy compliance, treatment sequence, other treatment modalities such as HIPEC, comorbidity, life-style factors, and ASA classification among others. These variables should ideally be included in national population-based datasets to do more detailed analysis and to improve comparability of the data.[38] In particular, from a patient-centred perspective, quality of life and individual preferences in the presence of incurable disease are important aspects for shared decision making. Finally, the different treatment approaches with a higher proportion undergoing surgery in Norway as compared to the Netherlands may be related to non-measurable factors, e.g. clinical traditions or different expectations from the patients in the two countries. The potential differences between countries and the effect on survival can therefore not be thoroughly investigated.

On the other hand, this study is unique in comparing both treatment and overall survival as well as using instrumental variable analysis between two European countries in patients with metastatic colorectal cancer. Furthermore, we used a large dataset with over 20,000 patients with national data covering the Netherlands and Norway.

In conclusion, the present population-based study, comparing both treatment strategies and overall survival of patients with incurable metastatic colorectal cancer between the Netherlands and Norway, showed treatment variation with especially more surgery and less radiotherapy in Norway. After adjustment for potential confounders, a better overall survival was observed in Norway compared with the Netherlands for all patients, and for patients <75 years, while we observed a worse survival in Norwegian patients aged ≥75 years. This may be partly the result of differences in treatment strategies,

although there may be other factors as well that impact on survival. However, survival differences between the Netherlands and Norway are small and clinical relevance may be questioned.

Our findings strongly underline that further research is needed to better define how to select patients with incurable metastatic colorectal cancer for various treatment options, and in particular who will and who will not benefit from surgical treatment of the primary tumour. This could eventually lead to individually tailored, optimal treatment of patients with incurable metastatic colorectal cancer.

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