Differences in pre-operative treatment for rectal cancer between Norway, Sweden, Denmark, Belgium and the Netherlands

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The members of the EURECCA consortium are given in the Appendix section.

Abstract

Several studies have shown remarkable differences in colorectal cancer survival across Europe. Most of these studies lacked information about stage and treatment. In this study we compared short-term survival as well as differences in tumour stage and treatment strategies between five European countries: Norway, Sweden, Denmark, Belgium, and the Netherlands.

For this retrospective cohort study all patients aged 18 years or older and operated on adenocarcinoma of the rectum without distant metastases and diagnosed in 2008 and 2009 were selected in national audit registries from Norway, Sweden, Denmark, Belgium, and the Netherlands.

Differences in pre-operative treatment between the countries were compared using univariable and multivariable logistic regression. One year relative survival and one year relative excess risk of death (RER) were compared between the five countries.

Large variation in the use of preoperative radiotherapy and chemoradiation was found between the countries. Even though, there was little variation in relative survival between the countries, except Sweden, which had a significant better one year RER of death among the elderly patients after adjustment. The differences in survival are expected to be caused by differences in peri-operative care, selection of patients, and especially management of elderly patients. The effects of preoperative treatment are expected to be seen on long term follow-up.

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Introduction

Several studies have shown remarkable differences in colorectal cancer survival across Europe. For rectal cancer, five-year relative survival in the period 2000–2007 ranged from 38.8% to 59.9% between European nations. The variation in outcome could be explained by case mix variation, differences in socioeconomic status and variation in registration. More importantly, many countries have their own guidelines resulting in variation in treatment plans. Different treatment strategies may lead to differences in survival. Currently it is unknown which country has a better treatment strategy compared with the other countries.

In the last two decades clinical audits have been initiated in several European countries to improve the outcome of rectal cancer patients. A clinical 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 and doctors. The European rectal cancer audits have not only successfully identified best practice and underperforming hospitals, but also achieved amongst others, a rise in survival, nationally. However, variation in outcome between the European countries remains. The EUropean REgistration of Cancer CAre (EURECCA) project was initiated by the European CanCer Organisation (ECCO) in order to decrease these differences and to improve cancer care through Europe. This project has the aim to generate the best care for all cancer patients by combining national audit structures.

Most of the previous studies concerning European survival differences lacked information about stage of disease and treatment strategies within countries and therefore, results should be interpreted with caution. The present study was undertaken to compare preoperative treatment of rectal cancer patients including the differences in tumour stage between five European countries participating in the EURECCA-project: Norway, Sweden, Denmark, Belgium, and the Netherlands.

Patients and methods

Patients

Patients diagnosed with rectal cancer in 2008 and 2009 were extracted from the Norwegian Colorectal Cancer Registry (NO), the Swedish Colorectal Cancer Registry (SE), the Danish Colorectal Cancer Group database (DK), Project on Cancer of the Rectum [PROCARE] of the Belgian Cancer Registry (BE) and the Netherlands Cancer Registry (NL). All registrations include roughly the entire national population except for the Belgian precare registration that included <50% of the Belgian rectal cancer patients in 2008–2009. From these national registrations, all patient were included that were aged 18 years and older with adenocarcinoma of the rectum (ICD-10 C20) without distant metastases, operated upon with a rectal resection, known age, stage of disease and treatment strategy, and a vital status known at date of follow-up.

Tumour stage was based on pathology reports (pathological stage). In case pathological stage was not available, clinical stage was used. Clinical stage is based on the results of echoendoscopy and magnetic resonance imaging (MRI). If neither pathological nor clinical stage was registered, patients were defined as having an unknown stage and were excluded. Preoperative treatment was divided into four groups: no preoperative treatment, preoperative radiotherapy, preoperative chemotherapy and unknown treatment. Patients were categorized in three age groups (<65 years, 65–74 years, and ≥75 years).

Statistical analyses

Differences in the characteristics between the countries were calculated using a chi squared test. Univariable and multivariable logistic regressions were performed to compare the use of preoperative treatment between the countries, and to compare the operative 30-days mortality between the countries. Time of follow-up was calculated from the day of surgery until death or the last day of follow-up. One year univariable relative survival analyses were made using the Hakulinen definition as the ratio of the survival observed among the patients and the survival that would have been expected based on the corresponding (age, gender, and year) general population. National life tables from the website www.mortality.org were used to estimate expected survival. Expected survival was estimated with Ederer II method. Relative Excess Risk (RER) of death were estimated using a multivariable generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times. Multivariable analyses were adjusted for age (in 1 year groups, used as continuous variable in the model), gender, and stage. Follow-up was truncated at 30 days or 1 year, respectively. Stratified multivariable RER of death analyses were performed for the three age groups. Sensitivity analyses have been performed to compare whether this would change the outcomes. Belgium was excluded from the sensitivity analyses because bias cannot be ruled out when <50% of the national population is included. All analyses have been tested for statistical interaction. In all analyses, a p-value of <0.05 was considered to be statistically significant.
**Results**

**Characteristics**

A total of 16,401 patients diagnosed with rectal cancer in 2008 and 2009 have been identified in the five clinical cancer registries. The median age of the patients was 67 years in NL, 70 years in SE, 70 years in DK, 70 years in NO, and 69 years in BE. About 20% of the patients from each country did not receive a resection of the tumour (NL 20.1%, SE 17.0%, DK 24.6%, NO 20.8%, and BE 17.0%). Non-resected patients were slightly older than the complete group; 71 years in NL, 75 years in SE, 75 years in DK, 77 years in NO, and 73 years in BE.

A total of 10,296 patients from the five countries were included in this study. Fig. 1 shows a flowchart of the inclusion and Table 1 shows the characteristics. 4107 patients were included from NL, 2433 from SE, 1510 from DK, 1170 from NO, and the remaining 1076 from BE. Patients from NL were younger compared to the patients of the other countries \((p < 0.001)\). No difference in gender distribution was found between the five countries. Both the clinical and the pathological stage distribution differed between the countries \((p < 0.001)\), the differences for pathological stage remained statistically significant when stage 0 \((\gamma \text{T0 after preoperative treatment})\) was excluded \((p < 0.001)\). Because the Danish registration does not record clinical stage only pathological stage was available from DK. In none of the following analyses, statistical interaction was found.

**Preoperative treatment**

All countries used preoperative treatment, either radiotherapy or chemoradiation, for rectal cancer patients. However, in DK 71.5% of the patients did not receive any preoperative treatment, compared to 69.3% in NO, 33.4% in BE, 33.1% in SE, and 14.2% in NL \((p < 0.001)\) (Table 1). Overall, the proportion of patients receiving preoperative radiotherapy varied by country \((p < 0.001)\), with NL and SE reporting high proportions of radiotherapy (52.8% and 52.3%, respectively). BE, NO, and DK had low proportions (14.7%, 9.7%, and 5.6%, respectively).

Fig. 2 shows the use of radiotherapy for each country organized by clinical stage. DK is excluded in this figure because of the lacking data on clinical stage. In NL radiotherapy was used in all stages, from 75.4% for stage I decreasing to 28.5% for stage III. In SE radiotherapy was
also administered in all stages (stage I 37.2%, stage II cT3 cN0 65.7%, stage II cT4 cN0 37.9%, and stage III 61.0%). The use of preoperative radiotherapy was low in NO (from 3.0% in stage I to 17.7% in stage III). In BE the administration of radiotherapy alone is not very common, except for clinical stage II cT3 cN0, where 22.1% of the patients received preoperative radiotherapy.

After multivariable adjustment for gender and stage the differences in the use of radiotherapy between patients <65 years and patients ≥75 years remained for DK, BE, and NL in that way that radiotherapy alone (instead of chemoradiation) is more frequently given to older patients than younger (OR = 1.85; p = 0.03 for DK, OR = 1.95; p = 0.002 for BE, and OR = 1.62; p < 0.001 for NL). In NO the use of radiotherapy remained stable with increasing age after adjustment (OR = 1.00; p = 0.9). In SE the use of radiotherapy decreased with increasing age (OR = 0.79; p = 0.02).

Table 1
Characteristics of the rectal cancer patients included stratified by country.

<table>
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<tr>
<th></th>
<th>The Netherlands</th>
<th>%</th>
<th>Sweden</th>
<th>%</th>
<th>Denmark</th>
<th>%</th>
<th>Norway</th>
<th>%</th>
<th>Belgium</th>
<th>%</th>
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<td>801</td>
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<td>414</td>
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<td>0</td>
<td>124</td>
<td>11.5</td>
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<td>79</td>
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<td>39.8</td>
<td>2433</td>
<td>23.6</td>
<td>1510</td>
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<td>1170</td>
<td>11.4</td>
<td>1076</td>
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Figure 2. The use of preoperative treatment per country organized by clinical stage.

Figure 3. The use of preoperative treatment per country organized by age group.
Regarding chemoradiation, BE had the highest usage (51.9%), followed by NL (33.0%), DK (22.4%), and NO (21.0%). SE used preoperative chemoradiation the least often (14.2%) (Table 1). The proportion of patients receiving chemoradiation increased with higher clinical stages in each country, whereas stage II cT4 cN0 was treated comparable with stage III (Fig. 2).

Stratified for age group, chemoradiation was administered less with increasing age for all countries ($p < 0.001$ for each country) (Fig. 3). After adjustment for gender and stage, the use of chemoradiation remained decreased with increasing age group for each of the countries (OR = 0.28; $p = 0.003$, OR = 0.43; $p < 0.001$ for SE, OR = 0.43; $p < 0.001$ for DK, OR = 0.21; $p < 0.001$ for NO, and OR = 0.30; $p < 0.001$ for BE).

Survival

The operative 30-days mortality rate was 2.5% in NL, 1.9% in SE, 3.0% in DK, 1.7% in NO, and 1.5% in BE, which did not differ significantly between the countries ($p = 0.08$). After multivariable adjustment for age, gender, and stage, SE, NO, and BE had a significant lower operative 30-days mortality rate as compared to NL (OR 0.58; 95% CI 0.41–0.83; $p = 0.003$, OR 0.53; 95% CI 0.32–0.87; $p = 0.012$, OR 0.52; 95% CI 0.30–0.89; $p = 0.017$, respectively), whereas the operative 30-days mortality was comparable between DK and NL (OR 0.99; 95% CI 0.69–1.43; $p = 0.9$).

Remarkable findings in this study were the large differences between the countries in the proportion of patients receiving preoperative radiotherapy or chemoradiation. Relative survival at 1 year was significantly better for patients from SE as compared to NL. However, Sweden has no automated link of death certificates to the cancer registration, which could result in some missed cases of death. When stratified for age groups, the differences in relative survival were only present in the patients aged 75 years and older.

Patients from NL were younger in comparison with other countries. When the datasets were compared without the selection criteria and therefore including all patients, the median age of the patients remained younger in the Netherlands (67 years in NL, 69 years in BE, and 70 years in NO, SE, and DK). The lower age of diagnosis does not come with a lower stage, as would be expected if the difference would be a result of screening. Brenner et al. have reported the age distribution in several European registries for colorectal cancer. Compared to NO and SE, less elderly patients from NL were included in this study. A possible explanation could be that the Dutch population is younger compared to the other countries, which is shown by Eurostat. Another possibility is that the age distribution for rectal cancer within the countries was different, resulting in less elderly patients within NL as compared to SE, DK, NO, and BE, supported by the evidence from the ECO-website (European Statistics by the European Commission).

The variation in the administration of both radiotherapy and chemoradiation is striking, as in DK less than 30% of the patients were treated preoperatively while in NL over 85% of patients received preoperative treatment. In BE, DK and NO preoperative chemoradiation was preferred, while in NL and SE preoperative radiotherapy was mostly administered. Besides variation in treatment, also variations between the guidelines are present (Attachment 1). Furthermore, these guidelines are not always followed strictly which can be seen in a higher administration of radiotherapy in T1 and T2 patients (TNM stage I) then the national guidelines prescribe. An interesting research proposal would be to compare whether the (preoperative) treatment given by each of the countries was in accordance to the guidelines. However, detailed information (such as tumour height and involvement of the mesorectal fascia) needed for such a comparison is not yet available from

![Figure 4. Graphic depiction of one year relative survival by country.](image-url)
Table 2
One-year multivariable* RER of death as compared to the Netherlands.

<table>
<thead>
<tr>
<th>The Netherlands</th>
<th>All ages</th>
<th>&lt;65 years</th>
<th>65-75 years</th>
<th>≥75 years</th>
</tr>
</thead>
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<td></td>
<td>RER</td>
<td>95% CI</td>
<td>p-Value</td>
<td>RER</td>
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<td>0.49-0.89</td>
<td>0.007</td>
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<td>Norway</td>
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<td>0.46-1.02</td>
<td>0.06</td>
<td>0.92</td>
</tr>
<tr>
<td>Belgium</td>
<td>0.66</td>
<td>0.42-1.03</td>
<td>0.07</td>
<td>0.55</td>
</tr>
<tr>
<td>Denmark</td>
<td>0.94</td>
<td>0.69-1.28</td>
<td>0.7</td>
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<tr>
<td>Norway</td>
<td>0.68</td>
<td>0.46-1.02</td>
<td>0.06</td>
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<td>0.66</td>
<td>0.42-1.03</td>
<td>0.07</td>
<td>0.55</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, and stage.

all registries. Since all guidelines are evidence-based, variation was expected to be minimal. However, it seems that the same literature can be interpreted in different ways. Another explanation could be the difference in time of development of the guidelines. Some guidelines are relatively old, and arise from the results of the Dutch TME-trial, in which the patients were randomised between Total Mesorectal Excision (TME) surgery with and without preoperative radiotherapy. During accrual of the trial, MRI staging was not standard and therefore less accurate. Nowadays, MRI staging is widely incorporated in all five countries included. Recently, the MERCURY study has shown that with MRI staging, T3 and N0 patients should not always receive preoperative treatment, suggesting that patients might have been overtreated in the last decade. Indications of overtreatment were also found in the most recent results from the TME-trial, which showed that preoperative radiotherapy significantly improved the cancer-specific survival in patients operated with a negative circumferential resection margin. However this benefit was offset by an increase in other causes of death, resulting in an equal overall survival compared with surgery alone. Similar data has been found in Sweden before the TME-era, indicating that radiotherapy can harm.

The wide-ranging variation in preoperative treatment could have an effect on short- and long term survival. Unadjusted survival did not differ significantly between the countries. After adjustment for age, gender, and stage,
SE, NO, and BE had lower operative 30-days mortality as compared to NL. It has been shown before that DK has an inferior short-term survival as compared to other European countries.\textsuperscript{21,22} SE had a significant better 1 year RER of death as compared to NL, after adjustment for several confounders. It is known that SE in general has a high quality health care with nationwide quality assurance programs, which might have contributed to the current results in short term survival.\textsuperscript{23}

As preoperative treatment is expected to have an effect on both the curative resection rate as well as on disease recurrence, it is expected to find the effects of the differences in treatment on recurrence and therefore, long term survival.\textsuperscript{24}

Although it is difficult to distinguish between the effect of peri-operative care and the effect of preoperative treatment on survival, it is to be expected that peri-operative care will probably result in survival differences within one year, since mortality in the first postoperative year is most likely due to non-cancer related disease.

Differences found at conditional 5 year survival (under the condition of surviving the first postoperative year) will probably be affected by preoperative and postoperative treatment, such as (chemo)radiotherapy and quality of surgery.\textsuperscript{25} The present study showed that the differences found in multivariable RER of death, when stratified by age group, was only present in the group of patients aged 75 years and older. Elderly patients are a heterogeneous group of patients, which might vary among the countries. Therefore, the differences found in RER of death between the countries in elderly patients could be more related to differences in surgery, peri-operative care, and differences in fitness of the elderly patients at time of surgery rather than to preoperative treatment. The differences in survival at 1 year suggest that survival in the elderly can be improved.

Long term follow-up is vital, since it could show whether differences in treatment strategies also result in survival benefit. Currently, the EURECCA consortium is performing ongoing research on the differences in long term survival between elderly patients within several countries. Furthermore, the administration of adjuvant chemotherapy in rectal cancer patients is being investigated. Possibly, due to the shorter life expectancy of elderly patients, the decrease in (local) recurrences due to preoperative radiotherapy and chemoradiation should be carefully weighed against treatment-related morbidity and mortality. One of the goals of EURECCA is to define multidisciplinary European guidelines for the treatment of colorectal cancer. During a consensus meeting in December 2012, experts from all disciplines involved in colorectal cancer treatment developed diagnostic and treatment algorithms, as a first initiative to achieve multidisciplinary European guidelines.\textsuperscript{26,27} Amongst others, the results of the present study contributed to the EURECCA consensus meeting. As a result the Dutch guidelines have been adjusted to less usage of radiotherapy in stage I and stage II rectal cancer patients.

**Strengths and limitations**

Several limitations are present in this study. Unknown is to what extent the differences in patient characteristics are due stage migration, variation in case-mix or differences in data registration. In the case of NL, patients are defined with a clinical unknown stage when no MRI is available. DK did not register preoperative (clinical) TNM stage, and neither collected information about stage 0 postoperatively (ypT0). But since DK had a relatively low administration of preoperative treatment, significant differences in clinical and pathological TNM stage are not expected. The use of staging by MRI is widely used in all five countries, which made preoperative staging more reliable. Another limitation is the selection bias probably present in the PROCARE database, which is based on voluntary participation of both hospitals and clinicians. The group of patients in PROCARE performed better compared to all patients within Belgium when the results of PROCARE are compared with the Belgium Cancer Registry. However, we have performed sensitivity analyses that did not result in changes in the outcome of the results. The strength of the current study is the large number of included patients with detailed information. To our knowledge this is the first study comparing five countries with detailed information on both rectal cancer treatment and short-term survival. All registries except for Belgium are national (clinical) cancer registries, with an estimated inclusion of over 95% of cases.

**Conclusions**

A large variation in administration of preoperative treatment has been found between NO, SE, DK, BE, and NL. After adjustment for age, gender, and stage, Sweden had a significant better relative survival for patients aged ≥75 years at 1 year compared to the Netherlands. The differences in 1 year relative survival are expected to be caused by differences in peri-operative care, selection of patients, and fitness of elderly patients. By comparing these items between the countries, which will be a next step of the EURECCA-project, differences in survival of elderly patients could be elucidated. To properly investigate this, randomized controlled trials (RCT’s) may be considered. RCT’s, however, are costly and time consuming and will not yield practice-changing results within years from the start. Furthermore, older patients are underrepresented if not excluded from RCT’s. International comparison of specific treatment protocols could serve as a good alternative to select ‘best practices’ and improve the risk/benefit ratio in the treatment of rectal cancer patients. This comparative effectiveness research can bridge the knowledge gap.
specifically in older cancer patients, who are by nature, heterogeneous in patient characteristics and treatment patterns. 

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Appendix

The members of the EURECCA consortium are given below:

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