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

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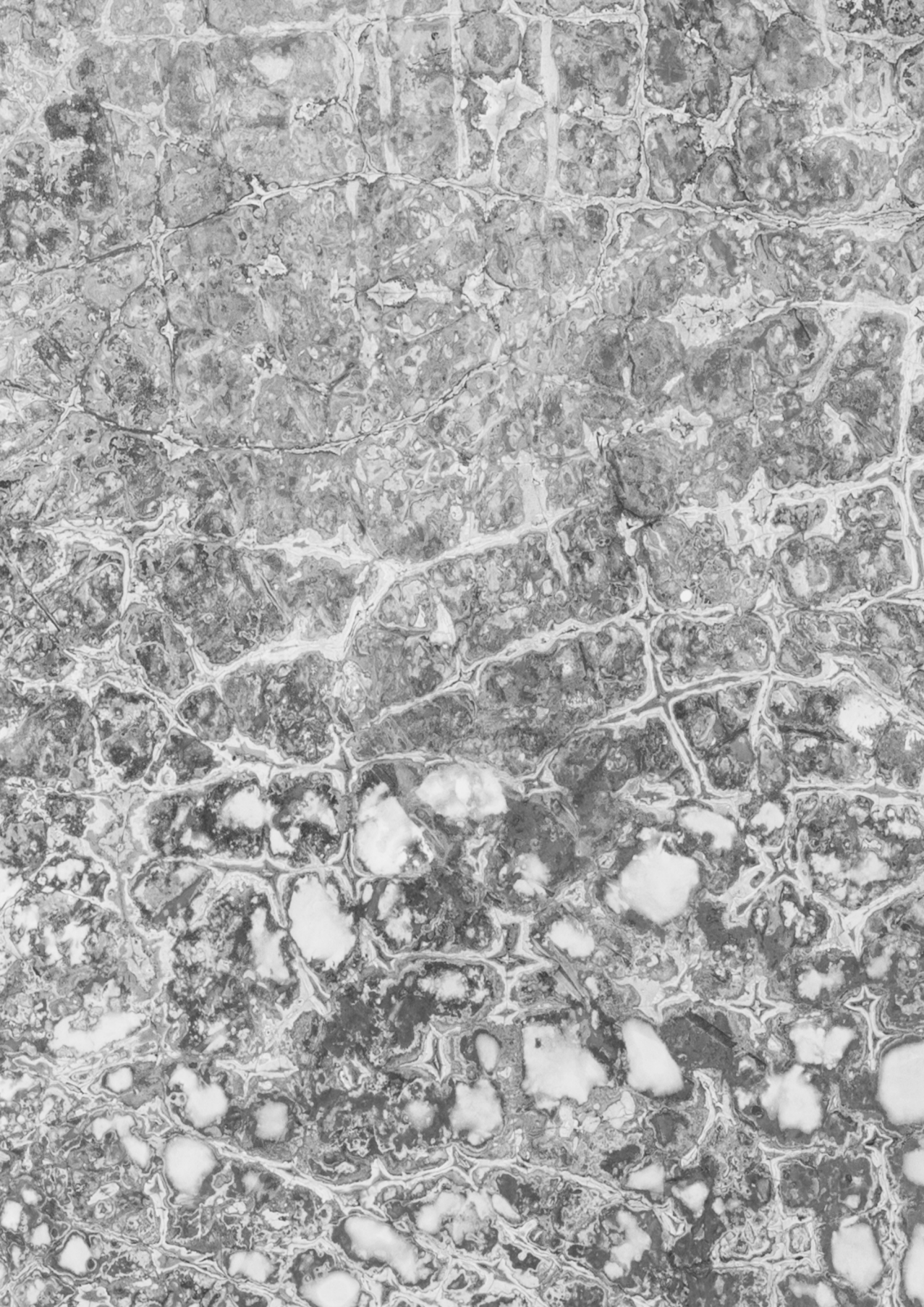

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Oncologic treatment strategies and relative survival of patients with stage I-III rectal cancer - a EURECCA international comparison between the Netherlands, Belgium, Denmark, Sweden, England, Ireland, Spain, and Lithuania

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ABSTRACT

Introduction

The aim of this EURECCA international comparison is to compare oncologic treatment strategies and relative survival of patients with stage I-III rectal cancer between European countries.

Material and methods

Population-based national cohort data from the Netherlands (NL), Belgium (BE), Denmark (DK), Sweden (SE), England (ENG), Ireland (IE), Spain (ES), and single-centre data from Lithuania (LT) were obtained. All operated patients with (y)pTNM stage I-III rectal cancer diagnosed between 2004 and 2009 were included. Oncologic treatment strategies and relative survival were calculated and compared between neighbouring countries.

Results

We included 57,120 patients. Treatment strategies differed between NL and BE ($p<0.001$), DK and SE ($p<0.001$), and ENG and IE ($p<0.001$). More preoperative radiotherapy as single treatment before surgery was administered in NL compared with BE (59.7% vs. 13.1%), in SE compared with DK (55.1% vs. 10.4%), and in ENG compared with IE (15.2% vs. 9.6%). Less postoperative chemotherapy was given in NL (9.6% vs. 39.1%), in SE (7.9% vs. 14.1%), and in IE (12.6% vs. 18.5%) compared with their neighbouring country. In ES, 55.1% of patients received preoperative chemoradiation and 62.3% postoperative chemotherapy.

There were no significant differences in relative survival between neighbouring countries.

Conclusion

Large differences in oncologic treatment strategies for patients with (y)pTNM I-III rectal cancer were observed across European countries. No clear relation between oncologic treatment strategies and relative survival was observed. Further research into selection criteria for specific treatments could eventually lead to individualised and optimal treatment for patients with non-metastasised rectal cancer.

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INTRODUCTION

Colorectal cancer is one of the most common cancers in Europe, with a total of 447,000 new cases and 215,000 deaths estimated to have occurred in 2012.[1] Rectal cancer accounts for approximately one third of all colorectal cancers.

The introduction of total mesorectal excision (TME) in rectal cancer treatment has led to substantial improvements in locoregional recurrence rates and survival.[2,3] The addition of preoperative short-course radiotherapy to TME further decreased the local recurrence rate by more than 50% compared with TME alone, although no overall survival benefit was demonstrated.[4] For patients with locally advanced rectal cancer, preoperative chemoradiation followed by TME became the standard treatment.[5-8] The role of adjuvant chemotherapy after preoperative (chemo)radiotherapy and TME has been extensively debated over the past years. Whereas adjuvant chemotherapy has been shown to be effective in patients treated without preoperative treatment, there is currently no clear scientific evidence to support the use of adjuvant fluorouracil-based chemotherapy after preoperative (chemo)radiotherapy and TME.[9-11]

Although survival of patients with colorectal cancer improved over the past years, rectal cancer survival still varies across Europe, with Eastern Europe having the lowest relative survival rates.[12] Survival differences might be explained by several factors, such as differences in demographics, socioeconomic status, lifestyle, screening or diagnostic procedures, stage at diagnosis, and health-care systems. Moreover, these differences might be attributable to differences in access to effective treatment or differences in patterns of care among countries.[13]

Randomised controlled trials (RCTs) are the gold standard to evaluate treatment effectiveness. However, RCTs tend to be expensive, slow, not always feasible, and strict inclusion criteria limit generalisability of the results.[14] Alternatively, comparative effectiveness research with large, ideally population-based datasets can provide evidence for optimal treatment strategies.

The aim of the present EURECCA international comparison is to compare oncologic treatment strategies and to compare relative survival of patients with stage I-III rectal cancer between European countries.

PATIENTS AND METHODS

Patients

We included national datasets selected from the Netherlands Cancer Registry (NL), the Belgian Cancer Registry (BE), the Danish Colorectal Cancer Group database (DK), the Swedish Colorectal Cancer Registry (SE), the English National Cancer Registration Service database Cancer Analysis System (ENG), the National Cancer Registry Ireland (IE) and selected all patients with (y)pTNM stage I-III rectal cancer (ICD-10 C20), who were diagnosed between 2004 and 2009 and who were surgically treated with curative intent. Besides, we obtained data from the Spanish Rectal Cancer Project (ES) including 103 out of 261 hospitals in Spain, and single-centre data from the Hospital of Lithuanian University of Health Sciences Kaunas Clinics (LT). Guidelines regarding preoperative and postoperative treatment strategies differ between these countries (Supplementary table 1).

We collected information on gender, age, year of diagnosis, (y)pTNM stage, tumour grade, preoperative treatment, postoperative treatment, and vital status at date of last follow-up. Age was categorised as <65 years, 65-74 years, and ≥75 years. Information on tumour stage was based on pathological reports. Clinical TNM stage was not available for some countries and missing for a substantial part in other countries, so stratification by cTNM stage was not possible. Preoperative treatment was defined as none, radiotherapy, chemoradiation, or unknown. Postoperative treatment was defined as none, chemotherapy, radiotherapy, chemoradiation, or unknown. For Sweden, postoperative treatment was complete for 2004-2006. For England, preoperative and postoperative treatment were defined as yes if a patient had received preoperative or postoperative treatment, and as unknown if a patient had surgery and no record of receiving preoperative or postoperative treatment, as a result of incomplete data.

Statistical analyses

Median follow-up was calculated according to the reverse Kaplan-Meier method.[15] For countries with national data, the analyses were compared side-by-side for neighbouring countries. Data from ES and single-centre data from LT were used for descriptive analyses, and not compared with another country. All (y)pTNM stages were analysed together. Stratification by (y)pTNM substage was not possible due to different guideline recommendations regarding preoperative treatment strategies.

The proportion of patients receiving different types of preoperative and postoperative treatment was calculated and compared with the chi-square test. Time of follow-up was calculated from date of diagnosis until death, or until end of follow-up (censored). Relative survival was calculated by the Ederer II method as the ratio of survival observed

among the patients with stage I-III rectal cancer and the survival that would have been expected based on the corresponding general population (matched by country, age, gender, and year of diagnosis). National life tables from www.mortality.org were used to estimate expected survival. Relative Excess Risks (RERs) of death were estimated using an adjusted generalised linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times. Crude and adjusted RERs were calculated. We adjusted for the following potential confounders: gender, age (as a continuous variable), year of diagnosis, and tumour grade. For the comparison DK-SE, we did not adjust for tumour grade because this information was not available for DK.

A p-value of <0.05 was considered as statistically significant. Analyses were performed with IBM SPSS Statistics 20.0 and STATA SE 12.0.

RESULTS

Overall, 56,878 patients were included; 11,768 patients from NL, 8,230 patients from BE, 4,761 patients from DK, 6,673 patients from SE, 20,991 patients from ENG, 1,689 patients from IE, 2,435 patients from ES, and 331 patients from LT. Table 1 shows patient and tumour characteristics. Median follow-up was 6.5 years (IQR 5.0-8.1).

Treatment strategies and relative survival for the Netherlands and Belgium
Figure 1a shows the treatment strategies, as well as the crude and adjusted relative survival for patients from NL and BE. Preoperative treatment strategy differed between NL and BE (p<0.001), with more radiotherapy as single treatment before surgery (59.7% vs. 13.1%) and less chemoradiation (19.1% vs. 38.9%) in NL compared with BE. Postoperative treatment strategy also differed between NL and BE, with more often no postoperative treatment (88.0% vs. 53.4%) and less often chemotherapy (9.6% vs. 39.1%) in NL compared with BE (p<0.001 for comparison postoperative treatment strategy NL-BE).

Five-year relative survival was 80.96% (95% CI 79.94-81.96%) in NL and 78.96% (95% CI 77.68-80.20%) in BE (Figure 2). After adjustment for potential confounders, no differences in relative survival were observed (RER 1.05, 95% CI 0.97-1.14; p=0.25, Figure 1a).

Treatment strategies and relative survival for Denmark and Sweden
Treatment strategies and relative survival for patients from DK and SE are shown in Figure 1b. In DK, a lower proportion of patients received preoperative radiotherapy as single treatment before surgery (10.4% vs. 55.1%), while a higher proportion of patients received chemoradiation (20.9% vs. 10.0%) compared with SE (p<0.001 for comparison

Table 1. Patient characteristics

	Netherlands (*n* = 11,768)	Belgium (*n* = 8,230)	Denmark (*n* = 4,761)	Sweden (*n* = 6,673)	England (*n* = 20,991)	Ireland (*n* = 1,689)	Spain (*n* = 2,435)	Lithuania (*n* = 331)
Gender								
Male	7,096 (60.3)	4,945 (60.1)	2,896 (60.8)	3,985 (59.7)	13,456 (64.1)	1,121 (66.4)	1,604 (65.9)	202 (61.0)
Female	4,672 (39.7)	3,285 (39.9)	1,865 (39.2)	2,688 (40.3)	7,535 (35.9)	568 (33,6)	831 (34.1)	129 (39.0)
Age (years)								
<65	4,818 (40.9)	2,888 (35.1)	1,754 (36.8)	2,212 (33.1)	7,339 (35.0)	712 (42.2)	930 (38.2)	113 (34.1)
65-74	3,789 (32.2)	2,562 (31.1)	1,609 (33.8)	2,110 (31.6)	7,180 (34.2)	542 (32.1)	742 (30.5)	131 (39.6)
≥75	3,161 (26.9)	2,780 (33.8)	1,398 (29.4)	2,351 (35.2)	6,472 (30.8)	435 (25.8)	763 (31.3)	87 (26.3)
Year of diagnosis								
2004	1,750 (14.9)	1,216 (14.8)	768 (16.1)	1,004 (15.0)	3,291 (15.7)	267 (15.8)	0 (0.0)	68 (20.5)
2005	1,781 (15.1)	1,322 (16.1)	775 (16.3)	1,068 (16.0)	3,429 (16.3)	278 (16.5)	0 (0.0)	85 (25.7)
2006	1,900 (16.1)	1,402 (17.0)	842 (17.7)	1,074 (16.1)	3,498 (16.7)	248 (14.7)	159 (6.5)	36 (10.9)
2007	2,082 (17.7)	1,433 (17.4)	785 (16.5)	1,174 (17.6)	3,529 (16.8)	316 (18.7)	362 (14.9)	33 (10.0)
2008	2,089 (17.8)	1,452 (17.6)	793 (16.7)	1,154 (17.3)	3,560 (17.0)	290 (17.2)	694 (28.5)	60 (18.1)
2009	2,166 (18.4)	1,405 (17.1)	798 (16.8)	1,199 (18.0)	3,684 (17.6)	290 (17.2)	1220 (50.1)	49 (14.8)
(y)pTNM stage								
I	3,782 (32.1)	2,271 (27.6)	1,261 (26.5)	1,887 (28.3)	5,711 (27.2)	275 (16.3)	817 (33.6)	55 (16.6)
II	3,274 (27.8)	2,339 (28.4)	1,721 (36.1)	2,101 (31.5)	7,023 (33.5)	300 (17.8)	771 (31.7)	136 (41.1)
III	3,915 (33.3)	2,652 (32.2)	1,718 (36.1)	2,534 (38.0)	8,257 (39.3)	422 (25.0)	847 (34.8)	139 (42.0)
I-III, unspecified	797 (6.8)	968 (11.8)	61 (1.3)	151 (2.3)	0 (0.0)	692 (41.0)	0 (0.0)	1 (0.3)
Grade								
I	493 (4.2)	1,237 (15.0)	0 (0.0)	450 (6.7)	975 (4.6)	64 (3.8)	0 (0.0)	187 (56.5)
II	5,618 (47.7)	5,018 (61.0)	0 (0.0)	2,574 (38.6)	16,669 (79.4)	1,277 (75.6)	0 (0.0)	130 (39.3)
III	1,060 (9.0)	1,025 (12.5)	0 (0.0)	287 (4.3)	2,213 (10.5)	145 (8.6)	0 (0.0)	14 (4.2)
IV	0 (0.0)	22 (0.3)	0 (0.0)	0 (0.0)	16 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	4,597 (39.1)	928 (11.3)	4,761 (100.0)	3,362 (50.4)	1,118 (5.3)	203 (12.0)	2,435 (100.0)	0 (0.0)

Data are presented as *n* (%)

preoperative treatment strategy DK-SE). Postoperative treatment strategy also varied between DK and SE (p<0.001). No postoperative treatment was given in 84.3% in DK vs. 75.8% in SE, while 14.1% of patients received postoperative chemotherapy in DK compared with 7.9% in SE. In 15.8% of patients from SE information on postoperative treatment was unknown.

Five-year relative survival was 81.65% (95% CI 80.00-83.24%) in DK and 81.18% (95% CI 79.67-82.63%) in SE (Figure 2). We observed no differences in adjusted relative survival (RER 0.95, 95% CI 0.85-1.07; p=0.38, Figure 1b).

Treatment strategies and relative survival for England and Ireland

Figure 1c shows treatment strategies and relative survival for patients from ENG and IE. In ENG, 15.2% of patients received preoperative radiotherapy as single treatment before surgery, and 15.6% received preoperative chemoradiation, compared with 9.6% and 34.6%, respectively in IE (p<0.001 for comparison preoperative treatment strategy ENG-IE). In 69.1% of patients from ENG, there was no record of receiving preoperative treatment.

Postoperative treatment strategy was also different between ENG and IE (p<0.001). A higher proportion of patients from ENG received postoperative chemotherapy compared with IE (18.5% vs. 12.6%). In 77.8% of patients from ENG there was no record of receiving postoperative treatment.

Five-year relative survival was 78.26% (95% CI 77.50-79.00%) in ENG and 76.84% (95% CI 74.05-79.50%) in IE. After adjustment for potential confounders, no difference in relative survival was observed between ENG and IE (RER 1.02, 95% CI 0.90-1.16;p=0.75, Figure 1c).

Treatment strategies and relative survival for Spain and Lithuania

Supplementary table 2 shows treatment strategies and five-year relative survival for both ES and LT. In ES, 55.1% received preoperative chemoradiation and 62.3% received postoperative chemotherapy. Five-year relative survival for ES was 81.82% (95% CI 79.00-84.46%).

In LT, 11.2% of patients received preoperative radiotherapy as single treatment before surgery, and 7.9% preoperative chemoradiation. Besides, postoperative chemotherapy was given in 12.4%, and postoperative chemoradiation in 13.6% of patients. Five-year relative survival was 84.04% (95% CI 77.21-90.12%).

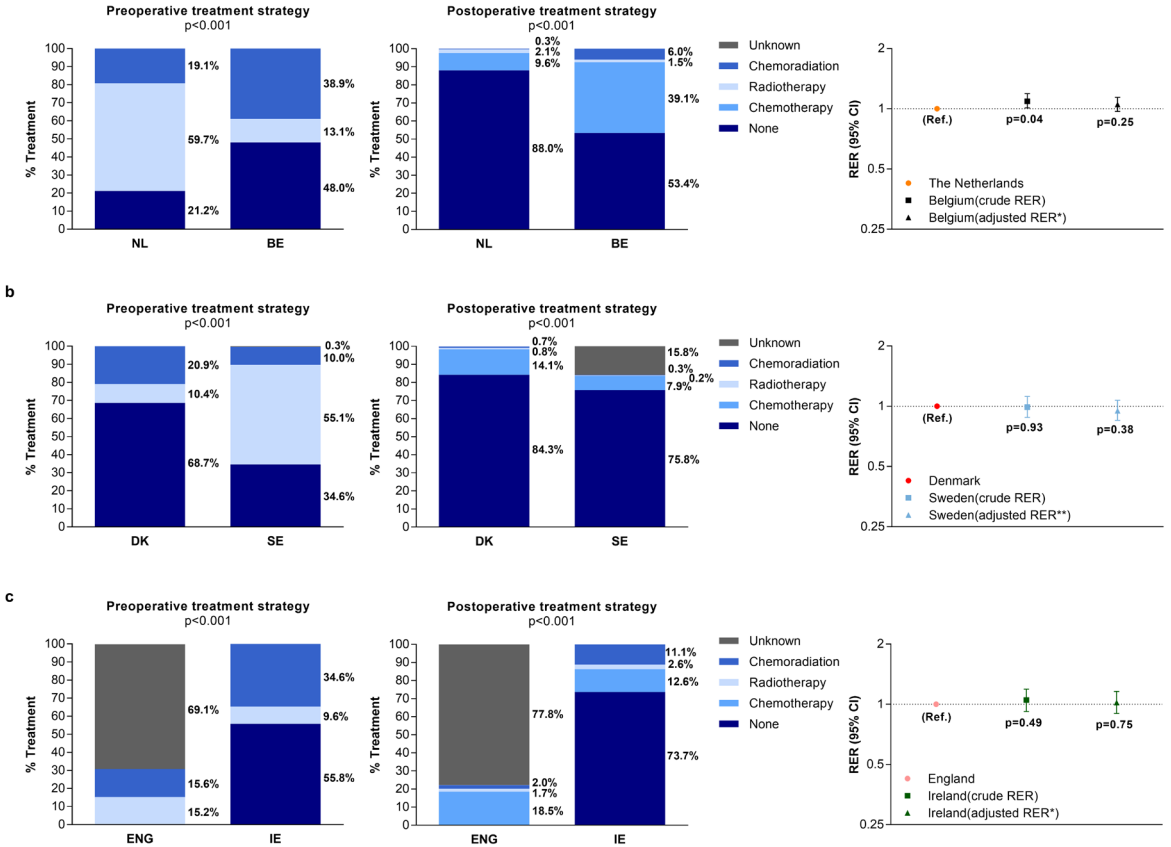

Figure 1. Treatment strategies and Relative Excess Risks (RERs) of death for a. The Netherlands and Belgium, b. Denmark and Sweden, and c. England and Ireland

* Adjusted for gender, age, year of diagnosis, grade

** Adjusted for gender, age, year of diagnosis

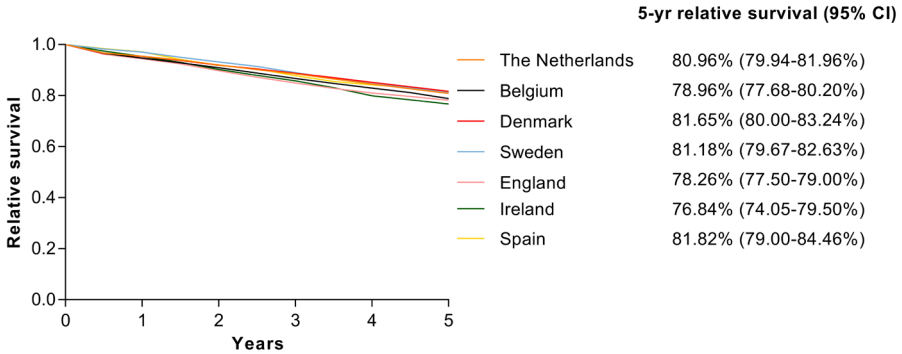

Figure 2. Relative survival

DISCUSSION

This study shows a large variation in both preoperative and postoperative oncologic treatment strategies between neighbouring countries. No differences in adjusted relative survival were observed between the Netherlands and Belgium, Denmark and Sweden, and England and Ireland. Therefore, we observed no clear relation between differences in treatment strategies and (adjusted) relative survival.

Striking differences were observed in preoperative and postoperative treatment strategies between the included European countries. More preoperative radiotherapy and less preoperative chemoradiation were given in the Netherlands compared with Belgium, in Sweden compared with Denmark, and in England compared with Ireland. In Lithuania, over eighty percent of patients received no preoperative treatment at all. Postoperative chemotherapy was more frequently administered in Belgium compared with the Netherlands, in Denmark compared with Sweden, and in England compared with Ireland. Over half of the Spanish patients received preoperative chemoradiation and about sixty percent received postoperative chemotherapy.

The observed differences in treatment strategies could at least partly be explained by differences in guidelines between the countries. Unfortunately, we were not able to compare guideline adherence with respect to preoperative treatment strategies since we had no information on clinical TNM stage, circumferential resection margin, and tumour height from the anal verge. Some guidelines have more recently been adjusted regarding pre- and postoperative treatment strategies. The Dutch guideline for example now recommends TME without preoperative treatment for patients with low risk resectable rectal cancer, defined as cT1-3N0, extramural invasion ≤5mm, and distance to the mesorectal fascia (MRF) of >1mm. For patients with intermediate risk resectable

rectal cancer (cT1-3N1 or cT3N0 with extramural invasion >5 mm, distance to the MRF >1 mm) preoperative short-course radiotherapy should be considered. Preoperative chemoradiation followed by TME is the standard of care for patients with high risk rectal cancer (cT3 with distance to the MRF ≤1 mm or cT4, and/or high probability of four or more positive lymph nodes in the mesorectum or positive lymph nodes outside the mesorectum on MRI.[16]

In addition, there are differences in guideline recommendations for postoperative chemotherapy, ranging from not recommending postoperative chemotherapy to recommending postoperative chemotherapy for patients with postoperative stage II and III disease. These guideline differences are reflected in our results.

The variation in guidelines and patterns of care regarding postoperative chemotherapy could be explained by inconclusive evidence on the effectiveness of postoperative chemotherapy after preoperative (chemo)radiotherapy and TME for patients with rectal cancer during the time period represented in the present study. In a systematic review and meta-analysis by Petersen and colleagues, a total of 21 eligible RCTs between 1975 and 2011 were identified. Patients who received adjuvant chemotherapy had improved overall survival (HR=0.83, 95% CI 0.76-0.91) and disease-free survival (HR=0.75, 95% CI 0.68-0.83) compared with patients who did not receive postoperative chemotherapy.[10] However, the majority of included studies were performed in patients who were surgically treated without preoperative treatment. Only two studies in this meta-analysis included patients who received preoperative (chemo)radiotherapy. First, the EORTC 22921 study showed no significant effect on overall survival and disease-free survival of the addition of fluorouracil-based postoperative chemotherapy after preoperative (chemo) radiotherapy in patients with clinical stage T3 or T4 resectable rectal cancer.[8] Second, the QUASAR study demonstrated a borderline significant improvement in overall survival for patients with rectal cancer treated with postoperative chemotherapy, but only a minority of these patients received preoperative radiotherapy.[17]

Interestingly, more recently published studies assessing the effectiveness of postoperative chemotherapy after preoperative (chemo)radiotherapy and surgery did not demonstrate a benefit of fluorouracil-based adjuvant chemotherapy regarding overall survival, disease-free survival, or distant recurrences.[9,11] During the accrual period of these trials there was no clear evidence of the advantage of combination chemotherapy over fluoropyrimidine monotherapy.[18,19] In a phase 2 study by Hong and colleagues, it was found that postoperative treatment with FOLFOX improved disease-free survival compared with fluorouracil and leucovorin in patients with ypTNM stage II or III rectal cancer.[20] Moreover, the German CAO/ARO/AIO-04 study also showed a significant improvement in disease-free survival with the addition of

oxaliplatin to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy in patients with clinically staged T3-4 or node positive rectal cancer, though no overall survival benefit was demonstrated.[21] However, both studies did not compare combination chemotherapy with observation. Therefore, the question whether postoperative combination chemotherapy results in better outcomes than observation remains unanswered.

Differences in patterns of care might contribute to differences in survival. Remarkably, although we observed large differences in patterns of care in the present study, no clear relation between these differences and relative survival was found. Crude analysis showed a worse relative survival for Belgium compared with the Netherlands, but no significant differences in relative survival were observed after adjustment for potential confounders. Also no differences in relative survival were observed between the other neighbouring countries.

This study has some limitations. Unfortunately, information on clinical TNM stage was either not available or missing in a considerable number of patients. As a result, we were not able to stratify the analyses by clinical stage. Moreover, we analysed all (y)pTNM stages together, because differences in preoperative treatment approaches would have resulted in incomparable data when analysing (y)pTNM substages separately. Other limitations of our study were that there might be unknown differences in data registration between the countries and that the populations of the participating countries differed to some extent. As an example, there were more patients aged 75 years and older in BE compared with NL. Although we adjusted the analyses for potential confounders, there may still be residual confounding by unidentified factors that we could not control for. For example, the impact of differences in screening or diagnostic procedures, or differences in health-care systems between the countries are unknown. Further, data on treatment was recorded as unknown in ENG if a patient had surgery and no record of receiving preoperative or postoperative treatment. During the time period 2004 – 2009 there would have been variation by region in the completeness of these data items in ENG. Therefore, no record of receiving preoperative or postoperative treatment could either mean that patients did not receive preoperative or postoperative treatment, or that it was not recorded when patients received preoperative or postoperative treatment. Information on type of surgical resection, quality of the resection, and whether the surgical resection margins were free or not would also have been relevant to adjust for taken into account that surgery is the most crucial factor for survival. Finally, we were unfortunately not able to obtain data on comorbidity, compliance to preoperative and postoperative treatment, type of chemotherapy, acute or late toxicity, and quality of life. However, our study provides unique insight into the enormous variation in patterns of care across European countries, and it is to our knowledge the first study comparing

both preoperative and postoperative treatment strategies as well as relative survival of patients with stage I-III rectal cancer. Furthermore, we used a large dataset including over fifty-seven thousand patients from eight countries. Importantly, national data covering the whole population were obtained from seven of these countries.

In conclusion, in this population-based study comparing oncologic treatment patterns and relative survival of patients with (y)pTNM I-III rectal cancer, we observed large differences in preoperative and postoperative treatment strategies across European countries. Moreover, we did not find a clear relation between oncologic treatment strategy and relative survival. Further research into selection criteria for specific treatments could eventually lead to individualised and optimal treatment for patients with non-metastasised rectal cancer.

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Supplementary table 1. Guideline recommendations by country during the time period represented in the present study

	Preoperative treatment	Postoperative treatment	Guideline adjusted?
The Netherlands	T1N0: no preoperative treatment. T2-T4: preoperative radiotherapy plus TME. In case of high, small tumours without lymph node metastases, it could be considered to omit preoperative radiotherapy. In case of positive circumferential resection margin (CRM) or more than 4 positive lymph nodes expected, preoperative chemoradiation could be considered.	Not possible to give a clear recommendation whether or not to administer postoperative chemotherapy.	Yes, 2014.
Belgium	T1-2N0: no preoperative treatment. Low tumour (0-5cm from the anal verge), T3-4N0 or TanyN+: preoperative chemoradiation. Mid and high tumours (5.1-15cm from the anal verge) T3N0 with CRM>2mm: preoperative radiotherapy. Mid and high tumours (5.1-15cm from the anal verge) T4N0 or CRM<2mm: preoperative chemoradiation. Mid and high tumours (5.1-15cm from the anal verge) TanyN+: preoperative chemoradiation.	Stage II-III: Stage II-III: (KCE 2007, Report 69 p. 38) -Postoperative chemotherapy should be considered for all patients who received preoperative radiotherapy without chemotherapy. -Postoperative chemoradiation is recommended in case a patient had no neo-adjuvant treatment.	Yes, 2016
Denmark	Until 2005: Short-course radiotherapy in mid (5-10 cm from the anal verge) and low (<5 cm from the anal verge) T3 and T4 tumours. All other: no preoperative treatment. Since 2005-2009: T1-2: low (<5 cm from the anal verge), mid (5-10 cm from the anal verge), and high (11-15 cm from the anal verge) tumours receive no preoperative treatment. T3: low and mid (MRF ≤ 5 mm) tumours: preoperative chemoradiation, mid (MRF > 5 mm) and high tumours: no preoperative treatment. T4: low and mid tumours: preoperative chemoradiation, high tumours: no preoperative treatment. In selected cases preoperative radiotherapy might be administered.	In selected cases postoperative chemotherapy might be administered.	Yes, 2009, 2014, 2015.
Sweden	T1-3a/b N0-1: no preoperative treatment. T3c/d N1-2: preoperative radiotherapy in case of no involved margins. T3-4Nany: with compromised margins: preoperative chemoradiation.	There are no indications for adjuvant chemotherapy.	Yes, 2014.

Supplementary table 1. Continued

	Preoperative treatment	Postoperative treatment	Guideline adjusted?
England	cT1 or cT2 or cT3a and no lymph node involvement (low risk): no preoperative treatment. any cT3b or greater, in which the potential margin is not threatened, or any suspicious lymph node not threatening the surgical resection margin, or the presence of extramural vascular invasion (moderate risk): consider preoperative radiotherapy. Consider preoperative chemoradiation for patients with tumours that are borderline between moderate (see above) and high risk (a threatened, <1mm, or breached resection margin, or low tumours encroaching onto the inter-sphincteric plane or with levator involvement). High-risk operable rectal cancer: offer preoperative chemoradiation.	Consider adjuvant chemotherapy after surgery for patients with high-risk stage II and all stage III rectal cancer.	Yes, 2014.
Ireland	T1-2N0, CRM clear: no preoperative treatment Early T3N0 or N1, CRM clear: upper and mid rectum preoperative radiotherapy or surgery only, lower rectum preoperative radiotherapy or chemoradiation and surgery CRM threatened by tumour or involved nodes or tumour beyond CRM or involved internal iliac/obturator nodes: preoperative chemoradiation and surgery.	Adjuvant chemotherapy should be considered for patients with node positive colorectal cancer. Patients with high-risk node negative disease should be individually counselled by an oncologic with regard to their level of risk and the possible benefits of fluoropyrimidine based chemotherapy.	No.
Spain	Stage II-III: preoperative chemoradiation is considered the treatment of choice.	Adjuvant chemotherapy is indicated for stage III patents who have been initially under staged.	No.
Lithuania	?	Adjuvant chemotherapy after surgery is recommended for patients with high-risk stage II and all stage III rectal cancer.	?

Supplementary table 2. Treatment strategies and five-year relative survival Spain and Lithuania

	Spain (%)	**Lithuania** (%)
Preoperative treatment		
None	42.0	81.0
Radiotherapy	2.9	11.2
Chemoradiation	55.1	7.9
Postoperative treatment		
None	31.1	66.8
Chemotherapy	62.3	12.4
Chemoradiation	6.7	13.6
Radiotherapy	0.0	7.3
Five-year relative survival (95% CI)	81.82% (79.00-84.46%)	84.04% (77.21-90.12%)