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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% post-operative chemotherapy. There were no significant differences in relative survival between neighbouring countries.

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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.

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 healthcare 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, 8230 patients from BE, 4761 patients from DK, 6673 patients from SE, 20,991 patients from ENG, 1689 patients from IE, 2435 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

Fig. 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 (Fig. 2). After adjustment for potential confounders, no differences in relative survival were observed (RER 1.05, 95% CI 0.97–1.14; $p = 0.25$, Fig. 1a).

Treatment strategies and relative survival for Denmark and Sweden

Treatment strategies and relative survival for patients from DK and SE are shown in Fig. 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 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 (Fig. 2). We observed no differences in adjusted relative survival (RER 0.95, 95% CI 0.85–1.07; $p = 0.38$, Fig. 1b).

Treatment strategies and relative survival for England and Ireland

Fig. 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; $p = 0.75$, Fig. 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.

Table 1
Patient characteristics.

	Netherlands ($n = 11,768$)		Belgium ($n = 8230$)		Denmark ($n = 4761$)		Sweden ($n = 6673$)		England ($n = 20,991$)		Ireland ($n = 1689$)		Spain ($n = 2435$)		Lithuania ($n = 331$)	
Gender																
Male	7096	(60.3)	4945	(60.1)	2896	(60.8)	3985	(59.7)	13,456	(64.1)	1121	(66.4)	1604	(65.9)	202	(61.0)
Female	4672	(39.7)	3285	(39.9)	1865	(39.2)	2688	(40.3)	7535	(35.9)	568	(33,6)	831	(34.1)	129	(39.0)
Age (years)																
<65	4818	(40.9)	2888	(35.1)	1754	(36.8)	2212	(33.1)	7339	(35.0)	712	(42.2)	930	(38.2)	113	(34.1)
65-74	3789	(32.2)	2562	(31.1)	1609	(33.8)	2110	(31.6)	7180	(34.2)	542	(32.1)	742	(30.5)	131	(39.6)
≥75	3161	(26.9)	2780	(33.8)	1398	(29.4)	2351	(35.2)	6472	(30.8)	435	(25.8)	763	(31.3)	87	(26.3)
Year of diagnosis																
2004	1750	(14.9)	1216	(14.8)	768	(16.1)	1004	(15.0)	3291	(15.7)	267	(15.8)	0	(0.0)	68	(20.5)
2005	1781	(15.1)	1322	(16.1)	775	(16.3)	1068	(16.0)	3429	(16.3)	278	(16.5)	0	(0.0)	85	(25.7)
2006	1900	(16.1)	1402	(17.0)	842	(17.7)	1074	(16.1)	3498	(16.7)	248	(14.7)	159	(6.5)	36	(10.9)
2007	2082	(17.7)	1433	(17.4)	785	(16.5)	1174	(17.6)	3529	(16.8)	316	(18.7)	362	(14.9)	33	(10.0)
2008	2089	(17.8)	1452	(17.6)	793	(16.7)	1154	(17.3)	3560	(17.0)	290	(17.2)	694	(28.5)	60	(18.1)
2009	2166	(18.4)	1405	(17.1)	798	(16.8)	1199	(18.0)	3684	(17.6)	290	(17.2)	1220	(50.1)	49	(14.8)
(y)pTNM stage																
I	3782	(32.1)	2271	(27.6)	1261	(26.5)	1887	(28.3)	5711	(27.2)	275	(16.3)	817	(33.6)	55	(16.6)
II	3274	(27.8)	2339	(28.4)	1721	(36.1)	2101	(31.5)	7023	(33.5)	300	(17.8)	771	(31.7)	136	(41.1)
III	3915	(33.3)	2652	(32.2)	1718	(36.1)	2534	(38.0)	8257	(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)	1237	(15.0)	0	(0.0)	450	(6.7)	975	(4.6)	64	(3.8)	0	(0.0)	187	(56.5)
II	5618	(47.7)	5018	(61.0)	0	(0.0)	2574	(38.6)	16,669	(79.4)	1277	(75.6)	0	(0.0)	130	(39.3)
III	1060	(9.0)	1025	(12.5)	0	(0.0)	287	(4.3)	2213	(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	4597	(39.1)	928	(11.3)	4761	(100.0)	3362	(50.4)	1118	(5.3)	203	(12.0)	2435	(100.0)	0	(0.0)

Data are presented as *n* (%).

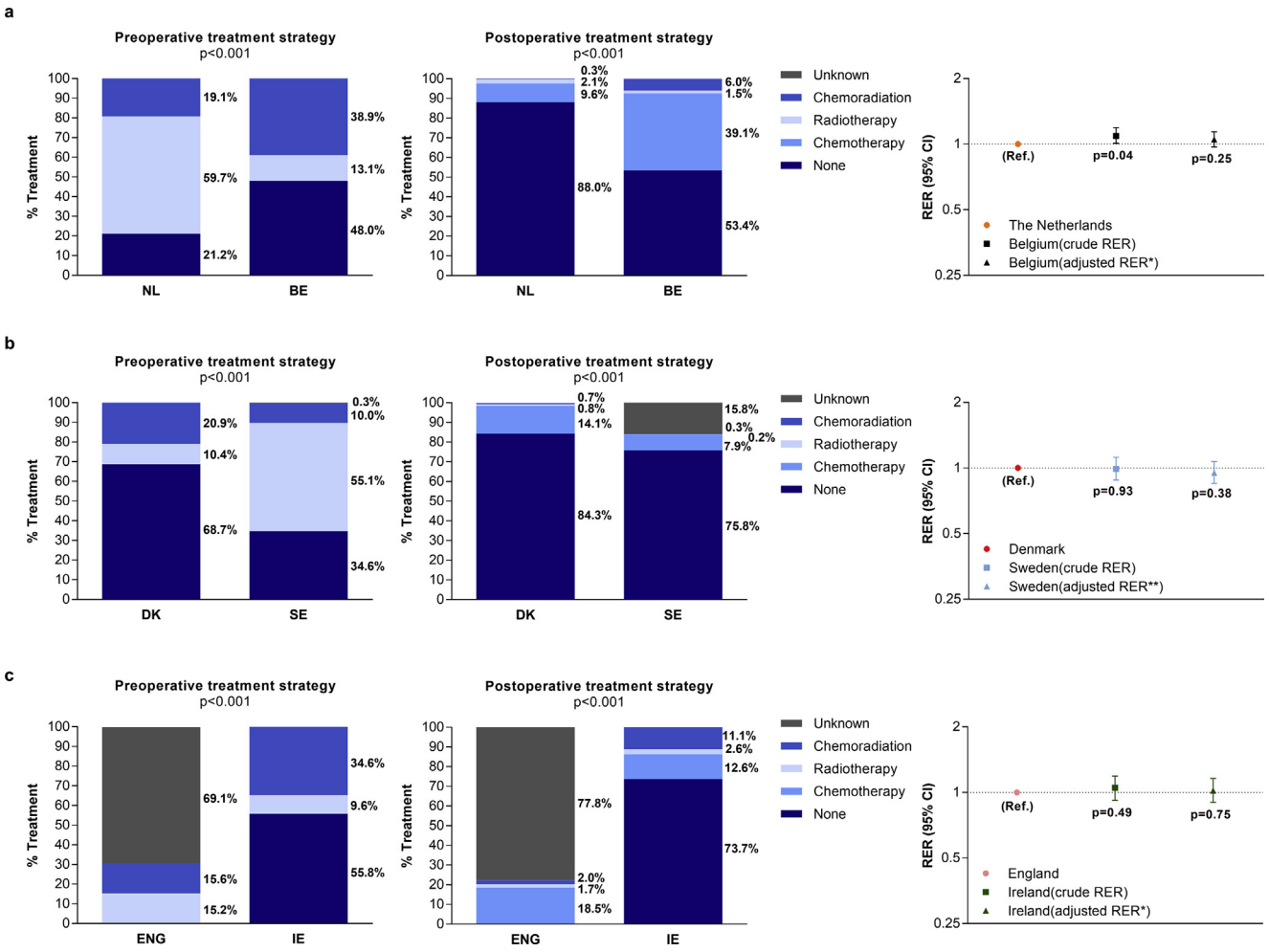

Fig. 1. Treatment strategies and Relative Excess Risks (RERs) of death for a. The Netherlands and Belgium, b. Denmark and Sweden, and c. England and Ireland, * Adjusted for gender, age, year of diagnosis, grade, **Adjusted for gender, age, year of diagnosis.

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%).

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

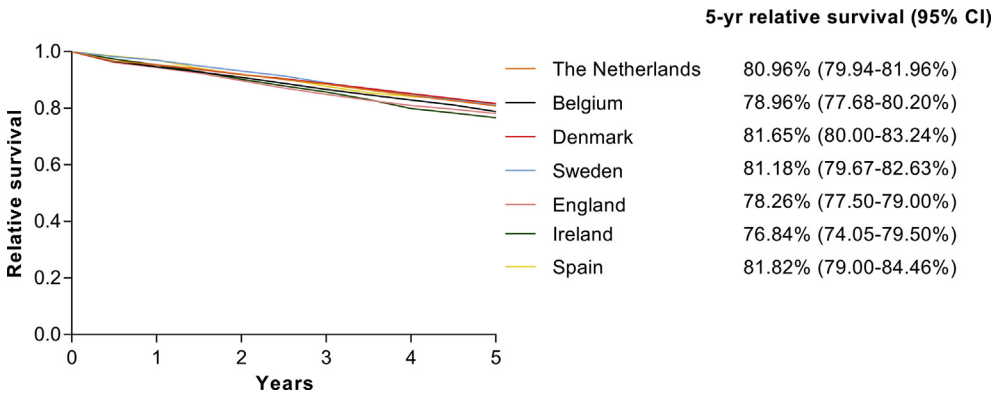

Fig. 2. Relative survival.

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 $\leq$5 mm, and distance to the mesorectal fascia (MRF) of >1 mm. 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 $\leq$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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Disclosure

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.05.025.

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