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One-year excess mortality and treatment in surgically treated patients with colorectal cancer: A EURECCA European comparison

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ABSTRACT

Background: Mortality in the first postoperative year represents an accurate reflection of the perioperative risk after colorectal cancer surgery. This research compares one-year mortality after surgery divided into three age-categories (18-64, 65-74, ≥75 years), focusing on time trends and comparing treatment strategies.

Material: Population-based data of all patients diagnosed and treated surgically for stage I-III primary colorectal cancer from 2007 to 2016, were collected from Belgium, the Netherlands, Norway, and Sweden. Stratified for age-category and stage, treatment was evaluated, and 30-day, one-year and one-year excess mortality were calculated for colon and rectal cancer separately. Results were evaluated over two-year time periods.

Results: Data of 206,024 patients were analysed. Postoperative 30-day and one-year mortality reduced significantly over time in all countries and age-categories. Within the oldest age category, in 2015–2016, one-year excess mortality varied from 9% in Belgium to 4% in Sweden for colon cancer and, from 9% in Belgium to 3% in the other countries for rectal cancer. With increasing age, patients were less likely to receive additional therapy besides surgery. In Belgium, colon cancer patients were more often treated with adjuvant chemotherapy ($p < 0.001$). For neoadjuvant treatment of rectal cancer, patients in Belgium and Norway were mostly treated with chemoradiotherapy. In the Netherlands and Sweden, radiotherapy alone was preferred ($p < 0.001$).

Conclusions: Despite improvement over time in all countries and age-categories, substantial variation exists in one-year postoperative mortality. Differences in one-year excess postoperative mortality could be due to differences in treatment strategies, highlighting the consequences of under- and over-treatment on cancer survival.

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1. Introduction

Colorectal cancer is the third most common cancer in men and the second most commonly occurring cancer in women. [1] Although other treatment options are being investigated [2], surgery continues to play an essential role in the treatment of colorectal cancer. An important outcome measure for surgery is postoperative mortality and is usually described as 30-day mortality. An earlier study by Dekker et al. revealed that the excess mortality (mortality adjusted for expected mortality in the general population) in the first postoperative year after colorectal cancer surgery is a more accurate reflection of the postoperative risk, in comparison with the 30-day mortality. Death in the first postoperative year, for stage I-III colorectal cancer patients, is in 25% of patients not expected to be from cancer itself or a recurrence but rather an adverse effect of treatment. [3] Across countries survival disparities for colorectal cancer exists. [4] Various EURECCA comparisons have been published, showing a wide variety of treatment strategies across European countries. [5-10]

Considering the importance of the first postoperative year, we used this outcome for comparative purposes of the postoperative course as this may best reflect treatment-related outcomes. The impact of the first-year mortality on long-term survival is profound and will impact cancer-related outcomes as well. Differences in one-year excess mortality between countries are interesting as they could be consequential to differences in treatment strategies. Identifying possible differences in one-year excess mortality and treatment strategies could be a starting point for critical evaluation of national guidelines and their implementation. Using population-based data of four European countries, Belgium, the Netherlands, Norway, and Sweden, the current research aims to make an international comparison of the one-year mortality after surgery and compare time trends and treatment of colorectal patients in three age categories.

2. Material and methods

2.1. Study design and data sources

This project is an observational, international cohort study of consecutively collected population-based data. Data have been collected from the national cancer registries of Belgium, the Netherlands, Norway, and Sweden. Belgian hospitals with care programs for oncological care, as well as all the pathology labs, are legally required to notify all cancer cases to the Belgian Cancer Registry. In the Netherlands, information about every patient with cancer is gathered in the Netherlands Cancer Registry, managed by the Netherlands Comprehensive Cancer Organisation. Data from Norway have been collected from the Cancer Registry of Norway. [11] All medical doctors in Norway are instructed by law to notify all new cancer cases. This registry is linked to the Norwegian Colorectal Cancer Registry, a specialized registry that contains detailed clinical information on all patients with colorectal cancer nationwide. [12] The Swedish Colorectal cancer registry provided clinical data on patients with colorectal cancer in Sweden. [13] All the cancer registries guaranteed the overall quality of data in terms of completeness (>95% of cancer patients in the population registered) and accuracy. No separate ethical approval was needed, as this study was based on de-identified registry data.

2.2. Procedures

Data were collected from all patients ≥18 years, diagnosed with primary colon or rectal cancer from January 2007 to December 2016, and undergoing surgical treatment. In case of patients diagnosed with multiple, simultaneous tumours, the tumour with the worst prognostic characteristics, using stage and grade, was chosen for all analyses. Stage was primarily based on pathological information and completed with clinical stage when necessary, using the 7th edition of the AJCC TNM staging. For rectal cancer, pathological information was based on either pT stage (after primary surgery) or ypT stage (after radiotherapy/chemoradiotherapy and surgery). Belgium and the Netherlands provided their data on stage from 2007 to 2009 using the TNM stage 6th edition, the years 2010–2016 were delivered using the TNM 7th edition. Included were stage I-III, leaving out metastatic disease (stage IV) and unknown stage. Colon cancer was defined by topographical codes C18-C19 and rectal cancer by code C20 of the International Classification of Diseases for Oncology. [14] In Sweden, topographical code C19 (rectosigmoid) was not defined as surgeons decide during surgery whether the tumour is part of the colon or the rectum. Only patients undergoing surgical resection were included in this study. Surgical treatment was defined as surgical removal of the tumour-bearing bowel segment, irrespective of curative or palliative intent. Patients with local excision of the tumour, including transanal endoscopic microsurgery, were excluded. In Norway, data on chemotherapy was not available. The assumption was made that patients received chemotherapy as per national guidelines. [15] Appendix A provides an overview of the data selection of each country.

2.3. Statistics

Patients were divided into three groups: <65 years, 65-74 years, and ≥75 years. All analyses were performed stratified by tumour location, country, stage, and age category. For the time trend analyses, periods consisting of two years were made. Thirty-day and one-year overall mortality were calculated, as well as treatment characteristics, using SPSS version 25.0. Differences were tested with chi-square tests. Finally, one-year excess mortality was calculated using the following formula: (observed numbers of death in the first year − expected number of deaths in the matched general population)/ (number of patients). The expected number of deaths was calculated using national life tables (www.mortality.org) matched for country, age, sex, and year of incidence. Time-trends for mortality were analysed using logistic regression with mortality as outcome and time periods as covariate, p-values over the years are reported.

3. Results

3.1. Patient characteristics

The surgical treatment rate of all patients ≥18 years diagnosed with stage I-III colorectal cancer and reliable follow-up between 2007 and 2016 varied from 64.3% in Belgium and Norway to 66.1% in Sweden and 66.9% in the Netherlands (appendix A). For the current analyses, data of 206,024 patients were included (Belgium 53,071 patients, the Netherlands 88,784 patients, Norway 25,548 patients, Sweden 38,621 patients). Details, stratified by tumour location, on distribution within age-categories, gender, year of diagnosis, and stage are displayed in Table 1.

3.2. Colon cancer, time trend analysis, stages

Time trends over the years, stratified for stage, age-category, and country, were all statistically significant ($p < 0.001$). Differences in stage distribution between countries in time period 2015-2016 were all statistically significant except for stage II in the older age category. Stage III disease remained the most common stage within

Table 1a
Characteristics of patients operated for colon cancer diagnosed in the period 2007–2016.

	Belgium			The Netherlands			Norway			Sweden		
	< 65 years	65–74 years	≥ 75 years	< 65 years	65–74 years	≥ 75 years	< 65 years	65–74 years	≥ 75 years	< 65 years	65–74years	≥ 75 years
	(*N* = 9,645)	(*N* = 11,280)	(*N* = 18,063)	(*N* = 17,402)	(*N* = 21,784)	(*N* = 24,919)	(*N* = 4,564)	(*N* = 5,651)	(*N* = 8,698)	(*N* = 5,585)	(*N* = 8,162)	(*N* = 12,775)
Gender												
Male	5,362 (55.6)	6,652 (59.0)	8,461 (46.8)	9,298 (53.4)	12,163 (55.8)	11,868 (47.6)	2,312 (50.7)	2,835 (50.2)	3,750 (43.1)	2,955 (52.9)	4,215 (51.6)	5,710 (44.7)
Female	4,283 (44.4)	4,628 (41.0)	9,602 (53.2)	8,104 (46.6)	9,621 (44.2)	13,051 (52.4)	2,252 (49.3)	2,816 (49.8)	4,948 (56.9)	2,630 (47.1)	3,947 (48.4)	7,065 (55.3)
Year of diagnosis												
2007–2008	1,691 (17.5)	1,979 (17.5)	3,489 (19.3)	3,294 (18.9)	3,525 (16.2)	4,863 (19.5)	806 (17.7)	950 (16.8)	1,655 (19.0)	1,131 (20.3)	1,466 (18.0)	2,391 (18.7)
2009–2010	1,808 (18.7)	2,032 (18.0)	3,525 (19.5)	3,341 (19.2)	3,611 (16.6)	4,991 (20.0)	852 (18.7)	1,065 (18.8)	1,715 (19.7)	1,131 (20.3)	1,544 (18.9)	2,497 (19.5)
2011–2012	1,907 (19.8)	2,157 (19.1)	3,717 (20.6)	3,316 (19.1)	4,079 (18.7)	4,952 (19.9)	919 (20.1)	1,118 (19.8)	1,682 (19.3)	1,110 (19.9)	1,677 (20.5)	2,499 (19.6)
2013–2014	2,122 (22.0)	2,781 (24.7)	3,762 (20.8)	3,249 (18.7)	4,640 (21.3)	5,338 (21.4)	973 (21.3)	1,206 (21.3)	1,784 (20.5)	1,053 (18.9)	1,694 (20.8)	2,572 (20.1)
2015–2016	2,117 (21.9)	2,331 (20.7)	3,570 (19.8)	4,202 (24.1)	5,929 (27.2)	4,775 (19.2)	1,014 (22.2)	1,312 (23.2)	1,862 (21.4)	1,160 (20.8)	1,781 (21.8)	2,816 (22.0)
Stage												
Stage I	2,313 (24.0)	2,856 (25.3)	3,373 (18.7)	3,621 (20.8)	5,326 (24.4)	4,975 (20.0)	1,012 (22.2)	1,238 (21.9)	1,826 (21.0)	858 (15.4)	1,492 (18.3)	2,109 (16.5)
Stage II	3,534 (36.6)	4,492 (39.8)	8,434 (46.7)	6,378 (36.7)	8,635 (39.6)	11,534 (46.3)	1,800 (39.4)	2,536 (44.9)	4,156 (47.8)	2,207 (39.5)	3,423 (41.9)	5,952 (46.6)
Stage III	3,798 (39.4)	3,932 (34.9)	6,256 (34.6)	7,403 (42.5)	7,823 (35.9)	8,410 (33.7)	1,752 (38.4)	1,877 (33.2)	2,716 (31.2)	2,520 (45.1)	3,247 (39.8)	4,714 (36.9)

Data are presented as n (%).

Table 1b
Characteristics of patients operated for rectal cancer diagnosed in the period 2007–2016.

	Belgium			The Netherlands			Norway			Sweden		
	< 65 years	65–74 years	≥ 75 years	< 65 years	65–74 years	≥ 75 years	< 65 years	65–74 years	≥ 75 years	< 65 years	65–74 years	≥ 75 years
	(*N* = 5,108)	(*N* = 4,288)	(*N* = 4,687)	(*N* = 9,767)	(*N* = 8,757)	(*N* = 6,155)	(*N* = 2,408)	(*N* = 2,153)	(*N* = 2,074)	(*N* = 3,936)	(*N* = 4,349)	(*N* = 3,814)
Gender												
Male	3,231 (63.3)	2,852 (66.5)	2,702 (57.6)	6,115 (62.6)	5,840 (66.7)	3,531 (57.4)	1,426 (59.2)	1,390 (64.6)	1,153 (55.6)	2,303 (58.5)	2,746 (63.1)	2,204 (57.8)
Female	1,877 (36.7)	1,436 (33.5)	1,985 (42.4)	3,652 (37.4)	2,917 (33.3)	2,624 (42.6)	982 (40.8)	763 (35.4)	921 (44.4)	1,633 (41.5)	1,603 (36.9)	1,610 (42.2)
Year of diagnosis												
2007–2008	1,023 (20.0)	847 (19.8)	977 (20.8)	1,864 (19.1)	1,453 (16.6)	1.158 (18.8)	452 (18.8)	350 (16.3)	390 (18.8)	791 (20.1)	785 (18.1)	806 (21.1)
2009–2010	1,039 (20.3)	847 (19.8)	959 (20.5)	1,877 (19.2)	1,575 (18.0)	1,194 (19.4)	480 (19.9)	420 (19.5)	435 (21.0)	759 (19.3)	807 (18.6)	787 (20.6)
2011–2012	1,022 (20.0)	846 (19.7)	981 (20.9)	1,949 (20.0)	1,711 (19.5)	1,267 (20.6)	436 (18.1)	420 (19.5)	417 (20.1)	802 (20.4)	842 (19.4)	781 (20.5)
2013–2014	1,058 (20.7)	972 (22.7)	900 (19.2)	1,867 (19.1)	1,918 (21.9)	1,351 (21.9)	537 (22.3)	497 (23.1)	412 (19.9)	789 (20.0)	898 (20.6)	731 (19.2)
2015–2016	966 (18.9)	776 (18.1)	870 (18.6)	2,210 (22.6)	2,100 (24.0)	1.185 (19.3)	503 (20.9)	466 (21.6)	420 (20.3)	795 (20.2)	1,017 (23.4)	709 (18.6)
Stage												
Stage I	1,750 (34.3)	1,504 (35.1)	1,382 (29.5)	1,784 (18.3)	1,924 (22.0)	1,403 (22.8)	586 (24.3)	586 (27.2)	541 (26.1)	1,113 (28.3)	1,325 (30.5)	1,116 (29.3)
Stage II	1,398 (27.4)	1,290 (30.1)	1,595 (34.0)	2,358 (24.1)	2,402 (27.4)	2,066 (33.6)	639 (26.5)	651 (30.2)	758 (36.5)	1,139 (28.9)	1,353 (31.1)	1,275 (33.4)
Stage III	1,960 (38.4)	1,494 (34.8)	1,710 (36.5)	5,625 (57.6)	4,431 (50.6)	2,686 (43.6)	1,183 (49.1)	916 (42.5)	775 (37.4)	1,684 (42.8)	1,671 (38.4)	1,423 (37.3)

Data are presented as n (%).

Table 2a
Stage time trends in percentages for colon cancer patients.

	Stage I						Stage II						Stage III					
	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	*P-value*	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	*P-value*	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	*P-value*
< 65 years						<0.001						0.003						<0.001
Belgium	18.3	20.6	21.3	26.1	31.6		39.8	39.2	38.8	33.5	33.2		41.9	40.2	39.9	40.4	35.2	
The Netherlands	18.2	17.9	18.1	20.1	27.9		38.6	39.7	37.9	36.5	31.8		43.2	42.4	44.0	43.4	40.3	
Norway	17.7	18.2	19.4	26.3	27.6		44.0	41.5	41.9	36.9	34.2		38.2	40.3	38.7	36.8	38.2	
Sweden	13.3	15.9	15.2	14.7	17.6		42.9	40.3	39.5	37.3	37.5		43.9	43.8	45.3	48.0	44.9	
65–74 years						<0.001						<0.001						<0.001
Belgium	19.4	20.7	22.3	30.7	30.7		43.4	43.3	40.0	36.5	37.6		37.2	36.0	37.7	32.8	31.7	
The Netherlands	19.5	21.1	22.3	23.0	32.0		43.4	41.5	40.1	40.8	35.0		37.1	37.4	37.6	36.1	32.9	
Norway	21.6	22.6	19.7	22.4	23.0		44.7	43.7	46.4	45.1	44.4		33.7	33.7	33.9	32.5	32.5	
Sweden	17.4	18.6	18.6	18.1	18.6		45.1	42.0	42.3	40.9	40.0		37.5	39.4	39.1	41.0	41.4	
≥ 75 years						0.006						0.375						<0.001
Belgium	16.2	17.8	17.8	20.3	21.1		47.4	47.6	47.1	45.3	46.2		36.4	34.5	35.1	34.4	32.8	
The Netherlands	18.0	18.6	19.1	23.3	20.6		46.9	48.4	47.2	42.8	46.3		35.1	33.0	33.7	33.9	33.1	
Norway	20.7	19.6	20.6	21.9	22.1		48.3	49.0	48.8	46.7	46.2		30.9	31.4	30.7	31.4	31.7	
Sweden	16.3	16.0	15.1	16.7	18.2		48.8	48.3	47.5	44.4	44.4		35.0	35.6	37.4	38.9	37.4	

Percentages are conducted from the stages within the same country and age category. *P-values* are for differences between countries in time period 2015-2016.

Table 2b
Stage time trends in percentages for rectal cancer patients.

	Stage I						Stage II						Stage III					
	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	*P-value*	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	*P-value*	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	*P-value*
< 65 years						<0.001						<0.001						<0.001
Belgium	30.8	33.8	32.5	36.2	38.2		29.4	26.5	29.3	26.4	25.3		39.8	39.7	38.3	37.4	36.5	
The Netherlands	22.0	16.4	15.7	16.4	20.5		30.5	28.9	22.3	21.2	18.9		47.5	54.8	62.0	62.3	60.5	
Norway	20.1	21.9	22.5	26.6	29.6		29.2	25.2	26.1	27.0	25.2		50.7	52.9	51.4	46.4	45.1	
Sweden	27.7	23.1	32.2	28.3	29.9		29.5	32.4	29.7	26.7	26.5		42.9	44.5	38.2	45.0	43.5	
65–74 years						<0.001						0.001						<0.001
Belgium	31.4	31.2	35.3	38.2	39.2		32.1	32.8	29.6	28.3	27.7		36.5	36.0	35.1	33.5	33.1	
The Netherlands	22.8	22.2	17.8	20.0	26.4		34.6	30.8	27.1	24.8	22.6		42.5	47.0	55.1	55.3	51.0	
Norway	22.0	22.4	27.1	31.4	31.1		31.4	31.4	31.7	29.8	27.5		46.6	46.2	41.2	38.8	41.4	
Sweden	28.3	28.9	27.7	32.5	33.9		32.1	31.1	34.6	30.1	28.4		39.6	40.0	37.8	37.4	37.7	
≥ 75 years						<0.001						<0.001						<0.001
Belgium	27.5	29.2	27.4	30.2	33.6		33.8	33.7	36.9	32.9	32.6		38.7	37.1	35.7	36.9	33.8	
The Netherlands	24.9	22.0	21.0	21.5	25.0		39.2	36.8	36.9	29.7	25.7		35.9	41.2	42.1	48.9	49.3	
Norway	24.4	23.7	24.5	30.3	27.6		40.3	39.8	36.0	32.0	34.8		35.4	36.6	39.6	37.6	37.6	
Sweden	29.7	28.1	28.3	30.1	30.3		34.9	34.3	33.5	32.3	31.9		35.5	37.6	38.2	37.6	37.8	

Percentages are conducted from the stages within the same country and age category. *P-values* are for differences between countries in time period 2015-2016.

the youngest age-category and stage II within the two other age-categories (details in Table 2a).

3.3. Rectal cancer, time trend analysis, stages

For stage III disease, a substantial increase was observed within the Netherlands within all age-categories, on average, from 42% to 54% over the years. This is contrary to Belgium, which showed a slight decrease in stage III diagnoses, on average, from 38% to 35%. Time trends over the years, stratified for stage, age-category, and country were all statistically significant ($p < 0.001$), except for stage III in the middle age-category in the Netherlands ($p = 0.262$) and stage III in the youngest age-category in Norway ($p = 0.392$) (details in Table 2b).

3.4. Colon cancer, treatment differences

In all countries and stages, the use of chemotherapy increased with stage and decreased with age. In Belgium, patients were more often treated with adjuvant chemotherapy in comparison with the other countries. For stage III disease in Belgium, this varied from 91.7% in the youngest age-category to 42.1% in the oldest age category. For the Netherlands, this was 86.6% to 25.7%, respectively, and for Sweden, 78.8% to 20.7%, respectively (Fig. 1a and appendix B.1).

3.5. Rectal cancer, treatment differences

In the majority of cases, rectal cancer patients in Belgium and Norway were treated with neoadjuvant chemoradiotherapy, while the Netherlands (stage I, II) and Sweden (all stages) preferred neoadjuvant radiotherapy alone (Fig. 1b). Furthermore, in Belgium, rectal cancer treatment was more frequently completed with adjuvant chemotherapy compared to the Netherlands and Norway in all stages and compared to stage I and II in Sweden (Fig. 1c and appendix B.2).

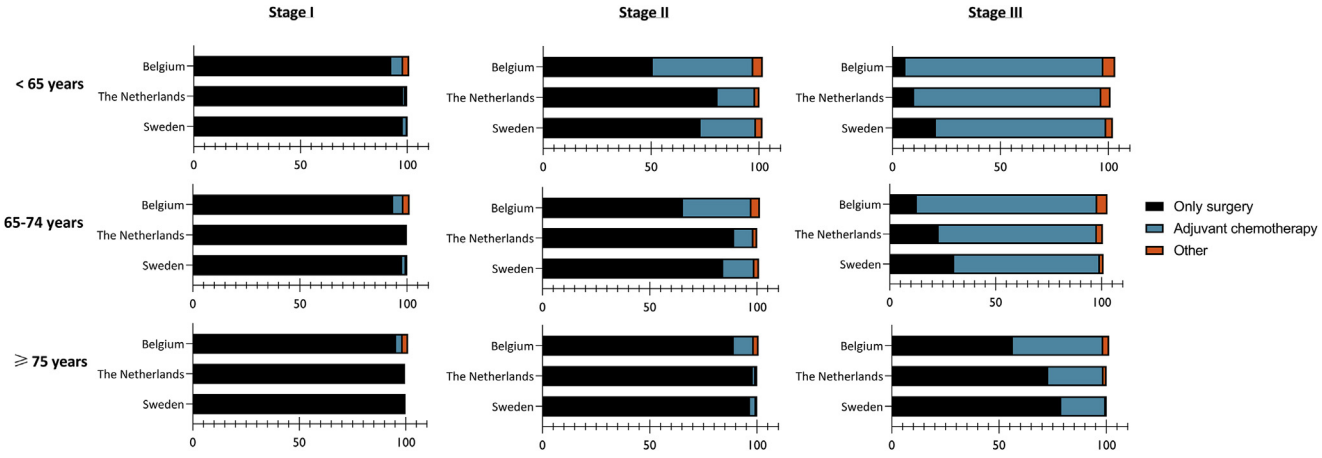

Fig. 1a. Treatment according to country, age and stage in colon cancer patients. Neoadjuvant and adjuvant treatment are combined; therefore, percentages can be above 100%. Differences between countries for adjuvant chemotherapy, stratified for age category and stage were calculated using chi-square. All differences had a *P-value* <0.001.

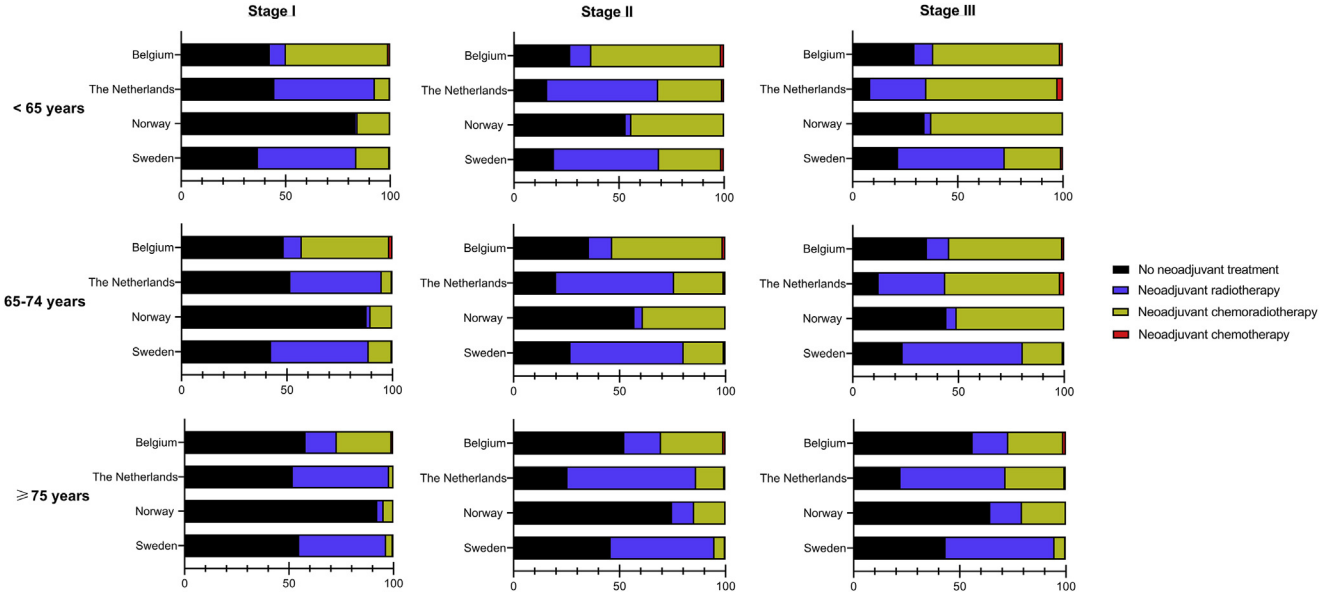

Fig. 1b. Neoadjuvant treatment, according to country, age and stage in rectal cancer patients. Differences between countries, stratified for age category and stage were calculated using chi-square. All differences between countries for neoadjuvant radiotherapy and chemoradiotherapy had a *P-value* <0.001.

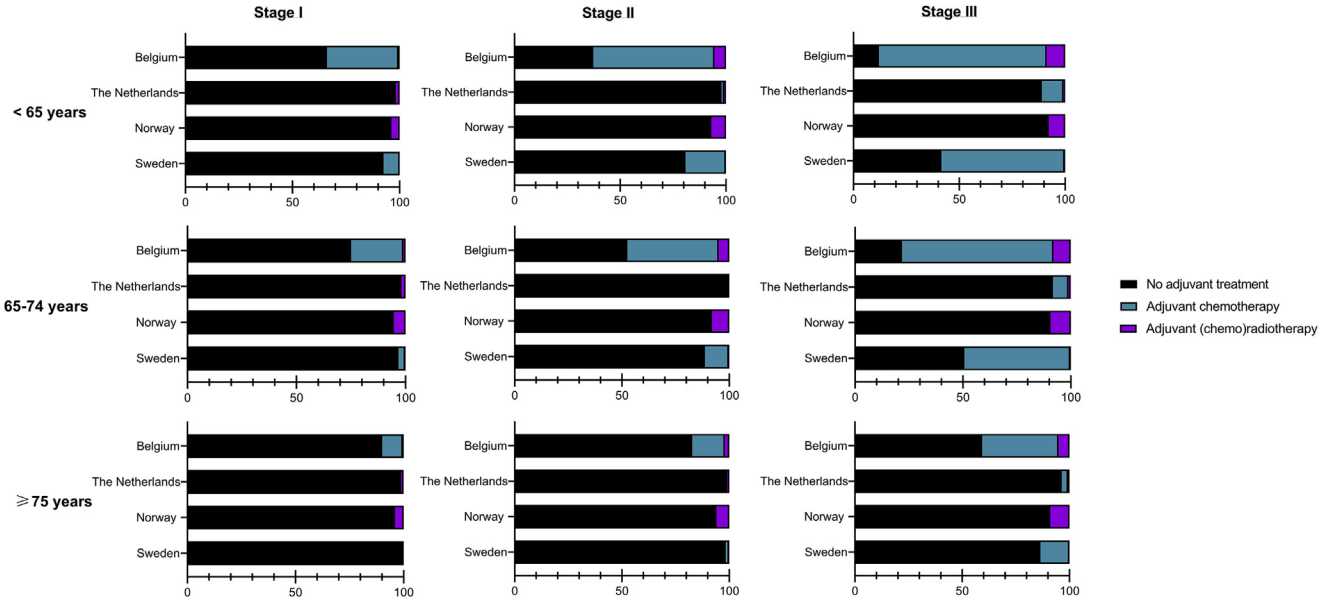

Fig. 1c. Adjuvant treatment, according to country, age and stage in rectal cancer patients. Differences between countries, stratified for age category and stage were calculated using chi-square. All differences between countries for adjuvant chemotherapy had a *P-value* <0.001.

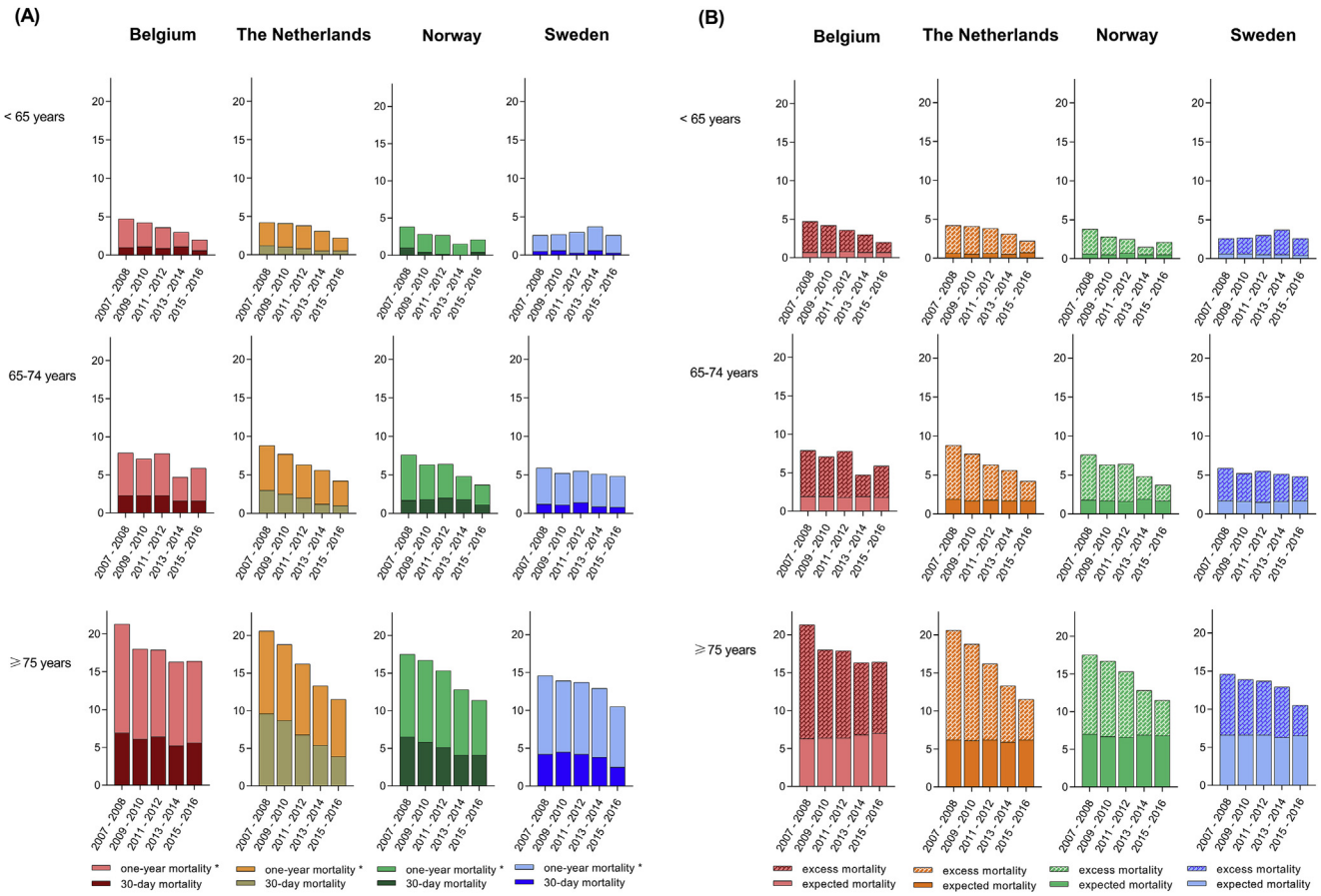

Fig. 2. (A) 30-day and one-year overall mortality in colon cancer patients. (B) One-year expected and excess mortality in colon cancer patients.
* One-year mortality is represented by the full bar.

Table 3a
Mortality time trends in percentages for colon cancer patients.

	≤ 30-day, overall mortality						1st year, overall mortality						1st year, excess mortality					
	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	*P-value*	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	*P-value*	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016
< 65 years						0.70						0.72					
Belgium	1.0	1.1	0.9	1.1	0.6		4.7	4.2	3.6	3.0	2.0		4.0	3.5	2.8	2.3	1.3
The Netherlands	1.2	1.0	0.8	0.5	0.5		4.2	4.1	3.8	3.1	2.2		3.6	3.6	3.2	2.6	1.5
Norway	1.0	0.4	0.1	0.0	0.4		3.8	2.8	2.5	1.5	2.1		3.2	2.3	1.8	1.0	1.6
Sweden	0.5	0.6	0.3	0.6	0.3		2.6	2.7	3.0	3.7	2.6		2.0	2.1	2.5	3.2	2.2
65–74 years						0.08						0.004					
Belgium	2.3	2.3	2.3	1.6	1.6		7.9	7.1	7.8	4.7	5.9		6.0	5.2	6.0	2.8	4.1
The Netherlands	3.0	2.5	2.0	1.2	1.0		8.8	7.7	6.3	5.6	4.2		6.9	6.0	4.5	3.9	2.5
Norway	1.7	1.8	2.0	1.8	1.1		7.6	6.3	6.4	4.8	3.7		5.8	4.6	4.8	2.9	2.0
Sweden	1.2	1.1	1.4	0.9	0.8		5.9	5.2	5.5	5.1	4.8		4.2	3.6	4.0	3.5	3.1
> 74 years						<0.001						<0.001					
Belgium	6.9	6.1	6.4	5.2	5.6		21.3	18.0	17.9	16.3	16.4	16.4	15.0	11.6	11.5	9.5	9.4
The Netherlands	9.6	8.7	6.8	5.4	3.9		20.6	18.8	16.2	13.3	11.5	11.5	14.4	12.7	10.0	7.4	5.3
Norway	6.5	5.8	5.1	4.1	4.1		17.5	16.7	15.3	12.8	11.5	11.5	10.5	10.0	8.7	5.9	4.7
Sweden	4.2	4.5	4.2	3.8	2.5		14.6	13.9	13.7	12.9	10.5	10.5	8.0	7.3	7.1	6.6	4.0

P-values are for differences between countries in time period 2015-2016.

3.6. Colon cancer, time trend analysis, mortality

Overall, 30-day and one-year mortality, stratified for age-category and country decreased over time ($p < 0.001$), with the largest decrease in the Netherlands (figures 2a and 2b). In time period 2015-2016, one-year overall mortality was statistically different between countries in the middle ($p = 0.004$) and oldest ($p < 0.001$) age-category (Table 3a). One-year expected mortality remained stable over the years and was comparable for all countries. The decreases in one-year overall mortality are due to reductions in excess mortality over the years. Within the oldest patient group, Belgium had a higher one-year excess mortality in the most recent years (9%), compared to the Netherlands, Norway, and Sweden (5%).

3.7. Rectal cancer, time trend analysis, mortality

Time trends for one-year overall mortality over the years, stratified for age-category and country, were all statistically significant ($p < 0.001$). Here too, one-year expected mortality was similar between the countries and over the years (figures 3a and 3b, Table 3b). While excess mortality among the youngest Belgian patients was average, the middle and oldest age-category had three times higher one-year excess mortality compared to the average. In the oldest age-category, one-year excess mortality was 9% in the most recent years compared to, on average, 3% in the other countries. Additional analyses with the most recent years learned that the higher one-year overall mortality was reflected in all stages in the oldest group in Belgium, statistically significant for stage II ($p = 0.007$) and stage III (<0.001) (appendix C). However, it was most pronounced in stage III, where a 20% one-year overall mortality was seen in Belgium, compared to an average of 10% in the other countries.

4. Discussion

The present study found minor differences in 30-day postoperative mortality and substantial differences in one-year postoperative excess mortality in an international cohort comparing surgically treated colorectal cancer patients. Excess mortality decreased over time in all countries. However, some striking differences across countries persisted over time, which could be related to differences in treatment strategies.

Cancer-related deaths in the first postoperative year are unlikely the result of primary stage I-III colorectal cancer itself, as recurrences usually appear after the first year of treatment. [16,17] Even when they do appear in the first year, they hardly ever lead to mortality in the first year after treatment. Additionally, research found that 25% of deaths in the first postoperative year were attributed to postoperative complications. [3] The one-year mortality reduction over the time periods in this study is most likely due to improvements in surgical procedures (laparoscopy), as well as improved perioperative and postoperative care. [18,19] However, a prolonged impact of treatment which could persist after hospital discharge should not be underestimated. [20] Attention for the time after discharge should be a focus for the improvement of treatment.

Improvement of care and quality assessment can be accomplished by clinical auditing, ultimately leading to demonstrable improvements in patient outcomes, partly as a result of a response to the awareness of being observed, causing a modification of behaviour. [21] The introduction of nationwide audits could partly explain the substantial improvement over time in the investigated countries. [22–25] This improvement is also enhanced by the emergence of multidisciplinary team meetings, where patients are

individually discussed by several specialists, leading to a more substantiated treatment plan for each patient. [26] The early introduction of multidisciplinary management in Sweden could also have contributed to the relatively low excess mortality in the early years of the current analyses. The same could be true for the centralization of treatment and further specialization. [13]

It can be beneficial to identify colorectal cancer at an earlier, asymptomatic stage, as screening typically leads to initial greater detection of and shift toward early-stage cancers, which could eventually lead to a decrease in incidence due to the removal of premalignant adenomas. [27] In Norway and Sweden, a pilot of national screening programs has started, without full implementation yet. In Belgium, it was launched in 2009 (on a national level in 2013) and in the Netherlands in 2014. [28] Its effect is already noticeable by the stage distribution shift over time. Stage III proportion decreased in favour of an important increase of stage I tumours, visible for colon and rectal cancer in Belgium and colon cancer in the Netherlands. For rectal cancer, the increasing use of chemoradiotherapy, and therefore down-staging of the pathological stage could also have been of influence. [29] Despite that, an increase in stage III diagnoses for rectal cancer was seen in the Netherlands. This may be an effect of stage migration, caused by a more thorough examination of lymph nodes. [30]

In general, with increasing age, patients were less likely to be treated with additional therapy. Yet differences in treatment strategies were found. Patients in Belgium received chemotherapy more often in colon cancer and rectal cancer. In the Netherlands and Sweden, patients with rectal cancer were more likely to receive neoadjuvant radiotherapy, while patients in Belgium and Norway were often treated with neoadjuvant chemoradiotherapy. Moreover, in Belgium, and to a lesser extent in Sweden, treatment of rectal cancer patients was frequently completed with adjuvant chemotherapy. A study of Vermeer et al., with colon cancer patients older than 80 years, demonstrated differences in adjuvant chemotherapy for stage III disease from 4% in Norway to 25% in Belgium [6]. In our data, colon cancer patients in Belgium, in all age-categories, received adjuvant chemotherapy more often than patients in the Netherlands or Sweden. Interestingly, the excess mortality was higher in Belgium than in the other countries. For rectal cancer, this difference in excess mortality was even greater (three times) for patients in the middle and oldest age-category with stage III disease, which may suggest the possibility of overtreatment. It has been argued before that it is essential to find a balance between under- and overtreatment, and adjuvant treatment should be considered carefully in older patients. [31,32]. Naturally, this balance should also be sought for young patients. In the current data, young colorectal cancer patients from Belgium and the Netherlands have comparable one-year mortality, while their treatment strategy concerning adjuvant chemotherapy is different.

The results of this study should be interpreted with regard to several limitations. No information on comorbidities and frailty, which significantly affect prognosis and treatment plan, were available for the current analyses. Data on postoperative complications, known for its negative influence on survival, were lacking as well. Also, there was no information on the number of emergency surgeries. Patients treated in an emergency setting are especially at risk for complications and mortality. [3,33,34].

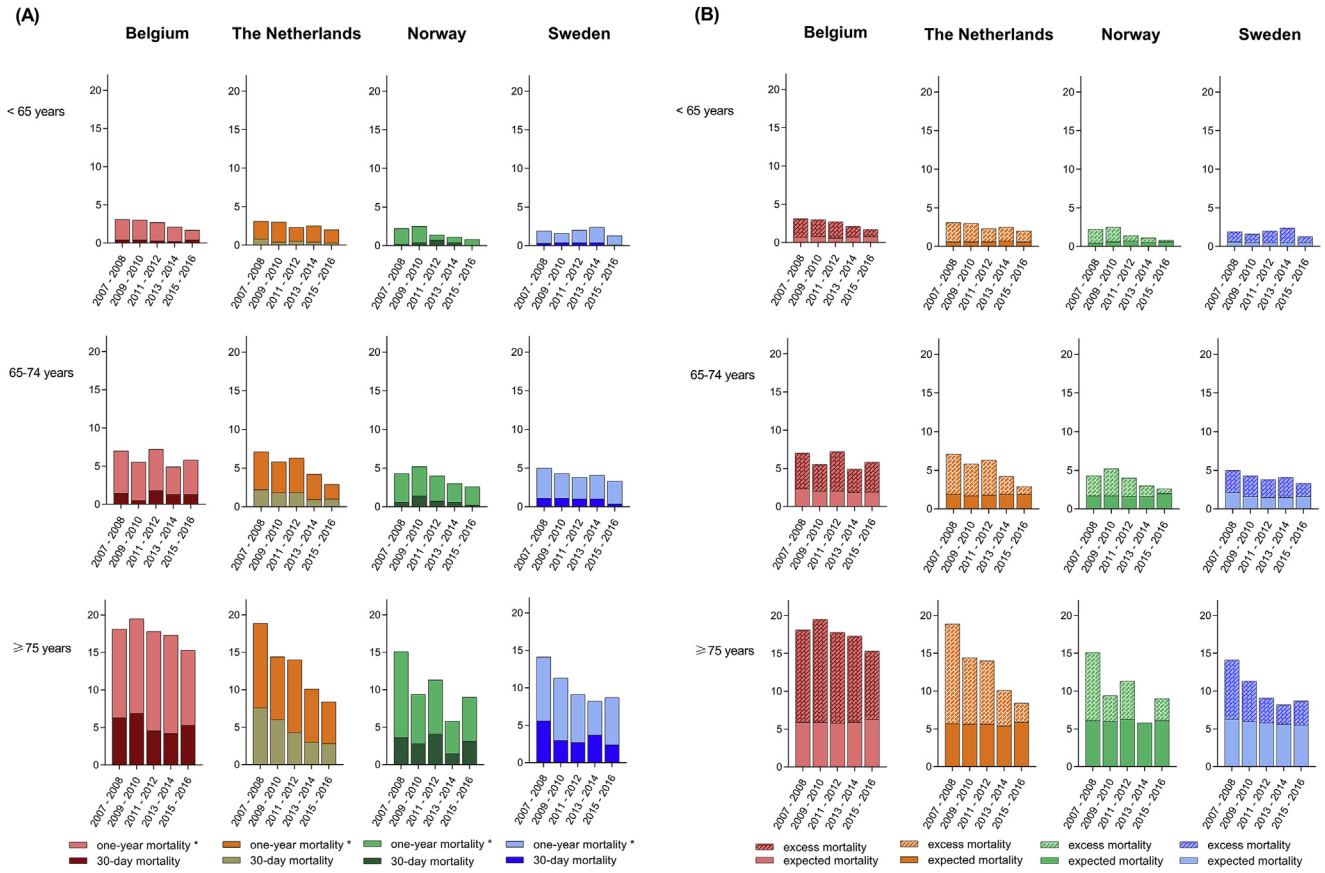

Fig. 3. (A) 30-day and one-year overall mortality in rectal cancer patients. (B) One-year expected and excess mortality in rectal cancer patients.
* One-year mortality is represented by the full bar.

Table 3b
Mortality time trends in percentages for rectal cancer patients.

	≤ 30-day, overall mortality						1st year, overall mortality						1st year, excess mortality					
	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	*P -value*	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	*P -value*	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	
< 65 years						0.40						0.20						
Belgium	0.4	0.4	0.3	0.2	0.4		3.1	3.0	2.7	2.1	1.7		2.4	2.2	2.1	1.4	0.9	
The Netherlands	0.8	0.4	0.5	0.4	0.3		3.1	3.0	2.3	2.5	2.0		2.5	2.4	1.7	1.8	1.4	
Norway	0.2	0.4	0.7	0.4	0.0		2.2	2.5	1.4	1.1	0.8		1.8	1.9	0.7	0.6	0.2	
Sweden	0.3	0.4	0.4	0.4	0.1		1.9	1.6	2.0	2.4	1.3		1.3	1.1	1.5	1.9	0.8	
65–74 years						0.06						0.001						
Belgium	1.4	0.5	1.8	1.3	1.3		7.0	5.5	7.2	4.9	5.8		4.7	3.5	5.2	3.1	3.9	
The Netherlands	2.2	1.8	1.8	0.9	1.0		7.1	5.8	6.3	4.2	2.9		5.2	4.1	4.5	2.3	1.0	
Norway	0.6	1.4	0.7	0.6	0.2		4.3	5.2	4.0	3.0	2.6		2.6	3.5	2.4	1.4	0.6	
Sweden	1.1	1.1	1.0	1.0	0.4		5.0	4.3	3.8	4.1	3.3		2.9	2.7	2.3	2.6	1.7	
≥ 75 years						0.005						<0.001						
Belgium	6.3	6.9	4.6	4.2	5.3		18.1	19.5	17.8	17.3	15.3		12.2	13.6	12.0	11.4	9.0	
The Netherlands	7.6	6.0	4.3	3.0	2.8		18.9	14.4	14.0	10.1	8.4		13.2	8.8	8.4	4.7	2.5	
Norway	3.6	2.8	4.1	1.5	3.1		15.1	9.4	11.3	5.8	9.0		9.0	3.4	5.0	*	2.9	
Sweden	5.6	3.0	2.7	3.7	2.4		14.1	11.3	9.1	8.2	8.7		7.8	5.3	3.3	2.6	3.2	

P-values are for differences between countries in time period 2015-2016.
* No excess mortality.

Population-based data with limited detailed patient and treatment information was used to compare treatment strategies, which makes it challenging to understand the entire process of treatment decisions. Age, comorbidities, frailty, but also patient preferences are known to influence treatment choices. Moreover, selection criteria vary per stage, country, hospital, and clinician. In addition, in some cases, maintaining quality of life is more desirable than receiving curative treatment. However, the use of population-based data is also the strength of this study as it provides robust data, compensating for the lack of detail. The data are in line with previous publications on the topic. [4,35–38]. Although, the current study is the first one to compare differences in age-categories between four European countries. Due to the mandatory nature of the national cancer registrations, we were able to offer a complete overview of the surgically treated adult patients diagnosed with colorectal cancer in four North-European countries in a period of 10 years.

5. Conclusion

Postoperative 30-day and one-year mortality of colorectal cancer patients decreased over time in Belgium, the Netherlands, Norway, and Sweden. However, substantial variations between countries exist. As population mortality in these countries is comparable, differences in excess one-year postoperative mortality could be due to differences in treatment strategies. This highlights the consequences of under- and over-treatment on cancer survival, especially in older patients and should be taken into consideration when evaluating national guidelines.

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Disclosure

All authors substantially contributed to the conception and design or analysis and interpretation of the data; drafting the article or revising it critically, and approved the final version. This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki. The national cancer registries provided anonymized patient data. Therefore, informed consent from patients or ethical approval was not required for this study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paperRenu R. Bahadoer, Esther Bastiaannet, Yyvette H.M. Claassen, Marianne van der Mark, Elizabeth van Eycken, Julie Verbeeck, Marianne G. Guren, Hartwig Kørner, Anna Martling, Robert Johansson, Cornelis J.H van de Velde, Jan W.T. Dekker

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.01.011.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.

[2] van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet 2018;391(10139):2537–45.

[3] Dekker JW, Gooiker GA, Bastiaannet E, van den Broek CB, van der Geest LG, van de Velde CJ, et al. Cause of death the first year after curative colorectal cancer surgery; a prolonged impact of the surgery in elderly colorectal cancer patients. Eur J Surg Oncol 2014;40(11):1481–7.

[4] Araghi M, Arnold M, Rutherford MJ, Guren MG, Cabasag CJ, Bardot A, et al. Colon and rectal cancer survival in seven high-income countries 2010-2014: variation by age and stage at diagnosis (the ICBP SURVMARK-2 project). Gut 2021 Jan;70(1):114–26.

[5] Claassen YHM, Vermeer NCA, Iversen LH, van Eycken E, Guren MG, Mroczkowski P, et al. Treatment and survival of rectal cancer patients over the age of 80 years: a EURECCA international comparison. Br J Canc 2018;119(4):517–22.

[6] Vermeer NCA, Claassen YHM, Derks MGM, Iversen LH, van Eycken E, Guren MG, et al. Treatment and survival of patients with colon cancer aged 80 Years and older: a EURECCA international comparison. Oncologist 2018;23(8):982–90.

[7] Claassen YHM, Bastiaannet E, van Eycken E, Van Damme N, Martling A, Johansson R, et al. Time trends of short-term mortality for octogenarians undergoing a colorectal resection in North Europe. Eur J Surg Oncol 2019;45(8):1396–402.

[8] Breugom AJ, Bastiaannet E, Boelens PG, Iversen LH, Martling A, Johansson R, et al. Adjuvant chemotherapy and relative survival of patients with stage II colon cancer - a EURECCA international comparison between The Netherlands, Denmark, Sweden, England, Ireland, Belgium, and Lithuania. European Journal of Cancer 2016;63:110–7.

[9] Breugom AJ, Bastiaannet E, Boelens PG, Van Eycken E, Iversen LH, Martling A, et al. 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. Eur J Surg Oncol 2018;44(9):1338–43.

[10] Breugom AJ, Bastiaannet E, Guren MG, Korner H, Boelens PG, Dekker FW, et al. Treatment strategies and overall survival for incurable metastatic colorectal cancer - a EURECCA international comparison including 21,196 patients from The Netherlands and Norway. Eur J Surg Oncol 2020;46(6):1167–73.

[11] Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Canc 2009;45(7):1218–31.

[12] Guren MG, Korner H, Pfeffer F, Myklebust TA, Eriksen MT, Edna TH, et al. Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993-2010. Acta Oncol 2015;54(10):1714–22.

[13] Kodeda K, Johansson R, Zar N, Birgisson H, Dahlberg M, Skullman S, et al. Time trends, improvements and national auditing of rectal cancer management over an 18-year period. Colorectal Dis 2015;17(9):O168–79.

[14] Fritz AGPC, Jack A, et al., editors. International classification of diseases for Oncology (ICD-O). 3rd edn. Geneva: World Health Organization; 2000.

[15] Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av kreft i tykktarm og endetarm [National Guideline CRC Norway]. 2019 [Available from: df.

[16] Detering R, Karthaus EG, Borstlap WAA, Marijnen CAM, van de Velde CJH, Bemelman WA, et al. Treatment and survival of locally recurrent rectal cancer: a cross-sectional population study 15 years after the Dutch TME trial. Eur J Surg Oncol 2019 Nov;45(11):2059–69.

[17] Westberg K, Palmer G, Hjern F, Johansson H, Holm T, Martling A. Management and prognosis of locally recurrent rectal cancer - a national population-based study. Eur J Surg Oncol 2018;44(1):100–7.

[18] Stormark K, Soreide K, Soreide JA, Kvaloy JT, Pfeffer F, Eriksen MT, et al. Nationwide implementation of laparoscopic surgery for colon cancer: short-term outcomes and long-term survival in a population-based cohort. Surg Endosc 2016;30(11):4853–64.

[19] Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. JAMA Surg 2017;152(3):292–8.

[20] Dekker JW, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. Ann Surg Oncol 2011;18(6):1533–9.

[21] Wickstrom G, Bendix T. The "Hawthorne effect"–what did the original Hawthorne studies actually show? Scand J Work Environ Health 2000;26(4):363–7.

[22] Van Leersum NJ, Snijders HS, Henneman D, Kolfschoten NE, Gooiker GA, ten Berge MG, et al. The Dutch surgical colorectal audit. Eur J Surg Oncol 2013;39(10):1063–70.

[23] Pahlman L, Bohe M, Cedermark B, Dahlberg M, Lindmark G, Sjodahl R, et al. The Swedish rectal cancer registry. Br J Surg 2007;94(10):1285–92.

[24] Wibe A, Moller B, Norstein J, Carlsen E, Wiig JN, Heald RJ, et al. A national strategic change in treatment policy for rectal cancer–implementation of total mesorectal excision as routine treatment in Norway. A national audit. Dis Colon Rectum 2002;45(7):857–66.

[25] Leonard D, Penninckx F, Kartheuser A, Laenen A, Van Eycken E, Procare. Effect of hospital volume on quality of care and outcome after rectal cancer surgery. Br J Surg 2014;101(11):1475–82.

[26] Basta YL, Bolle S, Fockens P, Tytgat KMAJ. The value of multidisciplinary team meetings for patients with gastrointestinal malignancies: a systematic review. Annals of Surgical Oncology 2017;24(9):2669–78.

[27] Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370(14):1298–306.

[28] Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64(10):1637–49.

[29] Feeney G, Sehgal R, Sheehan M, Hogan A, Regan M, Joyce M, et al. Neoadjuvant radiotherapy for rectal cancer management. World J Gastroenterol 2019;25(33):4850–69.

[30] Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med 1985;312(25):1604–8.

[31] Aparicio T, Navazesh A, Boutron I, Bouarioua N, Chosidow D, Mion M, et al. Half of elderly patients routinely treated for colorectal cancer receive a sub-standard treatment. Crit Rev Oncol Hematol 2009;71(3):249–57.

[32] Ko JJ, Kennecke HF, Lim HJ, Renouf DJ, Gill S, Woods R, et al. Reasons for underuse of adjuvant chemotherapy in elderly patients with stage III colon cancer. Clin Colorectal Canc 2016;15(2):179–85.

[33] McArdle CS, Hole DJ. Emergency presentation of colorectal cancer is associated with poor 5-year survival. Br J Surg 2004;91(5):605–9.

[34] Gooiker GA, Dekker JW, Bastiaannet E, van der Geest LG, Merkus JW, van de Velde CJ, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. Ann Surg Oncol 2012;19(8):2428–34.

[35] Breugom AJ, Bastiaannet E, Dekker JWT, Wouters M, van de Velde CJH, Liefers GJ. Decrease in 30-day and one-year mortality over time in patients aged >/=75 years with stage I-III colon cancer: a population-based study. Eur J Surg Oncol 2018;44(12):1889–93.

[36] Bos A, Kortbeek D, van Erning FN, Zimmerman DDE, Lemmens V, Dekker JWT, et al. Postoperative mortality in elderly patients with colorectal cancer: the impact of age, time-trends and competing risks of dying. Eur J Surg Oncol 2019;45(9):1575–83.

[37] Ketelaers SHJ, Orsini RG, Burger JWA, Nieuwenhuijzen GAP, Rutten HJT. Significant improvement in postoperative and 1-year mortality after colorectal cancer surgery in recent years. Eur J Surg Oncol 2019 Nov;45(11):2052–8.

[38] Brouwer NPM, Heil TC, Olde Rikkert MGM, Lemmens V, Rutten HJT, de Wilt JHW, et al. The gap in postoperative outcome between older and younger patients with stage I-III colorectal cancer has been bridged; results from The Netherlands cancer registry. Eur J Canc 2019;116:1–9.