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Tailored treatment for colon and rectal cancer

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Citation
Bahadoer, R. R. (2023, May 30). *Tailored treatment for colon and rectal cancer*. Retrieved from https://hdl.handle.net/1887/3619337

Version:	Publisher's Version
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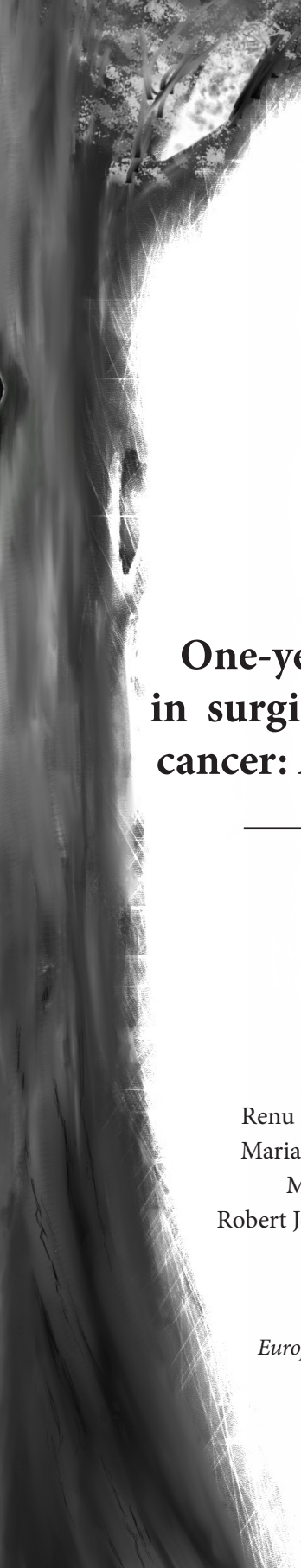
Downloaded from:	https://hdl.handle.net/1887/3619337

Note: To cite this publication please use the final published version (if applicable).

PART I - EURECCA



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

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European Journal of Surgical Oncology. 2021 Jul; 47 (7) 1651-1660

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.

Keywords: Colorectal Neoplasms, Mortality, Internationality, epidemiology, treatment

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.

Material and methods

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.

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] Supplementary table S1 provides an overview of the data selection of each country.

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.

Results

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 (supplementary table S1). 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.

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

	Belgium			The Netherlands		
	< 65 years (N = 9,645)	65-74 years (N = 11,280)	≥ 75 years (N = 18,063)	< 65 years (N = 17,402)	65-74 years (N = 21,784)	≥ 75 years (N = 24,919)
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)
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)
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)
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)
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)
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)
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)
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)
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)
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)

Data are presented as n (%).

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

	Norway			Sweden		
	< 65 years (N = 4,564)	65-74 years (N = 5,651)	≥ 75 years (N = 8,698)	< 65 years (N = 5,585)	65-74 years (N = 8,162)	≥ 75 years (N = 12,775)
Gender						
Male	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	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	806 (17.7)	950 (16.8)	1,655 (19.0)	1,131 (20.3)	1,466 (18.0)	2,391 (18.7)
2009-2010	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	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	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	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	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	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	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		
	< 65 years (N = 5,108)	65-74 years (N = 4,288)	≥ 75 years (N = 4,687)	< 65 years (N = 9,767)	65-74 years (N = 8,757)	≥ 75 years (N = 6,155)
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)
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)
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)
2009-2010	1,039 (20.3)	847 (19.8)	959 (20.5)	1,877 (19.2)	1,575 (18.0)	1,194 (19.4)
2011-2012	1,022 (20.0)	846 (19.7)	981 (20.9)	1,949 (20.0)	1,711 (19.5)	1,267 (20.6)
2013-2014	1,058 (20.7)	972 (22.7)	900 (19.2)	1,867 (19.1)	1,918 (21.9)	1,351 (21.9)
2015-2016	966 (18.9)	776 (18.1)	870 (18.6)	2,210 (22.6)	2,100 (24.0)	1.185 (19.3)
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)
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)
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)

Data are presented as n (%).

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

	Norway			Sweden		
	< 65 years (N = 2,408)	65-74 years (N = 2,153)	≥ 75 years (N = 2,074)	< 65 years (N = 3,936)	65-74 years (N = 4,349)	≥ 75 years (N = 3,814)
Gender						
Male	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	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	452 (18.8)	350 (16.3)	390 (18.8)	791 (20.1)	785 (18.1)	806 (21.1)
2009-2010	480 (19.9)	420 (19.5)	435 (21.0)	759 (19.3)	807 (18.6)	787 (20.6)
2011-2012	436 (18.1)	420 (19.5)	417 (20.1)	802 (20.4)	842 (19.4)	781 (20.5)
2013-2014	537 (22.3)	497 (23.1)	412 (19.9)	789 (20.0)	898 (20.6)	731 (19.2)
2015-2016	503 (20.9)	466 (21.6)	420 (20.3)	795 (20.2)	1,017 (23.4)	709 (18.6)
Stage						
Stage I	586 (24.3)	586 (27.2)	541 (26.1)	1,113 (28.3)	1,325 (30.5)	1,116 (29.3)
Stage II	639 (26.5)	651 (30.2)	758 (36.5)	1,139 (28.9)	1,353 (31.1)	1,275 (33.4)
Stage III	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 (%).

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

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).

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 (figure 1a and supplementary table S2a).

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 (figure 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 (figure 1c and supplementary table S2b).

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%).

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) (supplementary table S3). 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.

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

	Stage I						Stage II					
	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
Belgium	18.3	20.6	21.3	26.1	31.6		39.8	39.2	38.8	33.5	33.2	
The Netherlands	18.2	17.9	18.1	20.1	27.9		38.6	39.7	37.9	36.5	31.8	
Norway	17.7	18.2	19.4	26.3	27.6		44.0	41.5	41.9	36.9	34.2	
Sweden	13.3	15.9	15.2	14.7	17.6		42.9	40.3	39.5	37.3	37.5	
65-74 years						<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	
The Netherlands	19.5	21.1	22.3	23.0	32.0		43.4	41.5	40.1	40.8	35.0	
Norway	21.6	22.6	19.7	22.4	23.0		44.7	43.7	46.4	45.1	44.4	
Sweden	17.4	18.6	18.6	18.1	18.6		45.1	42.0	42.3	40.9	40.0	
≥ 75 years						0.006						0.375
Belgium	16.2	17.8	17.8	20.3	21.1		47.4	47.6	47.1	45.3	46.2	
The Netherlands	18.0	18.6	19.1	23.3	20.6		46.9	48.4	47.2	42.8	46.3	
Norway	20.7	19.6	20.6	21.9	22.1		48.3	49.0	48.8	46.7	46.2	
Sweden	16.3	16.0	15.1	16.7	18.2		48.8	48.3	47.5	44.4	44.4	

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.

Continuation Table 2a Stage time trends in percent ages for colon cancer patients.

	Stage III					
	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016	P-value
< 65 years						<0.001
Belgium	41.9	40.2	39.9	40.4	35.2	
The Netherlands	43.2	42.4	44.0	43.4	40.3	
Norway	38.2	40.3	38.7	36.8	38.2	
Sweden	43.9	43.8	45.3	48.0	44.9	
65-74 years						<0.001
Belgium	37.2	36.0	37.7	32.8	31.7	
The Netherlands	37.1	37.4	37.6	36.1	32.9	
Norway	33.7	33.7	33.9	32.5	32.5	
Sweden	37.5	39.4	39.1	41.0	41.4	
≥ 75 years						<0.001
Belgium	36.4	34.5	35.1	34.4	32.8	
The Netherlands	35.1	33.0	33.7	33.9	33.1	
Norway	30.9	31.4	30.7	31.4	31.7	
Sweden	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					
	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
Belgium	30.8	33.8	32.5	36.2	38.2		29.4	26.5	29.3	26.4	25.3	
The Netherlands	22.0	16.4	15.7	16.4	20.5		30.5	28.9	22.3	21.2	18.9	
Norway	20.1	21.9	22.5	26.6	29.6		29.2	25.2	26.1	27.0	25.2	
Sweden	27.7	23.1	32.2	28.3	29.9		29.5	32.4	29.7	26.7	26.5	
65-74 years						<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	
The Netherlands	22.8	22.2	17.8	20.0	26.4		34.6	30.8	27.1	24.8	22.6	
Norway	22.0	22.4	27.1	31.4	31.1		31.4	31.4	31.7	29.8	27.5	
Sweden	28.3	28.9	27.7	32.5	33.9		32.1	31.1	34.6	30.1	28.4	
≥ 75 years						<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	
The Netherlands	24.9	22.0	21.0	21.5	25.0		39.2	36.8	36.9	29.7	25.7	
Norway	24.4	23.7	24.5	30.3	27.6		40.3	39.8	36.0	32.0	34.8	
Sweden	29.7	28.1	28.3	30.1	30.3		34.9	34.3	33.5	32.3	31.9	

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.

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

	Stage III					
	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016	P-value
< 65 years						<0.001
Belgium	39.8	39.7	38.3	37.4	36.5	
The Netherlands	47.5	54.8	62.0	62.3	60.5	
Norway	50.7	52.9	51.4	46.4	45.1	
Sweden	42.9	44.5	38.2	45.0	43.5	
65-74 years						<0.001
Belgium	36.5	36.0	35.1	33.5	33.1	
The Netherlands	42.5	47.0	55.1	55.3	51.0	
Norway	46.6	46.2	41.2	38.8	41.4	
Sweden	39.6	40.0	37.8	37.4	37.7	
≥ 75 years						<0.001
Belgium	38.7	37.1	35.7	36.9	33.8	
The Netherlands	35.9	41.2	42.1	48.9	49.3	
Norway	35.4	36.6	39.6	37.6	37.6	
Sweden	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.

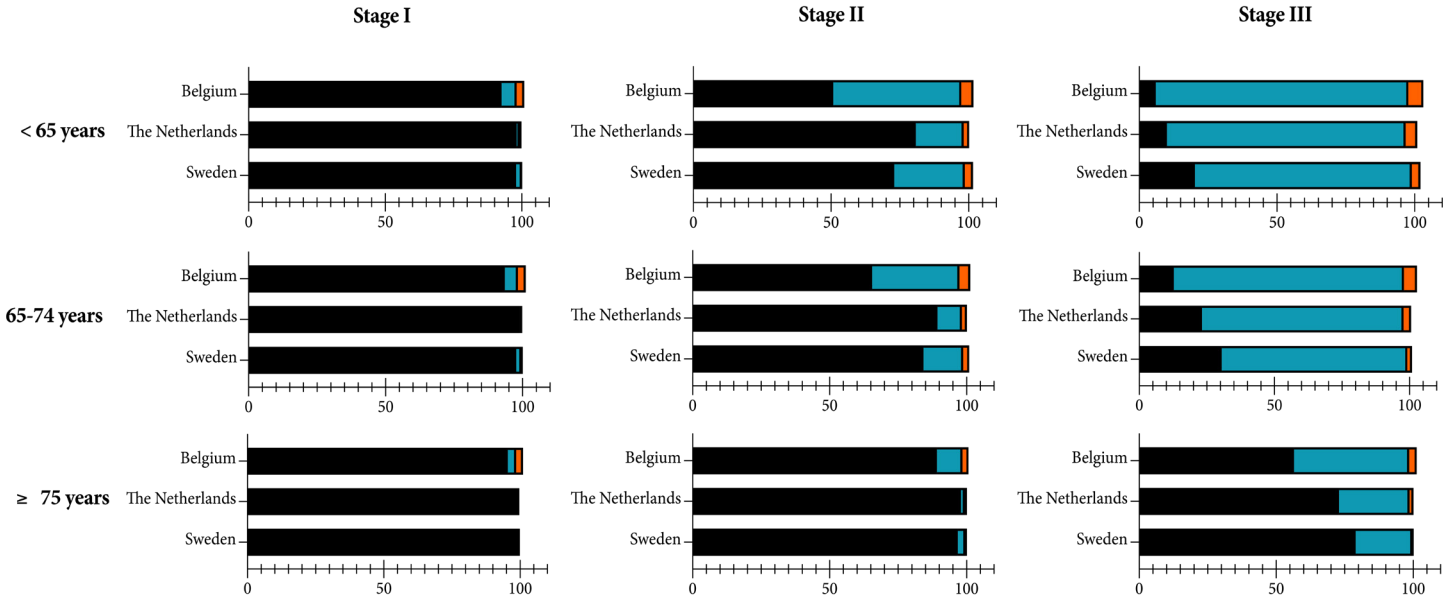

Figure 1a Treatment according to country, age and stage in colon cancer patients. Neoadjuvant and adjuvant treatment are combined; therefore, percentages can be above 100%. Differences between countries for adjuvant chemotherapy, stratified for age category and stage were calculated using chi-square.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

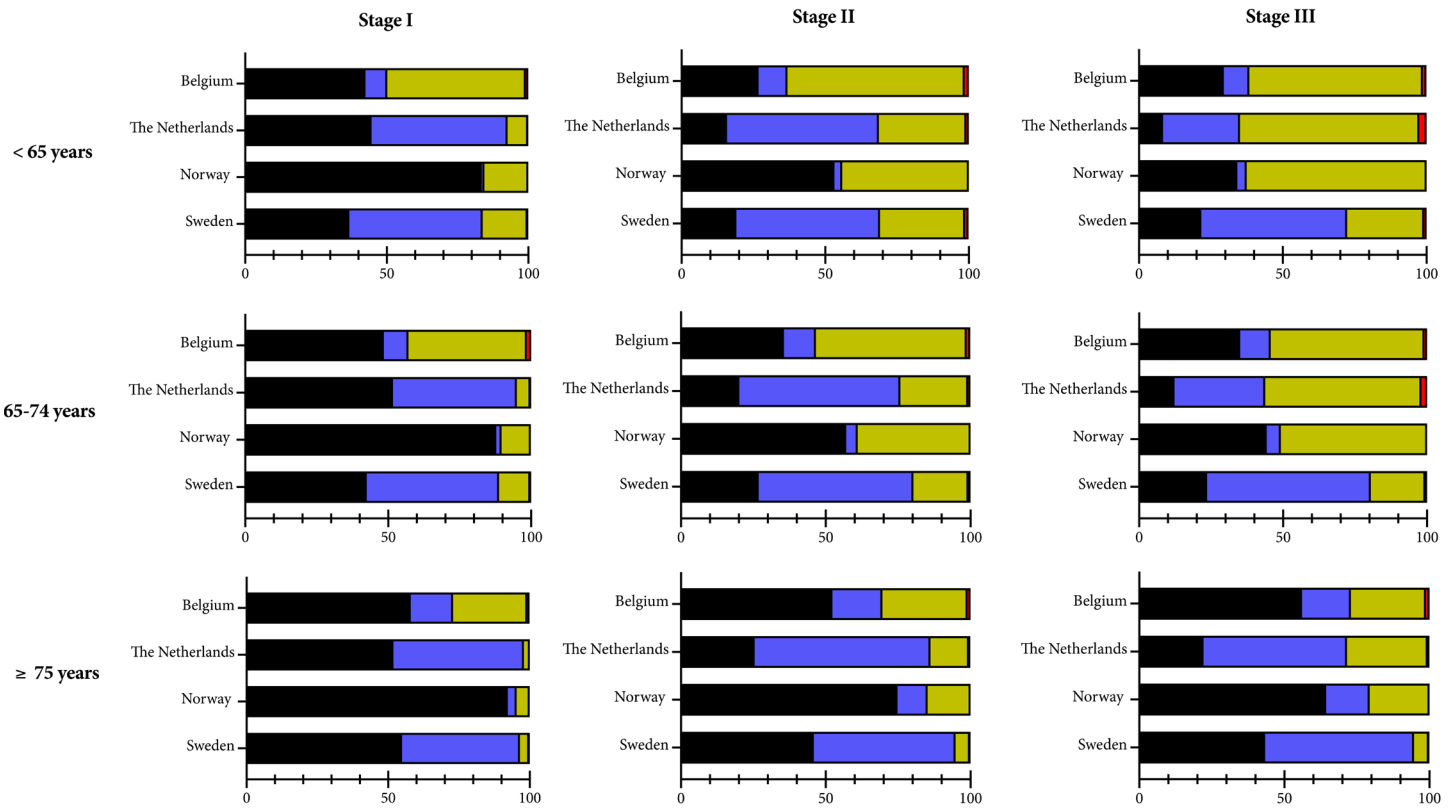

Figure 1b Neoadjuvant treatment, according to country, age and stage in rectal cancer patients. Differences between countries, stratified for age category and stage were calculated using chi-square. All differences between countries for neoadjuvant radiotherapy and chemoradiotherapy had a P-value <0.001.

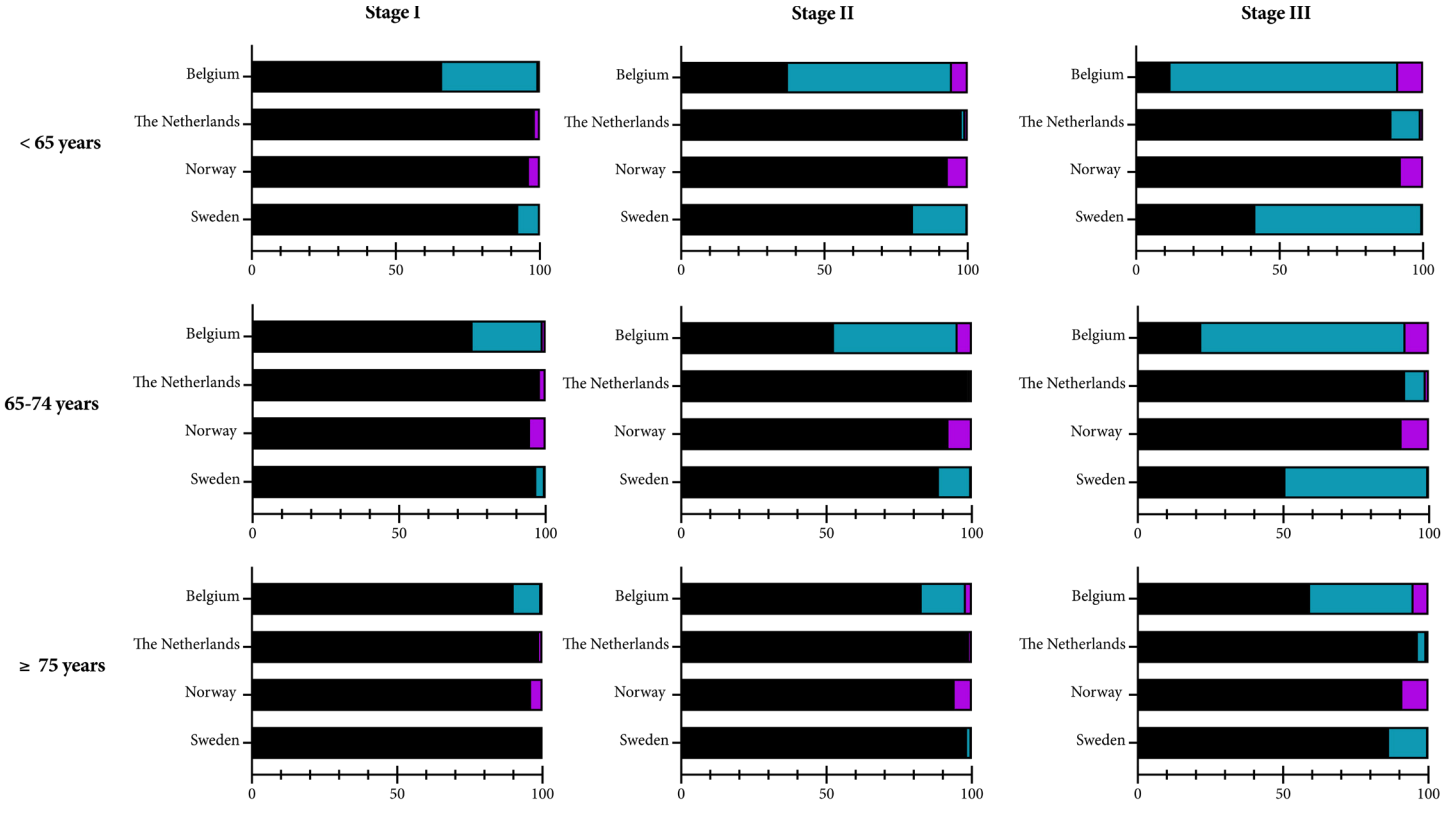

Figure 1c Adjuvant treatment, according to country, age and stage in rectal cancer patients. Differences between countries, stratified for age category and stage were calculated using chi-square. All differences between countries for adjuvant chemotherapy had a P-value <0.001.

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

	≤ 30-day, overall mortality						1st year, overall 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
< 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	
The Netherlands	1.2	1.0	0.8	0.5	0.5		4.2	4.1	3.8	3.1	2.2	
Norway	1.0	0.4	0.1	0.0	0.4		3.8	2.8	2.5	1.5	2.1	
Sweden	0.5	0.6	0.3	0.6	0.3		2.6	2.7	3.0	3.7	2.6	
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	
The Netherlands	3.0	2.5	2.0	1.2	1.0		8.8	7.7	6.3	5.6	4.2	
Norway	1.7	1.8	2.0	1.8	1.1		7.6	6.3	6.4	4.8	3.7	
Sweden	1.2	1.1	1.4	0.9	0.8		5.9	5.2	5.5	5.1	4.8	
> 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	
The Netherlands	9.6	8.7	6.8	5.4	3.9		20.6	18.8	16.2	13.3	11.5	
Norway	6.5	5.8	5.1	4.1	4.1		17.5	16.7	15.3	12.8	11.5	
Sweden	4.2	4.5	4.2	3.8	2.5		14.6	13.9	13.7	12.9	10.5	

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

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

	1st year, excess mortality				
	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016
< 65 years					
Belgium	4.0	3.5	2.8	2.3	1.3
The Netherlands	3.6	3.6	3.2	2.6	1.5
Norway	3.2	2.3	1.8	1.0	1.6
Sweden	2.0	2.1	2.5	3.2	2.2
65-74 years					
Belgium	6.0	5.2	6.0	2.8	4.1
The Netherlands	6.9	6.0	4.5	3.9	2.5
Norway	5.8	4.6	4.8	2.9	2.0
Sweden	4.2	3.6	4.0	3.5	3.1
> 74 years					
Belgium	15.0	11.6	11.5	9.5	9.4
The Netherlands	14.4	12.7	10.0	7.4	5.3
Norway	10.5	10.0	8.7	5.9	4.7
Sweden	8.0	7.3	7.1	6.6	4.0

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

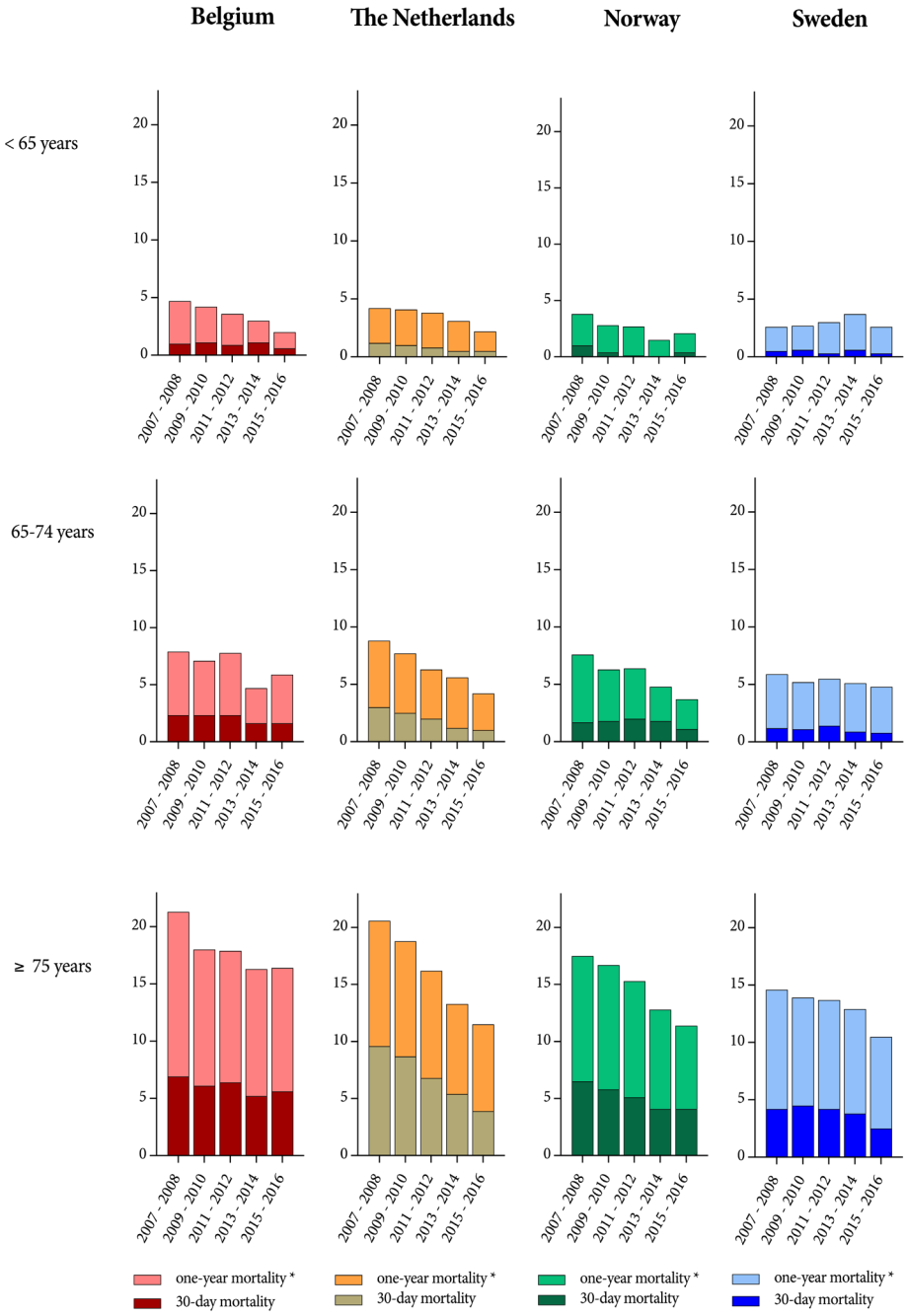

Figure 2 (A) 30-day and one-year overall mortality in colon cancer patients.

* One-year mortality is represented by the full bar.

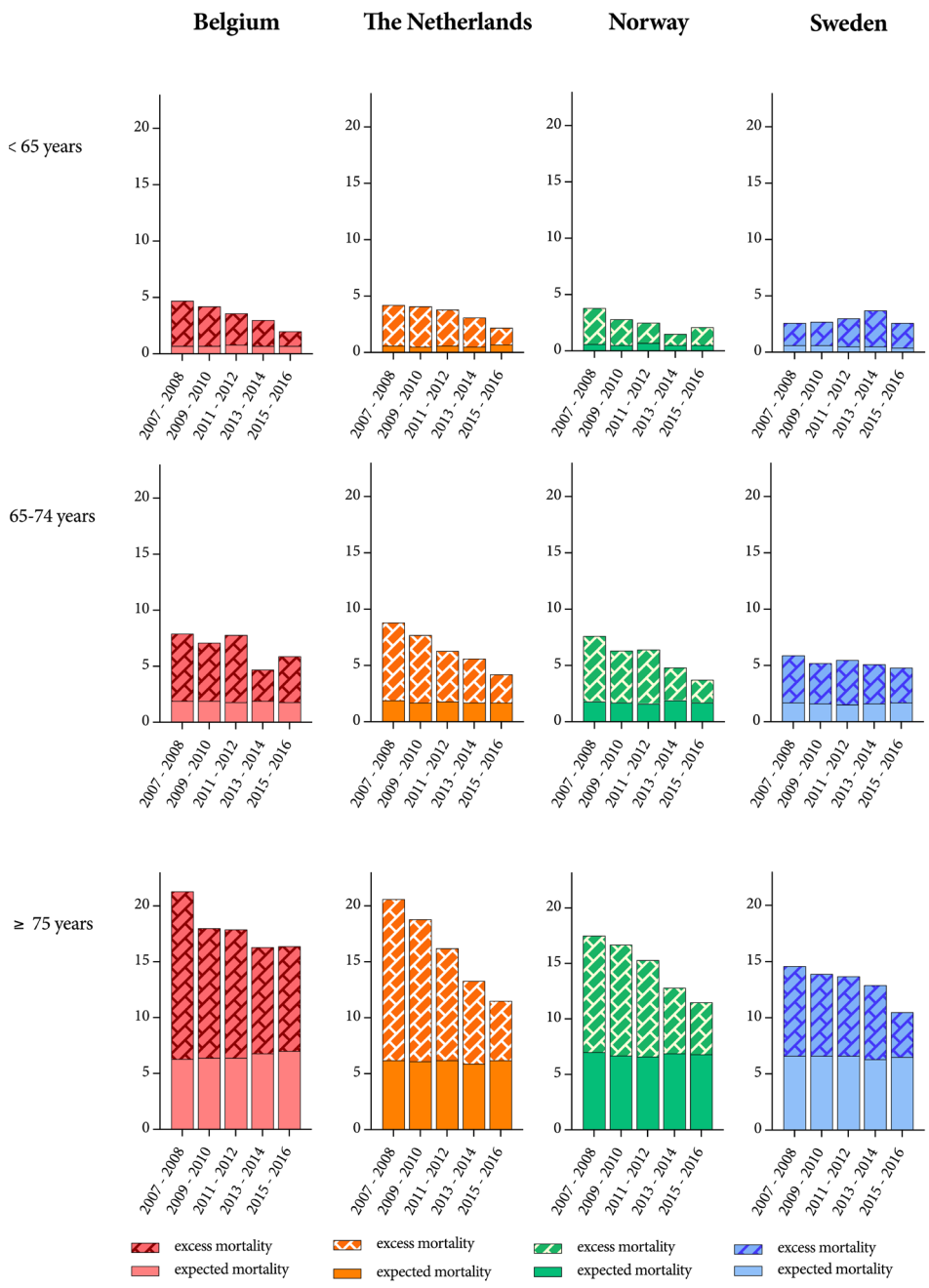

Figure 2 (B) One-year expected and excess mortality in colon cancer patients.

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

	≤ 30-day, overall mortality						1st year, overall 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
< 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	
The Netherlands	0.8	0.4	0.5	0.4	0.3		3.1	3.0	2.3	2.5	2.0	
Norway	0.2	0.4	0.7	0.4	0.0		2.2	2.5	1.4	1.1	0.8	
Sweden	0.3	0.4	0.4	0.4	0.1		1.9	1.6	2.0	2.4	1.3	
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	
The Netherlands	2.2	1.8	1.8	0.9	1.0		7.1	5.8	6.3	4.2	2.9	
Norway	0.6	1.4	0.7	0.6	0.2		4.3	5.2	4.0	3.0	2.6	
Sweden	1.1	1.1	1.0	1.0	0.4		5.0	4.3	3.8	4.1	3.3	
≥ 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	
The Netherlands	7.6	6.0	4.3	3.0	2.8		18.9	14.4	14.0	10.1	8.4	
Norway	3.6	2.8	4.1	1.5	3.1		15.1	9.4	11.3	5.8	9.0	
Sweden	5.6	3.0	2.7	3.7	2.4		14.1	11.3	9.1	8.2	8.7	

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

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

	1st year, excess mortality				
	2007 -2008	2009 -2010	2011 -2012	2013 -2014	2015 -2016
< 65 years					
Belgium	2.4	2.2	2.1	1.4	0.9
The Netherlands	2.5	2.4	1.7	1.8	1.4
Norway	1.8	1.9	0.7	0.6	0.2
Sweden	1.3	1.1	1.5	1.9	0.8
65-74 years					
Belgium	4.7	3.5	5.2	3.1	3.9
The Netherlands	5.2	4.1	4.5	2.3	1.0
Norway	2.6	3.5	2.4	1.4	0.6
Sweden	2.9	2.7	2.3	2.6	1.7
≥ 75 years					
Belgium	12.2	13.6	12.0	11.4	9.0
The Netherlands	13.2	8.8	8.4	4.7	2.5
Norway	9.0	3.4	5.0	*	2.9
Sweden	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.

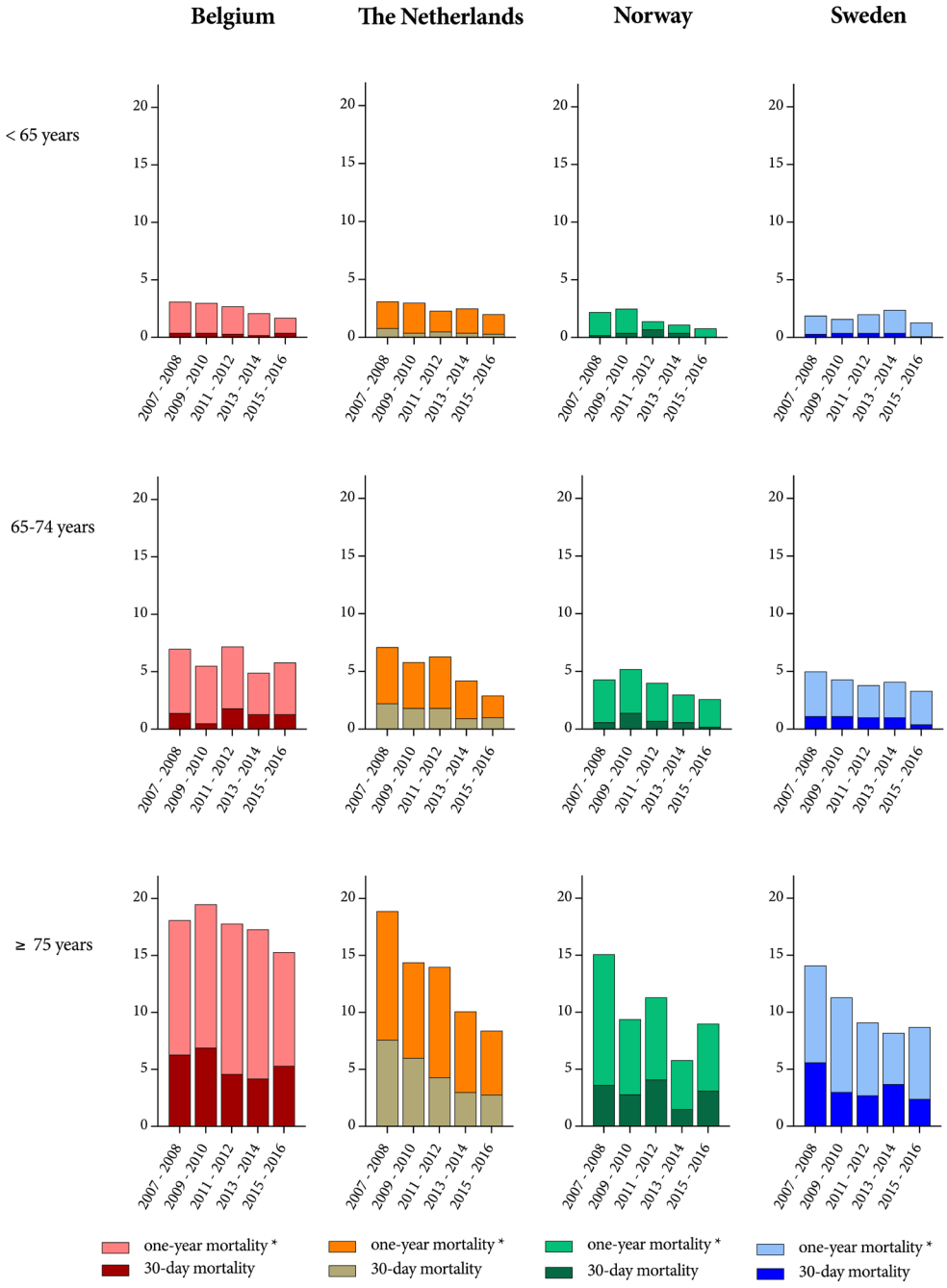

Figure 3 (A) 30-day and one-year overall mortality in rectal cancer patients.

* One-year mortality is represented by the full bar.

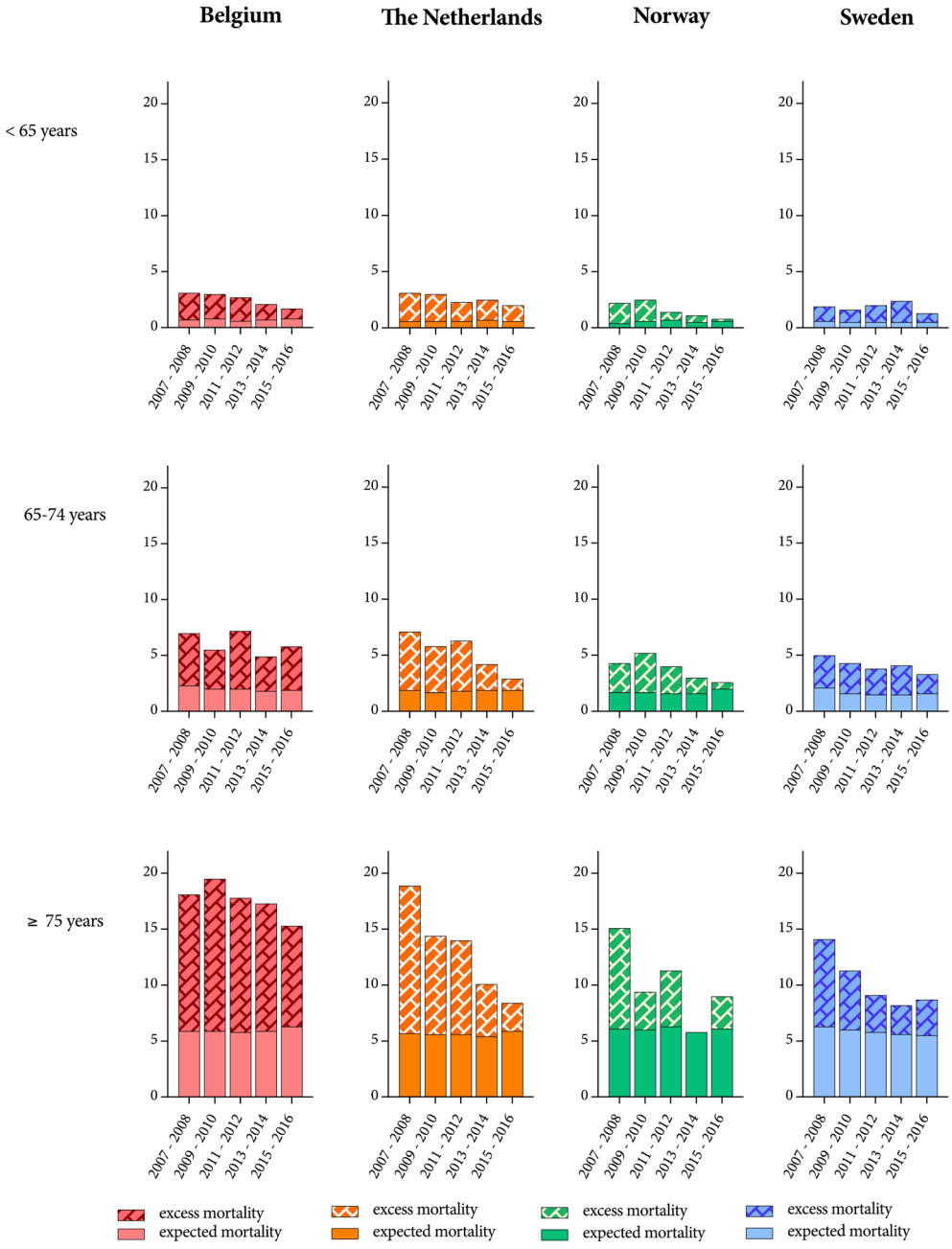

Figure 3 (B) One-year expected and excess mortality in rectal cancer patients.

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] 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.

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.

Funding The study was initiated by the European Registration of Cancer Care (EURECCA), which is funded by the European Society of Surgical Oncology. ESSO did not have a role in the study design, data collection, analysis, interpretation of the data, writing of the manuscript, or the decision to publish.

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 None declared. 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 paper.

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