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Tailored treatment for colon and rectal cancer

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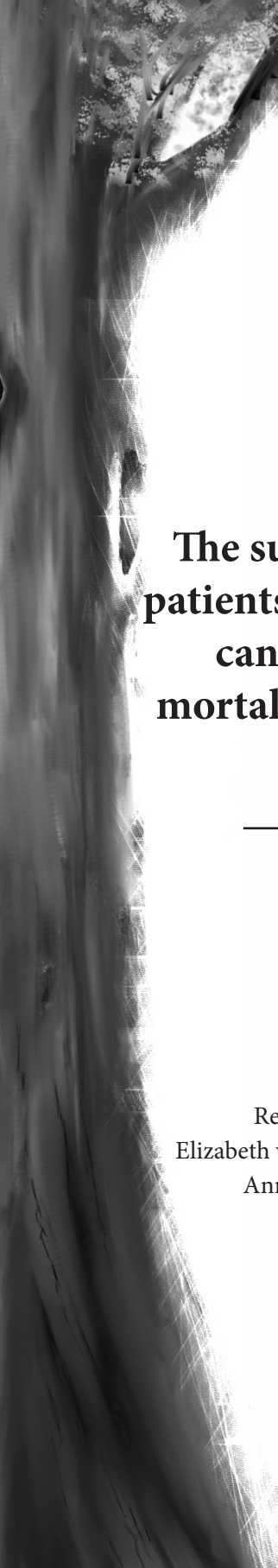
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The survival gap between young and older patients after surgical resection for colorectal cancer remains largely based on early mortality: A EURECCA comparison of four European countries

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Abstract

Background: A decade ago, it was demonstrated that the difference in survival between older patients and younger patients with colorectal cancer (CRC) was mainly due to mortality in the first postoperative year. Over the last few years, improvements - especially in perioperative care - have increased survival. The current research investigates whether a survival gap between younger and older patients with CRC still exists on a national level in four European countries.

Methods: Population-based data from Belgium, the Netherlands, Norway, and Sweden were collected from patients that underwent surgical resection for primary stage I-III CRC between 2007 and 2016. Relative survival and conditional relative survival (CS), with the condition of surviving the first postoperative year, were calculated for colon and rectal cancer separately, stratified for country and age category (<65, 65–75, ≥75 years). In addition, relative excess risk of death (RER) was estimated, and one-year excess mortality was calculated.

Results: Data of 206,024 patients were analyzed. In general, compared to patients <65 years, patients ≥75 years had a worse survival during the first year after surgery, which was most pronounced in Belgium (RER colon cancer 2.5 [95% confidence interval (CI) 2.3–2.8] and RER rectal cancer 2.6 [95% CI 2.3–2.9]). After surviving the first year, CS was mostly not statistically different between patients <65 years and patients ≥75 years with stage I-II, with the exception of stage II colon cancer in Belgium. However, CS remained worse in the largest part of the patients ≥75 years with stage III colon or rectal cancer (except for rectal cancer in Norway).

Conclusions: Although differences exist between the countries, the survival gap between young and older patients is based mainly on early mortality and remains only for stage III disease after surviving the first year.

Introduction

As the incidence of colorectal cancer increases with age, and life expectancy of the general population is increasing, a growing proportion of older patients is expected to be diagnosed with colorectal cancer.¹ In the past, surgical treatment options were not offered to older patients as frequently due to an increased complication rate and higher mortality rate in this population.^{2,3} Currently, with more frequent use of minimally invasive surgery and improvement of perioperative care within a multidisciplinary setting, these risks have decreased.⁴ Analyses of Dutch national data showed that the overall 30-day and one-year survival of older patients operated for colon cancer improved over time. Still, differences in short-term survival remained between the younger and older population⁵, although less prominent for relative survival.⁶ A recent Dutch study concluded that the relative survival of older patients with colorectal cancer has improved, leading to a similar cancer-specific survival compared with the younger population.⁷ In these studies, relative survival was used as an estimation of the cancer-specific survival, and calculated by dividing the observed survival in the cohort by the expected survival calculated from the matched (country, age, sex, and year) general population. This method can be used in the absence of cause of death in the cohort, or when cause of death is hard to establish, which is most often the case in older patients with multiple comorbidities. Calculating the relative survival for patients who survived the first postoperative year, the conditional relative survival, has shown age differences in early mortality. In 2011 Dekker et al. showed, in a regional dataset of the Netherlands, that decreased cancer-specific survival in older patients with colorectal cancer was mainly due to differences in early mortality. For those older patients who survived the first post-operative year, cancer-related survival aligned with younger patients.⁸ Correspondingly, Pilleron and colleagues analyzed data from patients with colon cancer aged between 50 and 99 years, and concluded that age-related disparities were no longer evident or considerably reduced if patients with localized disease survived the first six months after diagnosis.⁹ Recently, our group studied time-trends with focus on treatment and demonstrated improvement in overall one-year postoperative mortality over time in different age categories (< 65, 65–75, ≥75 years) in Belgium, the Netherlands, Norway, and Sweden. Results showed that substantial differences between countries and age categories still existed.¹⁰ For the current study, our

group focused on conditional relative survival with corresponding one-year excess mortality. It has not been investigated before whether the effect of disappearing age-related differences in conditional survival is also present on a national level for colorectal cancer in other European countries. Therefore, this study compared, with respect to different age categories, the one-year conditional relative survival (overall and according to tumor-stage) and corresponding excess mortality in Belgium, the Netherlands, Norway, and Sweden.

Methods

Study design and data sources

Observational data on consecutive patients have been collected for this international population-based cohort study from the national cancer registries of Belgium, the Netherlands, Norway, and Sweden. These countries were chosen based on their similar cancer incidence and life expectancy. Moreover, their national cancer registries guaranteed the overall quality of data in terms of completeness (>95% of patients with cancer in the population registered) and accuracy.¹¹ 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. All countries have a legal foundation that enables the collection of data concerning cancer cases in the context of public health.¹²⁻¹⁵

Procedures

Data were collected from all surgically treated patients diagnosed with primary colon or rectal cancer from January 2007 to December 2016. Colon cancer was defined by topographical codes C18-C19 and rectal cancer by code C20 of the International Classification of Diseases for Oncology.¹⁶ In Sweden, topographical code C19 (rectosigmoid) was not defined as the location of the tumor was decided by the surgeons at the time of surgery. For the current analyses, patients eighteen years and older diagnosed with stage I, II, III disease and recorded follow-up were included. Stage was based on pathological information and completed with clinical stage when necessary, using the 7th edition of the American Joint Committee on Cancer TNM staging. For rectal cancer, pathological information was based on either the

pTN or ypTN category. Belgium and the Netherlands provided their data on stage from 2007 to 2009 using the TNM stage 6th edition and from 2010 to 2016 using the TNM 7th edition. For patients diagnosed with multiple, simultaneous tumors, the tumor with the worst prognostic characteristics, using stage and grade, was chosen for all analyses. Surgical treatment was defined as surgical removal of the tumor-bearing bowel segment, irrespective of curative or palliative intent. Patients with stage IV disease were excluded, as well as patients who underwent local excision of the tumor, including transanal endoscopic microsurgery. Due to the high quality of the national registries there were no missing data on the baseline characteristics.

Statistics

All analyses were performed stratified by tumor location, country, and age category (younger than 65 years, 65–74 years and 75 years and older). To estimate cancer-related survival (in the absence of reliable information on the cause of death), relative survival (RS) was used, calculated by the Ederer II method as the ratio of the survival observed among the patients with cancer and the survival that would have been expected based on the corresponding (country, age, sex, and year) general population.¹⁷ The Ederer II method was used as the matched individuals were considered to be at risk until the corresponding cancer patient died or was censored. National life tables (www.mortality.org) were used to estimate expected survival, and survival time was calculated from the date of surgery to date of death. Afterwards, conditional relative survival (CS) was calculated with the condition of surviving the first postoperative year. With a multivariate generalized linear model, using a Poisson distribution, relative excess risk of death (RER) was estimated based on collapsed relative survival data, using exact survival times.¹⁸ We adjusted the models for overall mortality (OM, mortality in the first year due to any cause) and one-year excess mortality (EM). Expected mortality was based on the matched (country, age, sex, and year) general population, and EM was calculated using the following formula: (observed numbers of death in the first year – expected number of deaths in the first year (in the matched general population)) / (number of patients). The expected number of deaths was calculated by national life tables matched for age, sex, and year of incidence. With respect to the sizeable population of this study, a p-value of <0.001

was considered statistically significant. STATA/SE version 14.0 was used for the analyses.

Results

In Belgium, the Netherlands, Norway, and Sweden, 314,062 patients were diagnosed with colorectal cancer between 2007 and 2016. For the current analyses, the inclusion criteria were met by 53,071 patients from Belgium (64.3%), 88,784 patients from the Netherlands (66.9%), 25,548 patients from Norway (64.3%) and 38,621 patients from Sweden (66.1%). Supplementary Table A provides an overview of the data selection of each country. Patient characteristics, stratified by tumor location and age categories, are displayed in Table 1. The percentages of male patients with colon cancer were 53.6% (< 65 years), 55.2% (65–74 years), 46.2% (≥ 75 years). For patients with rectal cancer, these were 61.6% (< 65 years), 65.6% (65–74 years), and 57.3% (≥ 75 years). The proportion of patients ≥75 years with colon cancer was 43.4% (Belgium 46.3%, the Netherlands 38.9%, Norway 46.0%, Sweden 48.2%), considerably higher than the proportion patients ≥75 years with rectal cancer, 29.1% (Belgium 33.3%, the Netherlands 24.9%, Norway 31.3%, Sweden 31.5%). Patients aged eighteen years or older, diagnosed with stage I-III colorectal cancer and reliable follow-up in the national cancer registries undergoing surgical resection, were 90.2% (53,071 of 58,828) in Belgium, 89.3% (88,784 of 99,464) in the Netherlands, 92.3% (25,548 of 27,679) in Norway and 93.2% (38,621 of 41,437) in Sweden (Supplementary Table A).

Colon cancer, relative survival, and one-year conditional relative survival

As shown in Fig. 1a and Table 2a, in the Netherlands, Norway, and Sweden CS of older patients with stage I, II or III (combined) was similar among patients <65 years and patients 65–74 years after surviving the first postoperative year. Table 2a presents an additional overview of the RERs for RS and CS according to age and stratified for stage, with patients <65 years as a reference category. For stage I, patients ≥75 years in Norway and Sweden had similar RS compared to patients <65 years. In Belgium and the Netherlands, patients ≥75 years initially had a worse survival than patients <65 years, but this difference disappeared after surviving the first postoperative year. For stage II, worse RS of patients ≥75 years were found in Belgium, the Netherlands, and Norway. This difference disappeared after surviving

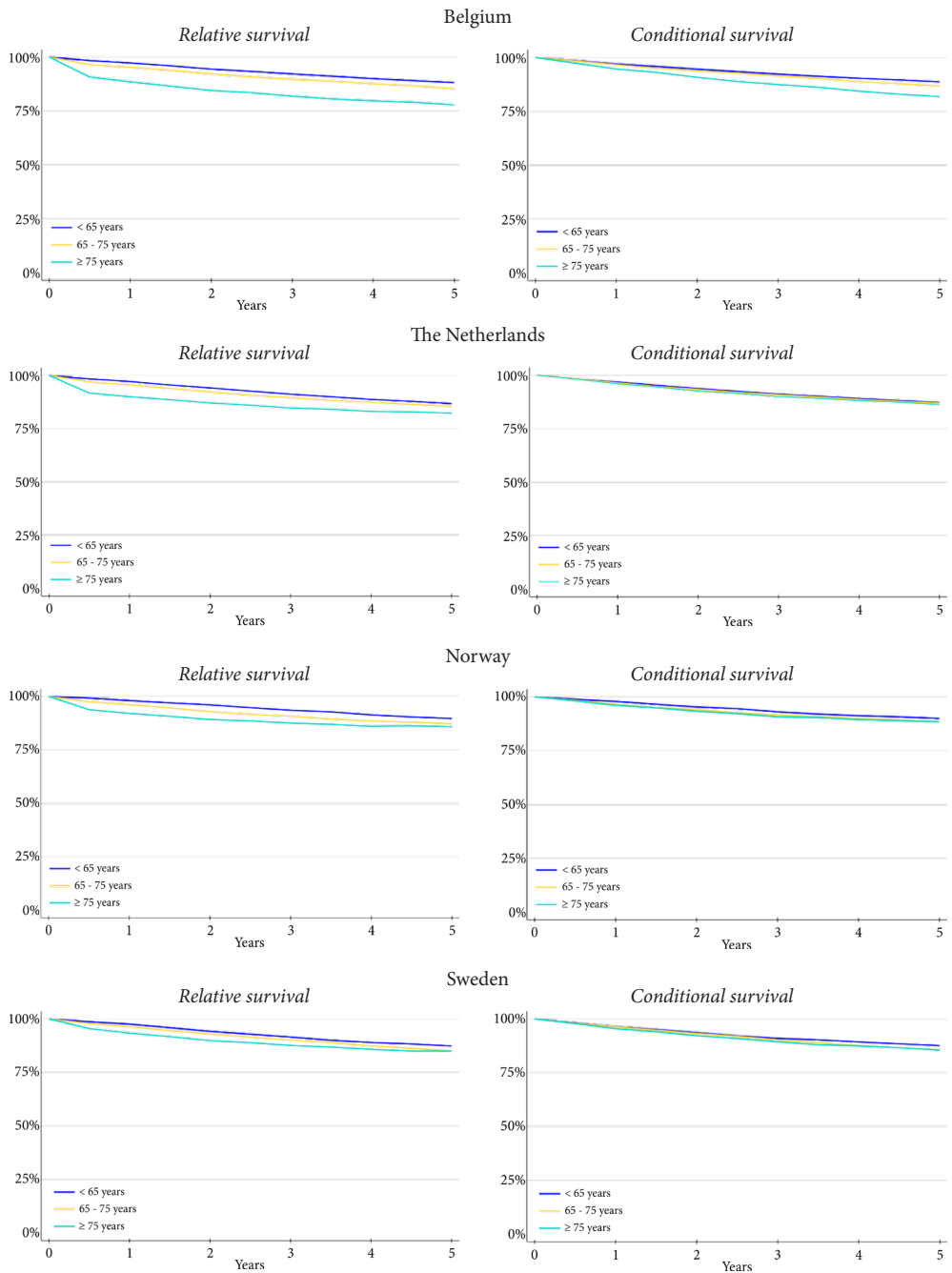


Figure 1a Relative and conditional survival of stage I-III operated colon cancer patients, according to age.

the first postoperative year in the Netherlands and Norway, but remained in Belgium. The difference for the patients 65–74 years remained as well in Belgium and was also present in the Netherlands. For stage III, CS remained worse for patients ≥ 75 years in all countries. For patients 65–74 years, survival aligned in CS in Belgium, the Netherlands, and Norway.

Rectal cancer, relative survival, and one-year conditional relative survival

Relative survival in patients ≥ 75 years with stage I, II and III combined improved after surviving the first postoperative year for patients with rectal cancer, leading to comparable CS between age categories (Fig. 1b). Table 2b presents an overview of RERs for RS and CS stratified for stage, with patients < 65 years as a reference category. The RS aligned in patients ≥ 75 years with stage I disease in Belgium and the Netherlands, leading to similar CS in all countries and all age categories. For stage II, the same trend was shown. For stage III, in all countries, RS of older patients was worse compared to patients < 65 years. This difference only disappeared in Norway after surviving the first postoperative year. Patients 65–74 years in Belgium and the Netherlands with stage III disease initially had a worse survival, which was similar for patients < 65 years after surviving the first postoperative year. (See Fig. 1b.)

One-year excess mortality

Table 3 provides an overview of one-year overall and one-year excess mortality. For colon cancer, in general, higher excess mortality was seen in females, with the exception of Norway, where excess mortality was higher for males. Excess mortality increased with age category. Patients 65–74 years and patients ≥ 75 years in Belgium and the Netherlands had similar, albeit higher, excess mortality compared to Norway and Sweden. Excess mortality also increased with stage and followed a trend of the lowest excess mortality in Sweden, followed by Norway, the Netherlands, and the highest in Belgium. In rectal cancer, excess mortality was consistently higher among men, increased with age and stage and showed a trend of the lowest excess mortality in Norway, followed by Sweden, the Netherlands, and highest in Belgium.

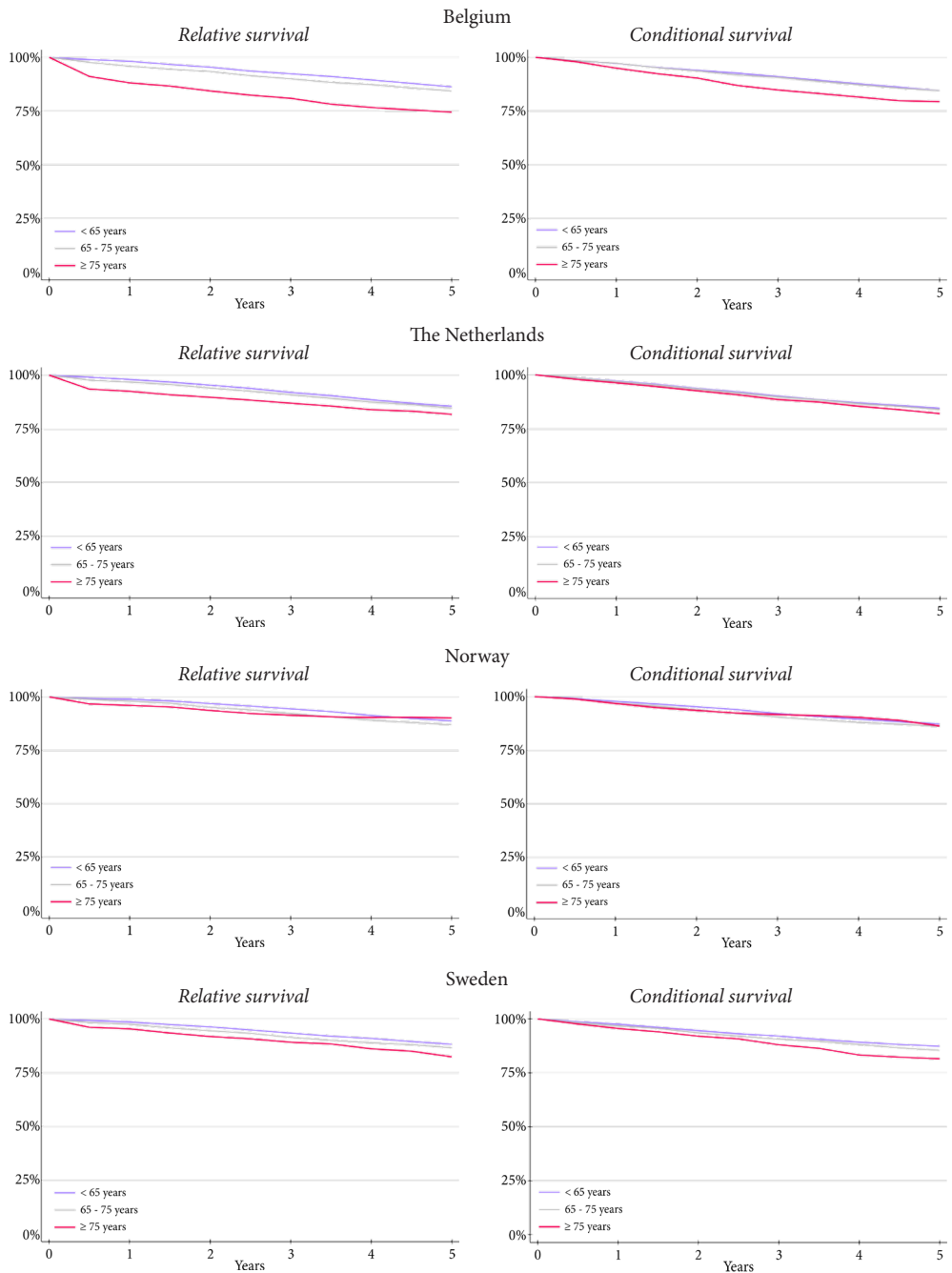


Figure 1b Relative and conditional survival of stage I-III operated rectal cancer patients, according to age.

Table I Characteristics of patients operated for colorectal 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
Colon cancer						
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)
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)
Rectal cancer						
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)
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 I Characteristics of patients operated for colorectal 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	65-74years N = 8,162	≥ 75 years N = 12,775
Colon cancer						
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)
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)
Rectal cancer						
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)
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(%).

Table 2a One-year relative and conditional survival of operated colon cancer patients, stratified by stage, shown as relative excess risk of death (RER) with corresponding 95% CI.

Belgium	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.3 (1.2-1.4)	1.2 (1.0-1.3)	1.2 (0.7-1.9)	N.A. *
>74 years	2.5 (2.3-2.8)	1.7 (1.5-1.9)	3.0 (2.0-4.5)	N.A. *
The Netherlands	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.1 (1.1-1.2)	1.0 (1.0-1.1)	1.9 (0.9-4.0)	1.2 (0.6-2.3)
>74 years	1.8 (1.7-1.9)	1.1 (1.0-1.2)	6.8 (3.5-13.3)	0.8 (0.2-3.7)
Norway	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.4 (1.2-1.6)	1.0 (1.0-1.4)	1.6 (0.6-4.2)	1.5 (0.7-3.4)
>74 years	2.0 (1.7-2.3)	1.3 (1.1-1.6)	1.8 (0.5-6.7)	N.A. *
Sweden	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.2 (1.0-1.3)	1.1 (1.0-1.3)	1.4 (0.6-2.9)	1.7 (0.8-3.3)
>74 years	1.4 (1.3-1.6)	1.2 (1.1-1.4)	N.A. *	0.9 (0.3-3.3)

RS relative survival, CS conditional survival N.A.* Not addressed due to relative survival above 100%, the results could not be presented in a RER (RS not different from the youngest age). Bold and italic: p-value ≤ 0.001

Continuation Table 2a One-year relative and conditional survival of operated colon cancer patients, stratified by stage, shown as relative excess risk of death (RER) with corresponding 95% CI.

Belgium	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.4 (1.1-1.7)	1.4 (1.1-1.8)	1.4 (1.2-1.6)	1.2 (1.1-1.4)
>74 years	2.5 (2.1-2.9)	1.5 (1.2-1.9)	2.8 (2.6-3.1)	2.1 (1.8-2.3)
The Netherlands	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.3 (1.1-1.5)	1.3 (1.1-1.5)	1.2 (1.1-1.3)	1.1 (1.0-1.2)
>74 years	1.7 (1.5-2.0)	1.0 (0.8-1.3)	2.2 (2.0-2.3)	1.5 (1.4-1.6)
Norway	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.8 (1.3-2.5)	1.3 (0.9-1.8)	1.4 (1.2-1.6)	1.3 (1.1-1.6)
>74 years	2.7 (1.9-3.7)	1.7 (1.1-2.4)	2.2 (1.9-2.6)	1.6 (1.3-1.9)
Sweden	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.2 (0.9-1.6)	1.1 (0.8-1.4)	1.3 (1.2-1.5)	1.3 (1.1-1.4)
>74 years	1.2 (0.9-1.7)	1.0 (0.7-1.4)	2.0 (1.8-2.3)	1.7 (1.5-1.9)

RS relative survival, CS conditional survival N.A.* Not addressed due to relative survival above 100%, the results could not be presented in a RER (RS not different from the youngest age). Bold and italic: p-value ≤ 0.001

Table 2b One-year relative and conditional survival of operated rectal cancer patients, stratified by stage, shown as relative excess risk of death (RER) with corresponding 95% CI.

Belgium	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.2 (1.1-1.4)	1.0 (0.9-1.2)	2.7 (1.3-5.8)	2.2 (1.2-3.8)
>74 years	2.6 (2.3-2.9)	1.5 (1.3-1.8)	6.9 (3.3-14.4)	0.6 (0.1-4.2)
The Netherlands	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.1 (1.0-1.2)	1.0 (1.0-1.2)	2.7 (1.1-6.8)	0.9 (0.4-1.9)
>74 years	1.5 (1.3-1.7)	1.2 (1.0-1.3)	6.2 (2.4-15.9)	0.7 (0.1-4.1)
Norway	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.2 (1.0-1.5)	1.2 (0.9-1.4)	1.0 (0.3-4.3)	0.9 (0.3-3.5)
>74 years	1.0 (0.7-1.5)	1.1 (0.8-1.5)	N.A. *	N.A. *
Sweden	All stages		Stage I	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.2 (1.0-1.4)	1.2 (1.0-1.4)	2.4 (1.0-5.6)	1.7 (0.8-3.5)
>74 years	1.6 (1.3-1.9)	1.5 (1.3-1.8)	0.4 (0.0-45.9)	0.5 (0.0-8.7)

RS relative survival, CS conditional survival N.A.* Not addressed due to relative survival above 100%, the results could not be presented in a RER (RS not different from the youngest age). Bold and italic: p-value ≤ 0.001

Continuation Table 2b One-year relative and conditional survival of operated rectal cancer patients, stratified by stage, shown as relative excess risk of death (RER) with corresponding 95% CI.

Belgium	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.0 (0.8-1.4)	0.8 (0.6-1.1)	1.3 (1.1-1.6)	1.1 (0.9-1.3)
>74 years	2.6 (2.1-3.2)	1.5 (1.2-1.9)	2.4 (2.1-2.8)	1.7 (1.5-2.0)
The Netherlands	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.0 (0.8-1.3)	1.0 (0.8-1.3)	1.2 (1.1-1.4)	1.2 (1.1-1.3)
>74 years	1.5 (1.2-1.9)	1.0 (0.8-1.4)	1.8 (1.6-2.1)	1.6 (1.4-1.8)
Norway	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.8 (1.1-2.9)	1.7 (1.1-2.7)	1.2 (0.9-1.5)	1.1 (0.8-1.4)
>74 years	1.5 (0.8-2.8)	1.5 (0.9-2.7)	1.6 (1.2-2.2)	1.5 (1.1-2.0)
Sweden	Stage II		Stage III	
	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref
65-74 years	1.2 (0.9-1.6)	1.1 (0.8-1.5)	1.2 (1.0-1.4)	1.2 (1.0-1.4)
>74 years	1.5 (1.0-2.1)	1.3 (0.9-1.9)	2.1 (1.7-2.5)	2.0 (1.7-2.4)

RS relative survival, CS conditional survival N.A.* Not addressed due to relative survival above 100%, the results could not be presented in a RER (RS not different from the youngest age). Bold and italic: p-value ≤ 0.001

Table 3 One-year overall and excess mortality rates in percentages

Colon cancer	Belgium			The Netherlands		
	N	OM	EM	N	OM	EM
Gender						
Male	20,475	11.0	6.9	33,329	9.5	6.0
Female	18,513	11.1	7.7	30,776	9.1	6.3
Age (years)						
< 65	9,645	3.4	2.7	17,402	3.4	2.8
65 - 74	11,280	6.6	4.7	21,784	6.2	4.5
≥ 75	18,063	18.0	11.4	24,919	16.1	9.9
Stage						
Stage I	8,542	6.2	2.9	13,922	5.0	2.1
Stage II	16,460	10.3	6.0	26,547	8.7	5.2
Stage III	13,986	15.0	11.5	23,636	12.4	9.5
Rectal cancer						
Rectal cancer	Belgium			The Netherlands		
	N	OM	EM	N	OM	EM
Gender						
Male	8,785	9.0	5.9	15,486	6.7	4.1
Female	5,298	8.0	5.6	9,193	5.0	3.1
Age (years)						
< 65	5,108	2.5	1.8	9,767	2.5	1.9
65 - 74	4,288	6.1	4.1	8,757	5.1	3.2
≥ 75	4,687	17.7	11.7	6,155	13.1	7.4
Stage						
Stage I	4,636	5.4	2.7	5,111	4.6	2.2
Stage II	4,283	9.6	6.5	6,826	6.8	4.1
Stage III	5,164	10.7	7.9	12,742	6.3	4.2

OM overall mortality, EM excess mortality

Continuation Table 3 One-year overall and excess mortality rates in percentages

Colon cancer	Norway			Sweden		
	N	OM	EM	N	OM	EM
Gender						
Male	8,897	9.5	5.4	12,880	8.5	4.5
Female	10,016	8.6	5.2	13,642	8.5	5.1
Age (years)						
< 65	4,564	2.5	2.0	5,424	2.9	2.5
65 - 74	5,651	5.6	3.9	7,731	5.3	3.9
≥ 75	8,698	14.7	7.9	11,109	13.0	7.5
Stage						
Stage I	4,076	5.2	1.6	4,459	3.9	0.2
Stage II	8,492	8.5	4.4	11,582	7.0	3.0
Stage III	6,345	12.2	8.7	10,481	12.2	8.8
Rectal cancer						
	Norway			Sweden		
	N	OM	EM	N	OM	EM
Gender						
Male	3,969	5.7	2.8	7,253	6.2	3.4
Female	2,666	3.8	1.4	4,846	4.1	1.8
Age (years)						
< 65	2,408	1.6	1.0	3,936	1.8	1.3
65 - 74	2,153	3.8	2.0	4,349	4.1	2.5
≥ 75	2,074	10.1	3.9	3,814	10.4	4.5
Stage						
Stage I	1,713	3.3	0.6	3,554	3.5	1.0
Stage II	2,048	5.3	2.2	3,767	5.4	2.6
Stage III	2,874	5.6	3.2	4,778	6.6	4.2

OM overall mortality, *EM* excess mortality

Patients ≥ 75 years

Fig. 2 focuses on patients ≥ 75 years, comparing countries. In Belgium and the Netherlands, the RS of patients ≥ 75 years with colon cancer was worse compared to Norway and Sweden (See Fig. 2a). In Belgium, the RS of patients with rectal cancer was also worse compared to the other countries. The steep decline at the beginning of the RS curves for all countries disappeared in the CS curves for both colon and rectal cancer. This led to a similar survival of this patient group within the investigated countries for the first two years after surviving the first postoperative year. Survival was most favorable in Norway and the least in Belgium. As expected, survival was worse when selecting only patients diagnosed with stage III disease (Fig. 2b).

The survival gap between young and older patients after surgical resection for colorectal cancer remains largely based on early mortality: A EURECCA comparison of four European countries

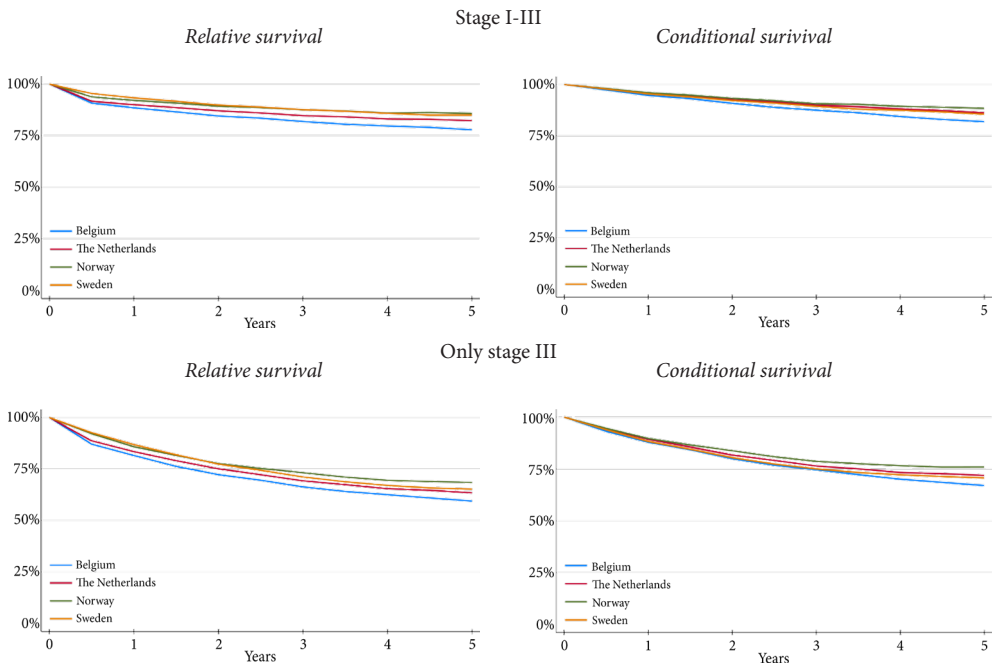


Figure 2a Relative and conditional survival of operated colon cancer patients, 75 years and older.

Discussion

Survival of patients that underwent surgical resection for stage I-III colorectal cancer between 2007 and 2016 in Belgium, the Netherlands, Norway, and Sweden was evaluated by analyzing relative survival. To confirm the importance of the first postoperative year on the survival of older patients, conditional survival was estimated with the condition of surviving the first postoperative year. The current study confirms that the survival of surgically treated older patients with colorectal cancer almost aligned with their younger counterparts (<65 years) after surviving the first postoperative year. The evident decline in survival of older patients during the first year after surgery was most notable in Belgium, followed by the Netherlands, and least in Norway and Sweden.

In line with previous studies,^{8,9} the greatest impact of age on survival was seen in stage III disease within all investigated countries, with the exception of patients with rectal cancer in

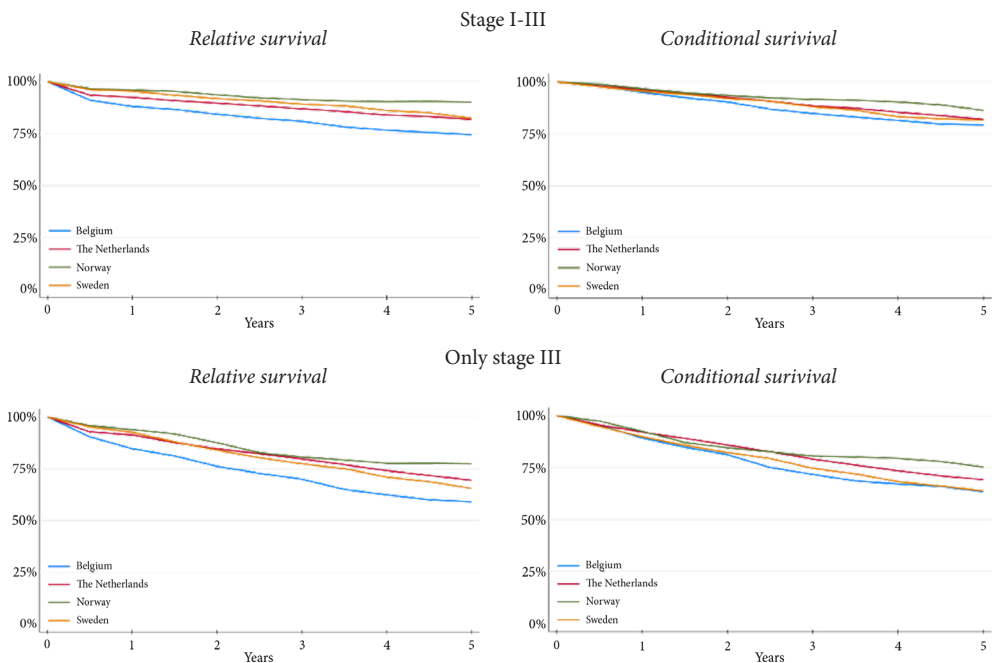


Figure 2b Relative and conditional survival of operated rectal cancer patients, 75 years and older.

Norway. In the last years, efforts have been made to reduce morbidity and mortality in older patients by effectively incorporating geriatric assessments, laparoscopy, enhanced recovery after surgery (ERAS) protocols, and prehabilitation programs.¹⁹ Perhaps the long-term effect of these efforts on a national level are still yet to come, given that large-scale implementation of specific care for the older patients can be a challenge. A single-center study in the Netherlands analyzed patients with colorectal cancer diagnosed between 2006 and 2012 and compared them with patients diagnosed between 2013 and 2017 in two age categories with a cut-off point of 75 years. The difference in one-year relative survival between the old and young group changed from 96.5% and 88.4%, p-value <0.001 (diagnosed 2006–2012) to 95.5% and 94.3%, p-value 0.429 (diagnosed 2013–2017). No distinction was made between stages.²⁰

Despite the improved CS for patients ≥ 75 years, survival remains least favorable in Belgium and most favorable in Norway. Our previous research¹⁰ showed that differences between Belgium, the Netherlands, Norway, and Sweden were most prominent in older patients, particularly for stage III rectal cancer. Patients ≥ 75 years with rectal cancer in Belgium received relatively less neoadjuvant treatment (less often and predominantly radiotherapy instead of chemoradiotherapy), but more often received adjuvant chemotherapy (36%) in comparison to the Netherlands (3%) and Sweden (13%).¹⁰ Norwegian data concerning the use of adjuvant chemotherapy were not available. However, this was not routinely recommended for patients with stage III colon cancer ≥ 75 years in the Norwegian guidelines.²¹ In addition, patients ≥ 75 years with colon cancer received adjuvant chemotherapy more often in Belgium than in the Netherlands or Sweden.¹⁰ A previous international study of patients aged 80 years and older, diagnosed between 2007 and 2010, demonstrated that in Belgium, 25% of patients with colon cancer stage III disease were treated with adjuvant chemotherapy, in contrast to 4% in Norway.²² This suggests for Belgian patients the possibility of undertreatment in case of neoadjuvant treatment for rectal cancer, but overtreatment in the case of adjuvant chemotherapy for colorectal cancer. Adjuvant combination chemotherapy is of uncertain benefit to older patients. Monotherapy is regarded as an appropriate treatment option, and a personalized treatment decision, taking comorbidity and performance status into account, is often recommended.²³ However, the added value of adjuvant chemotherapy in rectal cancer has never been substantiated.²⁴ The possibility of overtreatment is contrary to previous

literature, which suggested an absolute undertreatment of older patients.^{3,25-27} This stresses the importance to finding a good balance between under- and overtreatment. In addition, possible differences in quality of surgery and perioperative care with different degrees of implementation of centralization of care, minimally invasive surgery,²⁸ and clinical auditing could be partly responsible for the observed differences between countries.

Strikingly enough, a high RER in the first postoperative year among patients ≥ 75 years diagnosed with stage I colorectal cancer in Belgium and the Netherlands still existed. However, local excisions were more often performed in these countries: Belgium 3.8%, the Netherlands 4.7%, Norway 2.9%, and Sweden 0.6% (supplementary table S1). This procedure is done explicitly for stage I tumors and was not included in the current analyses. The patients ≥ 75 years diagnosed with stage I that underwent surgical resection were, therefore, probably patients that had tumors with high-risk features.²⁹ Patients with these high-risk features often require more extensive surgery, which might lead to a more complex recovery after surgery (a “complicated postoperative course”) which could explain the higher RER in Belgium and the Netherlands. Next to that, these patients have a higher risk of recurrence, which might also have influenced the mortality.

Not surprisingly, excess mortality increased with age and stage in all investigated countries. Overall, females with colon cancer had a higher excess mortality (compared to men with colon cancer). A possible explanation could be the high percentage of patients ≥ 75 years (43.4%) in the investigated population, of which the majority were female (56.6%). For rectal cancer, we noted a higher proportion of male patients, and these male patients with rectal cancer had a higher excess mortality (compared to women). A known challenge in the surgical treatment of rectal cancer is the anatomical complexity in the narrow wedge-shaped pelvis of males compared to female patients.³⁰ This may cause surgical resection to be more difficult, leading to an increased risk of postoperative complications in men and explaining the higher first postoperative year mortality.^{31,32}

The variation in surgical resection rate from 89.3% in the Netherlands to 93.2% in Sweden could be explained by differences in patient selection in different countries for patients of all ages.³³ Also, shared-decision-making in older patients may lead to refraining from surgery in case of (severe) comorbidity or a clinical (near) complete response after neoadjuvant

treatment. This watch-and-wait strategy is increasingly being practiced as a treatment for selected patients.³⁴ Evaluation of older patients demonstrated that they could avoid major surgery and a definitive colostomy, and have a proper anorectal and urinary function, with few cancer-related deaths.³⁵

To interpret the results of the present study, a few limitations should be taken into account. For the patients analyzed in this large cohort, information on comorbidities was lacking. Frailty weakens the ability to recover postoperatively and is an important predictor of postoperative morbidity and mortality. This is especially relevant to older patients who have a higher likelihood to be frail.³⁶ It is also known that patients treated in an emergency setting are more prone to a complicated postoperative course, especially in colon cancer.³⁷ Patients with emergency surgery were not excluded from the current analyses. As complete information on elective/emergency surgery was not available in this dataset, this subgroup could not be evaluated separately. Fortunately, the rise of national screening programs permits patients to be diagnosed at an earlier stage, presumably reducing the proportion of patients with colorectal cancer undergoing emergency surgery.³⁸ Despite the completeness of the data on patient and tumor characteristics in the cancer registries, a small percentage of the patients (0.05%) had missing data on follow-up. Due to the fact that information on the cause of death was lacking in this cohort study, we used relative survival as a measure, which has been shown to be a good estimation of the cancer-specific survival. We calculated this by dividing the observed survival in the cohort by the expected survival based on the country, sex, age, and year matched general population. Studying the actual cause of death in the first postoperative year is challenging, especially for older patients, but remains a focus for further research. Last, unfortunately, we did not have information on the γ P stage in all countries, so we were not able to stratify the results according to γ P or P stage. Despite the lack of these details, the current study was able to demonstrate the importance of the first postoperative year in older patients in four countries. The strength of this paper lies in the mandatory nature of the involved national cancer registries. This provides a robust base for a complete overview of four European countries over a continuous period of ten years, with focus on stage and age-distribution. For further improvement of care for older patients, a starting point for future research could be the first year after surgery. Perhaps improved patient selection, including

shared-decision-making in which the wishes and expectations of patients are carefully considered, could play a role here. In this respect, older patients with stage III disease may have the most to gain.

Conclusion

Although multimodality treatment, perioperative care, and consequently oncological outcome have improved in the past years, older patients with colorectal cancer still have a worse relative survival than their younger counterparts. Despite differences between countries, after surviving the first year, this survival gap is no longer apparent for patients diagnosed with stage I-II but remains for stage III. Together with a focus on early mortality, balancing under- and overtreatment - especially for stage III disease - is key to bridging the survival gap between younger and older patients with colorectal cancer that undergo surgical resection.

Declarations

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. The authors declare no conflicts of interest.

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Declaration of Competing Interest

None declared

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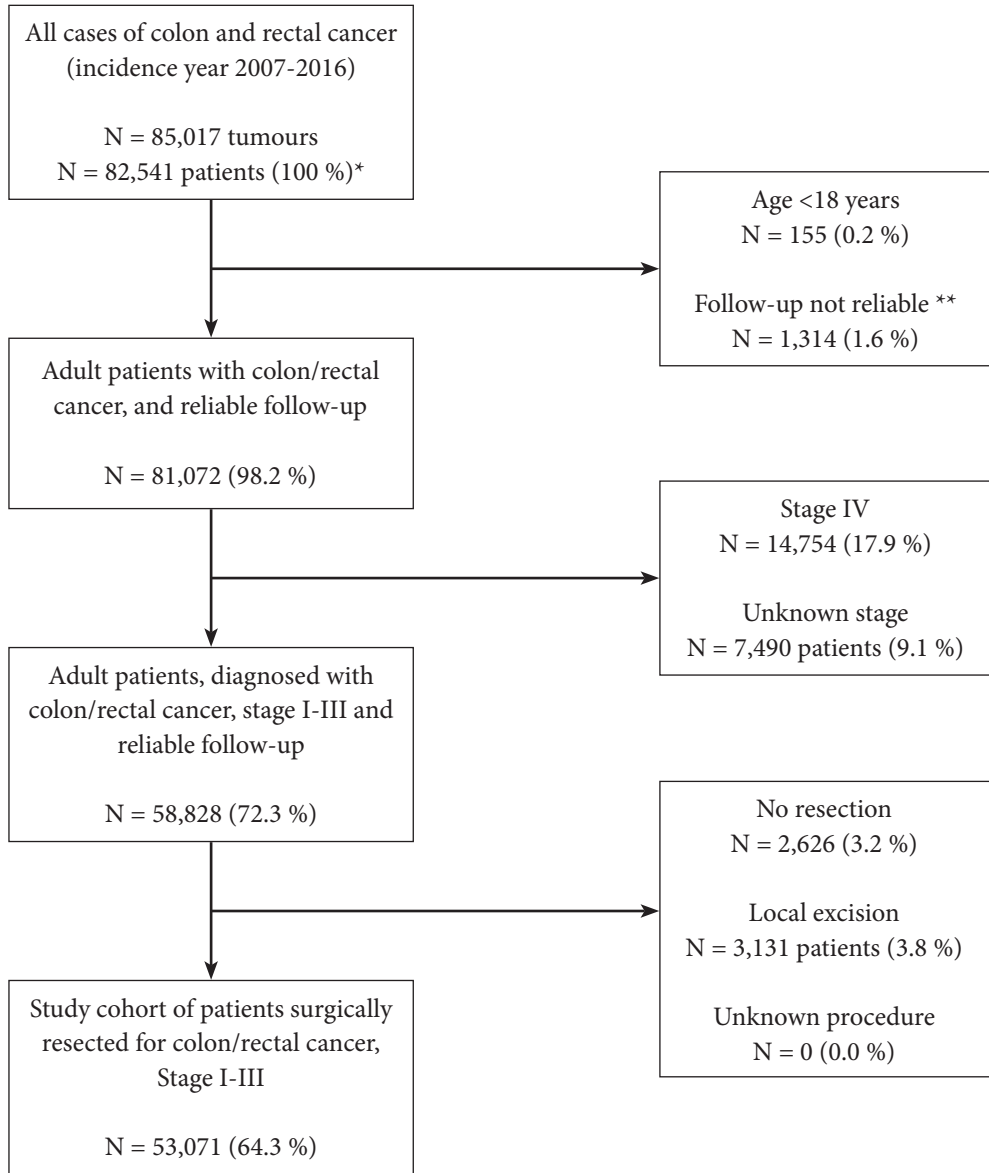
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Supplementary Appendix EURECCA

Supplementary Table S1a Flowchart patient selection Belgium.



Supplementary Appendix

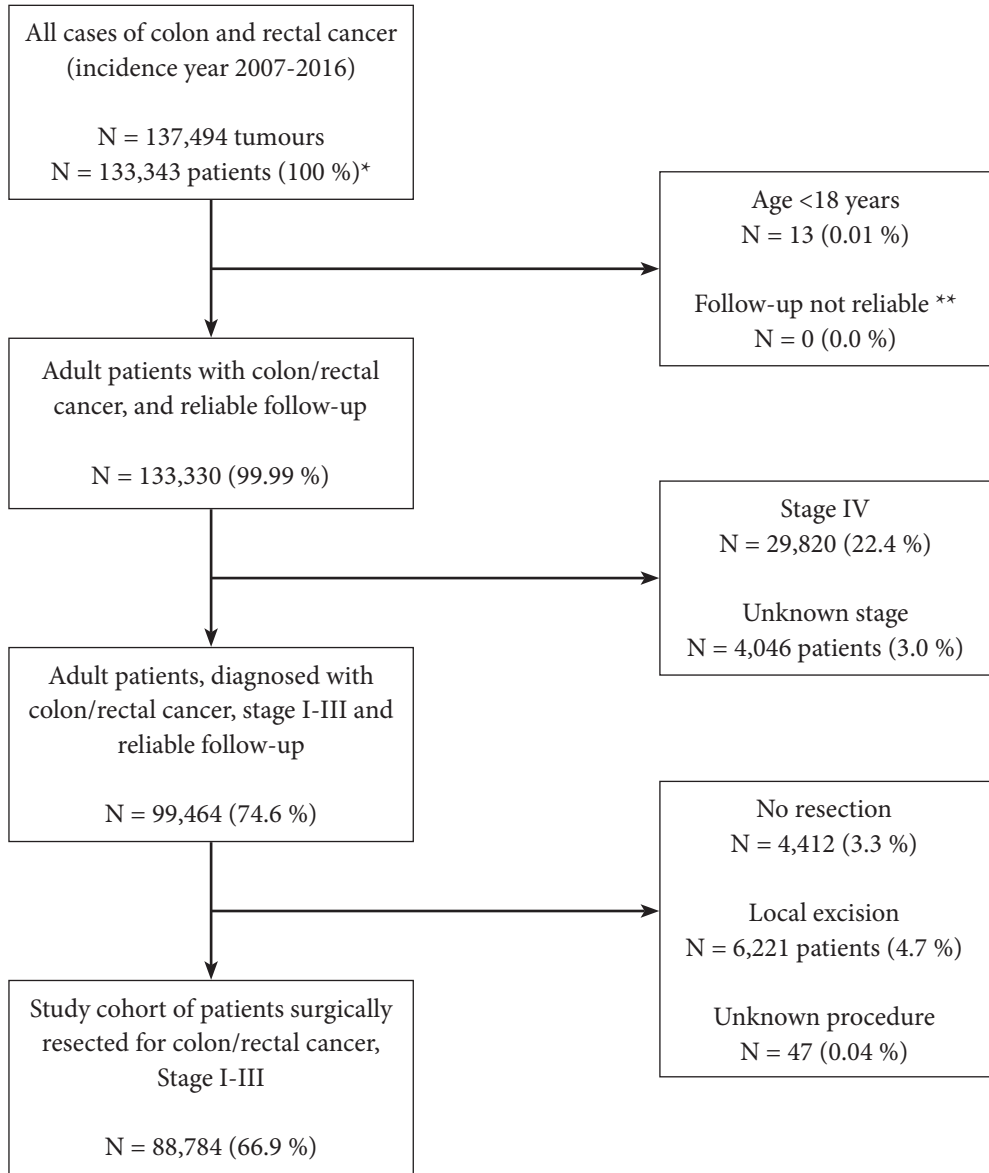
* First primary tumour selected. If multiple tumours were diagnosed on the same day, the highest stage or highest grade was chosen.

** Patients could not be linked with the administrative database, negative follow up (due to registration errors).

In 2018: total population 11,498,527 – number of new colorectal cancer cases 9,346

<https://gco.iarc.fr/today/data/factsheets/populations/56-belgium-fact-sheets.pdf> - accessed on 28th May 2020.

Supplementary Table S1b Flowchart patient selection The Netherlands.



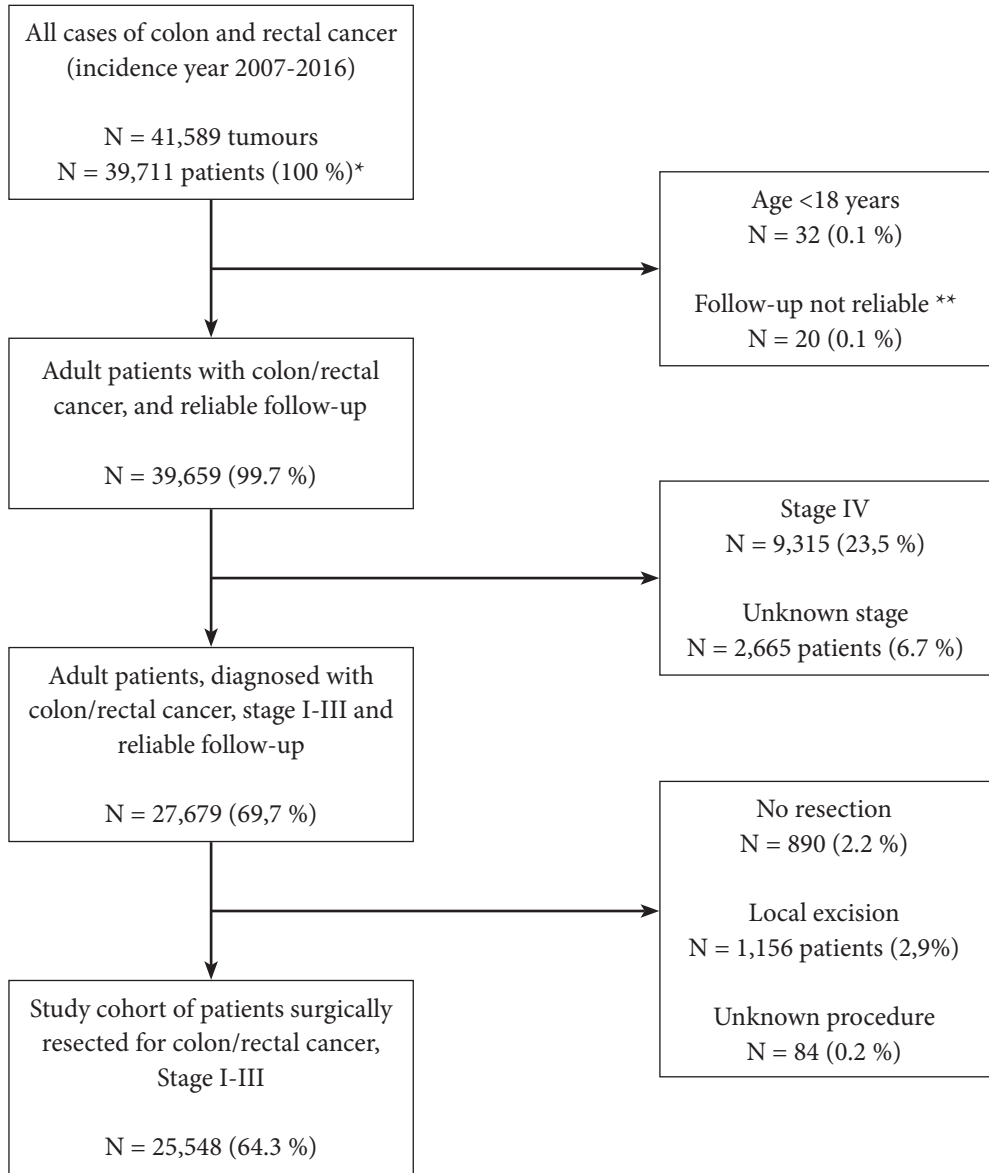
* First primary tumour selected. If multiple tumours were diagnosed on the same day, the highest stage or highest grade was chosen.

** Patients could not be linked with the administrative database, negative follow up (due to registration errors).

In 2018: total population 17,084,467 – number of new colorectal cancer cases 14,921

<https://gco.iarc.fr/today/data/factsheets/populations/528-the-netherlands-fact-sheets.pdf> - accessed on 28th May 2020.

Supplementary Table S1c Flowchart patient selection Norway.



Supplementary Appendix

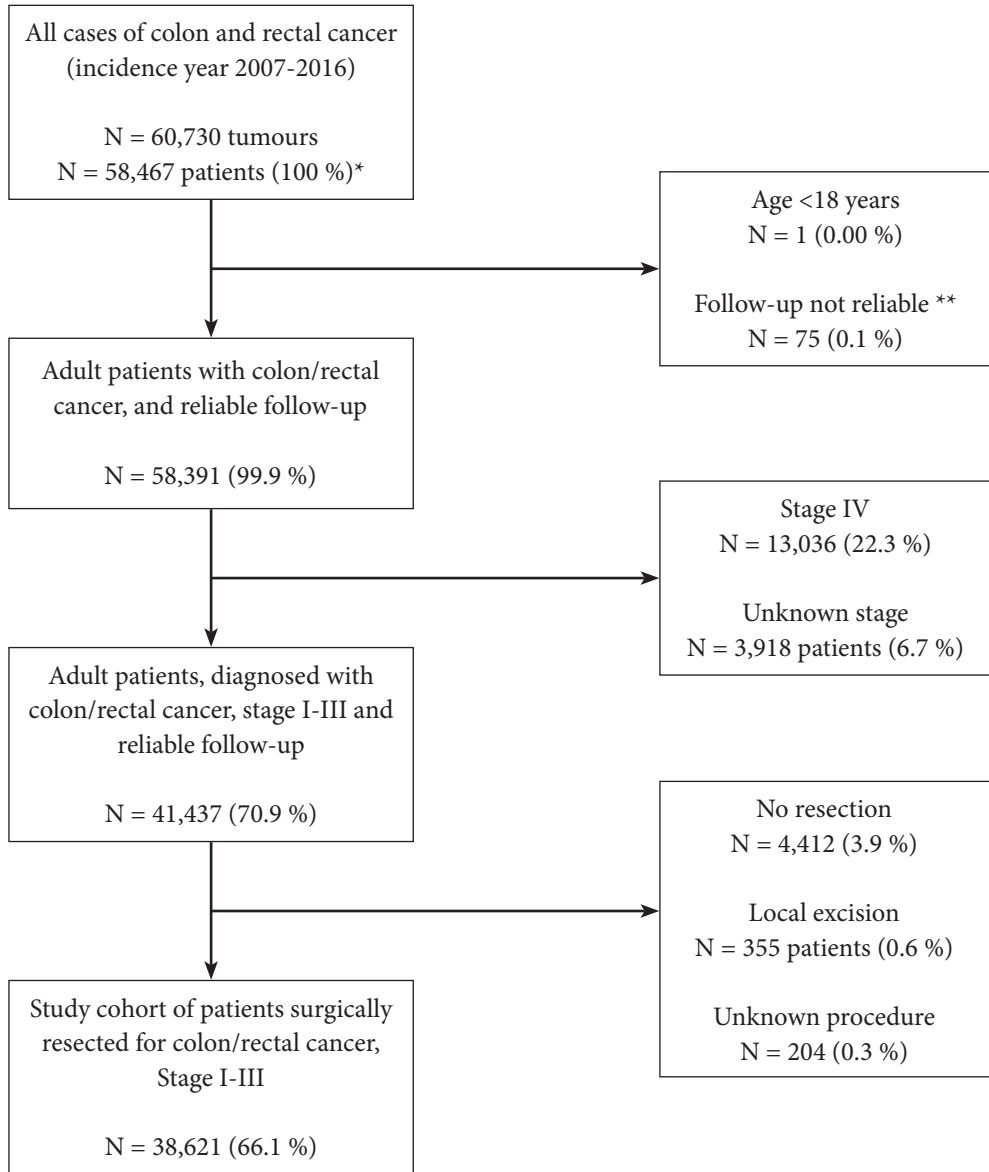
* First primary tumour selected. If multiple tumours were diagnosed on the same day, the highest stage or highest grade was chosen.

** Patients could not be linked with the administrative database, negative follow up (due to registration errors).

In 2018: total population 5,353,365 – number of new colorectal cancer cases 4,887

<https://gco.iarc.fr/today/data/factsheets/populations/578-norway-fact-sheets.pdf> - accessed on 28th May 2020.

Supplementary Table S1d Flowchart patient selection Sweden.



* First primary tumour selected. If multiple tumours were diagnosed on the same day, the highest stage or highest grade was chosen.

** Patients could not be linked with the administrative database, negative follow up (due to registration errors).

In 2018: total population 9,982,703 – number of new colorectal cancer cases 8,017

<https://gco.iarc.fr/today/data/factsheets/populations/752-sweden-fact-sheets.pdf> - accessed on 28th May 2020.

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
Belgium	(N = 2,313)	(N = 3,534)	(N = 3,798)	(N = 2,856)	(N = 4,492)	(N = 3,932)
Only surgery	2142 (92.6)	1796 (50.8)	229 (6.0)	2,670 (93.5)	2,943 (65.5)	502 (12.8)
Additional therapy	171 (7.4)	1,738 (49.2)	3,569 (94.0)	186 (6.5)	1,549 (34.5)	3,430 (87.2)
Neoadjuvant RT	3 (0.1)	6 (0.2)	4 (0.1)	5 (0.2)	9 (0.2)	12 (0.3)
Adjuvant RT	7 (0.3)	7 (0.2)	5 (0.1)	15 (0.5)	19 (0.4)	11 (0.3)
Neoadjuvant CT	28 (1.2)	87 (2.5)	120 (3.2)	41 (1.4)	102 (2.3)	110 (2.8)
Adjuvant CT	127 (5.5)	1,645 (46.5)	3,483 (91.7)	137(4.8)	1,434 (31.9)	3,348 (85.1)
Neoadjuvant CRT	18 (0.8)	15 (0.4)	25 (0.7)	13 (0.5)	21 (0.5)	24 (0.6)
Adjuvant CRT	10 (0.4)	38 (1.1)	52 (1.4)	8 (0.3)	29 (0.6)	36 (0.9)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I (N = 3,373)	Stage II (N = 8,434)	Stage III (N = 6,256)
Only surgery	3,220 (95.5)	7,525 (89.2)	3,533 (56.5)
Additional therapy	153 (4.5)	909 (10.8)	2,723 (43.5)
Neoadjuvant RT	7 (0.2)	18 (0.2)	13 (0.2)
Adjuvant RT	23 (0.7)	39 (0.5)	18 (0.3)
Neoadjuvant CT	44 (1.3)	97 (1.2)	101 (1.6)
Adjuvant CT	102 (3.1)	787 (9.3)	2,632 (42.1)
Neoadjuvant CRT	9 (0.3)	12 (0.1)	11 (0.2)
Adjuvant CRT	1 (0.0)	18 (0.2)	26 (0.4)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation**Supplementary Table S2a** Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I (N = 3,621)	Stage II (N = 6,378)	Stage III (N = 7,403)	Stage I (N = 5,326)	Stage II (N = 8,635)	Stage III (N = 7,823)
Only surgery	3554 (98.1)	5155 (80.8)	747 (10.1)	5,275 (99.0)	7,724 (89.4)	1,817 (23.2)
Additional therapy	67 (1.9)	1,223 (19.2)	6,656 (89.9)	51 (1.0)	911 (10.6)	6,006 (76.8)
Neoadjuvant RT	26 (0.7)	54 (0.8)	80 (1.1)	21 (0.4)	60 (0.7)	71 (0.9)
Adjuvant RT	-	5 (0.1)	5 (0.1)	1 (0.0)	7 (0.1)	3 (0.0)
Neoadjuvant CT	1 (0.0)	37 (0.6)	95 (1.3)	2 (0.0)	41 (0.5)	61 (0.8)
Adjuvant CT	39 (1.1)	1,107 (17.4)	6,427 (86.6)	24 (0.5)	771 (8.9)	5,839 (74.6)
Neoadjuvant CRT	1 (0.0)	32 (0.5)	121 (1.6)	2 (0.0)	42 (0.5)	79 (1.0)
Adjuvant CRT	-	3 (0.0)	14 (0.2)	1 (0.0)	3 (0.0)	5 (0.1)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I (N = 4,975)	Stage II (N = 11,534)	Stage III (N = 8,410)
The Netherlands			
Only surgery	4957 (99.6)	11,299 (98.0)	6,140 (73.0)
Additional therapy	18 (0.4)	235 (2.0)	2,270 (27.0)
Neoadjuvant RT	12 (0.2)	44 (0.4)	58 (0.7)
Adjuvant RT	-	11 (0.1)	5 (0.1)
Neoadjuvant CT	-	15 (0.1)	16 (0.2)
Adjuvant CT	5 (0.1)	156 (1.4)	2,164 (25.7)
Neoadjuvant CRT	1 (0.0)	11 (0.1)	35 (0.4)
Adjuvant CRT	-	3 (0.0)	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation**Supplementary Table S2a** Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I (N = 1,012)	Stage II (N = 1,800)	Stage III (N = 1,752)	Stage I (N = 1,238)	Stage II (N = 2,536)	Stage III (N = 1,877)
Norway						
Only surgery *	-	-	-	-	-	-
Additional therapy *	-	-	-	-	-	-
Neoadjuvant RT	-	-	2 (0.1)	-	2 (0.1)	2 (0.1)
Adjuvant RT	12 (1.2)	53 (2.9)	135 (7.7)	13 (1.1)	80 (3.2)	130 (6.9)
Neoadjuvant CT *	-	-	-	-	-	-
Adjuvant CT *	-	-	-	-	-	-
Neoadjuvant CRT	1 (0.1)	8 (0.4)	12 (0.7)	1 (0.1)	1 (0.0)	9 (0.5)
Adjuvant CRT	-	-	-	-	-	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I (N = 1,826)	Stage II (N = 4,156)	Stage III (N = 2,716)
Norway			
Only surgery *	-	-	-
Additional therapy *	-	-	-
Neoadjuvant RT	-	-	1 (0.0)
Adjuvant RT	11 (0.6)	73 (1.8)	121 (4.5)
Neoadjuvant CT *	-	-	-
Adjuvant CT *	-	-	-
Neoadjuvant CRT	-	3 (0.1)	2 (0.1)
Adjuvant CRT	-	-	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
Sweden	(N = 858)	(N = 2,207)	(N = 2,520)	(N = 1,492)	(N = 3,423)	(N = 3,247)
Only surgery	840 (97.9)	1,612 (73.0)	510 (20.2)	1,457 (97.7)	2,885 (84.3)	990 (30.5)
Additional therapy	18 (2.1)	595 (27.0)	2,010 (79.8)	35 (2.3)	538 (15.7)	2,257 (69.5)
Neoadjuvant RT	-	5 (0.2)	4 (0.2)	2 (0.1)	13 (0.4)	4 (0.1)
Adjuvant RT	-	-	-	-	-	-
Neoadjuvant CT	1 (0.1)	47 (2.1)	61 (2.4)	3 (0.2)	44 (1.3)	48 (1.5)
Adjuvant CT	18 (2.1)	564 (25.6)	1,985 (78.8)	28 (1.9)	495 (14.5)	2,230 (68.7)
Neoadjuvant CRT	1 (0.1)	15 (0.7)	12 (0.5)	3 (0.2)	12 (0.4)	3 (0.1)
Adjuvant CRT	-	-	-	-	3 (0.1)	1 (0.0)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2a Treatment details of patients operated for colon cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I (N = 2,109)	Stage II (N = 5,952)	Stage III (N = 4,714)
Only surgery	2,102 (99.7)	5,760 (96.8)	3,723 (79.0)
Additional therapy	7 (0.3)	192 (3.2)	991 (21.0)
Neoadjuvant RT	1 (0.0)	14 (0.2)	4 (0.1)
Adjuvant RT	-	-	1 (0.0)
Neoadjuvant CT	-	13 (0.2)	18 (0.4)
Adjuvant CT	5 (0.2)	165 (2.8)	976 (20.7)
Neoadjuvant CRT	1 (0.0)	6 (0.1)	-
Adjuvant CRT	-	-	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
Belgium	(N = 1,750)	(N = 1,398)	(N = 1,960)	(N = 1,504)	(N = 1,290)	(N = 1,494)
Only surgery	703 (40.2)	183 (13.1)	38 (1.9)	692 (46.0)	302 (23.4)	95 (6.4)
Additional therapy	1,047 (59.8)	1,215 (86.9)	1,922 (98.1)	812 (54.0)	988 (76.6)	1,399 (93.6)
Neoadjuvant RT	134 (7.7)	141 (10.1)	175 (8.9)	130 (8.6)	142 (11.0)	158 (10.6)
Adjuvant RT	4 (0.2)	5 (0.4)	5 (0.3)	4 (0.3)	13 (1.0)	5 (0.3)
Neoadjuvant CT	15 (0.9)	19 (1.4)	26 (1.3)	23 (1.5)	15 (1.2)	14 (0.9)
Adjuvant CT	585 (33.4)	800 (57.2)	1,555 (79.3)	360 (23.9)	548 (42.5)	1,048 (70.1)
Neoadjuvant CRT	855 (48.9)	863 (61.7)	1,182 (60.3)	622 (41.4)	672 (52.1)	798 (53.4)
Adjuvant CRT	6 (0.3)	71 (5.1)	164 (8.4)	10 (0.7)	50 (3.9)	116 (7.8)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I (N = 1,382)	Stage II (N = 1,595)	Stage III (N = 1,710)
Belgium			
Only surgery	778 (56.3)	745 (46.7)	611 (35.7)
Additional therapy	604 (43.7)	850 (53.3)	1,099 (64.3)
Neoadjuvant RT	206 (14.9)	276 (17.3)	287 (16.8)
Adjuvant RT	4 (0.3)	20 (1.3)	20 (1.2)
Neoadjuvant CT	13 (0.9)	16 (1.0)	21 (1.2)
Adjuvant CT	131 (9.5)	243 (15.2)	608 (35.6)
Neoadjuvant CRT	362 (26.2)	469 (29.4)	443 (25.9)
Adjuvant CRT	2 (0.1)	11 (0.7)	66 (3.9)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation**Supplementary Table S2b** Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I (N = 1,784)	Stage II (N = 2,358)	Stage III (N = 5,625)	Stage I (N = 1,924)	Stage II (N = 2,402)	Stage III (N = 4,431)
Only surgery	768 (43.0)	348 (14.8)	265 (4.7)	958 (49.8)	467 (19.4)	397 (9.0)
Additional therapy	1,016 (57.0)	2,010 (85.2)	5,360 (95.3)	966 (50.2)	1,935 (80.6)	4,034 (91.0)
Neoadjuvant RT	858 (48.1)	1,248 (52.9)	1,504 (26.7)	834 (43.3)	1,336 (55.6)	1,396 (31.5)
Adjuvant RT	29 (1.6)	14 (0.6)	28 (0.5)	34 (1.8)	14 (0.6)	34 (0.8)
Neoadjuvant CT	1 (0.1)	21 (0.9)	138 (2.5)	4 (0.2)	20 (0.8)	86 (1.9)
Adjuvant CT	6 (0.3)	31 (1.3)	574 (10.2)	2 (0.1)	16 (0.7)	313 (7.1)
Neoadjuvant CRT	129 (7.2)	717 (30.4)	3,509 (62.4)	93 (4.8)	561 (23.4)	2,406 (54.3)
Adjuvant CRT	2 (0.1)	4 (0.2)	15 (0.3)	2 (0.1)	3 (0.1)	12 (0.3)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I	Stage II	Stage III
The Netherlands	(N = 1,403)	(N = 2,066)	(N = 2,686)
Only surgery	714 (50.9)	522 (25.3)	541 (20.1)
Additional therapy	689 (49.1)	1,544 (74.7)	2,145 (79.9)
Neoadjuvant RT	647 (46.1)	1,255 (60.7)	1,327 (49.4)
Adjuvant RT	15 (1.1)	18 (0.9)	17 (0.6)
Neoadjuvant CT	-	8 (0.4)	16 (0.6)
Adjuvant CT	1 (0.1)	2 (0.1)	78 (2.9)
Neoadjuvant CRT	28 (2.0)	274 (13.3)	748 (27.8)
Adjuvant CRT	-	1 (0.0)	4 (0.1)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation**Supplementary Table S2b** Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	65-74 years					
	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
Norway	(N = 586)	(N = 639)	(N = 1,183)	(N = 586)	(N = 651)	(N = 916)
Only surgery *	468 (79.8)	296 (46.3)	314 (26.5)	484 (82.6)	320 (49.1)	320 (34.9)
Additional therapy *	118 (20.2)	343 (53.7)	869 (73.5)	102 (17.4)	331 (50.9)	596 (65.1)
Neoadjuvant RT	5 (0.9)	17 (2.7)	39 (3.3)	11 (1.9)	26 (4.0)	45 (4.9)
Adjuvant RT	22 (3.8)	44 (6.9)	91 (7.7)	31 (5.3)	52 (8.0)	86 (9.4)
Neoadjuvant CT *	-	-	-	-	-	-
Adjuvant CT *	-	-	-	-	-	-
Neoadjuvant CRT	91 (15.5)	282 (44.1)	739 (62.5)	60 (10.2)	253 (38.9)	465 (50.8)
Adjuvant CRT	-	-	-	-	-	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I (N = 541)	Stage II (N = 758)	Stage III (N = 775)
Norway			
Only surgery *	478 (88.4)	522 (68.9)	430 (55.5)
Additional therapy *	63 (11.6)	236 (31.1)	345 (44.5)
Neoadjuvant RT	17 (3.1)	79 (10.4)	116 (15.0)
Adjuvant RT	21 (3.9)	45 (5.9)	69 (8.9)
Neoadjuvant CT *	-	-	-
Adjuvant CT *	-	-	-
Neoadjuvant CRT	25 (4.6)	112 (14.8)	160 (20.6)
Adjuvant CRT	-	-	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation**Supplementary Table S2b** Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	< 65 years			65-74 years		
	Stage I (N = 1,113)	Stage II (N = 1,139)	Stage III (N = 1,684)	Stage I (N = 1,325)	Stage II (N = 1,353)	Stage III (N = 1,671)
Only surgery	397 (35.7)	184 (16.2)	95 (5.6)	551 (41.6)	325 (24.0)	154 (9.2)
Additional therapy	716 (64.3)	955 (83.8)	1,589 (94.4)	774 (58.4)	1,028 (76.0)	1,517 (90.8)
Neoadjuvant RT	524 (47.1)	570 (50.0)	854 (50.7)	614 (46.3)	723 (53.4)	951 (56.9)
Adjuvant RT	-	-	2 (0.1)	0 (0.1)	2 (0.1)	2 (0.1)
Neoadjuvant CT	3 (0.3)	14 (1.2)	14 (0.8)	4 (0.3)	9 (0.7)	10 (0.6)
Adjuvant CT	83 (7.5)	216 (19.0)	979 (58.1)	40 (3.0)	152 (11.1)	818 (49.0)
Neoadjuvant CRT	176 (15.8)	337 (29.6)	452 (26.8)	144 (10.9)	257 (19.0)	316 (18.9)
Adjuvant CRT	-	1 (0.1)	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Continuation

Supplementary Table S2b Treatment details of patients operated for rectal cancer diagnosed in the period 2007 – 2016.

	≥ 75 years		
	Stage I (N = 1,116)	Stage II (N = 1,275)	Stage III (N = 1,423)
Only surgery	609 (54.6)	579 (45.4)	550 (38.7)
Additional therapy	507 (45.4)	696 (54.6)	873 (61.3)
Neoadjuvant RT	465 (41.7)	623 (48.9)	730 (51.3)
Adjuvant RT	1 (0.1)	1 (0.1)	2 (0.1)
Neoadjuvant CT	2 (0.2)	3 (0.2)	3 (0.2)
Adjuvant CT	5 (0.4)	19 (1.5)	191 (13.4)
Neoadjuvant CRT	36 (3.2)	64 (5.0)	72 (5.1)
Adjuvant CRT	-	-	-

Data are presented as n(%). Pre- and postoperative treatment are not combined; therefore percentages can be above 100%.

RT radiotherapy CT chemotherapy CRT chemoradiotherapy.

*No information on chemotherapy administration.

Supplementary Table S3 Mortality time trends in percentages for patients with rectal cancer ≥ 75 years.

	≤ 30 day, overall mortality					P-value
	2007 - 2008	2009 - 2010	2011 - 2012	2013 - 2014	2015 - 2016	
Stage I						0.204
Belgium	4.5	6.4	2.6	4.0	3.4	
The Netherlands	7.3	6.1	4.5	2.4	3.7	
Norway	0.0	1.9	4.9	0.8	0.9	
Sweden	5.4	1.8	0.9	3.6	1.4	
Stage II						0.082
Belgium	7.0	8.7	7.2	5.1	6.0	
The Netherlands	8.4	5.2	4.3	3.5	2.0	
Norway	4.5	2.9	4.0	3.8	5.5	
Sweden	5.0	3.0	3.1	4.2	4.0	
Stage III						0.009
Belgium	7.1	5.6	3.4	3.6	6.5	
The Netherlands	7.0	6.7	4.3	3.0	2.7	
Norway	5.1	3.1	3.6	0.0	2.5	
Sweden	6.3	4.1	3.7	3.3	1.9	

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

Continuation Supplementary Table S3 Mortality time trends in percentages for patients with rectal cancer ≥ 75 years.

	1st year, overall mortality					P-value
	2007 - 2008	2009 - 2010	2011 - 2012	2013 - 2014	2015 - 2016	
Stage I						0.122
Belgium	10.8	16.4	13.8	13.2	9.2	
The Netherlands	16.7	9.5	11.7	6.6	7.4	
Norway	8.4	7.8	11.8	2.4	3.4	
Sweden	11.3	8.1	5.0	5.0	5.1	
Stage II						0.007
Belgium	19.4	19.5	18.2	18.2	16.2	
The Netherlands	18.9	14.6	12.8	11.7	7.5	
Norway	14.6	8.1	9.3	7.6	13.7	
Sweden	14.2	10.0	8.4	9.3	9.7	
Stage III						<0.001
Belgium	22.2	21.9	20.6	19.9	20.4	
The Netherlands	20.4	16.9	16.3	10.8	9.4	
Norway	20.3	11.9	12.7	7.1	8.9	
Sweden	16.4	14.9	12.8	9.8	10.8	

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