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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.

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1. 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 population [5], 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 post-operative 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.

2. Methods

2.1. 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].

2.2. 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.

2.3. 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.

3. 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

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

	Belgium			The Netherlands			Norway			Sweden		
COLON CANCER	< 65 years	65–74 years	≥ 75 years	< 65 years	65–74 years	≥ 75 years	< 65 years	65–74 years	≥ 75 years	< 65 years	65-74 years	≥ 75 years
	N = 9645	*N* = 11,280	*N* = 18,063	*N* = 17,402	*N* = 21,784	*N* = 24,919	*N* = 4564	*N* = 5651	*N* = 8698	*N* = 5585	*N* = 8162	*N* = 12,775
Gender												
Male	5362 (55.6)	6652 (59.0)	8461 (46.8)	9298 (53.4)	12,163 (55.8)	11,868 (47.6)	2312 (50.7)	2835 (50.2)	3750 (43.1)	2955 (52.9)	4215 (51.6)	5710 (44.7)
Female	4283 (44.4)	4628 (41.0)	9602 (53.2)	8104 (46.6)	9621 (44.2)	13,051 (52.4)	2252 (49.3)	2816 (49.8)	4948 (56.9)	2630 (47.1)	3947 (48.4)	7065 (55.3)
Stage												
Stage I	2313 (24.0)	2856 (25.3)	3373 (18.7)	3621 (20.8)	5326 (24.4)	4975 (20.0)	1012 (22.2)	1238 (21.9)	1826 (21.0)	858 (15.4)	1492 (18.3)	2109 (16.5)
Stage II	3534 (36.6)	4492 (39.8)	8434 (46.7)	6378 (36.7)	8635 (39.6)	11,534 (46.3)	1800 (39.4)	2536 (44.9)	4156 (47.8)	2207 (39.5)	3423 (41.9)	5952 (46.6)
Stage III	3798 (39.4)	3932 (34.9)	6256 (34.6)	7403 (42.5)	7823 (35.9)	8410 (33.7)	1752 (38.4)	1877 (33.2)	2716 (31.2)	2520 (45.1)	3247 (39.8)	4714 (36.9)

	Belgium			The Netherlands			Norway			Sweden		
RECTAL CANCER	< 65 years	65–74 years	≥ 75 years	< 65 years	65–74 years	≥ 75 years	< 65 years	65–74 years	≥ 75 years	< 65 years	65-74 years	≥ 75 years
	N = 5108	*N* = 4288	*N* = 4687	*N* = 9767	*N* = 8757	*N* = 6155	*N* = 2408	*N* = 2153	*N* = 2074	*N* = 3936	*N* = 4349	*N* = 3814
Gender												
Male	3231 (63.3)	2852 (66.5)	2702 (57.6)	6115 (62.6)	5840 (66.7)	3531 (57.4)	1426 (59.2)	1390 (64.6)	1153 (55.6)	2303 (58.5)	2746 (63.1)	2204 (57.8)
Female	1877 (36.7)	1436 (33.5)	1985 (42.4)	3652 (37.4)	2917 (33.3)	2624 (42.6)	982 (40.8)	763 (35.4)	921 (44.4)	1633 (41.5)	1603 (36.9)	1610 (42.2)
Stage												
Stage I	1750 (34.3)	1504 (35.1)	1382 (29.5)	1784 (18.3)	1924 (22.0)	1403 (22.8)	586 (24.3)	586 (27.2)	541 (26.1)	1113 (28.3)	1325 (30.5)	1116 (29.3)
Stage II	1398 (27.4)	1290 (30.1)	1595 (34.0)	2358 (24.1)	2402 (27.4)	2066 (33.6)	639 (26.5)	651 (30.2)	758 (36.5)	1139 (28.9)	1353 (31.1)	1275 (33.4)
Stage III	1960 (38.4)	1494 (34.8)	1710 (36.5)	5625 (57.6)	4431 (50.6)	2686 (43.6)	1183 (49.1)	916 (42.5)	775 (37.4)	1684 (42.8)	1671 (38.4)	1423 (37.3)

Data are presented as n(%).

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).

3.1. 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 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.

3.2. 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.)

3.3. 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

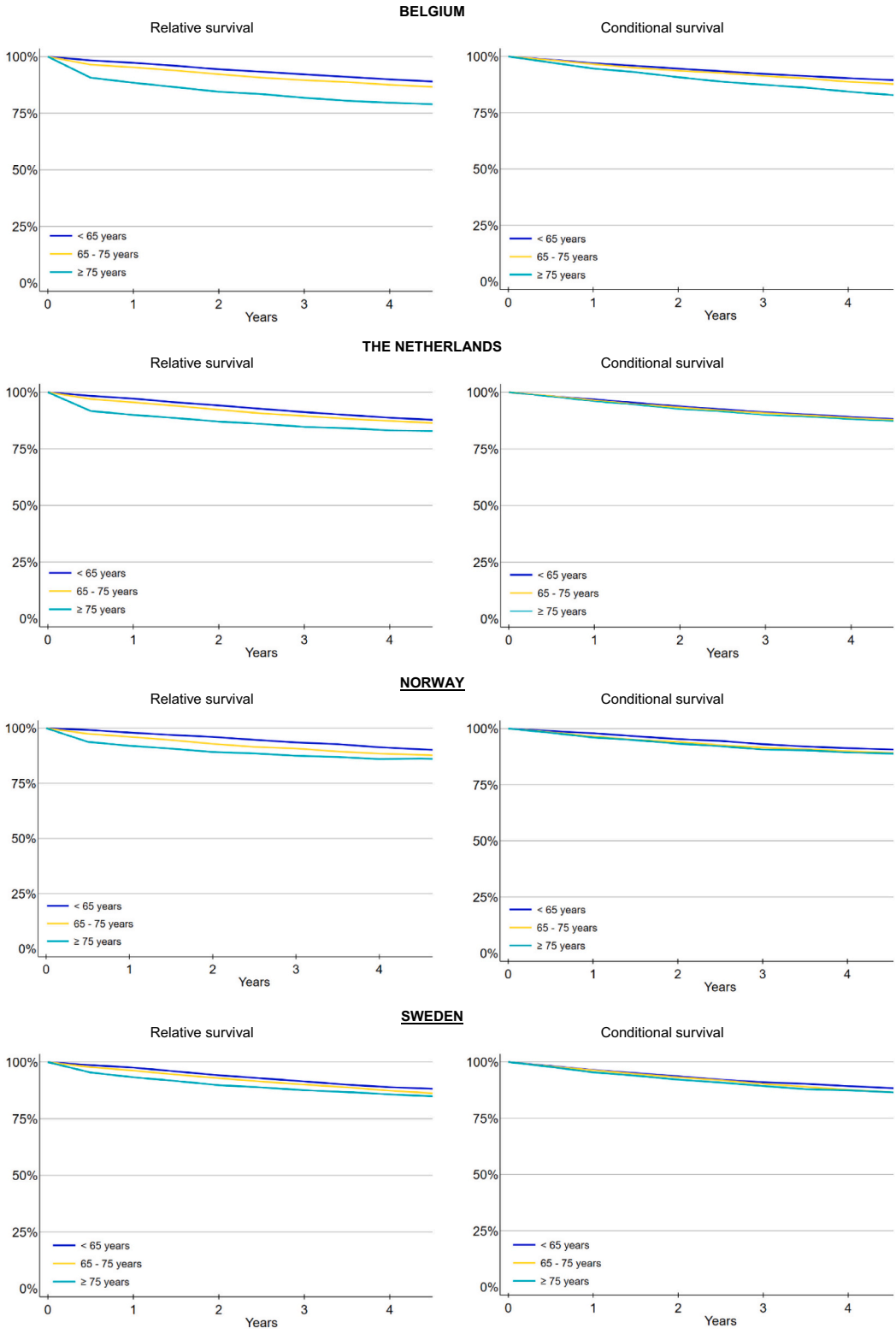

Fig. 1a. Relative and conditional survival of stage I-III operated **colon** cancer patients, according to age.

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.

3.4. *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

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		Stage II		Stage III	
	RS	CS	RS	CS	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref	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. *	***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 (2.3–2.8)***	***1.7 (1.5–1.9)***	***3.0 (2.0–4.5)***	N.A. *	***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	All stages		Stage I		Stage II		Stage III	
	RS	CS	RS	CS	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref	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)	***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	***1.8 (1.7–1.9)***	1.1 (1.0–1.2)	***6.8 (3.5–13.3)***	0.8 (0.2–3.7)	***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	All stages		Stage I		Stage II		Stage III	
	RS	CS	RS	CS	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref	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)	***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	***2.0 (1.7–2.3)***	1.3 (1.1–1.6)	1.8 (0.5–6.7)	N.A. *	***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	All stages		Stage I		Stage II		Stage III	
	RS	CS	RS	CS	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref	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)	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	***1.4 (1.3–1.6)***	1.2 (1.1–1.4)	N.A. *	0.9 (0.3–3.3)	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, *CI* confidence interval *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.

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).

4. 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 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 research [10] 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

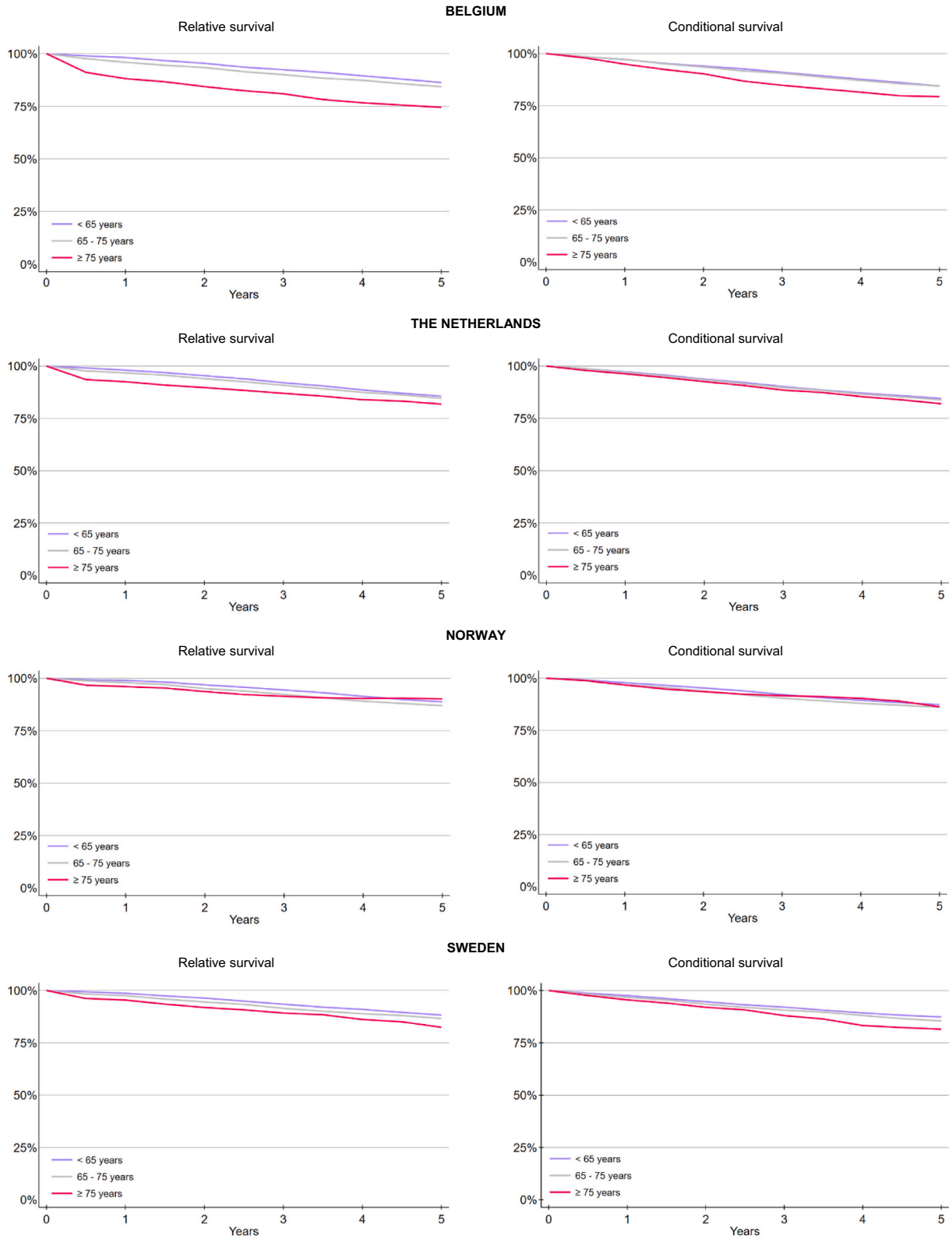

Fig. 1b. Relative and conditional survival of stage I-III operated **rectal** cancer patients, according to age.

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

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		Stage II		Stage III	
	RS	CS	RS	CS	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref	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)	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 (2.3–2.9)***	***1.5 (1.3–1.8)***	***6.9 (3.3–14.4)***	0.6 (0.1–4.2)	***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	All stages		Stage I		Stage II		Stage III	
	RS	CS	RS	CS	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref	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)	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 (1.3–1.7)***	1.2 (1.0–1.3)	***6.2 (2.4–15.9)***	0.7 (0.1–4.1)	***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	All stages		Stage I		Stage II		Stage III	
	RS	CS	RS	CS	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref	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)	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	1.0 (0.7–1.5)	1.1 (0.8–1.5)	N.A. *	N.A. *	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	All stages		Stage I		Stage II		Stage III	
	RS	CS	RS	CS	RS	CS	RS	CS
<65 years	Ref	Ref	Ref	Ref	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)	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	***1.6 (1.3–1.9)***	***1.5 (1.3–1.8)***	0.4 (0.0–45.9)	0.5 (0.0–8.7)	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, *CI* confidence interval *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 mortality (OM) and excess mortality (EM) rates in percentages. N = number of patients.

COLON CANCER	Belgium			The Netherlands			Norway			Sweden		
	N	OM	EM	*N*	OM	EM	*N*	OM	EM	*N*	OM	EM
Gender												
Male	20,475	11.0	**6.9**	33,329	9.5	**6.0**	8897	9.5	**5.4**	12,880	8.5	**4.5**
Female	18,513	11.1	**7.7**	30,776	9.1	**6.3**	10,016	8.6	**5.2**	13,642	8.5	**5.1**
Age (years)												
<65	9645	3.4	**2.7**	17,402	3.4	**2.8**	4564	2.5	**2.0**	5424	2.9	**2.5**
65–74	11,280	6.6	**4.7**	21,784	6.2	**4.5**	5651	5.6	**3.9**	7731	5.3	**3.9**
≥75	18,063	18.0	**11.4**	24,919	16.1	**9.9**	8698	14.7	**7.9**	11,109	13.0	**7.5**
Stage												
Stage I	8542	6.2	**2.9**	13,922	5.0	**2.1**	4076	5.2	**1.6**	4459	3.9	**0.2**
Stage II	16,460	10.3	**6.0**	26,547	8.7	**5.2**	8492	8.5	**4.4**	11,582	7.0	**3.0**
Stage III	13,986	15.0	**11.5**	23,636	12.4	**9.5**	6345	12.2	**8.7**	10,481	12.2	**8.8**

RECTAL CANCER	Belgium			The Netherlands			Norway			Sweden		
	N	OM	EM	*N*	OM	EM	*N*	OM	EM	*N*	OM	EM
Gender												
Male	8785	9.0	**5.9**	15,486	6.7	**4.1**	3969	5.7	**2.8**	7253	6.2	**3.4**
Female	5298	8.0	**5.6**	9193	5.0	**3.1**	2666	3.8	**1.4**	4846	4.1	**1.8**
Age (years)												
<65	5108	2.5	**1.8**	9767	2.5	**1.9**	2408	1.6	**1.0**	3936	1.8	**1.3**
65–74	4288	6.1	**4.1**	8757	5.1	**3.2**	2153	3.8	**2.0**	4349	4.1	**2.5**
≥75	4687	17.7	**11.7**	6155	13.1	**7.4**	2074	10.1	**3.9**	3814	10.4	**4.5**
Stage												
Stage I	4636	5.4	**2.7**	5111	4.6	**2.2**	1713	3.3	**0.6**	3554	3.5	**1.0**
Stage II	4283	9.6	**6.5**	6826	6.8	**4.1**	2048	5.3	**2.2**	3767	5.4	**2.6**
Stage III	5164	10.7	**7.9**	12,742	6.3	**4.2**	2874	5.6	**3.2**	4778	6.6	**4.2**

OM overall mortality, *EM* excess mortality.

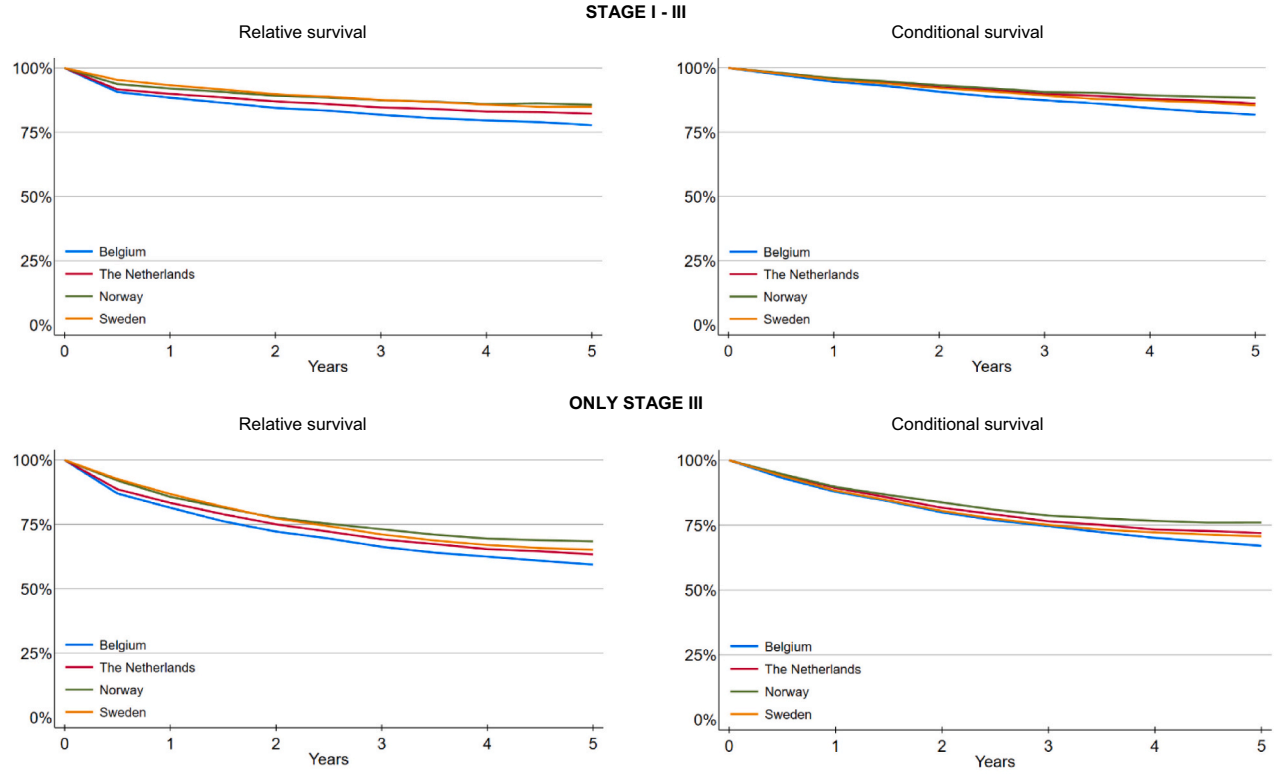

Fig. 2a. Relative and conditional survival of operated **colon** cancer patients, 75 years and older.

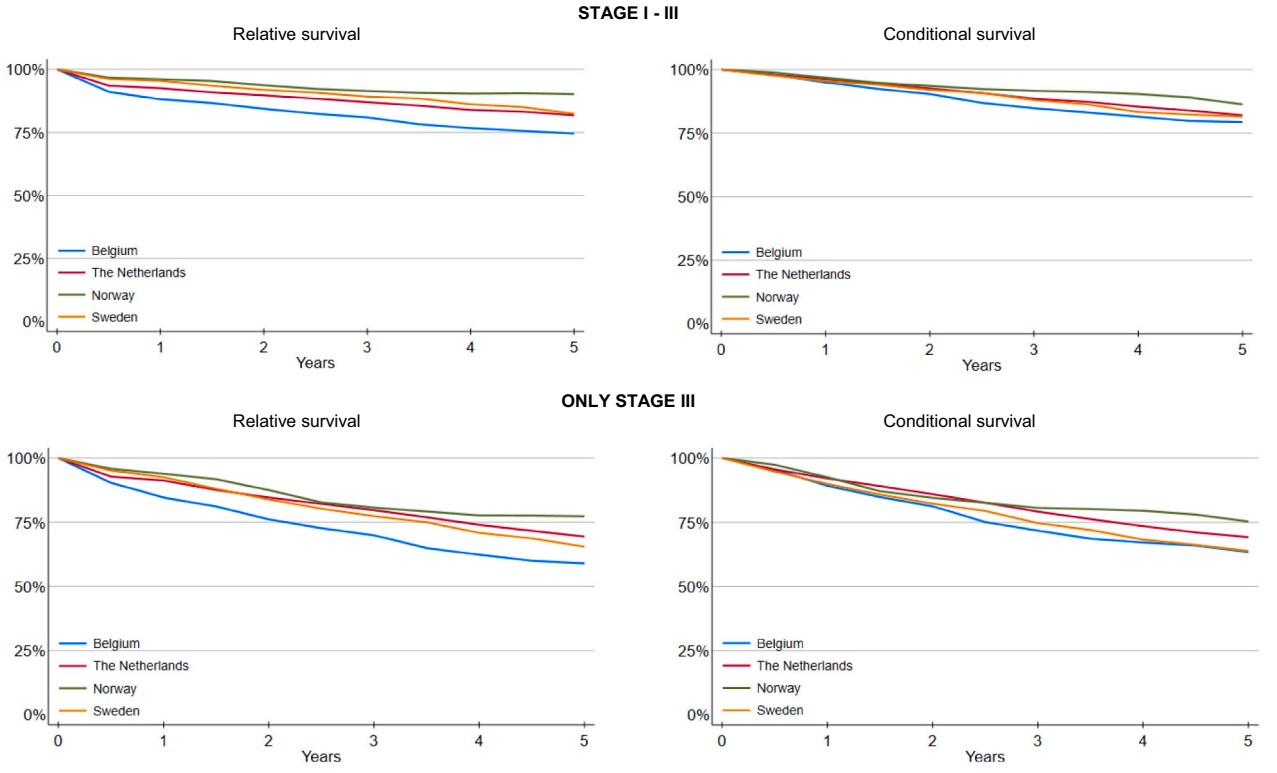

Fig. 2b. Relative and conditional survival of operated **rectal** cancer patients, 75 years and older.

often performed in these countries: Belgium 3.8%, the Netherlands 4.7%, Norway 2.9%, and Sweden 0.6% (appendix A). 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 yP stage in all countries, so we were not able to stratify the results according to yP 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.

5. 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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2022.04.011.

References

[1] Pilleron S, Sarfati D, Janssen-Heijnen M, Vignat J, Ferlay J, Bray F, et al. Global cancer incidence in older adults, 2012 and 2035: a population-based study. Int J Cancer 2019;144(1):49–58.
[2] Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol 2008; 9(5):494–501.
[3] Biondi A, Vacante M, Ambrosino I, Cristaldi E, Pietrapertosa G, Basile F. Role of surgery for colorectal cancer in the elderly. World J Gastrointest Surg 2016;8(9): 606–13.
[4] Ketelaers SHJ, Fahim M, Rutten HJT, Smits AB, Orsini RG. When and how should surgery be performed in senior colorectal cancer patients? Eur J Surg Oncol 2020; 46(3):326–32.
[5] Breugom AJ, Bastiaannet E, Dekker JWT, Wouters M, van de Velde CJH, Liefers GJ. Decrease in 30-day and one-year mortality over time in patients aged >/=75 years with stage I-III colon cancer: a population-based study. Eur J Surg Oncol 2018;44 (12):1889–93.
[6] Bos A, Kortbeek D, van Erning FN, Zimmerman DDE, Lemmens V, Dekker JWT, et al. Postoperative mortality in elderly patients with colorectal cancer: the impact of age, time-trends and competing risks of dying. Eur J Surg Oncol 2019;45(9): 1575–83.
[7] Brouwer NPM, Heil TC, Olde Rikkert MGM, Lemmens V, Rutten HJT, de Wilt JHW, et al. The gap in postoperative outcome between older and younger patients with stage I-III colorectal cancer has been bridged; results from the Netherlands cancer registry. Eur J Cancer 2019;116:1–9.
[8] Dekker JW, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. Ann Surg Oncol 2011;18(6):1533–9.
[9] Pilleron S, Charvat H, Araghi M, Arnold M, Fidler-Benaoudia MM, Bardot A, et al. Age disparities in stage-specific colon cancer survival across seven countries: an

ICBP SURVMARK-2 population-based study. Int J Cancer 2021;48(7):1575–85. https://doi.org/10.1002/ijc.33326. Epub 2020 Oct 14.
[10] Bahadoer RR, Bastiaannet E, Claassen YHM, van der Mark M, van Eycken E, Verbeeck J, et al. One-year excess mortality and treatment in surgically treated patients with colorectal cancer: a EURECCA European comparison. Eur J Surg Oncol 2021;47(7):1651–60. https://doi.org/10.1016/j.ejso.2021.01.011. Epub 2021 Jan 21.
[11] Bosetti C, Bertuccio P, Malvezzi M, Levi F, Chatenoud L, Negri E, et al. Cancer mortality in Europe, 2005-2009, and an overview of trends since 1980. Ann Oncol 2013;24(10):2657–71.
[12] Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, et al. Data quality at the Cancer registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer 2009;45(7):1218–31.
[13] Kodeda K, Johansson R, Zar N, Birgisson H, Dahlberg M, Skullman S, et al. Time trends, improvements and national auditing of rectal cancer management over an 18-year period. Colorectal Dis 2015;17(9):O168–79.
[14] Henau K, Van Eycken E, Silversmit G, Pukkala E. Regional variation in incidence for smoking and alcohol related cancers in Belgium. Cancer Epidemiol 2015;39(1):55–65.
[15] IKNL. Privacyverklaring. Available from, https://iknl.nl/privacyverklaring#8; 2022.
[16] Fritz AGPC, Jack A, et al., editors. International classification of diseases for oncology (ICD-O). 3rd ed. Geneva: World Health Organization; 2000.
[17] Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. Stat Med 2004;23(1):51–64.
[18] Suissa S. Relative excess risk: an alternative measure of comparative risk. Am J Epidemiol 1999;150(3):279–82.
[19] Montroni I, Ugolini G, Saur NM, Spinelli A, Rostoft S, Millan M, et al. Personalized management of elderly patients with rectal cancer: expert recommendations of the European Society of Surgical Oncology, European Society of Coloproctology, International Society of Geriatric Oncology, and American College of Surgeons Commission on Cancer. Eur J Surg Oncol 2018;44(11):1685–702.
[20] Ketelaers SHJ, Orsini RG, Burger JWA, Nieuwenhuijzen GAP, Rutten HJT. Significant improvement in postoperative and 1-year mortality after colorectal cancer surgery in recent years. Eur J Surg Oncol 2019;45(11):2052–8. https://doi.org/10.1016/j.ejso.2019.06.017. Epub 2019 Jun 13.
[21] Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av kreft i tykktarm og endetarm. National Guideline CRC Norway; 2019.
[22] Vermeer NCA, Claassen YHM, Derks MGM, Iversen LH, van Eycken E, Guren MG, et al. Treatment and survival of patients with Colon Cancer aged 80 years and older: a EURECCA international comparison. Oncologist. 2018;23(8):982–90.
[23] Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D, et al. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol 2015;26(3):463–76.
[24] Breugom AJ, Swets M, Bosset JF, Collette L, Sainato A, Cionini L, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16(2):200–7.
[25] Ko JJ, Kennecke HF, Lim HJ, Renouf DJ, Gill S, Woods R, et al. Reasons for underuse of adjuvant chemotherapy in elderly patients with stage III Colon Cancer. Clin Colorectal Cancer 2016;15(2):179–85.
[26] Babaei M, Jansen L, Balavarca Y, Sjovall A, Bos A, van de Velde T, et al. Neoadjuvant therapy in rectal Cancer patients with clinical stage II to III across European countries: variations and outcomes. Clin Colorectal Cancer 2018;17(1)[e129-e42].
[27] Papamichael D, Audisio R, Horiot JC, Glimelius B, Sastre J, Mitry E, et al. Treatment of the elderly colorectal cancer patient: SIOG expert recommendations. Ann Oncol 2009;20(1):5–16.
[28] Babaei M, Balavarca Y, Jansen L, Gondos A, Lemmens V, Sjovall A, et al. Minimally invasive colorectal Cancer surgery in Europe: implementation and outcomes. Medicine (Baltimore) 2016;95(22):e3812.
[29] Morino M, Risio M, Bach S, Beets-Tan R, Bujko K, Panis Y, et al. Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference. Surg Endosc 2015;29(4):755–73.
[30] Grass JK, Perez DR, Izbicki JR, Reeh M. Systematic review analysis of robotic and transanal approaches in TME surgery- a systematic review of the current literature in regard to challenges in rectal cancer surgery. Eur J Surg Oncol 2019;45(4):498–509.
[31] Dent OF, Chapuis PH, Renwick AA, Bokey EL. The importance of tumor stage and relative survival analysis for the association between sex and survival after resection of colorectal cancer. Ann Surg 2009;249(3):402–8.
[32] Dekker JW, Gooiker GA, Bastiaannet E, van den Broek CB, van der Geest LG, van de Velde CJ, et al. Cause of death the first year after curative colorectal cancer surgery; a prolonged impact of the surgery in elderly colorectal cancer patients. Eur J Surg Oncol 2014;40(11):1481–7.
[33] Benitez Majano S, Di Girolamo C, Rachet B, Maringe C, Guren MG, Glimelius B, et al. Surgical treatment and survival from colorectal cancer in Denmark, England, Norway, and Sweden: a population-based study. Lancet Oncol 2019;20(1):74–87.
[34] Lopez-Campos F, Martin-Martin M, Fornell-Perez R, Garcia-Perez JC, Die-Trill J, Fuentes-Mateos R, et al. Watch and wait approach in rectal cancer: current controversies and future directions. World J Gastroenterol 2020;26(29):4218–39.
[35] Haak HE, Maas M, Lambregts DMJ, Beets-Tan RGH, Beets GL, Dutch Watch-and-Wait C. Is watch and wait a safe and effective way to treat rectal cancer in older patients? Eur J Surg Oncol 2020;46(3):358–62.
[36] Miller SM, Wolf J, Katlic M, D'Adamo CR, Coleman J, Ahuja V. Frailty is a better predictor than age for outcomes in geriatric patients with rectal cancer undergoing proctectomy. Surgery. 2020;168(3):504–8.
[37] McArdle CS, Hole DJ. Emergency presentation of colorectal cancer is associated with poor 5-year survival. Br J Surg 2004;91(5):605–9.
[38] Geraghty J, Shawihdi M, Devonport E, Sarkar S, Pearson MG, Bodger K. Reduced risk of emergency admission for colorectal cancer associated with the introduction of bowel cancer screening across England: a retrospective national cohort study. Colorectal Dis 2018;20(2):94–104.