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Y.H.M. Claassen [a, *], E. Bastiaannet [a, b], E. van Eycken [c], N. Van Damme [c], A. Martling [d], R. Johansson [e], L.H. Iversen [f, g], P. Ingeholm [h], V.E.P.P. Lemmens [i, j], G.J. Liefers [a], F.A. Holman [a], J.W.T. Dekker [k], J.E.A. Portielje [b], H.J. Rutten [l, m], C.J.H. van de Velde [a]

[a] Department of Surgical Oncology, Leiden University Medical Center, the Netherlands
[b] Department of Medical Oncology, Leiden University Medical Center, Leiden, the Netherlands
[c] National Cancer Registry, Brussels, Belgium
[d] Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[e] Department of Radiation Science, Oncology, Umeå University, Umeå, Sweden
[f] Department of Surgery, Aarhus University Hospital, Aarhus, Denmark
[g] Danish Colorectal Cancer Group (DCCG.dk), Copenhagen, Denmark
[h] Department of Pathology, Herlev and Gentofte Hospital, Copenhagen, Denmark
[i] Netherlands Comprehensive Cancer Organization, Utrecht, the Netherlands
[j] Department of Public Health, Erasmus MC, Rotterdam, the Netherlands
[k] Department of Surgery, Reinier de Graaf Hospital, Delft, the Netherlands
[l] Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands
[m] GROW: School of Oncology and Developmental Biology, University of Maastricht, Maastricht, the Netherlands

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ABSTRACT

Background: Decreased cancer specific survival in older colorectal patients is mainly due to mortality in the first year, emphasizing the importance of the first postoperative year. This study aims to gain an overview and time trends of short-term mortality in octogenarians (≥80 years) with colorectal cancer across four North European countries.

Methods: Patients of 80 years or older, operated for colorectal cancer (stage I-III) between 2005 and 2014, were included. Population-based cohorts from Belgium, Denmark, the Netherlands, and Sweden were collected. Separately for colon- and rectal cancer, 30-day, 90-day, one-year, and excess one-year mortality were calculated. Also, short-term mortality over three time periods (2005–2008, 2009–2011, 2012–2014) was analyzed.

Results: In total, 35,158 colon cancer patients and 10,144 rectal cancer patients were included. For colon cancer, 90-day mortality rate was highest in Denmark (15%) and lowest in Sweden (8%). For rectal cancer, 90-day mortality rate was highest in Belgium (11%) and lowest in Sweden (7%). One-year excess mortality rate of colon cancer patients decreased from 2005 to 2008 to 2012–2014 for all countries (Belgium: 17%–11%, Denmark: 21%–15%, the Netherlands: 18%–10%, and Sweden: 10%–8%). For rectal cancer, from 2005 to 2008 to 2012–2014 one-year excess mortality rate decreased in the Netherlands from 16% to 7% and Sweden: 8%–2%).

Conclusions: Short-term mortality rates were high in octogenarians operated for colorectal cancer. Short-term mortality rates differ across four North European countries, but decreased over time for both colon and rectal cancer patients in all countries.

Introduction

Colorectal cancer is one of the most common types of cancer, accounting for an estimated number of 471,000 new cases and 228,000 deaths in Europe in 2012 [1]. Colorectal cancer is

* Corresponding author. Department of Surgery, K6-43 Leiden University Medical Center, PO Box 9600, 2300 RC, Leiden, the Netherlands.
E-mail addresses: y.h.m.claassen@lumc.nl (Y.H.M. Claassen), C.J.H.van_de_Velde@lumc.nl (C.J.H. van de Velde).

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predominantly a disease of the elderly, as approximately one fifth of all colorectal patients is older than 80 years [2]. This number is expected to increase as the population ages.

Several population based studies showed an impaired cancer related survival for older patients with colorectal cancer compared to their younger counterparts with colorectal cancer [3–5]. The EUROCARE-5 study showed a European average 5-year relative survival for colon and rectal cancer patients of 75 years or older of 49% and 44%, respectively, whereas 5-year relative survival for all ages were 57% and 56% [5]. Several aspects might explain these findings. Firstly, older colorectal cancer patients are more often diagnosed with an advanced stage of disease. Also they suffer more often from comorbidities that may contribute to a higher rate of postoperative complications, but also intervene with adjuvant treatments. Furthermore, they have a greater risk of dying due to complications or other diseases that are accelerated during cancer treatment [6–8].

A crucial component of the impaired cancer-specific survival in older colorectal cancer patients is the increased short-term mortality [9]. Short-term mortality is defined as mortality in the first postoperative year. Literature has shown that one-year mortality in colorectal cancer is highly influenced by age [10]. In a single-institution in Cleveland (Ohio, United States of America) 2485 patients with stages I-III colorectal adenocarcinoma who underwent an electively radical resection were included. In this study, octogenarians (patients of 80 years or older) had a one-year overall mortality of 37% after a colorectal cancer resection, whereas patients of 65 years or younger had a one-year mortality of 7% [10]. This study was limited by selection bias due to including patients for surgery of a single tertiary referral center and a limited number of patients.

Large population-based studies regarding short-term mortality in older colorectal cancer patients are scarce. Therefore, population-based data of colorectal cancer patients, aged 80 years or older, of Belgium, Denmark, the Netherlands, and Sweden were collected. The current study aimed to report short-term mortality rates (30-day, 90-day, one-year, and excess one-year mortality rates) of octogenarians with colorectal cancer in these four European countries. We focused on time trends of short-term mortality as a decrease of 30- and 90-day mortality was observed for both colon and rectal cancer over time in the Netherlands since 2005 [11].

Material and methods

Data and study population

Patients of 80 years or older, operated (irrespective of priority) for their primary colorectal cancer between January 1, 2005, and 31, December 2014, were included. Data were collected from the Belgian Cancer Registry, the Danish Colorectal Cancer Group database, the Netherlands Cancer Registry, and the Swedish Colorectal Cancer Registry. As in Sweden the colon cancer register was added from 2007 and forward, only Swedish data of colon cancer patients between 2007 and 2014 were available [12]. Colorectal cancer was defined as C18 (colon), C19 and C20 (rectal), according to the international Classification of Diseases and Related Health Problems [13]. Stage I-III of disease were included. The TNM Classification of Malignant Tumors (5th, 6th, or 7th edition) was used for defining tumor stage [14]. Tumor stage was based on pathological stage; in case this was missing clinical stage was used. Vital status and date of death were assessed either directly from the patient's medical record or through linkage of cancer registry data to population files on vital status. Follow up time was defined as the time from date of surgery until death or until end of follow up (censored). Surgery was defined as surgical resection of the tumor. Local excisions were included while construction of a stoma without tumor resection and endoscopic techniques were excluded. Patients were excluded from the analyses of 30-day, 90-day, and 1-year (excess) mortality in case the follow up data was missing. Of the follow-up data of the colon and the rectal cancer patients 0.1% and 0.2%, respectively, was missing.

Statistics

Short-term mortality analyses were performed separately for colon cancer and rectal cancer patients. Short-term mortality analyses consisted of the calculation of overall 30-day, overall 90-day, overall one-year mortality, and excess one-year mortality for each country. The excess 1-year mortality was calculated as: the observed mortality in one year minus the expected mortality divided by the number of patients in that specific selection. Expected mortality was calculated by matching the cohort to a general population file by age, sex and year. National life tables of the respective countries were used to estimate the expected survival. This is the most preferable method to obtain a prognosis of elderly as the risk of dying due to other causes is taken into account. Furthermore, short-term mortality over three time periods (2005–2008, 2009–2011, 2012–2014) was analyzed. Relative risk reduction of excess one-year mortality was calculated and defined as relative decrease from 2012 to 2014 compared to 2005–2008. The short-term mortality analyses were also performed for age subgroups (80–84 year, 85–89 year, and 90 + year). All analyses were compared between the participating countries.

STATA/SE version 12.0 was used for the statistical analyses.

Results

Patient and tumor characteristics

Between January 1, 2005 and 31, December 2014, a total of 45,302 colorectal patients of 80 years or older were identified. Among them, 35,158 patients were diagnosed with colon cancer and 10,144 patients with rectal cancer. Patient and tumor characteristics of the colon cancer and rectal cancer are presented in Table 1. In all countries the majority of colon cancer patients was diagnosed with stage II disease. For rectal cancer, the majority of patients had stage III disease. Of the colon cancer patients, 1.8% of the patients (average of the countries) had an unknown stage compared to 3.6% of the rectal cancer patients (average of the countries).

Overall 30-day, 90-day, and 1-year (excess) mortality

Table 2 shows an overview of the short-term mortality rates of octogenarians. The lowest 90-day mortality rate of colon cancer patients was found in Sweden (7.9%). Ninety-day mortality rate was 12.6% in Belgium, 13.6% in the Netherlands, and 14.9% in Denmark. Excess 1-year mortality rate for colon cancer patients varied from 8.6% in Sweden to 17.7% in Denmark. Also for rectal cancer patients, the lowest 90-day mortality rate was seen in Sweden (7.2% versus 10.9% in the Netherlands, 11.2% in Denmark, and 11.3% in Belgium). The excess 1-year mortality rate was the lowest in Sweden (5.3%) and the highest in Belgium (14.0%).

For colon cancer, in all countries ninety-day mortality rate increased with increasing age category (Belgium: 80–84 year: 9.9%, 85–89 year: 15.0%, 90 + year: 21.5%; Denmark: 80–84 year: 12.3%, 85–89 year: 15.7%, 90 + year: 29.0%, The Netherlands: 80–84 year: 10.9%, 85–89 year: 16.7%, 90 + year: 24.0%, Sweden: 80–84 year: 5.8%, 85–89 year: 10.1%, 90 + year: 13.3%). For rectal cancer, 90-day

Table 1
Patient and tumor characteristics of stage I-III colon and rectal cancer patients of 80 years and older who underwent surgery and were diagnosed during 2005 and 2014.

COLON CANCER				
	Belgium	Denmark	the Netherlands	Sweden
Total	10,513 (100)	4192 (100)	14,218 (100)	6235 (100)
Sex				
Male	4521 (43.0)	1686 (40.2)	6126 (43.1)	2610 (41.9)
Female	5992 (57.0)	2506 (59.8)	8092 (56.9)	3625 (58.1)
Grade				
I	1754 (16.7)	*	928 (6.5)	427 (6.8)
II	5773 (54.9)	*	9394 (66.1)	2912 (46.7)
III	1898 (18.1)	*	2398 (16.9)	1076 (17.3)
Unknown	1088 (10.8)	*	1498 (10.5)	1820 (29.2)
Stage				
I	1748 (16.6)	559 (13.3)	3066 (21.6)	972 (15.6)
II	5056 (48.1)	2240 (53.4)	6641 (46.7)	3010 (48.3)
III	3709 (35.3)	1393 (33.2)	4511 (31.7)	2253 (36.1)
Year of diagnosis				
2005–2008	3537 (33.6)	1566 (37.4)	5299 (37.3)	1496 (24.0)^
2009–2011	3147 (29.9)	1219 (29.1)	4544 (32.0)	2321 (37.2)
2012–2014	3829 (36.4)	1407 (33.6)	4375 (30.8)	2418 (38.8)
RECTAL CANCER				
	Belgium	**Denmark**	**the Netherlands**	**Sweden**
Total	2890 (100)	1103 (100)	3952 (100)	2199 (100)
Sex				
Male	1498 (51.8)	560 (50.8)	2020 (51.1)	1183 (53.8)
Female	1392 (48.2)	543 (49.2)	1932 (48.9)	1016 (46.2)
Grade				
I	471 (16.3)	*	213 (5.4)	183 (8.3)
II	1757 (60.8)	*	2083 (52.7)	1138 (51.8)
III	351 (12.1)	*	296 (7.5)	168 (7.6)
Unknown/NA	311 (10.8)	*	1360 (34.3)	710 (32.3)
Stage				
I	817 (28.3)	281 (25.5)	1212 (30.7)	682 (31.0)
II	1004 (34.7)	429 (38.9)	1257 (31.8)	738 (33.6)
III	1069 (37.0)	393 (35.6)	1483 (37.5)	779 (35.4)
Year of diagnosis				
2005–2008	1143 (39.6)	447 (40.5)	1598 (40.4)	904 (41.1)
2009–2011	915 (31.7)	348 (31.6)	1189 (30.1)	686 (31.2)
2012–2014	832 (28.8)	308 (27.9)	1165 (29.5)	609 (27.7)

* = not registered in Danish dataset.
^ = no data available of 2005 and 2006.

mortality rate rose as well with increasing age category (Belgium: 80–84 year: 9.0%, 85–89 year: 14.1%, 90 + year: 22.3%; 15.2%, Denmark: 80–84 year: 9.7%, 85–89 year: 15.2%, 90 + year: 10.9%, The Netherlands: 80–84 year: 10.1%, 85–89 year: 11.9%, 90 + year: 17.0%, Sweden: 80–84 year: 6.6%, 85–89 year: 7.4%, 90 + year: 12.7%).

Overall 30-day, 90-day, and 1-year (excess) mortality over time

A decrease of 30-day, 90-day, one-year mortality, and excess 1-year mortality rate is observed over time in colon cancer patients in Belgium, Denmark, the Netherlands, and Sweden (Fig. 1a). From 2005 to 2008 to 2011–2014 relative risk reduction of the excess 1-year mortality rate in colon cancer patients was more than 40% the Netherlands (42.7%, absolute difference: −7.6%), followed by Belgium (32.5%, absolute difference: −5.5%), Denmark (29.4%, absolute difference: −6.3%), and Sweden (23.0%, absolute difference: −2.3%). For rectal cancer, from 2005 to 2008 to 2011–2014 the highest relative reduction of excess 1-year mortality rate occurred in Sweden (70.0%, absolute difference: −5.8%), followed by the Netherlands (58.1%, absolute difference: −9.0%), Belgium (6.7%, absolute difference: −0.8%), and Denmark (3.8%, absolute difference: −0.5%).

Discussion

In this analysis including more than 45,000 patients aged 80 years or more undergoing a colorectal resection, the variety and time trends of short-term mortality were evaluated across four North European countries. Short-term mortality rates were high and substantial differences were seen between the countries. For both colon and rectal cancer patients short-term mortality rates decreased over time in all countries.

In literature it is shown that decreased survival in older colorectal cancer patients is mainly due to mortality in the first postoperative year [9,15]. This study showed high rates of short-term

Table 2
Overall 30-day, 90-day, and 1-year (excess) mortality of stage I-III colon and rectal cancer patients of 80 years and older who underwent surgery and were diagnosed during 2005 and 2014.

COLON CANCER				
	Belgium	Denmark	the Netherlands	Sweden
30-day mortality (%)	**7.8**	**11.4**	**10.3**	**5.5**
Stage I	5.8	6.3	7.4	2.8
Stage II	7.5	11.3	10.2	5.3
Stage III	9.0	13.4	12.5	7.0
90-day mortality (%)	**12.6**	**14.9**	**13.6**	**7.9**
Stage I	9.6	10.0	9.8	4.1
Stage II	12.1	14.3	13.3	7.2
Stage III	14.7	17.7	16.7	10.6
1-year mortality (%)	**23.3**	**23.6**	**22.4**	**17.1**
Stage I	14.9	15.7	14.9	8.4
Stage II	20.3	20.0	19.8	13.8
Stage III	31.4	32.7	31.2	25.4
Excess 1-year mortality (%)	**15.0**	**17.7**	**14.2**	**8.6**
Stage I	6.5	10.2	6.5	0.1
Stage II	11.6	14.1	11.4	5.0
Stage III	23.6	26.6	23.5	17.2
RECTAL CANCER				
	Belgium	**Denmark**	**the Netherlands**	**Sweden**
30-day mortality (%)	**6.4**	**7.3**	**7.5**	**4.7**
Stage I	4.2	3.9	5.3	3.2
Stage II	8.1	7.5	9.4	4.9
Stage III	6.5	9.7	7.8	5.9
90-day mortality (%)	**11.3**	**11.2**	**10.9**	**7.2**
Stage I	8.3	7.1	8.0	5.6
Stage II	13.0	11.0	12.6	8.0
Stage III	11.9	14.5	11.8	8.0
1-year mortality (%)	**22.1**	**18.3**	**18.9**	**13.6**
Stage I	16.2	12.1	13.6	9.2
Stage II	22.2	15.4	21.3	13.8
Stage III	26.5	26.0	21.2	17.1
Excess 1-year mortality (%)	**14.0**	**12.7**	**10.7**	**5.3**
Stage I	8.0	7.5	5.0	0.6
Stage II	14.3	10.0	13.3	5.6
Stage III	18.6	19.6	13.6	9.2

overall mortality in elderly patients undergoing a colorectal resection in different North European countries. These high mortality rates are in line with a recent Dutch study where a one-year overall mortality up to 24% was found in stage I-III colorectal cancer patients aged 85 or older [9,16]. Another study including patients of 80 or older who underwent an elective colectomy from the Surveillance, Epidemiology and End Results (SEER) database showed a considerable lower 90-day overall mortality and a 1-year overall mortality of 7% and 14%, respectively [17]. This difference might be explained by the fact that in our study both elective and emergency surgery were included of which the latter one is associated with higher postoperative mortality rates [18,19].

The lowest short-term mortality rates for both colon and rectal cancer in the current study were seen in Sweden. There is no specific focus or dedicated program for elderly on national basis. A reason for these findings could be that Swedish surgeons might use a stricter selection of patients with increasing age as the percentage of patients who did not undergo a resection increased over time [20]. Therefore, in Sweden a frail patient may have been included to a lesser extent, with resultant higher survival rates. Another explanation could be improved multidisciplinary management along with the successfully implementation of specialized centralization of rectal cancer surgery in Sweden [20]. As a result, even on regional level there are high volume hospitals and high volume surgeons for rectal cancer patients. On the other hand, these results could be a reflection of the in general better overall survival of Swedish people. In the EUROCARE-5 study an age-standardized one-year survival of 82.5% was found in Sweden compared to 77.6% in Europe [5]. National welfare programs and the Swedish health care system which is known for their lead in transparency of quality indicators and quality improvement might have contributed to this [21].

From 1989 to 2011 colorectal cancer mortality decreased for both men and women in Belgium, Denmark, the Netherlands and Sweden as shown in a retrospective analysis of the WHO mortality database [22]. Our study showed that overall one year mortality in both colon and rectal cancer decreased during the study period in these four countries. In the Netherlands better survival was observed in both types of cancer, whereas in Belgium and Denmark this was most pronounced in colon cancer patients and in Sweden in rectal cancer patients. The decrease of short-term mortality over time can be explained by improvements in several fields. Firstly, perioperative care has been improved by enhancement of anesthesia techniques, such as restriction in intravenous fluid supply and preventing hypothermia [23,24]. Furthermore the successfully implementation of the Enhanced Recovery After Surgery (ERAS)

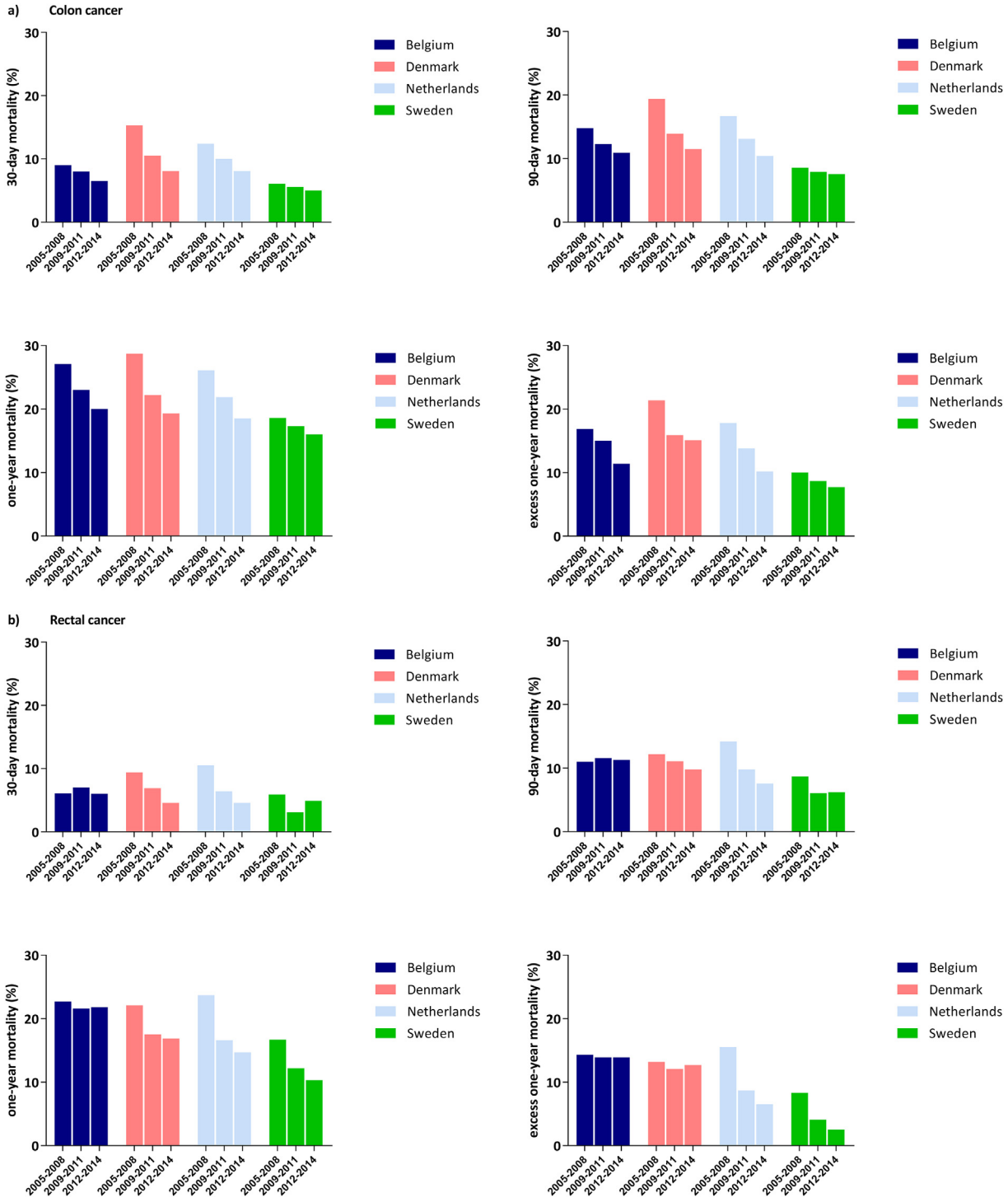

Fig. 1. Analyses of 30-day, 90-day, and 1-year (excess) mortality over time of colon cancer (a) and rectal cancer (b) patients of 80 years or older who underwent surgery and were diagnosed during 2005 and 2014.

program could have played a role. The last decades there has been more focus on the perioperative care for patients and the ERAS program has become standard in colorectal cancer patients after it was developed in 2001 [25]. This evidence-based care has led to major improvements in clinical outcomes and costs [25]. A recent study investigated the benefits of the ERAS program in elderly colorectal cancer patients undergoing elective colorectal surgery compared to case-matched patients with conventional care [26]. Clear improvements were observed in the ERAS group compared to the conventional group. As a result the authors concluded that the same benefits due to ERAS program can be expected in elderly compared to their younger counterparts and that ERAS should be implemented in elderly CRC patients without reservations [26]. Other initiatives focused on perioperative care and fast mobilization after surgery could have also contributed to the improvement over time. Counseling regarding nutrition and exercising preoperatively might have been an important factor as well. Another explanation could be the increasing utilization of a minimally

invasive approach [27]. Reduced mortality rates were seen with the minimally invasive approach compared to the open approach in a retrospective Dutch study and a Danish nationwide study, especially for the elderly [27,28]. Increasing use of bridge-to-surgery techniques with stent insertion or defunctioning stoma aiming to convert emergency cases to elective cases have also contributed to favorable change in short-term mortality [29]. Furthermore, the percentage of patients with colorectal cancer who underwent a resection decreased the last decade [30]. A better selection of vital patients (less frail patients) might also be partly responsible for the improvement over time. Finally, differences in the indication of (neo)-adjuvant chemo- and/or radiotherapy for older patients with colon- or rectal cancer could have played a role [31,32].

To our knowledge, this study contains the largest dataset regarding short-term mortality analyses of patients aged 80 or more undergoing a colorectal resection. Although we matched the excess mortality for age, sex, and stage, residual confounding between countries could have occurred. Confounders such as the number of comorbidities, frailty assessment, or emergency could have played a role in short term mortality differences between countries. The lack of data of frailty assessment can definitely be seen as a limitation of this study, Current cancer registries do not register this item but should consider to collect information such as frailty assessment, as that variable is highly important with interpreting results of elderly and mortality. Selection criteria for surgery within countries may be led by expected survival. This could result in selection bias in the comparison between countries. Which might have played a role in the current study, especially in this group of patients, as elderly are known for their heterogeneity.

Improved perioperative care and minimally invasive surgical approach seemed to have paid off with decreasing short-term mortality rates the last decade. Especially older frail patients are known to benefit from a minimally invasive approach due to reduced cardiopulmonary complications [33]. Further improvements in the perioperative care and increasing use of a minimally invasive approach might lead to a further decrease of short-term mortality rates.

Based on the findings of the current study we would like to address two points in order to improve the survival of elderly with colorectal cancer. First, our findings emphasize the importance of geriatric assessment. With this tool the presence of frailty can be identified, which is a strong predictor for both short- and long-term outcomes after gastrointestinal surgery [34]. Geriatric assessment can aid to indicate interventions aimed to optimize the condition of these elderly colorectal cancer patients before surgery with subsequently better postoperative outcomes. Second, short-term mortality rates are high in octogenarians with colorectal cancer and might indicate that a stricter selection of patients for surgery should be applied. This should be taken into consideration between clinician and patient in order to make a shared decision whether the risk accompanied with a major resectional surgery outweighs the benefit in terms of survival and of no risk of obstruction.

In conclusion, high short-term mortality rates were observed in octogenarians with colorectal cancer in a large population-based cohort. Short-term mortality differ across four North European countries. Short-term mortality rates decreased over time for both colon and rectal cancer patients in all countries.

Conflict Of Interest

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. No conflicts of interest for all authors. This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.03.041.

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