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Neoadjuvant Therapy in Rectal Cancer Patients With Clinical Stage II to III Across European Countries: Variations and Outcomes

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Abstract

This study is the largest observational study on neoadjuvant therapy in patients with stage II & III rectal cancer by including high-quality data from large population-based and clinical cancer registries. We observed large variations in administration of neoadjuvant chemo(radio)therapy across European countries. Our results support major survival advantages of patients treated with neoadjuvant radiotherapy.

Background—Neoadjuvant therapy improves survival of patients with clinical stage II and III rectal cancer in clinical trials. In this study, we investigated the administration of neoadjuvant radiotherapy (neo-RT) and neoadjuvant chemoradiotherapy (neo-CRT) and its association with survival in resected patients in 2 European countries (The Netherlands and Sweden) and at 3 specialist centers.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

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Materials and Methods—Administration of neoadjuvant treatment (all registries) and overall survival after surgery in The Netherlands and Sweden were assessed. Hazard ratios (HRs) were obtained using Cox regression adjusted for potential confounders.

Results—A total of 16,095 rectal cancer patients with clinical stage II and III were eligible for analyses. Large variations in administration of neo-RT and neo-CRT were observed. Elderly patients less often received neo-RT and neo-CRT. Patients with stage III disease received neo-CRT more frequently than neo-RT. Administration of neo-RT versus surgery without neoadjuvant treatment was significantly associated with improved survival in The Netherlands (HR, 0.62; 95% confidence interval [CI], 0.53–0.73) as well as in Sweden (HR, 0.79; 95% CI, 0.69–0.90). Administration of neo-CRT was associated with enhanced survival in The Netherlands (HR, 0.62; 95% CI, 0.50–0.78) but not in Sweden (HR, 0.97; 95% CI, 0.80–1.18). The mortality of patients treated with neo-CRT compared with neo-RT showed inconsistent results in population-based centers.

Conclusions—Our results support an association of neo-RT with enhanced survival among stage II and III rectal cancer patients. Comparing neo-CRT with neo-RT, larger variations and inconsistent results with respect to survival were observed across centers.

Keywords

Long-term outcomes; Neoadjuvant therapy; Rectal cancer; Survival; Variations

Introduction

Rectal cancer accounts for approximately 30% of all colorectal cancer cases.¹ The treatment of rectal cancer has improved during the past decades, leading to a decrease in local recurrence rates and improved survival.² At present, preoperative or neoadjuvant (chemo)radiotherapy, total mesorectal excision, and postoperative adjuvant chemotherapy are used as treatments for so-called locally advanced rectal cancer (LARC).³ A better way to decide on preoperative treatment for rectal cancer patients today is to subdivide them at diagnosis into 3 groups with low-, moderate-, or high-risk features, or as early, intermediate, and locally advanced; the 2 latter groups belong to what is referred to LARCs.^{3–7}

Preoperative or neoadjuvant therapy has been accepted as a treatment for increasing resectability, decreasing the rate of locoregional recurrence, and potentially improving survival in LARC patients.⁷ The therapeutic recommendations for treatment of rectal cancer vary between clinical guidelines in, for example, the United Kingdom,⁵ the rest of Europe,⁴ and the United States,⁸ and large variations in the pattern of care have been reported across European countries between 2008 and 2009.⁹ In this study by using more recent data (2007–2014) and a larger population of patients as part of the EurocanPlatform project (a consortium of major European cancer centers),¹⁰ we aimed to investigate the use of neoadjuvant treatment and its association with survival in resected rectal cancer patients with clinical stage II (cT3–4,N0,M0) and III (cTany,N+,M0).

Materials and Methods

This study was carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) and was approved by the ethics committee of the Medical Faculty of the University of Heidelberg, Germany.

Participating Centers and Study Populations

Data were obtained from 2 nationwide population-based and 3 institute-based clinical cancer registries from 4 European countries. The population-based registries include the Netherlands Cancer Registry (NCR) and the Swedish ColoRectal Cancer Registry (SCRCR). The institute-based registries are from the Portuguese Oncology Institute of Porto (IPO-Porto), the Netherlands Cancer Institute (NKI) in Amsterdam, and the Institute Jules Bordet (IJB) in Brussels (Belgium).

Information on basic patient and tumor characteristics, clinical and pathological Tumor, Node, Metastases stage, type of surgery, type of neoadjuvant therapy, count of examined lymph nodes, administration of adjuvant chemo(radio)therapy, and vital status were provided by the partners for the most recent period for which such data were available.

Rectal cancer cases included tumors that were topographically coded as C20.9 according to the International Classification of Diseases for Oncology, Third Edition.¹¹ We excluded cases with unknown information on the use or type of neoadjuvant therapy and cases with resection of rectum accompanied with other parts of the colon.

Statistical Methods

The distribution of basic patient and tumor characteristics across centers is presented. The annual age-standardized proportion of patients who received neoadjuvant radiotherapy (neo-RT) and neoadjuvant chemoradiotherapy (neo-CRT) in each center were computed using the age distribution from SCRCR in 2007 to 2014 as standard. The associations between sex, age group (< 65, 65–74, 75), clinical tumor stage (II, III), and administration of neo-RT or neo-CRT (compared with no neoadjuvant treatment) were investigated using multiple logistic regression models.

Overall survival of patients diagnosed in 2009 to 2014 was assessed up to 6 years after diagnosis using data from the registries in The Netherlands and Sweden. Institute-based centers were not included in survival analyses because of the limited number of cases. Overall survival was the time from diagnosis to death from any cause or date of the last contact. Hazard ratios (HRs) for the administration of neo-RT/neo-CRT compared with no neoadjuvant treatment and of neo-CRT compared with neo-RT were obtained using Cox regression models. Models were adjusted for sex, age group, clinical tumor stage, and adjuvant therapy including postoperative chemotherapy, radiotherapy, or a combination of both therapies. Because the start date of administration of adjuvant therapy was available from Sweden, adjuvant therapy was added as a time-varying factor in the analysis of the Swedish data by assigning a patient to the group of adjuvant therapy from his/her time of adjuvant therapy to the end of follow-up.

Results

Of 38,388 primary rectal cancer patients from the 5 European databases, 16,095 clinical stage II and III patients were eligible for analyses (Figure 1). Table 1 shows the frequencies of the administration of neoadjuvant therapy (neo-RT or neo-CRT) according to registry and center. In The Netherlands and Sweden, 90% and 79%, respectively, of the patients received neoadjuvant treatment. In both countries, neo-RT was more frequently administered than neo-CRT (NCR: 75% vs. 15%; SCRCR: 56% vs. 23%). The most common neoadjuvant treatment in the institute-based data was neo-CRT, with 68%, 71%, and 87% in IPO-Porto, NKI, and IJB, respectively. The maximum length of follow-up ranged from 45 months in Portugal to 111 months in Sweden.

The age distribution varied across the centers. Particularly, patients from the national population-based registries were on average older than patients from institute-based registries (mean: 66–68 vs. 61–65 years; Table 2). In all centers more clinical stage III than stage II rectal cancers were observed (between 64% [SCRCR] and 78% [IJB]). Administration of adjuvant therapy ranged from 8% in NKI to 55% in IJB.

Figure 2 shows the frequencies and trends of neo-RT and neo-CRT administration during 2007 to 2014. The population of patients receiving neoadjuvant treatment was higher in The Netherlands than in Sweden and slightly decreased over time in both countries. Whereas the population of patients who received neo-CRT increased over time in Sweden, an opposite pattern was observed in The Netherlands. Neo-CRT was the most common form of therapy in all institute-based registries, with no clear trend over time.

Table 3 shows the odds ratios (ORs) for the association of sex, age group, and clinical stage with neoadjuvant therapy administration after mutual adjustment for each of these factors. There was a significant tendency toward less frequent administration of neo-RT and neo-CRT with increasing age of patients in both population-based registries with stronger associations for neo-CRT. In 2 of the institute-based registries (IPO-Porto, IJB), such a trend was also observed for neo-CRT. Calculation of ORs was not possible or not meaningful for neo-RT administration because of low numbers of cases in IJB and NKI. Stage III rectal cancer patients received significantly more often neo-RT and neo-CRT than stage II patients in The Netherlands as well as in Sweden. Associations with stage were stronger for neo-CRT than for neo-RT.

Overall Survival of Patients

The overall HRs for death after adjustment for prognostic factors indicated significantly higher survival in the neo-RT group compared with the no neoadjuvant group in The Netherlands (HR, 0.62; 95% confidence interval [CI], 0.53–0.73) as well as in Sweden (HR, 0.79; 95% CI, 0.69–0.90; Table 4). The survival advantage of patients who received neo-RT was observed in both sexes and both clinical stages, and it increased with increasing age.

Administration of neo-CRT (compared with no neoadjuvant treatment) was significantly associated with higher survival rates of patients in The Netherlands (HR, 0.62; 95% CI, 0.50–0.78; Table 4). It was observed in all subgroups defined by sex, age (except for those

younger than 65 years), and clinical stage. In Sweden, we observed no survival difference in patients who received neo-CRT compared with those without neoadjuvant therapy (HR, 0.97; 95% CI, 0.80–1.18). The only exception was age group 75 years or older, in which administration of neo-CRT was associated with significantly enhanced survival (HR, 0.65; 95% CI, 0.46–0.94).

No significant survival difference was observed between administration of neo-CRT and neo-RT in The Netherlands (Table 4). In Sweden, patients who were treated with neo-CRT had significantly lower survival rates overall (HR, 1.32; 95% CI, 1.13–1.54), and in all subgroups except in the elderly (age 75 years or older). Adjusted overall survival curves are shown in Figure 3.

No substantial changes in the overall HRs for death were observed for neo-RT and neo-CRT in subgroup analyses among patients who did not receive postoperative chemo(radio)therapy (see Supplemental Table 1 and Supplemental Figure 1 in the online version). In contrast, neo-RT or neo-CRT was not associated with better overall survival in those who received adjuvant treatment (see Supplemental Table 2 and Supplemental Figure 2 in the online version).

Discussion

In this large retrospective cohort study, we investigated the administration of neoadjuvant therapy in rectal cancer patients with clinical stage II and III disease in different European countries and major clinical centers. During the study period from 2007 to 2014, a large variation with respect to neo-RT as well as neo-CRT administration was observed. Application of neo-RT compared with no neoadjuvant treatment was associated with significantly higher survival rates in The Netherlands as well as in Sweden. Survival advantages were observed for stage II as well as stage III and even for elderly patients. Results for neo-CRT were less consistent showing survival advantages in The Netherlands but not in Sweden.

The limitations of this study include the fact that some possible influential factors, such as patients' comorbidities and recurrence data were not available in sufficient completeness across registries to be considered in the survival analyses. Therefore, potential confounding by such factors could not be controlled for and the outcomes of patients were assessed solely on the basis of overall survival analysis. A major strength of the study includes the presence of high-quality long-term population-based data with large sample size and acceptable completeness of clinical stage data. Another strength of the study is the inclusion of institute-based as well as nationwide population-based data. The latter includes the full spectrum of patients including elderly patients who are often excluded from clinical trials, including randomized controlled trials (RCTs), and for whom evidence from RCTs is often limited or lacking.

The benefit of neoadjuvant therapy for rectal cancer patients, including downstaging/downsizing and reduced risk of local recurrence has been well demonstrated in RCTs and seen in observational studies.^{12,13} There are 2 main approaches to delivering neoadjuvant

therapy today: first, short-course neo-RT (5×5 Gy) followed by immediate surgery and second, long-course neo-RT (45–50.4 Gy) accompanied with chemotherapy (neo-CRT) or without chemotherapy followed by surgery after a 4- to 8-week break.³ Although there is good evidence to support both approaches, large variation in uptake of these therapeutic strategies has been previously reported among countries. For example, in the United States, long-course chemoradiotherapy is preferred,⁸ whereas some European countries (such as Sweden and The Netherlands) mainly use short-course radiotherapy except for the most locally advanced tumors, which are known as those reported to have cT3 with threatened or positive mesorectal fascia, or cT4 with a higher risk of not being radically removed or experiencing a recurrence, where chemoradiotherapy is recommended.^{3,4} Accordingly, we observed that only 15% and 23% of the patients received neo-CRT in The Netherlands and Sweden, respectively. In contrast, neo-CRT was most commonly provided to stage II and III rectal cancer patients in the 3 specialized medical centers included in our analysis (68%–87%). The differences between the specialized centers and the population statistics are striking and might have different explanations. Besides having younger patients, the case mix is not fundamentally different. Ongoing clinical trials might be an explanation, or simply that specialized centers choose a more extensive treatment than recommended.

Our results showed that stage III rectal cancer patients consistently more often received neo-CRT instead of neo-RT. A possible explanation for this finding is that stage III tumors are traditionally considered as more locally advanced and neo-CRT are often recommended.¹⁴ The National Comprehensive Cancer Network guidelines recommend neo-CRT for stage II as well as stage III rectal cancer patients.⁸ Canadian guidelines recommend administration of neo-CRT by excluding medically unfit patients who should be treated with preoperative radiotherapy alone.¹⁵ The European Society for Medical Oncology consensus guidelines indicate the equal value of neo-RT and neo-CRT in the treatment of rectal cancer with intermediate risk whereas in the locally advanced nonresectable cases neo-CRT is the recommended option in fit patients and recommend administration of concomitant chemotherapy for all patients if long-term radiation is used.^{3,4} Two Cochrane reviews of 6 RCTs in total reported that administration of neo-CRT compared with neo-RT for stage III rectal cancer patients had no effect on overall or disease-free survival but reduced the risk of local recurrence.^{16,17} A survival gain was seen only in the trial that included the “nonresectable” cases.¹⁸ Our findings, showing higher mortality rates of rectal cancer patients with neo-CRT compared with neo-RT in Sweden and comparable mortality in The Netherlands are likely a result of patient selection. In Sweden, neo-CRT is only recommended in the most advanced LARC patients, previously often considered as “nonresectable.” Our data also showed that patients who were treated with neo-CRT had substantially fewer positive lymph nodes in the surgical specimens compared with those who were treated with neo-RT or surgery alone (see Supplemental Table 3 in the online version). This finding is likely explained by the fact that most patients treated with neo-RT had surgery immediately after short-course radiotherapy whereas all patients treated with neo-CRT had a delay to surgery during which downstaging often occurs.

In most RCTs on the efficacy of neoadjuvant therapy, elderly patients were under-represented, and they are also less aggressively treated than younger patients in routine clinical practice.¹⁹ Our data also showed that neoadjuvant therapy was less frequently

applied in elderly patients. Among patients who received neoadjuvant therapy, elderly patients were less frequently treated with neo-CRT in all participating centers. There are several possible reasons that older patients less often receive neo-CRT, including poor performance status, existing comorbidity, and clinicians' tendency to avoid providing the more toxic and demanding neo-CRT to the elderly patient.²⁰ However, in a recent report from Sweden, Elliot et al indicated that the outcome of elderly patients might be optimized by a selection process, but comorbidity should be used cautiously for excluding patients from neoadjuvant treatment.²¹ Moreover, there is some evidence in the literature supporting a survival benefit of neoadjuvant therapy administration in elderly rectal cancer patients as well.^{19,22} A recent report from the National Cancer Data Base in the United States showed that administration of neoadjuvant therapy in LARC patients older than 80 years was associated with significantly enhanced survival.²³ In our analysis, we observed significantly better survival in patients aged 75 years or older treated with neo-RT or neo-CRT in The Netherlands as well as in Sweden. However, despite careful control for confounders, the potential of residual confounding must be kept in mind in an observational study such as ours. We cannot exclude confounding by preferential application of neo-RT or neo-CRT to more clinically fit elderly patients. The selection process might have been more pronounced in Sweden than in The Netherlands.

In contrast to colon cancer, very limited data are available from RCTs for rectal cancer supporting the value of adjuvant chemotherapy after neoadjuvant therapy and surgery.^{24–26} In a European consensus conference colon & rectum, administration of adjuvant chemotherapy in LARC patients can be considered according to the cost-benefits in a multidisciplinary team discussion.²⁷ We observed a negative interaction between neoadjuvant and adjuvant treatment in that neo-RT or neo-CRT was not associated with a survival benefit among patients who received postoperative chemotherapy. This is not surprising because it is likely that adjuvant chemotherapy was given to those with the worst pathology.

Conclusion

The results of this study are consistent with a survival advantage for rectal cancer patients who received neo-RT in 2 population-based European cancer registries (from The Netherlands and Sweden). Administration of neo-CRT compared with no neoadjuvant treatment was associated with better survival in The Netherlands, but not in Sweden, likely caused by a selection of patients with the most advanced cancers for neo-CRT in Sweden. We showed that elderly patients less frequently received neo-RT and neo-CRT whereas our results might indicate a survival benefit of neoadjuvant treatment in elderly rectal cancer patients as well.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points

- During the study period from 2007 to 2014, we observed a large variation with respect to neo-RT as well as neo-CRT administration across European centers.
- We showed that application of neo-RT compared with no neoadjuvant treatment was associated with significantly higher survival rates in stage II and III rectal cancer patients.
- Moreover, we showed that elderly patients less frequently received neo-RT and neo-CRT whereas our results might indicate a survival benefit of neoadjuvant treatment in elderly rectal cancer patients as well.
- This study is, to our knowledge, the largest observational study on this topic conducted to date including high-quality data from large population-based and clinical cancer registries.
- Disclosing variations in the administration of neoadjuvant therapy and monitoring its effect on outcomes of patients might strongly enhance efficient translation of relevant therapeutic innovations in clinical practice.

Figure 1. Flow Chart of the Inclusion of Rectal Cancer Patients According to Participating Center

Abbreviations: IJB = Institute Jules Bordet in Brussels; IPO-PORTO = Portuguese Oncology Institute of Porto; NCR = Netherlands Cancer Registry; Neo-CRT = neoadjuvant chemoradiation; Neo-RT = neoadjuvant radiotherapy; NKI = Netherlands Cancer Institute in Amsterdam; SCRCR = Swedish ColoRectal Cancer Registry.

Figure 2. The Age-Standardized Trend of Administration of Neoadjuvant Therapy Between 2007 and 2014

Abbreviations: IJB = Institute Jules Bordet in Brussels; IPO-PORTO = Portuguese Oncology Institute of Porto; NCR = Netherlands Cancer Registry; neo-CRT = neoadjuvant chemoradiation; neo-RT = neoadjuvant radiotherapy; NKI = Netherlands Cancer Institute in Amsterdam; no neoadj. = no neoadjuvant therapy; SCRCR = Swedish ColoRectal Cancer Registry.

Figure 3. Survival of Patients in The Netherlands and Sweden According to the Administration of (A) and (B) Neoadjuvant Radiotherapy (Neo-RT) or (C) and (D) Neoadjuvant Chemoradiation (Neo-CRT) and (E) and (F) Either Neo-RT or Neo-CRT Obtained From Cox Regression Models With Adjustment for Sex, Age Group, Tumor Stage, and Administration of Adjuvant Therapy

Table 1

Participating Centers and Application of Neoadjuvant Therapy in Patients With Rectal Cancer Clinical Stage II to III

Center	Country	Cases, n	Period of Diagnosis	Last Date of Follow-up	Maximum Months of Follow-up	Treatment, n (%)		
						No Neoadjuvant Therapy	Neoadjuvant Therapy	Neo-CRT
NCR ^a	Netherlands	9146	2009–2014 ^b	January 1, 2015	72	920 (10)	6814 (75)	1412 (15)
SCRCR ^a	Sweden	6427	2007–2014	March 31, 2016	111	1371 (21)	3576 (56)	1480 (23)
IPO-PORTO ^c	Portugal	247	2011–2012	September 30, 2014	45	18 (7)	62 (25)	167 (68)
NKI ^c	Netherlands	159	2007–2014	September 18, 2015	96	9 (6)	37 (23)	113 (71)
IJB ^c	Belgium	116	2007–2012	June 26, 2015	99	9 (8)	6 (5)	101 (87)

Emergent cases in Sweden were excluded; n = 28 (< 1%).

Abbreviations: IJB = Institute Jules Bordet in Brussels; IPO-PORTO = Portuguese Oncology Institute of Porto; NCR = Netherlands Cancer Registry; Neo-CRT = neoadjuvant chemotherapy; Neo-RT = neoadjuvant radiotherapy; NKI = Netherlands Cancer Institute in Amsterdam; SCRCR = Swedish ColoRectal Cancer Registry.

^aPopulation-based registry.

^bCases registered up to October 2014.

^cInstitute-based registry.

Table 2

Baseline and Clinical Characteristics of Patients With Rectal Cancer With Clinical Stages II to III

Characteristic	Center				
	NCR	SCRCR	IPO-PORTO	NKI	IJB
Sex					
Male	5805 (63)	3856 (60)	155 (63)	91 (57)	68 (59)
Female	3341 (37)	2571 (40)	92 (37)	68 (43)	48 (41)
Mean Age ($\pm$SD)	66 ($\pm$ 11)	68 ($\pm$ 11)	65 ($\pm$ 13)	61 ($\pm$ 12)	64 ($\pm$ 14)
Age Group, y					
Younger than 65	3786 (41)	2211 (34)	112 (45)	96 (60)	61 (53)
65–74	3153 (34)	2206 (34)	67 (27)	42 (26)	21 (18)
75 or older	2207 (24)	2010 (31)	68 (28)	21 (13)	34 (29)
Clinical Stage					
II (cT3–4,cN0,M0)	2667 (29)	2333 (36)	56 (23)	43 (27)	26 (22)
III (cTany,N+,M0)	6479 (71)	4094 (64)	191 (77)	116 (73)	90 (78)
Adjuvant Therapy^a					
No	8440 (92)	3710 (74)	146 (60)	146 (92)	50 (45)
Yes	706 (8)	1336 (26)	97 (40)	13 (8)	60 (55)

Data are presented as n (%) except where otherwise noted.

Abbreviations: IJB = Institute Jules Bordet in Brussels; IPO-PORTO = Portuguese Oncology Institute of Porto; NCR = Netherlands Cancer Registry; NKI = Netherlands Cancer Institute in Amsterdam; SCRCR = Swedish ColoRectal Cancer Registry.

^a Adjuvant therapy was not completely recorded in the SCRCR during 2007 to 2008 (n = 1381; 21%). Missing data on adjuvant therapy in IPO-PORTO (n = 4; 2%) and IJB (n = 6; 5%).

Odds Ratio of Administration of Neoadjuvant Therapy Regimen for Patients With Rectal Cancer Stages II to III, According to Clinical Characteristics

Table 3

Baseline Characteristics	Odds Ratio ^a (95% CI)					
	NCR	SCRCR	IPO-PORTO	NKI	IJB	
Neo-RT vs. No Neoadjuvant						
Sex						
Male	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
Female	1.06 (0.92–1.23)	0.93 (0.81–1.06)	2.63 (0.77–8.96)	0.70 (0.15–3.31)		NA
Age group, y						
Younger than 65	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)			
65–74	0.68 (0.57–0.82)	0.79 (0.66–0.95)	0.80 (0.17–3.73)	NA		NA
75 or older	0.42 (0.35–0.50)	0.36 (0.31–0.43)	1.54 (0.41–5.77)	NA		NA
Clinical stage						
II (cT3–4,N0,M0)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)			
III (cTany,N+,M0)	2.75 (2.38–3.16)	1.82 (1.60–2.07)	0.92 (0.27–3.15)	NA		NA
Neo-CRT vs. No Neoadjuvant						
Sex						
Male	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		1.00 (ref.)
Female	1.12 (0.92–1.37)	1.09 (0.91–1.31)	1.98 (0.60–6.56)	0.72 (0.17–3.02)		0.70 (0.16–2.98)
Age group, y						
Younger than 65	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		1.00 (ref.)
65–74	0.55 (0.44–0.69)	0.48 (0.39–0.59)	0.67 (0.18–2.52)	1.20 (0.21–6.74)		0.15 (0.01–1.78)
75 or older	0.16 (0.13–0.21)	0.06 (0.05–0.08)	0.16 (0.05–0.54)	NA		0.06 (0.01–0.57)
Clinical stage						
II (cT3–4,N0,M0)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)			1.00 (ref.)
III (cTany,N+,M0)	5.62 (4.59–6.89)	4.30 (3.56–5.20)	1.89 (0.58–6.14)	NA		1.63 (0.33–7.91)
Neo-CRT vs. Neo-RT						
Sex						
Male	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		

Baseline Characteristics	Odds Ratio ^d (95% CI)				
	NCR	SCRCR	IPO-PORTO	NKI	IJB
Female	1.02 (0.91–1.16)	1.05 (0.93–1.20)	0.75 (0.38–1.48)	1.21 (0.53–2.76)	NA
Age group, y					
Younger than 65	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
65–74	0.76 (0.67–0.86)	0.60 (0.52–0.69)	0.77 (0.32–1.84)	0.65 (0.26–1.62)	NA
75 or older	0.42 (0.35–0.50)	0.17 (0.14–0.21)	0.10 (0.05–0.22)	0.17 (0.06–0.49)	NA
Clinical stage					
II (cT3–4,N0,M0)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	NA
III (cTany,N+,M0)	1.95 (1.67–2.27)	2.34 (2.02–2.72)	2.03 (0.95–4.34)	2.03 (0.86–4.77)	NA

Abbreviations: IJB = Institute Jules Bordet in Brussels; IPO-PORTO = Portuguese Oncology Institute of Porto; NA = not applicable because of a small number of cases; NCR = Netherlands Cancer Registry; Neo-CRT = neoadjuvant chemoradiation; Neo-RT = neoadjuvant radiotherapy; NKI = Netherlands Cancer Institute in Amsterdam; ref. = reference; SCRCR = Swedish ColoRectal Cancer Registry.

^d Odds ratio estimate for neoadjuvant therapy. Odds ratio was obtained from multiple logistic regression models adjusted for gender, age group, and clinical tumor stage. Odds ratios shown in bold are statistically significant; $P < .05$. Odds ratios > 1 indicate more often administration of the respective neoadjuvant treatment.

Table 4

Hazard Ratio for the Association of Neoadjuvant Therapy Regimen With Overall Survival for Patients With Rectal Cancer With Clinical Stages II to III

Baseline Characteristic	Hazard Ratio (95% CI) ^a					
	The Netherlands			Sweden		
	Neo-RT vs. No Neoadjuvant	Neo-CRT vs. No Neoadjuvant	Neo-CRT vs. Neo-RT	Neo-RT vs. No Neoadjuvant	Neo-CRT vs. No Neoadjuvant	Neo-CRT vs. Neo-RT
Overall	0.62 (0.53–0.73)	0.62 (0.50–0.78)	1.03 (0.89–1.19)	0.79 (0.69–0.90)	0.97 (0.80–1.18)	<i>1.32</i> (1.13–1.54)
Sex						
Male	0.67 (0.54–0.82)	0.68 (0.51–0.91)	1.05 (0.87–1.25)	0.84 (0.70–1.00)	1.00 (0.78–1.29)	<i>1.28</i> (1.05–1.55)
Female	0.55 (0.42–0.72)	0.53 (0.37–0.77)	1.00 (0.78–1.28)	0.71 (0.57–0.88)	0.89 (0.65–1.22)	<i>1.42</i> (1.11–1.82)
Age at Diagnosis, y						
Younger than 65	0.90 (0.56–1.44)	1.06 (0.64–1.76)	1.22 (0.98–1.52)	0.81 (0.53–1.25)	1.51 (0.98–2.32)	<i>1.84</i> (1.41–2.41)
65–74	0.69 (0.49–0.98)	0.62 (0.40–0.95)	0.90 (0.69–1.16)	0.82 (0.61–1.11)	0.99 (0.69–1.41)	<i>1.38</i> (1.08–1.77)
75 or older	0.54 (0.44–0.67)	0.49 (0.35–0.69)	0.98 (0.73–1.31)	0.77 (0.65–0.91)	0.65 (0.46–0.94)	0.80 (0.57–1.13)
Clinical Stage						
II (cT3–4, cN0, M0)	0.68 (0.53–0.87)	0.70 (0.47–1.03)	1.07 (0.77–1.47)	0.84 (0.68–1.03)	1.29 (0.91–1.83)	<i>1.48</i> (1.08–2.04)
III (cTany, N+, M0)	0.57 (0.46–0.72)	0.59 (0.45–0.77)	1.02 (0.87–1.20)	0.75 (0.62–0.90)	0.84 (0.66–1.06)	<i>1.28</i> (1.07–1.52)

Period of study: 2009 to 2014. Hazard ratios shown in bold indicate statistical significance, $P < .05$. Hazard ratios shown in italic indicate statistically significant increased mortality rates.

Abbreviations: Neo-CRT = neoadjuvant chemoradiotherapy; Neo-RT = neoadjuvant radiotherapy.

^aHazard ratio (95% CI) was obtained according to subgroup of patients, from multiple Cox regression models adjusted for sex, age group, clinical tumor stage, administration of postoperative chemotherapy/chemoradiotherapy adjuvant therapy (as fixed covariate in the Netherlands National Cancer Registry; as time-varying covariate in the Swedish Colorectal Cancer Registry, where time to adjuvant therapy was available).