Frailty and outcomes in older cancer patients

Vlies, E. van der


3

TOLERABILITY, SAFETY AND OUTCOME OF NEOADJUVANT CHEMORADIOTHERAPY WITH CAPECITABINE IN PATIENTS AGED 70 YEARS OR OLDER WITH LOCALLY ADVANCED RECTAL CANCER

Ellen van der Vlies
*Lotte Jacobs**
Daan ten Bokkel Huinink
Haiko Bloemendal
Martijn P.W. Intven
Anke B. Smits
Bas L.A.M. Weusten
Peter D. Siersema
Niels van Lelyveld
Maartje Los

Clinical Colorectal Cancer 2018; 17:179-186

*both authors contributed equally

ABSTRACT

Background

In studies of colorectal cancer, the elderly have been frequently underrepresented because comorbid conditions and functional status often lead to study exclusion. For elderly patients with an indication for neoadjuvant chemoradiotherapy (nCRT), physicians usually decide using clinical factors whether nCRT should be offered. The aim of the present retrospective study was to assess the tolerability of nCRT with capecitabine and the surgical outcomes in patients aged ≥70 years with locally advanced rectal cancer.

Methods

Data from 1372 rectal cancer patients diagnosed from 2002 to 2012 at 4 Dutch hospitals were used. Patients aged ≥ 70 years were included if they had received nCRT, and their data were analyzed for treatment deviations, postoperative complications, mortality, disease-free survival (DFS), and overall survival (OS). The data were stratified into 3 age groups (70-74, 75-79, and ≥ 80 years).

Results

We identified 447 patients aged ≥ 70 years. Of these patients, 42 had received nCRT, and 37 (88%) had completed nCRT. Radiation dermatitis, fatigue, and diarrhea were reported in 62%, 57%, and 43% of the 42 patients, respectively. Of the 42 patients, 40 (95%) underwent surgery, 1 patient refused resection, and 1 patient died during nCRT of severe mucositis due to dihydropyrimidine dehydrogenase deficiency. The postoperative complication rate was 30%, and the 30-day mortality rate was 0%. A pathologic complete response was found in 7.5%. The 2- and 5-year DFS and OS rates were 58.5% and 40.7% and 81.0% and 58.2%, respectively.

Conclusion

The results of the present multicenter study have shown that if selected on clinical factors, nCRT with capecitabine is safe and well tolerated in elderly patients. No negative effect on surgical outcome was measured, and the beneficial effect (pathologic complete response, DFS, and OS) seemed comparable to that for younger age groups. We believe that elderly patients should not be excluded from nCRT on the basis of age only.

INTRODUCTION

Colorectal cancer (CRC) is a common disease worldwide, representing the third most commonly diagnosed malignancy.[1] With the improved life expectancy of elderly in general, the better diagnostic and staging techniques, and the CRC screening programs, physicians will increasingly see patients with CRC.[2,3] CRC predominantly affects elderly patients. The median age at diagnosis is 69-72 years, with 60% to 70% of all cases diagnosed in patients aged ≥65 years.[4-7] However, the aging process is associated with physiological, sociological and psychological transitions. As such, the risk of chemotherapy- and radiotherapy- related toxicity and postoperative morbidity could be increased. In addition, neoadjuvant chemoradiotherapy (nCRT) only affects the local recurrence rate but not the overall survival of rectal cancer patients; thus, the benefit for elderly patients is doubtful.[8]

In the past decade, several randomized controlled studies have confirmed the efficacy of nCRT and total mesorectal excision (TME) surgery resulting in a lower risk of local recurrence in rectal cancer patients.[8-16] In the Netherlands, nCRT for rectal cancer was introduced in 2006. Patients with a suspected positive resection margin along the mesorectal fascia and/or ≥4 suspected lymph nodes within the mesorectum and/or lymph nodes outside the mesorectal fascia on magnetic resonance imaging are considered eligible for nCRT. However, in studies on CRC, older patients have been frequently underrepresented because a comorbid condition and/or functional status often led to study exclusion.[17,18] In leading intervention studies such as the German Rectal Cancer study group and the ACCORD 12/PRODIGE 2 phase III study the median age of included patients is 62 and 63 years, respectively.[14,19] Few data on safety and beneficial effects of nCRT in the elderly are available.

The Dutch guidelines for CRC have advocated that the treatment principles of rectal cancer should not be different for younger and older patients. They should, however, be adapted when comorbidities and/or physiological changes are present.[20] In elderly rectal cancer patients with an indication for nCRT according to T/N stage, physicians usually decide on clinical factors whether nCRT should be offered to individual patients.

The aim of the present retrospective study was to assess the tolerability of nCRT with capecitabine and surgical outcomes in patients aged ≥70 years with locally advanced rectal cancer (LARC). We also assessed postoperative complications, mortality, disease-free survival (DFS) and OS.

METHODS

Patient population

The present retrospective multicenter study included data from the Dutch Comprehensive Cancer Centre of all patients with histologically confirmed rectal adenocarcinoma (stadium I-IV) from January 1, 2002 to December 31, 2012 from 4 Dutch hospitals (i.e. St. Antonius Hospital Nieuwegein and Utrecht, Diakonessenhuis Hospital Utrecht, Meander Medical Centre Amersfoort and University Medical Centre Utrecht) in the region of Utrecht, Netherlands. All patients aged ≥70 years who had received nCRT were included. The patient and treatment characteristics were obtained from the medical records. The medical ethics research committee approved the present study. (registration no., W13.018).

Treatment regimen

Patients received nCRT according to the applicable guidelines.[21] Clinical staging was determined by radiologic evaluation and the clinical TNM classification valid at diagnosis. The treatment of all patients was discussed in a multidisciplinary team that included oncologists, surgeons, radiation oncologists, gastroenterologists, pathologists and radiologists.

nCRT consisted of a regimen of chemotherapy and radiotherapy for 5 weeks followed by surgery 8 to 10 weeks later. The external beam radiotherapy dose was 50 Gy, delivered in 25 daily fractions of 2 Gy 5 times each week in supine position. Concomitant chemotherapy consisted of the oral 5-fluorouracil derivate capecitabine, 825 mg/m^2 twice daily, 7 days weekly.[21] Radical rectal resection was performed using to the TME technique by experienced colorectal surgeons specializing in colorectal oncology.[16]

Patient evaluation and follow up

Patients were monitored during and after nCRT for adverse events. The medical records were reviewed for gastro-intestinal, hematological and cardiac events, dermatitis, hand-foot syndrome, fatigue and death. The hematological toxicity was evaluated using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.[22]

The primary endpoint was the tolerability of nCRT and surgical outcomes in patients aged ≥70 years with LARC, including postoperative complications, mortality, DFS, and OS. Tolerability was defined as the number of treatment deviations with nCRT. The relative dose intensity was calculated and used as a reflection of treatment deviations, defined as the ratio of the actual delivered dose intensity of capecitabine to the standard

dose intensity of capecitabine (mg/m^2/week). The decision to deviate from the intended treatment schedule was the responsibility of the treating physician and not determined by a standardized protocol.

Statistical methods

The data were stratified by patient age into three groups (70-74, 75-79 and ≥80 years). The chi-square test and Fisher's exact test were used to analyze differences in proportions. All tests were two-sided and p-values (P<0.05) were considered to indicate statistical significance. DFS and OS were calculated using the Kaplan-Meier method and were calculated from the first day of nCRT. The statistical analysis was performed using SPSS Statistics for Windows, version 22.0 (IBM, Corp, Armonk, NY).

RESULTS

Baseline patient characteristics

A total of 447 rectal cancer patients aged ≥70 years were identified, with a median follow-up of 51 months [range 1-99 months]. Of these, 42 patients (9.4%) had received nCRT, with a median age of 74 years (interquartile range, 72-78). The cases of LARC were all diagnosed from 2006 to 2012. The Eastern Cooperative Oncology Group (ECOG) performance score was favorable for 88% of the patients at diagnosis. The distribution of distal tumors (≤5cm from the anal verge) and proximal tumors (>5cm from the anal verge) in the study cohort was equal. Baseline characteristics are listed in Table 1.

Table 1. Baseline Clinical Characteristics (N=42).

Characteristics	Patients (%)
Age	
70-74	23 (54.7)
75-79	12 (28.6)
≥80	7 (16.6)
Gender	
Male	26 (61.9)
Female	16 (38.1)
ECOG Performance score	
0	20 (47.6)
1	17 (40.5)
2	3 (7.1)
>2	2 (4.8)
Clinical T stage	
T1 or T2	3 (7.1)
T3	22 (52.4)
T4	17 (40.5)
Clinical N stage	
N0	6 (14.3)
N1	20 (47.6)
N2	16 (38.1)
Tumor height	
Lower rectum (≤5cm)	21 (50.0)
Higher rectum (>5cm)	21 (50.0)

Abbreviation: ECOG: Eastern Cooperative Oncology Group

Tolerability of nCRT

Overall, 37 patients (88.1%) completed the planned nCRT with capecitabine without treatment deviations, with no significant differences between the three age groups. The remaining 5 patients (11.9%) received ≤75% of the intended dose of capecitabine because of severe diarrhea (n=2), neutropenic fever (n=1), or severe mucositis due to dihydropyrimidine dehydrogenase (DPD)-deficiency (n=1). The patient with DPD-deficiency died of mucositis in the third week of nCRT. The intended radiation dose was given to all patients, except for the patient with DPD deficiency. Two patients required a dose delay because of diarrhea and fatigue. Patients with comorbidity or an ECOG performance status ≥2 did not experience more treatment deviations than the other patients (*P*=0.516 and *P*=0.231, respectively). Most patients (95.2%) experienced adverse events, with radiation dermatitis (61.9%), fatigue (57.1%) and diarrhea (42.9%) the most common (Table 2).

Table 2. Adverse events during nCRT according to age group (70-74, 75-79 and ≥80 years).

Adverse events	70-74 years (n=23)	75-79 years (n=12)	≥80 years (n=7)	P-value
Constipation	3 (13.0)	1 (8.3)	0	0.310
Diarrhea	9 (39.1)	5 (41.7)	4 (57.1)	0.448
Nausea/vomiting	2 (8.7)	0	3 (42.8)	0.067
Anorexia	4 (17.4)	2 (16.7)	1 (14.3)	0.856
Dehydration	0	0	1 (14.3)	0.067
Leucopenia	0	0	0	-
Thrombocytopenia				
CTC grade 1	1 (4.3)	1 (8.3)	0	0.821
Anemia				0.918
CTC grade 1	1 (4.3)	0	0	
CTC grade 2	0	1 (8.3)	0	
CTC grade 3	0	1 (8.3)	0	
Neutropenic fever	0	0	1 (14.3)	0.167
Dysuria-painful urination	3 (13.0)	5 (41.7)	1 (14.3)	0.482
Radiation dermatitis	15 (65.2)	7 (58.3)	4 (57.1)	0.649
Allergy	0	0	0	-
Hand-foot syndrome	1 (4.3)	1 (8.3)	0	0.821
Fatigue	13 (56.5)	6 (50.0)	5 (71.4)	0.641
Cardiac	0	0	0	-
Death	0	0	1 (14.3)	0.236

Abbreviation: CTC: Common toxicity criteria

Surgery procedures, postoperative complications, mortality and adjuvant chemotherapy
Of the 42 patients, 40 patients underwent surgery (95.2%); 1 patient refused resection and 1 patient died of DPD deficiency during nCRT. The median interval between the last day of nCRT and surgery 49 days [range 32-126 days]. Among the 40 patients, 10 patients (23.8%) had received a diverting stoma before starting nCRT. A primary anastomosis was performed in 3 patients, and the remaining group received a permanent colostomy. The pathology report showed R0 resections in 36 patients (90%). A pathologic complete response (pCR) was observed in 3 patients (7.5%).

Postoperative complications developed in 12 patients (30%), with 6 patients (15%) requiring reoperation because of anastomotic leakage (n=2) or drainage of a presacral abscess (n=4). Patients aged 70 to 74 years were significantly more often hospitalized within <30 days compared with the other patients (*P*=0.041). The reasons for repeat hospitalization were anastomotic leakage (n=1), wound infection (n=1), pneumonia (n=2) and presacral abscess (n=2). Postoperative intensive care admissions were indicated for only 2 patients (5%), 1 for a transfusion reaction and 1 because of respiratory problems. Patients aged ≥80 years were significantly longer, owing to discharge to a nursing home and a longer recovery period required for postoperative complications (*P*=0.034). The remaining postoperative complications and treatment efficacy did not significantly differ among the three age groups (Table 3). The overall 30-day mortality rate after surgery was 0%. Adjuvant chemotherapy was given to 8 patients. Of these 8 patients, 5 received capecitabine monotherapy and 3 received capecitabine and oxaliplatin (Table 3).

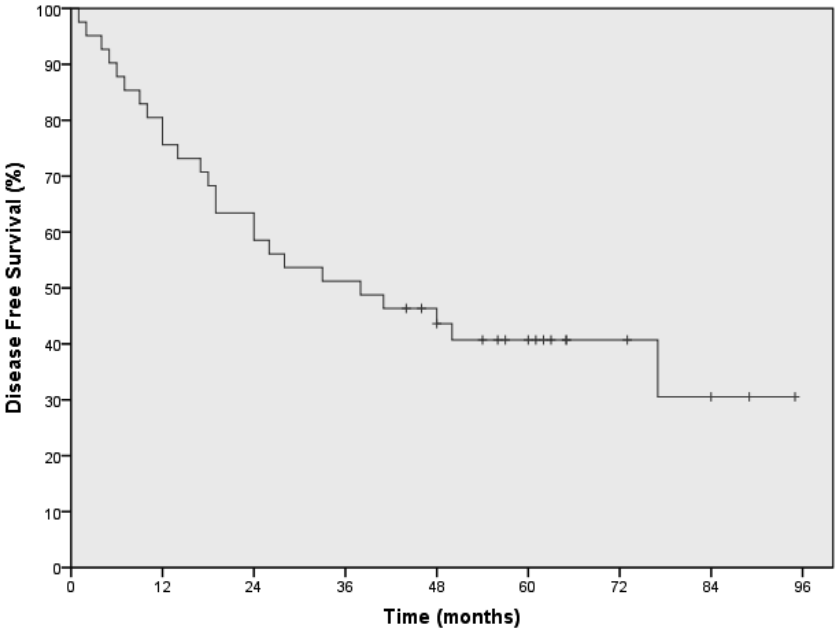
DFS and OS rates
The 2- and 5-year DFS rates were 58.5% and 40.7%, respectively, with a median of 38 months (SE 13.8, 95% CI 11.0-65.0) (Figure 1A). No significant differences were found in DFS among the three age groups (log rank *P*-value 0.468; figure 1B). Of the 42 patients, 31 patients (73.8%) developed disease recurrence, with 4 patients having local recurrence (9.5%) and 27 patients, distant metastasis (64.3%). The 2- and 5-year OS rates in all 42 patients were 81.0% and 58.2%, respectively, with a median OS of 67 months (Standard Error (SE) 13.5, 95% Confidence Interval (CI) 40.3-93.7%) (figure 2A). No significant differences were found in OS among the three age groups (log rank *P*-value 0.212; figure 2B).

Table 3. Surgery procedures and postoperative complications according to age group (70-74, 75-79 and ≥80 years).

	70-74 years (n=23)	**75-79 years (n=12)**	**≥80 years (n=7)**	**P-value**
Surgery	23 (100)	12 (100)	5 (71.4)	0.208
No surgery	0	0	2 (28.6)	
Diverting stoma	6 (26.1)	3 (25.0)	1 (14.3)	0.572
Type surgery				0.206
LAR	12 (52.2)	3 (25.0)	2 (40.0)	
APR	10 (43.5)	9 (75.0)	2 (40.0)	
Hartmann procedure	1 (4.3)	0	1 (20.0)	
Permanent colostomy	21 (91.3)	11 (91.7)	5 (100)	-
Temporary Ileostomy	0	0	0	
R0 resection rate	20 (86.9)	12 (100)	4 (80.0)	0.322
Days hospitalized, median(range)	7 (5-9)	7 (4-16)	10 (5-35)	0.034
Postoperative IC visit	1 (4.3)	0	1 (14.3)	0.124
Complications	9 (39.1)	1 (8.3)	2 (40.0)	0.440
Anastomotic leak	1 (4.3)	0	1 (20.0)	
Ileus	3 (8.7)	0	1 (20.0)	
Wound infection	1 (4.3)	1 (8.3)	0	
Pre-sacral abscess	4 (17.4)	0	0	
Re-hospitalization <30 days	6 (26.1)	0	0	0.041

Abbreviations; LAR: low anterior resection, APR: abdominoperineal resection, IC: intensive care

1A



1B

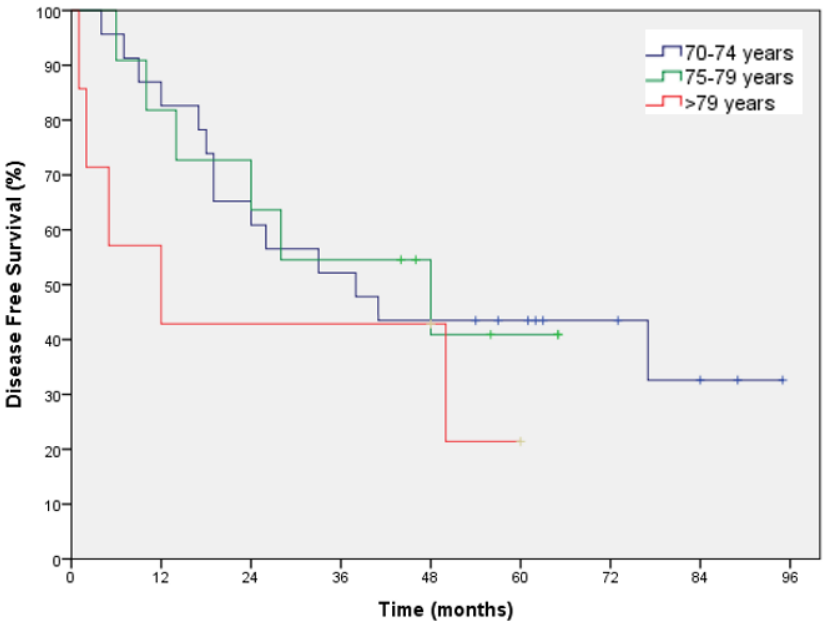
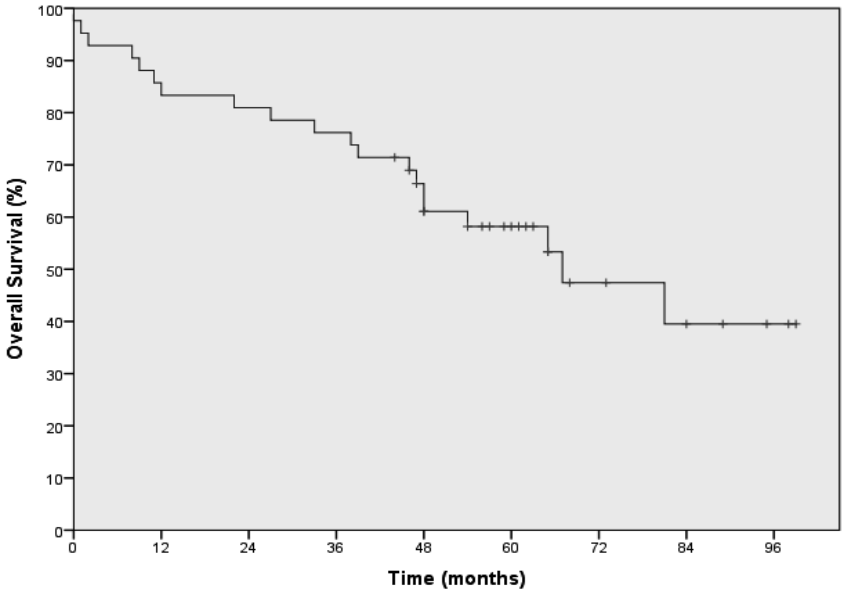


Figure 1. Kaplan-Meier estimates of DFS in all 42 patients (A) and age groups (B).

2A



2B

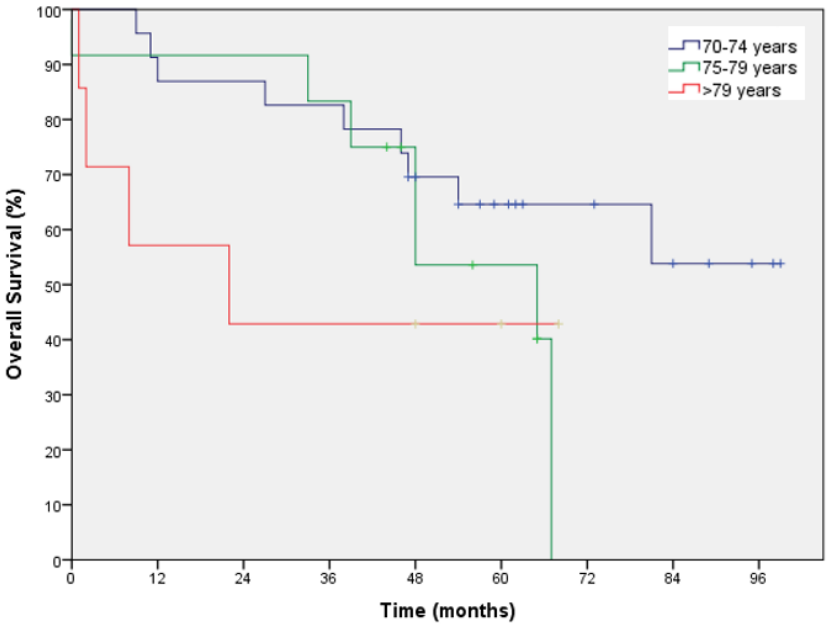


Figure 2. Kaplan-Meier estimates of OS in all 42 patients (A) and age groups (B).

DISCUSSION

The combination of nCRT with TME is the standard of care for patients with LARC in the Netherlands. To the best of our knowledge, the present multicenter study is the first to retrospectively evaluate the tolerability, safety and outcomes of nCRT with capecitabine in elderly patients with LARC.

Our results suggest that elderly patients with rectal cancer can receive nCRT followed by surgery because the tolerability of nCRT and the postoperative morbidity seemed acceptable. The clinical benefit, together with the good tolerability profile of nCRT, has been widely demonstrated in younger patients.[10-12,23] However, little is known about the tolerability of nCRT with capecitabine in the geriatric population with rectal cancer compared to the younger population. Kim et al. studied 45 younger patients (median age, 55 years) that reported that 95% of the patients completed nCRT with capecitabine.[24] The most commonly seen grade 3 adverse events were hand-foot syndrome (7%), fatigue (4%) and diarrhea (4%). No grade 3 or 4 hematological adverse events were observed, similar to our study in which 1 patient developed grade 3 anemia. Grade 3 nonhematological toxicity is a frequent reason for dose modification; however, these modifications were not often seen in the present study.

In general, the chemotherapeutic toxicity in our patients was comparable to that reported by retrospective studies of younger patients with LARC.[25,26] The ACCOR12/PRODIG 2 phase III trial compared the tolerability of nCRT with either capecitabine or capecitabine combined with oxaliplatin between older (≥70 year n=142) and younger patients (<70 patients n=442). Preoperative chemoradiotherapy resulted in a greater incidence of grade 3 toxicity (25.6% versus 15.8%, p=0.01) in the elderly. The grade 3 hematological toxicity rate was similar in the two age groups (<70 years: 4.1% vs. ≥70 years: 10.1%, p=0.66). Hematological toxicity was more common in the ACCORD/PRODIGD 2 phase III trial, which is likely explained by the addition of oxaliplatin. In the ACCORD/PRODIGD 2 phase III trial, 94.4% of the patients received the planned doses of capecitabine, similar to our study.[27]

Most of the studies that evaluated the geriatric population were small and used different radiotherapy techniques and/or chemotherapy schedules.[23,28-33] Only one study investigated the same schedule nCRT with capecitabine in elderly. Cefaro et al. retrospectively analyzed the data from 26 patients with a median age of 74 years. All patients completed the chemotherapy course as planned, expect for 1 patient, who developed hematologic toxicity. The tolerability of chemotherapy regimen in our study was lower, with 5 patients who received less than 75% of the planned

doses. The most frequent nonhematological toxicity in the study by Cefaro et al. was diarrhea in 62% of the patients. The incidence of diarrhea in our study was slightly lower (42.8%); however, the incidence of acute hematological toxicity was similar in both studies.[34]

A great concern exists that if elderly patients undergo nCRT and TME, they will be at an increased risk of postoperative complications and mortality compared with younger patients. Younger rectal cancer patients who undergo nCRT and surgery have a postoperative complication rate of 22.1% and a 30-day mortality rate of 0.7%.[35,36] This is comparable to the incidence of postoperative complications and the excellent 30-day mortality rate that we found in elderly patients (30% vs 0%, respectively).

Anastomotic leakage, which is considered the most severe surgical complication, is of particular interest. In our cohort, 3 patients received a primary anastomosis, and 2 of these patients developed anastomotic leakage (66.7%). This incidence is high compared with the incidence of anastomotic leakage after nCRT and surgery reported by Valenti et al. (4.2%).[36] Moreover, McDermott et al, in a systematic review, reported that the anastomotic leakage rate after rectal cancer surgery in general was 1% to 19% [37]. The rate was 8.4% according to the Dutch Surgical Colorectal Audit [38]. However, with only 3 patients with a primary anastomosis in our study cohort, the small sample size was too small to draw firm conclusions. Nevertheless, anastomotic leakage after low anterior resection has been associated with increased mortality in elderly patients.[39] Furthermore, mortality at 6 months in general increased significantly in patients ≥75 years compared to patients <75 years (57.1% versus 8.2%, relative risk = 6.94 (95% CI 2.99-16.11)), although no difference in the frequency of anastomotic leakage was observed between the two groups (11.5% versus 10.1%).[39]

In addition to these favourable surgical outcomes, we found a pCR in 3 patients (7.5%). This is slightly lower than pCR rates in previous published studies of capecitabine pretreatment 16% and 24%, respectively).[23,40] However, the number of patients in our study with pCR was too small to draw meaningful conclusions. We found a 5-year DFS rate of 40.7% and a 5-year OS rate of 58.2%, with no significant differences among the three age groups. These are comparable to the DFS and OS rates reported in previous studies of younger patients. A study by Kim et al. found a 5-year DFS of 52% and an OS rate of 58.1% in patients treated with nCRT and TME.[41] National studies of rectal cancer patients from Sweden, Denmark, the United Kingdom and Norway have reported overall 5-year OS rates between 44.8% and 63.4%.[42-45]

The major limitation of the present study was the retrospective design with a relatively small number of patients selected using clinical factors. Also, we were not informed about the outcomes of elderly patients who did not receive nCRT most likely because of age, comorbidity and/or frailty.

The results of the present multicentre study have shown that if elderly patients are selected using clinical factors, nCRT will be safe and well tolerated. We found no 30-day mortality after surgery and the beneficial effect (pCR, DFS and OS) seemed comparable to those for younger age groups. Therefore, we believe that elderly patients should not be withheld neoadjuvant treatment only because of age. Individual patient evaluation using a validated comprehensive geriatric assessment could be a useful tool in the decision-making process to prevent either under- and overtreatment of the elderly population with LARC.

REFERENCES

1. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(2):104-117. doi: 10.3322/caac.21220 [doi].
2. Papamichael D, Audisio R, Horiot JC, et al. Treatment of the elderly colorectal cancer patient: SIOG expert recommendations. *Ann Oncol*. 2009;20(1):5-16. doi: 10.1093/annonc/mdn532 [doi].
3. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: The challenges ahead. *Lancet*. 2009;374(9696):1196-1208. doi: 10.1016/S0140-6736(09)61460-4 [doi].
4. Kohne CH, Folprecht G, Goldberg RM, Mitry E, Rougier P. Chemotherapy in elderly patients with colorectal cancer. *Oncologist*. 2008;13(4):390-402. doi: 10.1634/theoncologist.2007-0043 [doi].
5. Muss HB. Older age--not a barrier to cancer treatment. *N Engl J Med*. 2001;345(15):1127-1128.
6. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer*. 2001;94(2):153-156. doi: 10.1002/ijc.1440 [pii].
7. Boyle P, Ferlay J. Cancer incidence and mortality in europe, 2004. *Ann Oncol*. 2005;16(3):481-488. doi: mdi098 [pii].
8. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med*. 2006;355(11):1114-1123. doi: 355/11/1114 [pii].
9. Preoperative short-term radiation therapy in operable rectal carcinoma. A prospective randomized trial. stockholm rectal cancer study group. *Cancer*. 1990;66(1):49-55.
10. Randomized study on preoperative radiotherapy in rectal carcinoma. stockholm colorectal cancer study group. *Ann Surg Oncol*. 1996;3(5):423-430.
11. Local recurrence rate in a randomised multicentre trial of preoperative radiotherapy compared with operation alone in resectable rectal carcinoma. swedish rectal cancer trial. *Eur J Surg*. 1996;162(5):397-402.
12. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: A systematic overview of 8,507 patients from 22 randomised trials. *Lancet*. 2001;358(9290):1291-1304. doi: S0140-6736(01)06409-1 [pii].
13. Camma C, Giunta M, Fiorica F, Pagliaro L, Craxi A, Cottone M. Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. *JAMA*. 2000;284(8):1008-1015. doi: jma00002 [pii].
14. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351(17):1731-1740. doi: 351/17/1731 [pii].
15. Ulrich A, Schwerdt J, Z'graggen K, Kienle P, Weitz J, Buchler MW. Acceptance of neoadjuvant short-term radiotherapy: A survey under surgeons and radiotherapists. *Langenbecks Arch Surg*. 2007;392(5):525-533. doi: 10.1007/s00423-006-0139-0 [doi].
16. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345(9):638-646. doi: 10.1056/NEJMoa010580 [doi].
17. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol*. 2003;21(7):1383-1389.
18. Hutchins LF, Unger JM, Crowley JJ, Coltman CA,Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med*. 1999;341(27):2061-2067. doi: 10.1056/NEJM199912303412706 [doi].

19. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: Results of FFCD 9203. *J Clin Oncol*. 2006;24(28):4620-4625. doi: 24/28/4620 [pii].
20. National Working Group on Gastrointestinal Cancers. Concept guideline colorectal cancer and colorectal liver metastasis. . 2013.
21. Glimelius B, Tiret E, Cervantes A, Arnold D, ESMO Guidelines Working Group. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24 Suppl 6:vi81-8. doi: 10.1093/annonc/mdt240 [doi].
22. National cancer institute. Common terminology criteria for adverse events (CTCEA) version 4.0. http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Updated 20102009.
23. De Paoli A, Chiara S, Luppi G, et al. Capecitabine in combination with preoperative radiation therapy in locally advanced, resectable, rectal cancer: A multicentric phase II study. *Ann Oncol*. 2006;17(2):246-251. doi: mdj041 [pii].
24. Kim JS, Kim JS, Cho MJ, Song KS, Yoon WH. Preoperative chemoradiation using oral capecitabine in locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys*. 2002;54(2):403-408. doi: S0360301602028560 [pii].
25. Krishnan S, Janjan NA, Skibber JM, et al. Phase II study of capecitabine (xeloda) and concomitant boost radiotherapy in patients with locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys*. 2006;66(3):762-771. doi: S0360-3016(06)00984-9 [pii].
26. de Bruin AF, Nuyttens JJ, Ferenschild FT, Planting AS, Verhoef C, de Wilt JH. Preoperative chemoradiation with capecitabine in locally advanced rectal cancer. *Neth J Med*. 2008;66(2):71-76.
27. Francois E, Azria D, Gourgou-Bourgade S, et al. Results in the elderly with locally advanced rectal cancer from the ACCOR12/PRODIGE 2 phase III trial: Tolerance and efficacy. *Radiother Oncol*. 2014;110(1):144-149. doi: 10.1016/j.radonc.2013.10.019 [doi].
28. Au HJ, Mulder KE, Fields AL. Systematic review of management of colorectal cancer in elderly patients. *Clin Colorectal Cancer*. 2003;3(3):165-171. doi: S1533-0028(11)70084-6 [pii].
29. Reddy N, Yu J, Fakih MG. Toxicities and survival among octogenarians and nonagenarians with colorectal cancer treated with chemotherapy or concurrent chemoradiation therapy. *Clin Colorectal Cancer*. 2007;6(5):362-366. doi: S1533-0028(11)70264-X [pii].
30. Pasetto LM, Friso ML, Pucciarelli S, et al. Rectal cancer neoadjuvant treatment in elderly patients. *Anticancer Res*. 2006;26(5B):3913-3923.
31. Guimas V, Boustani J, Schipman B, et al. Preoperative chemoradiotherapy for rectal cancer in patients aged 75 years and older: Acute toxicity, compliance with treatment, and early results. *Drugs Aging*. 2016;33(6):419-425. doi: 10.1007/s40266-016-0367-0 [doi].
32. Tougeron D, Roullet B, Paillot B, et al. Safety and outcome of chemoradiotherapy in elderly patients with rectal cancer: Results from two french tertiary centres. *Dig Liver Dis*. 2012;44(4):350-354. doi: 10.1016/j.dld.2011.10.017 [doi].
33. Margalit DN, Mamon HJ, Ancukiewicz M, et al. Tolerability of combined modality therapy for rectal cancer in elderly patients aged 75 years and older. *Int J Radiat Oncol Biol Phys*. 2011;81(5):e735-41. doi: 10.1016/j.ijrobp.2010.12.056 [doi].
34. Ausili Cefaro G, Genovesi D, Vinciguerra A, et al. Effects of preoperative radiochemotherapy with capecitabine for resectable locally advanced rectal cancer in elderly patients. *Tumori*. 2012;98(5):622-629. doi: 10.1700/1190.13204 [doi].

35. Garlipp B, Ptok H, Schmidt U, Meyer F, Gastinger I, Lippert H. Neoadjuvant chemoradiotherapy for rectal carcinoma: Effects on anastomotic leak rate and postoperative bladder dysfunction after non-emergency sphincter-preserving anterior rectal resection. results of the quality assurance in rectal cancer surgery multicenter observational trial. *Langenbecks Arch Surg*. 2010;395(8):1031-1038. doi: 10.1007/s00423-010-0708-0 [doi].
36. Valenti V, Hernandez-Lizoain JL, Baixauli J, et al. Analysis of early postoperative morbidity among patients with rectal cancer treated with and without neoadjuvant chemoradiotherapy. *Ann Surg Oncol*. 2007;14(5):1744-1751. doi: 10.1245/s10434-006-9338-8 [doi].
37. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *Br J Surg*. 2015;102(5):462-479. doi: 10.1002/bjs.9697 [doi].
38. Dutch surgical colorectal audit (DSCA) www.dcsa.nl
39. Rutten H, den Dulk M, Lemmens V, et al. Survival of elderly rectal cancer patients not improved: Analysis of population based data on the impact of TME surgery. *Eur J Cancer*. 2007;43(15):2295-2300. doi: S0959-8049(07)00545-X [pii].
40. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: A pooled analysis of individual patient data. *Lancet Oncol*. 2010;11(9):835-844. doi: 10.1016/S1470-2045(10)70172-8 [doi].
41. Kim NK, Baik SH, Seong JS, et al. Oncologic outcomes after neoadjuvant chemoradiation followed by curative resection with tumor-specific mesorectal excision for fixed locally advanced rectal cancer: Impact of postirradiated pathologic downstaging on local recurrence and survival. *Ann Surg*. 2006;244(6):1024-1030. doi: 10.1097/01.sla.0000225360.99257.73 [doi].
42. Kodeda K, Johansson R, Zar N, et al. Time trends, improvements and national auditing of rectal cancer management over an 18-year period. *Colorectal Dis*. 2015;17(9):O168-79. doi: 10.1111/codi.13060 [doi].
43. Bulow S, Harling H, Iversen LH, Ladelund S, Danish Colorectal Cancer Group. Improved survival after rectal cancer in denmark. *Colorectal Dis*. 2010;12(7 Online):e37-42. doi: 10.1111/j.1463-1318.2009.02012.x [doi].
44. Bown EJ, Lloyd GM, Boyle KM, Miller AS. Rectal cancer: Prognostic indicators of long-term outcome in patients considered for surgery. *Int J Colorectal Dis*. 2014;29(2):147-155. doi: 10.1007/s00384-013-1772-z [doi].
45. Guren MG, Korner H, Pfeffer F, et al. Nationwide improvement of rectal cancer treatment outcomes in norway, 1993-2010. *Acta Oncol*. 2015;54(10):1714-1722. doi: 10.3109/0284186X.2015.1034876 [doi].