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ORIGINAL ARTICLE

Feasibility of neoadjuvant therapy for elderly patients with locally advanced rectal cancer

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Abstract

Purpose The feasibility of neoadjuvant therapy (NAT) for elderly patients with rectal cancer has not been evaluated well.

Methods Between 2004 and 2014, 506 patients with locally advanced low rectal cancer underwent curative resection. Fifty-four were over 75 years old (elderly group), and 452 were under 75 years old (young group). The patients were divided into sub-groups according to whether they received NAT.

Results Nineteen (35.2%) patients from the elderly group and 348 (77.0%) from the young group received NAT. The proportion of patients who received NAT was significantly lower in the elderly group. In the elderly group, the median age and prevalence of co-morbidities were significantly lower in patients with than in those without NAT. The incidence of severe adverse events was similar in the two groups. On multivariate analysis, age was not related to postoperative complications in patients who received NAT. The 5-year local recurrence rate was significantly lower in the elderly patients who received NAT, and similar to that of the young patients who received NAT.

Conclusions Neoadjuvant therapy was feasible and should be considered as a treatment option for carefully selected elderly patients with locally advanced low rectal cancer.

Keywords Rectal cancer · Elderly patients · Chemoradiotherapy · Neoadjuvant therapy

Introduction

Rectal cancer is common worldwide, and its management is complex. The treatment strategy for rectal cancer has changed remarkably in the last three decades. Several randomized controlled trials (RCTs) have demonstrated that neoadjuvant therapy (NAT), including long-course chemoradiotherapy (CRT) or short-course radiotherapy (RT), reduces the local recurrence (LR) rate in patients with locally advanced rectal cancer [1–3]. In Western countries, NAT followed by total mesorectal excision is a standard treatment strategy for patients with locally advanced rectal cancer, whereas in Japan, NAT is not commonly given for rectal cancer [4, 5].

As the population ages, the number of elderly patients with rectal cancer increases [6, 7]. As elderly patients tend to have more co-morbidities than younger patients [8], delivering multimodal therapy to elderly patients with locally advanced rectal cancer can be challenging because they often have less tolerability to intensive treatment and an increased risk of severe adverse events [9]. Therefore, patients over 75 years of age were excluded from previous RCTs that validated the efficacy of NAT for locally advanced rectal cancer, and the safety and efficacy of NAT in elderly patients with locally advanced rectal cancer are not well known [1, 10, 11]. The aim of this study was to establish the safety and efficacy of NAT followed by surgery in elderly Japanese patients with locally advanced rectal cancer.

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Materials and methods

Neoadjuvant therapy was introduced gradually in our institution from 2004. The inclusion criteria for NAT for patients with rectal cancer are clinical stage II/III low rectal cancer and an age under 75 years [12, 13]. Low rectal cancer is defined as that with a distal margin below the peritoneal reflection, which is equivalent to 8 cm from the anal verge. We have no clear criteria for giving NAT to patients 75 years of age or older and discuss the indication for NAT at multidisciplinary team meetings on a case-by-case basis, considering the general condition of the patients, the presence of co-morbidities, the status of the primary tumor, and the advantages and disadvantages of NAT. The multidisciplinary team consists of colorectal surgeons and medical and radiation oncologists. NAT includes long-course oral 5-fluorouracil-based CRT with a total dose of 45–50.4 Gy and short-course RT (5 × 5 Gy) [13, 14]. A phase II study was started at our institution in 2013 to evaluate the efficacy and safety of preoperative systemic chemotherapy followed by long-course CRT in patients with low rectal cancer that was more locally advanced, with four or more involved mesorectal lymph nodes, lateral pelvic lymph node metastasis, or circumferential resection margin-positivity. The trial was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN number; 000011457). Forty patients who underwent systemic chemotherapy (six courses of FOLFOX plus bevacizumab) followed by CRT were included in this analysis. Total mesorectal excision was performed 1–16 weeks after the completion of radiotherapy.

Essentially, patients with pathological stage III or high-risk stage II (pT4, undifferentiated type, lymphovascular invasion positive) were directed to receive 5-fluorouracil-based adjuvant chemotherapy [4]. With respect to elderly patients, the choice of adjuvant treatment was at the attending surgeon's discretion or based on the patients' wishes. Patients were followed up every 3 months for the first 3 years and every 6 months thereafter. Blood tests including carcinoembryonic antigen (CEA) levels were done at every visit. Chest and abdominal computed tomography scans were performed every 6 months. This analysis was approved by the Clinical Research Review Board of the Cancer Institute Hospital.

Between July 2004 and December 2014, 527 consecutive patients who underwent curative resection for clinical stage II/III low rectal adenocarcinoma at our institution were reviewed retrospectively. Patients with synchronous colon cancer ($n = 10$), colitic cancer ($n = 4$), Lynch syndrome ($n = 2$), and familial adenomatous polyposis ($n = 1$) were excluded. Four patients who underwent synchronous pelvic exenteration were also excluded because this procedure is associated with a longer operation time, large blood loss, and high morbidity, and it was performed only in younger patients during this study period.

Finally, 506 patients were included in this retrospective study. These patients were divided into four groups according to their age (< 75 years and ≥ 75 years) and whether they received NAT (Fig. 1). The elderly patients treated with NAT were the "E-NAT group", the elderly patients treated without NAT were the "E-no NAT group", and the younger patients treated with NAT were the "Y-NAT group". To compare the clinical features between the E-NAT and E-no NAT groups and identify the factors affecting the selection of elderly patients for NAT, the following data were collected: starting point of the treatment, sex, age at surgery, American Society of Anesthesiologists (ASA)-performance status, co-morbidities, distance of the tumor from the anal verge, clinical T factor, and clinical N factor. Surgical and pathological data, including operative procedures, operation time, estimated blood loss, postoperative complications (Clavien–Dindo ≥ 2), postoperative hospital stay, mortality, pathological stage, circumferential resection margin status, histological type, lymphovascular invasion status, and whether adjuvant chemotherapy was given, were also compared between the E-NAT and E-no NAT groups to establish whether NAT affected the postoperative short-term outcomes of elderly patients. Among the patients who were treated with NAT, the following data were compared between the elderly and younger patients: type of NAT, adverse effects of NAT, whether combined resection was performed, 5-year cancer-specific survival (CSS), and 5-year LR rate. CSS was defined as the interval between the date of surgery to the date of cancer death or last follow-up. LR was defined as any recurrence within the pelvis. Independent risk factors for postoperative complications were evaluated to determine whether the age of the patients treated with NAT influenced the occurrence of postoperative complications. Pathological classification and staging were diagnosed according to the American Joint Committee on Cancer criteria. Adverse events during NAT were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events [15].

Statistical analysis was performed using a Bell Curve for Excel software, version 2.02 (Social Survey Research Information Co., Ltd., Tokyo, Japan). Data are presented as median values with ranges. Differences in categorical variables were compared using the Chi squared test or Fisher's exact test, as appropriate. Differences in continuous variables were analyzed with the Mann–Whitney *U* test. Survival curves were constructed by the Kaplan–Meier method with the log-rank test. Multivariate analysis using a Cox proportional hazard model was used to identify the independent risk factors for postoperative complications. Clinical

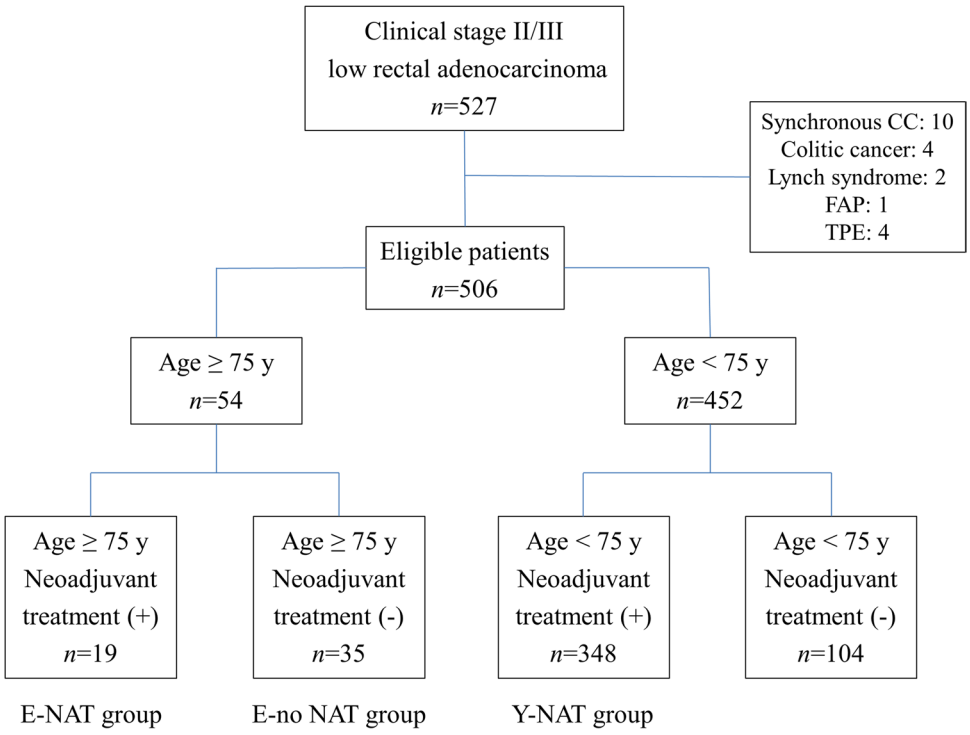

Fig. 1 CONSORT diagram. *CC* colon cancer, *FAP* familial adenomatous polyposis, *TPE* total pelvic exenteration

variables with a p value < 0.1 on the univariate analysis were included in the multivariate analysis. All p values < 0.05 were considered significant.

Results

The study population comprised 333 men and 173 women, with a median age of 61 (range 24–85) years. Of these patients, 54 (10.7%) were 75 years or older, with a median age of 77 (75–85 years), and the remaining 452 (89.3%) were younger than 75 years (Fig. 1). Nineteen of the elderly patients (35.2%) and 348 of the younger patients (77.0%) received NAT. The proportion of elderly patients treated with NAT was significantly lower ($p < 0.001$).

Table 1 shows the clinical differences between the E-NAT group and the E-no NAT group. The study period was divided into two intervals (2004–2009 and 2010–2014), and a significantly larger proportion of patients in the E-NAT group received this treatment in the later years ($p = 0.038$). The median age of the E-NAT group was significantly younger than that of the E-no NAT group ($p = 0.023$). ASA-performance status was similar between the groups, but the proportion of patients with co-morbidities was significantly lower in the E-NAT group than in the E-no NAT group (36.8% vs. 77.1%, $p < 0.001$). Regarding the remaining factors, including sex, location of the tumor, clinical T factor, and clinical N factor, there were no significant differences between the groups.

Table 2 shows the surgical and pathological differences between the E-NAT group and the E-no NAT group. None of the factors, apart from pathological stage and lymphovascular invasion, were significantly different between the E-NAT and E-no NAT groups. The rates of permanent stoma formation and postoperative complications were not significantly different between the groups. There was no mortality in either group. Pathological complete response (pCR) was achieved in four (21.0%) patients from the E-NAT group.

Table 3 shows the clinicopathological difference between the E-NAT and Y-NAT groups. Sex, age at surgery, and ASA-performance status differed significantly between the groups. The type of NAT used in the two groups also tended to be different, with systemic chemotherapy followed by CRT used frequently in the Y-NAT group. NAT was completed successfully in all patients in both groups. In the E-NAT group, only one patient (5.3%) had grade 3 toxicity and no patient had grade 4 toxicity. The incidence of adverse effects of NAT and the rate of permanent stoma were similar in the two groups. The postoperative pathological findings confirmed that no patient in the E-NAT group had a positive resection margin. Adjuvant chemotherapy was given significantly less often to patients in the E-NAT group than to those in the Y-NAT group ($p = 0.031$).

Table 4 shows the univariate and multivariate analyses for the risk factors for postoperative complications in patients treated with NAT. ASA-performance status, longer operation time, greater blood loss, and combined resections were significantly associated with postoperative complications

Table 1 Comparison of clinical characteristics between elderly patients treated with versus those treated without neoadjuvant therapy

	Neoadjuvant therapy (+) ($n=19$)	Neoadjuvant therapy (−) ($n=35$)	p values
Starting point of the treatment			0.038
2004–2009	3	16	
2010–2014	16	19	
Sex			0.602
Male	9	14	
Female	10	21	
Age in years (range)	76.9 (75–82)	78.6 (75–85)	0.023
ASA-performance status			0.606
1	2	6	
2	17	27	
3	0	2	
Co-morbidity			<0.001
None	12	8	
Yes	7	27	
One co-morbidity	2	13	
Two co-morbidities	2	8	
Three or more co-morbidities	3	6	
Tumor distance from the anal verge, mm (range)	49.7 (10–100)	52.8 (20–100)	0.682
Clinical T factor			0.361
1	0	2	
2	0	4	
3	15	25	
4	4	4	
Clinical N factor			0.799
N negative	11	19	
N positive	8	16	

Data are presented as the number of patients or medians (range)

ASA American Society of Anesthesiologists

on univariate analysis, but age was not (odds ratio = 0.606, $p=0.375$). On multivariate analysis, ASA-performance status, longer operation time, and greater blood loss were independent risk factors for postoperative complications.

The median follow-up period of this cohort was 51.2 months (6–137 months), and the 5-year CSS and LR rates of all patients were 90.7% with a 95% confidence interval (CI) of 85.6–92.2% and 5.9% (95% CI; 3.6–8.7), respectively. The 5-year CSS of the E-NAT, E-no NAT, and Y-NAT groups were 88.2% (72.9–100), 65.0% (45.8–84.1), and 93.7% (90.6–96.9), respectively (Fig. 2). The difference between the Y-NAT and E-NAT groups was not significant ($p=0.440$), and the 5-year CSS of patients in the Y-NAT group was significantly higher than that of patients in the E-no NAT group. The 5-year LR rates of the three groups were 5.2% (0–15.3), 18.4% (7.4–36.2), and 4.7% (4.2–7.1), respectively (Fig. 3). The differences between the E-NAT and the E-no NAT groups ($p<0.001$), and between the E-no NAT and Y-NAT groups ($p<0.001$) were significant. The difference between the E-NAT and Y-NAT groups was not significant.

Discussion

Colorectal cancer is the third most common cancer in men and the second most common cancer in women in Japan, with rectal cancer accounting for 38% of all colorectal cancers [7]. In Japan, surgery, including lateral pelvic lymph node dissection without NAT, is the standard treatment for low rectal cancer in patients with locally advanced disease [4]. To our knowledge, this is the first report analyzing the feasibility of NAT in elderly Japanese patients with locally advanced low rectal cancer.

This study showed that NAT did not affect the postoperative short-term outcomes in carefully selected elderly patients, and the rate of adverse effects of NAT was similar in elderly and younger patients with locally advanced low

Table 2 Comparison of surgical and pathological characteristics between elderly patients treated with and those treated without neoadjuvant therapy

	Neoadjuvant therapy (+) ($n=19$)	Neoadjuvant therapy (−) ($n=35$)	p values
Operative procedures			0.155
Sphincter-preserving surgery	13	16	
Abdominoperineal resection/Hartmann's procedure	6	19	
Operation time, min (range)	273 (197–450)	303 (184–554)	0.302
Estimated blood loss, mL (range)	50 (0–925)	50 (2–1170)	0.620
Postoperative complications			0.753
No	15	26	
Yes	4	9	
Postoperative hospital stay, days (range)	17 (11–26)	17 (15–31)	0.134
Pathological stage			<0.001
Pathological complete response	4	0	
I	5	0	
II	3	17	
III	7	18	
Circumferential resection margin			1.000
Negative	19	34	
Positive	0	1	
Histological type			0.607
Well/moderate	17	33	
Poor/mucinous/signet	2	2	
Lymphovascular invasion			0.017
Negative	6	2	
Positive	13	33	
Adjuvant treatment			0.728
No	15	29	
Yes	4	6	
FOLFOX/XELOX	2	0	
5-FU-related chemotherapy without oxaliplatin	2	6	

rectal cancer. The age of the patients with low rectal cancer treated with NAT was not associated with the occurrence of postoperative complications. Moreover, the 5-year LR rate of the elderly patients treated with NAT was significantly lower than that of the elderly patients treated without NAT and similar to that of the younger patients treated with NAT.

In this retrospective study, NAT was given significantly more often to elderly patients without co-morbidities than to those with co-morbidities, and the median age was significantly lower for elderly patients treated with NAT than for those treated without NAT. To optimize the treatment strategy for elderly patients with locally advanced rectal cancer, it is important to establish if elderly patients with rectal cancer would benefit from multimodal therapy. Several assessment tools have become available for evaluating the physical, physiological, and functional condition of elderly patients, although there have been few reports evaluating the utility of geriatric assessment of elderly patients with rectal cancer treated with multimodal therapy [16–18]. Cai et al. evaluated the feasibility of CRT or RT in 126 elderly patients (> 70 years) with rectal cancer and demonstrated that age and the Charlson co-morbidity score were independent prognostic factors for 3-year overall survival, but not for grade 3 toxicity [19, 20]. Tougeron et al. also examined the factors that influenced treatment tolerability in 125 elderly patients (≥ 70 years) with rectal cancer. They identified tumor stage as the independent prognostic factor for overall survival on multivariate analysis, whereas age and the Charlson co-morbidity score were not correlated with the prognosis [21]. Both of these studies included relatively large numbers of subjects; however, the study populations were heterogeneous and different from the present study, in which they included elderly patients with stage IV rectal cancer and those who received palliative RT or postoperative CRT after R1 resection. More recently, Suhool et al. evaluated the efficacy of routine assessment using the simplified Comprehensive

Table 3 Clinicopathological characteristics of patients with locally advanced low rectal cancer treated with neoadjuvant therapy

	Age ≥ 75 years ($n = 19$)	Age < 75 years ($n = 348$)	p values
Sex			0.032
Male	9	246	
Female	10	102	
Age in years (range)	76.9 (75–82)	57.2 (24–74)	< 0.001
Distance of the tumor from the anal verge, mm (range)	49.7 (10–100)	43.4 (5–100)	0.171
ASA-performance status			0.003
1	2	163	
2	17	184	
3	0	1	
Clinical stage			0.065
II	11	128	
III	8	220	
Type of neoadjuvant treatment			0.051
Long-course CRT (45/50.4 Gy)	16 (9/7)	304 (176/128)	
Short-course radiotherapy	2	5	
Systemic chemotherapy followed by CRT	1	39	
Adverse effects of neoadjuvant treatment			
≥ Grade 2 (%)	9 (47.4%)	134 (38.5%)	0.441
≥ Grade 3 (%)	1 (5.3%)	21 (6.0%)	1.000
Operative procedures			1.000
Sphincter-preserving surgery	13	243	
Abdominoperineal resection/Hartmann's procedure	6	105	
Pathological stage			0.687
Pathological complete response	4	60	
I	5	103	
II	3	89	
III	7	96	
Circumferential resection margin			1.000
Negative	19	342	
Positive	0	6	
Combined resection			0.487
No	16	307	
Yes	3	41	
Postoperative complications			0.448
No	15	237	
Yes	4	111	
Histological type			0.641
Well/moderate	17	323	
Poor/mucinous/signet	2	25	
Adjuvant treatment			0.031
No	15	182	
Yes	4	166	
FOLFOX/XELOX	2	80	
5-FU-related chemotherapy without oxaliplatin	2	86	

Data are presented as the number of patients or medians (range)

ASA American Society of Anesthesiologists, *CRT* chemoradiotherapy

Table 4 Clinical factors predicting postoperative complications of patients who received chemoradiotherapy

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Sex			0.230			
Female	1					
Male	1.357	0.825–2.231				
Age in years			0.375			
< 75	1					
≥ 75	0.606	0.195–1.852				
Co-morbidities			0.159			
No	1					
Yes	1.385	0.881–2.179				
ASA-performance status			0.009			0.046
1	1			1		
2/3	1.833	1.162–2.891		1.638	1.008–2.661	
Operation time, min			< 0.001			<0.001
< 350	1			1		
≥ 350	3.305	2.079–5.254		2.580	1.578–4.218	
Estimated blood loss, mL			< 0.001			
< 300	1			1		0.036
≥ 300	2.984	1.655–5.382		2.005	1.048–3.834	
Combined resection			0.005			0.062
No	1			1		
Yes	2.415	1.303–4.477		1.892	0.968–3.699	
Histological type			0.135			
Well/moderate	1					
Poor/mucinous/signet	1.818	0.830–3.983				
Adjuvant chemotherapy			0.134			
No	1					
Yes	1.407	0.900–2.199				

OR odds ratio, *CI* confidence interval, *ASA* American Society of Anesthesiologists

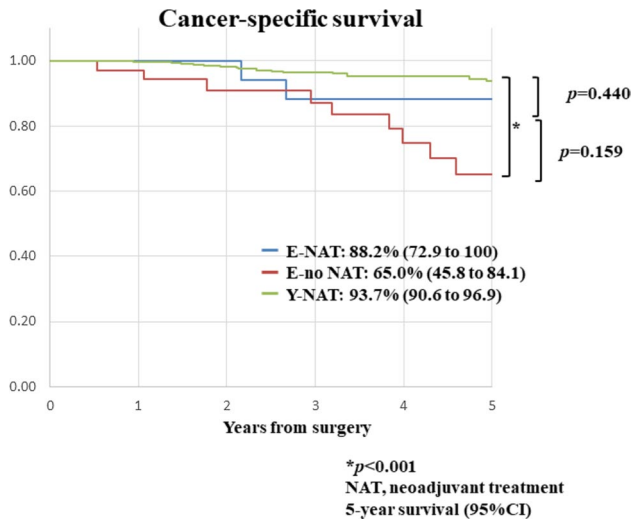

Fig. 2 Cancer-specific survival of elderly and younger patients

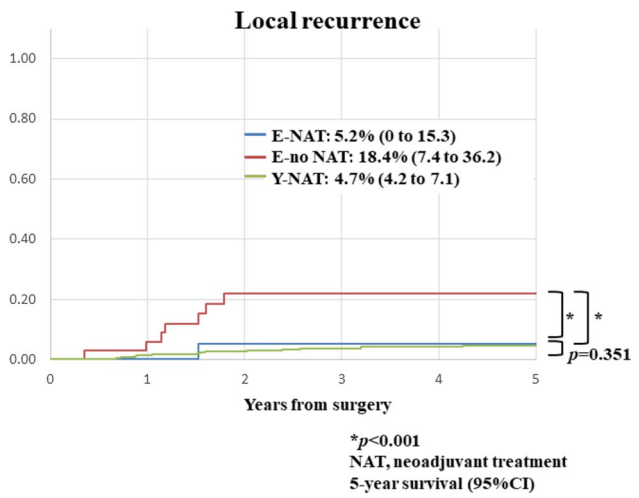

Fig. 3 Local recurrence rates in patients aged 75 years or older vs. and patients aged under 75 years

Geriatric Assessment score in elderly patients (≥ 75 years) with rectal cancer [22]. They argued that the study population had acceptable morbidity and rate of sphincter preservation using the score. Their study included only 15 elderly rectal cancer patients who received NAT, similar to the present study, which also included only 19 elderly patients treated with NAT. This number of patients was too small to draw any conclusion as to whether elderly patients with rectal cancer were suitable candidates for multimodal treatment, and further research is clearly needed.

To decide on the best treatment strategy for elderly patients with locally advanced rectal cancer, it is important to consider the advantages and disadvantages of a multimodal approach, including the risk of severe adverse events associated with NAT, the perioperative complication rate, the rate of sphincter preservation, and the rate of pCR. According to previous reports, the rate of postoperative complications ranged from 12.5 to 37%, the rate of grade 3 toxicity ranged from 12.5 to 34.9%, the rate of sphincter preservation ranged from 64 to 91.1%, and the pCR rate ranged from 14.7 to 21.8% [20–27]. In the present study, the rate of grade 3 toxicity was lower than that in the previous reports and the other rates were similar. Regarding the chronological distribution of the elderly patients treated with NAT, only three (16%) patients in the E-NAT group were treated with NAT within 6 years after the introduction of NAT in our institution, while 45% of the patients treated with NAT were 75 years of age or older in the later phase of this study period. After gaining experience with NAT for patients with locally advanced low rectal cancer, the indication for NAT was cautiously and gradually extended to elderly patients, which might be one of the reasons why the incidence of severe adverse effects was low in the present study. Moreover, elderly patients would be a heterogeneous population in terms of physiological tolerance, co-morbidity, and functional capacity, which may make it difficult to undergo standardized treatment. Currently, there is no clinically validated tool that can accurately predict treatment tolerance in elderly patients [26]. To prevent severe adverse events associated with NAT, case-by-case decision-making and individually tailored responses should be established by a multidisciplinary team consisting of specialists in each field.

According to previous reports, the 3–5-year overall survival of elderly rectal cancer patients after NAT ranged from 48.1 to 67.5%, but the 5-year CSS of these patients has rarely been reported [20, 22, 24, 28]. However, analysis of the CSS of elderly patients could be more important because of their likely increased risk of non-cancer-related death [26]. The 5-year CSS of the present E-NAT group was good, but not significantly different from that of the E-no NAT group. The reported 5-year LR rate ranged from 4 to 9%, similar to that in our series [21, 28]. The present study clearly showed that the local control effect of NAT was maintained in elderly rectal cancer patients.

The present study had some limitations. First, there were no clear criteria for selecting the elderly patients who were treated with NAT and this was a retrospective single-center study with a small number of elderly patients treated with NAT for locally advanced low rectal cancer. The odds ratio for postoperative complications in elderly patients treated with NAT was 0.606 compared with younger patients treated with NAT. Advanced age is generally considered an independent risk factor for postoperative complications [29, 30]. The discrepancy between the results of this study and those of previous studies was attributed to the small sample size and potential selection bias of elderly patients treated with NAT. Second, the background characteristics of the patients were potentially different among the three groups. The differences between the elderly patients treated with and those treated without NAT are described above, and differences also existed between the elderly patients treated with NAT and the younger patients treated with NAT. The ratio of female patients treated with NAT was significantly higher in the E-NAT group than in the Y-NAT group ($p = 0.032$). Notably, the average life span of women is longer than that of men and the risk of co-morbidity is lower in women than in men [31, 32]. As a result, elderly women were more frequently treated with NAT after case-by-case evaluation in this study. Moreover, the type of NAT was near-significantly different between the groups ($p = 0.051$), and the rate of adjuvant chemotherapy was significantly lower in the elderly patients than in the younger patients treated with NAT ($p = 0.031$). These differences between the groups might have influenced the results of the present study. Nevertheless, this study clearly demonstrated that certain elderly patients benefited from NAT, and the decision to give NAT to elderly rectal cancer patients should not be based solely on a patient's chronological age.

Conclusion

Based the findings of the present study, NAT should be considered as a treatment option for elderly patients with rectal cancer. It is crucial to establish clear criteria for selecting elderly rectal cancer patients who may derive benefit from NAT.

Author contributions TT and TN designed most of the study. TT analyzed the data. All coauthors contributed substantially to this study and fulfilled the requirements for authorship as per the guidelines of the International Committee of Medical Journal Editors. All authors have read and approved the final versions of the manuscript.

Compliance with ethical standards

Conflict of interest We have no conflicts of interest to declare.

Informed consent Additional informed consent was obtained from all participants whose identifying information is included in this article.

References

1. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731–40.
2. Breugom AJ, Van Gijn W, Muller EW, Berglund A, van den Broek CBM, Fokstuen T, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. Ann Oncol. 2015;26:696–701.
3. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish rectal cancer trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol. 2005;23:5644–50.
4. Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol. 2016;23:1–34.
5. Kotake K, Asano M, Ozawa H, Kobayashi H, Sugihara K. Tumour characteristics, treatment patterns and survival of patients aged 80 years or older with colorectal cancer. Colorectal Dis. 2015;17:205–15.
6. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics, 2006. CA Cancer J Clin. 2006;56:106–30.
7. Matsuda A, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H, Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in a study of 25 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol. 2008;2014(44):388–96.
8. Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg. 2006;203:865–77.
9. Bohac GC, Guaqueta D, Cheng DM, Aschengrau A, Hartshorn KL. Disparity in the use of combined modality therapy for rectal cancer in the older adult. J Geriatr Oncol. 2013;4:90–7.
10. Gérard JP, Conroy T, Bonnetain F, Bouché O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3–4 rectal cancers: results of FFCD 9203. J Clin Oncol. 2006;24:4620–5.
11. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudelko M, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol. 2004;72:15–24.
12. Nagasaki T, Akiyoshi T, Fujimoto Y, Konishi T, Nagayama S, Fukunaga Y, et al. Prognostic impact of neutrophil-to-lymphocyte ratio in patients with advanced low rectal cancer treated with preoperative chemoradiotherapy. Dig Surg. 2015;32:496–503.
13. Nagasaki T, Akiyoshi T, Fujimoto Y, Konishi T, Nagayama S, Fukunaga Y, et al. Preoperative chemoradiotherapy might improve the prognosis of patients with locally advanced low rectal cancer and lateral pelvic lymph node metastases. World J Surg. 2017;41:876–83.
14. Akiyoshi T, Ueno M, Matsueda K, Konishi T, Fujimoto Y, Nagayama S, et al. Selective lateral pelvic lymph node dissection in patients with advanced low rectal cancer treated with preoperative chemoradiotherapy based on pretreatment imaging. Ann Surg Oncol. 2014;21:189–96.
15. Cancer Therapy Evaluation Program (2017) Common terminology criteria for adverse events (CTCAE) v5.0. National Cancer Institute. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50.
16. Balducci L. Management of cancer in the older person: a practical approach. Oncologist. 2000;5:224–37.
17. 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;26:463–76.
18. Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer. 2012;118:3377–86.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–83.
20. Cai X, Wu H, Peng J, Zhu J, Cai S, Cai G, et al. Tolerability and outcomes of radiotherapy or chemoradiotherapy for rectal cancer in elderly patients aged 70 years and older. Radiat Oncol. 2013;8:86.
21. Tougeron D, Roullet B, Paillot B, Hamidou H, Tourani J, Bensadoun R, et al. Safety and outcome of chemoradiotherapy in elderly patients with rectal cancer : results from two French tertiary centres. Dig Liver Dis. 2012;44:350–4.
22. Suhool A, Moszkowicz D, Cudennec T, Vychnevskaia K, Malafosse R, Beauchet A, et al. Optimal oncologic treatment of rectal cancer in patients over 75 years old: results of a strategy based on oncogeriatric evaluation. J Visc Surg. 2018;155:17–25.
23. Ausili Cèfaro G, Genovesi D, Vinciguerra A, Augurio A, Di Tommaso M, Marchese R, et al. Effects of preoperative radiochemotherapy with capecitabine for resectable locally advanced rectal cancer in elderly patients. Tumori. 2012;98:622–9.
24. François E, Azria D, Gourgou-Bourgade S, Jarlier M, Martel-Laffay I, Hennequin C, 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;110:144–9.
25. Choi Y, Kim JH, Kim J-W, Kim JW, Lee K-W, Oh H-K, et al. Preoperative chemoradiotherapy for elderly patients with locally advanced rectal cancer-a real-world outcome study. Jpn J Clin Oncol. 2016;46:1108–17.
26. Jiang DM, Raissouni S, Mercer J, Kumar A, Goodwin R, Heng DY, et al. Clinical outcomes of elderly patients receiving neoadjuvant chemoradiation for locally advanced rectal cancer. Ann Oncol. 2015;26:2102–6.
27. Pasetto LM, Friso ML, Pucciarelli S, Basso U, Falci C, Bortolami A, et al. Rectal cancer neoadjuvant treatment in elderly patients. Anticancer Res. 2006;26:3913–23.
28. Jung B, Påhlman L, Johansson R, Nilsson E. Rectal cancer treatment and outcome in the elderly: an audit based on the Swedish rectal cancer registry 1995–2004. BMC Cancer. 2009;9:1–8.
29. Shahir MA, Lemmens VE, van de Poll-Franse LV, Voogd AC, Martijn H, Janssen-Heijnen ML. Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: a population-based study. Eur J Cancer. 2006;42:3015–21.

30. Perez DL, Caceres AN, Toscano NA, Casal NJ. Results of colon cancer surgery in patients over 75 years old. ANZ J Surg. 2018;88:11–5.
31. Abbott RD, Donahue RP, Kannel WB, Wilson PW. The impact of diabetes on survival following myocardial infarction in men vs women. The Framingham Study. JAMA. 1988;260:3456–60.
32. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res. 2010;11:122.