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Results of Tri-Modality Therapy for Rectal Cancer in Elderly Patients

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Abstract. *Background/Aim: Elderly cancer patients are more prevalent and require special attention. This study focused on the outcome of elderly (≥65 years) rectal cancer patients treated with tri-modality therapy. Patients and Methods: A total of 105 patients receiving neoadjuvant radio-chemotherapy and resection for locally advanced rectal cancers were retrospectively evaluated. Nine characteristics were analyzed for loco-regional control (LRC), metastases-free survival (MFS) and overall survival (OS) including tumor location, gender, age, performance status, radiotherapy technique, primary tumor/lymph node categories, downstaging and histological grading. Results: The 5-year rates of LRC, MFS and OS were 91%, 78% and 87%, respectively. Radio-chemotherapy was not completed in 12 patients (11%) due to toxicity; 18 patients (17%) experienced grade 3 toxicities. A total of 29 patients (28%) had surgical complications. On multivariate analyses, MFS was significantly associated with downstaging (p=0.003) and OS with lower histological grade (p=0.013). Conclusion: Tri-modality therapy resulted in promising outcomes and was tolerated reasonably well by elderly patients. Prognostic factors were identified that may help personalize future treatment.*

Due to demographic changes, the number of elderly cancer patients is constantly increasing (1). Many of these patients are unable to withstand common cancer treatments due to co-morbidities (decreased function of liver, kidneys and bone marrow) (2). Therefore, elderly patients require greater attention. It is often a challenge for the treating physicians to find the optimal balance between intensive treatment required to optimize survival from cancers and potentially serious toxicities. Side-effects may lead to discontinuation or, at least, interruption of treatment. For patients receiving radiotherapy, interruptions of the treatment of more than one week have been reported to have a negative impact on their prognoses (3, 4). More studies are required focusing particularly on elderly patients in order to better identify the most appropriate treatment regimens and avoid over- or under-treatment. The present study focused on elderly rectal cancer patients treated with neoadjuvant radio-chemotherapy followed by surgery.

Rectal cancer is one of the more common cancer types in Europe with incidences of 15-25 in 100,000 inhabitants per year (5). A very common treatment regimen for cancers of the lower (0-5.0 cm from the anal verge) and the middle (5.1-10.0 cm) third of the rectum include neoadjuvant radio-chemotherapy with doses of 50.4 Gy (5×1.8 Gy per fraction/week) plus concurrent 5-fluorouracil (5-FU) or capecitabine followed by surgery and postoperative chemotherapy (5-7). This regimen has also been used for rectal cancers of the upper third (10.1-15.0 cm) in patients with specific risk factors such as large tumors or extensive loco-regional lymph node metastases.

The present study evaluated outcomes in terms of loco-regional control (LRC), metastases-free survival (MFS), overall survival (OS), and the toxicities of this common treatment regimen in elderly patients (≥65 years). Additionally, this study aimed to identify prognostic factors associated with LRC, MFS and OS in this particular group.

Patients and Methods

A total of 105 elderly patients who received radio-chemotherapy for locally advanced non-metastatic rectal cancer between 2008 and 2018 were retrospectively analyzed. Twenty-three patients (22%) had stage II disease and 82 patients (78%) stage III disease. Planned radiotherapy doses were 50.4 Gy (5×1.8 Gy per week) to the tumor bed and pelvic lymph nodes. Planned concurrent chemotherapy included two cycles of 5-flourouracil (5-FU) alone (1000 mg/m^2/days 1-5) in 64 patients (61%), capecitabine alone (2×825

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mg/day during the period of radiotherapy) in 35 patients (33%), oxaliplatin alone (50-60 mg/days 1, 8, 22, 29) in 3 patients (3%), 5-FU plus oxaliplatin in 2 patients (2%) and capecitabine + oxaliplatin + bevacizumab in 1 patient (1%). All patients received a surgical resection after a median of 6.5 weeks (range=3-14 weeks), followed by up to six cycles of adjuvant chemotherapy.

Nine characteristics were analyzed with respect to associations with treatment outcomes in terms of loco-regional control (LRC), metastases-free survival (MFS) and overall survival (OS). These characteristics included tumor location (distance from the anal verge) (0-5.0 cm *vs.* 5.1-10.0 cm *vs.* 10.1-15.0 cm) (5), gender, age at the initiation of radiotherapy (≤72 years *vs.* ≥73 years, median age: 73 years), Karnofsky performance score (60-70% *vs.* 80-100%), radiotherapy technique (3D-conformal radiotherapy *vs.* intensity-modulated radiotherapy (IMRT) or volume-modulated arc therapy (VMAT)), clinical primary tumor category (cT1-2 *vs.* cT3-4), clinical lymph node category (cN0 *vs.* cN1-2), successful downstaging following radio-chemotherapy (no *vs.* yes) and histologic grading (grade 1-2 *vs.* grade 3). Patient characteristics are summarized in Table I. Successful downstaging was defined as a decrease by at least one stage according to the Union for International Cancer Control (UICC)) and was pathologically confirmed on surgical specimens. UICC-stage II is defined as T3-4 N0 M0 and stage III as T1-T4 N1-2 M0.

Univariate analyses with respect to LRC, MFS and OS were performed with the Kaplan–Meier method and the log-rank test. The characteristics that were significantly associated with treatment outcome ($p<0.05$) or showed a trend for such an association ($p<0.10$) were further included in multivariate testing using Cox regression analysis.

Table I. *Characteristics of the entire cohort of 105 patients.*

Characteristic	Numer of patients (%)
Tumor location	
0-5-0 cm	48 (46)
5.1-10.0 cm	47 (45)
10.1-15.0 cm	10 (10)
Gender	
Female	33 (31)
Male	72 (69)
Age at start of radiotherapy	
≤72 Years	52 (50)
≥73 Years	53 (50)
Karnofsky performance score	
60-70%	10 (10)
80-100%	82 (78)
Unknown	13 (12)
Radiotherapy technique	
3D-conformal radiotherapy	79 (75)
IMRT/VMAT	26 (25)
Clinical primary tumor category	
cT1-2	6 (6)
cT3-4	99 (94)
Clinical lymph node category	
cN0	23 (22)
cN1-2	82 (78)
Downstraging following radiochemotherapy	
No	30 (29)
Yes	75 (71)
Histologic grading	
Grade 1-2	73 (70)
Grade 3	20 (19)
Unknown	12 (11)

IMRT: Intensity-modulated radiotherapy; VMAT: volume-modulated arc therapy.

Results

Radio-chemotherapy could not be completed in 12 patients (11%) due to treatment–related toxicities. Radiotherapy included a planned total dose of 50.4 Gy that was completed in 104 patients (99%); radiotherapy was discontinued in 1 patient after 48.6 Gy due to grade 3 diarrhea and decreased performance status. Chemotherapy was completed in 95 patients (90%). In 10 patients (10%) chemotherapy had to be discontinued because of leucopenia (n=5), severe arterial hypertension (n=1), leucopenia+severe arterial hypertension (n=1), myocardial infarction (n=1), progressive polyneuropathy (n=1) or a paraneoplastic syndrome of inappropriate antidiuretic hormone secretion (n=1). In total, 18 patients (17%) experienced at least one grade ≥3 acute radio chemotherapy-related toxicity. Hematological toxicity (n=6), proctitis (n=4) and diarrhea (n=3) were the three most frequent toxicities. Postoperative complications occurred in 29 patients (28%). The three most frequent complications were wound-healing problems (n=9), anastomotic leakage (n=6) and pneumonia (n=4). One patient died in the night after surgery of an unknown reason.

On univariate analysis, none of the nine investigated characteristics was significantly associated, or showed a trend, with LRC (Table II). Therefore, no multivariate analysis was performed for LRC. On univariate analysis of MFS, successful downstaging following radio-chemotherapy was associated with improved MFS ($p=0.001$) (Table III). On subsequent Cox regression analysis, successful downstaging remained significant (risk ratio=4.58, 95% confidence interval=1.70-13.51, $p=0.003$). On univariate analysis of OS, improved treatment outcome was significantly associated with lower (G1-2) histologic grade ($p=0.005$) (Table IV). In addition, a higher Karnofsky performance score (80-100%) showed a trend towards better OS ($p=0.074$). Both characteristics were included in a Cox regression analysis, where the histologic grade was significant (risk ratio=7.45, 95% confidence interval=1.57-39.78, $p=0.013$) and the performance score did not reach significance (risk ratio=4.61, 95% confidence interval=0.64-23.26, $p=0.11$).

Discussion

Elderly cancer patients have been recognized as a group that is gaining importance and may require an adjustment of common treatment regimens taking into account the higher rates of significant co-morbidities and the reduced function of organs

Table II. *Loco-regional control rates*.

Characteristic	1 year (%)	2 years (%)	3 years (%)	4 years (%)	5 years (%)	*p*-Value
Entire cohort	100	91	91	91	91	
Tumor location						
0-5-0 cm	100	92	92	92	92	
5.1-10.0 cm	100	88	88	88	88	
10.1-15.0 cm	100	100	100	100	n.a.	0.63
Gender						
Female	100	83	83	83	83	
Male	100	94	94	94	94	0.20
Age at start of radiotherapy						
≤72 Years	100	94	94	94	94	
≥73 Years	100	90	90	90	90	0.45
Karnofsky performance score						
60-70%	100	100	100	n.a.	n.a.	
80-100%	100	92	92	92	92	0.53
Radiotherapy technique						
3D-conformal radiotherapy	100	93	93	93	93	
IMRT/VMAT	100	88	88	n.a.	n.a.	0.29
Clinical primary tumor category						
cT1-2	100	100	100	100	n.a.	
cT3-4	100	91	91	91	91	0.57
Clinical lymph node category						
cN0	100	95	95	95	95	
cN1-2	100	90	90	90	90	0.70
Downstraging following radiochemotherapy						
No	100	87	87	87	87	
Yes	100	94	94	94	94	0.30
Histologic grading						
Grade 1-2	100	96	96	96	96	
Grade 3	100	92	92	92	n.a.	0.49

IMRT: Intensity-modulated radiotherapy; VMAT: volume-modulated arc therapy; n.a.: not available.

(2). There is an increasing interest in research to improve the outcomes of these patients and tailor treatment regimens to their individual needs in different oncologic settings (8-13). Rectal cancer is common in this age group (1). Considerable research has been carried out to achieve better outcomes of patients treated for rectal cancer (14-19). However, most studies did not address the specific needs of elderly patients with rectal cancer. Therefore, the present study was performed to evaluate outcomes and toxicities of patients aged ≥65 years who received the "standard" treatment for locally advanced rectal cancer similar to that prescribed to younger patients (5-7).

The results of the present study were promising with LRC-, MFS- and OS-rates of 91%, 78% and 87%, respectively, at 5 years, particularly when taking into account that 78% of the patients had stage III disease. In a randomized trial of rectal cancer patients with stage II or III disease aged 30 to 76 years (median age=62 years) that compared preoperative radio-chemotherapy (50.4 Gy plus two cycles of 5-FU) followed by surgery and chemotherapy to surgery followed by radio-chemotherapy, the 5-year rates of LRC, MFS and OS in the preoperative arm were 94%, 64% and 74%, respectively (20). However, in the preoperative arm of the trial, only 54% of the patients had stage III disease compared to 78% in the present study. A more recent randomized trial compared preoperative short-course radiotherapy alone with 5x5 Gy to longer-course preoperative radio-chemotherapy (50.4 Gy plus continuous infusion of 225 mg/m^2 5-FU per day) in patients with stage II or III rectal cancer (21). In the longer-course arm, patients had a median age of 64 years (range=29-82 years), and the 5-year rates of LCR, MFS and OS were 94%, 70% and 70%, respectively. Since only 38% of their patients had stage III disease, treatment outcomes would be expected to be more favorable than in our current study (21). Successful downstaging was achieved in 45% of the patients receiving longer-course preoperative radio-chemotherapy in the randomized trial, which was a much lower rate than in our present study (71%) (21). This may be partially explained by the fact that in our study, 99% of the patients received the planned radiation dose of 50.4 Gy and 89% the planned chemotherapy compared to 93% and 84% in the randomized

Table III. *Metastases-free survival rates*.

Characteristic	1 year (%)	2 years (%)	3 years (%)	4 years (%)	5 years (%)	*p*-Value
Entire cohort	93	80	78	78	78	
Tumor location						
0-5-0 cm	98	81	77	77	77	
5.1-10.0 cm	88	75	75	75	75	
10.1-15.0 cm	100	100	100	100	n.a.	0.24
Gender						
Female	92	85	85	85	85	
Male	94	79	75	75	75	0.39
Age at start of radiotherapy						
≤72 Years	90	77	77	77	77	
≥73 Years	96	83	78	78	78	0.79
Karnofsky performance score						
60-70%	100	100	100	n.a.	n.a.	
80-100%	93	78	78	78	78	0.23
Radiotherapy technique						
3D-conformal radiotherapy	93	79	76	76	76	
IMRT/VMAT	95	89	89	n.a.	n.a.	0.50
Clinical primary tumor category						
cT1-2	100	100	100	100	n.a.	
cT3-4	93	79	77	77	77	0.31
Clinical lymph node category						
cN0	95	76	76	76	76	
cN1-2	93	82	79	79	79	0.88
Downstraging following radiochemotherapy						
No	85	60	52	52	52	
Yes	97	89	89	89	89	**0.001**
Histologic grading						
Grade 1-2	92	82	79	79	79	
Grade 3	93	85	85	85	n.a.	0.77

IMRT: Intensity-modulated radiotherapy; VMAT: volume-modulated arc therapy; n.a.: not available; bold: significant *p*-values.

trial. Moreover, the overall rate of surgery-related complications in our study was lower than in one of the previous randomized trials (28% *versus* 36%) (20) as were the rates of radio-chemotherapy-related grade ≥3 acute toxicities (17% *versus* 27%) (20). However, the present study is retrospective in nature and some complications or toxicities may have been missed. In spite of this, it appears that the elderly patients within the present study tolerated the tri-modality treatment sufficiently well with favorable survival and disease control.

In addition, prognostic factors were identified in this cohort of patients that may be used for personalization of the treatment. These factors included successful downstaging and histologic grade on both univariate and multivariate analyses and performance status on univariate analysis. These characteristics have been described previously as prognostic factors in patients of different age groups irradiated for rectal cancer (17, 19, 22).

In summary, radio-chemotherapy plus surgery resulted in promising outcomes in terms of LRC, MFS and OS when compared to previous randomized trials in patients of various ages. The tri-modality treatment given in the present study appeared sufficiently well tolerated by the elderly patients. Prognostic factors were identified that may help personalizing treatment in future studies.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there are no conflicts of interest related to this study.

Authors' Contributions

M.T., S.J., S.E.S. and D.R. participated in the design of the study. M.T., S.J. and D.R. provided data. S.E.S. and D.R. performed the analyses. M.T., S.J., S.E.S. and D.R. performed the interpretation of the data. D.R. and S.E.S. drafted the manuscript, which was reviewed and approved in its final form by all Authors.

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Table IV. *Overall survival rates*.

Characteristic	1 year (%)	2 years (%)	3 years (%)	4 years (%)	5 years (%)	*p*-Value
Entire cohort	99	96	87	87	87	
Tumor location						
0-5-0 cm	98	95	87	87	87	
5.1-0.0 cm	100	96	79	79	79	
10.1-15.0 cm	100	100	100	100	n.a.	0.59
Gender						
Female	100	100	90	90	90	
Male	99	94	86	86	86	0.44
Age at start of radiotherapy						
≤72 Years	100	100	91	91	91	
≥73 Years	98	92	82	82	82	0.22
Karnofsky performance score						
60-70%	90	90	68	n.a.	n.a.	
80-100%	100	96	87	87	87	0.074
Radiotherapy technique						
3D-conformal radiotherapy	99	95	85	85	85	
IMRT/VMAT	100	100	100	n.a.	n.a.	0.28
Clinical primary tumor category						
cT1-2	100	100	100	100	n.a.	
cT3-4	99	96	86	86	86	0.49
Clinical lymph node category						
cN0	100	88	88	88	88	
cN1-2	99	99	87	87	87	0.82
Downstraging following radiochemotherapy						
No	100	95	80	80	80	
Yes	99	96	90	90	90	0.45
Histologic grading						
Grade 1-2	100	98	91	91	91	
Grade 3	95	86	66	66	n.a.	**0.005**

IMRT: Intensity-modulated radiotherapy; VMAT: volume-modulated arc therapy; n.a.: not available; bold: significant *p*-value.

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