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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Clinical outcomes in elderly rectal cancer patients treated with neoadjuvant chemoradiotherapy: impact of tumor regression grade

Tumor regression grade after neoadjuvant chemoradiotherapy in elderly rectal cancer patients

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Abstract

Purpose The effect of neoadjuvant chemoradiotherapy (CRT) and the relationship between pathological complete response (pCR) with clinical outcomes has been evaluated in elderly locally advanced rectal cancer (LARC) patients.

Methods We retrospectively analyzed 117 LARC patients treated with conformal RT and concomitant fluoropirimidine-based chemotherapy. A dose of 4500 cGy, on the pelvis, up to 5500 cGy on the tumor was delivered. Multidisciplinary evaluation, including geriatric assessment, was previously performed to identify frail patients unsuitable for combined treatment.

Results The median age was 75 (range 70–88 years), and 103 (88%) patients had ECOG Performance Status (PS) = 0. All patients except one completed CRT. Ten (8.5%) patients temporarily suspended CRT for acute severe hematologic complication, diarrhea and/or proctitis and hypokalemia. Of the 103 operated patients (88%), a pCR, according to Mandard tumor regression grade (TRG) score, was obtained in 28 patients (27.2%), with TRG1-2 rate of 43.7%. The 3- and 5-year overall survival (OS) rates were 80.2% ± 4.2% and 68.0% ± 5.2%, 72.4% ± 4.5% and 57.8% ± 5.2% for disease-free survival (DFS), and 92.2% ± 2.8% and 89.5% ± 3.9% for loco-regional control. Patients with TRG1-2 had 3- and 5-year OS rates of 84.1% ± 6.6% and 84.1% ± 6.6% compared with 82.8% ± 5.5% and 67.7% ± 7.2% for patients with TRG3-5 ($p = 0.012$). The 3- and 5-year DFS rates for patients with TRG1-2 were 77.6% ± 7.0% and 74.2% ± 7.5% compared with 70.9% ± 6.3% and 54.7% ± 7.3% for patients with TRG3-5 ($p = 0.009$).

Conclusion Our results reported good tolerability and clinical outcomes of neoadjuvant CRT, with a benefit in patients ≥ 70 years, confirming the prognostic role of pCR on clinical outcomes.

Keywords Good performance status · Older patients · Outcomes · Rectal cancer · Radiotherapy · Pathological response

Introduction

Nowadays, colorectal cancer remains the second cause of death, affecting similarly both young and older patients, with a two-thirds of cases in patients aged more than 65 years (Siegel et al. 2013). Although this incidence is expected to be increased in the future, considering the mean-life expectancy, older patients were not always represented in clinical trials as the youngers, and they often resulted less aggressively treated, requiring individualized treatment approaches, because of their frailty and co-morbidities (Bergquist et al. 2016).

Regarding the prevalence of comorbidity and the related functional dependence, elderly patients are currently considered a heterogeneous population and a classification into young old (age 65–75 years), old (76–85), and oldest old (> 85) has been proposed for population studies (Balducci 2006).

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In addition, considering the important amount of elderly patients with cancer, the International Society of Geriatric Oncology (SIOG) recommended that patients with rectal cancer aged more than 65 years old should be evaluated for the most common physiological side-effects and physical and mental ability (Papamichael et al. 2015).

Neoadjuvant chemoradiotherapy (CRT), followed by total mesorectal excision (TME), is a standard of care for locally advanced rectal cancer (LARC) patients, with an increase in complete pathological response (pCR) rates (Kapiteijn et al. 2001). Furthermore, response to treatment, defined through tumor regression grade (TRG), might predict clinical outcomes, as disease-free survival (DFS) and overall survival (OS) (Martin et al. 2012).

Even if there are few clinical trials involving older patients with rectal cancer, they are always more often treated with curative intent, thanks to the increasing number of patients in good performance status (PS), half of them able to receive standard treatment (Guillerme et al. 2014). Furthermore, several studies reported that advanced age is neither a risk for complications after surgery nor after radiotherapy (RT), underlying the possibility to perform a treatment with curative intent (Jiang et al. 2015; Pfeffer and Blumenfeld 2017).

Moreover, the use of concurrent capecitabine had demonstrated its efficacy, with a low toxicity profile and safety, also in older patients, with the further advantage of the oral administration (Scheithauer et al. 2003).

In this contest, the aim of our retrospective analyses was to assess clinical outcomes and toxicities of neoadjuvant CRT in elderly patients (≥ 70 years) with LARC treated in our Institution.

Methods and materials

From 2001 to 2019, 117 (M:80; W:37) LARC patients, with ≥ 70 years, were treated in our Radiotherapy Department and retrospectively analyzed. Information about comorbidities and PS were carried out before starting CRT. Fragility was assessed by radiation oncologist according to the G8 scale and frail patients (G8 scale ≤ 14 score) underwent a geriatric assessment. Appropriate supportive therapy was then prescribed according to patient's comorbidities. Frail patients considered unfit for long-course CRT by geriatric assessment were proposed for short course RT and not included in this study. RT was performed by three dimensional (3D) conformal technique, with a dose of 4500 cGy (180 cGy/die) on the pelvic nodes, plus a sequential boost of 540 cGy (180 cGy/die; total dose 5040 cGy), or a concomitant boost of 1000 cGy (100 cGy/die, 2 times/week; total dose 5500 cGy) on the tumor and the corresponding mesorectum. During the last two years, a simultaneous integrated boost with intensity modulated radiotherapy (SIB-IMRT) procedure was used, to deliver a total dose of 5500 cGy (220 cGy/die).

All patients received concurrent chemotherapy with different schedules: 5-fluoracil and leucovorin (750 mg/mq-1000 mg/mq, 24 h-continous intravenous infusion, die 1–4) or capecitabine (825 mg/mq, 2 times a day, 7 days a week). Moreover, in patients enrolled in two Italian trials, cisplatin (Plafur: cisplatin 60 mg/mq, die 1 and 29, and 5-FU, 1,000 mg/mq, 24 h-continous intravenous infusion, die 1–4 and 29–32) or oxaliplatin (Xelox: capecitabine 1300 mg/mq/die, in a chronomodulated schema, 3 times a day [25% of the daily dose at 8 a.m., 25% at 6p.m., and 50% at 11 p.m.], 7 days a week, plus oxaliplatin 130 mg/mq per day, 2-h infusion on days 1, 19, and 38) had been added.

Six to eight weeks after CRT, surgery was performed with curative intent. Mandard TRG score was used to evaluate the pathologic response (Vecchio et al. 2005). The absence of residual cancer in resected specimen (TRG 1) was defined as pathologic complete response (pCR).

Acute and late toxicities were assessed using the Radiation Therapy Oncology Group (RTOG) scale and the RTOG/European Organization for Research and Treatment of Cancer (EORTC) late radiation scoring system (Cox et al. 1995). The 3-year and 5-year overall survival (OS), disease-free survival (DFS) and loco-regional control (LC) rates were calculated using the Kaplan–Meier method (Cox 1972). The follow-up was defined as the time interval between surgery and death for OS curve, the time interval between surgery and the first verified event for the DFS curve, and as the time between surgery and the local recurrence for the LC curve. Regards to patients who were not affected by any of these events, the observation time interval was defined as the period from surgery to the last follow-up examination. A p value of 0.05 or less was considered statistically significant. All statistical analyses were performed using SPSS software 13.0 (SPSS, Chicago, IL).

All research was performed in accordance with the actual version of declaration of Helsinki. No further ethical approval was necessary because this retrospective study was anonymous and non interventional.

Results

Patient population, treatment compliance and acute toxicity

A total of 117 LARC patients, aged ≥ 70 years, were included in the study. Tumor and treatment characteristics are reported in Table 1. The median age was 75 years (range 70–88 years): 80 (68.4%) patients were male, 37 (31.6%) female. One hundred and three (88%) patients had ECOG

Table 1 Tumor and patient characteristics ($n = 117$)

Age (years), median (range)	75 (70–88)		
	n (%)		*n* (%)
Gender		Type of surgery	
Male	80 (64.8)	AR	76 (65)
Female	37 (31.6)	TEM	1 (0.8)
		APR	23 (19.7)
Clinical stage		Other	3 (2.5)
T		No surgery	14 (12)
T2	14 (12)		
T3	97 (83)	Margin status	
T4	6 (5)	R0	98 (83.8)
N		R1	3 (2.5)
N0	36 (30.8)	No surgery	14 (12)
N1	59 (50.4)	Missing	2 (1.7)
N2	22 (18.8)		
		TRG	
Grade		1	28 (27.2)
1	17 (14.5)	2	17 (16.5)
2	68 (58.1)	3	35 (34)
3	5 (4.3)	4	18 (17.4)
NOS	9 (7.7)	5	2 (1.9)
Missing	18 (15.4)	Missing	3 (3)
Distance from anorectal ring (mm)		Pathological stage	
0–30	38 (32.5)	T	
31–50	29 (24.8)	T0	25 (24.2)
> 50	37 (31.6)	T1	8 (7.7)
Missing	13 (11.1)	T2	31 (30.1)
		T3	36 (35)
Radiotherapy total dose (cGy)		T4	0 (0)
5040	73 (62.4)	Missing	3 (3)
5500	44 (37.6)		
		N	
Chemotherapy schedule		N0	83 (80.6)
5-FU or Capecitabine	81 (69.2)	N1	14 (13.6)
Plafur	28 (24)	N2	2 (1.9)
Xelox	8 (6.8)	Missing	4 (3.9)

NOS not otherwise specified, *5-FU* 5-Fluorouracil, *Plafur* Cisplatin and 5-FU, *Xelox* Capecitabine and Oxaliplatin, *AR* anterior resection, *TEM* transanal endoscopic microsurgery, *APR* abdominoperineal resection, *R0* absence of tumor cells into resection margin, *R1* tumor cells into resection margin, *TRG* tumor resection grade

PS 0. Information on the main comorbidities was available in 93 patients (79.5%). Forty-eight (41%) patients were affected by hypertension or cardiovascular disease, with or without others concomitant comorbidities. Eleven (9.4%) patients were affected by diabetes and four (3.5%) by chronic obstructive pulmonary disease. Thirty (25.6%) patients had no comorbidities. All patients were considered suitable for CRT according to G8 scale and the geriatric assessment.

Ninety-seven patients (83.0%) presented cT3 tumors: 31 patients cT3N0, 66 patients cT3N + . Thirty-eight patients (32.5%) presented the tumor at a distance from the anorectal ring shorter than 30 mm, 29 (24.8%) between 31 and 50 mm, 37 (31.6%) at a distance longer than 51 mm.

Seventy-three (62.4%) patients were treated with a sequential boost, with a total dose of 5040 cGy, whereas a dose intensification with concomitant or simultaneous boost (total dose = 5500 cGy) was delivered in 44 patients (37.6%). All patients received concomitant chemotherapy: 5-fluoracil and leucovorin or capecitabine in 81 patients (69.2%); an intensification with the addition of cisplatin or oxaliplatin was given to 28 (24%) and 8 (6.8%) patients, respectively.

All patients completed neoadjuvant CRT, except one who died for heart attack during treatment. The cardiotoxicity of 5-FU could be related to this death, even if a sure correlation of this event with chemotherapy has not be proven.

Lower gastrointestinal toxicity was the most frequent acute side effect experienced: grade 1 in 39 patients (33.3%), grade 2 in 39 patients (33.3%) and grade 3 toxicity occurred in two patients (1.8%). Acute skin toxicities were reported as grade 1 in 22 patients (18.8%), grade 2 in 31 patients (26.5%) and grade 3 in only a patient (0.9%). Acute genitourinary (GU) toxicities were registered in 26 (22.2%, grade 1) and 3 patients (3.6%, grade 2), respectively. Acute hematologic toxicities were reported in 10 cases as grade 1 toxicities (half of them with leuconeutropenia, three cases of anemia and two of thrombocytopenia), 10 cases of grade 2 toxicities (five leucopenia, two anemia and three thrombocytopenia) and three cases of grade 3 toxicities (two cases of thrombocytopenia and a case of leucopenia). Ten (8.5%) patients temporarily suspended CRT (median days = 6, range = 5–18) for acute severe hematologic complication (grade 2–3 thrombocytopenia, grade 2 anemia, grade 2–3 leucopenia), diarrhea and/or proctitis, and hypokalemia. Of them, Capecitabine was administered in eight (6.8%) patients, whereas for the remaining two the first received Oxaliplan and Capecitabine (Xelox) and the last one Cisplatin and a 24 h-continous intravenous infusion of 5-FU (Plafur).

There were no reported severe neurological and liver toxicities.

Surgery and pathologic response

Surgery with curative intent including TME, abdominoperineal resection (APR) or transanal endoscopic microsurgery (TEM) was performed. TEM was made only for one patients with major clinical responses (yT0-T1). Fourteen patients (12%) did not undergo surgery: 11 patients for decline of PS and/or re-considered for high risk surgical complications, one died patient for heart attack, one patient for progression disease (peritoneal carcinosis). One patient got a clinical complete response and refused surgery.

Of the 103 operated patients (88%), a pathological complete response (TRG 1) was obtained in 28 patients (27.2%; 27 patients reporting pT0N0 and one patient with pT0N1), whereas a near to pathological complete response (TRG 2) was obtained in 17 patients (16.5%).

Post-operative complications occurred in 14 patients (13.5%) as three cases (2.9%) of wound dehiscence, two abscesses (1.9%) and nine cases (8.7%) of different complications, also with episodes of fistulae.

Late toxicity and outcomes

With a median follow-up of 45 months (range 6–163), 94 patients (80.3%) were evaluated for late toxicities. Thirty (31.9%) patients presented stoma, 23 of them undergoing an APR procedure and six patients not recanalyzed; a patient underwent APR for local relapse, after a prior anterior resection (AR), that caused a definitive stoma. Late rectal toxicity in terms of sphincter incontinence occurred in eleven (11.7%) patients and six (6.4%) patients reported moderate diarrhea with more than five bowel movements per day (G2 toxicity RTOG/EORTC scale). Only one patient presented late skin toxicity ≥ grade 3 and two late GI toxicity ≥ grade 3.

Four patients died for cardiac arrest, a patient for stroke and 11 patients for metastases. Unfortunately, we were not able to state if cardiac arrest was straight caused by 5-FU based chemotherapy. No previous cardiac events were reported in the medical history, although two of were affected by hypertension with good pharmacological benefit.

The 3-year OS, DFS and LC rates were 80.2% ± 4.2%, 72.4% ± 4.5% and 92.2%% ± 2.8%, respectively Fig. 1. The 5-year OS, DFS and LC rates were 68.0% ± 5.2%, 57.8% ± 5.2%, 89.5% ± 3.9%, respectively. Figure 2 shows the 3- and 5-year OS and DFS for patients with TRG1-2 compared to TRG3-5. Patients with TRG1-2 had significantly better OS, with 3- and 5-year rates of 84.1% ± 6.6% and 84.1% ± 6.6% compared with 82.8% ± 5.5% and 67.7% ± 7.2%, respectively, for patients with TRG3-5 ($p = 0.012$). A statistically significant difference in favor of TRG1-2 patients has also been reported for the 3- and 5-year DFS rates: 77.6% ± 7.0% and 74.2% ± 7.5% compared with 70.9% ± 6.3% and 54.7% ± 7.3%, respectively, for patients with TRG3-5 ($p = 0.009$).

Univariate analysis aiming to correlate clinical outcomes (OS, DFS and LC) with tumor length and distance from the anorectal ring, cN, cT and pN stage was performed, but a statistically significant correlation was not found for any of the analyzed. Stratification by TRG groups was not possible due to the population size.

Discussion

Nowadays, all malignancies affect older patients, with more than one-third occurring in patients aged more than 70 years (CRUK 2020). Older patients are often under-represented in clinical trials, with under-treatments and poorer outcomes respect to the youngers (Bergquist et al. 2016). Considering the heterogeneity of included ages and the performance

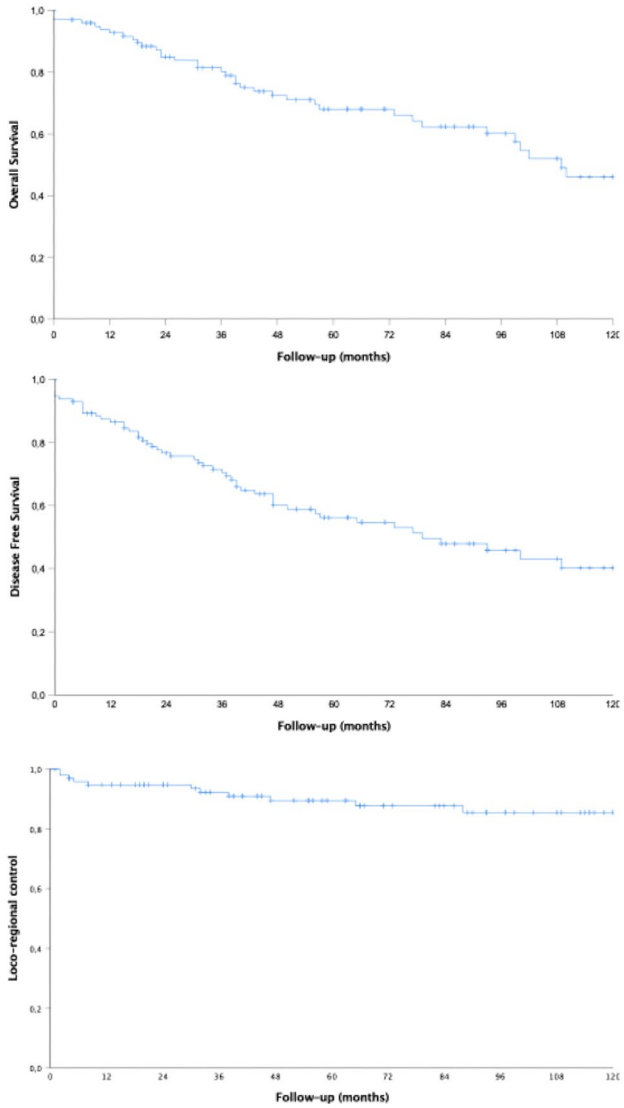

Fig. 1 Kaplan–Meier curves of cumulative overall survival, disease-free survival and loco-regional control for all patients

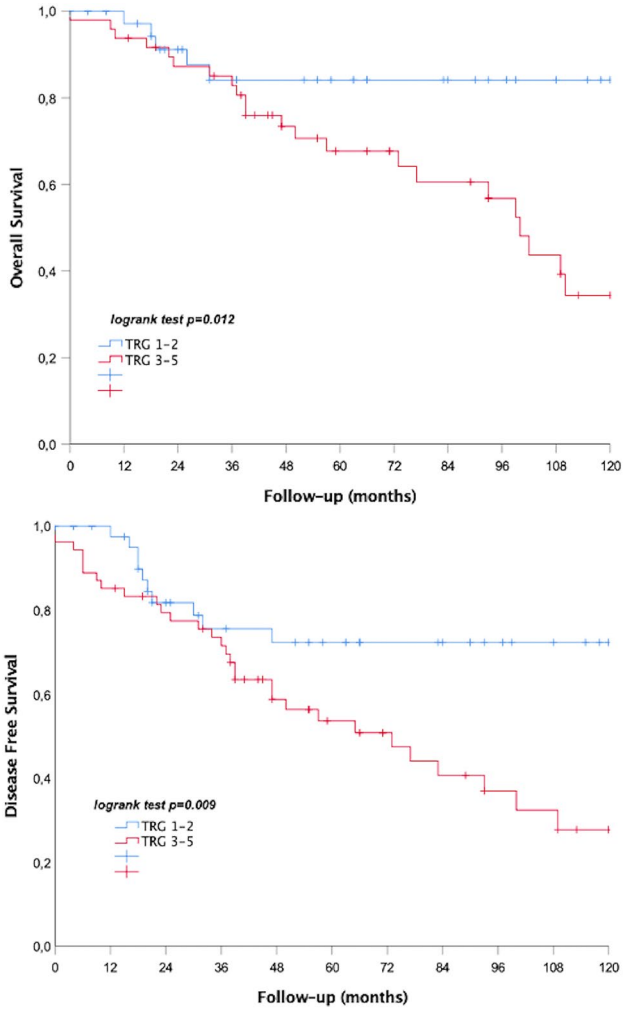

Fig. 2 Kaplan–Meier curves of cumulative overall survival and disease-free survival for patients with TRG1-2 and with TRG3-5

status of this patient's category, a personalized and tailored approach is necessary to be considered, to guarantee the best treatment choice for a curative intent.

Regards to rectal cancer, neoadjuvant long-course CRT and short-course RT (5 × 5 Gy), followed by radical surgery, are standards of care for patients with LARC, related to the risk factors for recurrence (Kapiteijn et al. 2001). Even if preoperative RT decreased local recurrence rate in patients aged > 70 years, in some situations, RT is used less frequently in older patients compared to young patients (Martijn and Vulto 2007). To effort the good results obtained also in older patients with LARC, several studies assessed that preoperative RT or CRT achieved a reduction in local recurrence and improved survival (Åsli et al. 2017; Vironen et al. 2004; Cai et al. 2013). The results of our retrospective analyses demonstrated that neoadjuvant CRT followed by surgery was well tolerated in older patients, reaching a TRG rate as for the youngest. Furthermore, thanks to the advance of modern RT, allowing an acceptable dose to adjacent organs at risk as small bowel, acute lower gastrointestinal toxicity could be reduced, attenuating the possibility of delay or interruption in CRT (Teoh and Muirhead 2016). On the other hand, as reported by many authors, performing surgical procedures could be debating. In fact, surgery could achieve good results in patients aged more than 80 years, with better survival compared to not-operated patients (Bhangu et al. 2014), as well as worse survival associated with higher rate of complications (Shahir et al. 2006; Margalit et al. 2011).

This retrospective analysis showed a good tolerability for older patients not only of neoadjuvant CRT but also of surgery, reporting a rate of 8.5% of severe acute toxicities requiring CRT interruption but with a recovery, a compliance for surgery in 86.4% of patients (89) and a

12% of post-operative complications. Considering the rate of CRT interruption, related to chemotherapy and/or radiotherapy toxicity, it could be favorable to pursue a treatment individualization. Indeed, pre-frail patients were not evaluated as specific subgroup in our analysis and this may have had an impact on treatment adherence. The percentage of acute toxicity reported in our study was inferior respect to others, as shown in Table 2, with toxicities ≥ G3 occurring only in a case (0.9%) for skin toxicity, 2 cases (1.8%) of GI and 3 cases (2.6%) of hematologic toxicity (thrombocytopenia and leucopenia) (François et al. 2014; Tougeron et al. 2014; Choi et al. 2016; Sung et al. 2019). This could be related to a selection of patients for a long-course CRT with good ECOG PS (0 = 88%), thanks to the multidisciplinary pre-treatment clinical evaluation, while short-course RT is usually proposed in patients with poor clinical conditions in our Institution.

The rate of permanent stoma was in line with literature, as reported in Table 2, this data is particularly significant in our analysis, taking into account that a 32.5% of patients had a tumor at a distance shorter than 30 mm from the anorectal ring, confirming the benefit of neoadjuvant CRT in terms of sphincter preserving-surgery. All patients with fecal incontinence underwent anterior resection. Nevertheless, since all patients were equally distributed in the 3 subgroups according to the distance of the tumor from the anorectal ring (< 30 mm, 31–50 mm, > 51 mm) and due to the small number of the population, a statistical correlation of the fecal incontinence rate with the type or surgery or to the distance of the tumor from the anorectal ring cannot be proven in our analysis. Finally, the low rate of postoperative complications occurring in fourteen patients (13.6%), as wound dehiscence, abscesses or fistulae, seems to confirm surgical tolerability. Our percentage was in line with that of younger patients (François et al. 2014).

Regarding pCR rate, our results (27.2%) were similar to other rates reported in literature, as the 14.7% of François et al. (2014), 14.8% of Sung et al. (2019) and 16% of Jiang et al. (2015) (Table 2). Moreover, it is well known the relationship between pCR and clinical outcomes. Good rates of pCR are directly related to DFS and OS (Sauer et al. 2004). Previous authors demonstrated as age > 70 year did not worsen clinical outcomes (Francois et al. 2014; Tougeron et al. 2014; Choi et al. 2016; Sung et al. 2019; Sauer et al. 2004).

OS and DFS in our study were in line with literature, as showed in Table 2, reporting 3- and 5-year OS rate of 80.2% ± 4.2% and 68.0% ± 5.2%, and 72.4% ± 4.5% and 57.8% ± 5.2% for DFS, respectively, 3- and 5- years LC rates 92.2%% ± 2.8% and 89.5% ± 3.9%, respectively.

Our results underlined how older patients were candidates for neoadjuvant CRT, with similar outcomes, even in non-clinical trial settings (Jiang et al. 2015).

Furthermore, we evaluated the possible correlation between TRG and clinical outcomes on elderly patients. This interesting estimation has been already performed in LARC patients irrespective of age. Rodel et al. suggested as TRG4 reached in 40 out of 340 patients, according to the Dworak classification, improved DFS after preoperative CRT (DFS = 86%, $p = 0.04$) (Rödel et al. 2005). This result on DFS was confirmed in the pooled analysis conducted by Maas et al., reporting a 5-year DFS rate of 83.3% for patients with pCR and 65.6% for those without pCR ($p < 0.0001$). The authors concluded as obtaining a pCR after CRT could be prognostically an indicator of favorable tumor profile, with an increased probability of DFS (Maas et al. 2010). TRG was also a predictor for local failure and OS (Vecchio et al. 2005). It significantly influences 5-year-local failure (TRG 1–2: 2% vs TRG 3–5: 17%, $p = 0.013$), metastasis-free survival (TRG 1–2: 91% vs TRG 3–5: 58%, $p < 0.001$) and OS (TRG 1–2: 89% vs TRG 3–5: 68%, $p = 0.004$) on 144 patients (Vecchio et al. 2005). Even if patients enrolled had a median age of 64 years (range 25–81), the authors reported a higher incidence of local failure for the youngest (< 50 years: 33%, 51–70 years: 9%, and > 70 years: 0%, $p = 0.001$) as well as a lower 5-year DFS (< 50 years: 45%, 51–70 years: 71%, and > 70 years: 8%, $p = 0.012$) (Vecchio et al. 2005). The association between pCR and clinical outcomes was confirmed in the meta-analysis of Martin and colleagues (Martin et al. 2012). Local failure resulted four times less expected to occur in complete responders respect to not-responders (OR 0.25, 0.10–0.59, $p = 0.002$), with a less frequent distant failure (OR 0.23, $p < 0.001$), a greater OS (OR 3.28, $p = 0.001$) and DFS (OR 4.33, $p < 0.001$) at 5 years for responders (Martin et al. 2012) Table 3.

To the best of our knowledge, this is the first study on elderly patients correlating TRG with clinical outcomes. We showed a statistically significant improvement in both OS ($p = 0.012$) and DFS ($p = 0.009$) for patients with a pCR respect to patients without pCR. This could validate the efficacy of CRT for elderly patients, with good rates of clinical outcomes for patients reaching pCR.

Conclusions

Our study showed good results in terms of tolerability and clinical outcomes in the elderlies, suggesting to establish similar treatment purpose as for the youngest. Neither acute toxicities causing a definitive CRT interruption nor surgical complications could worse patients quality of life. As for the youngest, pCR was confirmed as predictor of better outcomes also in elderly patients.

Table 2 Studies evaluating outcomes and toxicities in elderly rectal cancer patients

Author years	Study type	No.	Age	Treatment	Permanent stoma	R0	pCR	OS	DFS	Toxicities ≥ G3	
										Acute	Late
Tougeron et al. (2014)	R	125	> 70	nCRT + surgery	28%	90%	41% T down-staging	84% (2 yr) 76% (3 yr)	Not reported	15% (19 pts)	Not reported
François et al. (2014)*	R [Δ]	142	≥ 70	nCRT[Φ] + surgery	33%	88.6%	14.7%[¥]	80.5% (3 yr)	Not reported	25.6% (36 pts)	Not reported
Jiang et al. (2015)*	R	295	> 70	nCRT + surgery	Not reported	78%	16%	76% (5 yr)	Not reported	Not reported	
Choi et al. (2016)*	R	56	> 70	nCRT + surgery	8.9%	97.8%	15.6%[¥]	81.7% (3 yr) 67.5% (5 yr)	77.8% (3 yr) 60% (5 yr)	Diarrhea 16.1% (9 pts)	Neutropenia 1.8% (1pt)
Sung et al. (2019)*	R	310	≥ 70	nCRT + surgery[†]	9.7%	Not reported	14.8%	79.5% (5 yr)	65.5% (5 yr)	Hematologic: 16.1% (50 pts); non hematologic:14.8% (46 pts)	4.5% (14 pts)
Present study	R	117	≥ 70	nCRT + surgery	31.9%	83.8%	27.2%	80.2% (3 yr) 68.0% (5 yr)	72.4% (3 yr) 57.8% (5 yr)	5% (6 pts)	2.6% (3 pts)

no number, *R* resectability, *nCRT* neoadjuvant chemo-radiotherapy, *pCR* pathologic complete response, *OS* overall survival, *DFS* disease free survival, *R* retrospective, *yr* years

[Δ]Retrospective in phase III randomized trial

[Φ]Capecitabine or Capecitabine plus Oxaliplatin

*Compared to a younger population; nCRT: neoadjuvant chemoradiotherapy

[¥]Dworak regression grade

[†]Total mesorectal excision (TME)

Table 3 Studies evaluating outcomes in elderly rectal cancer patients according to pathological complete response

Author years	Study type	No.	Mean Age	pCR	No pCR	Local failure	Metastasis-free survival	DFS	OS
Rodel et al. (2005)	R	385	61	10.4% (TRG4)[¥]	52.2%, 3.8%, 15.3%, 8.3%	0% vs 4% vs 6% **$p = 0.33$**	–	86% vs 75% vs 63% **$p = 0.006$**	–
Vecchio et al. (2005)	R	144	64	32% (TRG 1–2)*	70% (TRG 3–5) *	2% vs 17% **$p = 0.013$**	91% vs 66% **$p = 0.004$**	91% vs 58% ***$p < 0.001$***	89% vs 68% $p =$ **0.004**
Maas et al. (2010)	P	3105	61	16%	84%	2.8% vs 9.7% ***$p < 0.0001$***	88.8% vs 74.9% ***$p < 0.0001$***	83.3% vs 65.6% ***$p < 0.0001$***	87.6% vs 76.4% ***$p < 0.0001$***
Martin et al. (2012)	MA	3363	60	24.4%	75.6%	0.7%	–	87.0% ***$p < 0.001$***	90.2% **$p = 0.001$**
Present study	R	117	75	43.7% (TRG 1–2)*	56.3% (TRG 3–5)*	–	–	77.6% vs 70.9% 74.2% vs 54.7% **$p = 0.009$**	84.1% vs 82.8% (3-y) 84.1% vs 67.7% (5-y) **$p = 0.012$**

Bold values indicate significance

no number, *pCR* pathological complete response, *DFS* disease free survival, *OS* overall survival, *R* retrospective, *P* pooled analysis, *MA* meta-analysis

*Mandard tumour regression grade

[¥]Dworak regression grade

Based on these considerations, age alone should not be a reason to deny a curative treatment. A multidisciplinary evaluation of older patients is recommended to offer the best individual approach, regards to their comorbidities and PS.

For this purpose, a prospective study involving a multidimensional geriatric assessment is currently underway in our Institution.

Author contributions LC, MT, GAC and DG designed and coordinate the study and the analysis. CR, LG, FCDG, ADP and SC collected the data. MDT and LC reviewed and approved data selection. CR and LC performed main data analysis and provided pictures elaboration. MM and MDN performed statistical data analysis. CR, MDT and LC drafted the manuscript. MT, CL and DG critically revised the study and the manuscript. All authors reviewed and approved the final manuscript.

Compliance with ethical standards

Conflict of interest None.

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