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Original Research Article

E_N_T_R_O_P_Y: Monocentric analysis of rectal cancer radio-chemotherapy treatment in patients of young age

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ABSTRACT

Purpose//objectives: A disproportionate incidence's increase of rectal cancer in patients younger than 50 years of age. The ESMO and NCCN recommendations are not age-specific and the literature is poor and conflicting. We decided to examine patients with rectal cancer treated in our centre in the last 15 years with curative neo-adjuvant radiochemotherapy comparing outcomes in the two groups under and over 55 years old.
Materials/methods: 788 rectal cancer patients were enrolled in this monocentric retrospective observational study (523 =>55 years and 265 < 55). All patients received neoadjuvant chemoradiation treatment. R statistical software v.4.1.3 was used for the entire analysis. The outcomes were death, local recurrence, and new distant metastases. Survival analysis was performed using the Kaplan-Meier method and the Log-rank was used to compare the two groups.
Results: All patients were classified in different risk groups, according to the ESMO 2017 rectal cancer clinical practice guidelines. 88 % of patients under 55 years old at the diagnosis belonged to the bad or advanced risk groups with an equal division. In patients over 55 years old, there was a clear dominance of the advanced risk class (62 % of the total). In multivariate analysis, OS and DFS decrease with increasing age and ESMO risk group. The other variables in multivariate were not significant. For Both OS, DFS and MFS, the curves separated significantly at 55 years of age, with a prevalence of metastasis development in the older group.
Conclusion: Elderly patients have a prevalence of advanced disease. Younger patients seem having a better OS at 3 and 5 years. ESMO risk group and age were the only variables affecting OS and DFS. Young patients have better MFS and DFS at 2 and 5 years than patients older than 55 years. The addition of oxaliplatin to fluoropyrimidine-based neoadjuvant chemotherapy resulted not significant in both groups.

1. Introduction

Over the past 10 years, the overall incidence of colorectal cancer in Europe has steadily increased, with annual increases ranging from 0.4 % to 3.6 % across different countries [1].

According to Eurostat, colorectal cancer is the second most common cancer in Europe, after breast cancer, and the second leading cause of cancer-related death, following lung [2].

Numerous studies have reported a disproportionate increase in the incidence of rectal cancer among patients younger than 50 years of age [1–5]. Possible reasons for this apparent "epidemic" of rectal cancer in younger patients could include the lack of routine screening in this age group, lifestyle factors common in economically developed countries (e.g., obesity, sedentary behavior, alcohol consumption, high intake of processed meats), as well as increasing urbanization and pollution. Although hereditary susceptibility and genetic factors should always be

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considered in young patients with rectal cancer, the majority of cases in this population are sporadic rather than familial [2,3,6,7].

The current standard of care for rectal cancer, as defined by the European Society for Medical Oncology (ESMO) [8] and the National Comprehensive Cancer Network (NCCN) [9] guidelines states surgical resection alone for very early and early risk groups and neoadjuvant radio-chemotherapy (NCRT) with subsequent surgical resection followed or not by systemic chemotherapy for intermediate, bad, or advanced risk groups.

However, these recommendations are not age-specific and are largely based on studies and data from patients over 50 years of age at diagnosis. There is limited literature on younger patients, and existing studies yield conflicting results when comparing outcomes between younger and older patients.

To address this gap in knowledge, we aimed to evaluate the outcomes of patients with rectal cancer treated at our center over the past 15 years with curative neoadjuvant radio-chemotherapy, comparing outcomes between patients under 55 years of age and those over 55 years of age.

2. Materials and methods

2.1. Patients

A total of 3,503 rectal cancer patients were assessed for eligibility in this study. Eight patients (0.2 %) were excluded because they were <18 years old at diagnosis. A total of 1,298 patients (37.1 %) were not included because they did not undergo concomitant CT with neoadjuvant radiotherapy. Additionally, 441 patients (12.6 %) underwent short-course radiotherapy; in 37 patients (1.1 %), the intent of the treatment was palliative. Furthermore, 312 patients (8.9 %) underwent adjuvant radiotherapy, and 619 patients (17.7 %) could not be included due to insufficient information. A flow-diagram of patient's selection is represented in Fig. 1.

A total of 788 rectal cancer patients were enrolled in this monocentric retrospective observational study (482 men and 306 women), all aged over 18 years at diagnosis. Among them, 523 patients (66.4 %) were aged 55 years or older, while 265 patients (33.6 %) were younger than 55.

Patient characteristics are reported in Table 1.

All patients underwent neoadjuvant chemoradiotherapy for low-medium-upper rectal cancer from January 2008 to July 2022 at the Fondazione Policlinico Universitario A. Gemelli IRCCS, Department of Radiation Oncology Gemelli Art – Rome. Inclusion and exclusion criteria are reported in Table 2.

Regarding follow-up, all patients were evaluated every 3–4 months for the first year, then every 6 months until the 5th year and after that, once year.

2.2. Staging

All cases were discussed both at diagnosis and during re-evaluation, which occurred 6–8 weeks after neoadjuvant therapy, in a multidisciplinary meeting involving radiotherapists, medical oncologists, radiologists, pathologists, and surgeons. For primary staging and restaging, all patients underwent pelvic MRI and CT scans of the chest and abdomen, while FDG-PET/CT was performed only in selected cases. The 7th and 8th editions of the TNM staging system were used according to the date of diagnosis (before or after December 2016). The 2017 ESMO rectal cancer clinical practice guidelines were followed to classify patients into different risk groups [8] Table 3.

2.3. Neoadjuvant chemoradiation treatment

All patients received NCRT with long-course radiotherapy (total prescribed dose between 50.4 and 60.1 Gy). Treatment was delivered using either 3D conformal radiotherapy or IMRT/VMAT, depending on the year of treatment (before or after 2010). Concomitant chemotherapy, based on disease stage and comorbidities, consisted of fluoropyrimidine ± oxaliplatin, according to different treatment schedules:

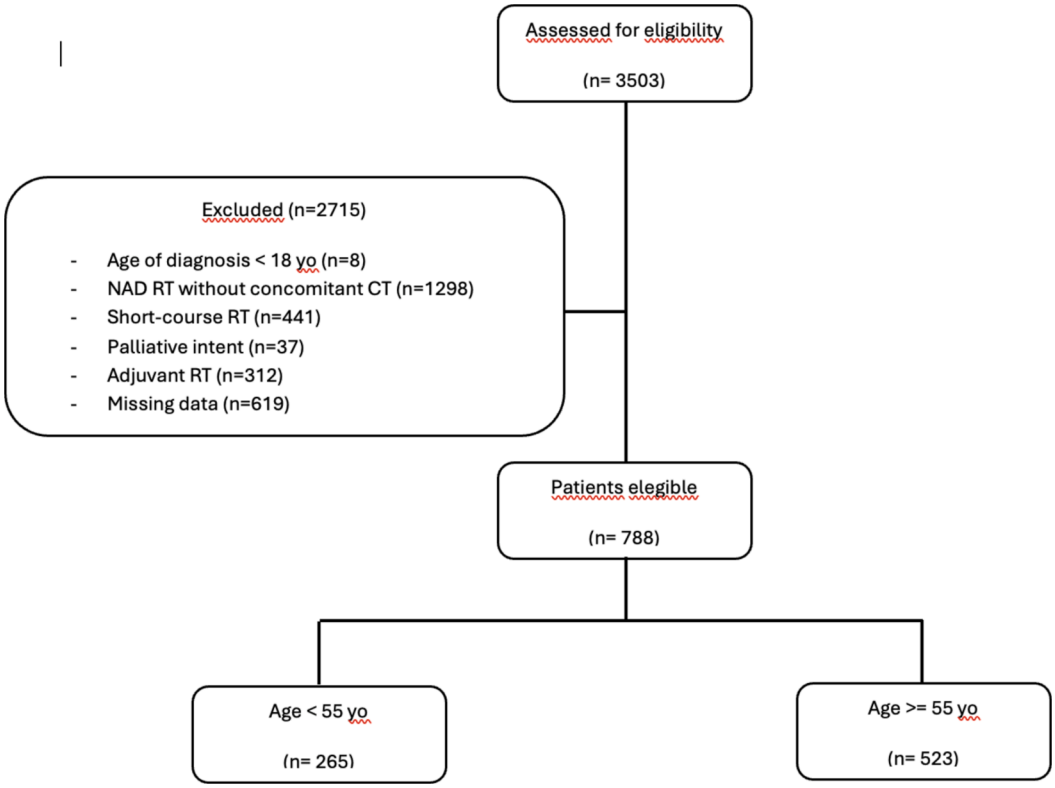

Fig. 1. Flow-diagram of patient's selection.

Table 1
Patient's characteristics.

Characteristics	n(%)
Total patients	788
Sex	
Females	306 (61.2)
Males	482 (38.8)
Age (in years)	
Range	23 – 82
Mean	60.4
Median	62
ESMO group	
Group 1	18 (2.3)
Group 2	83 (10.5)
Group 3	218 (27.7)
Group 4	461 (58.6)
Overall Treatment Time (OTT)	
Range	30 – 85
Mean	37.7
Median	36
CT Oxaliplatin based	
Yes	410 (52)
No	378 (48)
RT Dose delivered (Gy)	
Range	45–60.1
Mean	54.4
Median	55

- 5-fluorouracil iv 225 mg-mq-die in continuous infusion days 1–7 q7
- capecitabine per os 1650 mg-mq-die 1–7 q7
- capecitabine per os 1650 mg-mq-die days 1–5 q7 and avelumab iv 10 mg-kg-die g1 q14
- capecitabine per os 1300 mg-mq-die 1–7 days and oxaliplatin iv 60 mg-mq-die g1 q7
- 5-Fluorouracil 250 mg-mq-die days 1–7 and oxaliplatin iv 50 mg-mq-die 1, 8, 21, 28 during the 1st,2nd, 4th, and 5th week of radiotherapy

2.4. Surgery

Surgical treatment consisted of total mesorectal excision (TME), partial mesorectal excision (PME), or, in rare cases, Hartmann's procedure. In cases of local excision, various techniques, such as Transanal Minimally Invasive Surgery (TAMIS), Transanal endoscopic microsurgery (TEM), and transanal excision (TAE), were used.

2.5. Statistical analysis

Statistical analysis was conducted on the entire sample of patients as well as the two subgroups (under and over 55 years). The analysis was performed using R statistical software (version 4.1.3).

All variables were analyzed using descriptive statistical techniques. Qualitative variables were summarized as absolute frequencies and percentages. Comparisons of qualitative variables between the two groups were conducted using Fisher's exact test or the Chi-Square test, as appropriate. Quantitative variables were analyzed using Student's *t*-test for normally distributed data or the Mann-Whitney *U* test for non-normal distributions; the normality of data distribution was assessed with the Shapiro-Wilk test.

A p-value threshold of 0.05 was considered statistically significant, and results were presented with 95 % confidence intervals. Likelihood ratio (LR) test was used to evaluates the goodness-of-fit of statistical model, Wald p-value corresponds to the reported confidence intervals for HR.

The primary outcomes analyzed were death, local recurrence, and new distant metastases. Survival analysis assessed the time between the initiation of radiotherapy and death or the date of local or systemic disease recurrence, as determined by clinical examination, radiological imaging, or biopsy. For patients without events, survival time was calculated as the period between the initiation of radiotherapy and the most recent update of live/dead status (November 4, 2023).

Survival analysis was conducted using the Kaplan-Meier method, and the log-rank test was used to compare survival between the two groups.

The study was approved by the Internal Review Board (IRB) (protocol number: 0017106/23, dated May 31, 2023).

3. Results

A total of 788 patients who underwent neoadjuvant chemoradiation therapy at our center from January 2008 to July 2022 for rectal cancer were evaluated (523 patients 55 years or older and 265 under 55years

Table 3
ESMO rectal cancer clinical practice guidelines for diagnosis, treatment, and follow-up.

Risk group	TN substage
Very early	cT1 sm1 N0 (on ERUS and MRI)
Early (Good)	cT1-cT2; cT3a/b if middle or high, N0 (or also cN1 if high), MRF clear, no EMVI
Intermediate	cT3a/b very low, levators clear, MRF clear or cT3a/b in mid-or high rectum, cN1-2 (not extranodal), no EMVI
Bad	cT3c/d or very low localization levators threatened, cN1-N2 (extranodal), EMVI+, limited cT4aN0
Advanced (Ugly)	cT3 with any MRF involved, any cT4a/b, lateral node +

Table 2
Inclusion and exclusion criteria.

Inclusion criteria
- *Histologically documented adenocarcinoma of the rectum*
- *Diagnosis at over 18 years*
- *Undergoing neoadjuvant radiochemotherapy treatment followed or not by TME surgery*
- *Loung course radiotherapy*
- *Patients treated with curative intent*

Exclusion criteria
- *Age of diagnosis under 18*
- *Undergoing neoadjuvant radiotherapy treatment without concomitant chemotherapy*
- *Short-course radiotherapy*
- *Patients treated with palliative intent*
- *Adjuvant radiotherapy*

old). All patients were classified into different risk groups according to the ESMO 2017 rectal cancer clinical practice guidelines. The distribution of ESMO risk groups in patients under and over 55 years old is shown in Fig. 2.

The median follow-up period and the interquartile range (IQR) were 7.69 years and 3.84–11.82 years, respectively. No distribution trend was found among the various risk groups using the χ^2 test ($p = 0.001$).

Eighty-eight percent of patients under 55 years old at diagnosis belonged to the bad or advanced risk groups, with an equal division (97 patients bad and 136 advanced).

Similarly, in patients aged 55 years or older, 85 % belonged to the bad or advanced group; however, there was a clear dominance of the advanced risk class, accounting for 62 % of the total (121 patients bad and 325 advanced).

Overall survival at 5 and 10 years in the entire population was 78.9 % (CI 95 % 75.9 – 82.1) and 65.2 % (CI 95 % 61.3 – 69.5), respectively. Fig. 3.

The 3-year and 5-year overall survival (OS) rates were 89 % and 83 % in the Under 55 group and 84 % and 69 % in the 55 and Over group, respectively (Fig. 4).

Univariate ESMO risk analysis showed a significant impact on OS ($p < 0.001$). Fig. 5.

Table 4 summarizes the results of the Overall Survival (OS) univariate and multivariate analysis.

In multivariate analysis, the likelihood ratio test showed that overall survival (OS) decreases with increasing age and ESMO risk group ($p < 0.001$). The other variables in the multivariate analysis were not significant in terms of OS.

The impact of Oxaliplatin and overall treatment time (OTT) on OS in the advanced ESMO group was analyzed, yielding non-significant results both in the general population and in the two subsets: Under 55 and Over 55.

According to the ESMO risk group classification, 26.6 % of patients in the bad risk group and 71.8 % of those in the advanced risk group were treated with the addition of Oxaliplatin. The mean age of patients in the advanced risk group who underwent neoadjuvant chemoradiotherapy with either Oxaliplatin addition or fluoropyrimidine only was 58 and 64 years, respectively.

The OTT was 37 days in patients treated with fluoropyrimidine and Oxaliplatin and 35.5 days in those treated with fluoropyrimidine alone.

Disease-free survival (DFS) at 2 and 5 years in the entire population was 80.2 % (95 % CI: 77.3–83.3) and 70 % (95 % CI: 66.5–73.7), respectively (Fig. 6).

55 years old was the cutoff age to significantly separate the two curves ($p < 0.02$). Fig. 7.

The 2-year and 5-year DFS in both Under and Over 55 groups are represented in Table 5.

Table 6 summarizes the results of the Disease Free Survival (DFS) univariate and multivariate analysis.

In multivariate analysis, the likelihood ratio test showed that age <55 is associated with better disease-free survival (DFS) and ESMO risk group ($p < 0.001$). The other variables in the multivariate analysis were not significant in terms of DFS).

The role of Oxaliplatin and overall treatment time (OTT) in the advanced ESMO group did not show significant results for DFS, either in the general population or in the two subsets: Under 55 and Over 55 years

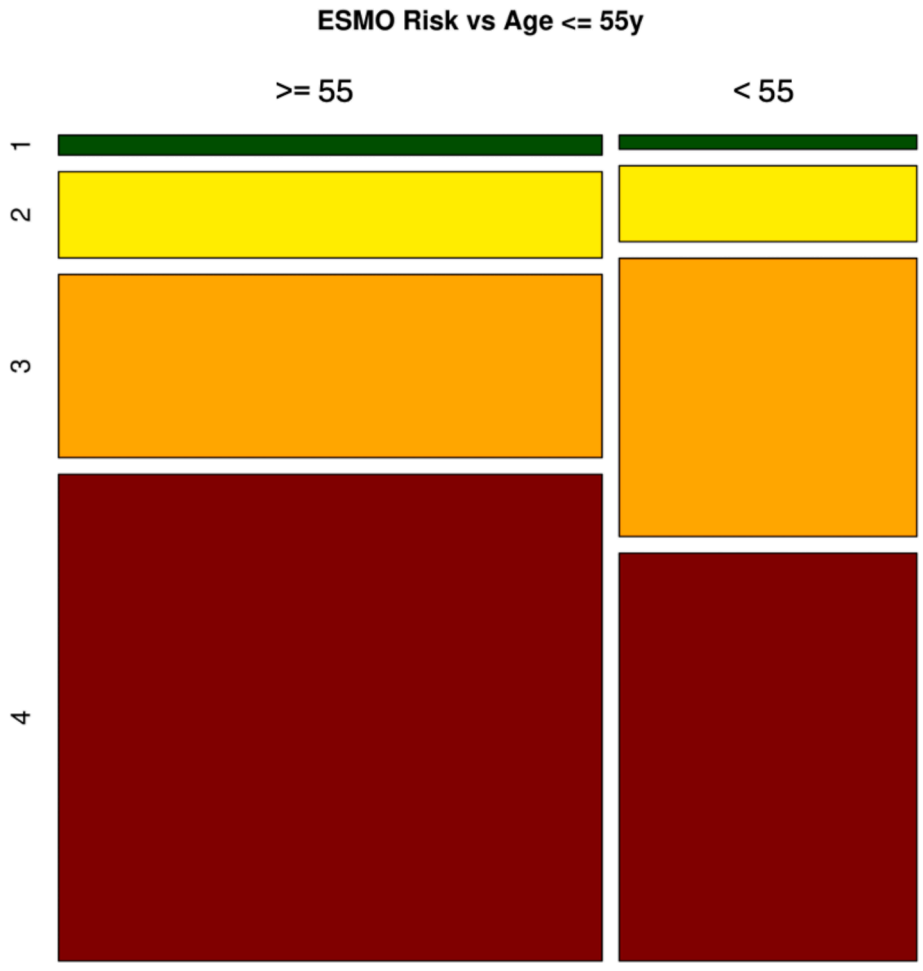

Fig. 2. ESMO risk groups in patients over and under 55 years old (χ 2 test, p = 0.001).

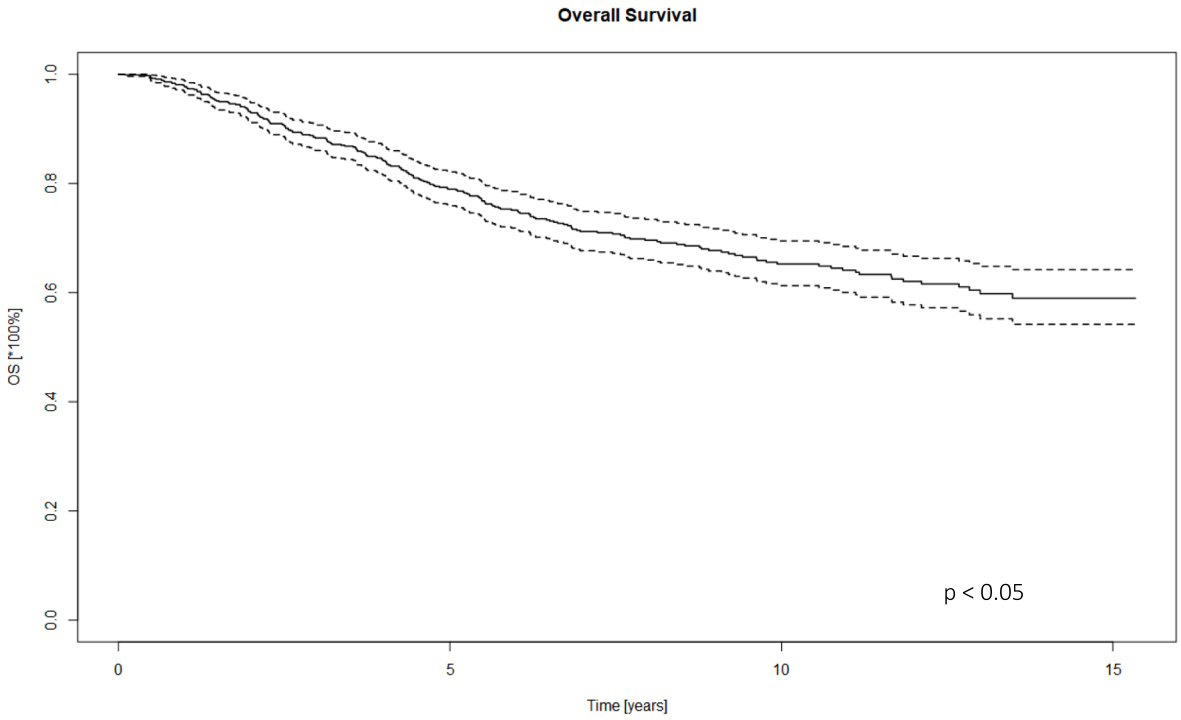

Fig. 3. Overall Survival.

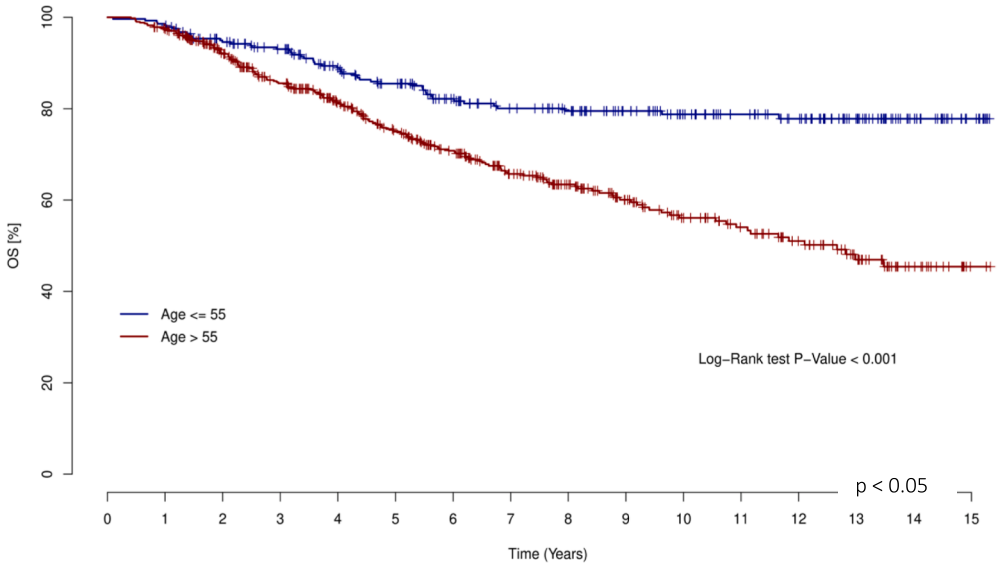

Fig. 4. Overall Survival Under and Over 55.

old.

Metastatic (M+) patients at diagnosis accounted for 7.5 % of the population (59/788), comprising 20 patients under 55 years of age (2.5 %) and 39 patients aged 55 or older (5 %). Among non-metastatic patients at diagnosis, 171 (23.7 %) developed distant metastases during follow-up: 48 patients under 55 years (6.6 %) and 123 patients aged 55 or older (17.1 %).

Local recurrence rates were 2.8 % (22/788) in the Under 55 group and 4.3 % (34/788) in the Over 55 group, respectively (Table 7).

Regarding metastasis-free survival (MFS), 40 patients with missing follow-up data were excluded from the analysis. The analysis showed that the risk of developing metastasis decreases in both the Under 55 and Over 55 groups after the fourth year. However, this result was not significant with the given age cutoff ($p = 0.8$; Fig. 8).

As for disease-free survival (DFS), the two curves separated significantly at 55 years of age ($p = 0.009$) Fig. 9); with a higher prevalence of

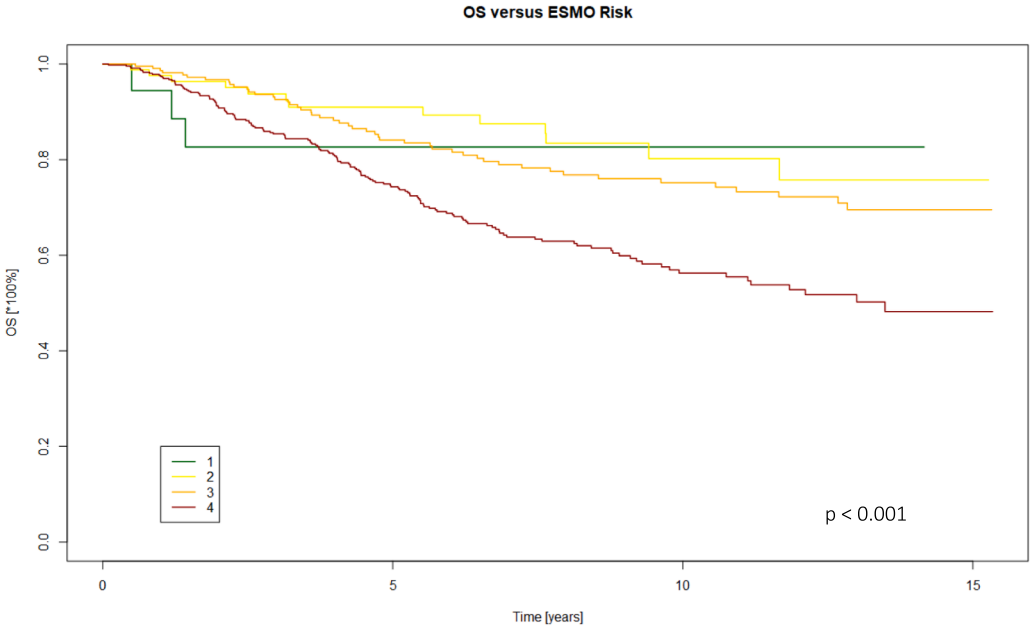

Fig. 5. Overall survival in ESMO risk groups.

Table 4
OS univariate and multivariate analysis.

	Overall Survival (OS)			
	Univariate p-Value*	***Multivariate p-Value***	***Hazard Ratio (HR)***	***95 % Confidence Interval (CI) HR***
Age	<0.001	<0.001	1.047	1.034 – 1.060
ESMO risk group (1–3 VS 4)	<0.001	<0.001	1.826	1.360–2.451
+ Oxaliplatin	0.03	NS	–	–
Overall Treatment Time (OTT)	<0.05	0.054	1.018	0.9997 – 1.038
Total Dose delivered (50.4 – 55 Gy)	NS	NS	–	–

Likelihood ratio test – $p < 0.001$.
Wald test – $p < 0.001$.
* Log-Rank test p-value.

metastasis development in the Over 55 group (Table 8).

Tables 9 summarize the results of the univariate and multivariate analyses for metastasis-free survival (MFS).

In multivariate analysis, local recurrence free survival (LRFS) appeared to decrease with increasing ESMO risk group (p=0.038) but the likelihood ratio test demonstrate that the model was not strong, probably due to the small number of local recurrence events. The other variables in the multivariate analysis were not significant in terms of LRFS.

In the overall sample, LRFS at 2 years was 96.1 % (95 % CI: 94.7–97.5) and at 5 years was 91.3 % (95 % CI: 89.0–93.7).

Tables 10 summarize the results of the univariate and multivariate analyses for LRFS.

4. Discussion

The increased incidence of rectal cancer among individuals younger than 50 years old has been demonstrated by several recent epidemiological studies [10–13].

To the best of our knowledge, only a few studies have focused on young locally advanced rectal cancer (LARC) patients following neoadjuvant chemoradiotherapy (NCRT) [14–21].

Although it has been hypothesized that rectal cancer in young patients may exhibit different biological behavior, with a higher risk of presenting at advanced stages and more aggressive histological features [6], our study found an equal distribution between bad and advanced ESMO risk groups in both young and elderly patients (around 80 % of the total population). However, there was a clear predominance of advanced cases (41 % advanced vs. 15 % bad) in the older group.

Besides indicating a serious prognosis, a locally advanced presentation can also result in a worse quality of life (QOL), particularly in young patients. This is because multimodality therapy may adversely affect functional outcomes, potentially leading to bowel dysfunction, sphincter loss, and the need for a permanent ostomy [22]. Additional concerns include urinary and sexual dysfunction, as well as infertility. These adverse events can lead to persistent anxiety, negative body image, embarrassment related to bowel movements, and impaired social functioning [23].

Although it is well known that genetic predisposition plays an important role in early-onset colorectal cancer (eoCRC), with hereditary cancer syndromes accounting for 2–5 % of all Colo-Rectal Cancer (CRC) cases, it is important to recognize that most patients have sporadic disease. [24,25]. Furthermore, most young patients with colorectal cancer (CRC) are symptomatic at the time of diagnosis, often experiencing general gastrointestinal symptoms such as abdominal pain and rectal bleeding, which are frequently mistaken for benign conditions. Therefore, it is strongly recommended that the diagnosis of CRC be carefully considered in young individuals presenting with alarming symptoms. [26].

Currently, no specific guidelines exist for the management of rectal cancer in young-onset patients, leading physicians to treat these patients similarly to those with late-onset disease. A recent evidence-based consensus on early-onset colorectal cancer (EOCRC) has been published, but it found insufficient evidence to recommend changes to endoscopic, surgical, or oncologic treatments based solely on age. [27].

Fluoropyrimidine-based chemoradiotherapy (5-FU or capecitabine)

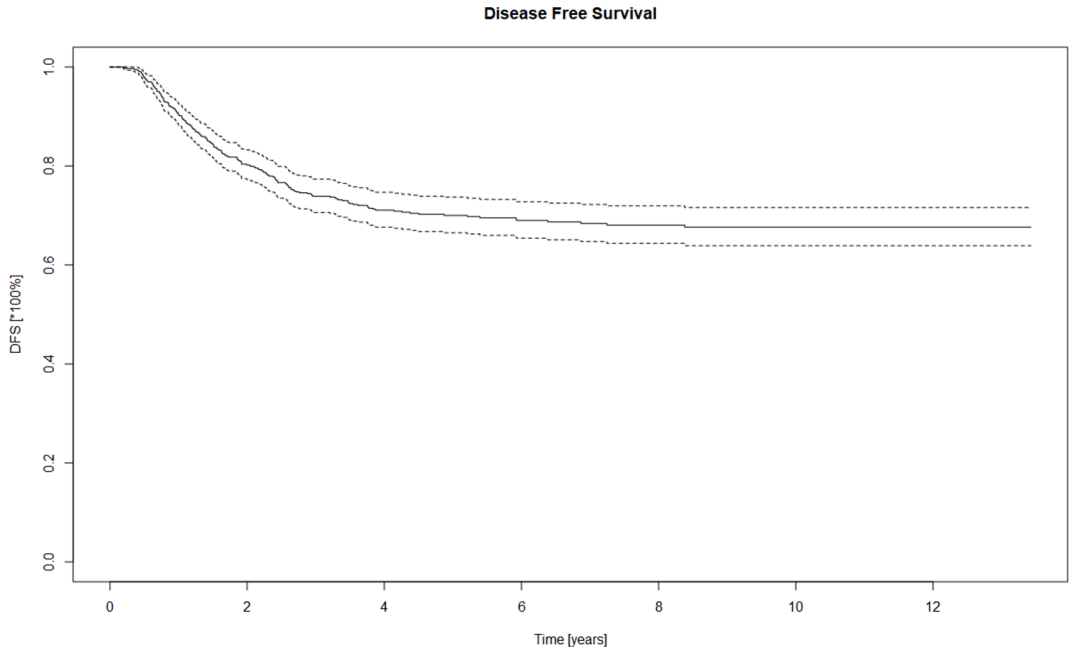

Fig. 6. Disease Free Survival.

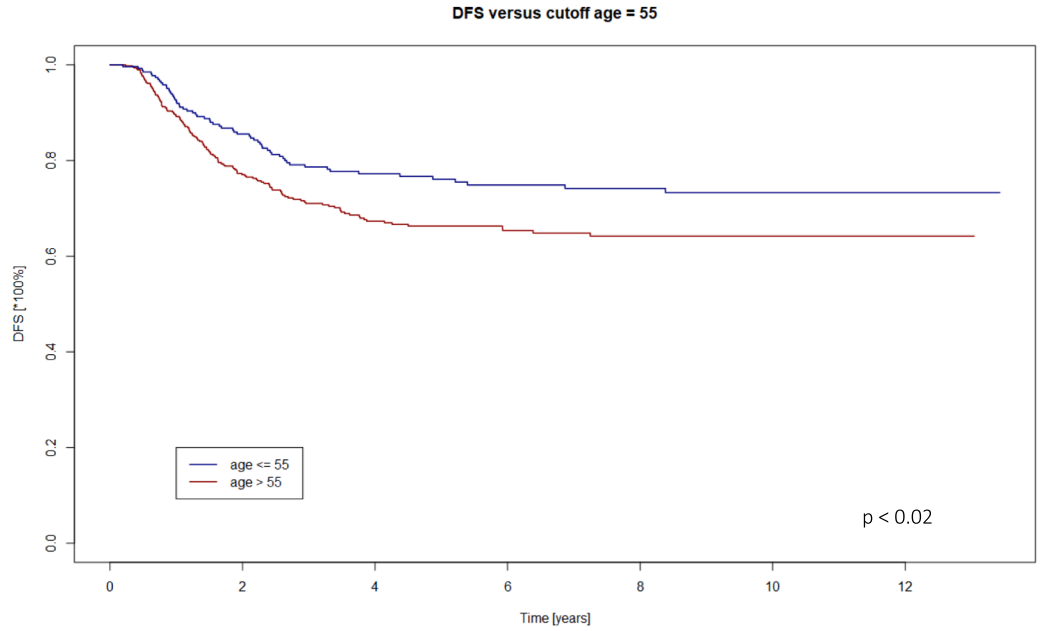

Fig. 7. DFS Under e Over 55.

Table 5
Disease free survival (DFS).

	Total	Under 55	Over 55
DFS 2 years	80.2 % (95 % CI 77.3–83.3)	85.3 % (95 % CI 80.9–89.8)	77.4 % (95 % CI 73.6–81.4)
DFS 5 years	70 % (95 % CI 66.5–73.7)	75.8 % (95 % CI 70.4–81.6)	66.7 % (95 % CI 62.3–71.5)

is currently considered the standard of care for locally advanced rectal cancer (LARC) in the neoadjuvant setting. However, the potential benefit of adding oxaliplatin to improve clinical outcomes remains unclear, as conflicting data persist in the literature.

Survival data for young rectal cancer are conflicting. Some studies have indicated a worse prognosis [14], while others have shown that younger patients have equivalent or better outcomes than older patients [18–21].

In the present study, we found that younger patients presented better overall survival (OS) at three and five years compared to patients 55 years old or older. Multivariate analysis revealed that the ESMO risk group and age were the only variables significantly affecting overall survival, confirming age as an important factor for survival benefits.

However, due to the lack of high-quality evidence, there is currently no uniform consensus regarding the impact of age on the efficacy of

Table 6
DFS univariate and multivariate analysis.

	Disease Free Survival (DFS)			
	*Univariate p-Value**	*Multivariate p-Value*	*Hazard Ratio (HR)*	*95 % Confidence Interval (CI) HR*
Age < 55**	0.020	0.016	0.688	0.507–0.932
ESMO risk group (1–3 VS 4)	0.004	0.010	1.473	1.096–1.980
+ Oxaliplatin	NS	NS	–	–
Overall Treatment Time (OTT)	NS	NS	–	–
Dose delivered (50.4 – 55 Gy)	NS	NS	–	–

Likelihood ratio test – $p < 0.001$.
Wald test – $p = 0.001$.
** Age factorized as age < 55 y in log-rank test and multivariable analysis.

Table 7
Patients' characteristics.

	M + at diagnosis	M + during follow-up	Local recurrence
Under 55	2.5 %	6.1 %	2.8 %
Over 55	5.0 %	15.6 %	4.3 %

NCRT and the outcomes of patients with locally advanced rectal cancer (LARC). A potential explanation for better outcomes in younger patients could be their superior physiological reserve and lower incidence of comorbidities.

A 55-year age cutoff was identified as a significant threshold, separating disease-free survival (DFS) and Overall Survival (OS) curves with improvements at both two and five years for younger patients compared to older ones. Furthermore, neither the total delivered radiotherapy dose, overall treatment time (OTT), nor the inclusion of oxaliplatin regimens in NCRT and/or adjuvant therapy demonstrated significance in either univariate or multivariate analysis for both DFS and OS.

Several randomized trials have investigated the addition of oxaliplatin to NCRT or perioperative chemoradiotherapy (CRT), yielding conflicting results [28–32]. Among these, the PETACC-6 and CAO/ARO/AIO-04 trials are particularly notable for their differing conclusions. While the PETACC-6 trial did not demonstrate any benefit from adding oxaliplatin, the CAO/ARO/AIO-04 trial reported age-dependent efficacy. Specifically, the CAO/ARO/AIO-04 trial found a significant improvement in disease-free survival (DFS) in younger patients (<60 years old) with the addition of oxaliplatin, whereas patients aged ≥70 years showed no benefit [33]. Importantly, no difference in overall survival (OS) was observed between the age groups.

However, this *meta*-analysis had significant limitations, primarily due to the varying doses and treatment schedules of 5FU/capecitabine and oxaliplatin used not only across different trials but also within the same trial (e.g., CAO/ARO/AIO-04). These discrepancies may explain why some studies showed significantly positive results while others did not. Notably, in the CAO/ARO/AIO-04 trial, the observed superiority may be attributed to the continuous administration of fluoropyrimidines throughout the entire course of both preoperative radiotherapy and adjuvant therapy, compared to the shorter administration in the control group. Additionally, the optimal timing for incorporating oxaliplatin—whether preoperative, postoperative, or both—to maximize disease-free survival remains undetermined. In our study, the addition of oxaliplatin to fluoropyrimidine-based neoadjuvant chemotherapy resulted not significant in terms of either overall survival, disease- or metastasis-free survival in both groups.

Even in the adjuvant setting, the use of oxaliplatin in the treatment of LARC patients remains controversial. Data from the SEER database [34] and ADORE trial [35] support the use of oxaliplatin in younger patients, particularly those who are ypN+, under 73 years of age, or have high-risk features. Nevertheless, adjuvant chemotherapy continues to be debated, especially for patients who have undergone preoperative chemoradiotherapy (CRT), as no study has definitively clarified its role in this context.

Adjuvant chemotherapy is currently recommended for patients with rectal cancer who have undergone upfront surgery and are in post-operative pathological stages II and III [1,2,36,37]. To date, only adjuvant fluoropyrimidines have been shown to improve survival. However, oxaliplatin-based adjuvant chemotherapy is widely used in patients with rectal cancer, primarily based on extrapolated findings from studies in patients with colon cancer [38,39].

At diagnosis, metastatic patients accounted for 7.5 % of the entire

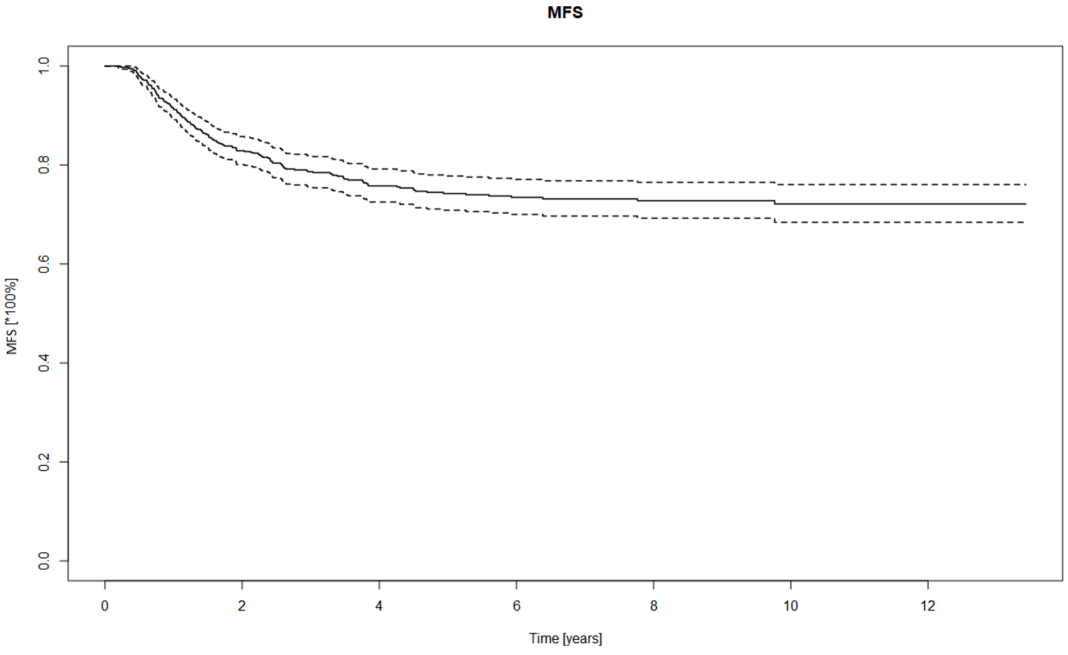

Fig. 8. Metastasis-Free Survival (MFS).

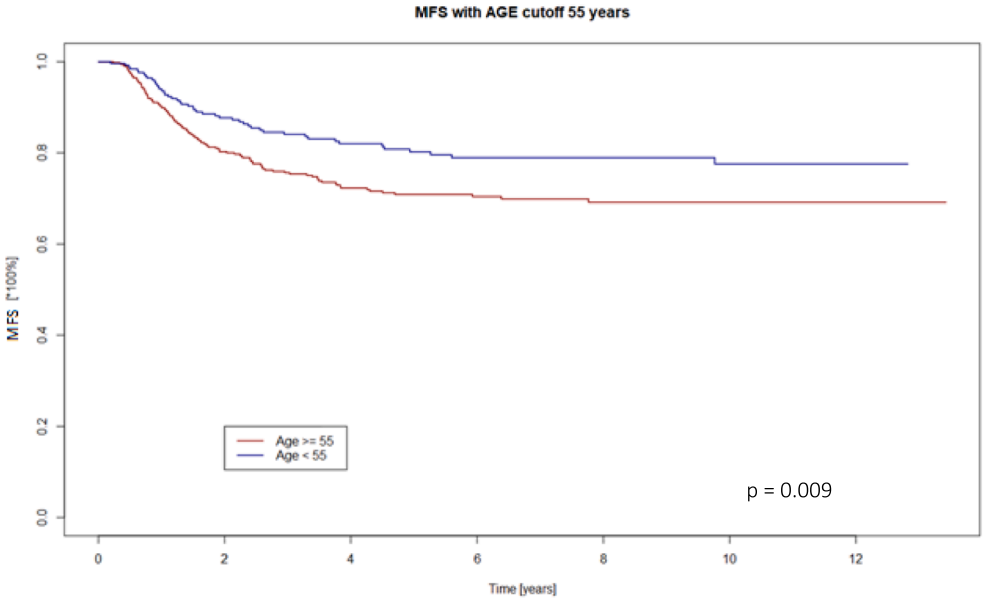

Fig. 9. MFS Under e Over 55.

Table 8
Metastasis free survival.

	Total	Under 55	Over 55
MFS 2 years	82.9 % (95 % CI 80.1–85.7)	87.7 % (95 % CI 83.6–91.2)	80.2 % (95 % CI 76.6–84)
MFS 5 years	74.2 % (95 % CI 70.9–77.8)	80.2 % (95 % CI 75.1–85.6)	70.9 % (95 % CI 66.5–75.5)

Table 9
MFS univariate and multivariate analysis.

	Metastasis-Free Survival (MFS)			
	Univariate p-Value*	***Multivariate p-Value***	***Hazard Ratio (HR)***	***95 % Confidence Interval (CI) HR***
Age < 55**	0.02	0.014	0.661	0.474–0.921
ESMO risk group (1 – 3 vs 4)	0.004	0.057	1.359	0.991–1.864
+ Oxaliplatin	NS	NS	–	–
OTT	NS	NS	–	–
Dose delivered (50.4 – 55 Gy)	NS	NS	–	–

Likelihood ratio test p = 0.004.
Wald test p = 0.005.
** Age factorized as age < 55 y in log-rank test and multivariable analysis.

Table 10
LRFS univariate and multivariate analysis.

	Local Recurrence Free Survival (LRFS)			
	Univariate p-Value*	***Multivariate p-Value***	***Hazard Ratio (HR)***	***95 % Confidence Interval (CI) HR***
Age < 55**	NS	NS	–	–
ESMO risk group (1–3 vs 4)	NS	0.038	1.869	1.035 – 3.375
+ Oxaliplatin	NS	NS	–	–
OTT	NS	NS	–	–
Dose delivered (50.4 – 55 Gy)	NS	NS	–	–

Likelihood ratio test p = 0.09.
Wald test p = 0.1.
** Age factorized as age < 55 y in log-rank test and multivariable analysis.

population. An age cutoff of 55 years emerged as significant, with a higher prevalence of metastasis development in the over-55 age group. Our study demonstrated that younger patients have better metastasis-free survival and disease-free survival at both two and five years compared to patients 55 years old or older.

Regarding local recurrence, the results were not statistically significant, likely due to the low number of local recurrences in the analyzed sample.

Our study has several limitations. First, it is a single-center, retrospective study. Second, genomic tests for RAS, BRAF, and microsatellite instability were not included. Third, comorbidities in elderly patients and treatment-related toxicity were not analyzed. Additionally, the substantially smaller sample size of young patients with rectal cancer compared to the larger number of elderly patients may have led to an overestimation of the differences between the two subgroups.

Due to these limitations, we are unable to either confirm or refute the findings of the CAO/ARO/AIO-04 trial.

To address these gaps, a multicenter prospective study would be beneficial. Such a study should incorporate genomic and clinical data and randomize patients younger and older than 55 years of age, who are candidates for neoadjuvant oxaliplatin-based chemoradiotherapy, into two treatment arms with standardized doses and fluoropyrimidine schedules.

4. Conclusions

In summary, this monocentric retrospective observational study, conducted on 788 rectal cancer patients (523 over 55 years and 265 under 55), treated with neoadjuvant chemoradiotherapy for low-, mid-, and upper-rectal cancer, showed that younger patients appear to have better overall survival (OS) and disease-free survival (DFS) at 3 and 5

years. ESMO risk group and age were the only variables significantly affecting OS and DFS. Furthermore, younger patients demonstrated superior metastasis-free survival (MFS) at 2 and 5 years compared to those 55 years old or older. The addition of oxaliplatin to fluoropyrimidine-based neoadjuvant chemotherapy did not result in significant benefit in either age group.

By integrating these findings with the epidemiological, clinical, and pathological characteristics of early-onset colorectal cancer (eoCRC) patients, some recommendations for managing rectal cancer in younger patients have been identified. Public health initiatives are essential to raise awareness and educate both physicians and patients about the risk of colorectal cancer (CRC) in young adults. A diagnosis of CRC should be carefully considered in young patients presenting with alarming symptoms. While a family history or genetic predisposition to CRC should be strongly evaluated, it is crucial to note that most cases are not genetically linked.

Currently, there is no evidence to support age-specific treatments (endoscopic, surgical, or chemoradiotherapy) for young patients with rectal cancer. Therapeutic decisions should be made in a multidisciplinary setting, considering radiological and histopathological characteristics as well as the patient's quality of life (QOL). Future studies aimed at defining specific phenotypes of eoCRC and understanding their responses to radiotherapy, chemotherapy, or immunotherapy could enhance clinicians' ability to tailor treatments to individual patients, ultimately improving outcomes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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