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Retrospective Analysis of Rectal Cancer: Late Versus Early Onset (RELEO study)

María Valero Revert[1], David Sánchez Garcia[1], Mariano Martinez Marín[1], Beatriz Grau Mirete[1], Cristina Bernabé Martinez[1], Elena Navarro Vicente[1], Marta Hernández Sáez[1], María Orengo López[1], Alejandro Moya Martinez[2,3], Francisco Pelegrín Mateo[4], Elena Asensio Martinez[1] and Javier Gallego Plazas[1]*

[1]*Medical Oncology Department, Elche University Hospital, Elche (Alicante), Spain.*

[2]*Biostatistics Service, Elche University Hospital, FISABIO, Elche (Alicante), Spain*

[3]*Department of Statistics, Mathematics and Computer Science, Miguel Hernández University, Spain.*

[4]*Medical Oncology Department, Vega Baja Hospital, Orihuela (Alicante), Spain.*

***Correspondence:**
Javier Gallego Plazas, Medical Oncology Department, Elche University Hospital, Elche (Alicante), Spain.

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ABSTRACT

Background: *The incidence of early-onset gastrointestinal cancer, particularly rectal cancer, is rising globally. Differences in disease presentation, treatment and outcomes in this population compared to older patients merits attention in the context of increasing aging.*

Methods: *RELEO studied rectal cancer patients consecutively treated in the Medical Oncology Department of Elche University and Vega Baja Hospitals between january 2010 and december 2023 in order to evaluate aspects related to the epidemiology, disease presentation, diagnosis and characteristics, as well as the therapeutic strategy and its results in young (<50 years) versus old patients (>70 years).*

Results: *765 patients with rectal cancer were included for the global population analysis. For the stage-matched comparison, 51 patients under 50 years of age and 102 (1:2) of the 292 patients over 70 years of age were included. Rectal adenocarcinoma in people under 50, compared to those over 70, was not associated with differential risk factors detectable in anamnesis, had neither particular location in the rectum nor more advanced clinical stage at diagnosis, and was not associated to worse prognosis. Patients under 50 years of age, compared to patients over 70, had less comorbidities ($p < 0.05$) better perfomancce status ($p<0.001$), and more symptoms at diagnosis [abdominal pain (41.2% vs. 24.5%; $p<0.05$), rectal bleeding (86.3% vs. 70.6%; $p<0.05$)]. Treatment was more intense in patients under 50, in both localized (neoadjuvant, $p<0.001$; adjuvant, $p=0.033$) and advanced disease (chemotherapy use, $p<0.001$; intensity, $p<0.001$; lines of chemotherapy, $p<0.001$), with statistically significant longer overall survival in stage III [76.0 (31.0-114.0) vs 37.0 months (22.0-83.0); $p=0.022$] and IV patients [28.5 (19.8-47.0) vs 8.5 months (3.8-15.0); $p=0.004$].*

Conclusion: *RELEO showed similar disease profile of rectal cancer regardless of age, with more fragility in older patients, conditioning treatment and survival. Further better adjusted studies are appropiate to clarify impact of age on rectal cancer.*

Keywords
Early-onset, Rectal, Cancer.

Introduction

Historically, cancer has been considered a disease predominantly associated with aging and with a multifactorial etiology [1]. Early Onset Cancer (EOC) is conventionally defined as one that is diagnosed between the ages of 18 and 49. There are several analyses worldwide that have observed a paradigmatic shift in the ages at which some of the most common cancers are diagnosed for reasons that have not been fully elucidated [2-5]. The GLOBOCAN database demonstrates an increasing incidence of colorectal, extrahepatic bile duct, gallbladder, liver, pancreas, stomach, breast, endometrium, bone marrow, thyroid, head and neck, kidney, and prostate cancer [6]. This growing and worrying trend has led different institutions (National Cancer Institute of the United States – NCI, European Society of Medical Oncology – ESMO) to consider it a priority in their lines of research, as well as to make efforts at the global level in order to determine the relative contribution that those known and those still unknown risk factors have in this epidemic of EOC and especially in relation to colorectal cancer in young adults (EO-CRC) [4,7].

Colorectal cancer (CRC) is the third most common tumor in the world and the second leading cause of cancer death [8]. In Spain, 44,294 new cases of CRC are estimated for the year 2024 (29,648 colon, 14,646 rectum), and 15,198 deaths from CRC were registered in 2022 (11,142 colon, 4,056 rectum), data that place it as the first tumour in incidence and the second in cause of death from cancer [9]. Incidence rates in people under 50 years of age have been increasing since the mid-1990s, mainly due to a growing incidence of rectal cancer [10]. Based on data from the American Association of Cancer Centers Registry, there has been an annual increase in colorectal cancer of 1.1% (95% CI; 0.3 -0.5) from 2006 to 2015. This increase includes an annual increase of 0.7% (95% CI; 0.5 – 0.9) for colon tumours and 1.7% (95% CI; 1.4 – 2.0) for rectal tumours. By 2023, 10% of all colon cancers and 22% of all rectal cancers in the United States were projected to be diagnosed in patients younger than 50 years of age [11]. Similarly, recent evidence demonstrates a rapidly increasing incidence of EO-CRC in other developed countries [12]. This circumstance is even more worrying when contrasted with the significant reduction in the incidence of CRC in patients over 50 years of age, justified in aspects such as screening programs and the reduction of risk factors [13].

We do not have specific data on the incidence of EO-CRC in Spain. The SECOC (Spanish Early-onset Colorectal Cancer) initiative, with a majority representation of centers in the Community of Madrid and Catalonia, and four participating autonomous regions, aims to prospectively recruit patients with EO-CRC to investigate the molecular bases and metabolic alterations, as well as factors related to lifestyle, other risk factors, and clinical-pathological data related to family history and follow-up [14]. We are confident that this prospective study can help advance knowledge about EO-CRC, as well as the specific characterization of this important health problem in Spain.

The Medical Oncology Department (MOD) of Elche General Universitary and Vega Baja Hospitals (EUH-VBH) covers a population of approximately 341,779 inhabitants. The Gastrointestinal Tumours Unit in this MOD began in 2010 an ambispective registry, consecutive in its prospective nature, of patients treated for a diagnosis of gastrointestinal cancer. It currently has more than 5,000 patients included.

In May 2024, an analysis of the MOD of EUH-VBH gastrointestinal cancer registry was carried out, including patients diagnosed between January 2010 and December 2023, evaluating the incidence trends of the different cancers in the population served and specifically in patients under 50 years of age (Table 1) [15].

TUMOR LOCATION / TENDENCY	ALL GASTRO-NTESTINAL CANCERS	COLON CANCER	RECTAL CANCER	ESOPHAGO-GASTRIC CANCER	SQUAMOUS CELL ESOPHAGEAL CARCINOMA	PANCREATIC DUCTAL CARCINOMA	NEURO-ENDOCRINE TUMOURS	BILIARY TRACT CANCER
GLOBAL INCIDENCE	↑	→	→	↓	↑	↑↑↑	↑↑	↑↑
INCIDENCE < 50 YEARS	↑↑	→	↑	↑	↓↓	↑	↑↑	↑
% PATIENTS < 50 YEARS	↑	→	↑↑	↑↑	↓↓	↓	↑↑	↓

Table 1: Trends in incidence of gastrointestinal cancers in EUH – VBH between January 2010 and December 2023 [15].

One of the noteworthy results of this analysis, which coincides with what has been previously reported in other countries [11], was the notable trend towards an increase in the proportion of patients under 50 years of age with rectal cancer, while colon cancer remained stable. A deeper exploration of the registry allowed us to identify 765 patients diagnosed with rectal cancer, 51 patients younger than 50 years, and 292 older than 70 years [15].

With this background, RELEO intends to retrospectively study rectal cancer in young (<50 years) versus old patients (>70 years) in order to evaluate aspects related to the epidemiology, disease presentation, diagnosis and characteristics, as well as the therapeutic strategy and its results.

Material and Methods

RELEO is a retrospective analytical cohort study conducted on the basis of the Gastrointestinal Cancer Registry of the MOD of EUH-VBH. Patients who met the inclusion criteria and did not meet the exclusion criteria for the study population were identified. The inclusion criteria were patients treated by the MOD of EUH-VBH for a rectal cancer diagnosis between january 2010 and december 2023, patients under 50 years of age (Group A) or over 70 years of age (Group B), and signed informed consent from the Gastrointestinal Cancer Registry of the MOD of EUH-VBH.

Once identified the population of patients under 50 years of age (Group A), a population of patients over 70 years of age was generated, including twice as many patients as in Group A (Group B) (1:2 ratio). The distribution of the population by clinical stage of disease at diagnosis in both Groups (A and B) had to be equivalent; consequently, each patient in Group A would be associated with

two patients in Group B with the same clinical stage. Patients in Group B would be identified as those treated consecutively, with the same clinical stage of disease as the Group A index case, by the MOD of EUH-VBH before and after the Group A index case.

Variables related to epidemiology, risk factors, comorbidities, family history of cancer, symptoms at diagnosis, diagnostic prodecures and time intervals, rectal cancer location, stage, prognostic factors, treatment strategy and results, as well as follow up were collected from the electronic medical records of the patients in order to proceed with the subsequent descriptive and analytical study.

Objectives of the study included to compare the characteristics of rectal cancer in patients younger than 50 years versus patients older than 70 years of age (Global population), the presentation and diagnostic process of rectal cancer in patients younger than 50 years versus patients older than 70 years of age (Group A vs B), as well as the therapeutic strategy and treatment results, according to the clinical stage at diagnosis, in patients under 50 years versus patients over 70 years of age (Group A vs B).

Statistical Analysis

A SPSS database was used for data collection and statistical analyses were performed in R versión 4.5.1 [16]. Two studies were conducted. First, the entire database was analyzed. Subsequently, a 1:2 ratio match was carried out between patients of different age groups, controlling for the date of inclusion and the clinical stage of each patient. For the comparison of quantitative variables between two groups, the normality of the data was initially evaluated using the Lilliefors test. In case the data followed a normal distribution, the Bartlett test was applied to check the homogeneity of variances, and the results were expressed as mean (standard deviation). If normality was not met, the Levene test was used to assess homogeneity, and the results were reported as median (Q1–Q3). For the comparison of means between groups, Student's t-test was used when the homogeneity of variances was met, and Welch's test was used otherwise. For the comparison of medians, the Wilcoxon test was applied. In the case of qualitative variables, absolute and relative frequencies (percentages) were reported. For the comparison between two qualitative variables, the Chi-square test or the exact Fisher test was used, depending on the suitability in each case.

Results

Of the 765 patients consecutively treated with rectal cancer in the MOD of EUH-VBH between January 2010 and December 2023, with a median age at diagnosis of 68 years (33-98), 343 (44.8%) patients under 50 (6.7%) or over 70 years of age (38.1%) were included. 51 (14.9%) of these 343 patients were under 50 years of age, while the remaining 292 (85.1%) were over 70 years of age at diagnosis, comprising the so-called "global study population".

For the stage-matched comparison between the two age groups, 51 patients under 50 years of age and 102 of the 292 patients over 70 years of age were included with a final population for this comparative analysis of 153 patients (1:2 ratio), a population referred to as the "stage-matched patient population" (Figure 1).

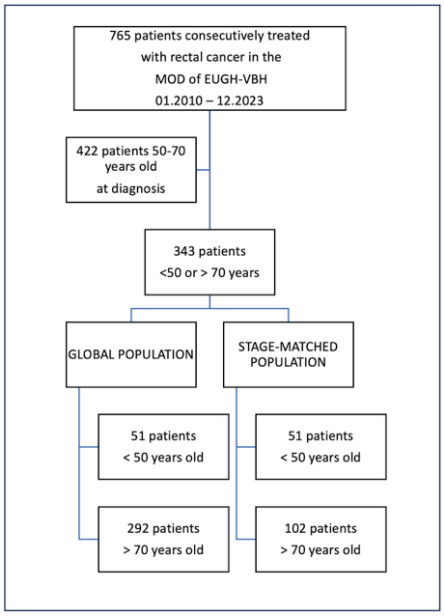

Figure 1: CONSORT diagram of patients included in RELEO.

Comparison of rectal cancer characteristics at diagnosis in patients younger than 50 years versus patients older than 70 years of age in the global population

The median age of both groups (<50, >70 years) in the global population reached statistically significant differences [45 (41.5-47.0) vs. 77.0 (74.0-82.0) years; p<0.001]. 60.8% of patients under 50 years of age were men, compared to 63.4% (185) of those over 70 years of age (p=0.755). The anatomical location of the primary tumor in the rectum (high, medium, low) and stage at diagnosis (I, II, III, IV) did not show statistically significant differences between the two groups (p=0.432 and p=0.123, respectively), although there were numerical differences in distribution according to localized vs. advanced stage between those under 50 and over 70 years of age (76.5% vs. 83.9% localized, 23.5% vs 16.1% advanced, respectively). However, statistically significant differences were observed between the two groups in ECOG performance status, both categorized from 0 to 4 (p<0.001) and grouped 0-1 vs 2-3 vs 4 (p=0.001), with a better performance status for the group of young patients (ECOG 0 in 52.9% vs 20.5% and ECOG 0-1 in 98.0% vs 78.1% of patients under 50 and over 70 years of age, respectively).

Regarding blood tests at diagnosis, a statistically significant deterioration of renal function was observed in patients over 70 years of age [creatinine clearance 116.2 (99.5-136.9) vs 61.8 (52.5-77.5) ml/min; p<0.001]. There were also statistically significant differences, although not clinically significant, in hemoglobin value [13.1 (11.5-14.7) vs 12.1 (10.8-13.7) g/dL; p=0.005], platelets count [293,000.0 (231,000.0-358,000.0) vs 250,000.0 (201,000.0-306,000.0) x µL; p=0.014], albumin [4.2 (3.7-4.5) vs 3.6 (3.2-3.9) g/dL; p<0.001], and glucose [96.0 (89.0-106.0) vs 104.0 (92.0-121.0) mg/dL; p=0.019] (Table 2).

	< 50 years N: 51	> 50 years N: 292	p
Age [Median (Q1 – Q3)]	45.0 (41.5 – 47.0)	77.0 (74.0 – 82.0)	< 0.001
Male [N (%)] Female [N (%)]	31 (60.8) 20 (39.2)	185 (63.4) 107 (36.6)	0.775
Anatomical location (%) (Upper – Medium – Low)	35.3 – 31-4 – 33.3	32.5 – 41.4 – 25.7	0.432
Stage (%) (I – II – III – IV)	11.8 – 5.9 – 56.9 – 23.5	14.0 – 17.1 – 51.7 – 16.1	0.123
ECOG (%) (0 - 1 – 2 – 3- 4)	52.9 – 45.1 – 2.0 – 0 – 0	20.5 – 57.5 – 15.8 – 4.8 – 0.3	< 0.001
ECOG (%) (1,2 – 3,4)	98.0 – 2.0	78.1 – 20.5	0.001
Creatinine Clearance (ml/min) [Median (Q1 – Q3)]	116.2 (99.5 – 136.9)	61.0 (52.5 – 77.5)	< 0.001

Table 2: Main findings of comparison of rectal cancer characteristics at diagnosis in patients younger than 50 years versus patients older than 70 years in the global population.

Presentation and diagnostic process of rectal cancer in patients younger than 50 years versus patients older than 70 years of age in the stage-matched population

The median age of both groups of patients matched by stage, as expected, reached statistically significant differences [45.0 years (41.5-47.0) vs. 78.5 years (75.0-83.0); p<0.001]. 60.8% of patients under 50 years of age were men, compared to 63.7% of those over 70 years of age (p=0.726). The anatomical location of the primary tumor in the rectum (high, medium, low) did not show statistically significant differences between the two groups (p=0.175). However, statistically significant differences were observed between the two groups in ECOG performance status, both categorized from 1 to 4 (p<0.001) and grouped 0-1 vs 2-3 vs 4 (p<0.001), with a better performance status for the group of young patients (ECOG 0 in 52.9% vs 16.7% and ECOG 0-1 in 98.0% vs 73.5% of patients under 50 and over 70 years of age, respectively).

Smoking habit was significantly more intense in those over 70 years of age [pack-years 20.8 (8.2) vs 50.9 (21.2); p<0.001], although active habit was mor frequent in those under 50 years of age (49.0% vs 6.9%); p<0.001). Alcohol exposure tended to be higher in people under 50 years of age (35.3% vs 19.6%; p=0.074). No differences in Body Mass Index (BMI) were demonstrated between the two groups (p=0.154).

Cardiovascular (Congestive Heart Failure - CHF, cerebrovascular disease), respiratory (Chronic Obstructive Pulmonary Disease - COPD) and Diabetes Mellitus (DM) comorbidities were more prevalent, with statistically significant differences, in the group of patients over 70 years of age (p < 0.05). The use of polypharmacy was also significantly higher in people over 70 years of age (mean 5.3 drugs vs. 1.0; p<0.001). Other conditions, such as acute myocardial infarction, peripheral vascular disease, dementia, liver disease, peptic ulcer, hemiplegia and hepatic steatosis, showed no statistically significant differences between the two groups. No corticosteroid use was identified in any of the groups. The use of immunosuppressants was very rare, with only two cases (2.0%) in the group over 70 years of age and none in the group of people under 50 years of age, with no statistically significant differences (p=0.553).

No relevant differences were found between groups in relation to the existence of a first-degree family history for different types of cancer. The only statistically significant difference in this regard was a greater evaluation by the Genetic Counseling Unit in patients under 50 years of age (35.3% vs. 6.9%; p<0.001).

The analysis of working activity, although with more than 50% of values lost in people over 70 years of age, showed a predominance of dynamic occupations in both groups, with a slightly higher proportion in those under 50 years of age, although without statistically significant differences (49.0% vs. 33.3%; p=1.0). Environmental exposure was more frequent in people under 50 years of age, also without statistical significance (47.1% vs. 33.3%; p=0.186)).

Incidental and screening diagnosis was infrequent and without statistically significant differences between those under 50 and over 70 years of age 0% vs 4.9%, p=0.170; and 0% vs 1.0%, p=1.000; respectively]. Considering symptoms and signs at diagnosis, those younger than 50 years of age had more frequent abdominal pain (41.2% vs. 24.5%; p<0.05) and rectal bleeding (86.3% vs. 70.6%; p<0.05), while anemia was more frequent in those over 70 years of age (33.3% vs. 57.8%; p<0.05). Bowel habit alterations were frequent in both groups with no statistically significant differences (64.7% vs. 55.9%, p=0.0384). Weight loss was present in both groups (43.1% vs 45.1%) with a similar distribution of loss percentage (p=0.629).

The medical specialty where most cases were diagnosed was Digestive Medicine (45.1% vs. 44.1% in those under 50 and over 70 years of age, respectively). Other specialties involved were Internal Medicine (27.5% vs 35.3%) and General Surgery (13.7% vs 12.7%). Diagnosis in the private health care setting only occurred in patients younger than 50 years (5.9%).

The time interval from symptom onset to histopathological diagnosis was numerically longer in patients younger than 50 years, without reaching statistical significance [60 (25.5-120.0) days vs. 37.5 (7.0-180.0); p=0.763]. There were no statistically significant differences neither in the time elapsed between the first consultation and the histopathological diagnosis of adenocarcinoma [55 days (15.8-113.0) in patients under 50 years of age, vs. 39 days (14.2-85.5) in patients over 70 years of age; p=0.131] nor in the time from histopathological diagnosis to completion of the disease extension study [4 days (0.0-9.0) vs. 4 days (0.0-13.0); p=0.815]. However, there was a statistically significant difference in the time interval from histopathological diagnosis to the establishment of the therapeutic plan, which was shorter in those under 50 years of age [21 days (14.0-32.0) vs. 28 days (18.2-40.0); p<0.05].

Prognostic factors of rectal cancer in patients younger than 50 years versus patients older than 70 years of age in the stage-matched patient population

In blood tests at diagnosis, greater deterioration of renal function was observed in patients over 70 years of age [creatinine clearance 116.2 (99.5-136.9) vs 61.7 (44.1-74.5) ml/min; p<0.001]. There were also statistically significant differences, although not clinically significant, in the levels of hemoglobin [13.1 (11.5-14.7) vs 11-8 (10.1-13.7) g/dL; p=0.001], platelets count [293,000000.0 (231,000.0-358,000.0) vs 251,000.0 (205,000.2-300,000.0) x µL; p=0.0032], albumin [4.2 (3.7-4.5) vs 3.6 (3.1-4.0) g/dL; p<0.001], and glucose [96.0 (89.0-106.0) vs 105.0 (92.0-127.2) mg/dL; p=0.022].

In the comparative analysis within each age cohort between localized (I, II and III) and advanced (IV) stages, statistically significant differences between stages stand out for both age cohorts in the values of lactate dehydrogenase (LDH) [175 (151.8-353.5) localized disease in patients under 50 years of age vs 377.0 (192.0-504.5) in patients over 70 years of age, p=0.037; 206 (168.0-382.8) advanced disease in patients under 50 years of age vs 365.5 (225.5-488.5) in patients over 70 years of age, p=0.001], carcinoembryonic antigen (CEA) [2.9 (1.5-9.8) vs 32.1 (7.9-396.5), p=0.001; 2.9 (2.0-6.9) vs 47.2 (5.6-314.3), p<0.001; respectively] and carbohydrate antigen (CA) 19.9 [9.9 (3.2-20.8) vs 103.5 (78.2-234.8), p<0.001; 11.7 (4.1-25.0) vs 125.0 (17.7-643.4), p<0.001; respectively].

In the cohort of patients under 50 years of age, differences were observed between localized and advanced stages also in the neutrophil-lymphocyte ratio (NLR) [2.4 (1.9-3.2) vs 3.4 (2.7-4.3), p=0.027]; while in the cohort of patients over 70 years of age, differences in albumin [3.7 (3.2-4.1) vs 3.3 (3.1-3.6), p=0.010] and alkaline phosphatase (ALP) values [74.5 (64.8-84.0) vs 108.5 (75.0-154.0), p<0.001] were observed. There were no differences neither in grade of differentiation nor in location of the primary tumor in the rectum at diagnosis between patients younger than 50 and older than 70 years (p=0.874 and p=0.880, respectively). In patients with localized disease, there were no differences in the prognostic factors evaluated by magnetic resonance imaging (MRI) between the two age groups: clinical lymph node involvement (p=0.795), extramural venous invasion (p=0.468), and mesorectal fascia threat (p=0.564); however, it should be noted that these parameters were not evaluated at diagnosis in between 12.3% and 16.7% of patients.

In patients with advanced disease (stage IV), no differences were found in the number (p=0.721) or location of distant metastases (p 0.292-1.0). The proportion of patients with Kirsten rat sarcoma oncogen (KRAS) mutation was higher in patients younger than 50 years, but it did not reach statistical significance (90.9% vs 56.2%, p=0.090); while no differences were observed in the frequency of neuroblastoma RAS (NRAS) or B-Raf proto-oncogene (BRAF) mutations (p=1,000).

The Glasgow and Goustave Roussy Immune Score (GRIM) prognostic scores, grouping stages I to IV, calculated in 67.3% and 76.5% of patients, respectively, showed statistically significant differences (p=0.004 in both cases), with a more favorable prognosis in patients younger than 50 years of age. The modified Glasgow prognostic score, however, did not show statistically significant differences between the two groups in 77.8% of patients analyzed (p=0.133) [17,18]. Biological age could be calculated using PhenoAge [19] in 56.9% of the patients, showing statistically significant differences between the two groups: [47.6 (9.3) in patients under 50 years of age, vs. 87.4 (10.9) in patients over 70 years of age; p<0.001]. The mean biological age of patients over 70 years of age was markedly higher than the chronological age (87.4 vs. 78.6, respectively), compared to that calculated for those under 50 years of age (47.6 vs. 45.0, respectively). The statistically significant differences achieved in the result of these scores by grouping patients with localized and advanced disease (stages I to IV) already mentioned were maintained for GRIM (p=0.011) and PhenoAge (p<0.001) in patients with localized disease, and for Glasgow (p=0.008) and PhenoAge (p<0.001) in patients with advanced disease (stage IV).

Prognostic models of advanced colorectal cancer calculated in 97.2% of patients in this subgroup (stage IV) achieved statistically significant differences in the Grupo Español Multidisciplinar de Cáncer Digestivo (GEMCAD) and Köhne models (p=0.012 and p=0.011, respectively), with a better prognosis for patients younger than 50 years of age. However, no statistically significant differences were found when applying the Groupe Coopèrateur Multidisciplinaire en Oncologie (GERCOR) prognostic model (p=0.419) [20].

Therapeutic strategy against rectal cancer, depending on the clinical stage at diagnosis, in patients younger than 50 years versus patients older than 70 yearsof age in the stage-matched population

In localized disease, no statistically significant differences were found in the surgical procedure performed (p=0.234), length of hospital stay for surgery (p=0.066), or in postoperative wound complications (p=0.741). However, statistically significant differences were observed in anastomotic dehiscence, occurring in 10.5% of those under 50 years of age compared to 1.3% of

Stage IV patients	< 50 years N: 12	> 70 years N: 24	
First line treatment: N (%) - Monochemotherapy - Doublet chemotherapy - Triplet chemotherapy - Only radiotherapy - Only best supportive care	 0 (0.0) 8 (66.7) 4 (33.3) 0 (0.0) 0 (0.0)	 4 (16.7) 6 (25.0) 0 (0.0) 1 (4.2) 13 (54.2)	 < 0.001
First line targeted therapy: N (%) - Yes - No	 9 (75.0) 3 (25.0)	 3 (12.5) 21 (87.5)	 < 0.001
Number of lines of therapy [Median (Q1– Q3)]	3.0 (2.0 – 3.0)	0.5 (0.0 – 1.8)	< 0.001
Stage IV patients treated with chemotherapy	**< 50 years N: 12**	**> 70 years N: 10**	
First line treatment toxicity . N (%) - G1-2 - G3-4	 7 (58.3) 5 (41.7)	 4 (40) 6 (60)	 0.670
Residual Neurotoxicity: N (%) - No - G2	 7 (58.3) 5 (41.7)	 8 (80.0) 2 (20.0)	 0.381
Treatment related admission in hospital: N (%) - No - Yes	 11 (91.7) 1 (8.3)	 6 (60.0) 4 (40.0)	 0.135
Treatment modification - No - Yes - Interruption	 6 (50.0) 4 (33.3) 2 (16.7)	 4 (40.0) 3 (30.0) 3 (30.0)	 0.864

Table 3: Treatment of stage IV rectal cancer patients in the stage mached population.

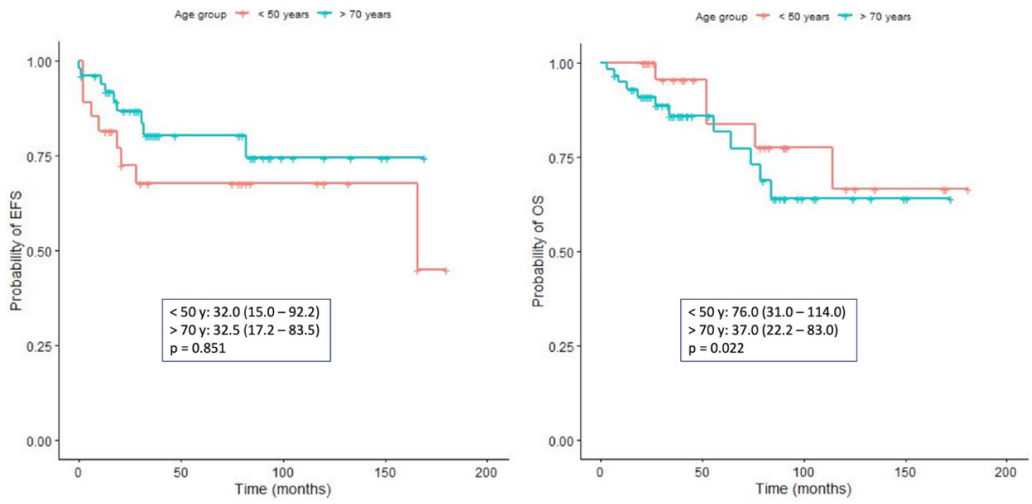

Figure 2: Kaplan-Meier Estimates of Event Free Survival (EFS) and Overall Survival (OS) in clinical stage III matched populations.

those over 70 years of age (p=0.048). No statistically significant differences were observed in the performance of ostomy (p=0.069), but it was transient in 42.1% of those under 50 years of age compared to 21.1% of those over 70 years of age. Organ preservation was achieved in the same proportion of patients in both groups (5.3%).

There were statistically significant differences in the neoadjuvant treatment applied according to age (p<0.001), with a greater use of neoadjuvant chemotherapy and chemoradiotherapy in patients under 50 years of age (31.6% vs 10.5%) and greater use of exclusive radiotherapy in those over 70 years of age (0% vs 31.6%). Similarly, statistically significant differences were observed in adjuvant therapy use in favor of patients under 50 years of age (34.2% vs 14.5%; p=0.033).

Similarly, there were statistically significant differences in the treatment administered to patients with advanced disease according to age, both in their intention (more radical in patients under 50 years of age, p=0.008; more symptomatic in those over 70 years, p<0.001) and modality (higher chemotherapy use in patients under 50 years, p<0.001) and in their intensity (more intense in patients under 50 years, p<0.001) and duration (more lines of chemotherapy in patients under 50 years, p<0.001) (Table 3).

Treatment outcomes of rectal cancer, in patients younger than 50 years versus patients older than 70 years of age in the stage-matched population

The median follow-up of the stage-matched population sample is 4.8 years (2.3-9.5) for patients younger than 50 years and 2.8 years (1.1-6.1) for those over 70 years of age. There was a statistically significant difference in median follow-up between both age cohorts (p<0.001).

There were differences, although not statistically significant, in the median event free survival (EFS) between the 18 stage I

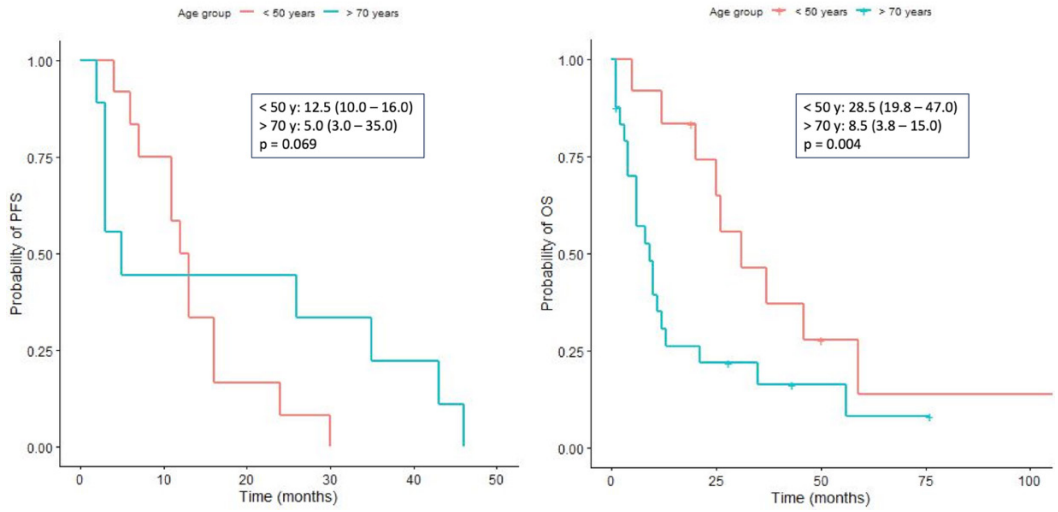

Figure 3: Kaplan-Meier Estimates of Progression Free Survival (PFS) and Overall Survival (OS) in clinical stage IV matched populations.

rectal cancer patients younger than 50 and older than 70 years [128.5 (82.2-142.5) vs. 66.0 (48.0-98.2), respectively; p=0.111]. Similarly, differences in median overall survival (OS) at this stage did not reach statistical significance [130.0 (88.8-143.5) vs 78.0 (59.2-99.5), respectively; p=0.083].

Median EFS of 6 stage II patients was 20.0 months (15.5-43.0), with no statistically significant differences between patients under 50 and over 70 years of age [22.0 (20.0-30.0) vs. 16.0 (14.0-58.0), respectively; p=0.655]. Differences in median OS between patients younger than 50 years and older than 70 at this stage did not reach statistical significance [68.0 (47.5-113.5) vs 16.0 (9.5-48.8), respectively; p=0.121].

Median EFS of the 87 stage III patients was 32.5 months (15.2-84.0), with no statistically significant differences between patients younger than 50 and older than 70 years (p=0.851). However, differences in the median OS according to age at this stage did reach statistical significance favoring patients under 50 years of age [76.0 (31.0-114.0) vs 37.0 (22.0-83.0), respectively; p=0.022]. Regarding disease recurrence, only numerical differences were observed in the proportion of local and distant relapses in stages II and III grouped between patients under 50 and over 70 years of age (2.6% vs 6.6% local and 26.3% vs 9.2% distant relapse, respectively; p=0.603).

At the time of this analysis, 75% [9] of patients under 50 years of age and 91.6% [22] of patients over 70 years of age with stage IV rectal cancer had died, while 16.7% [2] of patients under 50 years of age and 8.3% [2] of patients over 70 years of age were still alive with disease recurrence. Among the 22 stage IV patients treated with chemotherapy (12 under 50 years of age, 10 over 70 years of age), there were no differences in first line chemotherapy toxicity severity (p=0.670), hospital admissions (p=0.135), or treatment modifications (p=0.864) (Table 3). Median progression free survival (PFS) of the 36 patients with stage IV disease was 12 (5.0-24.0) months, with only clinically significant differences between patients younger than 50 and older than 70 years [(12.5 (10.0-16.0) vs 5.0 (3.0-35.0); p=0.669]. Nevertheless, clinically and statistically significant differences were found in median OS, with longer OS in patients younger than 50 years [28.5 months (19.8-47.0) vs 8.5 months (3.8-15.0), respectively; p=0.004].

Disscusion

According to the results of the RELEO study, rectal adenocarcinoma in people under 50 years of age, compared to those over 70 years of age, is not associated with differential risk factors detectable in anamnesis, has neither particular location in the rectum nor more advanced clinical stage at diagnosis, and is not associated to worse prognosis. Nevertheless, patients over 70 years of age show worse functional status and more comorbidities. On the other hand, rectal adenocarcinoma in patients under 50 years of age, compared to patients over 70, causes more symptoms at diagnosis, tends to take longer time to be diagnosed and shorter to be treated once diagnosed; and patients under 50 are also treated more intensively in both localized and advanced disease with clinicallly significant longer survival times in localized disease and statistically significant in advanced disease.

In the RELEO study the distribution by sex as well as clinical stage at diagnosis showed no differences between the two age cohorts in the global population. However there was a tendency to a higher proportion of advanced stages (III and IV) in those under 50 years of age. Previous reports in the literature have suggested that patients with EO-CRC present with more advanced disease owing to a tumor biology that is inherently more agressive, although recent reports have not confirmed this findings [21-24]. In our global population and the stage-matched cohort of only rectal cancer patients, differences in rectal tumor location could not be demonstrated. Previous analysis including colon and rectal cancer patients have reported more fequent location in left colon and rectum for EO-CRC but have not focused in tumor location within the rectum [25].

Worse functional status and higher comorbidity burden have been associated to older age at diagnosis of colorectal cancer [26]; in

our global cohort we could confirm worse functional status in patients older than 70 years and more impaired renal function. Difference in functional status favoring younger patients was also demonstrated in the population matched by stage; this fact could have influenced in differences in treatment intensity and outcomes in both localized and advanced sidease. As expected, further study of comorbidities in the stage matched population confirmed higher burden of them and more polypharmacy in patients over 70 years.

Biological age provides additional prognostic information beyond chronological age, especially in predicting health outcomes and functional status in older adults [27]. In our study based on Phenoage [17], biological age was higher than the chronological age, with higher differences in those over 70 years of age. Divergences between biological and chronological age tends to increase with advancing age, as cumulative exposures and genetic factors exert greater influence on physiological decline and disease risk [28].

The incidence of rectal cancer in people under 50 years of age in our study could not be justified by risk factors usually included in the anamnesis (obesity, toxic habits, professional activity, comorbidities, concomitant treatments, family history) at diagnosis. Although reasons for the rise in EO-CRC remain unknown, major hypotheses have focused on metabolic disorders and health behaviors, environmental risk factors, psychosocial states and stressors and medication use among younger generations causing accelerated biological aging [29,30]. Some strategies such us prospective cohort studies through life course, investigation of novel environmental exposures and early carcinogénesis, and comprehensive collections of paired clinicopathologic variables, biospecimens and exposome data, have been proposed in order to increase our knowledge [31].

Patients under 50 years of age in our study had abdominal pain and rectal bleeding as more frequent reasons for consultation, while those over 70 years of age had anemia as main cause for diagnostic procedures. These findings agree with those of the ColoCare study were younger patients with left-sided colon and rectal cancers were more likely to present with symptomatic disease compared to older patients [32]. It has also been described how younger patients also tend to experience longer delays from symptom onset to diagnosis, frequently due to lower clinical suspicion, resulting in a higher proportion of advanced-stage disease at presentation [33,34]. In our series of patients, time elapsed between the onset of symptoms and histopathological diagnosis also tended to be longer in patients under 50 years of age, while time between histopathological diagnosis and the establishment of the therapeutic plan was significantly shorter.

There is strong evidence that advanced rectal cancer is associated with higher tumor marker and inflammatory parameter levels compared to localized rectal cancer [35,36]. As previously reported in the literature, in both cohorts of patients in our study, those under 50 and over 70 years of age, advanced disease was associated with significantly higher LDH, CEA, and CA 19.9 values. These results were consistent with greater systemic inflammation, identified in LDH, and a higher tumor burden, reflected in higher CEA and CA 19.9 values, in the advanced stages. In those younger than 50 years, advanced disease was also associated with higher NLR values, reflecting a greater impact on inflammation parameters in patients under 50 years of age in the face of advanced disease; while in those over 70 years of age it was associated with lower albumin values and higher ALP values. reflecting a greater impact on nutritional status due to advanced disease in older patients.

The adverse prognostic factors for MRI in localized disease were similar in patients younger than 50 and older than 70 years in our study. Previous reports have shown the presence of MRI-detected adverse prognostic features as strong predictors of poor outcomes regardless of age, with prognostic value consistent across age groups [37,38].

Regardinga advanced disease, only the frequency of KRAS mutation differed between both groups, being significantly more frequent in people under 50 years of age, with location and number of metastases showing no differences. No other histopthaological or molecular features, usually described to be more agressive in younger populations, were observed in our stdudy [25].

The GRIM and Glasgow prognostic scores were more favorable in people under 50 years of age; this was also the case for GEMCAD and Köhne scores in cases of advanced disease for this group. There is evidence that prognostic score results for advanced colorectal cancer can differ depending on patient age, but age itself is not consistently an independent prognostic factor when adjusting for other clinical variables [38]. Younger patients with localized rectal cancer often receive more intense perioperative treatment, including higher rates of neoadjuvant chemoradiotherapy, adjuvant chemotherapy, and multiagent regimens, even in low-risk stage II disease, compared to older patients, although guidelines recommend similar management regardless of age [25,31,39,40]. Patients under 50 years of age with localized disease in our study received more intense neoadjuvant treatment and adjuvant treatment was more frequently used in them compared to those over 70 years of age.

Despite more intense perioperative treatment is more frequently administered to younger patients with localized rectal cancer, this does not consistently lead to better DFS or OS compared to older patients with stage-specific outcomes agenerally similar across age groups [25,34,40]. Although conditioned by the small sample size, only trends towards better EFS and OS were observed in patients under 50 years of age with both stage I and II. In the case of stage III disease, this favorable trend in EFS was accompanied by a statistically significant difference in OS in favor of those under 50 years of age.

Regarding advanced disease, younger patients are more frequently treated with intense chemotherapy (triplet chemotherapy combinations, biologic agents) while older patients are less likely to receive chemotherapy for metastatic rectal cancer; consequently

younger patients may experience higher rates of treatment-related adverse events due to more aggressive regimens. However, this increased treatment intensity does not consistently translate into improved disease-specific outcomes. Survival rates and PFS are generally similar between younger and older patients when adjusted for stage and other prognostic factors [25,34,40,41]. Patients under 50 years of age with advanced rectal cancer in our study were treated more frequently with chemotherapy, and this chemotherapy was more intense and in in more lines of treatment compared to those over 70 years of age. Among patients receiving chemotherapy for advanced disease, there were no differences in the severity of toxicity, admissions, or the need to modify treatment according to age. Although we observed a tendency for higher PFS and a statistically significant difference in OS in favor of those under 50 years of age with advanced disease this finding could be explained by differentces in treatment strategies justified by worse performance status and more comorbidities in patients over 70 years of age.

In summary our study of rectal adenocarcinoma in stage-matched populations of patients under 50 and over 70 years of age showed that in patients over 70 years of age, with a similar disease profile to those under 50, their comorbidities and their biological age caused a greater impact of the disease, conditioning less intense antineoplastic treatment and limiting their prospects for survival.

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