Rectal Cancer in Adolescent and Young Adult Patients: Pattern of Clinical Presentation and Case-Matched Comparison of Outcomes

ORIGINAL CONTRIBUTION

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BACKGROUND: Rectal cancer in adolescents and young adults (age ≤39) is increasing. Early diagnosis is a challenge in this subset of patients.

OBJECTIVE: This study aims to analyze the presentation pattern and outcomes of sporadic rectal cancer in adolescents and young adults.

DESIGN: This is a retrospective study.

SETTING: This study was conducted at 3 European tertiary centers.

PATIENTS: Data on adolescents and young adults operated on for sporadic rectal cancer (January 2008 through October 2019) were analyzed. To compare outcomes, adolescents and young adults were matched to a group of patients aged ≥40 operated on during the same period.

MAIN OUTCOME MEASURES: The primary outcomes measured were clinical presentation and long-term outcomes.

RESULTS: Sporadic rectal cancers occurred in 101 adolescents and young adults (2.4%; mean age, 33.5; range, 18–39); 51.5% were male, and a smoking habit was reported by 17.8% of patients. The rate of a family history for colorectal cancer was 25.7%, and of these patients, 24.7% were obese. Diagnosis based on symptoms was reported in 92.1% patients, and the mean time from first symptoms to diagnosis was 13.7 months. The most common symptom at diagnosis was rectal bleeding (68.8%), and 12% and 34% of the adolescents and young adults presented with locally advanced or metastatic disease at diagnosis. Consequently, 68.3% and 62.4% adolescents and young adults received neoadjuvant and adjuvant treatments. The rate of complete pathological response was 24.1%; whereas 38.6% patients had stage IV disease, and 93.1% were microsatellite stable. At a mean follow-up of 5 years, no difference in cancer-specific survival, but a lower disease-free survival was reported in adolescents and young adults ($p < 0.0001$) vs the matched group. Adolescents and young adults with stages I to II disease

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had shorter cancer-specific survival and disease-free survival ($p = 0.006$; $p < 0.0001$); with stage III disease, they had a shorter disease-free survival ($p = 0.01$).

LIMITATIONS: This study was limited by its observational, retrospective design.

CONCLUSIONS: The significantly delayed diagnosis in adolescents and young adults may have contributed to the advanced disease at presentation and lower disease-free survival, even at earlier stages, suggesting a higher metastatic potential than in older patients. See **Video Abstract** at http://links.lww.com/DCR/B537.

CÁNCER DE RECTO EN PACIENTES ADOLESCENTES Y ADULTOS JÓVENES: CUADRO DE PRESENTACIÓN CLÍNICA Y COMPARACIÓN DE DESENLACES POR CASOS EMPAREJADOS

ANTECEDENTES: El cáncer de recto en adolescentes y adultos jóvenes (edad ≤ 39) está aumentando. El diagnóstico temprano es un desafío en este subgrupo de pacientes.

OBJETIVO: Analizar el cuadro de presentación y los desenlaces en adolescentes y adultos jóvenes con cáncer de recto esporádico.

DISEÑO: Estudio retrospectivo.

ÁMBITO: Tres centros europeos de tercer nivel.

PACIENTES: Se analizaron los datos de adolescentes y adultos jóvenes operados de cáncer de recto esporádico (enero de 2008 - octubre de 2019). Para comparar los desenlaces se emparejó a adolescentes y adultos jóvenes con un grupo de pacientes mayores de 40 años operados en el mismo período de tiempo.

PRINCIPALES VARIABLES ANALIZADAS: Cuadro clínico, resultados a largo plazo.

RESULTADOS: Los cánceres de recto esporádicos en adolescentes y adultos jóvenes fueron 101 (2,4%, edad media: 33,5, rango 18-39). El 51,5% eran hombres, el 17,8% de los pacientes fumaba. El 25,7% tentía antecedentes familiares de cáncer colorrectal. El 24,7% eran obesos. El diagnóstico con base en los síntomas se informó en el 92,1% de los pacientes, el tiempo promedio desde los primeros síntomas hasta el diagnóstico fue de 13,7 meses. El síntoma más común en el momento del diagnóstico fue el sangrado rectal (68,8%). 12% y 34% de adolescentes y adultos jóvenes presentaron enfermedad localmente avanzada o metastásica en el momento del diagnóstico. Por lo tanto, el 68,3% y el 62,4% de adolescentes y adultos jóvenes recibieron neoadyuvancia y adyuvancia. La tasa de respuesta patológica completa fue del 24,1%; mientras que el 38,6% estaban en estadio IV. El 93,1% eran microsatelite estable. Con una media de seguimiento de 5 años, no se observaron diferencias en la sobrevida específica del cáncer, pero se informó una menor sobrevida libre de enfermedad en adolescentes y adultos jóvenes (p <0,0001) frente al grupo emparejado. Los adolescentes y adultos jóvenes en estadios I-II tuvieron una sobrevida específica por cáncer y una sobrevida libre de enfermedad más corta ($p = 0,006$; p <0,0001); el estadio III tuvo una sobrevida libre de enfermedad más baja ($p = 0,01$).

LIMITACIONES: Diseño observacional y retrospectivo.

CONCLUSIONES: El diagnóstico notablemente demorado en adolescentes y adultos jóvenes puede contribuir a la presentación de una enfermedad avanzada y a una menor sobrevida libre de enfermedad, incluso en estadios más tempranas, lo cual implica un mayor potencial metastásico en comparación con pacientes mayores. Consulte **Video Resumen** en http://links.lww.com/DCR/B537. *(Traducción—Dr. Juan Antonio Villanueva-Herrero)*

KEY WORDS: Adolescent; Clinical presentation; Outcomes; Rectal cancer; Young.

Approximately 70,000 adolescent and young adults (AYAs; age 15–39) are diagnosed with cancer each year in the United States,[1] accounting for 5% of the overall cancer diagnoses. Although the absolute number of colorectal cancer (CRC) cases remains low in AYAs,[2,3] its incidence is on the rise.[2,4–10] Specifically, the increased incidence of rectal cancer (RC) in younger patients is more significant for patients in the age interval 20 to 34 years.[3,11] In addition, a study including data from the Surveillance, Epidemiology, and End Results program of the American National Cancer Institute showed that, among people aged 35 to 39 years, 32% of tumors occurred in the rectum.[12] A recent report from the American Cancer Society[13,14] warns that the incidence of CRC (in which typically 90% of patients are over 50 years of age) is increasing sharply in each generation born since 1950. Individuals born in the 1990s have double the risk of developing colon cancer, and the risk of developing RC is quadrupled in comparison with adults born in the 1950s at their same age. Although the implementation of screening programs results in earlier diagnosis and improved survival, the worrying rise in AYAs reverses this trend.[15,16] Early diagnosis of AYA-RC poses a challenge, particularly in those patients without a known predisposition (eg, familial adenomatous polyposis (FAP), hereditary nonpolyposis CRC (HNPCC) or Lynch syndrome, IBD) and due to the absence of awareness of patients and care providers of potential alarm symptoms. In addition, in published series, controversy exists regarding pathological features, stage at presentation, and outcomes.[17–20] This study aims to analyze patient

characteristics, presentation pattern, and outcomes in AYA patients operated on for sporadic RC and to correlate outcomes with a group of matched patients aged ≥40 operated on in the same period.

METHODS

Data on patients operated on for RC from January 1, 2008 to October 31, 2019 were retrospectively collected from prospectively maintained databases of 3 European tertiary centers. An additional chart review was performed if needed. Eleven AYA patients were excluded because they were affected by predisposing conditions (1 attenuated FAP, 2 FAP, 5 HNPCC, and 3 IBD). Data of the remaining 101 AYA patients with sporadic RC were analyzed: patient characteristics, presentation pattern, pathology data, time from first symptoms to diagnosis, neoadjuvant/adjuvant treatments, and long-term outcomes. To analyze outcomes, AYAs were matched one-to-three to a group of patients aged ≥40 operated on for sporadic RC in the same period. Among the 4210 patients ≥40 years of age, 210 were excluded before the matching because they were affected by a predisposing condition (1% FAP, 2.8% HNPCC, 1.2% IBD). The matching criteria used were distance of the tumor from anal verge, because our focus was on RC, and anastomotic failure, because it is recognized to have an impact on local recurrence. No emergency procedures were performed both in AYA patients and in the matched group. Obesity was defined as a BMI ≥30 kg/m^2. Family history was defined as at least one first/second/third-degree relative affected by CRC in patients not fulfilling the Amsterdam or Bethesda criterion for HNPCC or the clinical criteria for FAP. Hereditary nonpolyposis CRC (or Lynch syndrome) was defined by the presence of deleterious mutation in a DNA mismatch repair gene. Patients with a histologically proven diagnosis of IBD were also excluded. All patients in the AYA group underwent a genetic assessment. The Institutional Review Board of the 3 centers approved the study.

Statistical Analysis

Continuous variables were reported using means and SDs; categorical variables were reported using frequencies and percentages. A one-to-three propensity score matching was used to determine the group of patients aged ≥40 according to the following covariates: distance of the tumor from anal verge and anastomotic failure. Logistic regression analysis was performed to estimate the association between obesity and outcomes. The prognostic effect of obesity was estimated using cancer-specific survival (CSS) and disease-free survival (DFS) Cox regression model. Linear and exponential regression analyses were performed to analyze the correlation between age at diagnosis and the time in months between first symptoms and diagnosis. Cancer-specific survival and DFS analyses were conducted using the Kaplan-Meier method. For patients who had died or been lost to follow-up, data were censored at the time of death or last documented follow-up. All statistical tests were 2-sided and analyses were performed using SPSS (Statistical Package for the Social Sciences, version 25.0; SPSS Inc, Armonk, New York) software. A p value <0.05 was considered statistically significant.

RESULTS

Of 4210 patients with RC operated on in the study time frame, 101 were younger than 39 and affected by sporadic RC (2.4%; mean age, 33.5; range, 18–39). Fifty-two of 101 (51.5%) patients were male; a smoking habit was reported by 18 of 101 (17.8%). The rate of family history for colorectal cancer was 25.7%. Twenty-five of 101 (24.7%) patients were obese (mean BMI, 24.73). Table 1 shows patients' demographics in detail. Obesity was not a risk factor for CSS (OR, 0.22; 95% CI, 0.02–1.39; $p = 0.17$), whereas it was a risk factor for DFS, although not significant (OR, 1.66; 95% CI, 0.67–4.38; $p = 0.35$). At Cox regression analysis, obese subjects had a HR of 1.74 (95% CI, 0.88–3.45) for disease progression in comparison with nonobese patients (HR, 0.57; 95% CI, 0.29–1.14), although not significant ($p = 0.11$). Diagnosis based on symptoms was reported in 92.1% of AYA patients; the mean time from first symptoms to diagnosis was 13.7 months. The most common symptom at diagnosis was rectal bleeding (64/101; 68.8%) followed by changes in bowel habits (18%). Table 2 shows the other symptoms in detail. No linear or exponential correlation was found between age at diagnosis and time in months from first symptoms to diagnosis ($p = 0.71$; $p = 0.56$). Twelve of 101 (12%) and 34 of 101 (34%) AYA patients presented with locally advanced or metastatic disease at diagnosis; 12.9% were pluri-metastatic or

TABLE 1. Patient demographics

Variable	*AYA (age ≤39) (n = 101)*
Age, years, mean ± SD (range)	33.5 ± 4.77 (18–39)
Sex, n (%)	
Male	52 (51.5)
Female	49 (48.5)
BMI, kg/m^2, mean ± SD	24.73 ± 5.39
Obesity, n (%)	25 (24.7)
Overweight, n (%)	34 (33.6)
Normal	41 (40.5)
Underweight	1 (1.2)
Common familiar CRC, n (%)	26 (25.7)
Smoker, n (%)	
Yes	18 (17.8)
No	80 (79.2)
Ex	3 (3.0)

Values are given as mean (±SD) or n (%).
AYA = adolescent and young adults; CRC = colorectal cancer.

TABLE 2. Pattern of clinical presentation

Variable	AYA (age ≤39) (n = 101)
Reason for diagnosis, n (%)	
Symptoms	93 (92.1)
Screening	7 (6.9)
Incidental	1 (1.0)
Symptoms at diagnosis, n (%)	
Rectal bleeding	64 (68.8)
Chronic abdominal pain	5 (5.4)
Change in bowel habits	17 (18.2)
Rectal pain	1 (1.1)
Bloating	5 (5.4)
Weight loss	1 (1.1)
Mean time from symptoms to diagnosis, mo	13.7 + 9.8
Locally advanced disease at diagnosis, n (%)	12 (11.9)
Metastatic disease at diagnosis, n (%)	34 (33.7)
Liver	17 (50.0)
Lung	3 (8.8)
Liver and lung	5 (14.8)
Peritoneum	6 (17.7)
Liver and peritoneum	1 (2.9)
Kidney	–
Liver and presacral	1 (2.9)
Ovary	1 (2.9)
Pluri-metastatic/carcinomatosis, n (%)	13 (12.9)

Values are given as mean (±SD) or n (%).
AYA = adolescent and young adults.

presented with carcinomatosis (Table 2). Consequently, 69 of 101 (68.3%) and 63 of 101 (62.4%) AYA patients received neoadjuvant and adjuvant treatments (Table 3). After neoadjuvant chemoradiation, 24.1% patients achieved a complete pathological response (ypT0N0); whereas 38.6% patients had stage IV disease. Most of sporadic RCs in AYA patients were microsatellite stable (93.1%). Two microsatellite instable AYA-RCs were stage 0, three were stage 2, one was stage 3, and one was stage 4.

At a mean follow-up of 5 years, no difference in CSS ($p = 0.99$) but a lower DFS was reported in AYA patients ($p < 0.0001$), when compared to the matched group of patients aged >40 (mean age, 67.3 ± 16.52; range, 40–91) (Table 4; Fig. 1). Cancer-specific survival and DFS curves did not change after exclusion of patients with stage IV disease, microsatellite instability (MSI) cases, and cases with common familial CRC (Figs. 2–4). A stage-specific analysis was also performed merging stages I and II (because there were only 4 stage I AYA patients). Adolescent and young adult patients with stage I to II disease had a reduced CSS and DFS ($p = 0.006$; $p < 0.0001$), whereas AYA patients with stage III disease showed a reduced DFS compared with patients aged ≥40 ($p = 0.01$) (Figs. 5 and 6).

DISCUSSION

Our study focuses on a rare subgroup of patients developing RC. In fact, because of the low overall incidence of

TABLE 3. Pathology stage, microsatellite status, and neoadjuvant/adjuvant treatment

Variable	AYA (age ≤39) (n = 101)
TNM stage, n (%)	
Stage 0 (complete response)	13/54 (24.1)
Stage I	4/88 (4.5)
Stage IIa	22/88 (25.0)
Stage IIb	2/88 (2.3)
Stage IIIa	8/88 (9.1)
Stage IIIb	10/88 (11.4)
Stage IIIc	8/88 (9.1)
Stage IV	34/88 (38.6)
Microsatellite status	
MSI	7 (6.9)
MSS	94 (93.1)
Neoadjuvant therapy, n (%)	69 (68.3)
Chemotherapy	11/69 (15.9)
Radiotherapy	4/69 (5.8)
Chemoradiotherapy	54/69 (78.3)
Adjuvant therapy, n (%)	63 (62.4)

Values are given as mean (±SD) or n (%).
AYA = adolescent and young adults; MSI = microsatellite instability; MSS = microsatellite stable.

CRC in the AYA population and the unique age range that straddles a both "pediatric" and "adult" cohort, few studies have explored CRC, and in particular RC, in AYAs.[6,10,21] Only 26% of AYA patients reported a family history for CRC. This, together with the lack of screening programs for the population of this age group and an underestimation of symptoms by patients and doctors, may have likely contributed to the more advanced stage at diagnosis and consequently to a lower DFS. Nevertheless more patients presented with metastatic disease at diagnosis; CSS did not differ in the 2 groups. However, the worst prognosis observed in AYAs diagnosed at stages I to II may suggest a different biology of RC in this specific group of patients.

TABLE 4. Cancer-specific survival and disease-free survival in the 2 groups

Variable	AYA (age ≤39) (n = 101)	Matched group (age ≥40) (n = 300)	p value
Age, y, mean ± SD (range)	33.5 ± 4.77 (18–39)	67.3 ± 16.52 (40–91)	
Follow-up time, days, mean ± SD	1992.52 + 216.03	1989.89 ± 209.79	0.973
Vital status, n (%)			0.074*
Alive	88 (87.1)	280 (93.3)	
Dead	13 (12.9)	20 (6.7)	
Status at the last follow-up, n (%)			<0.0001
Cancer-free	49 (48.5)	255 (84.6)	<0.0001
Local recurrence	2 (2)	3 (1.2)	0.749
Metastases	50 (49.5)	42 (14.2)	<0.0001

Values are given as mean (±SD) or n (%).
AYA = adolescent and young adults.
*Yates correction has been applied.

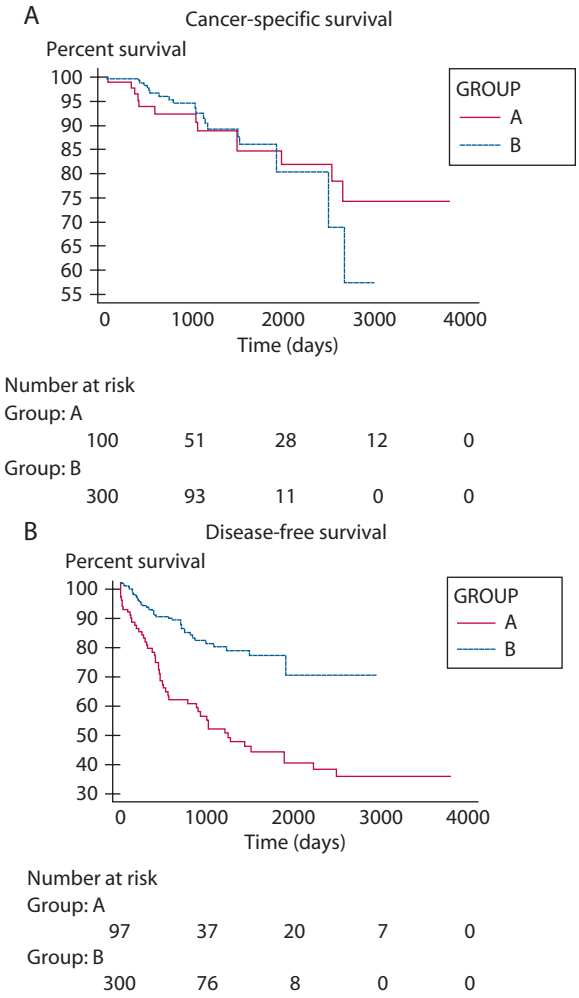

FIGURE 1. Cancer-specific survival (A) and disease-free survival (B) curves. A, AYA; B, matched group. AYA = adolescent and young adults.

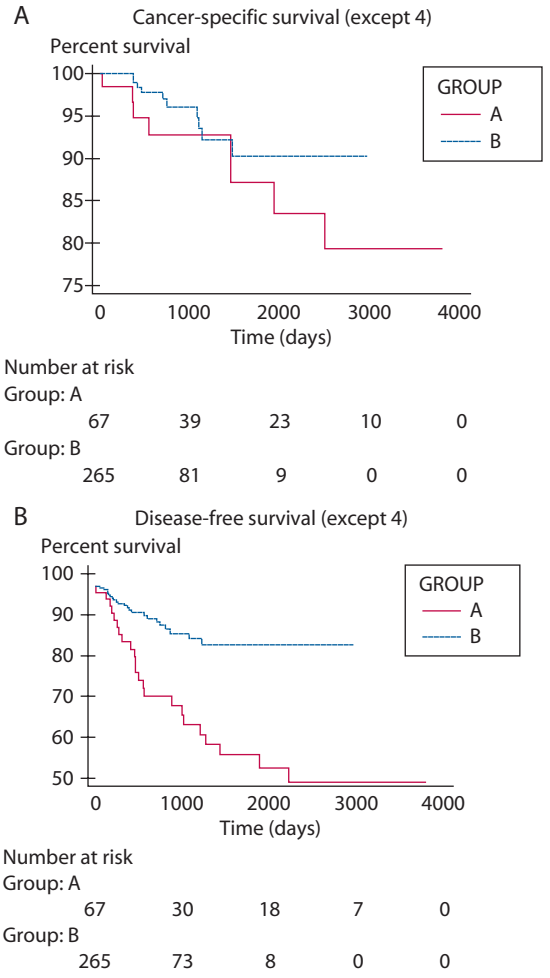

FIGURE 2. Cancer-specific survival (A) and disease-free survival (B) curves without stage IV patients. A, AYA; B, matched group. AYA = adolescent and young adults.

Adolescent and young adult CRC tends to present at more advanced clinical stages[6,7,13,16,22] and with more aggressive tumor features compared with similar tumors in older patients.[16,19,23–25] This may be due to more frequent delayed diagnosis in AYAs and possibly to a different tumor biology (ie, more aggressive variants). In the present study 33% of AYA-RC patients presented with distant metastases and 12% with locally advanced disease. Mean time from symptoms to diagnosis was more than 1 year in AYA-RC. According to literature data, young patients are diagnosed at more advanced stages than older patients, even when screening-detected cancers are excluded.[26] The scarce awareness (not only of young people, but also of parents and physicians) that CRC can occur in this age group certainly contributes to the delayed diagnosis. A recent survey by the Colorectal Cancer Alliance[27] reported that 63% of survey respondents with young-onset CRC (≤50 years of age, 43% of these being ≤39) had waited 3 to 12 months to see a doctor after the onset of symptoms, often because they did not suspect their symptoms as a possible presentation of CRC. However, even when visiting their physicians, most patients were initially misdiagnosed: 67% of respondents saw at least 2 physicians, and some as many as 4, before receiving the proper diagnosis of CRC. Physicians most commonly misdiagnosed patients as having hemorrhoids or IBD. Most of the survey respondents (71%) were diagnosed at stage III or IV, which subjected them to aggressive therapies and a substantial decrease in their physical and emotional quality of life, as well as life expectancy. Hence, physicians need to be aware of the increasing rate of AYA-CRC, because they can play a critical role in decreasing the mortality by recognizing the signs and symptoms of the disease early on and therefore recommending a timely diagnostic when symptoms appear, regardless of the patient's age. In addition, physicians have an immediate opportunity to improve the detection of CRC in younger patients by maintaining awareness that CRC mostly occurs in individuals with no family history or apparent risk factors and is increasingly occurring in individuals <50 years of age. No correlation between age and time in months from first symptoms to diagnosis was found. This finding may possibly be related

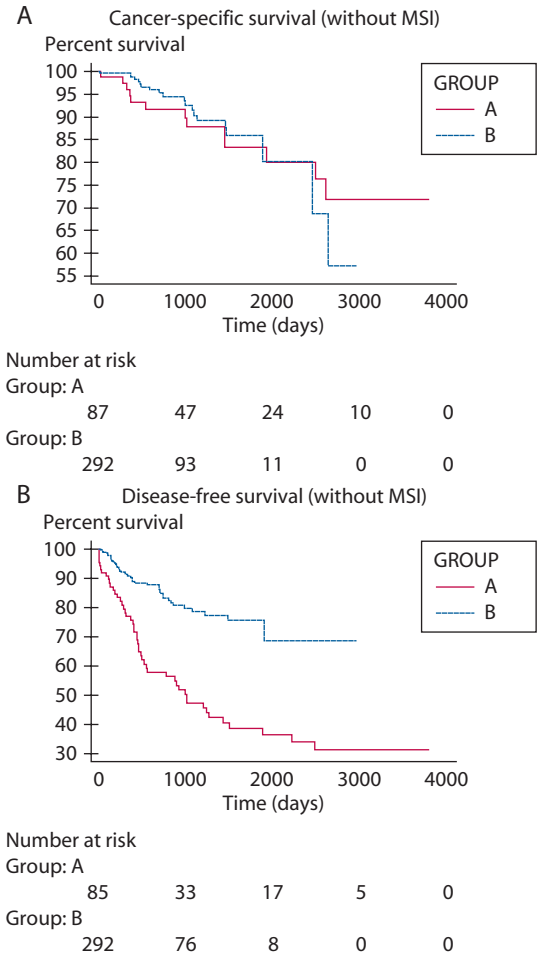

FIGURE 3. Cancer-specific survival (A) and disease-free survival (B) curves without MSI cases. A, AYA; B, matched group. AYA = adolescent and young adults; MSI = microsatellite instability.

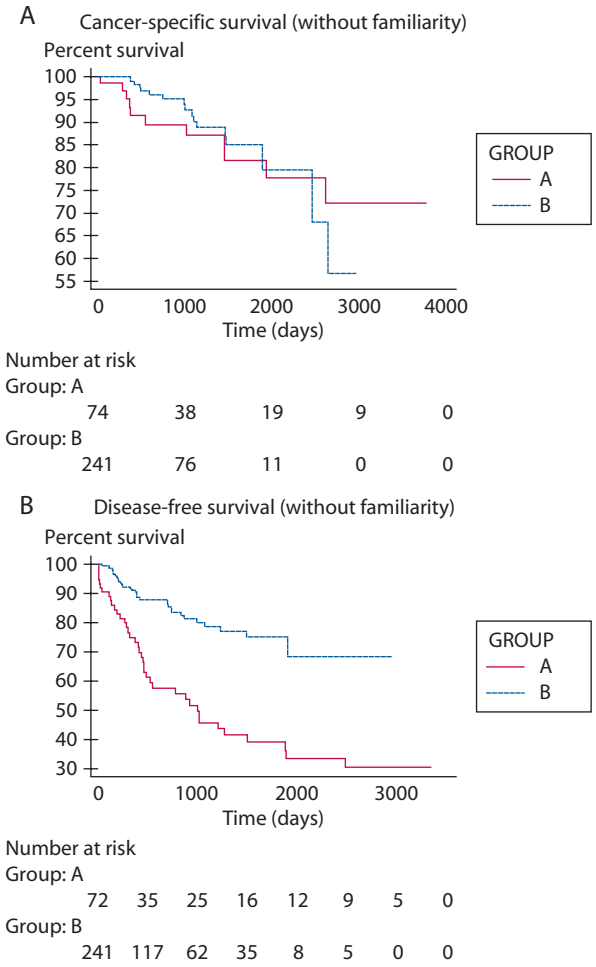

FIGURE 4. Cancer-specific survival (A) and disease-free survival (B) curves without common familial CRC cases. A, AYA; B, matched group. AYA = adolescent and young adults; CRC = colorectal cancer.

to the very young subset of patients in our study. However, the analysis of this correlation warrants further insight with a larger sample of patients. Another possible strategy to reduce CRC in AYAs is to change the cutoff to begin CRC screening. In fact, most current guidelines recommend beginning screening for average-risk patients at age 50.[28–32] However, it is becoming increasingly recognized that sporadic cancers in patients aged ≤50 represent a large number of CRC cases, with growing morbidity and mortality, because a high rate of these patients present with stage III or IV disease. Interestingly, the biggest increase in CRC is occurring among people younger than 40 years of age, suggesting that consideration should be given to starting screening at age 40.[2,3,14] In this regard, the American Cancer Society recently updated the screening guidelines recommending to start screening at age 45 for the normal-risk population, whereas the U.S. Multi-Society Task Force for Colorectal Cancer recommends screening at age 40 for all patients with a family history of CRC at any age. Our data are consistent with the current literature and underline the importance to continue analyzing the incidence data of CRC in the young to set an appropriate threshold age for the beginning of screening.

Cancer-specific survival did not differ among AYA patients and the group of older patients, whereas DFS was significantly worse in AYA patients. These findings did not change if patients with MSI or patients with familial CRC were excluded from the analysis. Interestingly, AYA patients showed a significantly shorter CSS and DFS at earlier pathology stages and a significantly higher complete pathological response rate after neoadjuvant chemoradiotherapy. As far as we know these data have not previously been reported in the literature and might support the theory of a different biology of AYA-RC.[33,34] Hence, sporadic AYA-RCs seem to have a good response to chemoradiotherapy but at the same time tend to recur more rapidly. Our data may suggest that RC in the young represents a different biological entity, which in turn influences response to multimodal therapy and cancer natural history.

Microsatellite instability in CRC arising in the young ranges from 7% to 41%[35–37] depending on the age of onset. This relatively high proportion of MSI tumors in young

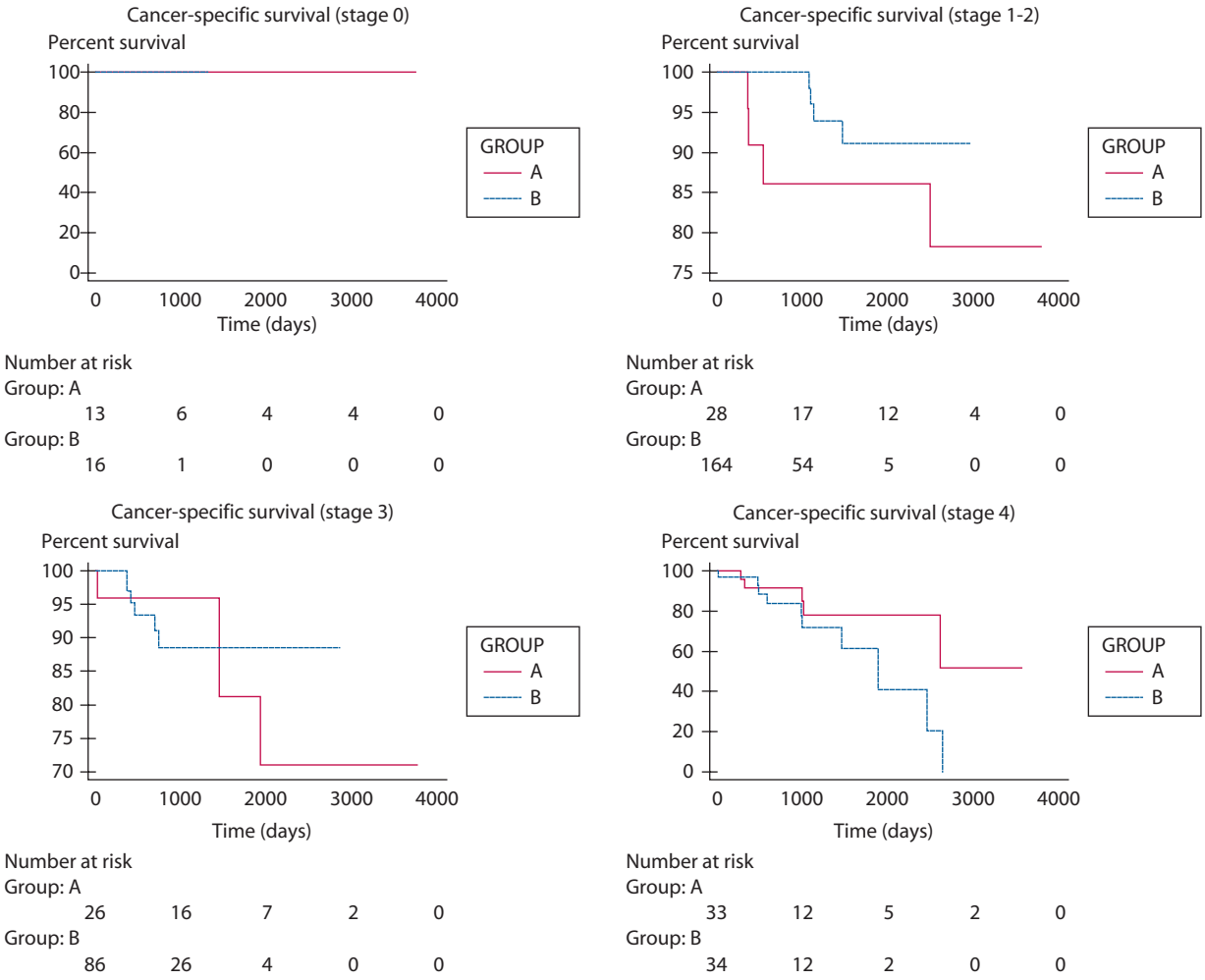

FIGURE 5. Cancer-specific survival curves by stage. A, AYA; B, matched group. AYA = adolescent and young adults.

patients with CRC has been attributed to the high proportion of patients with HNPCC in that age group. However, approximately 15% to 20% of sporadic CRCs in the young population also show MSI. Rectal cancers arising in the young have a lower expression of MSI than colon cancers (5.55% vs 27.7%; $p = 0.04$).[38] In our study, the rate of MSI was 6.9%, which is consistent with literature data. Interestingly, we did not report an association between survival and microsatellite status.[39] However, MSI cases in our study group were too few to draw definitive conclusions. There are no data in the literature regarding the correlation of microsatellite status and other clinical/genetic characteristics of AYA-RCs, an aspect that warrants further studies.

Population-based studies showed that men are more likely to develop left-sided colon cancer and RC than women. These differences were attributed to genetic, epigenetic, and hormonal factors.[40] Sex distribution specifically in AYA-RCs has not been described yet. In our series, 51.5% of patients were men; our findings are in accordance with 2 studies focused on CRC in AYAs[6,10] that showed an overall slightly higher, but not statistically significant, incidence of CRC in males.[10] Nevertheless, a specific analysis according to cancer site was not performed in these studies. Further studies are required to effectively assess the incidence by sex among AYA-RC patients and better understand potentially related factors.

Although obesity is a known risk factor for the development of CRC, in our series 24.7% of patients were obese and 33.6% were overweight. Despite the descriptive nature of our data, evidence seems to support the hypothesis of attributing the increasing trend of CRC in the most recent generations to a shift in lifestyle factors: Western dietary pattern (with abundance of red and processed meat[41] and high-fat diet[42]), coupled with lack of physical activity,[43,44] resulting in obesity.[43–45] A recent population-based study[46] (1.8 million adults followed over 23 years) analyzing the association between BMI in late adolescence and the risk of CRC concluded that being overweight or obese in adolescence was associated with an increased risk of subsequent colon cancer both in men and women, whereas only obesity was associated with an increased risk of RC. The shorter DFS and the

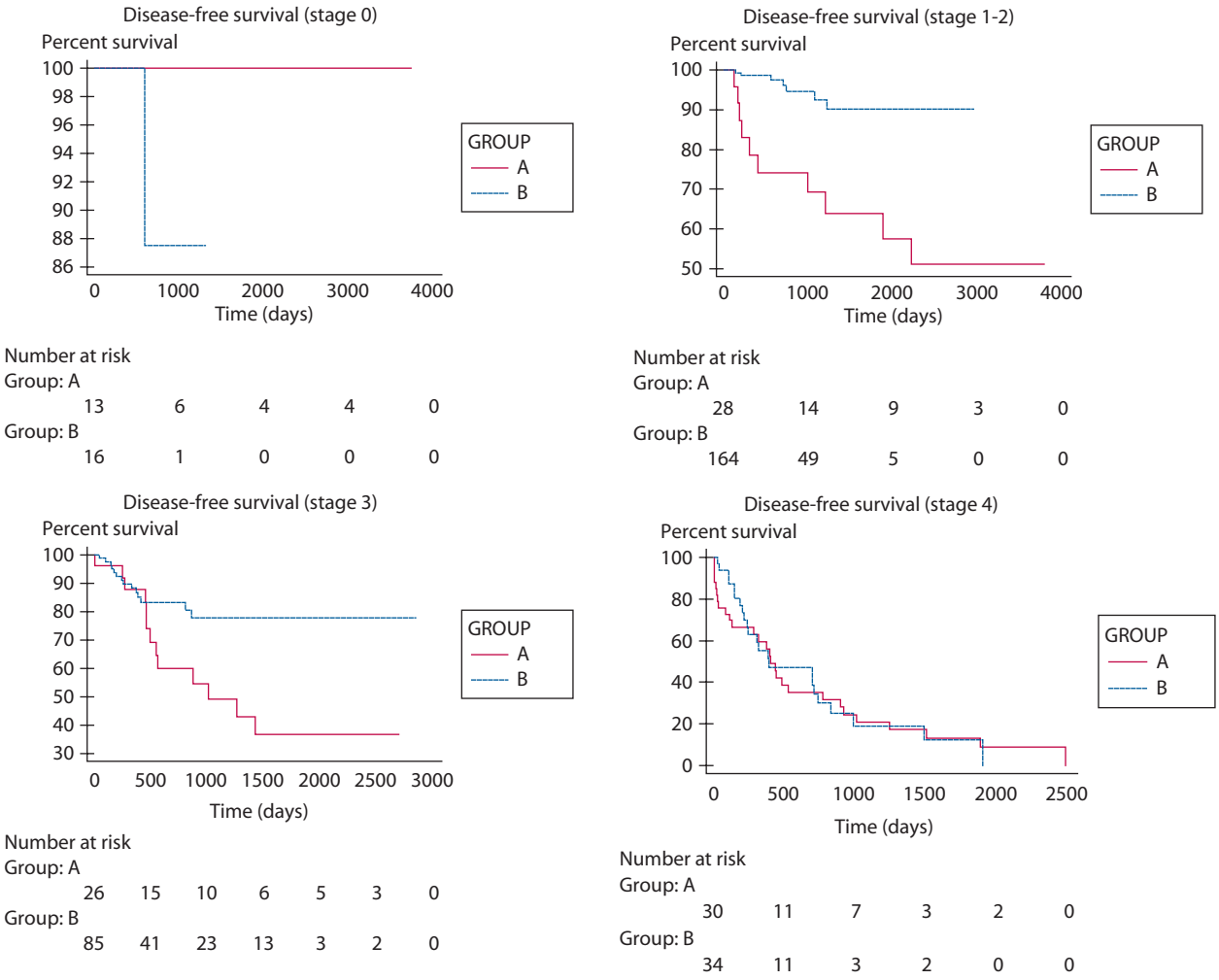

FIGURE 6. Disease-free survival curves by stage. A, AYA; B, matched group. AYA = adolescent and young adults.

faster disease progression in obese patients did not result in statistical significance in our study. However, these findings warrant further analysis because our data are too limited to draw definitive conclusions.

Tobacco smoking has been previously reported as a risk factor of early-onset CRC (<50 years).[47,48] However, this habit was reported only in 18% of AYAs. A possible explanation could be related to the age interval of the study group, in which risk factors other than tobacco smoking probably should be explored.

Although a limitation of this study is its observational retrospective design, the large study population from 3 centers offers a significant amount of clinical data, considering the rare subset of patients examined.

CONCLUSIONS

Our data call for increasing awareness on RC in AYA patients, a disease with a growing incidence for which the presence and prompt investigation of symptoms are critical for a timely diagnosis at an early, curable stage. Future interventions should target strategies for earlier diagnosis, closer surveillance, and a greater understanding of its biology, etiology, and risk factors.

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