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Original Article

Classifying early-onset colorectal cancer according to tumor location: new potential subcategories to explore

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Abstract: Early-onset Colorectal Cancer (ECRC) represents a significant and increasing proportion of Colorectal Cancer (CRC), but it is a heterogeneous entity that probably encompasses specific subclasses. On the premise that the carcinogenetic mechanism and progression of CRC may differ with location, we analyzed molecular and clinical characteristics of ECRC according to tumor location in order to identify more homogeneous subgroups of CRC. Right-sided ECRC is a subset in which most Lynch Syndrome cases are found, with earlier stages at diagnosis and better prognosis. At this location the CpG Island Methylator Phenotype (CIMP) is predominant and Chromosomal Instability (CI) is rare. Left-sided ECRC appears as a transitional or intermediate location, except for CI tumors, that seem to predominate at this location. Finally, rectal ECRC shows Microsatellite Stability, CIMP low-0 and low CI - with recurrent altered chromosomal regions in common with left-sided ECRC-, possibly in relation with Microsatellite And Chromosomal Stable tumors, but with an unexpected familial component and worse prognosis. All this suggest that the molecular basis of ECRC varies with tumor location, which could affect the clinical management of patients.

Keywords: Early-onset colorectal cancer, microsatellite instability, CpG island methylator phenotype, chromosomal instability, tumor location

Introduction

Early-onset CRC (ECRC) represents 11% of colon cancers and 18% of rectal cancers [1-4]. Currently, it is not generally considered as a subgroup of hereditary CRC, and Microsatellite Instability (MSI) does not explain the majority of cases [5-8]. Although ECRC could be a specific subgroup of CRC [6], it is a heterogeneous entity that probably encompasses particular subclasses of CRC [7, 8]. Some studies have demonstrated that right- and left-sided CRCs exhibit different genetic, biological and demographical characteristics, suggesting that the carcinogenetic mechanism and progression of CRC may differ with tumor location [9-11]. Thus, the anatomic site of CRC could help to subclassify ECRC and to identify more homogeneous subgroups of CRC. To our knowledge, this should be the first analysis of molecular and clinical characteristics of ECRC according to tumor location.

Material and methods

We collected a total of 88 consecutive individuals with ECRC younger than 45 years old; six cases with Familial Adenomatous Polyposis

Table 1. Clinical, pathological and familial features of the global group, and the comparison of the different location groups within early-onset CRC

	Early-onset CRC n (%)	Right colon Early-onset CRC n (%)	Left colon Early-onset CRC n (%)	Rectum Early-onset CRC n (%)	p (X^2)
Patients	82 (100)	20 (24)	35 (43)	27 (33)	
Mean age of onset (SD)[1]	39.6 (4.9)	39.1 (6)	39.3 (4.2)	40.2 (4.9)	NS
Sex					
Male	49 (59.8)	10 (50)	22 (63)	17 (63)	
Female	33 (40.2)	10 (50)	13 (37)	10 (37)	NS
Tumour differentiation[2]					
Poor	8/60 (13.3)	4/16 (25)	3/24 (12.5)	1/20 (5)	NS
Mucin production[2]	19/60 (32)	6/16 (37.5)	8/24 (33)	5/20 (25)	NS
"Signet ring" cells[2]	4/60 (7)	0/16 (0)	2/24 (8)	2/20 (10)	NS
Astler-Coller modified					
A	23 (28)	4 (20)	12 (34)	7 (26)	
B	26 (32)	12 (60)	12 (34)	2 (7)	
C	14 (17)	3 (15)	3 (9)	8 (30)	
D	19 (23)	1 (5)	8 (23)	10 (37)	0.002
Global Survival in months (SD)[1]	58.5 (34.8)	81.6 (34.5)	55.4 (32.6)	44.6 (29.4)	<0.001
Disease-Free Survival in months (SD)[1]	50.8 (39.9)	72.4 (42.6)	48.7 (37.2)	36.7 (35.2)	0.006
Associated polyps	46 (56)	14 (70)	21 (60)	11 (41)	NS
Mean number (SD)[1]	1.8 (2.5)	3 (3.2)	1.6 (1.9)	1.2 (2.3)	0.046
Type					
Adenomatous	22 (48)	5 (36)	10 (48)	7 (64)	NS
Hyperplastic	8 (17)	2 (14)	4 (19)	2 (18)	
Mixed	16 (35)	7 (50)	7 (33)	2 (18)	
Multiple primary neoplasms	11 (13)	5 (25)	4 (11)	2 (7)	NS
Synchronous or metachronous CRCs	5 (6)	4 (20)	0 (0)	1 (4)	0.01
Family history of cancer					0.006
Amsterdam II-positive families	15 (18)	8 (40)	6 (17)	1 (4)	
Aggregation for Lynch-related neoplasms	27 (33)	7 (35)	6 (17)	14 (56)	
Aggregation for Lynch-unrelated neoplasms	9 (11)	1 (5)	6 (17)	2 (8)	
Sporadic cases	31 (38)	4 (20)	17 (48)	10 (37)	

[1]Statistical analysis was carried out using Student's t test. [2]Percentages shown are based on varying total numbers as some cases were excluded because only one biopsy was taken (stage D), or because tumors were severely dysplastic with "in situ" carcinoma, and it was not possible to study any other characteristic. SD: Standard Deviation. NS: Not Significant. CRC: Colorectal Cancer.

were excluded. All patients, or a first degree relative when the proband was deceased, provided written consent. Clinicopathological, familial and follow-up characteristics of all cases and comparisons between location groups are shown in **Table 1**. Molecular analysis involves MSI analysis and screening for germline mutations in Mismatch Repair (MMR) genes [6]; CpG Island Methylator Phenotype (CIMP) characterization; and Chromosomal instability (CI) was evaluated by comparative genomic hybridization (CGH) array, and methods and calculation of the Genomic Instability Index (GII, defined as the fraction of altered genome) as recently reported [13]. For associations between tumor location and other discrete variables, statistical analyses were performed using Pearson's Chi Square (X^2) Test for parametric variables, and Fisher's Exact Test for non-parametric variables. For continuous variables, Student's t test was used.

Results

The earliest modified Astler-Coller tumor stages (A and B) were observed in 80% of the right-sided ECRCs, whereas the most advanced stages (C and D) predominated in rectal cases. The highest mean-number of associated polyps as well as the highest frequency of multiple, synchronous or metachronous, CRCs where associated with right location, decreasing progressively throughout the left colon and the rectum. Amsterdam II criteria were fulfilled by 40% of right-sided ECRC cases, and there was also an important rate of Lynch Syndrome (LS)-related tumors in rectum cases (56%). Prognosis worsened gradually from right colon

Table 2. Molecular characteristics of early-onset CRC according to tumor location

	Right colon Early-onset CRC n (%)	Left colon Early-onset CRC n (%)	Rectum Early-onset CRC n (%)	p (X^2)
MSI	6/20 (30)	6/35 (17)	0/26 (0)	0.016
MMR gene mutations	6 (30)	4 (11)	0	0.009
CIMP				0.005
CIMP-0	2 (12.5)	14 (45)	11 (52)	
CIMP-Low	6 (37.5)	14 (45)	8 (38)	
CIMP-High	8 (50)	3 (10)	2 (10)	
Molecular classification				0.007
MSI- CIMP High	3 (19)	1 (3)	0 (0)	
MSI- CIMP Low-0	2 (12.5)	4 (13)	0 (0)	
MSS- CIMP High	5 (31)	2 (6.5)	2 (9.5)	
MSS- CIMP Low-0	6 (37.5)	24 (77.5)	19 (90.5)	
GENOMIC INSTABILITY[1]				
GII				
Gains	0.048321	0.124064	0.115086	NS
Losses	0.020220	0.227445	0.018711	0.009
Normal	0.870251	0.692384	0.830362	0.05
CNA per case (SD)	91.5 (45)	121 (128)	61.6 (77)	0.14
Total gains per case (SD)	43 (22)	55 (67)	34 (47)	NS
Total losses per case (SD)	48.5 (22)	66 (63)	28 (32)	0.03
Mean of whole altered chromosomes (SD)	1.5 (2)	3 (3)	3.5 (4)	0.14

[1]Statistical analysis was carried out using Student's t test. CIMP: CpG Island Methylator Phenotype. CNA: Copy Number Alterations. GII: Genomic Instability Index. MSI: Microsatellite Instability. SD: Standard Deviation. NS: Not Significant. MMR: Mismatch Repair. CRC: Colorectal Cancer.

cases, with best prognosis, to rectal cases, with worst prognosis, like Global Survival and Disease-Free Survival. All clinical data are shown in **Table 1**.

Eighty-one of the 82 early-onset cases were studied. Twelve were defined as MSI (15%) and the remaining 69 were defined as Microsatellite Stable (MSS) (**Table 2**). MSI was present in 30% of right-sided ECRC, in 17% of left-sided ECRC, and in 0% of rectum cases. Ten cases showed a pathogenic germline mutation in one of the MMR genes: two in MLH1 and four in MSH2 in right colon cases, and two in MLH1 and two in MSH6 in left colon cases. One left colon case showed hypermethylation of the MLH1 promoter as sporadic case, and none LS case appeared in rectal location.

CpG Island Methylator Phenotype (CIMP) characterization was carried out in 68 of the 82 early-onset tumours (**Table 2**). Right-sided CRCs showed an important component of CIMP (high in 50% and low in 37.5%). Left-sided and rectal CRCs demonstrated a low frequency of CIMP-High (10%).

We classified ECRC into four categories [12] based on CIMP status [6] and the results of the microsatellite study. Right-sided ECRCs showed the most even distribution of the four categories. Left-sided and rectal ECRCs were mainly MSS-CIMP low-0 (**Table 2**).

Quantitative analysis of CI in tumours according to location is shown in **Table 2**. The highest GII was observed in left-sided ECRCs, and the subgroup of Losses showed significant differences between the three tumour locations. Left-sided ECRCs also exhibited the highest number of copy number alterations (CNAs) per case, and the lowest number of CNAs per case was observed in rectal ECRCs. However, this latter group showed the highest mean number of whole chromosome aberrations.

Univariate and multivariate analysis performed with R Statistical Software® [13] were carried out in order to identify minimum recurrently lost or gained regions at the different locations (Supplementary Table 1). Recurrent gains and losses were more frequent in right-sided ECRCs. The only recurrent region that was

observed in all three tumor locations was gain of 19p13.3-q13.24. Five regions were common to right- and left-sided ECRCs: losses at 1q12-q21.2, 5q13.2, 9p12-p13, 9p13.1, and 10q11.22. Other frequently altered regions were: gains at 7q22.1 and losses at 16p13.12-p12.3, in right-sided ECRCs; losses at 9q21.11 and 11q14.2-14.3, and gains at 20q11.21-q11.22, in left-sided ECRCs; and losses at 14q11.1-11.2, and gains at 17q21.31-q21.32, and 22q11.1 in rectal ECRCs. Based on the comparative analysis between tumor locations, two main groups of differentially altered chromosomal regions emerge: one predominantly associated with left-sided ECRCs, and another one common to left-sided and rectal ECRCs (Supplementary Table 2).

Discussion

Early-onset CRC is being considered a specific and distinct subtype of CRC according to molecular, morphological and genetics features [8]. In order to better characterize carcinogenesis and its correlation with clinical, pathological and familial patterns, our group of research described the three main ways of CRC pathogenesis (microsatellite, chromosomal instability, and CpG island methylation) in the different tumour locations (right colon, left colon, and rectum) [5, 6]. A molecular classification of CRC should be established in order to practical implications for diagnosis, prognosis and treatment, and, for that purpose and before a necessary comparison with late-onset CRC, an in-depth analysis of early-onset CRC must be done.

Right-sided ECRC shows, as a group in which most LS cases are found, some of its features, including earlier stages at diagnosis, more associated polyps, synchronous and metachronous CRC, and better prognosis. At this location CIMP-High is predominant and CI is rare, although recurrently altered chromosomal regions are observed (>40%) [9]. Left-sided ECRC appears as a transitional or intermediate location, except for CI tumors that seem to predominate at this location, as well as sporadic cases. Finally, rectal ECRC shows mainly MSS, CIMP low-0 and low CI, possibly in relation with Microsatellite and Chromosomal Stable (MACS) tumors [14, 15], but with recurrent altered chromosomal regions in common with left-sided ECRC as well, and an unexpected familial component (Lynch-related tumors aggregation without diagnosis of Lynch Syndrome) and worse prognosis (not only explained by the advanced stage of diagnosis).

The most frequent common region, gain in 19p13.3-q13.42, has already been reported as more frequent in early-onset CRC population [16], in which only 20-50% cases showed LOH of this region, as well as in Peutz-Jeghers syndrome [17, 18]. Regarding the most frequent regions commonly altered within right and left colon, only losses of 1q12-q21.2 have previously been reported in this subset of age [16], being the others rarely reported in association with sporadic CRC [19]. With respect to the most frequent regions for each group of location alone, only gain of 7q22.1 in right colon cancer (related with GAEC1) [20], and loss of 14q11.1-11.2 in rectal cancer (related with NDRG2) [21], have been previously associated with CRC; 11q13.3 region has been related to some cases of lymph node metastasis [22], and 2p24.3 showed evidence of linkage with cases of Familial CRC type X [23].

All these findings strongly suggest that molecular basis of ECRC varies with tumor location and may have a significant impact on the clinical management of patients. Next step should be the analysis and comparison of all these parameters within late-onset CRC regarding tumor location, in order to continue our differential characterization of ECRC, and also a complete definition and knowledge of the implications of the most important altered chromosome regions of each colon location.

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Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

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Supplementary Table 1. Most frequent chromosomal regions altered for each early-onset CRC location

Right colon				Left colon				Rectum			
Chromosome	region		%	Chromosome	region		%	Chromosome	region		%
chr1	p36.23	p34.2	54	chr1	p36.23	p36.22	46	chr1	q21.1	q21.1	42
chr1	q12	q21.2	69	chr1	p36.22	p35.3	50	chr5	q13.2	q13.2	42
chr1	q21.1	q21.2	62	chr1	p36.11	p36.11	46	chr6	p21.31	p21.2	47
chr5	q13.2	q13.2	69	chr1	p35.3	p35.1	46	chr8	p23.1	p23.1	47
chr7	p22.3	p22.2	62	chr1	q21.1	q21.1	61	chr9	p13.1	p13.1	42
chr7	p22.2	p22.1	54	chr5	q13.2	q13.2	64	chr9	p12	p12	42
chr7	q11.23	q11.23	62	chr6	p21.31	p21.2	46	chr9	p12	q21.11	47
chr7	q11.23	q11.23	62	chr7	p22.3	p22.3	46	chr9	q21.11	q21.11	42
chr7	q21.3	q22.1	54	chr7	q11.23	q11.23	46	chr10	q11.22	q11.22	47
chr7	q22.1	q22.1	69	chr7	q22.1	q22.1	46	chr11	q14.1	q14.1	42
chr9	p13.1	p13.1	69	chr9	p12	p11.2	57	chr11	q24.3	q25	42
chr9	p12	q13	77	chr9	q13	q13	57	chr11	q25	q25	47
chr9	p12	p11.2	85	chr9	q21.11	q21.11	57	chr12	q13.11	q13.2	47
chr9	q13	q21.11	69	chr9	q33.3	q34.3	46	chr14	q11.1	q11.2	53
chr9	q33.3	q34.3	62	chr10	q11.21	q11.22	57	chr17	q12	q21.32	47
chr10	q11.22	q11.22	77	chr11	p11.12	p11.12	61	chr17	q21.31	q21.32	53
chr10	q21.3	q22.1	54	chr11	q12.3	q13.3	46	chr17	q22	q25.3	47
chr11	p11.12	p11.12	62	chr11	q13.1	q13.2	50	chr18	q12.3	q12.3	42
chr11	q13.1	q13.2	54	chr11	q14.2	q14.3	57	chr19	p13.3	q13.43	58
chr12	q13.13	q13.2	54	chr13	q33.3	q34	46	chr20	p11.1	q13.2	47
chr14	q24.2	q24.3	54	chr14	q32.31	q32.32	46	chr22	q11.1	q11.1	53
chr16	p13.3	p13.3	54	chr16	p13.3	p13.3	46	chr22	q11.1	p22.33	47
chr16	p13.12	p12.3	69	chr16	q21	q22.1	54				
chr16	p13.11	p13.11	62	chr17	q21.1	q21.31	46				
chr17	p11.2	p11.2	54	chr17	q22	q25.3	46				
chr17	q21.31	q21.32	62	chr17	q24.3	q25.3	50				
chr17	q24.3	q25.3	62	chr19	p13.3	p13.11	54				
chr19	p13.3	q13.42	69	chr19	p13.11	p13.11	57				
chr19	q13.2	q13.2	54	chr19	q13.33	q13.43	46				
chr19	q13.42	q13.43	62	chr20	q11.1	q13.33	50				
chr21	q22.3	q11.1	62	chr20	q11.21	q11.23	54				
chr21	q22.3	q22.3	69	chr20	q11.21	q11.22	57				
chr22	q12.1	q13.31	54	chr20	q12	q13.12	54				
				chr20	q13.2	q13.2	46				
				chr22	q11.1	q11.1	50				
				chr22	q11.1	q11.21	46				

Green: gained region. Red: lost region.

Supplementary Table 2. Recurrently lost or gained chromosomal regions at the three tumor locations

Chromosome	*p*-value	Right colon freq	Left colon freq	Rectum freq	START	END
1	0.03667446	0.22	**0.47**	0.27	p36.32	p36.32
1	0.03667446	0.22	**0.47**	0.27	p36.21	p36.13
1	0.03667446	0.22	**0.47**	0.27	p36.21	p36.21
1	0.03667446	0.22	**0.47**	0.27	p36.31	p36.23
1	0.02296994	0.15	**0.42**	0.32	p36.13	p36.13
1	0.03667446	0.22	**0.47**	0.27	p33	p33
1	0.03667446	0.22	**0.47**	0.27	p21.2	p21.2
1	0.03667446	0.22	**0.47**	0.27	p35.3	p35.1
1	0.03667446	0.22	**0.47**	0.27	p32.3	p32.3
1	0.03667446	0.22	**0.47**	0.27	p34.1	p34.1
1	0.03667446	0.22	**0.47**	0.27	p36.33	p36.33
1	0.04053749	0.18	**0.47**	0.27	p32.1	p31.3
1	0.03698053	0.17	**0.45**	0.32	p31.1	p31.1
2	0.00620656	0.12	*0.27*	*0.30*	q11.2	q11.2
2	0.01121651	0.12	*0.28*	*0.30*	p22.1	p21
2	0.01395518	0.12	*0.30*	*0.30*	p24.3	p24.3
2	0.01395518	0.12	*0.30*	*0.30*	p14	p13.3
2	0.01633463	0.12	*0.32*	*0.30*	p23.1	p22.3
2	0.01633463	0.12	*0.32*	*0.30*	p16.2	p16.1
3	0.04279354	0.20	**0.45**	0.23	p13	p13
3	0.0307224	0.22	**0.45**	0.23	p21.31	p21.31
3	0.0307224	0.22	**0.45**	0.23	p14.1	p14.1
4	0.03678661	0.17	*0.35*	*0.32*	p12	p11
4	0.01935295	0.15	*0.35*	*0.32*	p13	p13
5	0.01747245	0.17	**0.47**	0.28	p13.3	p13.3
6	0.04279354	0.20	**0.45**	0.23	q13	q13
6	0.04279354	0.20	**0.45**	0.23	p21.33	p21.32
6	0.04279354	0.20	**0.45**	0.23	p23	p23
6	0.03554386	0.18	**0.43**	0.20	q12	q12
6	0.03554386	0.18	**0.43**	0.20	q12	q13
6	0.04279354	0.20	**0.45**	0.23	p12.2	p12.2
8	0.0440678	0.18	**0.47**	0.32	p12	p12
8	0.0440678	0.18	**0.47**	0.32	q12.3	q12.3
8	0.0440678	0.18	**0.47**	0.32	q22.2	q22.2
10	0.04569747	0.13	*0.32*	*0.30*	q24.1	q24.1
11	0.03120876	0.22	*0.32*	*0.28*	q13.2	q13.3
12	0.03667446	0.22	**0.47**	0.27	p11.21	p11.1
12	0.03667446	0.22	**0.47**	0.27	p13.1	p13.1
14	0.04895096	0.13	**0.27**	0.28	q23.2	q23.2
16	0.04279354	0.20	**0.45**	0.23	q11.1	q11.1
16	0.04279354	0.20	**0.45**	0.23	q22.1	q22.1
16	0.02204329	0.22	**0.43**	0.22	q12.1	q12.2
16	0.0307224	0.22	**0.45**	0.23	p13.11	p12.3
17	0.03667446	0.22	**0.47**	0.27	p12	p11.2
17	0.03667446	0.22	**0.47**	0.27	q25.3	q25.3
17	0.02543652	0.20	**0.38**	0.17	q22	q22
17	0.04160357	0.20	**0.40**	0.18	q21.32	q21.32

20	0.04885665	0.22	**0.42**	0.22	q13.13	q13.2
20	0.04885665	0.22	**0.42**	0.22	q13.12	q13.13
21	0.04232093	0.07	0.30	*0.23*	q22.11	q22.11
21	0.04232093	0.07	*0.30*	*0.23*	p11.2	p11.2
21	0.04122866	0.07	*0.32*	*0.23*	q21.1	q21.1

Numbers in bold indicate chromosomal regions predominantly altered in left-sided Early-onset Colorectal Cancer (ECRC). Numbers in italics indicate chromosomal regions altered with comparable frequencies in left-sided and rectal ECRC.