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ORIGINAL ARTICLE

Worse histological grade of proximal colorectal tumors and its relation with stage

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Summary

Purpose: *Accumulated data seem to support the concept that proximal and distal colorectal cancers (CRC) should be considered as different disease entities. We investigated a particular aspect of this assumption by examining variation of stage and grade distribution according to tumor site in a Greek patients' group.*

Methods: *A total of 200 cases having had undergone surgery for primary CRC was retrospectively analysed. Fifty-seven proximal tumors were compared to 143 distal lesions regarding tumor stage (TNM I-IV) and grade of differentiation (well, moderate and poor). Grade distribution by site was also examined within each particular stage and within additional stage categories (I-II, III-IV, I-III, II-IV, II-III).*

Results: *There was an almost significant trend of distal tumors for earlier stage (I) presentation (p=0.055), whereas proximal cancers were more frequently diagnosed with stages II-III (p=0.08). Poorly differentiated lesions displayed a strong predilection for proximal site (p=0.002), while tumors with moderate differentiation were preferentially found distally (p=0.001). Such segmental differences in grade distribution were also ascertained within most particular stages and all additional stage subsets (especially the last three). Moreover, both the proximal and the poorly differentiated lesions showed a parallel decrease in their incidence during the study period.*

Conclusion: *The consistently recorded worse histological pattern of proximal tumors implies a different biological behavior of these lesions possibly due to distinct tumorigenic pathways involved in their development, whereas their tendency for late stage presentation demands further investigation before considered supportive to this concept.*

Key words: grade, proximal and distal colorectal cancer, stage, tumor site

Introduction

CRC – one of the most common malignancies in Western countries [1] – has been generally considered as the same disease entity, despite the well known differences in clinical and macroscopic presentation and surgical treatment of proximal and distal tumors. However, further segmental variations in age, gender and race incidence [2,3], combined with a proximal shift in the anatomical distribution of CRC within the large bowel [4] suggest that distinct genetic and environmental factors may be involved in the development of right and left-sided tumors [5,6].

Data from the molecular biology field support this aspect, indicating specific segmental predilections of the different tumorigenic pathways of CRC [6,7] and revealing distinct molecular patterns according to tumor location [8-14]. Whether these findings provide enough evidence to identify proximal and distal cancers as different biological entities is a matter of ongoing discussion [5,6,13,14].

From the clinical point of view, segmental differences in features with considerable prognostic significance, such as tumor stage and grade have been also observed, indicating a worse clinicopathological profile of proximal tumors [2,3,15-17]. The expected adverse impact of these findings on survival has been recently reported [18,19]. However, others have found a favorable proximal behavior in terms of earlier stage [10], better outcome [12,14,20] and response to chemotherapy [21].

Considering this discrepancy and the reported relations of stage and grade with the underlying tumori-

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genic pathways [7,8,10,12,20], we studied the segmental distribution of these variables in a cohort of Greek patients. We especially focused on segmental differences of grade within particular stages, in an attempt to determine whether such variations were consistently present during disease progress or were confined to certain stages. In addition, we investigated potential changes in the anatomical, stage and grade distribution of CRC over the study period, assuming that the possibly existing links between these features may be also reflected in their variation with time.

Methods

Study population

The hospital records of 236 patients having had undergone surgery for CRC between 1998 and 2003 in the 2nd Surgical Department, "Tzaneio" Hospital, Piraeus, were retrospectively analysed. After the omission of synchronous lesions with double location, recurrences, hereditary cancers and those with unclear pathology reports, 200 cases were finally included in the study. We therefore obtained a homogeneous sample of primary, sporadic and –also– untreated cases (without neoadjuvant therapy - not performed at the chosen study period).

Clinicopathological classification

We classified tumors as stage I, II, III, IV (TNM classification). Stage 0 lesions (3 cases) were incorporated into stage I. Grade categories included well (G_1), moderate (G_2) and poor (G_3) differentiation (WHO classification). For the study purposes, the entire cohort and each particular stage or grade were divided into proximal (cecum, ascending and transverse) and distal (descending, sigmoid and rectum), in relation to the splenic flexure [2,6,14,16,17]. Cases were also classified by the time of surgery into 3 time intervals (1998-1999, 2000-2001, 2002-2003).

Table 1. Clinicopathological characteristics of the entire cohort

Characteristics	*Number of cases (%) Total n=200*
Stage (TNM)	
I	29 (14.5)
II	84 (42)
III	68 (34)
IV	19 (9.5)
Grade	
G_1	13 (6.5)
G_2	170 (85)
G_3	17 (8.5)
Gender	
Male	118 (59)
Female	83 (41)
Age (years)	
Mean	69.1
Median	70
Range	32-93
Site	
Proximal	57 (28.5)
Distal	143 (71.5)
Time of operation	
1998-1999	63 (31.5)
2000-2001	72 (36)
2002-2003	65 (32.5)

Statistical analysis

We analysed segmental distribution of stage and grade using x^2 (with Yates correction when necessary) and Fisher's exact test – both appropriate for categorical comparisons. We specifically examined segmental distribution of grades within particular stages and within the following disease categories: stage I-II (early), III-IV (advanced), I-III (non metastatic), II-III (locally advanced and regional) and II-IV (excluding I). Potential variation of grade by stage was also investigated in overall series and in each particular segment. In all analyses, we tested for differences (between sites or stages) regarding each particular grade category, avoiding integration of well and moderate cases - considered as clinicopathologically and prognostically disparate disease entities [22]. Moreover, we compared site, stage and grade distribution of cases between the 3 different time intervals using the same tests. All p values were two-sided and statistical significance was put at the level of 0.05.

Results

The clinicopathogical characteristics of the studied cohort are listed in Table 1. There were 200 cases (118 males and 82 females with a mean age of 69.1 years) including 57 (28.5%) proximal and 143 (71.5%) distal cancers. The vast majority of cases (76%) had disease stage II-III and moderate grade (85%). Patients were almost uniformly distributed into the 3 time periods.

Segmental comparisons for each one stage and grade are presented in Table 2. There were no signifi-

Table 2. Differences in stage and grade between right and left-sided tumors

Parameters	*Total n=200 n (%)*	*Right n=57 n (%)*	*Left n=143 n (%)*	*p*-value (x^2, Yates)*
Stage				
I	29 (14.5)	4 (7)	25 (17.5)	NS (0.055)[§]
II	84 (42)	27 (47.5)	57 (40)	NS[†]
III	68 (34)	21 (37)	47 (33)	NS[†]
IV	19 (9.5)	5 (8.5)	14 (9.5)	NS
Grade				
G_1	13 (6.5)	5 (8.5)	8 (5.6%)	NS
G_2	170 (85)	41 (72)	129 (90.2)	0.001
G_3	17 (8.5)	11 (19.5)	6 (4.2)	0.002

[*]P values for comparisons of segmental distribution in particular stages or grades (tables 2×2). P values for comparison of overall stage and grade distribution by site (contingency tables), not shown in this column, were NS for stage and 0.002 for grade. [§]p=0.04 after exclusion of 3 cases with stage 0 disease. [†]p=0.08 for integrated stages II-III. NS: non significant

cant segmental differences regarding stage distribution. However, the proportion of cases with stage I was higher in distal than in proximal site (17.5 vs. 7%, p=0.055). In fact, when comparison was limited to T1/T2 N0M0 lesions (by removing Tis cases) this finding became significant (p=0.04). On the other hand, proximal tumors were more frequently presented in stages II-III (84.5 vs. 73%, p=0.08).

Clearly different segmental patterns were observed regarding grade distribution (Table 2). Poorly differentiated tumors (G_3) were more frequently found in proximal than in distal site (19 vs. 4%, p=0.002). Conversely, for lesions with moderate differentiation (G_2) a distal preponderance was well documented (90 vs. 72%, p=0.001).

Specific analysis (Table 3) confirmed the existence of proximal predilection for G_3 tumors within stages II, III, and both early and advanced disease (p=0.035, 0.04, 0.03 and 0.048, respectively). Significantly higher frequencies of distal tumors with moderate grade were found in stages I, III and in advanced disease (p=0.02, 0.02 and 0.025, respectively). Moreover, a prevalence of well differentiated proximal tumors was recorded in stage I. Also, in the 3 additional stage categories (created by excluding either stage I, or IV, or both – see methods), the proportion of poorly differentiated lesions was significantly higher in proximal than in distal site (p=0.0015, <0.001 and 0.002, respectively; Figure 1A). In the same categories, the significance of the ascertained predilection of distal tumors for moderate grade was also maintained (p=0.008, <0.001 and 0.007, respectively; Figure 1B).

Interestingly, grade was found connected not only with tumor site, but also with stage (Table 4 and Figure 2). In particular, the recorded ratios early/advanced stage for well, moderate and poor grade were 2.25 (9/4), 1.43 (99/71) and 0.41 (5/12), respectively (Figure 2), indicating clear predilections of well and poorly differentiated cancers for early (especially stage I) and advanced disease (III-IV), respectively (Table 4). At sub-

Table 3. Grade distribution within stages

*Stage**	*Total N (%)*	*Right N (%)*	*Left N (%)*	*p-value (x^2 Yates, Fisher)§*
I				
G_1	6 (21)†	3 (75)†	3 (12)	0.02
G_2	23 (79)	1 (25)	22 (88)	0.02
G_3	– (0)	– (0)	– (0)	–
Total	29 (100)	4 (100)	25 (100)	
II				
G_1	3 (3.5)	-(0)	3 (5.25)	NS
G_2	76 (90.5)	23 (85)	53 (93)	NS
G_3	5 (6)	4 (15)	1 (1.75)	0.035
Total	84 (100)	27 (100)	57 (100)	
Early stage				
G_1	9 (8)	3 (9.5)	6 (7.3)	NS
G_2	99 (87.5)	24 (77.5)	75 (91.5)	NS (0.08)
G_3	5 (4.5)	4 (13)	1 (1.2)	0.03
Total	113 (100)	31 (100)	82 (100)	
IIIG_1	4 (6)	2 (9.5)	2 (4.2)	NS
G_2	55 (81)	13 (62)	42 (89.3)	0.02
G_3	9 (13)	6 (28.5)	3 (6.5)	0.04
Total	68 (100)	21 (100)	47 (100)	
IV				
G_1	– (0)	– (0)	– (0)	–
G_2	16 (84)	4 (80)	12 (86)	NS
G_3	3 (16)	1 (20)	2 (14)	NS
Total	19 (100)	5 (100)	14 (100)	
Advanced stage				
G_1	4 (4.5)	2 (7.5)	2 (3.3)	NS
G_2	71 (81.5)	17 (65.5)	54 (88.5)	0.025
G_3	12 (14) †	7 (27)	5 (8.2)	0.048
Total	87 (100)	26 (100)	61 (100)	

*For brevity's sake only early (I-II) and advanced (III-IV) stage categories were included in this table (besides particular stages). §P values only for segmental comparisons of grade within stages. Corresponding values for comparisons of grade frequencies between stages are not shown in this column. †Marked frequencies differed significantly from those of the same grade observed in other stages; in the column "Total" p values - for G_1 (stage I vs. II-IV) and for G_3 (Advanced vs. Early stage) - were 0.003 and 0.02 respectively. Similarly, in the column "Proximal" p value for G_1 (stage I vs. II-IV) was 0.0013. NS: non significant

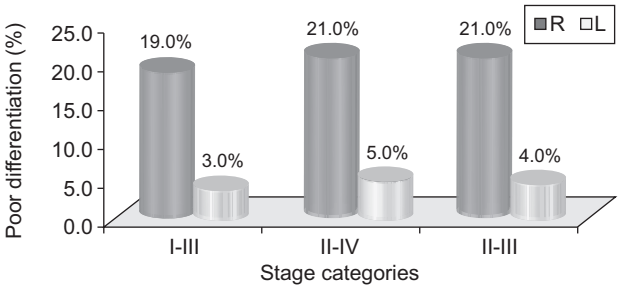

Figure 1A. Segmental distribution of poor differentiation in additional stage categories. The proportion of poor grade was significantly higher in proximal (R) than in distal (L) site in the following disease categories: Stage I-III: 19 vs. 3%, p<0.001; Stage II-IV: 21 vs. 5%, p=0.0015; Stage II-III: 21 vs. 4%, p=0.002.

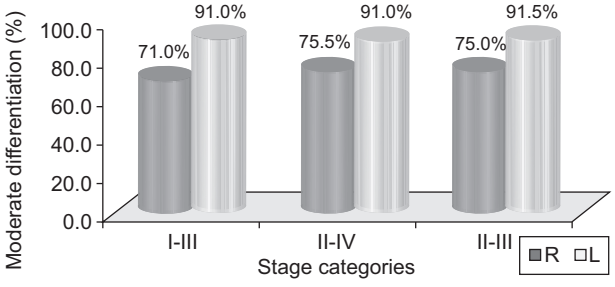

Figure 1B. Segmental distribution of moderate differentiation in additional stage categories. The proportion of moderate grade was significantly higher in distal (L) than in proximal (R) site in the following disease categories: Stage I-III: 91 vs. 71%, p<0.001; Stage II-IV: 91 vs. 75,5%, p=0.008; Stage II-III: 91,5 vs. 75%, p=0.007.

Table 4. Relation between stage and grade

A

Grade	*Total N*	*Stage I N (%)*	*Stage II N (%)*	*Stage III N (%)*	*Stage IV N (%)*
G_1	13	6 (46)	3 (23)	4 (31)	– (0)
G_2	170	23 (13.5)	76 (45)	55 (32)	16 (9.5)
G_3	17	– (0)	5 (29.5)	9 (53)	3 (17.5)
Total	200	29 (14.5)	84 (42)	68 (34)	19 (9.5)

As indicated in Table 4A, particular stage distributions of G_1 and G_3 tumors were clearly opposed to each other, while that of G_2 was similar to the overall stage distribution. For simplification and better statistical evaluation data were converted into the form shown below (Table 4B), by integrating stages I-II and stages III-IV.

B

Grade	*Total n*	*Early stage (I-II) n (%)*	*Advanced stage (III-IV) n (%)*	*p-value (x^2)*
G_1	13	9 (70)	4 (30)	NS*
G_2	170	99 (58)	71 (42)	NS*
G_3	17	5 (29.5)	12 (70.5)	0.02*
Total	200	113 (56.5)	87 (43.5)	0.045**

*p values for comparisons of stage distribution between a given grade and the integrated others (for instance G_1 vs. G_2-G_3) - tables 2×2. **p value for comparison between overall early and advanced stage distribution by grade (contingency table). In addition, separate comparisons of stage distribution between two particular grades yielded significant p values for G_3 vs. G_1 (p=0.003) and for G_3 vs. G_2 (p=0.023). NS: non significant

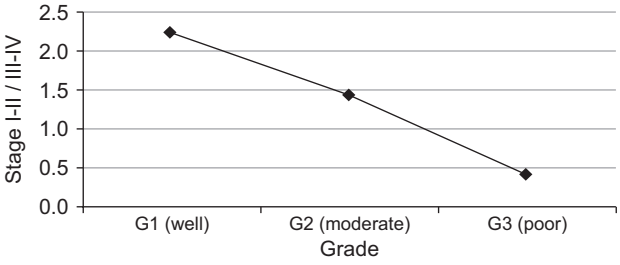

Figure 2. Variation of early / advanced stage ratio by grade. The changes in the I-II / III-IV ratio accompanying the worsening of grade are presented, indicating a striking reduction of this ratio from 2.25 for well differentiated tumors to 0.41 for poorly differentiated lesions. Variation was more pronounced between G2 and G3 (1.43 vs. 0.41) than between G1 and G2 (2.25 vs. 1.43). This was reflected in the significance of the observed differences (p values were 0.003 for G3 vs. G1, 0.023 for G3 vs. G2 and non significant for G2 vs. G1 respectively - Table 4B).

group analysis, the former trend remained significant only for the proximal site, while the latter became insignificant for both segments (Tables 3,4).

As regards changes in site, stage and grade distribution during the study period (Figure 3), a parallel decrease in the proportion of both proximal and poorly differentiated lesions was recorded between the first two (1998-2001) and the last (2002-2003) time intervals

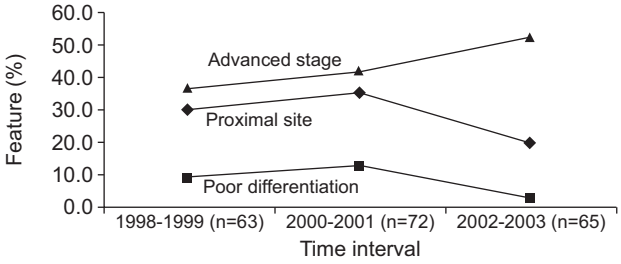

Figure 3. Changes in the distribution of site, grade and stage during study period. As indicated in this figure, the pattern of the observed variation in incidence during the study period, was similar for poor grade and proximal site but different for advanced stage. With the exception of the reduction in poor grade recorded between 2000-2001 and 2002-2003 (p=0.04), the other time-related changes of the examining features approached but did not reach the level of significance (p values varied between 0.055 and 0.08; see Results).

(32 vs. 20%, p=0.06 for site and 11 vs. 3%, p=0.055 for grade). The reduction of poor grade was significant for the particular comparison between the middle and the last interval (12.5 vs. 3%, p=0.04). By contrast, an increase in the proportion of advanced stage (III-IV) was observed between the first and the last interval (36.5 vs. 52%, respectively, p=0.07).

Discussion

Segmental differences of CRC regarding disease stage and grade have been widely examined and reported [2,3,10,11,14,15-19]. Proximal tumors were more frequently found with poor differentiation [11,14,15-19] and higher stage [2,3,16-19] - the latter partially attributable to delayed diagnosis due to their less symptomatic clinical onset [17,19], combined with inadequate screening strategies - especially regarding the use of colonoscopy [3,19]) and also to a possible understaging of distal tumors because of the lower number of lymph nodes evaluated distally [18,23].

Our findings, in line with others [11,14,15-19], indicated a clear predilection of poorly differentiated lesions for proximal site, whereas tumors with moderate differentiation were more frequently observed distally. Although marginal, differences in stage were also recorded. Like others [17-19], we found a higher proportion of stage II and III tumors in the proximal group, whereas stage I disease was more frequently found distally. The incidence of stage IV was similar in both groups, consistent with previous and recent data [3,19].

We had previously demonstrated similar segmental variations regarding stage and grade in a different (non Greek) cohort [16]. Interestingly, in that study, proximal predilection shown by G_3 lesions was specifi-

cally ascertained only for early disease. Similar findings were also reported by others [14,23]. However, those studies –analyzing grade segmental distribution within only one [14] or two stages [23]– didn't provide global information on the issue. We now confirmed this finding in both early and advanced stage and other disease categories (I-III, II-IV, II-III) as well, with a considerably strong statistical significance for the latter subsets. The consistency of this trend implies the existence of an indigenous link between poor grade and proximal site – an assumption supported by the parallel change in the distribution of poorly differentiated and right-sided cancers during the study period. Indeed, poor differentiation is a common phenotypic feature of the microsatellite instability (MSI) genetic pathway, almost exclusively seen in proximal cancers [6,7]. Moreover, the larger CPG island methylator phenotype (CIMP) epigenetic mechanism has been also associated with proximal site and poor differentiation [6,10]. On the other hand, the chromosomal instability (CIN) pathway, being the major tumorigenic mechanism in CRC, is more frequently found distally [6-8,13] and is associated –compared with MSI– with relatively better grade [8,12,20]. Notably, in our sample, moderate grade emerged as a very common feature of distal tumors, consistently observed in all stage categories in a proportion varying from 86 to 93% of cases with this location.

Besides genetic causes, interaction between grade and stage - previously reported [15,22,24] and also ascertained here – may partially account for the observed segmental differences. Thus, the late stage presentation of proximal tumors could be accompanied by higher rates of worse differentiation as a result of the predominance of more malignant and aggressive clones of tumor cells during disease progress [16]. Conversely, the consistent trend of proximal tumors for poor differentiation probably contributes to higher stage, because lesions with this grade are more likely expected to disseminate [15,24]. However, the observed predilection of well differentiated lesions for proximal site, specifically depicted within stage I, possibly suggests that proximal tumors may initially be more indolent. Accordingly, their worse histological profile within other stages could be in part a result of their trend for higher stage – mostly attributable to delayed diagnosis [3,17,19]. Nevertheless, the fact that poor histological type (accompanied or not by higher stage) was more commonly found proximally may warrant a larger use of total colonoscopy to exclude tumors with this anatomical location.

The worse clinicopathological profile of proximal tumors (in terms of higher stage and grade) found in the current and previous studies [15-19], although –regarding stage– was not always the case [10,11], is probably suggestive of an unfavorable outcome, as indicated by large studies [18,19,24]. However, in those series, specific analysis revealed that survival for proximal tumors with stage II disease, was either better [18] or equal [19] to that seen for distal lesions of the same stage. This finding, consistent with previous data from series examining particular stages [12,14,20,21], could be possibly attributed to the higher proportion of MSI tumors associated with proximal site [6,7], lower stage [25] and better outcome [12,20,21]. However, given that MSI is a rather minor subset [13] (accounting for approximately 25-30% of proximal tumors [6]), other molecular factors with potentially favorable prognostic influence, such as diploidy [12], low loss of heterozygosity (LOH) burden [20] and lower p53 mutation rate [8,11,14] (all correlated with proximal site and lower stage) may also account for these results, probably counteracting the adverse impact of worse grade. They may also contribute to the previously mentioned better histological pattern of proximal cancers with stage I disease - potentially comprising a genetically distinct and biologically indolent minor tumor subset (besides MSI).

Currently, poor differentiation is considered a relative indication for chemotherapy in stage II disease, while the role of MSI in treatment response is under ongoing investigation (phase III trials) [26,27]. Considering the high proportion of poor grade among MSI tumors [25,28], the known predilection of both features for proximal site [6,15,16-19,28] and the trend for better response reported for tumors with this location [21], evaluation of MSI status could be used in the future to assist therapy decision in stage II / G_3 CRC (preferentially proximal).

The limitations of this study are the relatively small number of cases and the short study period. However, in terms of stage, grade and site distribution (Table 1), our sample was generally comparable to larger series examining both colon and rectal tumors [10,11,17]. On the other hand, the observed variations of these features during the study period (Figure 3), demand additional investigation. Validation of them in the next time interval could be furthermore supportive of the connection between poor grade and proximal site (suggested by their parallel change with time). Most importantly, it could be also indicative of a possibly reduced effectiveness of diagnostic procedures for CRC in the area covered by Tzaneio hospital (as suggested by the observed increase in the incidence of advanced stage between 1998 and 2003 and –perhaps– by the concurrent decrease in the incidence of proximal tumors). Finally, the strong link between poor differentiation and proximal site has been recently reconfirmed in a large study [29], indicating the former as one of the clinicopatho-

logical features consistently discriminating right from left-sided CRC, whereas other characteristics (including advanced stage) were found connected with particular colonic segments (cecum, splenic flexure).

In conclusion, an apparently worse histological pattern of proximal tumors was consistently observed within almost all stage categories. Whether this finding is (mostly) a phenotypic characteristic of the underlying distinct genetic pathways responsible for proximal tumorigenesis, or a result (in part) of the late stage presentation of these lesions is a matter of further investigation. The potential impact of these observations on disease outcome, treatment and screening strategies should be also ascertained, particularly regarding the necessity of more generalized use of total colonoscopy.

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