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# Relationship between degree of cellular differentiation in colorectal cancer and topographical distribution

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## ABSTRACT

**Objectives:** to demonstrate the relationship between degree of cellular differentiation in colorectal cancer and topographical distribution in 215 patients diagnosed with colorectal cancer from 1997 to 2000.

**Material and methods:** 215 patients (129 men and 86 women) were studied prospectively with a mean age of 64 years (range: 23-84 years). In all patients we performed a full colonoscopy with several biopsies (in patients with colon stenosis we used barium enema), radiographic studies (CT, abdominal ultrasounds), and laboratory tests for serum tumour markers (CEA, Ca 19-9, alpha-fetoprotein). The topographic location of colorectal cancer was: rectum 35%, sigmoid colon 31%, descending colon 10%, transverse colon 6%, ascending colon 9%, caecum 5%, and we included anorectal cancer 4%.

**Results:** according to histological differentiation we found: A) well-differentiated tumours 101/215 (47%); B) moderately-differentiated tumours 98/215 (45.5%), and C) poorly-differentiated tumours 16/215 (7.5%). We found no significant association among histological differentiation, topographic location, stage according to the Astler-Coller classification, sex or age (p = ns). The prevalence of well-differentiated tumours in men was 49% and 43% in women; of moderately-differentiated cancers in men was 43%, and 49% in women; for poorly-differentiated tumours in men was 7.5%, and 7.2% in women. Regarding tumour location, 165 cancers were found in the left colon: 80 were well differentiated, 77 moderately differentiated and 8 poorly differentiated. In the transverse colon we found 12 tumours: 7 well differentiated, 3 moderately differentiated and 2 poorly differentiated. 30 cancers were localized in the right colon: 11 well differentiated, 15 moderately differentiated and 4 poorly differentiated. In the anorectum 8 tumours were found: 3 well differentiated, 3 moderately differentiated and 2 poorly differentiated.

According to staging classification, well differentiated tumours (101/215) were more common in Dukes' C2 (20.7%) and B1 (32.6%), moderately differentiated cancers (98/215) were in B1 (28.5%) and C2 (20.4%), and poorly differentiated tumours (16) were more common in Dukes' C2 (25%), without differences among other stages (p = ns).

**Conclusions:** according to our results we have found that histological differentiation of colorectal cancer has no association with topographic location, and it is independent of sex or age. We have not found any relationship either between histological differentiation and stage in the Astler-Coller classification, but well differentiated cancers were more common at any location, age or sex.

**Key words:** Colorectal cancer. Topographic location. Histological differentiation.

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## INTRODUCTION

*Colon cancer constitutes the third cause of death from neoplasms after breast cancer and lung cancer, representing 15% of all malignant tumours diagnosed in women and 14% of those in men. Colon cancer incidence increases steadily and rates of survival after 5 years for cases diagnosed early are 90%, decreasing to hardly 35% in advanced stages. In Spain mortality rates for 100,000 inhabitants/year are considered 22 for men and 19 for woman (2), considering about 11,000 person/years are diagnosed with colon cancer in late stages. In Andalusia, rates of mortality are 17.75 per 100,000 inhabitants and year. Population aging relates to the biggest incidence of colorectal cancer. Incidence rates are also higher in developed countries, this being related to certain dietary patterns and better quality of life, as they are somewhat higher in urban populations (3).*

*The degree of tumour penetration in the intestinal wall according to the classification by Astler-Coller (4)*

*and Dukes (5,6) has greater prognostic value, tumours with thin penetration presenting a better outcome, and survival approaching 90% after 5 years when the tumour is limited to the mucosa. Cellular differentiation, and its influence in prognosis, is the central subject of our work. It is well known that, in general, the more differentiated a tumour, the better the prognosis; it is interesting to study the possible relationship between the variable "differentiation" and stage at diagnosis time, as well as a potential link to topographical localization of the neoplasm inside the colon, and patient age and gender.*

## MATERIAL AND METHODS

*215 patients with colorectal cancer were studied prospectively, 129 men and 86 women, with a mean age of 64 years (range: 34-90 years for men and 23-84 for women) (Fig. 1). Patients were referred from the various areas belonging to the Sanitary Area of University Hospital Virgen Macarena, with an influence area composed of 483,434 inhabitants conforming an urban-rural population with a growth of the age group above 65 years and a severe decrease in infantile population. Symptoms were mainly short-standing rectal bleeding, constipation associated with abdominal pain, long-standing sporadic rectal bleeding, or anaemia due to iron deficiency that was refractory to treatment. The studied patients were not included in programs of colorectal cancer detection. Besides a clinical history and physical exploration, the procedure for diagnosis included a full colonoscopy; in patients with colon stenosis we performed a barium enema with the purpose of establishing the existence of other lesions. In all patients, we performed analytical tests and laboratory tests for serum tumour markers (CEA, CA 19.9 and Alpha-Fetoprotein), as well as CT and abdominal ultrasonography studies, with a special interest in discarding hepatic metastases or the existence of compromising tumours in neighbouring or adjacent organs.*

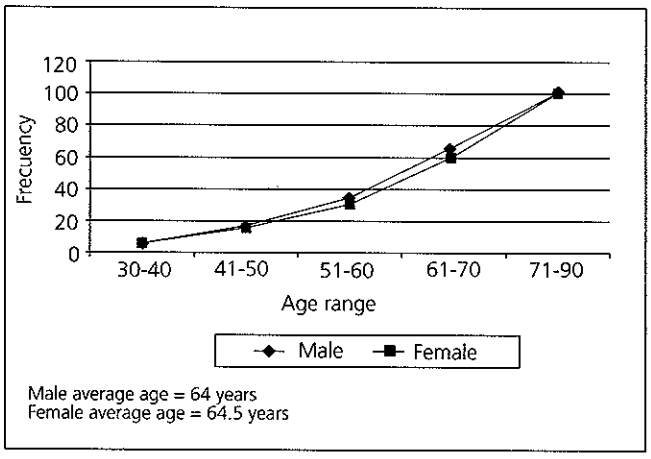


Fig. 1.- *Series: age and gender (N 215).*

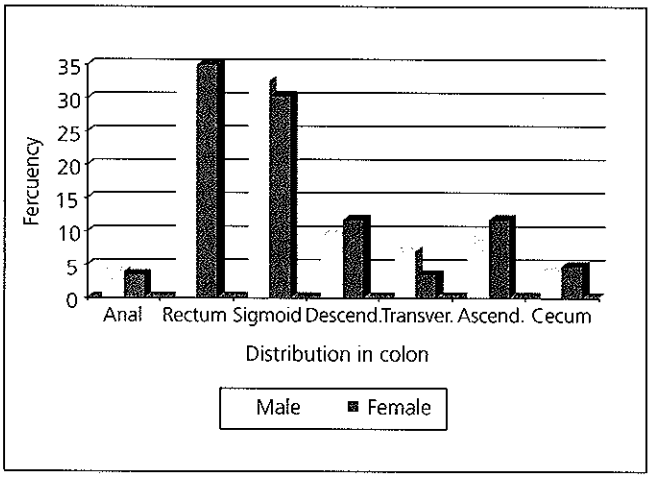


Fig. 2.- *Tumor location by Gender. The tumor distributions in colon by sex haven't differential statistical significance (p=NS).*

*The surgical pieces were analysed to establish their stage according to the Dukes and Astler-Coller classifications, as well as the degree of cellular differentiation and other general tumour characteristics. The distribution of our patients according to degree of cellular differentiation (well differentiated, moderately differentiated and poorly differentiated), and the location of tumours in the colon is shown in figure 2 and table I.*

*Presently the study does not analyse rates of survival, because our main objective was to establish the relationship existing between cellular differentiation and stage, topographical location of the tumour, age and gender.*

Statistical method: *we used descriptive statistics to express the general characteristics of our series according to the various variables analysed. We used the Chi-square and the exact Fisher tests for qualitative variables, and t Student for quantitative variables.*

## RESULTS

*In our study series, 129 men and 86 women, the mean age for both genders was 64 years and the distribution of colorectal cancer, according to gender, was: for men 76.6% of the lesions were located in the left colon, 6.9% in the transverse colon, 12.3% in the right colon, and 3.8% with anorectal involvement. For women, 76.7% of the lesions were located in the left colon, 3.5% in the transverse, 16.2% in the right colon, and 3.5% in the anorectum; globally the distribution of colorectal cancer does not present significant differences between both groups (Fig. 2). The distribution of colorectal cancer for cellular differentiation neither represented significant differences in the studied series. We observed a homoge-*

**Table I. Degree of cellular Differentiation by Tumour Distribution in Colon**

| Colon location | Well differentiated 101/215 | Moderately differentiated 98/215 | Poorly differentiated 16/215 | Total% 215 |
|---|---|---|---|---|
| Anal tract | 37,5 | 37,5 | 25 | 100 |
| Rectum | 51,2 | 45 | 3,8 | 100 |
| Sigmoid | 51,5 | 41 | 7,5 | 100 |
| Descending and splenic flexure | 28,5 | 71,5 | 0 | 100 |
| Transverse | 58,3 | 25 | 16,7 | 100 |
| Ascending and hepatic flexure | 47,3 | 42,2 | 10,5 | 100 |
| Cecum | 18,2 | 63,4 | 18,4 | 100 |

p= NS depending on degree of cellular differentiation and tumour site in distinct colon localizations

*neous distribution in different localizations: poorly differentiated ones are least frequent, being equally distributed in all groups; globally, well differentiated tumours represent 47%, moderately differentiated tumours 45.5%, and poorly differentiated ones 7.5%. Neither difference was observed as statistically significant for cellular differentiation between rectal cancer and other non-colonic localizations (p=NS); distribution according to localization and cellular differentiation is shown in table I.*

*When we try to establish the relationship between cellular differentiation and stage according to the classifications by Dukes and Astler-Coller, well differentiated tumours (47%, 101/215) were more common in stages A (14/101), B1 (33/101) and C2 (21/101); moderately differentiated tumours (45.5%, 98/215) in Dukes' B1 (28/98), B2 (18/98) and C2 (20/98); and poorly differentiated tumours (7.5%, 16/215) in C2 (4/16), B2 (3/16) and C3 (3/16); differences were statistically significant for number of neoplasms in the different areas of the colon – more tumours in the left colon – but not for cellular differentiation (p = NS), as we show in figure 3 and table I. In 104 patients (48.3%) we found metastases distributed as follows: 83% in nodes, 9% in liver, 4% in uterus after invasion, 2% in peritoneum, 1% in pancreas and stomach, 1% in liver and skin. Most metastatic cancers were located mainly in the left colon, in the recto-sigmoid area. Our work shows a correlation lack between degree of cellular differentiation, stage and tumour site within the colon; we have also been able to check that these factors are seemingly unrelated to age or gender.*

*We deduct that cellular differentiation and stage (tumour stratification) are the factors determining tumour aggressiveness, rather than their localization in the colon, independently of age and gender.*

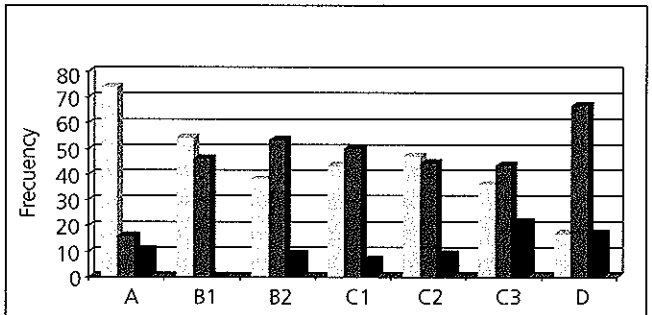


Fig. 3.- *Degree of cellular differetiation in Dukes Astler-Coller System. Overall, no statistical signification between degree of cellular differentiation and tumour stage is found (p=NS).*

## DISCUSSION

*In this prospective study we analyse the relationship between cellular differentiation and tumour aggressiveness, specified as stage, and a possible association with the topographical distribution of tumours, age at diagnosis and patient gender. In our series the mean age of patients was 64 years, range 23-90 years; 9.6% were younger than 40, and 90.4% were over 41 years. These data, coinciding for most authors, confirm the necessity to es-*

*tablish controlled studies in the at-risk population younger than age 50. In our study most patients were diagnosed in advanced stages, 41.3% in stage C of Dukes, Astler and Coller, and 6% in stage D. The detection of occult bleeding allows colorectal cancer to be diagnosed in early stages, with a sensitivity between 48 and 80%, and a specificity between 97.7 and 99%. It has been shown to reduce mortality from colon cancer by 15-33%, depending on method. Nevertheless, diagnosing this common pathology in an early stage is always effective (7-10). Colonoscopy is the gold standard for this diagnosis, since it allows direct visualization of the lesion, biopsy sampling of tumours, and prevention by excising adenomas, precursory lesions of colon cancer (13,14). All patients in our series were initially diagnosed by colonoscopy, and none had manifested symptoms that could be directly related to a colorectal cancer in previous years. The silent and confusing evolution of these neoplasms demands a vigilant attitude for colonic symptoms of recent appearance in a 40 year-old subject, and one should not presume in these cases rectal bleeding is fundamentally originated by haemorrhoid processes, just as it happened in most of our patients. Based in our work, rectal bleeding in young patients is not always haemorrhoidal in nature, as 9.6% of our patients were younger than 40 years.*

*They are few the works mentioning a relationship between degree of cellular differentiation and tumour stratification as a prognostic factor together tumour site within the colon, and we could check that tumours present the same degree of aggressiveness regardless of tumour location. Even being the left colon (from the splenic flexure to the rectum) the most frequent site for these tumours –76.6% in our series– this localization is not synonymous of higher aggressiveness; it is only the place where more colorectal cancers were found. This area of the colon is also preferred by adenomas; we could not relate degree of cellular atypia (high or low grade) to localization or gender (53), but the fact that more neoplasms were found in this area does not justify that aggressiveness be in connection with localization. According to results, an adenoma would not become an adenocarcinoma sooner in the left colon* versus *one in the right or transverse colon; all localizations would have the same possibilities to express aggressiveness from the sequence adenoma-carcinoma, and to the same extent in both genders. As a dependant variable for frequency of these neoplasms –as seen in most reported studies– we found age, oldest age being directly related to adenoma and carcinoma development –mean age of 60 and 64, according to our studies (53).*

*In our results –coinciding with other works (22, 35, 41)– we observed that degree of cellular differentiation, and stage according to Dukes and Astler-Coller do not relate to tumour site within the colon, which is a common characteristic for both genders. Once a neoplasm has developed, tumour aggressiveness is independent of age, gender and site.*

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