COLORECTAL CANCER IN YOUNG ADULTS 20 TO 40 YEARS OLD: A POPULATION-

by

Federica Domati\textsuperscript{1}, Stefania Maffei\textsuperscript{1}, Shaniko Kaleci\textsuperscript{1}, Carmela Di Gregorio\textsuperscript{2}, Monica Pedroni\textsuperscript{1}, Luca Roncucci\textsuperscript{1}, Piero Benatti\textsuperscript{1}, Giulia Magnani\textsuperscript{1}, Luigi Marcheselli\textsuperscript{1}, Luca Reggiani Bonetti\textsuperscript{2}, Francesco Mariani\textsuperscript{1}, Antonio Maria Alberti\textsuperscript{3}, Valerio Rossi\textsuperscript{3} and Maurizio Ponz de Leon\textsuperscript{1}.

Dipartimento di Medicina Diagnostica, Clinica and Sanità Pubblica, Università di Modena e Reggio Emilia\textsuperscript{1} (Italy); Divisione di Anatomia Patologica, Policlinico, Modena\textsuperscript{2}; ALTEG (Associazione per la Lotta ai Tumori dell’Età Giovanile\textsuperscript{3}) (Roma; Italy).

Running title: Colorectal cancer in Young adults.

Keywords: Colon, Cancer, Dukes, Survival, Early onset.

Financial support: This work has been carried out with the financial support of AIRC (Associazione Italiana Ricerca Cancro). Francesco Mariani was supported by a grant from Fondazione Umberto Veronesi.

Correspondence To:
Maurizio Ponz de Leon, M.D.
Department of Diagnostic Medicine, Clinical and Public Health Medicine Policlinico, Via del Pozzo 71, 41100 Modena, Italy.
Tel. + 39 59 4222269;
Fax. +39 59 4222958;
E-mail: deleon@unimore.it

Conflict of interest:
There are no conflicts of interest

The word of the manuscript: 3,096
Total number of tables: 5
Total number of figures: 5
**Objectives**: We proposed to investigate: A) clinical features of patients with colorectal malignancies developed before the age of 40 years; B) assessment of survival; C) possible factors involved in the etiology and pathogenesis of these rare neoplasms

**Materials and Methods**: The study included all patients with a diagnosis of colorectal neoplasm developed before age 40 registered in the local specialized Registry. Besides stage and morphology, the 57 detected patients were studied for familial aggregation of cancer.

**Results**: Despite the relevant increase over time of all registered patients, the incidence of early-onset tumors remained stable or showed a slight decline. Adenocarcinomas represented 68% of all cases (versus 98% in adults and elderly patients), the remaining being carcinoid tumors, Kaposi sarcoma, squamous carcinomas and lymphoma. Hereditary cases represented 10.5% of all adenocarcinoma, a fraction significantly higher than that seen in older patients (0.5%). Moreover, familial aggregation was found in 21% of the cases. There was a tendency to better survival for individuals with tumors diagnosed in the most recent decade.

**Conclusions**: The incidence of colorectal cancer developing ≤40 years was rather stable over a 25 years period, and showed a definite preponderance of the male sex. Hereditary cases and familial aggregation of tumors were consistently more frequent in “juvenile” cases; more in general, a well-defined etiology could be established in nearly 15% of patients. Survival was significantly more favorable, though the difference from older patients was mainly due to the present of carcinoid tumors, Kaposi sarcoma and squamous carcinoma.
According to recent world-wide epidemiological observations (1), incidence rates of colorectal cancer continue to rise in most Western as well as Developing countries, in spite of the efforts in screening and early detection of these common malignancies (2, 3). In contrast, figures on the incidence of early onset colorectal neoplasms are not consistent, some studies indicating a tendency to an increase (4, 5, 6), whereas others would suggest a relative stability of the rates (7, 8). Part of these discrepancies can be attributed to the different age-limits proposed for the definition of early onset (or ‘juvenile’) tumors, which have been set at age 40, 45 or 50 depending on the authors and proposal of the studies (4, 6, 9).

Apart their incidence, clinical and biological features of early onset tumors can be different; as recently pointed out (10), there is evidence that a given proportion of cancers developing in young adults may exhibit etiologic, biologic and pathogenetic properties which are at variance with those observed in adults and elderly persons. Moreover, the relatively young age of patients can allow therapeutical approaches (both medical and surgical) which might appear hazardous or inappropriate for an older population. Finally, early onset colorectal tumors (≤ 40 years) are rare diseases, and we got many example, especially in the most recent decades, of new molecular pathways or models of carcinogenesis which have been conceived by careful observations of the properties of rare neoplasms (11, 12). Through the data of a continuous 25-year registration of colorectal malignancies, the main purposes of the present investigation were: First, to describe the main clinical and epidemiological features, including stage and morphology, of patients with malignant tumors developed before the age of 40 years. Second, to analyze survival of these patients according to a number of variables; Third, to investigate possible factors involved in the etiology and pathogenesis of these rare neoplasms. When relevant, the results were compared with those observed in the large majority (>40 years) of the registrared patients.
The general organization, the main purposes and the results of the specialized Colorectal Cancer Registry of Modena have been described previously in detail (13, 14, 15, 16). The registration covers Modena (Northern Italy) and 10 surrounding municipalities for a total of 265,227 residents (males 128,288, females 136,939) at census 2001. An active registration of all malignancies of the large bowel developing in the population started the 1st January 1984 and is ongoing. In the present analysis, the 25-year period 1984-2008 was taken into consideration. Besides basic anagraphic data, the registration form takes accurate records of localization of tumors in the various subsites of the large bowel (International Classification of Disease, Tenth revision) (17), main diagnostic procedures (the diagnosis was based on endoscopy in the large majority of cases), pathological stage, morphological diagnosis, familial aggregation of neoplasms (of the large bowel and of other organs), type of surgical approach, adjuvant or palliative chemotherapy, and radiotherapy. Moreover, from the beginning of the Nineties years each registered patient was actively followed-up through an informatic network gathering all information concerning health of resident population, so that local recurrences, distant metastasis and clinical status (alive or dead) could easily be recorded.

**Stage and Morphology**

Epithelial tumors of the large bowel were staged following the guidelines of the TNM classification (18), which closely corresponds to the Dukes staging into four main categories (19). Thus, in stage I tumors (Dukes A), lesions spread through the muscolaris mucosae into the submucosa (T1) or reach the muscular wall (T2). In stage II (Dukes B) the neoplasms go beyond the muscular wall into the pericolic tissues (T3) and may reach the serosal surface (T4) or infiltrate surrounding organs, but without evidence of lymphatic or haematogenous dissemination. In stage III (Dukes C) lymphatic involvement is present, unregarding the dimension and the degree of infiltration of the primary tumors (C-1, 1 to 3 metastatic lymph nodes; C-2, 4 or more metastatic
Finally, in stage IV (Dukes’ D) there is evidence of distant haematogenous metastasis, usually in the liver and/or lung. Morphologic diagnosis was assessed with the criteria of the International Classification of Diseases for Oncology (20), which closely corresponds to the SNOMED classification. Tumors were coded with five-digit numbers, the first four referred to various histological types, the fifth to malignancy (=3 in all cases) (21). Ambiguous definitions such as carcinoma in situ, foci of neoplastic cell or severe dysplasia were not regarded as cancer unless a clear infiltration of the muscularis mucosae was evident at histology.

**Familial Aggregation of Tumors and Hereditary**

One of the main purposes of the Registry was the study of familial aggregation of neoplasms and, thus, the detection of hereditary tumors of the large bowel (22). From the beginning of registration (1984) each patient (i.e., incident case) was contacted directly, through other family members or the family doctor - and a careful gynaecological tree of the first-degree relatives was traced. All cases of cancer among relatives were recorded and, when possible, verified by clinical charts and other certificates, especially morphologic diagnoses (23). In the suspicion of Lynch syndrome, Familial Adenomatous Polyposis (FAP) or other more rare hereditary diseases, the pedigree was extended to second and third degree relatives; moreover, from 1994 suspected cases were systematically analyzed for the presence of Microsatellite Instability (MSI), lack of expression of the main genes of the mismatch repair system (MMR) and, when possible (patient alive and willing to undergo genetic testing), search of constitutional mutation in APC or in the MMR genes (MSH2, MLH1,MSH6). For the purposes of present study familial cases were defined as the presence or at least one family member affected by colorectal malignancies; hereditary cases were defined by detection of constitutional mutations in one of the genes predisposing to colorectal tumors.

**Molecular Analysis**

Microsatellite instability was evaluated as previously described in more details (9, 24). Paraffin embedded tumour tissue was microdissented, incubated in xilene and pelleted for 5 min.
After washing in ethanol, samples were dried and DNA extracted with standard procedure. MSI was evaluated with 4 Microsatellite markers (BAT 25, BAT26, NR24 and CAT25), using a fluorescence-based PCR. DNA from tumour tissues was amplified by PCR, subsequently run on a CEQ 8000 sequencer, and then analyzed with the Fragment Analysis System (Beckman Coulter). Tumour positive for MSI were identified as those in which instability was detected with at least three markers.

For immunohistochemical analysis of the proteins encoded by the 3 main genes involved in DNA MMR (hMSH2, hMLH1 and hMSH6), tumor tissues were sectioned (4 um) and slides submitted to microwave antigen retrieval, as previously described (9). Various monoclonal antibodies were used at optimal dilution. With the use of diaminobenzidine as chromogen, staining was carried out in a NEXES Automatic Staining System, after counterstaining with haematoxylin.

Again, sequence analysis of APC and of the main MMR genes has previously been reported in more details (25, 26). Genomic DNA was extracted by peripheral blood cells and directly sequenced after amplification obtained with primers located in the flanking intones approximately 50 base pairs from the respective intron/exon borders, in order to detect all possible splice junction mutations. Direct sequencing of the PCR products were executed using Dye Terminator Cycle Sequencing Kit (Beckman Coulter) and reactions were run on a CEQ 8000 capillary sequencer according to the manufacturer’s instructions. To exclude the possibility of large genomic deletions of hMLH1, hMSH2 and hMSH6, all patients were analysed by Multiplex Ligation-dependent Probe Amplification (MLPA). Pathogenic mutations were detected twice and confirmed in a second blood sample of the patient. The purposed of the study was clearly explained and an informed consent was obtained.
The statistical significance of differences between means was assessed with Student's t test, \( X^2 \) test or Fisher's exact test, as appropriate. Life table analysis and Long-Rank tests were used to evaluate differences in survival and their significance. All analyses were carried out using the Statistical Package for Social Sciences (SPSS) software.

Trend analysis of juvenile colorectal carcinoma was assessed with the joinpoint Regression Program. The software analyzes the data and fits the best joinpoint model that the data allow throughout the examined period. The program started with a straight line and tested whether mere joinpoint (points where the trend changed) were statistically significant and should be added to the model. In this way the program tests if an apparent change of trend is statistically significant. Moreover, the program evaluates the Estimated Annual Percentage Change (EAPC) and its confidence interval (95%); \( p < 0.05 \) was considered as statistically significant (27). The EAPC was computed with the linear regression of the natural logarithm of the crude rate as function of the year of diagnosis and testing the hypothesis that the regression parameter was zero; furthermore the "joinpoint method" identifies the presence of change point in the temporal trend. The trend was considered significant with \( p \)-value \( < 0.05 \). The statistical test was performed with 4000 Monte Carlo permutation method.
Table 1 shows the main clinical features of the 57 patients registered for colorectal malignancies over a 25-year period. The incidence for quinquenium was rather stable or, considering the gradual increase of total registered patients, tended to a slight decline. The male sex was constantly more represented, approximately 3 times more frequent than the female sex. Male: Female ratio was 2.5 in individuals younger than 40 years and 1.2 in older subjects with colorectal carcinoma.

Details on morphology are shown in Table 2 and 3. While adenocarcinoma was by far the most frequent histological type in tumors developed after the age of 40 (98% of the total), carcinoid tumors, squamous carcinoma, Kaposi sarcoma (associated with AIDS) and lymphomas were all appreciably more frequent in younger subjects. Moreover, mucinous carcinomas and, more in general, high-grade lesions were more frequent in patients under the age of 40 years. As far as stage was concerned (Table 4), stage II lesions were significantly more frequent in older individuals; in contrast, stage IV lesions were appreciably more frequent in younger patients. The fraction of total harvested lymph nodes in the resected specimens did not differ significantly between the two groups; however, the finding of more than 30 lymph nodes was observed more frequent in subjects younger than 40 years. In the latter group, 15.8% of the tumors were localized in the appendix, 19.3% in the right colon, 31.6% in the left colon and 32% in the rectum (including the rectosigmoid junction); the corresponding figures in older patients were 0.2%, 34.5%, 31.6% and 29.3%.

As expected (Table 5), hereditary cancer syndromes were significantly more frequent among patients with early onset tumors than in older individuals; however, it is worth noting that the large majority of patients with Lynch syndrome (i.e. with constitutional mutations of \textit{MSH2}, \textit{MLH1} or \textit{MSH6} genes) were detected in patients above the age 40 years (26 vs 4). Similarly, familial cases were nearly the double in subjects younger than 40 years; despite the documented or suspected
in all cases, in the majority (68.2%) of patients with early onset colorectal neoplasia the disease presented in sporadic form.

Figure 1 shows cancer-specific survival in the two groups of patients; from Panel A a significantly better survival was clearly evident for younger individuals; however, the difference disappeared in Panel B, in which adenocarcinomas only were taken into consideration. It follows that the more favourable overall prognosis had to be attributed to the presence of patients with carcinoid tumors, squamous carcinoma and Kaposi sarcoma. This contention is further illustrated in Figure 2, which takes into consideration survival in these subgroups of patients. Finally, Figure 3 (Panel A and B) illustrates survival of the 57 patients younger the 40 years in the two periods of registration 1984-1998 and 1999-2007 (cases of 2008 were not included because the follow-up did not reach five years). Prognosis was undoubtedly better for patients registrared in the more recent decade, though the difference tended to attenuate when considering only patients with adenocarcinoma.

Figure 4 shows a trend of the crude incidence rates of juvenile colorectal cancer (x 100,000 residents/year) between 1986 and 2008. The reference population was that of the 2001 census. The shape of the curve shows a not significant increase of juvenile colorectal carcinoma throughout the study period, with percent of annual variations (EAPC) of 2.4 (IC95%, -14.0 +22.0) during the year 1986-2008. Figure 5 shows the linear regression of the natural logarithm of the crude rate as function of the year of diagnosis; the data confirmed a non significant trend (IC95% -0.11; 0.12; P=0.100).
The results of the present long-term population based investigation can be summarised as follows. The incidence of early onset (<40 years) colorectal carcinoma was rather stable between 1984-2008, and showed a definite predominance of the male sex. Adenocarcinoma was the most prevalent histological type; however, the frequency of carcinoid tumors, squamous carcinus, Kaposi sarcomas, lymphomas and mucinous carcinomas was significantly higher than those observed in individuals older than 40 years. Familiar aggregation of tumors and hereditary cases were constantly more frequent under the age of 40 years; more in general, a well defined etiology (hereditary or viral disease) could be established in about 15 % of patients. Finally, in the whole study group (57 patients) survival was significantly more favorable when compared to older patients, though the difference tended to disappear when only patients with carcinomas were considered.

Siegel et al (4) by analyzing the SEER (Surveillance, Epidemiology an End Results) data showed that overall incidence rates of colorectal cancer in adults under age 50 tended to increase by approximately 1.5-1.6% per year. Again from the SEER study Meyer et al (5) reported a gradual increase of incidence of rectal cancer, between 1973 and 2005, in individuals younger that 40 years; joinpoint analysis revealed that the increase of incidence began in 1984. Similarly, Ganopatly et al (6) found a definite tendency to an increased incidence of colorectal cancer in patients of less than 40 years of age over a 20-year period. At variance with these observations, and in accordance with the finding of the present study, other investigations (28, 29) reported little or no change of incidence rates. Possible reasons for the conflicting results include: A) different population examined, B) different age cut-off in defining early onset terms (40, 45, 50 years), and C) possible differences in the definition of infiltrating carcinoma.

Although colorectal cancer is usually considered a neoplasm affecting both sexes at the same extent, as a matter of fact in most Western series the disease appears more prevalent in men than in women (30, 31). It is of interest to note that in selected series, such as patients with early
among males seems even higher (32, 33), at least in same series.

Indeed, we observed a male ratio of 1.2 in the whole group of 4,843 registered patients, whereas in the 57 individuals younger that 40 the ratio was 2.5. It is too early to suspect presence of additional risk factors in relatively young male patients with colorectal cancer (or protective factors in females), but this aspects probably deserves more attention.

The majority of neoplasms arising in patients under age 40 were adenocarcinomas, however, their fraction was consistently lower than that observed in maturity onset malignancies (68 vs 98%). it follows that a relevant portion of tumors were of different histological types, including carcinoid tumors (usually localized in appendix, and with a favorable prognosis) squamous carcinoma (of the anus), Kaposi sarcoma (associated with AIDS infection) and lymphomas; these finding confirm previous reports in similar series (34, 35). In addition, as already reported among adenocarcinomas the fraction of mucinous carcinoma was significantly higher then in patients with colorectal cancer diagnosed over age 40 (36). Taking into account that these more rare tumors (i.e. Carcinoid, Squamous carcinus, Kaposi sarcoma and Lymphomas) usually show a more benign clinical course (Figure 2), the findings may explain the more favorable survival of relatively young patients illustrated in Figure 1A. As a matter of fact any difference in survival almost disappeared when adenocarcinoma only were considered (Figure 1B). The more favorable 5-years survival observed in the last decade of registration in patients with early onset tumors is not surprising, and it has been reported in general for colorectal neoplasm, in which over the last 30 years cancer specific survival passed from 40-45% to nearly 60% (37, 38). The better survival can be due to several factors, including more accurate interventions, with the recovery of more than 20 lymph nodes (39), diffusion of screening and consequent diagnosis of early tumors (2, 3), and the availability of more powerful drugs for adjuvant and palliative therapies (40).

Hereditary factors were more prevalent in relatively young individuals than in older patients. Indeed, 4 patients had Lynch syndrome or FAP (10.5% of 38 patients with adenocarcinoma) versus 26 (0.5%) in the older population. It should be painted out that this is only a minimum estimate
hereditary diseases were screened only for MLH1, MSH2, MSH6 gene. Recent observation suggest the mutations in the PTEN gene can be associated with early colorectal carcinoma (41); PTEN mutations induce the Cowden/Bannayan phenotype, however, in many individuals the clinical stigmata of the diseases can be scanty, and may escape detection (42,43). Similarly, early onset colorectal carcinoma can be associate with PMS2, EPCAM and even STK11 mutations (44, 45, 46); it follow that our estimate of the contribution of hereditary factors to the developments of early colorectal carcinoma can be underestimated to a certain extent. Familiarity was present in 21% of our patients under 40 and in 10.9% of older patients with colorectal cancer; through this group is rather heterogeneous, it might include additional cases with hereditary syndromes not related to FAP and MMR genes.

A final consideration concerns the etiology of early onset (<40 years) colorectal cancer; putting together the 4 patients with Lynch syndrome and FAP, the 3 patients with Kaposi sarcoma (linked to HIV infection) and the 2 subjects with squamous carcinoma of the anus (closely related to papillomavirus infection), it follows that at least in 9 individuals (15.8%) the disease could be reconduced to a know etiology. Thus, while in the common patients with colorectal cancer a clear etiological factor can be identified in 2-3% of all affected individuals (23), approximately 16.0% of patients with early onset disease recognize precise genetic or environmental factors. It follows that these should always be suspected in individuals with colorectal cancer developed before the age of 40 years.
This work has been carried out with the financial support of AIRC (Associazione Italiana Ricerca Cancro). Francesco Mariani was supported by a grant from Fondazione Umberto Veronesi. Thanks are also due to the Regione Emilia Romagna and to the Fondazione Cassa di Risparmio (Modena) for generous support. Parts of this work have been presented at the X° meeting of AIFEG (Italian Association for the studies of Hereditary Tumors), Padova 8-9 October 2012.

2. Church TC. Screening for Colorectal Cancer-Which Strategy is the Best? JNCI 2011;7:103.


Table 1. Main clinical features of the 57 patients with colorectal cancer diagnosed before the age of 40 years during the period 1984-2008 (25 years).

Table 2. Main histological types of the 57 patients with colorectal cancer developed ≤40 years vs 4,786 patients > 40 years (total registered patients: 4,843).

Table 3. Type of Adenocarcinoma and tumor grade in the 38 patients with colorectal carcinoma ≤40 years vs 4,692 patients with carcinoma > 40 years (total registered adenocarcinomas= 4,730)

Table 4. Tumor Stage (Dukes/TNM) in 38 patients with adenocarcinomas developed ≤40 vs 4,692 patients with adenocarcinoma diagnosed > 40 years.

Table 5. Hereditary, familiality and sporadic colorectal cancer cases in the 38 patients with adenocarcinoma diagnosed before the age of 40 years and in the 4,692 patients with neoplasms detected after the age of 40.
Five-year survival in the 57 patients with colorectal cancer diagnosed ≤40 and 4,786 cases with cancer developed after the age of 40 (Panel A).

Five-year survival of patients with colorectal adenocarcinoma in the two groups (38 vs 4,692) (Panel B).

**Figure 2.** 5-year survival according to main histological types in patients with early ones colorectal cancer. (57 cases divided in Adenocarcinomas, Carcinoid Tumors, Kaposi Sarcoma, Squamous Carcinoma).

**Figure 3.** Five-years survival by period of registration (1984-1997 vs 1998-2007) in the 55 patients with colorectal cancer diagnosed before the age of 40 years (Panel A). Five-year survival limited to the 37 patients with adenocarcinoma (Panel B).

**Figure 4.** Joinpoint analysis of the crude incidence rates of juvenile colorectal cancer (x 100,000 residents/year) between 1986 and 2008.

**Figure 5.** Linear regression of the natural logarithm of the crude rate as function of the year of diagnosis.
<table>
<thead>
<tr>
<th>(n° registrated patients)</th>
<th>Age of diagnosis mean ± SD (Range)</th>
<th>Sex M/F</th>
<th>Localization Colon/Rectum</th>
<th>Living / Deceased at 5 years</th>
<th>Tumor Recurrence No/Yes</th>
<th>Type of Recurrence Local/ Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984 – 1988 (560)</td>
<td>36±2.45 (33-38)</td>
<td>3/1</td>
<td>3/1</td>
<td>1/3</td>
<td>3/1</td>
<td>1/0</td>
</tr>
<tr>
<td>1989 – 1993 (803)</td>
<td>34.4±4.8 (24-40)</td>
<td>8/4</td>
<td>10/2</td>
<td>6/6</td>
<td>10/2</td>
<td>1/1</td>
</tr>
<tr>
<td>1994 – 1998 (972)</td>
<td>33.3±6.4 (17-40)</td>
<td>10/4</td>
<td>11/3</td>
<td>11/3</td>
<td>13/1</td>
<td>0/1</td>
</tr>
<tr>
<td>1999 – 2003 (1,123)</td>
<td>33.3 ± 6.4 (19- 40)</td>
<td>11/3</td>
<td>7/7</td>
<td>12/2</td>
<td>11/3</td>
<td>2/1</td>
</tr>
<tr>
<td>2004 – 2008 (1,285)</td>
<td>35.9±4.5 (27-40)</td>
<td>9/4</td>
<td>7/6</td>
<td>10/3</td>
<td>11/2</td>
<td>0/2</td>
</tr>
<tr>
<td>Totale (4,843)</td>
<td>34.1±5.3 (17-40)</td>
<td>41/16</td>
<td>38/19</td>
<td>40/17</td>
<td>48/9</td>
<td>4/5</td>
</tr>
</tbody>
</table>

* Percent of total registered patients in that five-year period.
<table>
<thead>
<tr>
<th></th>
<th>Adenocarcinoma N° (%)</th>
<th>Carcinoid * Tumors N° (%)</th>
<th>Squamous Carcinoma N° (%)</th>
<th>Kaposi Sarcoma N° (%)</th>
<th>Lymphoma N° (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 40 years</td>
<td>38 (68.0)</td>
<td>13 (22.9)</td>
<td>2 (3.5)</td>
<td>3 (5.2)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>(n°57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 40 years</td>
<td>4,692 (98.0)</td>
<td>21 (0.4)</td>
<td>43 (0.8)</td>
<td>0</td>
<td>17 (0.3)</td>
</tr>
<tr>
<td>(n°4,786) #</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p=0.098</td>
<td>p&lt;0.001</td>
<td>p=0.195</td>
</tr>
</tbody>
</table>

* Including Neuroendocrine carcinoma (NEC) (8246.3), Large-cell neuroendocrine carcinoma (8013.3), Small-cell neuroendocrine carcinoma (8041.3), Mixed neuroendocrine carcinoma (8244.3).

# Including 11 Lyomiosarcoma, 2 Melanoma

其中包括所有表3中描述的类别。

包括神经内分泌癌（NEC）（8246.3），大型细胞神经内分泌癌（8013.3），小细胞神经内分泌癌（8041.3），混合神经内分泌癌（8244.3）。

包括11例淋巴肉瘤，2例黑色素瘤。
<table>
<thead>
<tr>
<th></th>
<th>Mucinous Adenocarcinoma</th>
<th>Indifferetiated Carcinoma</th>
<th>Signet-ring cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N° (%)</td>
<td>N° (%)</td>
<td>N° (%)</td>
</tr>
<tr>
<td>G1-G2*</td>
<td>G3**</td>
<td>G1-G2*</td>
<td>G3**</td>
</tr>
<tr>
<td>≤40 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(38) *</td>
<td>20 (52)</td>
<td>9 (23.6)</td>
<td>3 (7.8)</td>
</tr>
<tr>
<td>&gt;40 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4,692) **</td>
<td>3,183 (67.8)</td>
<td>585 (12.4)</td>
<td>131 (2.7)</td>
</tr>
</tbody>
</table>

# Including Adenocarcinoma in adenoma (8210.3), Adenocarcinoma in villous adenoma (8261.3), Micropapillary carcinoma (8265.3) and Adenocarcinoma (8140.3): tumors with > 50% of mucinous (8480.3)

<table>
<thead>
<tr>
<th>G1-G2*</th>
<th>G3**</th>
<th>G1-G2*</th>
<th>G3**</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤40 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(38) *</td>
<td>20 (52)</td>
<td>9 (23.6)</td>
<td>3 (7.8)</td>
</tr>
<tr>
<td>&gt;40 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4,692) **</td>
<td>3,183 (67.8)</td>
<td>585 (12.4)</td>
<td>131 (2.7)</td>
</tr>
</tbody>
</table>

* G1 well differentiated neoplasms and G2 moderately differentiated.
** G3 poorly differentiated tumours.
+ In 2 patients information on grade was not available
++ In 694 patients information on grade was not available
<table>
<thead>
<tr>
<th>Groups</th>
<th>TNM I/Dukes A N° (%)</th>
<th>TNM II/Dukes B N° (%)</th>
<th>TNM III/Dukes C N° (%)</th>
<th>TNM IV/Dukes D N° (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 40 years (38)*</td>
<td>7 (18.4)</td>
<td>7 (18.4)</td>
<td>10 (26.3)</td>
<td>12 (31.0)</td>
</tr>
<tr>
<td>&gt; 40 years (4,692)**</td>
<td>800 (17.5)</td>
<td>1,451 (30.9)</td>
<td>1,115 (23.7)</td>
<td>948 (20.2)</td>
</tr>
</tbody>
</table>

\[ p < 0.828 \quad p < 0.113 \quad p < 0.713 \quad p < 0.083 \]

* 2 out of 38 were not staged.

** 378 out of 4,692 were not staged (8.0%).
<table>
<thead>
<tr>
<th></th>
<th>Hereditary Cases</th>
<th>Familial cases</th>
<th>Sporadic cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N° (%)</td>
<td>N° (%)</td>
<td>N° (%)</td>
</tr>
<tr>
<td>≤ 40 years</td>
<td>(38)</td>
<td>4* (10.5)</td>
<td>8 (21.0)</td>
</tr>
<tr>
<td>&gt; 40 years</td>
<td>(4,692)</td>
<td>26** (0.5)</td>
<td>512 (10.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.005</td>
<td>0.029</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* 3 patients had Lynch syndrome (2 MSH2 mutations, 1 MLH1 mutations, all 3 MSI positive). One patient had FAP (APC +). No patients had MuTYH mutations.

**19 patients had Lynch syndrome (12 with MSH2 mutations, 5 with MLH1 and 2 with MSH6 mutations, all MSI positive); Seven patients had Familial Adenomatous Polyposis, in five due to constitutional APC mutations, in two to biallelic MuTYH alterations.
Panel A

p=0.004
p=0.326
p=0.011
Panel A

<table>
<thead>
<tr>
<th>Months</th>
<th>Percent Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>10</td>
<td>0.8</td>
</tr>
<tr>
<td>20</td>
<td>0.6</td>
</tr>
<tr>
<td>30</td>
<td>0.4</td>
</tr>
<tr>
<td>40</td>
<td>0.2</td>
</tr>
<tr>
<td>50</td>
<td>0.0</td>
</tr>
</tbody>
</table>

1998-2007 years (n=31)
1984-1997 years (n=24)

p=0.270