Location and Age at Onset of Colorectal Cancer in Hungarian Patients between 1993 and 2004. The High Number of Advanced Cases Supports the Need for a Colorectal Cancer Screening Program in Hungary

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Abstract. Background: In recent decades, the incidence of proximal colorectal cancer (CRC) in North America and Western Europe has steadily increased, while that of the distal tumors has shown a corresponding decrease. Our aim was to investigate the change in age at diagnosis, the gender, location and cancer stage of CRC cases over the last 12 years in a large number of Hungarian patients. Patients and Methods: The clinical and histological data of 1694 CRC patients (M/F: 917/777, age at diagnosis: 65.2±SD 12.5 years), diagnosed at the First Department of Medicine and the First Department of Surgery of Semmelweis University, Budapest, Hungary, between January 1, 1993 and December 31, 2004, were analyzed retrospectively. Results: CRCs were rectal or left-sided in 70% and proximal (transverse, ascending or cecum) in 30% of the cases. The proportion of rectal carcinomas increased over the observed period (1993-1998: 31.6% vs. 1999-2004: 42.1%, p=0.001), while the proportion of proximal tumors remained stable. Eleven percent of CRCs were diagnosed under the age of 50 years. The age at diagnosis did not differ between males and females, but was lower in patients with rectal tumors compared to other localizations (p=0.02); 75.7% of the CRCs were T3-T4 at diagnosis and lymph node metastases could be detected in 47.7%. Conclusion: In contrast to Western European and North American trends, the proportion of proximal CRCs did not increase in Hungary over the observed period. Almost two-thirds of all cancers were left-sided. The high percentage of locally advanced tumors and lymph node metastases supports the need for colorectal screening programs.

Colorectal adenocarcinoma (CRC) is the second most common cause of death in developed countries. It is preceded only by lung cancer in mortality statistics as the leading cause of malignant deaths. Approximately 700,000 new cases are discovered and almost half a million patients die of the disease each year (1). CRC mortality has almost tripled in Hungary in the past four decades. While it was the cause of death in 1,898 cases in 1965, this number had risen to 5,095 by 2003. This increase seems to have halted in recent years; approximately 7,000-7,500 new cases are diagnosed annually, although exact incidence data are not available (2).

It was previously reported that 70% of CRCs involve the left colon, while 30% occur in the proximal colon. It is also known, based on epidemiological studies, that substantial geographical differences exist in the incidence of CRC. Several factors, such as eating habits, race and differences in genetic background, are believed to account for those differences (3).

Recent data have indicated a redistribution in the localization of colorectal carcinomas in North America and Western Europe (4-8). Numerous reports cite an increase in the incidence of right-sided CRCs, parallel with decreasing tumor numbers in the distal colon. The proportion of the right colonic segment has risen from 30% to 35%, while that of the rectum fell from 20% to 15%. A progressive increase of CRC incidence has been observed in both genders and a gradual shift towards the right-sided localization has been described in the elderly in the United States (9), as also confirmed by Australian and Asian
studies (8, 10). Colorectal cancer has become more frequent even in Greece, where the CRC incidence was traditionally low and a tendency towards a shift to the right side in localization had been observed in patients above 65 years of age (7). It is still not clear if this increase is truly the result of the rise of right-sided tumor frequency, or just a shift of proportions. It is, however, known that proximally, locally advanced stage lesions are more frequent (11).

The aim of our study was to investigate the changes in age at diagnosis, gender, location and cancer stage of CRC cases over the last 12 years in a large number of Hungarian patients.

Patients and Methods

The histologically-confirmed consecutive CRC cases diagnosed at the First Department of Medicine and the First Department of Surgery of Semmelweis University, Budapest, Hungary, between January 1, 1993 and December 31, 2004, were retrospectively analyzed.

A total of 1,694 CRC patients (male/female: 917/777, mean age at diagnosis: 65.2 ± SD 12.5 years) were included in the analysis. The CRC patients were divided into two subgroups; distal tumors located in the rectum or left colon and proximal tumors, if the tumor was located in the transverse or ascending colon/cecum.

Twelve subjects developed synchronous tumors (11 males and 1 female, mean age at diagnosis: 68.8, SD 11.6 years, 6 rectum and transverse colon, and 5 rectum and ascending colon/cecum). All patient materials and records were assessed following a study protocol approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (152/2004).

Statistical analysis. Normality was tested by the Shapiro Wilk’S W test. For comparison, the D-test and ANOVA test with a post hoc Scheffe test were applied. The possible relationships between gender, localization, TNM classification and age-group distribution were assessed using the $\chi^2$ and Yates-corrected $\chi^2$ tests. The results are mean±SD, if not stated otherwise. A $p$ value of <0.05 was considered significant. All calculations were performed on Statistica 6.1 (Statsoft Inc., OK, USA).

Results

The mean age at diagnosis did not differ significantly in men or women (64.8 ± SD 12.0 years vs. 65.8 ± 12.9 years). However, according to the age-group distribution, the proportion of female patients diagnosed after the age of 70 years was higher than males (M/F: 30.1% vs. 40.0%, $p=0.01$, Yates-$\chi^2$). The difference remained significant when the age distribution was analyzed according to the number of patients diagnosed in different decades of life (see Figure 1, $p=0.03$, $\chi^2$). Of all the CRC patients, 11% were under 50 years of age. In 2.5% of the patients, the carcinoma was diagnosed under 40 years of age, while 0.5% of the patients were under 30 years of age at diagnosis. Among the patients under the age of 30, FAP (familial adenomatous polyposis) was the final diagnosis in 3 cases and HNPCC (hereditary non-polyposis colorectal cancer) in 2, based on the family history and clinical characteristics of the patients; however, the data available on the risk factors and family history were limited.
An association was found between gender and disease location: male patients more frequently developed distal tumors (rectum and left-sided: 73.1% vs. right colon: 26.9%; females, rectum and left-sided: 66.0% vs. right colon: 34.0%, p = 0.002, Yates-χ²).

The clinical data for the CRC patients, according to the age at diagnosis, are provided in Table I. In the group of patients diagnosed under the age of 50 years, the cancer stage at diagnosis was more frequently advanced (T3-T4: 85.4% vs. 74.4%, p = 0.005), and the presence of lymph node metastasis was also more frequent. No difference was found in the location or gender.

The analysis of the relationship between location and TNM classification revealed that rectal tumors were diagnosed slightly earlier (rectum: 64.1±12.1 years vs. left colon: 66.1±12.2 years vs. right colon: 66.0±12.9 years, p = 0.03 for all groups, ANOVA, Scheffé post hoc) and at an earlier stage (T1: 5.6%, T2: 26.5%, T3: 61.5%, T4: 6.4%) compared to both left- and right-sided CRCs (T1: 4.8% and 3.1%, T2: 17.3% and 15.9%, T3: 68.0% and 71.2%, T4: 9.9% and 9.8%, p = 0.0008). At the same time, no difference was observed in the presence of metastases.

Almost 60% more tumors were diagnosed in the period between 1999 and 2004. The mean age at diagnosis was significantly lower (Table II). The proportion of rectal tumors and the prevalence of patients with lymph node metastasis was higher in this period (40.9% for 1993-1998 vs. 52.1% for 1999-2004, p = 0.0002). Regarding the cancer site, the ratio of proximal tumors did not change; at the same time, rectal lesions accounted for a larger proportion of distal cancers.

**Discussion**

Between 1993 and 2004, an increase in the number of CRC cases was detected. Almost 75% of the cancers were diagnosed at a locally advanced (T3-4) stage and almost half of the patients already had lymph node metastases at diagnosis. It was also unsatisfactory that no significant change in the TNM classification could be detected over the observed period. Furthermore, the tumors in those patients under 50 years of age were found to be even more advanced, irrespective of the cancer site or gender. An explanation remains to be found for the increase in CRC cases and the high number of locally advanced cases diagnosed in Hungarian patients.

Several factors might have contributed. It is known that vegetables, fruits, fiber and microelements might have a protective effect against CRC (12, 13). One explanation might be that a high meat and fat content are characteristic of the Hungarian cuisine, which, together with a lack of physical activity, may increase the cancer risk (14). There is also limited awareness of the high lifetime risk of CRC among patients in Hungary, making it possible that patients...
only seek medical advice with more severe symptoms (e.g., blood in the stool, weight loss), which often have already been present for months. In addition, there is, to date, no screening program underway in Hungary.

Recent North American and Western European epidemiological data have described an increase in the incidence of CRC along with a shift in the cancer site. Jubelier et al. (15) analyzed the data from the West Virginia Cancer Registry (n=7895). They reported that the number of right-sided cancers had increased from 30.5% to 37.6% and that the patients were more frequently males. The prevalence of right-sided tumors had rapidly increased in males over 85 years old, and in females over 75 years of age. The North American Central Cancer Registry detected 131,780 CRC cases between 1992 and 1997. The statistics showed that the proportion of proximal cancers had increased from 31.9% to 37.0%. There was a difference between the Caucasian and colored populations: right-sided CRC were more frequent in blacks, especially in females (16).

Based on the statistical analysis of the 87,695 CRC cases of the past 20 years, Japanese authors have found that the CRC incidence has increased 2.5-fold. Distal tumors are more frequent in males. In the past 5 years, the number and proportion of right-sided tumors are on the rise in both genders (17). The Chinese Cancer registry also demonstrated a rapid increase in CRC incidence during a 23-year period (1972-1994). The proportion of distal colon and rectum tumors decreased compared to proximal cancers (18). There was a significant difference with regard to age and gender. At 55 years of age, the proportion of proximal and distal tumors changed in the 2 genders. Men over the age of 55 years were more likely to develop distal or rectal lesions, while, at a younger age, this was more typical of women. An increase of CRC incidence in both men and women was also demonstrated by Norwegian epidemiological data from 1958 to 1997. However, an increase in the proportion of right-sided tumors could not be demonstrated (19). Some data suggest that proximal tumors are more often diagnosed at a locally advanced stage (11). In the present work, we found that both genders participated equally in the rise in the number of cases. We failed to detect a relationship between age at diagnosis and cancer location. Distal tumors, as in the Asian results, were more frequent in men, while the proportion of proximal tumors was higher in women. In recent years, it has become clear that the location is not the only difference between proximal and distal lesions. An analysis of surgically-resected colon segments revealed distinct genetic differences between the two sites (20). Molecular biological research has confirmed that not only anatomical and functional, but also genetic, differences lie in the background of the divergence in tumor localization (21, 22).

However, in contrast to previous reports, no proximal shift was observed; in fact, rectal tumors were more often diagnosed, while the proportion of proximal tumors remained stable. This data emphasizes that, in this regard, Hungary does not follow the international trends.

The high proportion of locally advanced and metastatic cancers in our study supports the need for the introduction of colorectal screening programs in Hungary. Several options are available: fecal occult blood test (FOBT), sigmoidoscopy or colonoscopy. FOBT is relatively simple and cheap, although the major limitation of its use is the need for continuous patient compliance. If performed properly, CRC mortality can be decreased by 15-30% (23-25). Another possibility is screening colonoscopy, but the high cost and available endoscopic capacity usually limit its use. The optimal time of onset is not known; usually an age of approximately 50 years is suggested (26). The only country where colonoscopic screening is routinely performed in about 40 centers as part of a public health program is Poland; 50,148 screening colonoscopies were performed between 2000 and 2004 and a total of 416 (0.8%) CRC and 2,380 (4.7%) 1 cm or greater adenomas were detected. It was concluded that one-time screening colonoscopies could be done at 50 years of age in men and, later, around 60-65 years, in women (Jaroslaw Regula, personal communication). In Hungary, with respect to financial considerations, annual or biannual stool blood tests and, in positive cases, colonoscopy in people over the age of 50 years might be the preferred method (27). Although in our study the mean age at diagnosis of CRC did not differ in men and women, the data in Figure 1 indicate that the peak incidence for men was around 50-60 years of age, while this occurred in women 5-10 years later. The distribution of patients according to age groups was also significantly different. This, in concordance with the Polish data, support an earlier onset of screening colonoscopy in males (around 50 years of age) compared to women (around 55-60 years of age).

The prognosis is highly variable across different parts of the world. While in the United States the 5-year survival rate is around 62% (28), and some publications even report a 70-75% 5-year survival in Dukes’ B2/C patients (29, 30), in Eastern Europe (including Hungary) the results are more modest (25-35%), which may, at least, be partially explained by the large number of locally advanced cases with a high proportion of patients with lymph node metastasis detected in our study. A screening program could also be valuable in the detection of cancer at an earlier stage, resulting in a more favorable treatment outcome.

In summary, in contrast to North America and Western Europe, proximal CRC did not become more frequent in Hungary during the observation period. Almost two-thirds of all CRC cases were distal and distal cancer was more frequent in men. The high proportions of advanced cases with lymph node metastases support the need for the introduction of a colorectal screening program in Hungary.
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