

COLORECTAL CANCER: WHAT HAS CHANGED IN DIAGNOSIS AND TREATMENT OVER THE LAST 50 YEARS?

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Aims and background: This overview focuses on what has changed in the diagnosis and treatment of colorectal cancer over the last 50 years.

Methods: The most important international registers (SEER, European and Italian) as well as the literature have been consulted. Furthermore, many prognostic factors are analyzed with the aim to understand the reasons why 5-year survival has improved over the last two decades.

Results: Since the biologic characteristics of the tumor cannot be changed, improved survival must be supported by concomitant multiple factors, such as earlier diagnosis (as given

by a more informed educational behavior and the advent of screening) as well as the wide use of colonoscopy and the technical improvement of surgical and medical treatment. However, it seems that the greatest improvement in survival is limited to 5-year controls, whereas long-term survival does not appear to show any significant improvement.

Conclusions: We can hypothesize that our efforts have just delayed the inevitable end: death. Nevertheless, further research should be done to confirm this hypothesis, perhaps in the field of molecular biology, which may also be the right approach to understanding the biologic aggressiveness of each tumor.

Key words: colorectal cancer, epidemiology, survival, treatment.

Introduction

All malignant tumors are potentially fatal, and many factors influence the final outcome of the disease. These are mainly the tumor's stage, its biologic characteristics, the combination of diagnostic methods and therapeutic choices. Progress made in the survival of patients treated for various types of carcinoma over the last few decades is partly due to better population screening for some cancers (e.g., breast, uterocervical, colorectal and prostate), leading to earlier detection and increased public awareness, improved diagnostic tools, surgical techniques and greater efficacy of anticancer drugs.

A first step towards a rational analysis of the temporal variations in tumor survival and, in particular, of colorectal cancer cannot be made without a comparative analysis of statistical data observed over the last 50 years. The aim of the first part of this review is to analyze trends in incidence, prevalence, mortality and survival in colorectal cancer to enable a correlation with progress achieved in the field of clinical diagnosis and treatment. The choice has fallen on colorectal cancer because the disease is the second cancer killer of both men and women, and technology has dramatically improved the diagnostic and therapeutic approach.

Materials and methods

This review systematically compares epidemiological data published by the SEER group of American tumor registries (Surveillance, Epidemiology and End Results)

with those collected nationally by the Italian Tumor Registry Association and those reported by the European Community. Incidence, mortality and survival statistics, as well as environmental factors are considered in the analysis. Diagnostic and therapeutic methods that have led to better patient survival have also been examined¹⁻³.

In view of the number of factors that have played a role in modifying patient outcome, only literature with a statistical-epidemiologic content and with medical specialization was consulted. It is evident that of the many factors that influence survival, often only one element is analyzed in the literature. However, it would be worthwhile to analyze all factors so as to recognize those which are 'independent' and the order of importance in a multifactorial analysis.

Results

Incidence

SEER have published estimates of incidence for colorectal cancer starting from 1950. Scanning approximately three decades, incidence rose from less than 50 cases per 100,000 population/year at the beginning of the observation period, to 58 cases per 100,000 population/year⁴. Between 1973 and the end of the 1980s, incidence is reported as peaking to about 62 cases per 100,000 population/year. However, a substantial drop was observed in the period 1989-2001, going from 62 to 47.7 cases per 100,000 population/year⁵.

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Figures 1 and 2 illustrate the incidence curve for the whole period available, differentiating between tumors of the colon from those of the rectum. The drop is present overall in both tumor sites. It should be noted that the SEER data were collected from a multiethnic population such as the American one⁶. Analysis by race indicates the white population has a lower incidence of colon cancer over the given period than the black population (even more evident when only males are compared). These differences are probably due to diverse levels of exposure to the traditional risk factors for colorectal cancer but also, as in the specific case of the colon-rectum, to incidence variations supported by the different awareness and intervention of the analyzed populations in regard to the precursors of colorectal cancer mainly represented by adenoma^{4,7,8}.

According to data published in 1999, 5-year survival was between 40 and 59% in European countries⁹. This difference in survival is due to the varied organizational behavior of the European Union countries, to the different ways factors such as stage of disease are obtained, access to optimal treatment and the social status¹⁰.

Colorectal cancer is the second most frequent cancer in Italy today in both males and females, claiming 33,000 new cases and 18,000 deaths every year. Analysis of data from Italian cancer registries showed an in-

creased incidence in cancers of the colon and rectum. However, this trend was not regularly distributed between genders. The increase was greater for males, peaking in the 90's, whereas average annual variation in females was smaller, with a relatively strong increase concentrated between 1986 and 1990, but stabilizing since that date. It is also noteworthy that the number of people being screened in the USA is relatively low at 44%, and this figure is even lower in Italy. The USA-Italy comparison leads to some further considerations: the different trends in incidence could be due to the diverse use of endoscopy and colorectal (fecal occult blood test) screening programs and the different black populations in the two countries¹¹. Tumors of the right colon are more frequent in the United States than in Italy (37% vs 24%), whereas tumors of the rectum are more common in Italy (36% vs 30%).

Apart from cultural factors that may stem from racial differences in multiethnic populations such as that of the USA, it is noteworthy that in the area covered by SEER between 1970 and 2000, a 16% increase in right colon cancer was revealed, and diagnosis was often made through endoscopic examination¹². In fact, the use in the United States of the pancolonscope is not comparable to such use in Italy, where the examination is reserved almost exclusively for the symptomatic popula-

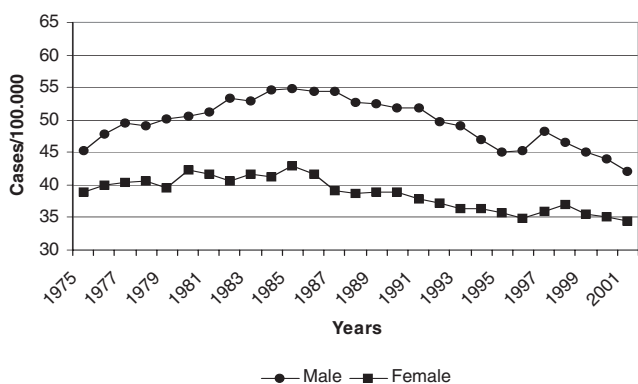


Figure 1A - Incidence colon cancer: Male / Female.

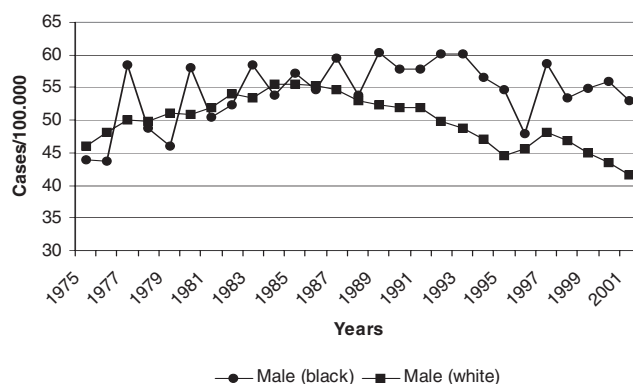


Figure 1B - Incidence colon cancer: Black male / White male.

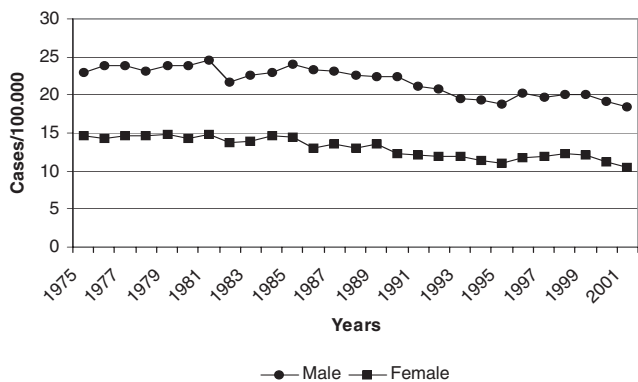


Figure 2A - Incidence rectal cancer: Male / Female.

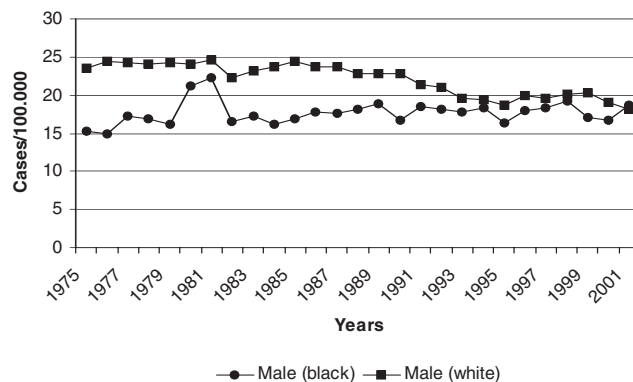


Figure 2B - Incidence rectal cancer: Black male / White male.

tion and as a second-level screening examination after the fecal occult blood test. The widespread use of endoscopic examinations in most countries has reduced the incidence of colorectal cancer by removing colon adenomas considered to be precursors of malignant lesions. The Italian group SCORE conducted a study on 9911 patients submitted to sigmoidoscopy screening, from which 1070 cases of adenomatous polyps were detected¹³.

Smart¹⁴ reported findings on the incidence of colorectal cancer based on stage over the period 1973-1984, which indicate on one part a trend towards localized and regional disease diagnosed *in situ*, and on the other a drop in so-called advanced disease¹⁵. It is presumable that these results can be obtained through screening. Eurocare 3 also reported that screening contributes greatly to the improvement in survival and has played a role in modifying incidence of colorectal cancer over the last decades³.

Prevalence

Tumor prevalence is the sum of newly generated cases in the population and excised cases where patients are still living with or without recurrence. When calculating prevalence, data on incidence and mortality rates are used to give an estimate of the number of living cases in a population over a given time. Even though it is extremely difficult to calculate¹⁶, prevalence is a fundamental indicator of the complex activity of healthcare programming that expresses the validity of treatment to which the population is submitted. The most reliable Italian data from cancer registries refer to approximately 12% of the population and estimate prevalence up to December 1992 of 96.5 cases of colon cancer and 54.3 cases of rectal cancer every 100,000 population. Translated into absolute numbers, this gives 83,000 cases, thereby confirming the importance of this disease on a national level¹⁷.

Mortality

It is well known that screening has an important role in reducing mortality from colorectal cancer^{18,19}. An exact and differentiated analysis of mortality from cancer of the colon and rectum proves difficult. In fact, incidence given by specific tools, such as tumor registries, is differentiated for the two sites, colon and rectum, whereas death certificates express only those statistics that combine the two sites.

Mortality rates were greatly reduced over the period observed in areas covered by the SEER program involving the white population of both sexes. The black American female population showed substantial stability, whereas the males presented a modest increase. In contrast, mortality in Italy slightly dropped in both genders. After peaking towards the end of the '80s, the total rates slowly diminished and, in 1997, returned to the 1986 level (males) or slightly below (females).

Survival

The SEER data show that 5-year survival increased from 50% in 1975 to 63% in 2000. Five-year survival in Italy has improved remarkably, going from 41% over the period 1986-1989 to 47% in 1990-1994, and this progress also involved the medium-high age population²⁰. Even though more pessimistic affirmations are reported in the literature, it would appear that over the last decades mortality from carcinoma (especially colorectal) at 5 years has greatly diminished. Nevertheless, it has also been reported that 10 and 15-year survival rates are unchanged²¹⁻²³. Survival is mainly determined by stage at diagnosis and has a weaker relation to prognostic factors linked to the patient and to the tumor itself. Adequacy of treatment at the time of first detection and disease recurrence is also important.

The role of medical and surgical treatment

It is obvious that over the last decades diagnostic techniques have become more sophisticated and the population has greater awareness of health problems. Consequently, there has been a net increase in cases diagnosed at an early stage and therefore susceptible to improved survival. Screening has had an important role in this outcome. In fact, studies in the screened population showed that the number of colorectal cancers in stage A and B has moved from 30-40% to 60-70%⁴, a trend also confirmed by Smart¹⁴. An analysis carried out by Nelson *et al.*¹⁵ with consultation of SEER data demonstrated a progressive increase in cases classifiable as *in situ* and therefore susceptible to so-called conservative treatment with greater survival. Cheng *et al.*²⁴ observe an increase in the percentage of localized cancers thanks to screening, passing from 31.9% to 37% in the descending colon to 41.5% in the distal colon.

It has also been observed that what was "adequate" in the '50s has changed, so that today we can attribute a more dynamic than static significance to the concept of 'adequate'. In the past, the oncologic criteria of radicality was considered respected when the intestinal resection was caudally at least 5 cm from the tumor. This margin has been gradually reduced to at least 2 and sometimes even 1 cm^{25,26}. There is still controversy over the extent of lymphadenectomy. According to an international convention, the minimum number of lymph nodes to be removed and examined must be between 12 and 15. Regrettably, as reported in SEER data²⁷, only 37% of U.S. patients undergoing surgery between 1987 and 2001 had an 'adequate' lymphadenectomy. This percentage is most certainly less in Italy.

Over the years, the extent of lymphadenectomy for colon cancer has not changed, and therefore its impact on survival is not significant. Lymphadenectomy for sigmoid-rectal tumors is much more controversial. Treatment of rectal cancer has undergone many important changes over the last 20 years. With the advent of mechanical staplers, the number of Miles operations has dramatically dropped to be replaced by low anterior re-

section^{28,29}. Data comparing Miles with anterior resection have shown survival to be identical. The most important improvement was of a psychological nature (lack of permanent colostomy).

Removal of the mesorectum became the gold standard in the 1980-1990s³⁰. Surgeons agree that it is mandatory to remove the mesorectum in cases of cancer of the lower sigma and rectum, but resection can be more limited in cancers of the proximal sigma and left colon. Almost all studies reported a drop in local recurrence from 15-20% to <10% and often improved survival^{31,32-34}. A second important factor is the advent of total mesorectal excision, confirming reduction in local recurrence in many studies.

There are at least two schools of thought for regional lymphadenectomy in cases of rectal carcinoma. Many Japanese surgeons perform an extended lymphadenectomy characterized by a lateral lymph node dissection, whereas western surgeons prefer the so-called traditional method^{35,36}. Some authors³⁷⁻³⁹ have compared traditional with extended lymphadenectomy in Dukes B and C cases, respectively. Five-year survival using the traditional method in Dukes B cases varied in these studies from 58% to 74.8%, whereas it was 23% to 36.6% in Dukes C. In the same stages but with extended lymphadenectomy, the range was 58% to 86% for Dukes B and 40 to 65.5% for Dukes C cases. These same authors concluded that extended lymphadenectomy should be performed solely or preferably on Dukes C cases where improvement in survival is greater, whereas the high incidence of urogenital complications compromises the cost-effectiveness of results in Dukes B cases.

Analysis of data regarding stage at time of detection has great importance on survival, the entity of which is inversely proportional to the stage of disease. However, Moreira *et al.*³¹ reported in 1994 no significant statistical difference in any stage of rectal cancer and believed the discriminating factor to be the presence of angio- and neuro-invasiveness. The number of lymph nodes removed and examined is important for a correct staging only when there is common intent between surgeon and pathologist. It would be particularly useful to have a bench preparation of the surgical specimen to enable detection of lymph nodes smaller than 5 mm in diameter. Kotanagi *et al.*⁴⁰ reported in 1993 findings of a study on 133 metastatic lymph nodes, 50% of which were less than 5 mm in diameter. Andreola *et al.*⁴¹ found that of 1793 isolated lymph nodes from 50 rectal resections (median, 36 per patient), those smaller than 5 mm in diameter represented 45.4% and metastases were present in 50% of them. A higher percentage (78%) was found by Herrera and Villarreal⁴², but lymph node isolation was made with the clearing technique.

Another task of the pathologist should be to analyze the circumference of the mesorectum⁴³⁻⁴⁵. Disease recurrence is more likely when neoplastic infiltration is found at less than 1 mm from the surgical margin.

Prognostic importance of lymph node micrometastases is controversial. Some authors believe there is no significance, whereas others believe there is^{46,47}.

Medical treatment

It is more difficult to assess the impact of chemotherapy alone in improving survival. Over the course of the years, dozens of drugs have been experimented in advanced stages of disease as well as in adjuvant stages. Results on the tumor have not always been the same as the outcome on survival.

The best results have been achieved with the use of an association of radio- and chemotherapy in a neoadjuvant stage of rectal carcinoma. Neoadjuvant treatments, mainly radiotherapy and the new chemotherapeutic regimen, have not just contributed with tumor down-staging to limit the number of Miles operations, but they have also determined complete remission in some cases^{48,49}.

As it is known that the most frequent postoperative site of recurrence of colorectal cancer is the liver and that metastases occur following the portal route, several authors have administered adjuvant 5-fluorouracil via the portal route. However, results were disappointing, especially in Dukes C stage disease.

With regards to efficacy of adjuvant chemotherapy, Beart *et al.*⁵⁰ reported in 1991 that substances administered till then (alkylating agents, thiotepa, alkylating substances) had not given comforting results, whereas better success was obtained with 5-fluorouracil and folinic acid (41% drop in recurrence rate and 33% in death rate) in cases of colon cancer. Wolmark *et al.*⁵¹ confirmed the results obtained using 5-fluorouracil, semustine and vincristine.

Smith *et al.*⁵² reported the 10-year results of a randomized trial on 1166 patients treated with 5-fluorouracil, semustine and vincristine vs control: 5-year survival was 67% vs 59%, and disease-free survival 58% vs 51% for Dukes B and C cases. Laurie *et al.*⁵³ reported a 3.5-year survival after administration of levamisole alone in 401 patients, in association with 5-fluorouracil and control of 68%, 71% and 55%, respectively, with 63%, 63% and 43% disease free. It is therefore true to say that (given the disease-free percentage), the greater part of the 37%, 37% and 57% not disease free will die after 3.5 years of observation.

In 2003, findings were published of a new association of antineoplastic drugs, 5-fluorouracil + leucovorin and irinotecan or oxaliplatin. Lievre and Mitry⁵⁴ confirmed the superiority of these drugs in improving survival.

A recent study⁵⁵ on 2246 patients compared results of an adjuvant therapy, FOLFOX vs LV and 5-fluorouracil, in stage II and III cases. After a 3-year observation period, 72.2% disease-free survival was found after treatment with FOLFOX and 65.3% after LV and 5-fluorouracil. Compared with the trial of Laurie *et al.*⁵³, a slight increase in the disease-free period was noted. However, it is necessary to verify the number of deaths at time of analysis, as well as how many deaths were a consequence of recurring disease recorded at the end of the 3-year observation period. Nonetheless, based on numerous randomized clinical trials, there is no doubt that there is an improvement in 5-year survival and disease-free period.

When local recurrence occurs, it can be treated with chemotherapy, radiotherapy, or both when only one site is involved. Local recurrence can sometimes be removed by performing lower anterior resection, the Miles operation or resecting the sacrum below the S2 vertebra²⁹. About 30% of patients are still alive at 5 years.

Advanced cases with multiple metastases are treated with chemotherapy. Over the last 20 years, anticancer medical treatment has achieved encouraging results in 5-year survival, the best of which are at present obtained with FOLFOX or FOLFIRI and, in selected cases, with monoclonal antibodies.

In the 1980s, Adson and Van Heerden^{56,57} published results of surgical treatment of hepatic metastases. Since then, surgery has been continually adopted albeit in highly selected cases. Treatment with radiofrequency or cryosurgery is more recent. Surgery would seem to be the optimal treatment in about 10% of cases when metastatic spread involves just the liver or lungs, since it has proven to give greater survival than other treatments. Surgery alone is preferable in cases of single metastasis or when the number of metastases is <4 and limited to one lobe. Five-year survival reported worldwide is 27-30% and near 40% when liver metastasis is single. Chemotherapy has shown good results in about 15-20% of cases previously judged unresectable to then become resectable.

Discussion

If increased incidence means the number of patients diagnosed with cancer, we can presume that merit is due to improved diagnostic tools which enable safer and quicker diagnosis than in the past. Starting in the 1950's, incidence of colorectal cancer increased, reaching 53 cases per 100,000 population. The most likely reasons for this increase is improved health education of cohorts born after the 1950's, the advent of endoscopy, the progressive life expectancy in many populations and, to a lesser extent, the diffusion of screening. If the increase in incidence is a true result of the etiologic process, the problem is more complicated and involves primary prevention. Findings from clinical data confirm the trend towards improved stage at time of diagnosis in already invasive forms and the removal of adenomatous and mainly villous polyps considered as potentially capable of transforming into carcinoma.

It is more difficult to give significance to the distinct rise in prevalence, although survival improvement confirms the impact of early detection and consequent drop in more advanced stages, as well as the efficacy of treatment.

Annual death rates should combine time of detection and treatment performed with a "curative" intent so an opinion can be expressed on the efficacy of therapies applied over the years.

The application of a multidisciplinary therapeutic approach and the quality of technical ability can explain

the present improvement in survival. The difficulty lies in establishing what can be considered adequate therapy. It must be said in this respect that what was once considered adequate treatment has undergone changes over the years. Over the last two decades, the inferior site of large bowel resection has dropped from 5 to 2 cm without modifying the concept of radicality. It has been established that ligation should be performed at the origin of the inferior mesenteric vessels in left colon-sigma carcinomas. However, when no lymph node metastases are detected, ligature may even be performed at the lower emission of the left colic artery. Also in this case, adequate lymphadenectomy and conservation of hypogastric nerves in the proximal tract of their route can be performed. In the obvious presence of metastatic lymph nodes in the proximal tract of the mesenteric vessels, extended lymphadenectomy is indicated.

The extent of lymphadenectomy has been a controversial subject for many years. It has a significantly superior staging, the reliability of which is directly proportional to the number of lymph nodes removed and examined, which must be more than 12. Thus, close collaboration between the surgeon and pathologist is mandatory.

Considerations regarding rectal cancer are more complex because improved surgical techniques (total mesorectum excision and lateral pelvic lymphadenectomy in Dukes C cases) and results of adjuvant or neoadjuvant clinical trials, with radio- and chemotherapy, have contributed to a considerable improvement in 5-year survival. There is better health awareness of the population, because over the last 20 years screening has permitted an early diagnosis of carcinoma with marked neoplastic down-staging and consequent improvement in prognosis.

Lastly, it is without doubt that the advent of more active drugs (oxaliplatin, irinotecan, and therapeutic schedules FOLFOX, FOLFIRI, monoclonal antibodies) has contributed to improve survival in treated patients. These positive findings are in adjuvant and neoadjuvant phases. The latter has already generated some optimism. Refinement of diagnostic and therapeutic techniques has allowed an increase in survival but this does not always lead to definite recovery.

In the 1950's and 60's, patients presenting hepatic metastases intraoperatively could expect to survive six months, improving to one year with the arrival of more efficient drugs. With the arrival of liver resection, about 10% of patients could undergo surgery with the aim to reach 5-year survival in 27-30% of them.

In conclusion, it can be safely said that the observed improvement in survival, estimated at 16-18% over the last 20 years, with a yearly increase of 1-1.5 points, is the result of a combination of skills, non of which can claim the entire merit for this success. Nevertheless, as some authors of the SEER analyses claim that death from colorectal cancer has remained more or less unchanged at 10 and 15 years, suspicion arises that the reported increase in survival could be interpreted as a result limited to 5 (and maybe 10) years, therefore read-

able as just a delay due to progress in medical technology, or to death predetermined by still little known alterations in a molecular biology setting. We must not forget however that biological prognostic factors of the tumor could be the real added value for a correct evaluation of survival and treatment results. Their identification will be the main object of research in future years, but already today a wider use of thymidylate synthase and telomerase tests could lead to a more rational indication of adjuvant chemotherapy. Research into molecular biology is more sophisticated and in the near future

may lead to the identification of those genes responsible for, or involved in, carcinogenesis. Lastly, as already mentioned, due to the descriptive lack on death certification in Italy, we have to analyze separately data relating to cancers of the colon and rectum. In the first case, hepatic metastases are more frequent and local recurrence is rarer, whereas in the second case recurrences are very frequent.

It is to be hoped that in the near future there will be a more informed certainty of the uncertain and greater understanding of the certain.

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