

# Current Changes in the Management and Outcome of Patients with Curable Colorectal Cancer

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**ABSTRACT:** **Background:** Major changes in the evaluation and treatment of curable colorectal cancer (CRC) have emerged in the last two decades. These changes have led to better patient outcome over time.

**Objectives:** To evaluate the impact of these changes as reflected in the difference in long-term outcome of a consecutive group of recently laparoscopically operated curable CRC patients and a consecutive group of patients operated 20 years earlier in the same department.

**Methods:** Data of the new group were taken from our prospectively collected data of patients who underwent elective laparoscopic surgery for CRC in recent years. Data regarding patients operated on 20 years ago were retrieved from previous prospectively collected data on the long-term survival of CRC patients operated in the same department.

**Results:** The recently operated group comprised 203 patients and the previous group 199 patients. Perioperative mortality was 0.5% in the new group versus 1.5% in the old group (not significant). There were more early-stage and more proximal tumors in the recently operated group. A Kaplan-Meier 5-year survival analysis revealed no difference between stage I patients of the two groups. However, there was a significant increase in 5-year survival in the new group for stage II (85% vs. 63%,  $P = 0.004$ ) and for stage III patients (57% vs. 39%,  $P = 0.01$ ). This trend was maintained after removing the rectal cancer patients from the calculated data.

**Conclusions:** We have demonstrated improved survival for stage II and III CRC patients over a 20-year period in the same medical center. This change most likely reflects advances both in imaging techniques leading to more accurate staging and in adjuvant treatments.

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**KEY WORDS:** colorectal surgery, colorectal cancer, survival

related to the stage at diagnosis. Treatment for curable CRC consists of adequate oncological surgery and adjuvant treatment when indicated.

The approach to colorectal cancer has changed over the last decade in several aspects. More emphasis is given to screening programs [2] since they lead to early detection and the resultant increased survival [3]. Operative procedures have become less invasive and well tolerated by patients due to the increased use of laparoscopy [4]. This process was somewhat slow to evolve owing to early concerns related to oncological safety [5] that were later resolved [6–8]. Since the early 1990s adjuvant treatment after surgery became the standard of care in node-positive patients and in selected stage II patients. This together with new potent chemotherapeutic drugs that have emerged in recent years have led to a substantial increase in the overall survival of advanced CRC patients [9].

The purpose of the present study was to evaluate how all the abovementioned changes were reflected in the outcome of patients with curable colorectal cancer operated in the same medical center over a long period. This was done by comparing patient and tumor characteristics and long-term survival between patients who were operated almost two decades ago [10] and a consecutive group of patients who recently underwent laparoscopic surgery by a dedicated surgical team from the same department.

## PATIENTS AND METHODS

The 'old' group of patients comprised consecutive patients who were electively operated for curable colorectal cancer in our department during the period 1984–1987. The 'new' group of patients comprised consecutive elective patients operated laparoscopically during the period September 2003 to December 2009 by a dedicated laparoscopic team from the same department.

Data for the old group were extracted from an existing database on patients' long-term survival that we used in a previous study published in 1997 [10]. This group of patients included all consecutive patients electively operated during this period. Data for the new group were retrieved from our prospectively collected data on all patients undergoing laparoscopic colorectal surgery. Almost all the procedures were

Carcinoma of the colon and rectum is the third most common cancer in North America, with an incidence of 147,000 new cases and 50,000 cancer-related deaths per year [1]. The prognosis of patients with colorectal cancer is

CRC = colorectal cancer

performed or directed by one of two surgeons dedicated to this approach. Long-term data in this group were collected from our outpatient clinic data files and personal contact when necessary. The data collection was approved by the institutional review board.

**STATISTICS**

Statistical analysis was performed using the chi-square test, *t*-test, Mann-Whitney non-parametric test, and long rank test for Kaplan-Meier survival curves. *P* value less than 0.05 was considered significant.

**RESULTS**

**THE OLD GROUP**

This group consisted of 199 patients, for whom follow-up was available for 184 (92.4%). In all of them follow-up time was > 5 years. None of these patients received adjuvant chemotherapy, while 14 rectal cancer patients received adjuvant radiotherapy.

**THE NEW GROUP**

This group consisted of 203 patients, for whom follow-up was available for 202 (99.5%). Fourteen percent of the patients had completed at least 5 years of follow-up since their operation. Mean follow-up time in this group was 30 months. None of the stage I patients received adjuvant treatment while 33% and 75% of stage II and III patients respectively received some form of adjuvant treatment.

**GROUP COMPARISON**

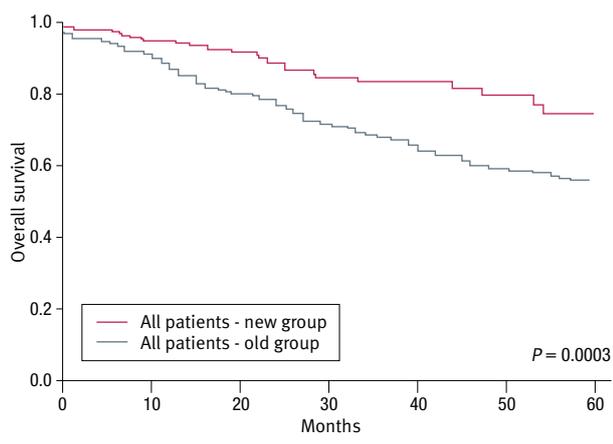
Mean age, the ratio between males and females, and operative mortality did not differ between the two groups. Stage distribution revealed more early stages in the new group. Also found were more right-sided tumors and fewer rectal tumors in the new group [Table 1].

**Table 1.** Demographic data, mortality, stage distribution and tumor location

	Old group N=199	New group N=203	<i>P</i> value
Mean age (yrs)	70.2 ± 12.4	69.9 ± 11.1	NS
M/F ratio	1.16	0.83	NS
Peri-operative mortality	3 (1.5%)	1 (0.5%)	NS
<b>Stage</b>			
I	28 (14%)	66 (32.3%)	< 0.01
II	108 (54.3%)	72 (35.3%)	0.02
III	63 (31.6%)	65 (31.9%)	NS
<b>Location</b>			
Rt. colon	54 (27%)	94 (46.3%)	0.007
Lt. colon/sigma	83 (42%)	72 (35.4%)	NS
Rectum	56 (28%)	33 (16.2%)	0.02

NS = not significant

**Figure 1.** Kaplan-Meier 5-year overall survival analysis for all patients: new group versus old group (75% vs. 57%, *P* = 0.003)



**LONG-TERM OVERALL SURVIVAL**

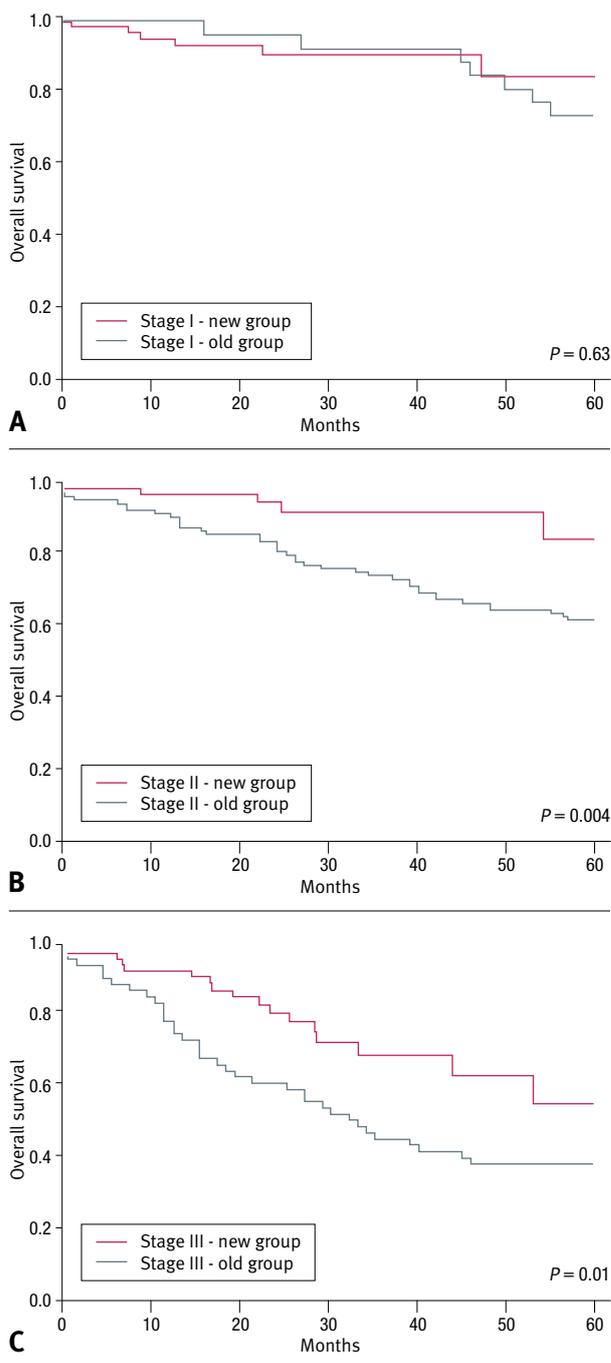
Survival comparison between the two groups demonstrated increased overall survival in the new group (75% versus 57% 5-year survival, *P* = 0.0003) [Figure I]. Survival comparison according to disease stage revealed a similar 5-year overall survival in stage I. However, an increased overall survival in stage II (85% vs. 63% 5, *P* = 0.004) and in stage III (57% vs. 39%, *P* = 0.01) was demonstrated in the new group [Figure 2]. This trend was maintained also after removing the rectal cancer patients from the calculated data (84% vs. 62% 5-year survival in stage II patients, *P* = 0.01 and 64% vs. 41% in stage III patients, *P* = 0.03).

**DISCUSSION**

Over the past 20 years the approach to and treatment of colorectal cancer have changed in many aspects. Implementation of screening programs, the use of less invasive surgical methods (i.e., laparoscopy), and the concept and development of better adjuvant treatments have modified both our treatment approach and patient outcome. These changes are reflected in the present study, which demonstrates the different outcome of operated patients with CRC over a 20-year period in the same department.

Comparing the two groups of patients in terms of stage and location of the cancer revealed an earlier stage and more right-sided tumors in the new laparoscopic group. The prevalence of an earlier-stage cancer in the new group may reflect an overall change over the last decade due to more public awareness and the availability of screening programs that result in early detection of colorectal cancer. Gross et al. [11] demonstrated a significant increase in probability of being diagnosed at an early stage in a population that was reimbursed for screening colonoscopy since 1998 compared to before. Fazio and col-

**Figure 2.** Kaplan-Meier 5-year overall survival analysis: new group versus old group. **[A]** Stage I patients (84% vs. 73%, not significant). **[B]** Stage II patients (75% vs. 57%,  $P = 0.003$ ). **[C]** Stage III patients.



laborators [3] reported the same trend for public education and screening programs. The change in tumor location in our study may reflect a universal process of rightward shift over time, with more proximal tumors diagnosed in recent decades [12]. This

phenomenon may be attributed to better screening of the proximal colon, increased routine performance of full colonoscopy, and general dietary changes over the past few decades [13].

Our study included a consecutive group of patients who were operated laparoscopically by a dedicated laparoscopic team. This fact may have produced some bias with regard to comparison of the group's characteristics since this group did not include patients who underwent open procedures for any reason (i.e., team decision or operation by non-laparoscopic surgeon). Obviously, the traditional open surgical approach was used in the old group of patients as laparoscopy was not a possible surgical approach 20 years ago.

The difference in tumor location may also be attributed to a change in referral patterns over 20 years. It may be that the laparoscopic approach was applied to more patients with right colonic tumors because rectal cancer patients were referred or chose other dedicated colorectal surgeons who did not employ laparoscopic surgery. However, we have no way of evaluating the impact of the change in referral patterns on the case-mix of our new group of patients. Nevertheless, we can presume that the surgical approach (i.e., laparoscopy versus open) had no impact on the difference between the long-term outcome, since it was repeatedly confirmed that laparoscopy has postoperative benefits but does not change patient survival compared to the open approach [6,7]. Unfortunately, in this study we could not compare postoperative recovery parameters between the two groups as these data were not available for the old group.

A change in surgical approach that could have an impact on survival is the introduction and implementation of the TME technique (total mesorectal excision) in recent years for rectal cancer patients. The TME approach demonstrated a lower local recurrence rate [14] and improved overall survival [15]. Unfortunately, in our study we could not assess the rectal cancer patients separately because the numbers were too small for significant survival analysis. However, evaluation of the colon cancer-only patients in our series revealed the same trend of better survival in the new group. This underlines the fact that the survival improvement is due to several factors, though location (colon versus rectum) might be one of them.

Data regarding quality measures for oncological resection as reflected in resection margins and the number of harvested nodes were available for the present laparoscopic group. The surgical margins and the mean number of harvested lymph nodes in this group concur with the standards of adequate oncological resection [16-18]. These data were not available for the old patient group; however, we can presume that the quality of surgery was not different 20 years ago as the same surgical oncology principles existed then and now.

This study demonstrated no change in long-term outcome for stage I CRC patients over the years. This result is reason-

able since the prognosis of stage I patients following adequate surgery is very good, with no need for further treatment apart from close follow-up. However, we have shown a significant improvement in survival for stage II and III CRC patients. We believe that the survival improvement can be attributed to the substantial advance in adjuvant therapy and better staging due to improved imaging techniques. The introduction of the 5 FU/leukoverin adjuvant treatment as the standard of care for stage III patients and selected stage II patients and the recent addition of oxaliplatin has substantially increased patient survival [19]. It is important to note that adjuvant chemotherapy was not the standard of care in the years 1984–1987 in our department.

In addition to the improvement in adjuvant treatment, the improved imaging techniques have probably contributed to more accurate staging. The improved sensitivity of computed tomography and the development of the positron emission tomography scan may have enhanced the accuracy of staging evaluation in discovering small metastases that could not be identified 20 years ago. This may lead to the exclusion of stage IV patients from our present patients who may not have been excluded 20 years ago and were likely considered to be in a lower stage.

The surgical principles of colon cancer resection that are currently practiced were the same as those followed when our old group was operated and even long before [20]. However, the recent focus on the number of retrieved lymph nodes may influence the pathologist as well as the surgeon to perform a more extensive dissection. Recent studies have emphasized the importance of the number of retrieved and examined nodes in the resected specimen. Increased lymph node evaluation may lead to better staging and may have an impact on long-term survival [21]. This perception did not exist 20 years ago and thus it is possible that some patients who were considered stage II in our old group were understaged due to less accurate pathological evaluation or less extensive surgery leading to a worse long-term survival in this group. Yet, as mentioned earlier, we do not have the data on the number of evaluated nodes in our old patient group to support this assumption.

General improvement in survival of colorectal cancer patients over the last decade was demonstrated in several studies using databases of cancer registries [22,23]. The major reason for this improvement is the enhanced prognosis of patients with regional tumor spread undergoing curative surgery [22]. Many of the reasons for this change that were suggested by others [23] were demonstrated and discussed in our study.

In conclusion, we have demonstrated improved overall survival for stage II and III CRC patients undergoing curative surgery over a 20-year period. This study is unique in that it compares two groups of patients operated by teams from the same department over a long period. Our results are in accordance with epidemiological reports from large database registries. Today, a colorectal cancer patient has a higher probability of being diagnosed at an early stage, having

a proximal tumor, undergoing laparoscopic surgery, receiving adjuvant treatment when indicated, and living longer than was possible two decades ago.

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