Colorectal cancer-screening program improves both short- and long-term outcomes: a single-center experience in Trieste

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Abstract

Screening programs (SC) have been proven to reduce both incidence and mortality of CRC. We retrospectively analyzed patients who underwent surgical treatment for CRC between 01/2011 and 01/2017. The current screening program in our region collects patients aged from 50 to 69. For this reason, out of a total of 600 patients, we compared 125 patients with CRC founded during the SC to 162 patients who presented with symptoms and were diagnosed between 50–69 years old (NO-SC). 45% patients in the SC group were diagnosed as AJCC stage I vs 27% patients in the NO-SC group; 14% vs 20% were stage II, 14% vs 26% were stage III, and 3% vs 14% were stage IV (p 0.002). We found a significant difference in surgical approach: 89% SC vs 56% NO-SC patients had laparoscopic surgery (p 0.002). In the NO-SC group, 16% patients underwent resection in an emergency setting. Only 5% patients in the SC group had postoperative complications vs 14% patients in the NO-SC group (p 0.03). We had a 2-year OS of 86%, being 95% in the SC group and 80% in the NO-SC group (p 0.002). Likewise, the whole 2-year DFS was 77%, whereas it was 90% in the SC group and 66% in the NO-SC group (p 0.002). Screening significantly improves early diagnosis and accelerated surgical treatment. We obtained earlier stages at diagnosis, a less invasive surgical approach, and lower rates of complications and emergency surgery, all this leading to an improvement in both OS and DFS.

Keywords Colorectal cancer · Cancer screening program · Short-term outcomes · Long-term outcomes · Colorectal surgery

Abbreviations

CRC	Colorectal cancer
USPSTF	US Preventive Services Task Force
FOBT	Fecal occult blood test
FIT	Fecal immunochemical test
CT	Computed tomographic colonoscopy
gFOBT	Guaiac fecal occult blood test
ASA score	American Society of Anesthesiologists physical status classification score
AJCC	American Joint Committee on Cancer
OS	Overall survival
DFS	Disease-free survival

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Introduction

Colorectal cancer (CRC) is the third most common type of non-skin cancer in both men and women. It is the second leading cause of cancer death in the United States after lung cancer. In 2016, an estimated 134,490 people in the United States were diagnosed with colorectal cancer and 49,190 people died from it [1].

Incidence rates of colorectal cancer show a positive relationship with an increasing level of economic development [2]. Even so, the 5-year survival rate decreases with lower levels of income, with rates reaching 60% in high-income countries in comparison to 30% or less in low-income countries [3].

Screening has been proven to reduce both incidence and mortality of CRC [4–7]. For this reason, all expert medical groups, including the US Preventive Services Task Force [7]

(USPSTF), strongly recommend screening. Although minor details of the recommendations may vary, these groups generally recommend that people at average risk of colorectal cancer get screened at regular intervals, beginning at age 50 years [1–3, 7]. The USPSTF advices screening to continue until age 75; after 75, the decision to screen is to be based on patient's life expectancy, health status, presence of comorbidities and previous screening results. Routine screening of people aged 86 years or older is not recommended by the USPSTF [5–7].

People at increased risk because of family history of colorectal cancer or previous polyps' resections or a medical history of inflammatory bowel disease or certain inherited conditions may start screening at younger age and/or have more frequent screening.

CRC screening is available in many countries with high and upper-middle incomes worldwide and is delivered by organized programs or on opportunistic basis.

Participation rates in such screening are highly variable among countries and settings but have typically been below 40% [8].

Insurance status and access to primary care are the main determinants of participation. Additional obstacles include costs, logistic challenges, lack of provider involvement, language barriers, cultural beliefs, and lack of awareness of colorectal cancer screening [9, 10].

There are several methods available for colorectal cancer screening [11], generally divided in noninvasive and invasive tests. Noninvasive stool-based tests to detect blood include the guaiac fecal occult blood test (gFOBT) [12] and the more sensitive fecal immunochemical test (FIT) [13]. Invasive endoscopic methods, which use optical approaches to directly examine the rectum and colon, include sigmoidoscopy and colonoscopy [14].

Colonoscopy is used both as a primary screening tool and as secondary level examination for patients who tested positive with other screening methods. In addition, computed tomographic (CT) colonography was developed as a noninvasive visualization technique [15].

During colonoscopy, any abnormal growths in the colon and the rectum can be removed and sent to pathology, including growths in the upper parts of the colon that are not reached by sigmoidoscopy. Studies suggest that colonoscopy reduces deaths from colorectal cancer by about 60–70% [7, 11].

Experts recommend colonoscopy every 10 years for people at average risk as long as their test results are negative [16, 17].

Newer noninvasive techniques have also recently emerged, and are based on visual inspection (e.g., video capsule endoscopy [18]) or on the analysis of biomarkers in stool (e.g., multitarget-stool DNA [19]), blood (e.g., methylated septin 9 DNA), or breath (e.g., exhaled breath analysis of volatile organic compounds [20]).

Studies have shown that gFOBT can help to reduce the number of deaths due to colorectal cancer by 15–33% [12, 21] when performed every 1–2 years in people aged 50–80 years.

In Friuli Venezia Giulia region of Italy, a screening program for men and women aged 50–69 is currently ongoing and allows patients to undergo gFOBT every 2 years up to the age of 74. If the test results positive, the patient is then recalled and suggested to undergo to a colonoscopy.

The aim of our study is to analyze the impact of this screening program on clinical outcomes and survival in patients undergoing surgery for CRC.

Methods

Study population

We retrospectively analyzed a total of 600 patients whom underwent surgical treatment for CRC between January 2011 and January 2017 in the department of General Surgery, Cattinara University Hospital, Trieste. The institutional ethical board approved the study and informed consent was obtained from each patient. Individual information was collected from the patients, their physician or the registers of death of the municipalities of residence.

Study design

The current screening program in Friuli Venezia Giulia region collects all men and women aged 50–69. For this reason, out of a total of 600 patients we compared 125 patients who were found to have a CRC during the screening program (SC) to 162 patients who presented with symptoms and were diagnosed when aged 50–69 without prior screening (NO-SC). Adhesion to the regional program was 60.3% in 2015.

Statistical analysis

Summary statistics of clinical and instrumental variables at enrolment were expressed as mean and standard deviation, or median and interquartile range, or counts and percentage, as appropriate. Comparisons between groups were made with the ANOVA test on continuous variables, using the robust Brown–Forsythe test when appropriate. The Chi-square test was used for discrete variables. Kaplan–Meier curves and the log-rank tests were calculated and compared between groups of patients defined according to SC/NO-SC evolution.

Results were considered statistically significant when $p < 0.05$. All calculations were performed using IBM SPSS 19.0 for Windows and the R package version 3.10.

Results

Characterization of patients

The study population included 287 of 600 enrolled patients, with at least five clinical evaluations during the follow-up period (3–6–12–18–24 months).

The baseline characteristics of the patients are reported in Table 1. The median age was 65 years (IQR 62–70 years).

The large majority of patients had an ASA score of 2 (61%) and was treated after the first evaluation (i.e., enrollment). 90% of patients underwent surgery in elective setting vs 6% who were operated in emergency setting. 65% of the overall study population was treated by a laparoscopic surgery approach.

At 2-year follow-up time, 72% of patients was disease free, 10% was alive with a tumor and 15% died (100% because of CRC in the SC group, 72%, because CRC vs 28% because of other causes).

45% of patients in the SC group were diagnosed as AJCC [22] stage I in comparison to 27% of patients in the NO-SC group (p value 0.002); 14% of patients in the SC group were stage II vs 20% in the NO-SC group also, 14% of patients in the SC group were stage III vs 26% in the NO-SC group and 3% stage IV in comparison to 14% in the NO-SC group (p value 0.002).

We found significant difference between groups when looking at surgical approach: 89% of patients in the SC group had laparoscopic surgery in comparison to 56% of NO-SC patients (p value 0.002).

Furthermore, 16% of patients underwent resection in an emergency setting in the NO-SC group in comparison to 0% in the SC group. Moreover, 14% of patients in the NO-SC group had a Clavien–Dindo classification up to grade III vs only 5% of patients in the SC group (p value 0.03).

2-year overall survival (OS) in the total study population was 86% (Table 2). There was a statistically significant difference between the two groups as OS was 95% in the SC group and 80% in the NO-SC group (p value 0.002).

2-year Disease-Free Survival (DFS) was 77% in the total study population, 90% in the SC group and 66% in the NO-SC group (p value 0.002).

Figure 1 shows OS curves and DFS curves of patients according to the AJCC stage. Patients with stage IV disease at diagnosis presented a similar rate of events in the OS and DFS curves (p value 0.0001).

On the other hand, the DFS curves (Fig. 2) of patients undergoing regional screening compared with the NO-SC group diverged significantly at the 24-month follow-up time point (SC group: 92% [CI 86–99%]; NO-SC group: 76% [68–86%]; p value 0.004).

The OS curves, shown in Fig. 3, demonstrate that the cumulative events during the follow-up period were less for SC patients in comparison to NO-SC patients, with better outcome for the former group (SC GROUP: SC Group: 92% [CI (86–99%); NO-SC GROUP: 82% [CI (77–86%)]; p value 0.0002, log-rank test).

Discussion

The present study describes for the first time the natural history of CRC since the beginning of the screening program in the city of Trieste.

Screening for CRC became widely available after many studies identified a benefit in terms of incidence and mortality rates. In particular, a landmark study by Mandel et al. showed a 33% reduction in cumulative mortality from CRC with the use of FOBT [23]. Other subsequent studies confirmed these results [24–26].

FOBT is the most basic type of test for CRC screening and became the test of choice in Friuli Venezia Giulia region after a cost-effectiveness analysis demonstrated its advantages in a mass-screening setting.

However, it is reported that the predictive value of FOBT for the diagnosis of CRC is only around 10% [27].

Fecal Immunochemical test (FIT) has been shown to have greater sensitivity and specificity for the detection of adenomas and CRC in comparison to classic gFOBT [28, 29]. An organized FIT screening program in Florence showed improvement of 22% in CRC incidence [30].

Unfortunately, FIT also showed low sensitivity for the detection of colon polyps [31].

The only technique able to bypass this issue remains colonoscopy, which has shown higher sensitivity and specificity, providing also the opportunity to resect polyps and adenomas, therefore, lowering the incidence of CRC. Numerous studies showed that CRC mortality decreased of around 68–88% in people undergoing screening colonoscopy [32–35], even though more studies have shown that this advantage is mainly related to left sided lesions [36]. Furthermore, colonoscopy requires sedation and the results are hindered by compliance with bowel preparation. These characteristics limit its use on a mass-screening basis [33, 36, 37]. It remains, however, the examination of choice when prior tests have given a positive result.

Numerous clinical trials are currently comparing screening techniques with the aim of finding the best: the CONFIRM trial (NCT01239082) is investigating one-time colonoscopy vs annual FIT plus colonoscopy at a positive result.

Table 1 Baseline patient characteristics

	Overall population (287)	Screening (125 patients)	No Screening (162 patients)	*p* value
Median age [25°p–75°p]	65 [6–70]	64 [62–69]	66 [62–70]	
Males	**68%**	66%	69%	0.69
ASA				
1	19,5%	35%	4%	0.009
2	61%	55%	67%	
> 2	19,5%	10%	29%	
Stage				
0	13%	21%	8%	0.002
I	33%	45%	27%	
II	17%	14%	20%	
III	22%	14%	26%	
IV	12%	3%	14%	
NOT CLAS.	3%	3%	5%	
pT				
0	3%	3%	3%	0.000
IS	10%	15%	6%	7
1	14%	26%	9%	
2	21%	23%	21%	
3	30%	26%	34%	
4	18%	3%	24%	
NOT CLASS.	4%	4%	4%	
pN				
N0	67%	81%	58%	0.000
N +	27%	15%	36%	6
NOT CLASS.	6%	4%	6%	
Tumor location				0.38
Sigma	30%	35%	30%	
Ascending	19%	20%	18%	
Rectum	25%	22%	31%	
Other	26%	23%	21%	
Regime				
Elective	90%	100%	84%	0.002
Emergency	6%	0%	16%	
Surgery				
Laparoscopy	65%	89%	56%	0.002
Open	33%	11%	44%	
Conversion				
Yes	14%	9%	16%	0.14
No	83%	91%	84%	
Local recurrences				0.07
Yes	4%	1%	6%	
No	97%	99%	94%	
Distant recurrences				0.06
Yes	**14%**	9%	18%	
No	**82%**	91%	82%	
Follow-up				
Disease free	72%	90.2%	66.4%	0.01
Alive with tumor	10%	4.4%	13.4%	
Died	15%	5.4%	20.2%	
Other complications	**9%**	5%	14%	0.036

Bold values are median [first, third quartiles]

Table 2 2-year overall survival and disease-free survival

Variables	Screening (125 patients) (%)	No Screening (162 patients) (%)	*p* value
OS	95	80	0.002
DFS	90	66	0.002

Other studies are also comparing FIT to colonoscopy [38] or colonoscopy or FIT to no screening [39, 40].

In our experience, our regional program based on the use of gFOBT significantly improved early diagnosis of CRC: in fact, we found tumors at earlier stages in patients who underwent screening (45% AJCC stage I in SC patients vs 27% in NO-SC patients, $p = 0.002$).

We were, therefore, able to use a less invasive surgical approach more often in the SC group of patients (89% of laparoscopic procedures in SC patients vs 56% in NO-SC patients), recording lower rates of complications (5% complication rate in SC patients vs 14% in NO-SC patients, $p = 0.03$) and of conversion to open surgery (9% in the SC group vs 16% in the NO-SC group, in the absence of statistical significance) (Table 1).

These data are in accordance with results from the most important trials in the field [23–26, 41] and clearly show that this screening approach provides a significant advantage in terms of DFS (90% in the SC group vs 66% in the NO-SC group, $p = 0.002$) and OS (95% in the SC group vs 80% in the NO-SC group, $p = 0.002$) (Table 2).

In contrast to what was previously reported in the literature [36], we did not find significant differences in the detection efficacy of the screening program in relation to the cancer anatomical location, but this could be due to the fact that colonoscopy was only used as a second level screening technique after the FOBT returned a positive result.

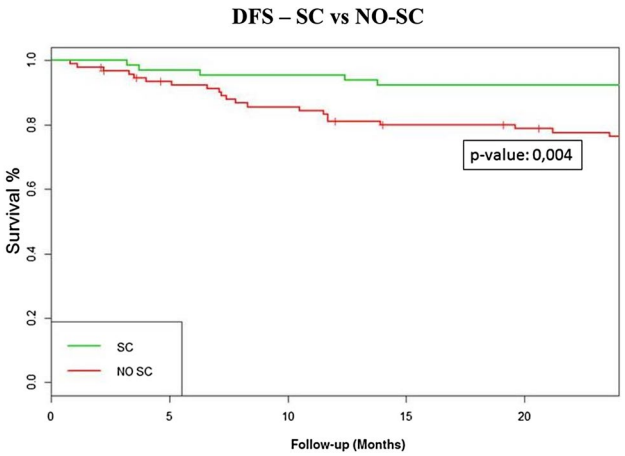

Fig. 2 2-year DFS rate

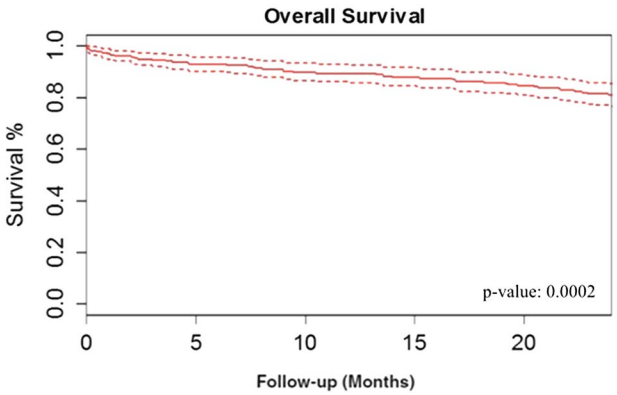

Fig. 3 Overall survival curves, shown in Fig. 3, demonstrate the cumulative events

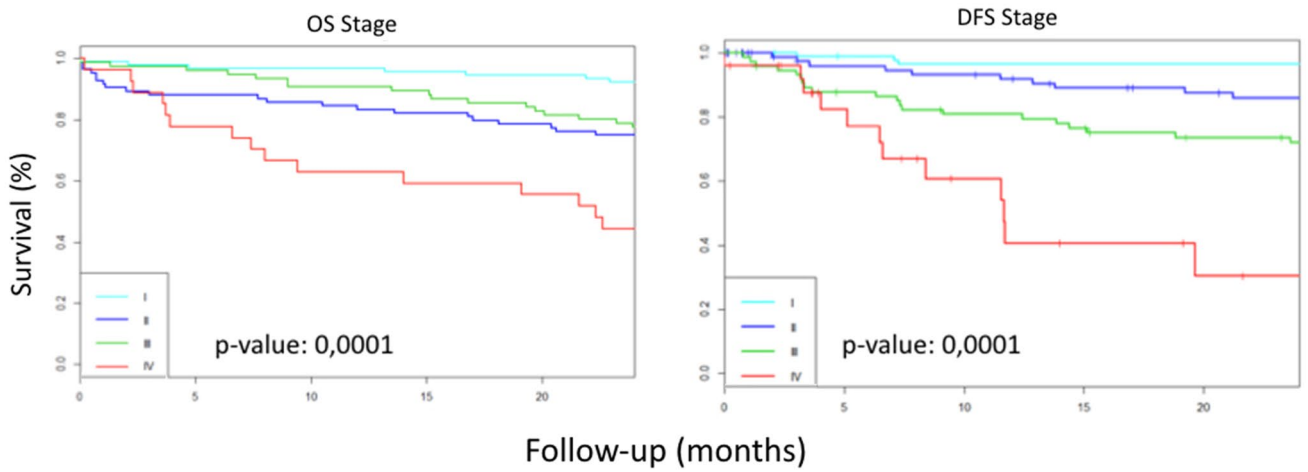

Fig. 1 Kaplan–Meier Survival Curves: long-term OFS and DF AJCC stage related

One limitation of this study is, however, the short follow-up time, which limits the analysis of clinical outcomes measures. The differences detected between the two groups in terms of DFS and OS could potentially diminish with a longer follow-up period.

Several national organizations have published guidelines on strategies to reduce colorectal cancer mortality, including the National Comprehensive Cancer Network [6], the US Multi-Society Task Force [17], and the American College of Gastroenterology [42].

The 2016 US Preventive Services Task Force recommendations do not support any specific testing strategy or strategies over others, but rather highlight the importance of screening patients at average risk for colorectal cancer between 50 and 75 years of age, with tailored screening for those between 76 and 85 years of age [26].

While screening has been shown to reduce CRC mortality, screening rates have not increased in the last 10 years and are stable at around 60% [43]. Adherence to screening programs remains traditionally low [44, 45]. Moreover, drop-out rates after one-time participation are also relatively high [46, 47].

At our center, adherence to the screening program remains at around 50%.

To improve this aspect and, therefore, to obtain even better results from CRC screening, newer, noninvasive techniques are being developed, which could "attract" people who are traditionally reluctant to undergo colonoscopy for instance [48]. Methylated septin 9 blood test identifies hyper-methylated septin 9 DNA in the bloodstream, which is thought to derive from CRC cells. The test shows 70% of sensitivity and 90% of specificity for CRC detection in retrospective studies [49, 50]. Unfortunately, following prospective trials reported similar specificity, but lower sensitivity, especially for early stages CRC [17]. Exhaled breath analysis of volatile organic compounds is also being investigated and showed encouraging results, but more randomized studies comparing this to other available techniques are needed [20, 51].

In view of the lack of clear results and sufficient data from randomized clinical trials on the newest screening techniques, currently used strategies such as FOBT and FIT are still considered the best options in terms of cost-effectiveness and non-invasiveness for mass-screening.

The cost-effectiveness literature of interventions to increase participation in screening programs mostly does not address the problem of how to calculate an incremental cost per year of life gained, but generally does a cost-consequence analysis and calculates the cost per test performed or the incremental cost per person earned at screening.

The European guidelines identify several papers evaluating the cost-effectiveness of colorectal screening [52].

The three cancer screenings currently recommended (pap test, mammography and FOBT) are very cost-effective interventions, with a low cost per year of life gained. Consequently, to try to earn a person at the single screening episode, up to € 40 can be dedicated in the case of the Pap test, € 130 in the case of mammography, € 800 in the case of sigmoidoscopy and € 80 in the case of FOBT, remaining under the € 30,000 for QALY (cost per quality adjusted life year) or LYG (cost per life year gained), cost unanimously considered as the cost-effectiveness limit [53–58].

As reported by Idigoras Rubio et al. an increase of 5-year survival rate of 23.4% of the participants in the screening program suggests that incidence and mortality rates of CRC will decrease in the near future for participants in screening program [59].

An effort needs to be made to improve other aspects, such as socio-economic disparities, patient education and adherence to the programs. Patient education material dissemination and multiple successive invitations to participate to screening programs could be some of the most effective and simple ways to improve patient participation rates.

In addition, patient stratification according to risk of CRC could further improve screening efficacy, cost-effectiveness and ultimately patient compliance, as invasive screening strategies could be then specifically used only on high-risk patients, sparing the average population.

Conclusion

In conclusion, even in the presence of limitations such as the retrospective nature of the study and the short follow-up time, we confirmed the impact of the screening program on clinical outcomes measures and survival rates in patients with CRC in our region.

In our study, we do not only explain that participate to the screening mean a low-grade tumor detection and a reduction of mortality and recurrences, but we want to emphasize that early diagnosis means accelerated surgical treatment.

An accelerated surgical treatment means a less invasive surgical approach, lower rates of complications and emergency surgery who can lead to an improvement in both OS and DFS.

The possibility of a patient selection bias also exists, even though all patients were enrolled at the same institution in accordance to homogeneous and clear inclusion criteria.

Implementation of tools to achieve higher participation to screening programs could ultimately further reduce incidence and mortality from CRC. Adoption of less invasive screening techniques will definitely benefit patients adherence to screening once results from randomized studies are available. Finally, a cancer-risk patient stratification

approach could improve screening cost-effectiveness and patient compliance.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest for all authors regarding the publication of this manuscript and no financial issues to disclose.

Research involving human participants The manuscript reports an observational retrospective study, so, on the basis of the resolution of the Authority for the Protection of Personal Data (Gazzetta Ufficiale N° 72—March 26, 2012—http://www.garanteprivacy.it/garante/doc.jsp?ID=1878276). This study has been conducted in accordance with the ethical standards of the Declaration of Helsinki. The institutional ethical board approved the study and the informed consent was obtained under the institutional review board policies of hospital administration.

Statement of informed consent Informed consent was obtained from all individual participants included in the study. There are no relationships with industry.

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