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Propensity Score-Matched Analysis of Minimal Invasive Surgery versus Open Surgery for Colorectal Cancer in Older Patients

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Synopsis

The efficacy of open versus minimal invasive surgery of colorectal cancer older patients is not clearly established even though surgeons deal with older patients. The study assesses the minimal invasive approach in older patients undergoing colorectal cancer surgery.

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Rezumat

Analiza comparativă a abordului minimal invaziv cu cel clasic în cazul pacientilor vârstnici cu cancer colorectal, pe baza scorului de propensiune

Introducere: În ultimii ani se observă o creştere constantă a numărului de pacienți vârstnici adresați serviciilor chirurgicale, datorată, în mare parte, îmbunătățirii speranței de viață. Această categorie populațională este puțin reprezentată în marile trialuri, ceea ce face dificilă aplicarea tratamentelor standardizate. Eficiența tehnicilor chirurgicale minimal invazive comparativ cu cele clasice în cancerul colorectal, patologie frecvent întâlnită la vârste înaintate, reprezintă un subiect sensibil în literatura

de specialitate. Studiul de față are ca obiectiv identificarea pontențialelor beneficii ale abordului minimal invaziv la pacienții vârstnici cu neoplazii colorectale.
Material şi Metode: A fost analizată baza de date a Clinicii de Chirurgie Generală a Institutului Clinic Fundeni, între anii 2012 şi 2015, având ca şi criterii de selecție a cazurilor: vârsta ≥ 65 şi diagnosticul de adenocarcinom colonic sau rectal. După aplicarea criteriilor de excludere au fost identificate 975 de cazuri: 842 operate prin abord classic (OS) şi 133 operate prin abord minimal invaziv (MIS). Reducerea bias-ului de selecție s-a efectuat în baza scorului de propensiune.
Rezultate: După corelarea scorului de propensiune în ambele grupuri, s-a observat că pacienții operați minimal invaziv (MIS) au înregistrat o durată mai scurtă de spitalizare postoperatorie în comparație cu cei operați classic (OS) ($p = 0.025$). În privința datelor preoperatorii, există o pondere semnificativă a intervențiilor deschise în cazul pacienților cu afecțiuni respiratorii cronice ($p=0.039$). Prezența bolilor respiratori s-a asociat şi cu creşterea ratei de complicații postoperatorii conform clasificării Clavien-Dindo ($p < 0.001$) şi implicit cu numărul de zile de spitalizare ($p = 0.028$).
Concluzii: Alegerea abordului minimal invaziv în cancerul colorectal nu trebuie să fie influențat de vârsta cronologică a pacienților. În cadrul studiului a fost demonstrată lipsa inferiorității abordului minimal invaziv în comparație cu abordul clasic, la pacienții vârstnici, în termeni ce analizează morbiditatea postoperatorie şi durata de internare. Pentru validarea beneficiilor chirurgiei minimal invazive la pacienții vârstnici, sunt în continuare necesare studii prospective pe loturi mari şi omogene de pacienți.

Cuvinte cheie: chirurgie minimal invazivă, chirurgie clasică, abordul laparoscopic, chirurgie robotică, îngrijirea pacienților vârstnici, cancer colorectal, scor de propensiune

Abstract

Introduction: Currently, surgeons deal with an older patient cohort, confronting new challenges brought by the raised life expectancy. This population is unrepresented in surgical trials; therefore, the optimal therapy is still a matter of debate. The efficacy of open versus minimal invasive management of colorectal cancer (CRC) in an elderly cohort is not clearly established. The current study assesses the minimal invasive approach in elderly patients undergoing colorectal surgery.
Material and Methods: The General Surgery Department database was inquired between 2012 and 2015 using the following filters: age ≥ 65 and rectal or colon adenocarcinoma. After applying the exclusion criteria, 975 cases were obtained: 842 underwent open surgery (OS) and 133 underwent minimal invasive surgery (MIS). A propensity score matching was performed to reduce patient selection bias.
Results: After the propensity score matching, the MIS group had a shorter postoperative hospital stay than the OS group ($p = 0.025$). From the preoperative variables, the presence of chronic lung disease was significantly higher in the OS group ($p = 0.039$). The presence of chronic lung disease positively associates with the Clavien-Dindo classification ($p < 0.001$) and with the number of days from surgery to discharge ($p = 0.028$).
Conclusion: The chronological age alone should not be a limit to MIS granting that it showed no inferiority to the OS in terms of postoperative morbidity, correlating with lower postoperative stay in the elderly. Further prospective studies are needed to assess the outcome of MIS in elderly population.

Key words: minimal invasive surgery, open surgery, elderly care, colorectal carcinoma, laparoscopic approach, robotic approach, propensity score

Introduction

Currently, surgeons deal with an older patient cohort and therefore, are confronting with new challenges. Life expectancy has raised and so has the incidence of neoplastic disease, especially that of colorectal cancer (CRC) (1). Even though many definitions of the elderly were proposed, depending on the life expectancy and the country, in most developed countries the cut off was set at 65 years, although a shared definition has not yet been reached (2,3). Approximately 70% of the newly diagnosed colon cancers occur in patients older than 65 years, CRC being an age-associated malignancy (4). They tend to have locally invasive CRC with a higher prevalence of the right colon involvement (4). Compared with their younger counterparts (35-69 years old), patients older than 70 years receive 50% less treatment (4). Elderly patients are less likely to receive guideline-recommended therapies (5).

In the past 25 years, the approach in general surgery has shifted from the open to minimal invasive techniques aided by the improvement in technology and by the clear benefits proved by numerous studies (6,7): decreased morbidity, better pulmonary function, early return to normal function, less blood-loss, and shorter hospital stay with similar oncological results as open surgery (OS) (8). This shift in the surgical management also affects the elderly, which now represent a significant proportion of patients with CRC. Laparoscopic surgery is becoming the gold standard of treatment for many pathologies (9), including CRC with 1A levels of evidence (10) making it the treatment of choice. Given the fact that there is a lack of clinical trials designed for the elderly, the optimal therapy is not well established for this population. They are unrepresented in surgical trials (2,4), with most studies being observational and so there is few data on the optimal surgical management for this age group (8). Schiphorst et al (8) evaluated the register of National Institute of Health clinical trial and of International Standard Randomized Controlled Trial Number for randomized trials on laparoscopic surgery for CRC. Of the 52 study protocols available, 44% exclude the elderly simply because of age or comorbidities (10) and in 86% of trials, the mean age of the enrolled patients is below 70 without any specification on concomitant comorbidities (8). Only seven (13%) trials had no restrictions on the maximum age, American Society of Anesthesiologists (ASA)-score, or any form of physical suitability (8).

The specific physiological changes during laparoscopy involve a clear understanding of the surgical technique and the comorbidities from which the elderly suffer (9). Age should not be a barrier to treatment and neither our preconceived ideas. More studies are needed to better understand the risk-benefit ratio of minimal invasive surgery (MIS) in elderly patients with CRC and to combat the age discrimination of these patients, termed "age-ism", with the necessary evidence-based arguments.

Surgery is considered challenging for this patient group due to their frailty caused by reduced physiological reserves and frequent comorbidities (10). Comparing OS versus MIS in CRC over an age limit would lead to new evidence regarding the surgical therapy of choice for this group. Significant controversy remains when it comes to MIS in the elderly as some studies report increased risk of complications, whereas others consider it safe (11). The question that future guidelines need to address is if MIS is a safe approach for CRC elderly patients.

The main goal of this study is to evaluate the characteristics and the differences in the short term outcome after MIS and OS approach in CRC elderly patients, defined as individuals of 65 years old or older. The secondary goal is to identify preoperative risk factors for postoperative complications.

Materials and Methods

Study Design and Setting

The study is a retrospective propensity score match case-control. Initially, the database from the General Surgery Department was inquired between 2012 and 2015 for patients

older than 65 years with malignant colorectal pathology undergoing elective surgery using the following filters: age ≥ 65 and diagnosis of rectal or colonic adenocarcinoma.

The extracted data included age, gender, primary tumor location, type of surgery (radical or palliative), tumor stage, days from surgery to discharge, symptoms, ASA Score (12), New York Heart Association (NYHA) Functional Classification (13), comorbidities (14), diabetes, type of anastomosis, protective stoma, Clavien-Dindo classification (15), neoadjuvant chemo- or radiotherapy, multiorgan resections and surgical margins < 2 cm. Uncontrolled diabetes was defined as blood glucose à jeun of 180 milligram per deciliter or higher in a previously diagnosed patient with diabetes. The Clavien-Dindo classification is an instrument that stratifies the postoperative complications in 5 grades, depending on the type of treatment needed, minimizing the risk of bias, and allowing a thorough comparision (10).

Propensity score match case-control was used to limit selection biases, to compare the results with a control group that had undergone OS for the same tumor location, stage, and type of surgery (radical or palliative), with the same age and gender of the patient.

Ethics

Informed consent was obtained from all patients who underwent surgery and approval from the Local Ethics Committee and Research Board was obtained for the use of the patient data in this study.

Investigation and Treatment Management

All patients underwent colonoscopy with multiple biopsies in order to confirm de CRC diagnosis. For CRC staging, a thoracic, abdominal and pelvis computer tomography with intravenous and oral contrast was performed and for rectal cancer the local protocol included a pelvis magnetic resonance imaging to evaluate the local extension of the disease. The cases were extensively discussed in the tumor board. Systematic geriatric assessment was not a standard practice at the time of the study, being introduced only recently into the clinic. The decision to perform OS or MIS belonged to the primary surgeon. All patients underwent mechanical bowel preparation with polyethylene glycol prior to surgery and received antibiotic prophylaxis one hour prior to incision. A partial colectomy with total mesocolon excision was performed for colon cancer patients and a rectal resection with total mesorectal excision for rectal cancer after neoadjuvant chemoradiation (45-50.4 Gy with 5-fluorouracil or capecitabine) if indicated by the tumor board. No Enhanced Recovery after Surgery (ERAS) protocol was in place at the time of the study. A liquid diet was introduced on the second day postoperatively and solid diet after passing the first flatus. The peritoneal drainage was suppressed after the first stool and a day after, the patient was discharged with reevaluation at a week.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows (version 23.0, IBM, Chicago, IL). Categorical variables were described in frequencies and percentages. Continuous variables were represented as mean ±SD or median and range, after checking for normality. Categorical variables were compared using the Chi-square test, Mann–Whitney test, and Fisher's exact test. Continuous variables with quasi-normal distributions were compared using Student's T-test and those with a severe deviation from normality, with appropriate nonparametric tests. For correlation analyses, Spearman's Rho coefficient was used.

A propensity score matching was performed to reduce patient selection bias. This methodology greatly reduces effect size bias and confers non-randomized studies experimental design characteristics.

The propensity score matching was performed using Python extension for SPSS. Covariates used to calculate the propensity score were based on the previously published studies (11,16-18). As a first step, the

propensity score was estimated using logistic regression. The covariates used in this step were age, gender, primary tumor location, the type of surgery (radical or palliative) and tumor stage. After the estimation of the propensity score, the patients from the two groups were matched using a one-to-one nearest neighbor matching with a caliper of 0.15. Using this procedure, 27% of the cases were matched from the initial sample (266 patients, 133 from each group).

For all analyses, p-values < 0.05 were considered statistically significant.

Quality Assessment of Propensity Scores

The covariates used in calculating the propensity score were age, gender, primary tumor location, the type of surgery (radical or palliative), and tumor stage. A logistic regression was performed, with the above covariates, saving predicted probabilities and logit transformations as they are used in the matching process (propensity score). The dependent variable was specified to be the patient's treatment group [Group 1 – Open Surgery (OS) and Group 2 - Minimal Invasive Surgery (MIS)].

The logistic regression model was examined to evaluate the quality of propensity scores. The correct separation into groups compared to the null hit rate indicated a 36% improvement (86% versus 50%). An inferential goodness-of-fit test (Hosmer–Lemeshow) was also performed and suggested good model fit - Chi-square = 8.151 (p = 0.419). This demonstrated that the patients' selection was not random and could be reasonably predicted because of the covariates used in the estimation of propensity scores.

Differences in the probability of performing OS or MIS (i.e., selection bias) were then compared using independent T-test samples. This initial assessment is important in evaluating the magnitude of bias and any improvement after the propensity score matching. Results indicated that the groups were statistically different in their propensity scores or initial likelihood of being selected intro the MIS group (p < 0.001, SMD = 0.436). This difference in SMD (standardized mean difference) suggests that the two groups should not be directly compared when estimating the effects of the type of surgery.

Nearest Neighbor Matching within a Specified Caliper

Propensity scores were used to match the patients receiving MIS to those receiving OS. Because an exact match is difficult to obtain on 5 covariates, even for a large sample size, a distance measure (a caliper) was specified *a priori*. Specifically, a caliper of 0.15 standard deviations of this score was used as a reasonable distance for reducing bias between groups (a larger value of the caliper will lead to more pairs matched, but with a less power of bias reduction). After matching with a 0.15 caliper, a number of 266 patients were matched (133 from each group), which is remarkable – all patients from the MIS group were matched with a patient from the OS group (which is 6 time larger than MIS group).

Post-Matching Analyses to Evaluate Balance

To evaluate balance as a result of the propensity score matching model, Rosenbaum (2010) (19) and Rosenbaum and Rubin (1983, 1984)(20,21) suggests the standardized difference in the mean propensity score between the 2 groups should be less than 0.20 and the ratio of the propensity score variances in both groups should be near one (the recommended limits are 0.80 – 1.20). For covariates, continuous or categorical, statistical differences should not be significant in the matched sample. The results of the balance evaluation are presented in *Supplementary Table 1* and *Table 1*. Once balance is achieved on the propensity scores and covariates, groups can be compared directly on the outcome of interest (the effect of the surgical approach).

Results

Included Patients – Unmatched Cohort

We started by observing that the percentage of patients over 65 undergoing CRC surgery, both

Table 1. Covariates score balance before and after propensity score matching.

	Before matching. (975 patients)			After matching on matched sample (266 patients)		
Categorical covariates	OS group (n = 842)	MIS group (n = 133)	p-value*	OS group (n = 133)	MIS group (n = 133)	p-value*
Gender						
Male	61% (514)	53% (70)	0.102	56%	53%	0.712
Female	39% (328)	47% (63)		44%	47%	
Primary Tumor location						
Right colon	28% (236)	27% (36)		28%	27%	
Lower rectum and anal canal	16% (135)	18% (24)	0.442	19%	18%	0.708
Superior rectum and rectosigmoid junction	24% (202)	29% (39)		30%	29%	
Left colon	28% (236)	21% (28)		20%	21%	
Synchronous tumors	4% (33)	5% (6)		3%	5%	
Type of surgery						
Radical	81% (682)	92% (122)	0.001	92%	92%	0.820
Palliative	19% (160)	8% (11)		8%	8%	
Tumor stage						
0	2% (17)	8% (11)		5%	8%	
I	14% (118)	22% (29)		22%	22%	
II A	36% (303)	35% (47)		40%	35%	
II B	1% (8)	-		1%	-	
II C	1% (8)	1% (1)	<0.001	-	1%	0.654
III A	2% (17)	3% (4)		2%	3%	
III B	18% (152)	19% (25)		19%	19%	
III C	5% (42)	2% (3)		1%	2%	
IV A	16% (135)	7% (9)		8%	7%	
IV B	1% (8)	2% (3)		1%	2%	
IV C	4% (34)	1% (1)		1%	1%	
Continuous covariates						
Age in years (mean ±SD)	73 ± 6	73 ± 5	0.955	72 ± 5	73 ± 5	0.759

* Mann–Whitney test and Fisher's Exact test for categorical covariates and t-test for continuous covariates

OS and MIS, is steadily and continuously increasing over the years (*Fig. 1*), further supporting the need of analyzing the efficacy of the therapeutic approach in this population.

One thousand one hundred forty-three cases were acquired. One hundred sixty-eight were excluded on the following criteria: ostomy formation for neoadjuvant radiotherapy in rectal cancer, emergency reintervention (included as postoperative complication 3b Dindo-Clavien classification), intervention for local recurrence or hepatic metastasis (liver-first approach), intervention for local recurrence in patients that had initial surgery in another surgical center. From the 975 included cases, 842 had OS and 133 had minimal invasive surgery (*Fig. 2*).

The mean age was 73 years old with 60% of the patients being males. In what concerns the primary tumor location the majority 28% were located on the right colon, followed by the left colon 27%, superior rectum and rectosigmoid junction 25%, lower rectum and anal canal 16% and in 4% of cases there were synchronous tumors. Regarding the tumor stage, 3% were stage 0, 15% stage I, 38% stage II (36%

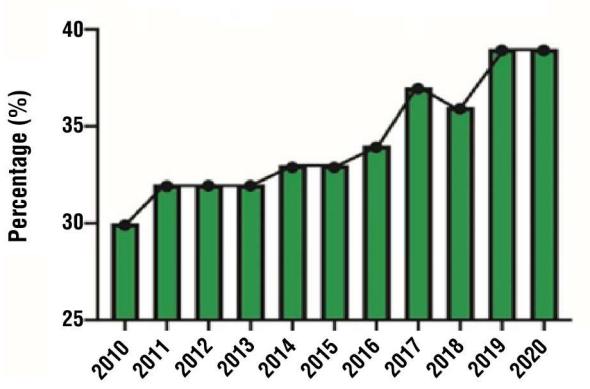

Figure 1. Percentage of elderly (≥ 65 years) who had surgery in Fundeni Clinical Institute (2010-2020)

stage IIA, 1% stage IIB and 1% stage IIC), 25% stage III (2% stage IIIA, 18% stage IIIB and 5% stage IIIC) and 19% stage IV (15% stage IVA, 1% stage IVB and 3% stage IVC). Of all the surgeries in this cohort 86% was performed by open approach. From the 14% of the MIS approach 73% were laparoscopic (97 patients) and 27% robotic (36 patients). We recorded a conversion rate of 7.52% (10 cases), these patients were included in the OS group due to the greater surgical trauma. In 18% of cases, the type of surgery was palliative. In 67% of patients an anastomosis was performed (25% had a mechanical one) from which 21% had a protective stoma. The percentage of the patients from the cohort that had a stoma, irrespective if terminal (33% from the entire cohort) or protective stoma (14% from the entire cohort), was 47%. 83 patients (8.5%) had surgical resection margins less than 2 centimeters.

Propensity Score Matched Case-Control Analysis

In *Table 1*, the baseline characteristics of the matching variables are depicted before and after the propensity score matching analysis. Before matching the percentage of palliative surgery in the OS group was statistically significantly higher than in the MIS group (p=0.001), this was probably due to the fact that in the OS group there were also statistically significant more patients with advanced

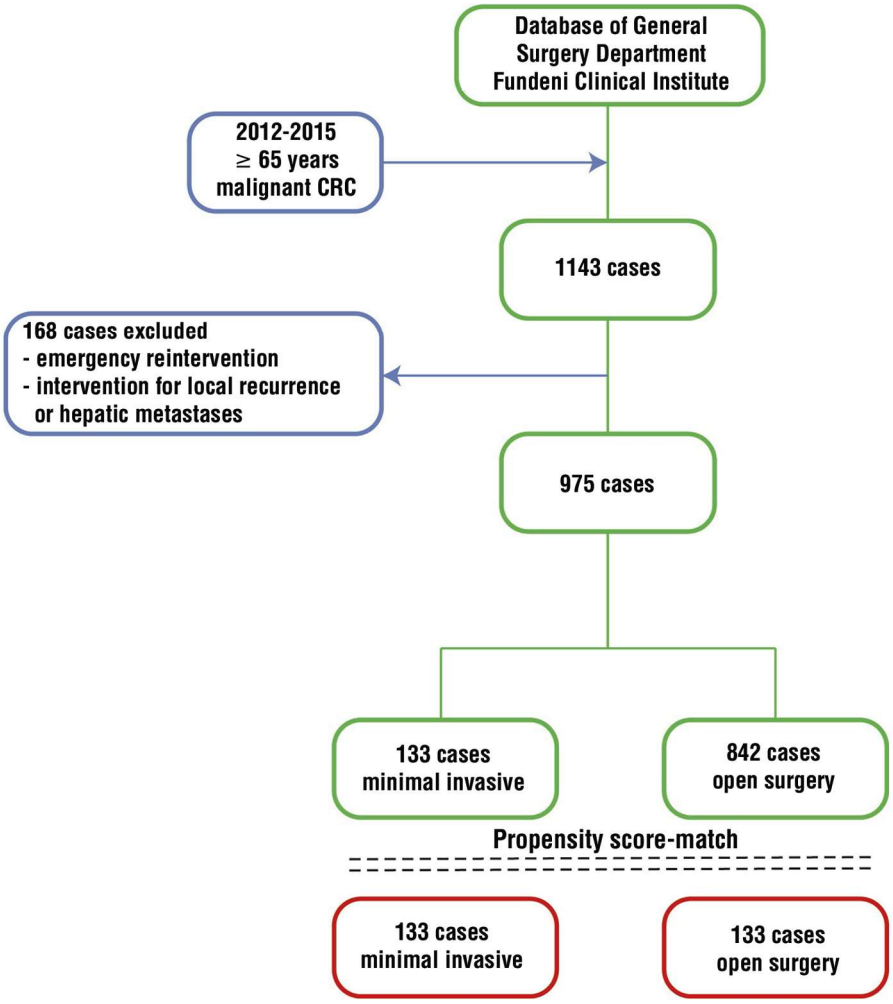

Figure 2. Flowchart illustrating the selection process

CRC ($p < 0.001$). After the propensity score match, we observe that there were no more statistically significant differences between the variables used. The mean age was 72 years old for the OS group and 73 years old for the MIS group, and both groups had slightly higher percentages of males. The tumors located in the superior rectum and recto-sigmoid junction enriched both groups, followed by tumors located in the right colon. After propensity score matching approximately two third of the cases had tumors staged 0-IIC in both groups.

An additional set of variables that were not used for the propensity matching were compared between the MIS and OS group. In *Table 2* the preoperative characteristics of the patients are shown. The only statistically significant different preoperative variable between the two groups was the presence of lung disease ($p = 0.039$), grey-marked.

Regarding intra- and postoperative variables (Table 3.) we observed much more to be statistically significant different between MSI and OS group (grey-marked). There are statistically significant differences between the groups in what concerns the type of anastomosis: more stomas and more manual anastomosis in the OS group and more mechanical anastomosis in the MIS group ($p \leq 0.001$). As well, for the protective soma variable there were more cases for which this did not applied either because it was a terminal stoma or because it was a right hemicolectomy in which a protective ostomy has no role ($p = 0.024$). Even though there were no statistically significant differences between the groups in regard with postoperative complications ($p = 0.699$), registered in Table 3 using Dindo-Clavien classification, the days from surgery to discharge were statistically significant different with a shorter stay for the patients in MIS group ($p = 0.025$).

Table 2. Post propensity score matched case-control comparative analysis of preoperative variables

Characteristics	OS group (n = 133)	MIS group (n = 133)	p-value*
Symptoms			
Screening	12%	17%	
Anemia	21%	16%	0.494
Abdominal Pain	9%	10%	
Lower gastrointestinal (GI) bleeding	29%	31%	
Transit disorders	29%	26%	
Unexplained weight loss (yes)	47%	48%	0.902
ASA score			
1	1%	8%	
2	29%	32%	0.140
3	62%	50%	
4	8%	10%	
NYHA classification			
0	69%	65%	
1	2%	4%	0.555
2	18%	20%	
3	11%	11%	
Cardiac pathology (yes)	72%	75%	0.489
Chronic Lung disease (yes)	14%	6%	0.039
Endocrine pathology (yes)	21%	22%	0.881
Liver pathology (yes)	8%	5%	0.316
Vascular pathology (yes)	20%	24%	0.374
Diabetes			
No	80%	80%	
Controlled	9%	5%	0.752
Uncontrolled	11%	16%	
Neurological conditions and disorders (yes)	8%	8%	1.000
Neoadjuvant radiotherapy (yes)	7%	11%	0.276
Neoadjuvant chemotherapy (yes)	5%	9%	0.111

*Mann–Whitney test (also for continuous variables with non-normal distribution) and Fisher's exact test

Estimating the Effect of Preoperative Variables on Postoperative Variables in the Entire Post-Matched Cohort

In order to investigate the effect of the statistically significant preoperative variables on the matched group and to assess if they are risk factors for postoperative complications a group subanalysis was performed. Taking into consideration the types of variables (categorical and quantitative), a Chi-square test of independence and a t-test were used. We performed this analysis in order to understand which of the statistically significantly different pre-operative parameters can impact post-operative endpoints. We observed that chronic lung disease and Clavien-Dindo classification are significantly associated (Chi-square test, $p < 0.001$). There is a significant difference (t-test, $p = 0.028$) in the number of days from surgery to discharge between the patients with chronic lung disease (mean number of days is 16) and those without chronic

Table 3. Post propensity score matched case-control comparative analysis of intraoperative and postoperative variables

Characteristics	OS group (n = 133)	MIS group (n = 133)	p-value*
Days from surgery to discharge. (median, range)	9 (5 – 58)	8 (5 – 58)	0.025
Type of anastomosis			
Stoma	29%	20%	
Manual	49%	23%	<0.001
Mechanical	22%	57%	
Protective stoma			
Not applied	82%	70%	
No	16%	27%	0.024
Yes	2%	3%	
Clavien-Dindo classification (n = 262)			
0	58%	58%	
1	3%	5%	
2	19%	22%	
3a	11%	7%	0.699
3b	3%	4%	
4a	2%	1%	
4b	-	1%	
5	4%	2%	
Multi-organ resections (yes)	17%	14%	0.307
Surgical resection margins less than 2 cm (yes)	12%	11%	0.847

*Mann–Whitney test (also for continuous variables with non-normal distribution) and Fisher's exact test

lung disease (mean number of days is 11).

Thirty-six patients from the matched cohort had uncontrolled diabetes (15 from the OS group and 21 from MIS group). There is no significant association between the presence of uncontrolled diabetes and the surgical approach (Chi-square test, p = 0.282). When analyzing the entire cohort, this variable did not reach a statistically significant association neither with Clavien-Dindo classification (Chi-square test, p = 0.120) nor with days from surgery to discharge (T-test, p = 0.337).

Discussion

The percentage of patients over 65 diagnosed with CRC is increasing as previously reported in the literature (4) and as we observed in our clinical practice, best described in *Fig. 1.* This made us aware of the importance in treatment management of this specific group of patients. Prior to the design of the study, we conducted a literature survey in order to better understand the management of these patients and to properly identify the targeted cohort. The elderly patients receive less active and intensive treatment than their younger counterparts, even though they can tolerate similar regimens and are more likely to be admitted as emergencies as National Cancer Equality Initiative states (22). We identified the following issues in treating them: sub-optimal treatment, ineffective assessment, comorbidities and multidrug-use, lack of education in elderly care, lack of social support, and age discrimination (2). The multiple studies in the literature (4,23-45) that compare the elderly with their younger counterparts have clearly shown that we are dealing with a particular category of patients with special needs and specific therapeutic management. The present study enrolled only elderly people in order to evaluate the short outcomes of the different approaches.

We chose to exclude the emergency cases because emergency surgery is associated with higher postoperative complication and mortality rate (46) and specifically in the older patients (≥ 65 years old) is associated with a postoperative complication rate ranging from 57.8% (47) to 65.7% (46) and a thirty-day mortality rate ranging from 10.4% (46) to 26.5% (47). We aimed to assess if MIS may have some advantages for CRC elderly patients in terms of early outcome or at least it is not inferior to OS.

The covariates used to calculate the propensity score were based on the previously published studies (11,16-18) to reduce the selection bias and to construct a randomized experimental-like situation.

The mean age of the entire pre-match cohort was of 73 years old, with 605 patients between 65-74 years old, 345 patients between 75-84 years old, and 25 patients over 85 years old. The oldest patient in the cohort was 92 years old. As previously reported in the literature (40), we also identified a predominance of right colon cancer (28%) in the pre-match cohort. Also, 19% of the patients had stage IV CRC (4).

Fourteen percent of all elderly patients with CRC underwent MIS in our center. They are frequently disqualified from minimal

invasive approach based solely on their chronological age. From which 73% underwent a laparoscopic approach and 27% a robotic one. De'Angelis et al (48) did not find any differences between the two MIS approaches on short term outcomes (postoperative morbidity, mortality, time to first flatus, return to regular diet and length of hospital stay), nor on the long term outcome (similar 1, 2 and 3 years overall and disease free survival). The only difference was found in the operative time, being longer for the robotic approach (48). Considering this we decided that both approaches can be studied together comparatively with the OS group.

The conversion rate (CR) was 7.52% (10 cases) due to intraoperative hemorrhage (2 cases), local tumor extension (5 cases) and important adhesions from previous surgery (3 cases). This is at the lower edge of the data published so far in general population (49) and similar with the data published on the older patient cohort: ranging from Chern et al (50) – 2% CR to Son et al (51) -11.1% CR. *Supplementary Table 2* summarizes the CR published so far in CRC older patients. Cases that underwent exploratory laparoscopy or were converted to open surgery were included in the OS group due to the greater surgical trauma, the associated higher blood loss and the parietal incisions that would interfere with the advantages offered by MIS (10).

Thirty three percent of patients had a terminal stoma and in 14% had a protective stoma resulting in a 47% of cases from the entire pre-match cohort having some type of stoma. Van Loon et al (52) reports that up to 35% of Dutch elderly patients have an ostomy after CRC surgery and that elderly patients with end ostomy experience significantly worsened 60-day, 90-day and 3-year overall and relative survival. Even though the mortality rate reaches 57% in older patients compared with their younger counterpart in case of anastomotic leakage after rectal surgery (52), the decision to from an ostomy should be thoroughly analyzed by the surgeon and considering the above mentioned should be tailored to the patient after a correct assessment and not by taking into account only the chronological age.

After propensity score matching, approximately two third of the cases had tumors stage 0 to IIC. This is due to the fact that early stages of CRC were selected to MIS group taking into consideration the learning curve needed to master MIS.

After assessing the preoperative variables there were no statistically significant differences, besides the presence of chronic lung disease, indicating a relatively uniform cohort. There were no significant differences between the groups regarding the symptoms suggesting that the clinical presentation is not a decision factor in selecting the type of approach. Both groups had the same number of patients that had unexplained weight loss, thus concerns regarding nutritional deficiencies did not influence the approach. Chen et al (1) identified sarcopenia and hypoalbuminemia as independent risk factors for patients over 65 years, despite the surgical approach, and the MIS for colon cancer as a protective factor for postoperative complications. The ASA score, NYHA classification, the presence of cardiac, endocrine, liver, vascular pathologies, as well as the presence of neurological conditions and disorders and diabetes, controlled or uncontrolled, did not differ statistically significant between groups, suggesting the feasibility of the MIS approach for this type of patient. The incidence of postoperative complications was significantly associate with the presence of more than one comorbidity prior to surgery (48). The group comparison demonstrates no differences in terms of neoadjuvant treatment.

MIS demonstrated a statistically significant advantage in terms of days from surgery to discharge, emphasizing even more benefits to elderly patients. The absence of laparotomy greatly shortens the period of postoperative convalescence and related complications are avoided (hemorrhage, hematomas, infections, incisional hernias, and eviscerations). Even though the postoperative hospital stay seems long comparing with the ERAS (53) protocols that are now in practice (9 days for OS and 8 days for MIS), at the time of the study this

protocol was not in place in our clinic. Further assessing the literature, the postoperative hospital stay after CRC surgery in older patients varies for MIS between 9 (54,55) days-14.2 (51) days and for OS between 10 (54) days to 17.8 (51) days.

More ostomies were recorded in the OS group and predictably more mechanical anastomosis in the MIS group, even though the patients who needed ostomy formation prior to neoadjuvant radiotherapy in rectal cancer were excluded. The study identified group fewer protective ostomies performed in the MIS. There were no differences in multiorgan resections or the presence of safety surgical resection margins suggesting that is not an impediment to MIS and that is a safe approach, with a similar percentage of safety margins.

The MIS is still not as widespread in the elderly as in the younger, because of some limited indications: longer operating times, a reduction in cardiac preload and an increased risk of postoperative atelectasis (10). Roscio et al (10) stated that prolonged pneumoperitoneum or reverse Trendelenburg position does not cause significant intra- or postoperative problems in patients over 70 years. Furthermore, the European Association for Endoscopic Surgery (EAES) underlined, grade B evidence, that MIS is not contraindicated in patients with a reduced cardio-pulmonary function if the pneumoperitoneum is maintained at 12 mmHg (56). Despite that, the elderly and those with preexisting ischemic heart disease or cerebro-vascular disease are considered particularly vulnerable for potential myocardial and cerebral ischemia in the reverse Trendelenburg position, which results in reduced venous return (57,58). These can be avoided by returning to the horizontal position every 2 hours (57). Since then, Mosquera et al. (11) demonstrated significant benefits from the MIS approach in medically unfit patients and Feroci et al (59) reported a lower mortality in high-risk patients, undergoing MIS compared with OS, defined by age, ASA score and comorbidities. In *Supplementary Table 3* the most relevant studies from the PubMed database on the subject were summarized.

In *Supplementary Table 3*, the estimated blood loss was significantly lower for the MIS approach. Elderly benefit from it giving the fact that older patients with intraoperative blood loss ≥ 200 ml had worse overall survival rates, this being an independent risk factor for postoperative adverse events (60).

Many studies report fewer complications for MIS colon resection than OS (11), decreased length of stay and morbidity in patients older than 80 years (61) and mortality (62). The study did not attain any statistically significant difference between groups, suggesting that is a safe approach for CRC surgery in the older patients, at least as good as the OS approach. Regarding the risk factors for postoperative complications, Niitsu et al (63) identified the operation time ≥180 minutes and the selection of laparoscopic approach (the operative time was higher for laparoscopy). Even though the study did not show the superiority of the MIS, in terms of postoperative morbidity, the shorter hospital stay in MIS patients may beneficial. There is an increasing trend for older patients with CRC OS to require home health or nursing home placement (64), by faster reintegration and shorter hospital stay MIS may help them.

The only significant statistical difference was observed for lung diseases (LD- see *Supplementary Table 4* for the subcategories included). These comorbidities were higher in the OS group, raising question marks about the management of these patients and the difficulties in providing an adequate peripheral oxygenation management during anesthesia and tolerating the pneumoperitoneum or the anti-Trendelenburg position. This is a selection bias due to not offering the possibility of MIS to patients with low lung capacity.

Inoue et al (65) identified pulmonary disease as an independent risk factor for postoperative complications. Additionally, the study estimated the effect of LD on the Clavien-Dindo classification and on the number of days from surgery to discharge and found a positive association between them.

Evaluating the postoperative complications in these patients, the study shows that only 10% had postoperative pulmonary complications alone consisting primarily of pneumonia and the complications covered various conditions. Even though the reason for the LD association with postoperative complications in laparoscopic surgery for colorectal cancer has not been elucidated, other studies report it (40,58, 65-67). LD as comorbidity is a reliable risk factor for surgical site infections (66,67). It appears that these patients are not fit for MIS as 87.5% had complications (varying from Clavien-Dindo classification 1 to 5), unlike OS, which had 66%, this is a subgroup analysis. Further studies are needed to achieve statistical significance.

Diabetes is an independent factor in colorectal surgery for developing postoperative complications, especially surgical site infection (68) and has increased 30-day mortality risk (69). The study confirmed no statistical differences among groups. Considering the facts, the study additionally evaluates the effect of uncontrolled diabetes, on Clavien-Dindo classification and on days from surgery to discharge, failing to prove a statistical association between them. This supports the use of perioperative insulin-based regiments in patients with diabetes mellitus.

Limitations

An important limitation is given by the retrospective study design, which we tried to overcome by using propensity score matching case-control in order to give experimental design characteristics for an objective evaluation and to also reduce the effect size bias. To our knowledge it is the largest study of this type on this subject conducted in an eastern European population. This may be beneficial for this specific population type with different health care systems, different cultural approaches, and different genetic background.

Another weakness is that no frailty testing prior to surgery was performed because systematic geriatric assessment was not a standard practice at the time of the study being recently introduced into the clinic. We tried to rectify this through the ASA score and careful evaluation of comorbidities.

Even though the present study emphasizes the short-term aspects of the postoperative CRC elderly patients, we consider that long-term monitoring in order to evaluate the oncological parameters (overall survival, disease free survival, etc.) and the oncological safety of MIS is an important research direction.

Conclusions

The elderly are a heterogeneous population, and the chronological age alone should not be a limit to MIS, granting the fact that it is effective and safe for CRC patients. Minimally invasive approach showed no inferiority to the open approach in terms of postoperative morbidity, correlating with lower postoperative stay in the elderly. Chronic lung disease is associated with the postoperative complications and postoperative hospital stay. Further prospective studies are needed to assess the outcome of MIS in elderly population.

Conflict of Interest

The authors declare no conflicts of interest.

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Data Statement

Data available on request from the corresponding author.

Author's Contributions

C.-E.M. and D.G. share first authorship. C.-E.M. and D.G. conceived and designed the analysis, collected the data, and wrote the paper. C.A., A.V., T.S., M.L. collected the data.

R.P.-P. performed the analysis. M.P.D reviewed and edited the manuscript, performed data visualization, verified the methodology. G.I.P and C.V. supervised and reviewed the final manuscript. All authors reviewed the results and approved the final version of the manuscript.

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Disclosure

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Appendix

Supplementary Table 1. Propensity score balance before and after propensity score (PS) matching.

	Before matching (975 patients)				After matching (266 patients)			
	OS group (n = 842)	MIS group (n=133)	SMD	Variance ratio	OS group (n = 133)	MIS group (n=133)	SMD	Variance ratio
PS (Mean ± SD)	0.865 ±0.048	0.844 ±0.045	0.436	1	0.846 ±0.044	0.844 ±0.045	0.002	1

Supplementary Table 2. Conversion rate (CR) literature assessment in CRC older patients

Year, Author	CR %
2020, Chern et al (1)	2%
2016, Niitsu et al (2)	2.9%
2014, Fujii et al (3)	3%
2016, Nishikawa et al (4)	3.2%
2006, Feng et al (5)	3.9%
2016, Moon et al (6)	7%
2015, Hinoi et al (7)	7.4%
2017, Yamamoto et al (8)	7.9%
2021, Son et al (9)	11.1%

Supplementary Table 3. A compendium of most relevant studies that evaluated MIS in CRC older patients

Year, Author, Journal	Study type, Number of participants OS/MIS	Enrollment Age and criteria	Elective /Emergency	Outcome	
				Short-term	Long-term
2006, Feng et al (5), Aging Clin Exp Res.	R-matched, 102/51	>70 years	E	- less OM in L - less EBL for L - shorter time to first flatus for L - less postoperative analgesia for L	-
2011, Robinson et al (10), J Surg Res.	R, 195/47	≥ 65 years	NOS	- similar OT - less EBL for L - shorter TROD for L - shorter PHS for L	- similar Ov.Surv. and DFS
2014, Fujii et al (3), Surg Endosc.	P, 100/100	≥75 years	E	- higher OT for L - less EBL for L - lower OM for L - similar PHS	
2015, Niitsu et al (2), J. Gastroenetrol.	R, 295/103	≥ 80 years and ECOG≥2	E	- less EBL for L - higher OT for L	- similar Ov.Surv.
2015, Hinoi et al (7), Ann Surg Oncol.	R – PSM, 459/459	≥80 years, stage 0-III CRC	NOS	- higher OT for L - less EBL for L - shorter PHS for L colon surgery - lower OM for L colon surgery - shorter TROD for L	- similar Ov.Surv., DFS, CSS
2016, Moon et al (6), Cancer Med.	R- PSM, 71/71	≥80 years	E	- shorter OT for OS - similar EBL - shorter PHS stay for MIS - shorter time to first flatus for MIS - OM higher in the OS	- similar Ov.Surv. and RFS
2016, Nishikawa et al (4), Surg Endosc.	R, 88/62	≥80 years and Em (all em cases were performed OS)	E	- less EBL for MIS - shorter PHS for MIS - similar morbidity and mortality	-

Year, Author, Journal	Study type, Number of participants OS/MIS	Enrollment Age and criteria	Elective /Emergency	Outcome	
				Short-term	Long-term
2016, Shigeta et al (11), Surg Today.	R, 55/52	≥ 80 years	E	- OM lower for L - similar OT - lower EBL for L - shorter TROD for L - shorter PHS for L	- similar CSS
2017, Ishibe et al (12), Surg Endosc.	P, 92/98	≥ 75 years	E	-	- similar 3-year Ov.Surv. and 3-year RFS - local recurrence rate higher for L in rectal cancer
2017, Yamamoto et al (8), J Gastroenterol.	R - PSM, 153/153	≥80 years, stage 0-III CRC, history of previous surgeries	NOS	- less EBL for L - longer OT for L - lower OM for L - shorter TROD for L - shorter PHS for L	- similar Ov.Surv. and DFS
2019, Zhou et al (13), BMC Surg.	R- PSM, 93/93	>80 years	E	- less EBL for L - lower OM for L - lower time to first flatus for L - lower PHS for L	- similar Ov.Surv. and DFS
2020, Hashida et al (14), Surg Laparosc Endosc Percutan Tech.	R, 26/82	≥ 85 years	NOS	- similar OT - less EBL for L - 2 major postoperative complications in OS, no major postoperative complication in L	- similar DFS
2020, Chern et al (1), BMC Surg.	R, 662/305	≥ 75 years	E	- higher TNM stage and higher patients with albumin <3.5 g/dl in OS - shorter PHS for L - similar OM	- no differences in Ov.Surv., CSS and cumulative recurrence rate
2021, Miguchi et al (15), Asian J Endosc Surg.	R - PSM, 48/48	≥ 80 years	E	- longer OT for L - less EBL for L - OM higher in OS	- similar 5-year CSS, 5-year Ov.Surv., 5-year RFS
2021, Takahashi et al (16), Anticancer Res.	R – PSM, 76/76	≥ 80 years	NOS	- short-term outcomes better for L (fewer postoperative complications and less delirium)	- similar 5-year Ov.Surv.
2021, Son et al (9), Int J Clin Oncol.	R, 104/190	≥ 80 years	E	- longer OT for L - shorter TROD for L - shorter PHS for L - OM lower for L	- similar 3-year Ov.Surv. and RFS

CSS -cancer specific survival, DFS-disease free survival, E- elective, EBL- estimated blood loss, Em-emergency, L-laparoscopy, MIS - minimal invasive surgery both laparoscopy and robotic, NOS-not otherwise specified, OM- overall morbidity, OS- open surgery, Ov.Surv. -overall survival, OT- operative time, P- Prospective randomized controlled trial, PHS - postoperative hospital stay, PSM-propensity score match, RFS- recurrence free survival, R-retrospective, TROD - time to reassume oral diet

Supplementary Table 4. Chronic Lung disease subcategories included in the present study

Chronic lung disease	• Personal history of pulmonary tuberculosis
	• Surgical resection of pulmonary neoplasia
	• Pulmonary thromboembolism
	• Asthma
	• Pulmonary hypertension
	• Chronic obstructive pulmonary disease (COPD)
	• Pachypleuritis
	• Recurrent pulmonary edema

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