Outcomes of laparoscopic surgery for pT3/pT4 colorectal cancer in young *vs.* old patients

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ABSTRACT

BACKGROUND: Laparoscopy for locally advanced colorectal cancer is not standardized yet and its potential risks and benefits in elderly patients are still under debate. The aim of this study was to evaluate clinical and oncologic results of laparoscopic surgery for pT3/pT4 lesions in both old and young people.
METHODS: Between 2006 and 2015, 115 patients aged <70 years and 112 patients aged ≥70 years underwent elective laparoscopic surgery for pT3/pT4 colorectal cancer presenting without distant metastasis at the Department of General Surgery, Trieste. Characteristics of the study populations, including demographic, operative and tumor features, were prospectively collected and short-term and long-term clinical, pathologic and oncologic outcomes were retrospectively analyzed.
RESULTS: No difference was found in terms of tumor features, type and duration of surgery, and quality of resection. Old patients were found to have significantly higher rates of conversion (P=0.02) and postoperative mortality(P=0.03), whereas postoperative complications and reintervention rates ~~-a~~lthough higher in the elderly ~~-d~~id not differ on sta - tistical analysis (P=0.13 and P=0.19, respectively). Local and distant recurrence rates were not statistically different between the two groups (P=0.64 and P=0.34, respectively). Adjuvant chemotherapy was more frequently offered to young people (P<0.001), who were considered significantly healthier than old ones (P<0.001). Overall survival was significantly lower among the elderly (P=0.001), but 5-year disease-free survival did not differ between the two groups (P=0.09).
CONCLUSIONS: Laparoscopic surgery for locally advanced lesions is feasible, but old patients present an increased risk of conversion and postoperative morbidity and mortality, which may alter long-term outcomes determining an apparent decrease in survival.

KEY WORDS: Colorectal neoplasms; Laparoscopy; Aged; Adult.

Colorectal cancer is the most common type of gastrointestinal cancer and one of the leading causes of cancer-related mortality in both women and men.[1, 2] Its etiology is multifactorial and encompasses genetic, environmental and individual features (*e.g.* diet, diabetes, obesity, inflammatory conditions of the digestive tract).[2, 3] Surgery remains a mainstay of treatment and laparoscopy has been shown to be a safe and effective alternative to open procedures, determining similar oncologic results by offering at the same time all the advantages of a minimally invasive approach (*i.e.* quick recovery, faster return of bowel function, less postoperative pain, shorter duration of hospital stay, better cosmesis).[3-10] However, its role for locally advanced lesions is not standardized yet.[11-14] In addition, risks and benefits of minimally invasive techniques in elderly patients are still under debate. It is well known that age can influence outcome after major surgery, especially because of the frequent coexistence of associated comorbidities (*e.g.*

cardiac, pulmonary, renal, and immunological disorders) that might negatively interfere with postoperative outcomes.[15-18] However, age itself should not be a hindering factor when considering the best surgical option for medically fit patients.[18-23]

The aim of this study was to evaluate clinical and oncologic results of laparoscopy surgery for pT3/pT4 colorectal cancer in the elderly compared to a young population, with particular regard to postoperative complication and reintervention rates, overall survival, and disease-free survival.

Materials and methods

The study is a retrospective analysis of a prospective collected database of the Department of General Surgery, University Hospital of Trieste. All patients who underwent elective laparoscopic surgery for pT3/pT4 colorectal cancer presenting without distant metastasis (M0) between January 2006 and December 2015, were considered for the analysis. Definition of pT3/pT4 colorectal cancer included either T3 tumor attached to other organs and/or abdominal structures or T4 neoplasia on histopathologic examination according to the depth of penetration into the bowel layers, as outlined by the AJCC staging system.[24]

All patients underwent elective laparoscopic surgery with curative intent following oncologic principles. Patients requiring emergency procedures (*i.e.* in case of acute bowel obstruction and/or perforation), patients undergoing open surgery as a first approach, and patients undergoing palliative surgery, were not included in the study. Patients with recurrent colorectal cancer were also excluded from the study.

For each patient, the preoperative work-up consisted of colonoscopy with biopsy, contrast-enhanced computed tomography (CT) of the abdomen and chest, and pelvic magnetic resonance imaging (MRI) in case of rectal cancer.

Surgical procedures were performed by either dedicated colorectal surgeons or surgical trainees under direct supervision of skilled colorectal surgeons.

All patients were divided into two age groups. The "young" group included patients <70 years old, whereas the "old" group included patients ≥70 years old. Patients were compared in terms of: demographic parameters (*i.e.* age, gender, American Society of Anesthesiology [ASA] score), tumor's characteristics (*i.e.* location of tumor, dimension of tumor, positive lymph nodes, staging, grading, histopathology, adjuvant chemotherapy), clinical, pathologic and oncologic outcomes (*i.e.* type of operation performed, duration of intervention, resection margin status, number of lymph nodes harvested, conversion rate, postoperative complication rate, reoperation rate, postoperative mortality rate, length of hospital stay, local recurrence, metachronous metastatic disease, overall survival, and disease-free survival). Quality of radical surgery was classified according to the AJCC residual tumor definition.[24] Conversion was defined as any non-planned open procedure performed after an initial laparoscopic approach. Postoperative complications were evaluated according to the Dindo-Clavien classification, considering them as major for a grade ≥2.[25] Reoperation rate was defined as any additional interventional procedure performed within the first 30 days from primary surgery. Postoperative mortality considered any death occurring within the first thirty days from primary surgery.

According to local protocols based on international guidelines,[26] neoadjuvant chemoradiotherapy was routinely advocated for all patients with stage III rectal cancer, whereas adjuvant chemotherapy was offered to all medically fit stage III patients. As recommended by international protocols,[26] all patients entered a 5-year follow-up assessment consisting of: clinical evaluation, regular laboratory assay including dosage of carcinoembryonic antigen (CEA) and gastrointestinal cancer antigen (GICA), abdominal ultrasound every six months and/or chest-abdominopelvic CT scan once a year, and full colonoscopy at one, three and five years from surgery. Positron Emission Tomography (PET) scanning was selectively performed on the basis of individual suspicious evidence.

Diagnosis of recurrence was established by means of radiologic findings, increased oncomarkes, and/or tissue biopsy. Overall survival (OS) was calculated from the date of surgery to

either the last visit recorded or death. Disease-free survival (DFS) was measured from the first day of treatment to the date of either last follow-up assessment or disease recurrence, whichever came first.

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in this study.

Statistical analysis

Quantitative results were reported in terms of median (range), whereas qualitative variables were reported in terms of absolute frequencies and percentages. All statistical analyses were performed using SPSS v. 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were assessed using the Fisher's exact test or χ^2 test, when appropriate. Continuous variables were evaluated by using the Mann-Whitney U-test and Wilcoxon Rank Sum test, when appropriate. The Kaplan-Meier method was used to generate survival curves and comparison relied on Log-rank test. A P value of less than 0.05 was considered to be statistically significant.

Results

A total of 227 patients undergoing elective laparoscopic surgery with curative intent for pT3/pT4 M0 colorectal cancer over a ten-year timeframe were considered eligible for the study. Of these, 115 were included in the young group (age <70 years at the time of diagnosis) and 112 were included in the old group (age ≥70 years at the time of diagnosis). Characteristics of patient populations are summarized in Table I.

Overall median follow-up period was 46 (0-146.5) months. Median age at the time of diagnosis was 62 (45-69) years in the young group and 77 (70-90) years in the old group, respectively. No statistically significant difference was found in terms of gender, with a slight prevalence of males in both groups. ASA score resulted significantly lower in the young group (P<0.001), with most patients (89%) presenting essentially healthy or with only mild systemic disease (*i.e.* ASA score I and II).

TABLE I.—*Study population characteristics.*

Characteristics	Young group (N.=115)	Elderly group (N.=112)	P value
Age, years	62 (45-69)	77 (70-90)	<0.001
Sex			0.89
Males	74 (64%)	74 (66%)	
Females	41 (36%)	38 (34%)	
ASA score			<0.001
1-2	102 (89%)	58 (52%)	
3-4	13 (11%)	54 (48%)	
Tumor location			0.29
Right colon	21 (18%)	32 (29%)	
Transverse colon	8 (7%)	5 (4%)	
Left colon	7 (6%)	9 (8%)	
Sigmoid colon	39 (34%)	35 (31%)	
Rectum	38 (33%)	31 (28%)	
Diffuse	2 (2%)	0 (0%)	

Results are reported as median (range) or as number of patients (percentage).
ASA: American Society of Anesthesiology.

Results of the study populations were comparable in terms of tumor's location and histopathologic characteristics, type and duration of surgical procedure, and radicality of resection.

Multivisceral resection was achieved in 4 patients, two per group (P=1.00).

Conversion rates were significantly higher in the old population (P=0.02), where about one third of patients underwent a switch from laparoscopy to laparotomy during primary surgery. Reasons to convert included non-cancer related intra-abdominal adhesions (N.=9), unexpected bulky tumor (N.=8), organ injuries (N.=2), appearance of hemodynamic instability (N.=1), and technical problems (*i.e.* inability to properly expose the operation field (N.=7), unsafe resection maneuvers (N.=19), difficulties in performing the anastomosis (N.=11).

Median length of hospital stay was 8 (3-59) days in the young group and 9 (4-72) days in the old group, respectively (P=0.21). Postoperative complications were recorded in 30% of young patients and in 40% of old patients (P=0.13), with reintervention rates of 7% and 13%, respectively (P=0.19). The most common problems recorded in both groups included surgical site infection, anastomotic dehiscence, postoperative ileus, pneumonia, and intra-abdominal fluid col-

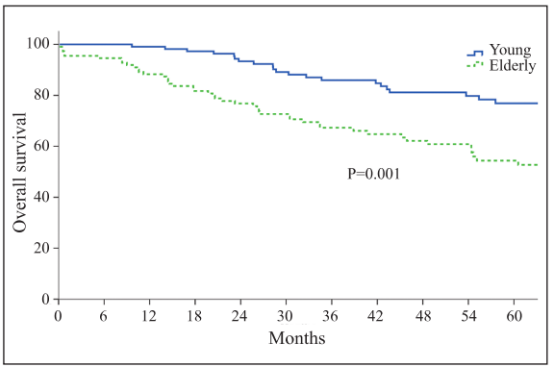

Figure 1.~~O~~verall survival at 5 years.

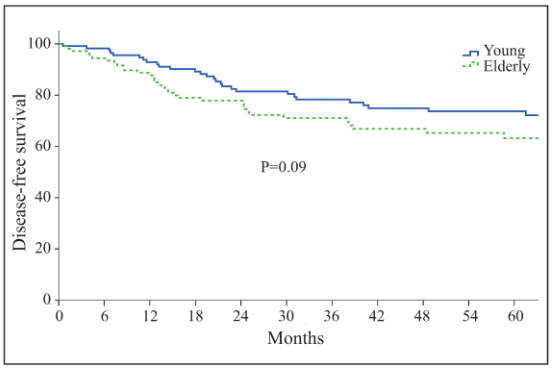

Figure 2.~~D~~isease-free survival at 5 years.

lection. Postoperative mortality was reported for five patients (5%) in the old group, whereas no death was recorded within 30 days from primary surgery in the young group (P=0.03). The causes of death in these five patients were septic shock secondary to anastomotic dehiscence (N.=2) or to pneumonia (N.=1) and pulmonary embolism (N.=2).

Adjuvant chemotherapy was more frequently offered to patients in the young group, with nearly double of young subjects undergoing further oncologic therapy compared to old ones (74% *vs*. 39%, respectively; P<0.001). Local and distant recurrence rates were not statistically different between the two groups, globally presenting in 24% of young patients and 31% of old patients, respectively (P=0.30). Specifically, local recurrence was reported in nine patients (8%) in the young group and in 11 patients (10%) in the old group (P=0.64), whereas metachronous metastatic disease was reported in 22 patients (19%) in the young group and in 28 patients (25%) in the old group (P=0.34).

Overall survival rate was found to be significantly different between the two groups, with 77% of young patients being alive at 5 years from diagnosis compared to 54% of old patients (P=0.001). However, 5-year DFS did not significantly differ between the young and the old groups (63% and 74%, respectively; P=0.09).

The Kaplan-Meier curves for OS and DFS are displayed in Figure 1, 2. Clinical, pathologic and oncologic outcomes are summarized in Table II.

Discussion

Surgery is a mainstay of treatment for colorectal cancer and laparoscopy is a safe and effective alternative to open procedures, offering similar long-term outcomes with the associated advantages of minimally invasive approaches (*e.g.* quick recovery, less postoperative pain, shorter duration of hospital stay).[4-10, 14, 16-20]

In the present study, we evaluated short- and long-term results of elective laparoscopic surgery for pT3/pT4 colorectal cancer in the elderly compared to a younger population. The cut-off age was arbitrarily set at 70 years. This study demonstrated how laparoscopic surgery has similar results in the elderly compared to younger patients, although it implies a higher risk of conversion.

According to our analysis, ASA score was significantly lower in the young group, in which the majority of patients presented essentially healthy or with only mild systemic disease (*i.e.* ASA score I and II). This result is not surprising when we consider that, although old age itself should not define frailty, elderly people are generally more susceptible to disease and disability, and advanced age is frequently associated with significant comorbidity and limited functional reserve.[17, 27]

No significant difference was found in terms of type of operation, duration of intervention, and quality of surgery. However, conversion rates were significantly higher in the old group compared to the young patients. According to a meta-analysis by Clancy *et al.*,[28] average

TABLE II.—*Clinical, pathologic and oncologic outcomes.*

Parameters	Young group (N.=115)	Elderly group (N.=112)	P value
Length of operation, min	153 (60-380)	158.5 (45-340)	0.34
Type of intervention			0.19
Right hemicolectomy	21 (18%)	32 (29%)	
Transverse colon resection	6 (5%)	5 (4%)	
Left hemicolectomy	17 (15%)	22 (20%)	
Anterior resection	63 (55%)	49 (44%)	
Other	8 (7%)	4 (3%)	
Conversion	21 (18%)	36 (32%)	0.02
Quality of surgery			0.79
R0	114 (99%)	111 (99%)	
R+ (R1, R2)	1 (1%)	1 (1%)	
N. of lymph nodes harvested	15 (1-53)	15 (2-48)	0.66
T stage			0.26
pT3	94 (82%)	84 (75%)	
pT4	21 (18%)	28 (25%)	
N stage			0.08
pN0	67 (58%)	52 (46%)	
pN+	48 (42%)	60 (54%)	
Grading			0.12
G1	21 (18%)	10 (9%)	
G2	74 (64%)	81 (72%)	
G3	20 (18%)	21 (19%)	
Postoperative complications	35 (30%)	45 (40%)	0.13
Postoperative mortality	0 (0%)	5 (5%)	0.03
Reintervention	8 (7%)	14 (13%)	0.19
Length of hospital stay, days	8 (3-59)	9 (4-72)	0.21
Adjuvant chemotherapy	85 (74%)	44 (39%)	<0.001
Global recurrence	28 (24%)	35 (31%)	0.30
Local recurrence	9 (8%)	11 (10%)	0.64
Distant metastasis	22 (19%)	28 (25%)	0.34

Results are reported as median (range) or as number of patients (percentage).

conversion rate in laparoscopic colorectal cancer is 17.9% (±10.1%) and factors negatively associated with completion of laparoscopic surgery are male gender, rectal tumor, T3/T4 tumor, node-positive disease, and lower body mass index. However, given that main reasons to convert included adhesions and tumor fixation in both groups, the disparity in conversion rates might not only be dependent on individual patient factors or surgeon's relative experience. Although the correlation between age and conversion has already been reported by other authors,[29-31] it is possible that concerns for potential anesthetic problems, technical difficulties and intra-operative decisions concerning oncologic resection contributed to the decision to convert more easily in the elderly, in whom the goal of treatment is to provide them with the best possible quality of life with the lowest physiological cost.

As far as short-term outcomes are concerned, postoperative complications were recorded in 40% of patients in the old group compared to 30% of those in the young group. Reintervention rates were nearly doubled in the elderly population and length of hospital stay was generally slightly longer in the old group than in the young group. Although all these data were not considered significant on statistical analysis, it is quite clear that old patients are at increased risk for multiple adverse outcomes because of their increased vulnerability, lower functional reserve and more probable failure to thrive.[27] Under this perspective, it is no wonder to find that postoperative mortality was significantly higher in the old group, where five deaths (5%) occurred within 30 days from primary surgery compared to none in the young group.

When considering oncologic long-term outcomes, old patients were less likely to receive adjuvant chemotherapy than young patients. This result is in accordance with the previously reported higher ASA score in the elderly set, which may justify why oncologists would frequently not consider old people medically fit for further treatments. Moreover, OS rates are significantly lower in the elderly group, with 54% of patients being alive at 5 years from surgery compared to 77% of patients in the young group. However, no statistical difference was found in terms of 5-year DFS and recurrence rates between the two sets of patients, thus leading us to conclude that old people are more likely to die from other causes than cancer, which can result in an apparent decrease in OS. Our results are in accordance with literature data, stating that age, gender and TNM stage are the most powerful predictors of oncologic outcomes and cancer-free survival.[13-20, 28, 32]

Limitations of the study

Being a single-center experience based on retrospective non-randomized analysis, the possibility of generalizing the results of this study to other patients is potentially limited. In addition, the sample size is small, and the follow-up period might not be long enough.

Conclusions

In this study, we manage to confirm that laparoscopic surgery for pT3-pT4 colorectal cancer is generally safe and feasible, although higher conversion rates should be anticipated in the elderly compared to younger patients. Besides, it should be remembered that old people tend to present an increased risk of postoperative morbidity and mortality, which may alter long-term outcomes determining an apparent decreased survival.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Gabriele Bellio and Marina Troian contributed equally to this work. Gabriele Bellio and Marina Troian: data acquisition, analysis and interpretation, manuscript drafting. Arianna Pasquali: data acquisition, critical revision of the manuscript. Nicolò De Manzini: data acquisition and interpretation, critical revision of the manuscript. All authors have read and approved the final manuscript.

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