Diseases of the Colon & Rectum Publish Ahead of Print

DOI: 10.1097/DCR.0000000000003961

ORIGINAL CONTRIBUTION

Rectal Cancer in the Elderly: To Operate or Not to Operate? A Nationwide Retrospective Study of the Italian Society of Surgical Oncology–Colorectal Cancer Network Collaborative Group

Running head: Rectal cancer surgery for the elderly

Rossella Reddavid, M.D., Ph.D.[1] • Ugo Elmore, M.D.[2] • Danila Azzolina, M.A., Ph.D.[3] • Jacopo Moro, M.D.[4] • Simona Ceraolo, M.D.[5] • Paola De Nardi, M.D.[6] • Alberto Biondi, M.D.[7] • Roberto Persiani, M.D.[8] • Leonardo Solaini, M.D.[9] • Donato Paolo Pafundi, M.D.[10] • Desiree Cianflocca, M.D.[11] • Diego Sasia, M.D.[12] • Marco Milone, M.D., Ph.D.[13] • Giulia Turri, M.D.[14] • Michela Mineccia, M.D.[15] • Francesca Pecchini, M.D.[16] • Gaetano Gallo, M.D.[17] • Daniela Rega, M.D.[18] • Simona Gili, M.D.[19] • Fabio Maiello, M.D.[20] • Andrea Barberis, M.D., S.C.[21] • Federico Costanzo, M.D.[22] • Monica Ortenzi, M.D.[23] • Andrea Divizia, M.D.[24] • Caterina Foppa, M.D., Ph.D.[25] • Gabriele Anania, M.D.[26] • Antonino Spinelli, M.D., Ph.D.[27] • Giuseppe S. Sica, M.D., Ph.D.[28] • Mario Guerrieri, M.D.[29] • Roberto Polastri, M.D.[30] • Francesco Bianco, M.D.[31] • Paolo Delrio, M.D.[32] • Micaela Piccoli, M.D.[33] • Alessandro Ferrero, M.D.[34] • Corrado Pedrazzani, M.D.[35] • Giovanni D. De Palma, M.D.[36] • Felice Borghi, M.D.[37] • Claudio Coco, M.D.[38] • Davide Cavaliere, M.D.[39] • Domenico D'Ugo, M.D.[40] • Riccardo Rosati, M.D.[41] • Maurizio Degiuli, M.D.[42]

1 University of Turin, Department of Oncology, Division of Surgical Oncology and Digestive Surgery, San Luigi University Hospital, Orbassano (Turin) Italy

2 Department of Gastrointestinal Surgery, IRCCS San Raffaele Scientific Institute, "Vita-Salute" San Raffaele University, School of Medicine, 20132 Milan, Italy.

3 Department of Environmental and Preventive Sciences, University of Ferrara, Via Fossato di Mortara 64B, 44100, Ferrara, Italy

4 University of Turin, Department of Oncology, Division of Surgical Oncology and Digestive Surgery, San Luigi University Hospital, Orbassano (Turin) Italy

5 Department of Clinical and Biological Sciences, University of Turin, 10124 Turin, Italy

6 Department of Gastrointestinal Surgery, IRCCS San Raffaele Scientific Institute, "Vita-Salute" San Raffaele University, School of Medicine, 20132 Milan, Italy.

7 Fondazione Policlinico Universitario A.Gemelli IRCCS. Università Cattolica del Sacro Cuore, Roma

8 Fondazione Policlinico Universitario A.Gemelli IRCCS. Università Cattolica del Sacro Cuore, Roma

9 General and Oncologic Surgery, Morgagni-Pierantoni Hospital, Ausl Romagna, Forlì, Italy

10 Fondazione Policlinico Universitario A. Gemelli – IRCCS - UOC Chirurgia Generale 2.

11 Department of Surgery, S. Croce e Carle Hospital, Cuneo, Italy

12 Department of Surgery, S. Croce e Carle Hospital, Cuneo, Italy

13 University of Naples "Federico II", Department of Clinical Medicine and Surgery, Department of Gastroenterology, Endocrinology and Endoscopic Surgery, Naples, Italy

14 Division of General and Hepatobiliary Surgery, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy

15 Department of General and Oncological Surgery, "Umberto I" Mauriziano Hospital, Turin, Italy

16 Unita’ Operativa di chirurgia generale, d’urgenza e nuove tecnologie, OCSAE, Azienda Ospedaliero Universitaria di Modena, Italy

17 Department of Surgery, Sapienza University of Rome, Rome, Italy

18 Colorectal surgical Oncology, Abdominal Oncology Department, Fondazione Giovanni Pascale IRCCS, Naples, Italy

19 General Surgery Unit, San Leonardo Hospital, ASL-NA3sud, Castellammare di Stabbia-Naples, Italy

20 Department of Surgery - General Surgery Unit, Hospital of Biella, Biella, Italy

21 Chirurgia Generale ed Epatobiliopancreatica; E.O. Ospedali Galliera, Genova

22 S.C. Chirurgia Generale ed Epatobiliopancreatica; E.O. Ospedali Galliera, Genova

23 Clinica Chirurgica Universita' Politecnica delle Marche, Ospedali Riuniti Ancona, Italy

24 Minimally Invasive and Gastrointestinal Surgery Unit, Università e Policlinico Tor Vergata, Rome, Italy

25 Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20072 Pieve Emanuele, Milan, Italy. IRCCS Humanitas Research Hospital -, via Manzoni 56, 20089 Rozzano, Milan, Italy

26 AOU Ferrara, Department of Surgical Morphology and Experimental Medicine, Ferrara, Italy

27 Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20072 Pieve Emanuele, Milan, Italy. IRCCS Humanitas Research Hospital -, via Manzoni 56, 20089 Rozzano, Milan, Italy

28 Minimally Invasive and Gastrointestinal Surgery Unit, Università e Policlinico Tor Vergata, Rome, Italy

29 Clinica Chirurgica Universita' Politecnica delle Marche, Ospedali Riuniti Ancona, Italy

30 Department of Surgery - General Surgery Unit, Hospital of Biella, Biella, Italy

31 General Surgery Unit, San Leonardo Hospital, ASL-NA3sud, Castellammare di Stabbia-Naples, Italy

32 Colorectal surgical Oncology, Abdominal Oncology Department, Fondazione Giovanni Pascale IRCCS, Naples, Italy

33 Unita' Operativa di chirurgia generale, d'urgenza e nuove tecnologie, OCSAE, Azienda Ospedaliero Universitaria di Modena, Italy

34 Department of General and Oncological Surgery,"Umberto I" Mauriziano Hospital, Turin, Italy

35 Division of General and Hepatobiliary Surgery, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy

36 University of Naples "Federico II", Department of Clinical Medicine and Surgery, Department of Gastroenterology, Endocrinology and Endoscopic Surgery, Naples, Italy

37 Oncologic Surgery Unit Candiolo Cancer Institute, FPO-IRCCS, (Turin), Italy

38 Università Cattolica del Sacro Cuore - Fondazione Policlinico Universitario A. Gemelli – IRCCS - UOC Chirurgia Generale 2.

30 General and Oncologic Surgery, Morgagni-Pierantoni Hospital, Ausl Romagna, Forlì, Italy

40 Fondazione Policlinico Universitario A.Gemelli IRCCS. Università Cattolica del Sacro Cuore, Roma

41 Department of Gastrointestinal Surgery, IRCCS San Raffaele Scientific Institute, "Vita-Salute" San Raffaele University, School of Medicine, 20132 Milan, Italy.

42 University of Turin, Department of Oncology, Division of Surgical Oncology and Digestive Surgery, San Luigi University Hospital, Orbassano (Turin) Italy

Funding/Support: None reported.

Financial Disclosures: None reported.

Correspondence: Rossella Reddavid, M.D., Ph.D., University of Turin, Department of Oncology, Surgical Oncology and Digestive Surgery, San Luigi University Hospital, Regione Gonzole 10, 10040 Orbassano (Turin) Italy. Email: rossella.reddavid@unito.it

ABSTRACT

BACKGROUND: Patients older than 70 account for 44% of all rectal cancer cases. Although surgery is the gold standard treatment, elderly patients can also be offered other treatments, such as total neoadjuvant therapy with watch and wait.

OBJECTIVE: This study aimed to investigate whether postoperative 90-day mortality is increased in the elderly compared to younger patients.

DESIGN: This nationwide retrospective study included all consecutive resections of rectal cancer between 2005-2016 using data from the RALAR study. Patients were divided into 2 groups based on their age: non-elderly <70 years and elderly ≥ 70.

SETTING: Data were obtained from 19 Italian referral centers for colorectal surgery.

PATIENTS: A total of 3,573 patients underwent rectal surgery: non-elderly (2,071 [57.9%]) and elderly (1,502 [42%]).

MAIN OUTCOME MEASURES: The primary endpoint was 90-day postoperative mortality. Secondary endpoints included intensive care unit stay, hospitalization, surgical and general postoperative complications, overall survival, disease-specific survival, and recurrence rate.

RESULTS: Ninety-day postoperative mortality was comparable between groups (0.41% non-elderly vs 1.05% elderly, $p = 0.087$). Elderly patients were monitored more frequently in intensive care unit and developed more postoperative general complications, while no differences were found between the groups in terms of postoperative surgical complications. Hospitalization was longer in elderly (median [IQR]: 12.3 [9.7] vs 11.1 [14.6] days). Five-year overall survival was higher in non-elderly (77.3%) compared to elderly (45.8%, adjusted OR 1.70, 95% CI: 0.57, 5.65), while the disease-specific survival was similar between groups.

LIMITATIONS: There are limitations inherent in this retrospective study, i.e., the long accrual period and the unknown proportion of patients who didn’t undergo surgery.

CONCLUSIONS: Although elderly patients experience a higher rate of postoperative general complications without an increase in postoperative mortality, rectal surgery yields similar surgical and oncological outcomes compared to younger patients. This study suggests that age alone shouldn't exclude someone from surgery. See **Video Abstract**.

CÁNCER RECTAL EN PERSONAS MAYORES: ¿OPERAR O NO OPERAR? ESTUDIO RETROSPECTIVO A NIVEL NACIONAL DEL GRUPO COLABORATIVO DE LA RED DE CÁNCER COLORRECTAL DE LA SOCIEDAD ITALIANA DE ONCOLOGÍA QUIRÚRGICA

ANTECEDENTES: Los pacientes mayores de 70 años representan el 44 % de todos los casos de cáncer rectal. Aunque la cirugía es el tratamiento de referencia, a los pacientes de edad avanzada también se les pueden ofrecer otros tratamientos, como la terapia neoadyuvante total con vigilancia y espera.

OBJETIVO: El objetivo de este estudio fue investigar si la mortalidad postoperatoria a los 90 días es mayor en los pacientes de edad avanzada en comparación con los pacientes más jóvenes.

DISEÑO: Este estudio retrospectivo a nivel nacional incluyó todas las resecciones consecutivas de cáncer rectal entre 2005 y 2016 utilizando datos del estudio RALAR. Los pacientes se dividieron en dos grupos según su edad: no ancianos <70 años y ancianos.

ENTORNO: Los datos se obtuvieron de 19 centros de referencia italianos para cirugía colorrectal.

PACIENTES: Un total de 3573 pacientes se sometieron a cirugía rectal: no ancianos (2071, 57,9 %) y ancianos (1502, 42 %).

PRINCIPALES MEDIDAS DE RESULTADO: El criterio de valoración principal fue la mortalidad postoperatoria a los 90 días. Los criterios de valoración secundarios incluyeron la estancia en la unidad de cuidados intensivos, la hospitalización, las complicaciones quirúrgicas y generales postoperatorias, la supervivencia global, la supervivencia específica de la enfermedad y la tasa de recurrencia.

RESULTADOS: La mortalidad postoperatoria a los 90 días fue comparable entre los grupos (0,41 % en los no ancianos frente al 1,05 % en los ancianos, p = 0,087). Los pacientes de edad avanzada fueron monitorizados con mayor frecuencia en la unidad de cuidados intensivos y desarrollaron más complicaciones generales posoperatorias, mientras que no se encontraron diferencias entre los grupos en cuanto a complicaciones quirúrgicas posoperatorias. La hospitalización fue más prolongada en los pacientes de edad avanzada (mediana [IQR]: 12,3 [9,7] frente a 11,1 [14,6] días). La supervivencia global a cinco años fue mayor en los no ancianos (77,3 %) en comparación con los ancianos (45,8 %, OR ajustado 1,70, IC del 95 %: 0,57, 5,65), mientras que la supervivencia específica de la enfermedad fue similar entre los grupos.

LIMITACIONES: Este estudio retrospectivo presenta limitaciones inherentes, como el largo periodo de acumulación y la proporción desconocida de pacientes que no se sometieron a cirugía.

CONCLUSIONES: Aunque los pacientes de edad avanzada experimentan una mayor tasa de complicaciones generales postoperatorias sin un aumento de la mortalidad postoperatoria, la cirugía rectal produce resultados quirúrgicos y oncológicos similares a los de los pacientes más jóvenes. Este estudio sugiere que la edad por sí sola no debería ser motivo para excluir a alguien de la cirugía. (*AI-generated translation*)

KEY WORDS: Elderly; Postoperative complication; Rectal cancer; Surgery; Survival; Treatment.

INTRODUCTION

Colorectal cancer (CRC) ranks as the second most frequent cause of cancer-related deaths with 935,000 deaths worldwide in 2020. A significant rise in CRC mortality is estimated in the next 20 years, reaching almost 1,600,000 deaths/year.[1] This dramatic projection is largely related to an aging population, leading to cancer being defined as a disease of old age.

The median age of diagnosis of rectal cancer (RC) is 70 and statistics report that its incidence significantly increases in the elderly, reaching its peak at 85.[2] RC is a complex disease requiring a targeted multidisciplinary approach to select patient-tailored surgical treatment and perioperative therapy to increase postoperative and survival outcomes.[3,4]

Management of RC patients is further complicated in elderly and super-elderly patients who are often affected by multiple and severe diseases, requiring more intensive postoperative observation and support in postoperative care unit (PACU), intensive care unit (ICU), rehabilitation programs and post-acute care facilities.

Several authors reported that even when elderly patients are treated for a potentially fatal cancer, they will often die from other causes.[5] Hence, it seems that the treatment of elderly and super-elderly patients with cancer can lead to only a small increase in life expectancy.

Furthermore, data available on these categories of patients are limited because they are rarely included in clinical trials, which often exclude elderly individuals.[6] Therefore, they are either overtreated based on guidelines validated on younger patients or undertreated based on arbitrary choices.

In this last decade, the treatment of elderly patients has been gaining more attention due to a rising aging population.

In 2018, Hathout et al.[7] conducted a literature review and established a treatment algorithm to aid the oncologist in management planning and decision-making in elderly patients with RC. The authors set the elderly cutoff at 70 years, even though the definition of elderly can vary from 70 to 75 years, depending on the study. Several international societies investigated the best treatment approach for seniors with RC producing recommendations to provide solutions to these main problems: "Is the patient going to die with cancer or of cancer? Is the treatment producing more benefits than harm?"[8,9].

Our multicenter retrospective study, which included 5,398 patients with RC who underwent surgery, assessed the overall anastomotic leak rate (10.2%), identified the independent risk factors and developed a clinical prediction model to calculate the probability of leakage.[10] This subset of patients was employed here to identify if 90-day postoperative mortality is increased in the elderly compared to younger patients undergoing RC surgery.

METHODS

The setting of the present study is summarized briefly as the details have been reported in the previous paper.[10]

Study Design and Patients

A national, multicenter, retrospective study under the patronage of the Colorectal Cancer Network of the Italian Society of Surgical Oncology was conducted. Patient data were collected from 19 Italian referral centers for colorectal surgery in line with STROBE guidelines.[11] IRB approval was obtained by the AOU San Luigi Gonzaga human research institutional review board (protocol number 15525). Each participating hospital acquired the local committee's approval.

All consecutive individuals with RC who underwent resection in an elective setting between January 2000 and December 2016 were collected retrospectively from each center dataset.

Given the wide accrual period and the large number of patients, we excluded those enrolled between 2000 and 2005 to better generalize our results to current medical practice, considering the significant advancements in medicine over the past 25 years.

Inclusion and exclusion criteria were the same of the previous RALAR study,[10] except for the exclusion of patients who underwent emergency surgery.

We employed the definition of elderly as ≥70 years according to most of the recent literature.[7,12] Patients were divided into 2 groups based on their age: non-elderly (NE) <70 years and elderly (E) ≥ 70.

Due to the retrospective design, the sample size was determined by available data, and a priori estimation was not feasible.

Study Variables, Preoperative Work-up, Treatments, and Pathology

Factors related to baseline, disease, surgical treatment, postoperative and survival were collected and analyzed. All individuals underwent the same staging evaluations according to the ESMO guidelines.[13] Based on tumor clinical stage, patients received preoperative treatment or upfront surgery. Three types of intervention were included: rectal anterior resection, intersphincteric resection and total proctocolectomy with ileo-anal anastomosis. Surgery was conducted with different approaches, i.e. open or minimally invasive (laparoscopic/robotic) according to the individual preference and skills of the operating surgeon.

The 8th edition of the International Union Against Cancer/American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system was adopted in the analyses for the Pathologic Classification.[14]

Endpoints of the Study

The primary endpoint was 90-day postoperative mortality, that is a better measure of postoperative outcome compared to 30-day mortality, allowing the inclusion of a greater number of mortality outliers.[15]

Secondary endpoints included the ICU stay, hospitalization, surgical postoperative complications (Clavien Dindo>2), general postoperative complications, overall survival (OS), disease-specific survival (DSS) and recurrence rate.

Statistical Analysis

The age was categorized into two groups: <70 and ≥70 years. Other clinical variables were similarly processed to ensure they were suitable for analysis. Separate tables were created to compare demographic and clinical characteristics across the age groups. The absolute and relative frequencies are reported for the categorical variables and the median with interquartile ranges for the quantitative ones. The Wilcoxon test was used to compare groups for the quantitative variables, and the χ^2 test, or Fisher's Exact test when appropriate, for the categorical ones.

The primary outcome was 90-day postoperative mortality, with time-to-event data analyzed from the date of surgery to the date of death. Logistic regression models were fitted to evaluate the associations between age and various binary perioperative outcomes. Restricted cubic splines were used to model age to allow for non-linear relationships. The models were adjusted for potential confounders in multivariable models, including clinically relevant variables identified from the literature and expert judgment: age category (<70 vs ≥70), ASA classification, obesity (BMI ≥30), TNM stage, operative time, neoadjuvant treatment, and year of surgery. These variables were retained regardless of univariable significance to account for potential confounding. Adjusted odds ratios (aORs) and 95% confidence intervals were reported. A sensitivity analysis using an Inverse Probability of Treatment Weighting (IPTW)[16] for balancing the age effect on the primary outcome has been performed as a sensitivity analysis and reported in the supplementary material. The Covariate Balance Propensity Score (CBPS)[17] has been estimated. The adjusted variables in the matching process were chosen as the multivariable models according to literature evidence and clinical judgment.[18–20] The Covariate Balance plot and the 90 days mortality effect weighted for the Propensity Score have been reported. Inverse probability of treatment weighting (IPTW) was applied to create a pseudo-population in which covariates were balanced across age groups.

The key assumption underlying the IPTW method is the common support (overlap) assumption, meaning that for each covariate pattern, there is a positive probability of being in either age group. We evaluated this assumption by visually inspecting the propensity score distribution and covariate balance before and after weighting. As demonstrated by standardized differences approaching zero across covariates, adequate balance was achieved.

Competing risk analysis for the long-term secondary outcomes,[21] with Fine and Gray models, was also performed by reporting the cumulative incidence function to account for the competing risk of cancer-related death, death for other causes, and disease relapse. Our primary objective was prognostic rather than etiologic to quantify the cumulative probability of relapse or death in the presence of competing risks. Therefore, we used Fine and Gray models, which estimate the sub distribution hazard ratios and directly inform on the cumulative incidence function (CIF) for clinical decision-making. The CIF was used to estimate the probability of experiencing a specific event, such as cancer-related death, death from other causes, or disease relapse over time, while appropriately accounting for the presence of competing events. For example, the CIF for cancer-related death estimates the risk of dying from cancer before the occurrence of competing events, such as death from other causes.

Specifically, patients who were alive and had not experienced recurrence at last follow-up were right-censored, assuming that this censoring is non-informative, i.e., it arises solely from administrative or follow-up time limitations and is unrelated to the underlying event process. CIF curves were plotted for each event of interest (death and relapse) stratified by age categories.

A complete case analysis has been performed after verifying that the patient characteristics do not affect the missing mechanism via a logistic regression model.

All statistical analyses were conducted in R, and results were considered statistically significant at a *p* value < 0.05. The analyses were performed using R 4.3.2 and the rms and cmprsk packages.[22–24]

RESULTS

Patient Characteristics and Perioperative Treatments

A total of 3,573 patients who underwent surgery for RC were included in the present study. Individuals were divided into 2 groups based on their age at diagnosis: group NE (2,071, 57.9%) and group E (1,502, 42%). The median age of group NE was 60.0 [53.4;65.1] and group E was 75.8 [72.3;79.9].

The distribution of gender was unbalanced within the groups with a significant prevalence of males, especially in group E (p=0.04). The median BMI was similar between the groups (p=0.43), while both the Charlson Comorbidity Index (CCI) and the ASA scores were dramatically higher in E group (9.7% and 42.8% respectively) than in group NE and E (p<0.001). Neoadjuvant treatment (NAT) was administered mainly in group NE, unlike group E (p<0.001) (Table 1).

Operative Details

Laparoscopic surgery was performed on more than half of the patients in each group, with NE being the highest (58.1%). Open surgery was used more often on E patients, while the robotic technique was similarly used in both groups. E individuals underwent low-tie ligation (LL) of an inferior mesenteric artery (IMA) more frequently than their counterpart (17.2% vs 12.6%, $p < 0.001$), while a diverting stoma was significantly less frequent fashioned in NE patients ($p = 0.008$). Operative time was longer in NE compared to the other group (231 minutes vs 210 in E, $p = 0.002$). Drainage was placed in almost all patients with no differences found between groups (Table 1).

Pathological Characteristics

Group NE was characterized by a lower cancer location and a higher number of distant metastases compared to E, while pathological tumor grading was less advanced in this group. No differences were found between groups regarding node metastases and TNM stage (Table 1).

Postoperative Outcomes

The age risk profile, calculated via restricted cubic splines for the significant age effects on postoperative endpoints indicated a worsening in prognosis starting from 70 years corresponding to the change in the slope of the prediction curve for Length of Stay and general complication (Supplemental Fig. 1 at http://links.lww.com/DCR/C566).

E patients were monitored in the ICU more frequently after surgery (8.62%) than the other group (NE = 5.06%, $p < 0.001$). Furthermore, they developed more postoperative general complications (14.8% vs 12.3% in E and NE respectively, $p = 0.033$) (Table 2). No significant differences were found in postoperative surgical complications, especially the onset of the anastomotic leak was similar between groups.

Hospitalization was longer in E (12.3 days vs 11.1 days, $p = 0.004$), while 90-day mortality was slightly higher in E without a significant difference compared to NE (1.05% vs 0.41%, $p = 0.087$). Furthermore, the pooled multivariable analysis confirmed that age was not an independent risk factor for 90-day mortality, unlike the ASA score and perioperative treatments. The operative period didn't significantly affect the 90-day mortality risk (Table 3).

The propensity score sensitivity analysis demonstrates an adequate covariate balance (Supplemental Fig. 2 at http://links.lww.com/DCR/C566); the sensitivity analysis reporting the propensity-adjusted odds ratio per 10-year increase in age yielded a not significant OR of 1.69 (0.99 – 2.89, $p = 0.07$).

This suggests a non-significant increase in mortality risk for elderly patients, consistent with the findings from the main multivariable model.

Survival Outcomes

Survival analyses included 2,407 patients with a median follow-up time of 4.38 years. The mortality was significantly higher in E (544 (54.2%) compared to NE 319 (22.7%, $p < 0.001$). Interestingly, more than 70% of E died from other causes, with a significant difference compared ($p < 0.001$) to NE.

The 5-year OS was significantly higher in NE (77.3%) compared to E (45.8%, $p < 0.001$, Supplemental Fig. 1 at http://links.lww.com/DCR/C566), confirmed by Fine and Grey regression multivariable analysis (Table 3).

Competing risk analysis demonstrated that other cause mortality was strictly affected by age, especially over 84, along with other covariates (TNM stage and ASA score, Supplemental Fig. 1 at http://links.lww.com/DCR/C566, Supplemental Table 1 at http://links.lww.com/DCR/C566).

The cumulative incidence of DSS competing risks was similar across age groups ($p = 0.160$).

The multivariable model evidenced an improvement of DSS in patients submitted to surgery after 2009 (Supplemental Table 1 Panel C at http://links.lww.com/DCR/C566).

Recurrence of cancer was diagnosed in 707 patients (25.1%) without significant differences between groups ($p = 0.963$). The liver was the most common site (264 patients; Table 2 in

Supplement http://links.lww.com/DCR/C566). The median time of recurrence was significantly shorter for E (4.58) compared to NE (5.27 respectively, $p < 0.001$). However, competing risk analysis showed that recurrence was not affected by age but only by TNM stage>III (Fig. 1, Supplemental Table 1 at http://links.lww.com/DCR/C566).

Complete case analyses have been performed because patient characteristics do not affect the missing mechanism (Supplemental Table 4 at http://links.lww.com/DCR/C566).

DISCUSSION

To the best of our knowledge, this study represents one of the largest in literature focusing on RC surgery in elderly patients, investigating short-term and survival outcomes. The main finding was that DSS in seniors is almost the same as in younger patients. Furthermore, the 90-day mortality is similar between the groups without significant differences. Postoperative mortality rate assessment is crucial in deciding if surgery is the best treatment option for elderly patients. RC is one of the most common tumors worldwide, accounting for 44% in the elderly.[25] Currently, no universal guidelines are available, although a few multidisciplinary recommendations have been developed recently.[8,9] The data provided by this study can help the multidisciplinary team refer elderly patients with rectal cancer to the best treatment options.

The use of minimally invasive surgery (MIS) is largely represented in this study (>60%) despite recruiting starting in 2005, when MIS was in its early stages for RC: the first RCT (MRC CLASSIC) of the laparoscopic approach in RC was published in 2005.[26] MIS for RC has become an accepted and well-researched practice over the last two decades, becoming a mainstay for the enhanced recovery after surgery (ERAS) protocol.[27] Compared to open surgery, MIS is strongly recommended for CRC surgery in elderly patients due to its proven advantages in reduced postoperative complications, time to oral diet, and hospitalization.[2,6,8]

Alternative treatment modalities for seniors have been investigated (short-course RT and long waiting, less extensive surgery,[28] watch and wait with organ preservation[29]) to challenge the traditional presumption that postoperative outcomes are worse in the elderly as compared with younger patients. This belief stems from biased analyses of data published in the past decade, such as the absence of a younger counterpart, exclusion of open and emergency surgeries, and series from low-volume surgeons and hospitals. Furthermore, most studies focused only on 30-day mortality without analyzing postoperative morbidity.[30] To date, most authors have identified 90-day mortality as a preferred indicator of postoperative outcome over the 30-day death rate because it allows the inclusion of more mortality outliers.[4] To address these issues, 90-day mortality and postoperative complication rates were investigated along with factors related to postoperative outcomes. In this study, overall 90-day mortality was very low (0.69%), without a significant difference between the groups (0.41% vs 1.05%, $p = 0.087$). These mortality rates were lower than those reported in literature, which range from 1.7% to 6.2% in NE and 6.8% to 14.1% in seniors (≥ 80 years), confirming the high-quality performance of the centers involved. It's important to mention that although there is a statistically non-significant increase in 90-day mortality, the odds ratio is quite high at 1.9, with a large confidence interval that is just barely below 1. This is probably due to the low 90-day mortality rates; further studies with a larger sample size are needed to validate our findings.

Another well-established assumption limiting access to surgery for seniors is that they experience more postoperative complications, especially higher leakage rates, than younger patients. Several studies have demonstrated that age alone is not an independent risk factor for postoperative surgical complications, while emergency presentation and locally advanced cancers are strictly related with higher morbidity and mortality.[10] Nevertheless, seniors are less often diagnosed through screening and more frequently with complicated- and locally-advanced cancers.[31] In 2016 Pirrera conducted a large retrospective study comparing patients with CRC aged <80 to older patients, concluding that advanced age is not a contraindication to elective CRC surgery, despite being associated with worse postoperative outcomes in emergency settings.[32] In our cohort, postoperative surgical complications with Clavien Dindo more than 2 were similar between groups, with lower rates (26.8% in NE and 29.4% in E, $p = 0.31$) than those reported in literature (32.7% to 53.7% for patients ≥ 80, and 19.7% to 55.9% for those <80).[33]

This study suggests that advanced age directly correlates with increased general postoperative complications, leading to prolonged ICU stays and hospitalization. This is likely to be due to worse performance status (higher ASA score and CCI) and increased frailty. Frailty is widely recognized as a predictor of postoperative complications, mortality, longer hospitalization, increased readmissions, loss of independence, and higher healthcare costs.[34] Ogata et al. have shown that an appropriate preoperative frailty assessment can be useful for selecting patients for surgery and for identifying those who may benefit from prehabilitation prior to surgery.[35] The same authors previously conducted a retrospective study[36] comparing three age groups of patients with CRC submitted to curative surgery: younger than 60, between 60 and 79, and 80 and older. The study showed that while the long-term disease-free survival of patients over 80 years was similar to that of younger age groups, more than half of the older patients died of reasons unrelated to cancer. Our findings align with literature data showing a comparable DSS across groups while the five-year OS rate was significantly worse for E patients as most older patients died from causes other than cancer.

It’s important to mention that our favorable short- and long- term outcomes may be largely attributable to the high quality of centers involved, otherwise we can’t consider this fact as a bias because of most of the literature concurs in stating that patients with RC should be treated in referral centers to improve outcomes especially in complex cases.[37]

Although radical surgery represents the current benchmark treatment for RC, the National Cancer Intelligence Network reported that in the UK, seniors with CRC undergo less surgery compared to younger patients.[38] This is mainly due to the decreased use of multimodal treatments. Spinelli et al. identified two main reasons for this difference in management between seniors and their younger counterparts.[39] First, most clinicians are unable to distinguish between age and aging; indeed, age alone should no longer be considered a limitation, as many tools now better identify frail patients.[40] Second, seniors are often discriminated against due to the widespread preconception about life expectancy: in Europe life expectancy at birth was on average 80.6 years in 2022 (83.3 for women, 77.9 for men).[41]

This study has some limitations. First, this is a retrospective study characterized by missing data, resulting in a lack of details including the absence of perioperative geriatric assessment and postoperative quality of life evaluations. Second, the accrual period was very long, during which time numerous improvements were made in perioperative therapies, surgical techniques, postoperative management, and post-acute care. Third is the unknown proportion of patients who did not undergo surgery and were referred for alternative treatments or palliative care.

CONCLUSIONS

Therefore, although elderly patients have a higher risk of postoperative medical complications due to their baseline comorbidities, without a corresponding increase in post operative mortality, we would suggest that they can undergo surgical treatment with outcomes comparable to those of younger patients. The data provided by this study can help the multidisciplinary team refer elderly patients with rectal cancer to the best treatment options. Further studies are needed to evaluate more patient-centered items, such as frailty, socioeconomic and cognitive status, and post-treatment quality of life.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249.
2. Montroni I, Ugolini G, Saur NM, et al. Personalized management of elderly patients with rectal cancer: Expert recommendations of the European Society of Surgical Oncology, European Society of Coloproctology, International Society of Geriatric Oncology, and American College of Surgeons Commission on Cancer. *Eur J Surg Oncol*. 2018;44:1685–1702.
3. Deschner BW, VanderWalde NA, Grothey A, Shibata D. Evolution and current status of the multidisciplinary management of locally advanced rectal cancer. *JCO Oncol Pract*. 2021;17:383–402.
4. Sofia S, Degiuli M, Anania G, et al. Textbook outcome in colorectal surgery for cancer: an Italian version. *J Clin Med.* 2024;13:4687.
5. Miura Y, Nishio K, Kitamura Y, Goto T, Yano M, Matsui S. Surgical risk assessment for super-elderly patients. *Geriatr Gerontol Int*. 2022;22:271–277.
6. Reddavid R, Sofia S, Puca L, et al. Robotic rectal resection for rectal cancer in elderly patients: a systematic review and meta-analysis. *J Clin Med*. 2023;12:5331.
7. Hathout L, Maloney-Patel N, Malhotra U, et al. Management of locally advanced rectal cancer in the elderly: a critical review and algorithm. *J Gastrointest Oncol*. 2018;9:363–376.
8. Podda M, Sylla P, Baiocchi G, et al. Multidisciplinary management of elderly patients with rectal cancer: recommendations from the SICG (Italian Society of Geriatric Surgery), SIFIPAC (Italian Society of Surgical Pathophysiology), SICE (Italian Society of Endoscopic

Surgery and new technologies), and the WSES (World Society of Emergency Surgery) International Consensus Project. *World J Emerg Surg*. 2021;16:35.

9. Claassen YHM, Vermeer NCA, Iversen LH, et al. Treatment and survival of rectal cancer patients over the age of 80 years: A eurecca international comparison. Br J Cancer. 2018;119:517-522.

10. Degiuli M, Elmore U, De Luca R, et al; collaborators from the Italian Society of Surgical Oncology Colorectal Cancer Network Collaborative Group. Risk factors for anastomotic leakage after anterior resection for rectal cancer (RALAR study): A nationwide retrospective study of the Italian Society of Surgical Oncology Colorectal Cancer Network Collaborative Group. *Colorectal Dis*. 2022;24:264–276.

11. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.

12. Topal U, Yüksel · S, Songür · M Z, Teke · Z, Kepkep · N D, Bektaş · H. Safety and feasibility of robotic surgery in geriatric patients with rectal cancer. 2024;28:152.

13. Glynne-Jones R, Wyrwicz L, Tiret E, et al; ESMO Guidelines Committee. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl 4):iv22–iv40.

14. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours - 8th edition. Union Int Cancer Control. Published online 2017:272.

15. Byrne BE, Mamidanna R, Vincent CA, Faiz O. Population-based cohort study comparing 30- and 90-day institutional mortality rates after colorectal surgery. *Br J Surg*. 2013;100:1810–1817.

16. Bettega F, Mendelson M, Leyrat C, Bailly S. Use and reporting of inverse-probability-of-treatment weighting for multicategory treatments in medical research: a systematic review. *J Clin Epidemiol*. 2024;170:111338.

17. Imai K, Ratkovic M. Covariate balancing propensity score. *J R Stat Soc Series B Stat Methodol*. 2014;76:243–263.

18. Talmor D, Kelly B. How to better identify patients at high risk of postoperative complications? *Curr Opin Crit Care*. 2017;23:417–423.

19. Mahajan A, Esper S, Oo TH, et al. Development and validation of a machine learning model to identify patients before surgery at high risk for postoperative adverse events. *JAMA Netw Open*. 2023;6:e2322285.

20. Gaba F, Mohammadi SM, Krivonosov MI, Blyuss O; GO SOAR Collaborators. Predicting risk of post-operative morbidity and mortality following gynaecological oncology surgery (PROMEGO): a global gynaecological oncology surgical outcomes collaborative led study. *Cancers (Basel)*. 2024;16:2021.

21. Austin PC, Steyerberg EW, Putter H. Fine-Gray subdistribution hazard models to simultaneously estimate the absolute risk of different event types: cumulative total failure probability may exceed 1. *Stat Med*. 2021;40:4200–4212.

22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.

23. Harrell E, Frank M. Package “rms” Title Regression Modeling Strategies.; 2024.

24. R: The R Project for Statistical Computing. https://www.r-project.org. Accessed August 7, 2024.

25. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. *CA Cancer J Clin*. 2023;73:233–254.

26. Guillou PJ, Quirke P, Thorpe H, et al; MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet*. 2005;365:1718–1726.
27. Gustafsson UO, Scott MJ, Hubner M, et al. Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS®) society recommendations: 2018. *World J Surg*. 2019;43:659–695.
28. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. *Lancet Oncol*. 2017;18:336–346.
29. Habr-Gama A, Gama-Rodrigues J, São Julião GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. *Int J Radiat Oncol Biol Phys*. 2014;88:822–828.
30. Ahmed S, Howel D, Debrah S; NORCCAG (Northern Region Colorectal Cancer Audit Group). The influence of age on the outcome of treatment of elderly patients with colorectal cancer. *J Geriatr Oncol*. 2014;5:133–140.
31. Ming-Gao G, Jian-Zhong D, Yu W, You-Ben F, Xin-Yu H. Colorectal cancer treatment in octogenarians: elective or emergency surgery? *World J Surg Oncol*. 2014;12:386.
32. Pirrera B, Vaccari S, Cuicchi D, et al. Impact of octogenarians on surgical outcome in colorectal cancer. *Int J Surg*. 2016;35:28–33.
33. Park H, Parys S, Tan J, Entriken F, Hodder R. Post-operative outcomes in the elderly following colorectal cancer surgery. *ANZ J Surg*. 2021;91:387–391.
34. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. *Age Ageing*. 2018;47:193–200.

35. Ogata T, Sadakari Y, Nakane H, et al. The five-item modified frailty index predicts long-term outcomes in elderly patients undergoing colorectal cancer surgery. *World J Surg Oncol*. 2023;21:268.

36. Ogata T, Yoshida N, Sadakari Y, et al. Colorectal cancer surgery in elderly patients 80 years and older: a comparison with younger age groups. *J Gastrointest Oncol*. 2022;13:137–148.

37. Choi JDW, Shepherd T, Cao A, El-Khoury T, Pathma-Nathan N, Toh JWT. Is centralization for rectal cancer surgery necessary? *Colorectal Dis.* 2024;26:1753-1757.

38. National Cancer Intelligence Network — Health Economics Research Centre (HERC). https://www.herc.ox.ac.uk/downloads/health_datasets/browse-data-sets/national-cancer-intelligence-network. Accessed March 8, 2025.

39. Spinelli A, Montroni I. Personalized treatments for elderly patients affected by rectal cancer. *Colorectal Dis*. 2017;19:879–880.

40. Huisman MG, Audisio RA, Ugolini G, et al. Screening for predictors of adverse outcome in onco-geriatric surgical patients: A multicenter prospective cohort study. *Eur J Surg Oncol*. 2015;41:844–851.

41. Mortality and life expectancy statistics - Statistics Explained. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Mortality_and_life_expectancy_statistics#Life_expectancy_at_birth Accessed September 14, 2024.

LEGENDS

1. Long-term survival outcomes. Cumulative incidence of (A) overall mortality (HR 2.51 [95% CI: 1.69-4.01, $p < 0.001$]), (B) other causes mortality (HR 2.33 [95% CI: 1.44-3.77, $p = 0.001$]), (C) disease-specific mortality (HR 2.73 [95% CI: 0.68-11.00, $p = 0.160$]), and (D) relapse (HR 1.11 [95% CI 0.86-1.44, $p = 0.420$]).

Table 1

Patient characteristics and surgical outcomes					
	Overall	**<70 years**	**≥70 years**	**P-value**	**Analyzed patients**
	N=3573	N=2071	N=1502		
Age	67.0 [58.4;74.6]	60.0 [53.4;65.1]	75.8 [72.3;79.9]	<0.001	3573
Sex				0.049	3573
M	2201 (61.6%)	1247 (60.2%)	954 (63.5%)		
BMI	25.3 [22.9;27.8]	25.3 [22.9;28.0]	25.3 [22.8;27.7]	0.430	2230
CCI				<0.001	2817
<2	1563 (55.5%)	980 (61.3%)	583 (47.8%)		
2-3	669 (23.7%)	375 (23.5%)	294 (24.1%)		
3-4	291 (10.3%)	157 (9.82%)	134 (11.0%)		
4-5	134 (4.76%)	44 (2.75%)	90 (7.38%)		
>5	160 (5.68%)	42 (2.63%)	118 (9.68%)		
ASA score >II	814 (29.0%)	315 (19.3%)	499 (42.4%)	<0.001	2808
Perioperative treatment	1686 (65.5%)	1096 (71.5%)	590 (56.7%)	<0.001	2573
Tumour distance from the AV (cm)	8.00 [6.00;12.0]	8.00 [5.00;11.0]	9.00 [6.00;12.0]	0.032	3494
Cancer location				0.091	3193
High	949 (29.7%)	532 (28.7%)	417 (31.1%)		
Medium	1459 (45.7%)	839 (45.3%)	620 (46.2%)		
Low	785 (24.6%)	480 (25.9%)	305 (22.7%)		
(y)pT				<0.001	3428
0	327 (9.54%)	217 (10.9%)	110 (7.64%)		
1	437 (12.7%)	278 (14.0%)	159 (11.0%)		
2	879 (25.6%)	521 (26.2%)	358 (24.9%)		
3	1592 (46.4%)	868 (43.6%)	724 (50.3%)		
4	193 (5.63%)	105 (5.28%)	88 (6.12%)		
(y)pN				0.900	3507
0	2272 (64.8%)	1323 (64.9%)	949 (64.6%)		
1	803 (22.9%)	461 (22.6%)	342 (23.3%)		

2	432 (12.3%)	253 (12.4%)	179 (12.2%)		
pM				0.007	3521
1	312 (8.86%)	204 (9.98%)	108 (7.32%)		
(y)pTNM				0.680	3573
<III	2228 (62.4%)	1285 (62.0%)	943 (62.8%)		
≥III	1345 (37.6%)	786 (38.0%)	559 (37.2%)		
Type of Approach				<0.001	3505
Laparoscopic	2072 (59.1%)	1249 (61.4%)	823 (56.0%)		
Open	1216 (34.7%)	651 (32.0%)	565 (38.4%)		
Robotic	217 (6.19%)	135 (6.63%)	82 (5.58%)		
IMA ligation				<0.001	3335
Low tie	437 (13.1%)	211 (10.9%)	226 (16.1%)		
Stoma				0.044	3524
Colostomy	327 (9.28%)	198 (9.70%)	129 (8.70%)		
Ileostomy	1728 (49.0%)	1028 (50.4%)	700 (47.2%)		
No	1469 (41.7%)	815 (39.9%)	654 (44.1%)		
Combined multiorgan resection	542 (16.1%)	314 (16.2%)	228 (15.9%)	0.864	3370
Operative Time (min)*	234 [180;298]	240 [180;300]	222 [180;291]	0.006	3125
Pelvic drain	3317 (98.2%)	1917 (98.3%)	1400 (98.1%)	0.848	3378

Data are median (IQR) or n (%); BMI: Body Mass Index; CCI: Charlson Score Index; ASA: American Society of Anesthesiologists; AV: Anal verge; IQR: Interquartile range; IMA: Inferior Mesenteric Artery;

*Time from first incision to closure of the surgical incision.

(y)pT, pathological T stage according to the 8th edition of the TNM classification after neoadjuvant treatment (Y) when administered; (y)pN, pathological N stage according to the 8th edition of the TNM classification after neoadjuvant treatment (Y) when administered; pM, pathological M stage according to the 8th edition of the TNM classification; (y)pTNM, pathological TNM stage according to the 8th edition of the TNM classification after neoadjuvant treatment (Y) when administered

Table 2

Ninety-day mortality and post-operative secondary outcomes							
	Overall	**<70 years**	**≥70 years**	**Effect** (Univariable)**	**P-value (Univariable)**	**Effect** (Adjusted*)**	**P-value (Adjusted*)**
	N=3573	N=2071	N=1502				
ICU	190 (6.57%)	84 (5.06%)	106 (8.62%)	1.77 [1.32;2.38]	<0.001	1.28 [1.02;1.62]	0.04
General complications	472 (13.3%)	252 (12.3%)	220 (14.8%)	1.24 [1.02;1.51]	0.033	1.32 [1.10;1.58	0.028
Surgical complications CD ≥ III	397 (28.0%)	211 (26.8%)	186 (29.4%)		0.348	1.24 [0.86; 1.21]	0.8
Anastomotic leak	377 (10.6%)	210 (10.1%)	167 (11.1%)	1.11 [0.89;1.38]	0.665	0.87 [0.68; 1.11]	0.45
Length of stay (days)	11.6 (12.8)	11.1 (14.6)	12.3 (9.66)	1.01 [1.00;1.02]	0.004	1.03 [1.01-1.05]	0.002
90-day mortality	18 (0.69%)	6 (0.41%)	12 (1.05%)	2.54 [0.97;7.44]	0.087	1.70 [0.57,5.65]	0.34

ICU: Intensive Care Unit; CD: Clavien Dindo Classification

Data are median (IQR), or n (%).

*Adjusted for Age, Status, and Obesity

** The effect is an OR (Odds Ratio) for the categorical outcomes, and AME (Average Marginal Effect) for numeric outcomes

Table 3

Primary outcome (90-day mortality). The descriptive statistics for alive and deceased patients have been reported together with the Univariable and Multivariable estimates with 95% CI.

	Descriptive			Univariable			Multivariable		
Characteristic	Alive, N = 3,555[1]	90-day mortality, N = 21[1]	**Valid Cases***	**Crude OR[2]**	**95% CI[2]**	**p-value**	**Adjusted OR[2]**	**95% CI[2]**	**p-value**
Age			3,573						
<70	2,065 (58%)	6 (33%)		—	—		—	—	
>=70	1,490 (42%)	12 (67%)		2.77	1.07, 7.98	0.042	1.70	0.57, 5.65	0.34
Staging pTNM			3,573						
<II	2,215 (62%)	13 (72%)		—	—		—	—	
>III	1,340 (38%)	5 (28%)		0.64	0.20, 1.69	0.4	0.39	0.09, 1.24	0.12
ASA			2,808						
I-II	1,990 (71%)	4 (24%)		—	—		—	—	
III-IV	801 (29%)	13 (76%)		8.07	2.85, 28.7	<0.001	6.72	2.05, 30.2	**<0.001**
Obesity	289 (13%)	3 (19%)	2,230	1.54	0.35, 4.80	0.5	1.55	0.35, 5.09	0.52
Year of Surgery			3,573						
2005-2009	1,294 (36%)	6 (33%)		0.87	0.30, 2.26	0.8	1.06	0.29, 3.19	
>=2010	2,261 (64%)	12 (67%)							0.92

Neoadjuvant Therapy									
Yes	1,682 (66%)	4 (24%)	2,573	0.16	0.04, 0.45	0.001	0.30	0.08, 0.91	**0.033**

[1] n (%)

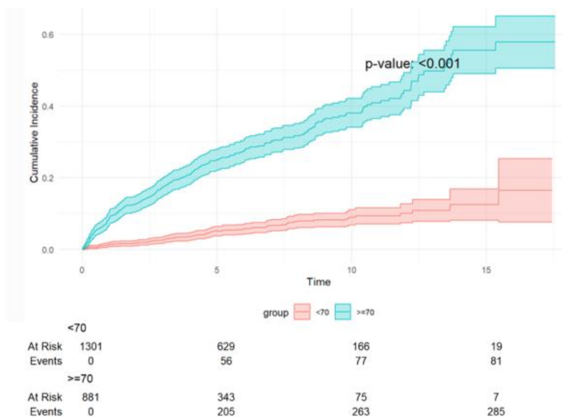
[2] OR = Odds Ratio, CI = Confidence Interval

BMI: Body Mass Index; ASA: American Society of Anesthesiologists; (y) pTNM, pathological TNM stage according to the 8th edition of the TNM classification after neoadjuvant treatment (Y) when administered

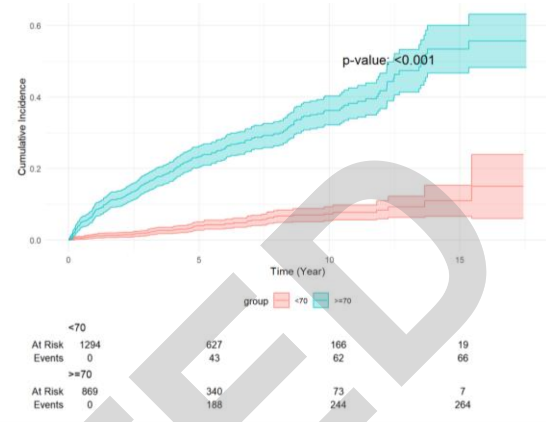
* Valid cases are those that have complete and non-missing data

Figure 1. Long-term survival outcomes

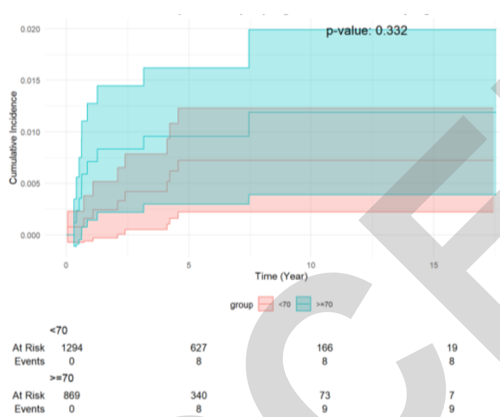
Panel A (Cumulative Incidence of Overall Mortality)



Panel B (Cumulative Incidence of Other Causes Mortality)



Panel C (Cumulative Incidence of Disease specific Mortality)



Panel D (Cumulative Incidence of Relapse)