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Minimally invasive surgery for T4 colon cancer is associated with better outcomes compared to open surgery in the National Cancer Database

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ABSTRACT

Minimally invasive surgery (MIS) is favored for T1-T3 colon cancer resection due to improved short and long-term outcomes. Recommendations regarding T4 cancers remain controversial due to a paucity of clinical trials or large datasets assessing outcomes.

We aim to compare outcomes for pT4 colon cancer patients treated with MIS or open surgery (OS) in the National Cancer Database (NCDB). We analyzed adults having MIS or OS for stage II or III pT4 colon cancers between 2010 and 2014 using propensity-score matching, Cox and logistic regression modeling.

Of 21 998 T4 patients, 7532 (34.2%) underwent MIS, 14 466 (65.8%) OS and 22.3% were MIS converted to OS. After propensity score matching, 5624 patients in each cohort were included. MIS was associated with improved postoperative mortality (3.4 vs. 7.2%, $p > .001$), surgical margins, optimal lymph node harvest, adjuvant chemotherapy use and 5-year survival (46% vs. 41%, $P < .001$).

MIS was associated with improved short and long term outcomes for T4 colon cancers compared to OS on multivariate analysis. Based on these findings, well selected pT4 colon cancers can be considered appropriate for MIS however, prospective clinical trials are needed to better define the role of MIS in T4b colon cancer.

Introduction

Since the first report of port-site metastasis after laparoscopic colectomy for colon cancer in 1993, multiple studies on the oncological safety of the laparoscopic approach for the treatment of this disease have been performed [1,2]. Several randomized controlled trials have established that laparoscopic surgery for T1-T3 colon cancer is safe and may yield equivalent or potentially better results than open resection [2,3,4]. Evidence has increasingly favored the laparoscopic approach for improved short-term outcomes, namely decreased perioperative blood loss, earlier recovery of bowel function, earlier return to oral intake, shorter hospital stay, and lower morbidity [5]. The long-term oncologic outcomes (5-year disease-free and overall survival) are equivalent in laparoscopic and open resection in the majority of studies [1,3].

In contrast to the quantity and level of evidence supporting the use of minimally invasive surgery for T1-T3 colon cancer, studies investigating the role and outcomes of MIS for T4 cancers are very limited [6]. T4 cancers are associated with significantly worse outcomes overall and, because they often require en bloc resection of the invaded structures in order to attain negative margins, pose a technical challenge to surgeons that may limit the feasibility and impact results of MIS [7,8,9,10]. Cancers that perforate the visceral peritoneum (T4a) are associated with a higher risk of peritoneal recurrence with some experts suggesting an increase in risk with MIS [11].

In most of the available randomized clinical trials comparing MIS and OS for colorectal cancer, T4 tumors are part of the exclusion criteria [12,13,14,15]. As a result, only a few relatively small

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observational cohort studies are available on this topic. They suggest no difference in progression-free and overall survival between patients with T4 colon cancer treated with MIS or OS, but had significant limitations including being single institution cohorts with insufficient power to detect differences in survival [7,15,16,17,18,19,20,21,22,23].

Due to lack of data, recommendations regarding the use of MIS for the resection of T4 colon cancer remain controversial. The objective of this study was to analyze a large cohort of patients with T4 colon cancer sourced from a national cancer-specific database to compare survival outcomes and predictive factors between patients undergoing MIS (laparoscopic and robotic) versus OS for pathological stage T4 (pT4) colon cancers.

Methods

This study was reviewed and approved by the Institutional Review Board.

Data source

The National Cancer Database (NCDB) is an oncology database sponsored by the American College of Surgeons and the American Cancer Society. It collects information from more than 1500 Commission on Cancer (CoC)-accredited facilities in the United States and contains more than 34 million patient records. The NCDB captures approximately 70% of newly diagnosed cancer cases nationwide. Each record collects standardized patient-level data elements including demographic and socio-economic information, tumor characteristics, treatment facility characteristics, first courses of treatment, and survival status [24,25].

Patient selection and variables of interest

Retrospective data from the NCDB was used to analyze demographic variables, clinical factors, treatment characteristics, and survival outcomes in patients undergoing either MIS or OS for T4 colon cancer between 2010 and 2014. Patients with records documenting a diagnosis of adenocarcinoma of the colon, AJCC stage II or III, pathologic stage T4 (pT4), age $\geq$18 years, and who underwent surgical resection were included. Patients who had metastatic disease (AJCC stage IV or documentation of M1 status), rectosigmoid or rectal cancer, or missing information on critical variables of interest (histologic diagnosis, stage, location of tumor, surgical approach, vital status, follow-up time, or chemotherapy use) were excluded from the analysis. Detailed explanations of the variables collected in the NCDB are publicly available (https://www.facs.org/quality-programs/cancer/ncdb).

Readmissions are defined by the NCDB as planned or unplanned admissions to the same hospital as surgery, for the same illness, within 30 days of discharge following hospitalization for surgical resection of the primary tumor.24 Surgical procedures of the colon (C18.0-C18.9) were identified with the 'Surgery of the Primary Site Codes' #30, 32, 40, 41, 50, 51, 60, 61, 70, and 80. Procedures classified as "laparoscopic" or "robotic" in the NCDB were considered minimally invasive (MIS). The NCDB does not collect data on cause of death; therefore, all-cause mortality was used in survival calculations. Survival time is reported in the NCDB as the time between date of initial diagnosis and date of death or date of last follow-up.

Statistical analysis

Propensity score matching was used to attempt to compensate for the probable selection bias and create two comparable cohorts in terms of demographic, clinical, and treatment factors. A 1-to-1 ratio for matching by propensity scores without replacement was performed, stratified by tumor size (<50 mm versus $\geq$50 mm), where a 'nearest neighbor' algorithm was used with a caliper of .001. Propensity scores were calculated from a multivariate logistic regression model with all demographic factors and the clinical and treatment factors known preoperatively (Charlson-Deyo score, surgery extent, and tumor size) included as covariates. Demographic, clinical, and treatment factors were compared between the two surgical groups using Pearson's $\chi 2$ test. A multivariate logistic regression model was used to determine predictive factors associated with the type of surgical procedure, 30-day mortality, and 30-day readmission rates between MIS and OS groups. The Kaplan-Meier method was used to estimate overall survival and comparisons between groups were made with the log-rank test. A Cox proportional hazard model was utilized to evaluate the impact of demographic, clinical, and treatment factors on overall survival. All aforementioned analyses were performed using both unmatched and matched datasets with the exception of analysis for surgical procedure where only unmatched data set was used.

Heterogeneity in the comparisons between MIS and open procedures was also examined for selective clinical and treatment factors using the matched data. An interaction term between clinical or treatment factors and surgical approach was tested for statistical significance using the Likelihood ratio test in a Cox proportional hazard model, from which adjusted hazard ratios for each subgroup would be calculated along with 95% confidence intervals (CI). As a sensitivity analysis, investigators repeated selective analyses using only patients who survived beyond 30 days after surgery. Propensity score matching was performed separately using the same previously described method. All hypothesis tests were two-sided and statistical significance was assessed at the level of $\alpha = 0.05$. An intention-to-treat (ITT) analysis was performed with regards to surgical approach (MIS or OS), whereby patients undergoing MIS converted to open (MISCO) were analyzed in the MIS group. As-treated analysis was also performed, where MISCO patients were included in the OS group. All statistical analyses were conducted using R 3.3.2 (R Core Team, Vienna, Austria).

Results

Patient characteristics

A total of 33 215 patients with pT4 colon cancer were identified in the NCDB between 2010 and 2014. After applying eligibility criteria, 21 998 records were fit for analysis. Of these, 7532 (34.2%) underwent MIS and 14 466 (65.8%) underwent OS. A total of 1681 patients in the MIS group underwent conversion to OS (MISCO) for a conversion rate of 22.3%. Demographic, clinical, and treatment characteristics are shown in Tables 1 and 2.

Definitions

Community CP: The facility accessions more than 100 but fewer than 500 newly diagnosed cancer cases each year and provides a full range of diagnostic and treatment services, but referral for a portion of diagnosis or treatment may occur.

Comprehensive Community CP: The facility accessions 500 or more newly diagnosed cancer cases each year. The facility provides a full range of diagnostic and treatment services either on-site or by referral.

Academic/Research Program: The facility participates in postgraduate medical education in at least four program areas, including internal medicine and general surgery. The facility accessions more than 500 newly diagnosed cancer cases each year,

Table 1
Demographic characteristics of study population by surgical approach.

Total, No.	All Unmatched Cohort			Propensity-score Matched Cohort		
	Minimally Invasive No. (%)	Open No. (%)	P Value	Minimally Invasive No. (%)	Open No. (%)	P Value
	7532	14 466		5612	5612	
Age, y						
<65	2806 (37.3)	5251 (36.3)	0.17	1805 (32.2)	1766 (31.5)	0.44
≥65	4726 (62.7)	9215 (63.7)		3807 (67.8)	3846 (68.5)	
Sex						
Male	3523 (46.8)	6621 (45.8)	0.16	2576 (45.9)	2563 (45.7)	0.82
Female	4009 (53.2)	7845 (54.2)		3036 (54.1)	3049 (54.3)	
Race						
White	6435 (86)	12 050 (83.8)	<0.001	4991 (88.9)	4930 (87.8)	0.32
Black	753 (10.1)	1778 (12.4)		486 (8.7)	542 (9.7)	
Asian	215 (2.9)	424 (2.9)		110 (2)	113 (2)	
Other	82 (1.1)	126 (0.9)		25 (0.4)	27 (0.5)	
Insurance						
Medicare	4336 (58.2)	8523 (59.9)	<0.001	3584 (63.9)	3629 (64.7)	0.71
Not insured	276 (3.7)	793 (5.6)		175 (3.1)	156 (2.8)	
Private insurance	2444 (32.8)	3899 (27.4)		1631 (29.1)	1605 (28.6)	
Medicaid	332 (4.5)	899 (6.3)		198 (3.5)	193 (3.4)	
Other government	60 (0.8)	112 (0.8)		24 (0.4)	29 (0.5)	
Income[b]						
< $30 000	789 (10.8)	1967 (14)	<0.001	600 (10.7)	599 (10.7)	0.21
$30 000 - $35 999	1173 (16)	2590 (18.4)		891 (15.9)	838 (14.9)	
$36 000 - $45 999	1962 (26.8)	4120 (29.3)		1502 (26.8)	1593 (28.4)	
≥ $46 000	3386 (46.3)	5362 (38.2)		2619 (46.7)	2582 (46)	
Education						
≥29%	1059 (14.5)	2501 (17.8)	<0.001	783 (14)	817 (14.6)	0.84
20–28.9%	1541 (21.1)	3432 (24.4)		1169 (20.8)	1162 (20.7)	
14–19.9%	1728 (23.6)	3361 (23.9)		1288 (23)	1276 (22.7)	
<14%	2981 (40.8)	4743 (33.8)		2372 (42.3)	2357 (42)	
Facility[a]						
Community CP	761 (10.3)	2095 (14.8)	<0.001	554 (9.9)	596 (10.6)	0.63
Comprehensive Community CP	3593 (48.7)	6622 (46.9)		2857 (50.9)	2835 (50.5)	
Academic/Research Program	2110 (28.6)	3709 (26.3)		1533 (27.3)	1513 (27)	
Integrated Network CP	910 (12.3)	1683 (11.9)		668 (11.9)	668 (11.9)	

a CP = cancer program.

and it offers the full range of diagnostic and treatment services either on-site or by referral.

Integrated Network CP: The organization owns, operates, leases, or is part of a joint venture with multiple facilities providing integrated cancer care and offers comprehensive services. At least one facility in the category is a hospital and must be a CoC-accredited cancer program.

There were no significant differences in regards to comorbidities ($P = .38$) or clinical stage of disease ($P = .17$) between the two groups. However, the proportion of patients with pathologic stage III was higher in the MIS group than in the OS group (60.6% (4563 patients) vs 58.6% (8470 patients); $P = .004$).

Incidence of positive surgical margins was lower for MIS compared to OS (18.6% (1386 patients) vs 22.3% (3183); $P < .001$). The proportion of patients postoperatively staged as pT4b was lower in the MIS group (28.8% (2086 patients) vs 39.5% (5429 patients); $P < .001$). Resections of contiguous organs were less frequently performed in the MIS group (13.2% vs 19.4%; $P < .001$), but the proportion of patients receiving resection of ≥12 lymph nodes was larger in the MIS group (90.8% vs 86.9%; $P < .001$). The proportion of patients with pathologic stage II that received adjuvant chemotherapy was 1097 (37.0%) in the MIS group compared to 2073 (34.6%) in the OS group ($P = .028$). For pathologic stage III, 3075 (67.4%) of patients in the MIS group and 4809 (56.8%) of patients in the OS group ($P < .001$) received adjuvant chemotherapy.

Outcomes

After 1:1 ratio propensity score matching, 5612 patients from each group were included in the matched dataset. The demographic, clinical, and treatment factors used for matching were well balanced between the two cohorts (Tables 1 and 2). From the multivariate logistic regression to calculate the propensity scores, factors associated with the use of MIS were the following: Black race (OR, 0.87; 95% CI, 0.78–0.96; $P = .006$), no insurance (OR, 0.70; 95% CI, 0.59–0.84; $P < .001$), private insurance (OR, 1.21; 95% CI, 1.10–1.32; $P < .001$), Medicaid (OR, 0.79; 95% CI, 0.67–0.92; $P = .003$), income ≥$46,000 (OR, 1.31; 95% CI, 1.15–1.49; $P < .001$), comprehensive community cancer program (OR, 1.48; 95% CI, 1.34–1.63; $P < .001$), academic/research program (OR, 1.62; 95% CI, 1.46–1.79; $P < .001$), integrated network cancer program (OR, 1.49; 95% CI, 1.32–1.68; $P < .001$), colectomy with contiguous organ resection (OR, 0.66; 95% CI, 0.60–0.72; $P < .001$), proctocolectomy with contiguous organ resection (OR, 0.55; 95% CI, 0.42–0.72; $P < .001$), and tumor size ≥ 50 mm (OR, 0.79; 95% CI, 0.74–0.84; $P < .001$).

Mean (±SD) length of hospital stay was 7.04 (±6.19) days for patients undergoing MIS and 8.66 (±7.51) days for OS ($P < .001$). Postoperative mortality at 30 days was 3.4% for MIS and 7.2% for OS ($P < .001$). The rate of readmission within 30 days of surgical discharge date was not significantly different between MIS and OS (10.3% vs 9.4%; $P = .93$).

The forest plot in Fig. 1 summarizes the relative impact of relevant variables on overall survival based on multivariate analysis using matched data. The MIS approach was independently associated with a significantly lower risk of death (HR, 0.80; 95% CI, 0.75–0.85; $P < .001$). Other significant factors that adversely impacted survival were age ≥65 years, lower education level, higher comorbidity score, pT4b, positive surgical margin, advanced

Table 2
Clinical and treatment characteristics of study population by surgical approach.

Total, No.	All Unmatched Cohort			Propensity-score Matched Cohort		
	Minimally Invasive No. (%)[a]	Open No. (%)	*P* Value	Minimally Invasive No. (%)	Open No. (%)	*P* Value
	7532	14 466		5 612	5 612	
Clinical T stage						
cTX	4021 (57.2)	7307 (54.7)	<0.001	3007 (57.4)	2888 (55.4)	<0.001
cT1 - cT3	1063 (15.1)	1525 (11.4)		818 (15.6)	625 (12)	
cT4	1943 (27.7)	4538 (33.9)		1415 (27)	1704 (32.7)	
Clinical stage group						
II	1020 (49.5)	2399 (51.4)	0.17	746 (49.4)	856 (49.1)	0.87
III	1040 (50.5)	2271 (48.6)		764 (50.6)	889 (50.9)	
Pathologic stage group						
II	2969 (39.4)	5996 (41.4)	0.004	2228 (39.7)	2248 (40.1)	0.71
III	4563 (60.6)	8470 (58.6)		3384 (60.3)	3364 (59.9)	
Pathologic T stage						
pT4a	5151 (71.2)	8304 (60.5)	<0.001	4008 (71.4)	3656 (65.1)	<0.001
pT4b	2086 (28.8)	5429 (39.5)		1604 (28.6)	1956 (34.9)	
Charlson-Deyo score[b]						
0	5172 (68.7)	9974 (68.9)	0.38	3 860 (68.8)	3 832 (68.3)	0.80
1	1735 (23)	3235 (22.4)		1 308 (23.3)	1 338 (23.8)	
≥ 2	625 (8.3)	1257 (8.7)		444 (7.9)	442 (7.9)	
Chemotherapy						
None	3176 (42.2)	7 050 (48.7)	<0.001	2410 (42.9)	2735 (48.7)	<0.001
Before surgery	54 (0.7)	225 (1.6)		31 (0.6)	63 (1.1)	
After surgery	4172 (55.4)	6 882 (47.6)		3087 (55)	2702 (48.1)	
Other	130 (1.7)	309 (2.1)		84 (1.5)	112 (2)	
Radiotherapy						
None	7101 (94.3)	13 468 (93.1)	<0.001	5310 (94.6)	5248 (93.5)	0.02
Before surgery	9 (0.1)	66 (0.5)		6 (0.1)	14 (0.2)	
After surgery	265 (3.5)	665 (4.6)		196 (3.5)	250 (4.5)	
Other	157 (2.1)	267 (1.8)		100 (1.8)	100 (1.8)	
Lymph nodes sampled						
<12	690 (9.2)	1 893 (13.1)	<0.001	444 (7.9)	652 (11.6)	<0.001
≥12	6 817 (90.8)	12 524 (86.9)		5 168 (92.1)	4 960 (88.4)	
Pathologic N stage						
pN0	2 988 (39.9)	6 097 (42.3)	0.003	2 274 (40.5)	2 284 (40.7)	0.59
pN1	2 455 (32.8)	4 539 (31.5)		1 776 (31.6)	1 812 (32.3)	
pN2	2 039 (27.3)	3 765 (26.1)		1 562 (27.8)	1 516 (27)	
Surgery Extent						
Colectomy	6 463 (86.5)	11 502 (80.3)	<0.001	4 912 (87.5)	4 976 (88.7)	0.32
Colectomy w/ cont. organ	909 (12.2)	2 509 (17.5)		650 (11.6)	590 (10.5)	
Proctocolectomy	22 (0.3)	42 (0.3)		6 (0.1)	5 (0.1)	
Proctocolectomy w/ cont. organ	76 (1)	274 (1.9)		44 (0.8)	41 (0.7)	
Surgical Resection Margins[c]						
Negative	6 058 (81.4)	11 081 (77.7)	<0.001	4 595 (81.9)	4 429 (78.9)	<0.001
Positive	1 386 (18.6)	3 183 (22.3)		1 017 (18.1)	1 183 (21.1)	
Tumor Size						
< 50mm	3 245 (44.2)	5 227 (37.2)	<0.001	2 324 (41.4)	2 324 (41.4)	>0.99
≥ 50mm	4 097 (55.8)	8 811 (62.8)		3 288 (58.6)	3 288 (58.6)	

[a] Percentages were calculated after excluding the missing cases from the denominator. w/=with; cont.= contiguous
[b] A 0 score means patients had none of the conditions in the mapping table (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes).
[c] Surgical resection margins status is recorded as it appears in the pathology report. Pathology reports for colon resection typically report proximal, distal, radial and mesenteric margins.

pathological N stages, and larger tumor size (≥50 mm). Conversely, Asian race, not insured or private insurance, treatment at an academic/research program or integrated network cancer program, use of chemotherapy, and optimal lymph node sampling (≥12) were associated with longer survival.

MIS was associated with significantly longer survival time (Fig. 2a). Median overall survival was 56.4 months (95% CI, 54.0–58.4) for MIS and 42.2 months (95% CI, 39.4–46.0) for OS. Five-year OS was 46.0% for MIS and 40.5% for OS ($P < .001$). In a subgroup analysis, the 5-year overall survival was 45.2% for MISCO and 46.1% for non-converted MIS. The log-rank test indicated a significant survival difference among non-converted MIS, MISCO, and OS ($P < .001$; Fig. 2b).

Fig. 3 presents the results of a series of multivariate Cox regression models to examine the heterogeneity of the comparison between MIS and OS for various subgroups defined by selective clinical and treatment factors. There was no significant heterogeneity for most factors ($p > 0.05$) except for pathologic stage group and pathologic N stage. The survival benefit of MIS was significantly higher for stage II patients (HR: 0.68; 95% CI, 0.61–0.76) than stage III patients (HR, 0.86; 95% CI, 0.76–0.98; $P < .001$). As for pathologic N stage, the more advanced the cancer was, the less improvement of overall survival MIS would provide over OS ($P < .001$). The survival benefit was largest for pN0 patients (HR, 0.69; 95% CI, 0.62–0.76), less significant for pN1 patients (HR, 0.77; 95% CI, 0.66–0.89), but inconclusive for pN2 patients (HR, 0.94; 95% CI, 0.81–1.08).

HR: Hazard ratio, CI: Confidence interval.

As a sensitivity analysis, we repeated the analyses of overall survival for patients who had survived beyond 30 days after surgery. After propensity score matching, 5400 patients from each

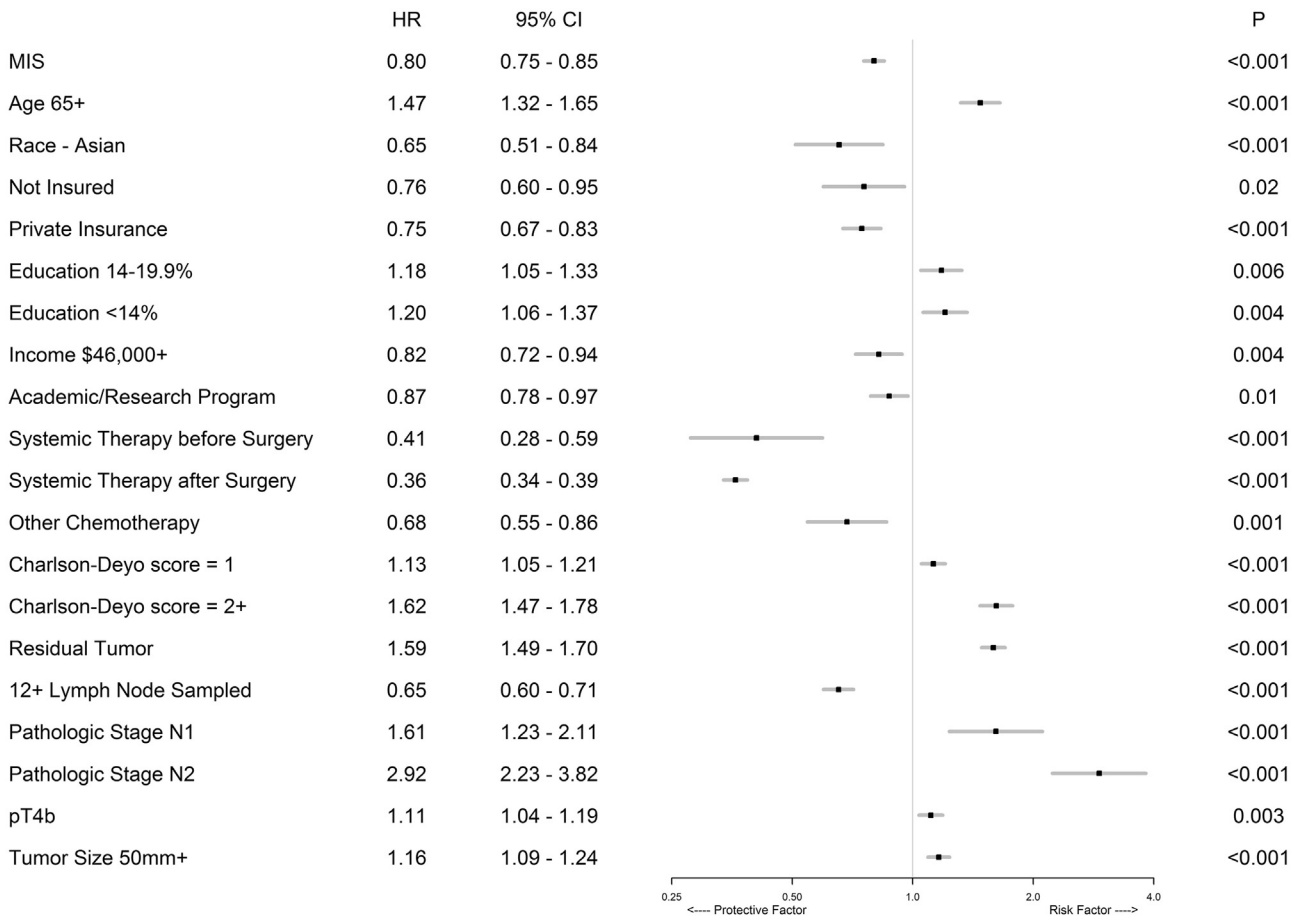

Fig. 1. Forest plot of adjusted hazard ratios and 95% CIs of factors significantly associated with overall survival in patients undergoing surgical resection of pT4 colon cancer
Legend: The baseline groups for the factors listed above are: MIS, age <65 years, race-white, Medicare insurance, education ≥29%, annual income <$30 000, Community cancer program, pathologic stage II, no chemotherapy, no radiotherapy, Charlson-Deyo score = 0, no residual tumor, lymph nodes sampled <12, pathologic N stage 0, pT4a and tumor size <50 mm. HR: Hazard ratio, CI: Confidence interval.

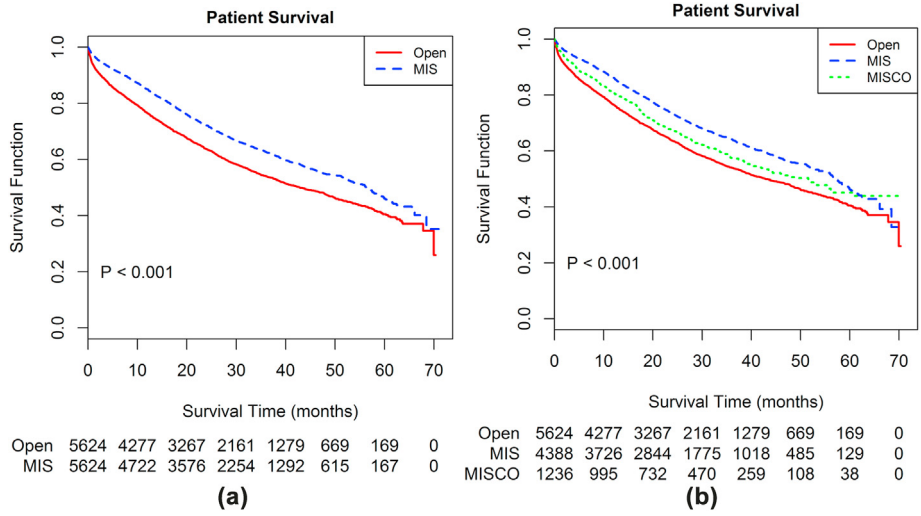

Fig. 2. Kaplan-Meier estimates of overall survival in patients with pT4 colon cancer by surgical approach.**Legend: a)** Overall survival in patients undergoing open surgery (solid line) and minimally invasive surgery (broken line). Log rank test: $P < .001$. b) Overall survival in patients undergoing open surgery (solid line), minimally invasive surgery converted to open (dotted line), and minimally invasive surgery not converted to open (broken line). Log rank test: $P < .001$.

group were matched. In these patients, 5-year overall survival rates were 43.3% for OS and 48.3% for MIS. A Cox proportional hazard model concluded a 17% reduction in risk of mortality for MIS patients (HR, 0.83; 95% CI, 0.78–0.89; $P < .001$).

As an exploratory analysis, we evaluated clinical factors, overall survival and 30-day mortality allocating the MISCO patients in the

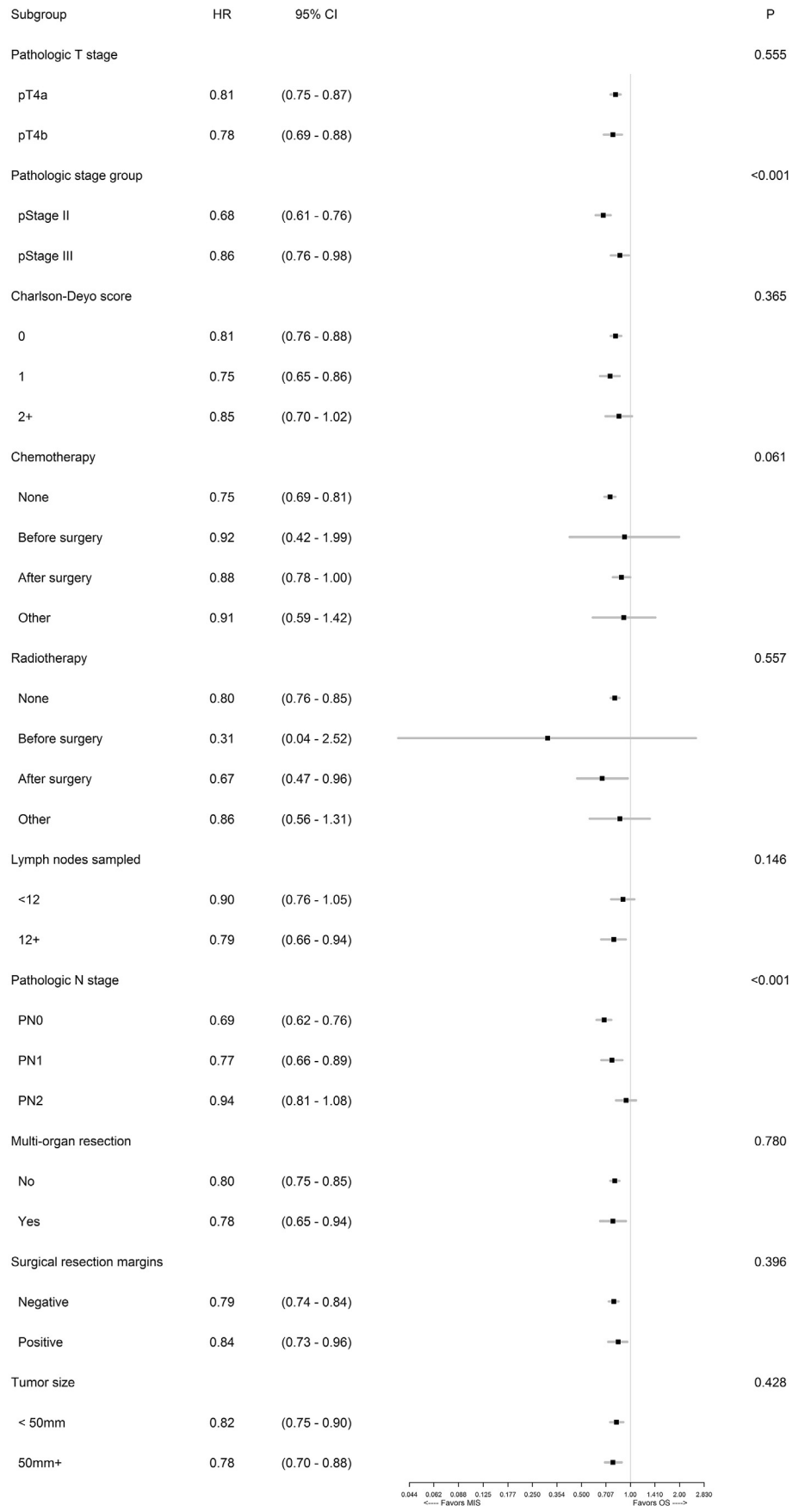

Fig. 3. Forest plot of adjusted HRs and 95% CIs for various subgroups categorized by selective clinical and treatment factors.
Legend: P values indicate the significance level of the interaction terms.

OS rather than the MIS group according to the "as treated" principle. The results were largely unchanged and confirmed improved overall survival and 30 −day mortality in the MIS group with a small change in hazard ratios further emphasizing the difference in favour of MIS. The details of this analysis are presented in Supplementary Table 1 and Supplementary Table 2.

Discussion

The results of this study show that more than one third (34.2%) of surgically treated pT4 colon cancer cases recorded in the NCDB between 2010 and 2014 were performed laparoscopically or robotically. This percentage is remarkable because T4 colon cancers have traditionally been considered a relative contraindication for MIS [11,14,26]. Inaccurate preoperative clinical staging could account for this high proportion of MIS treated pT4 tumors. Clinical diagnosis of T4 is challenging, as the sensitivity of computed tomography (CT) for detecting the accurate depth of transmural invasion is approximately 70% [27,28]. In the MIS group, the primary tumor could not be preoperatively staged (cTX) in the majority (57.2%) of patients and only 27.0% of patients were staged as cT4 preoperatively. Therefore, investigators further hypothesize that in approximately three quarters of patients, limitations in preoperative imaging and clinical under-staging may have led to the choice of MIS, but in at least one quarter of cases the use of MIS in T4 tumors was a deliberate choice of the surgeon.

Prior small observational cohort studies noted equivalent outcomes in terms of postoperative mortality, complications, and survival, between MIS and OS for T4 tumors but the present study observed that MIS was associated with lower 30-day mortality and longer overall survival compared to OS.7,16–22 This central finding differs from the current literature, which has shown no statistically significant difference in overall survival between T4 colon cancer treated with MIS or OS.7,16–20,23 Previous studies have significant limitations being of a single-institution and retrospective in nature, as well as not sufficiently powered to detect true differences in survival. In contrast, the present analysis incorporated data from more than 20 000 patients, increasing the power and ability to detect differences in survival. Furthermore, they represent the results of treatments provided across a wide range of clinical settings in terms of type of health facility, environment and providers (thus reflective of the "real world") rather than a selected group of uniform institutions, which is typically the case for results of clinical trials.

The survival benefit in the MIS group persisted when adjusting for potential confounders (including age, disease stage, lymph node status, comorbidity score, resection margin status, tumor size and use of chemotherapy) and by using several statistical methodologies, such as propensity score matching to minimize bias. Not surprisingly, several factors were associated with shorter survival times, with the most relevant being pathologic stage III, Charlson-Deyo comorbidity score of $\geq$2, and positive surgical resection margins. However, surgical approach (MIS vs. OS) remained a significant independent predictor on multivariate analysis and after propensity score matching despite a higher proportion of patients with pathologic stage III and pN2 in the MIS group (irrespective of "intention to treat" or "as treated" analysis). The reasons for a higher proportion of pathological stage III patients in MIS group are unknown but could be related to more accurate staging due to a higher average lymph node retrieval. The survival advantage of the MIS group persisted even after patients who died within 30 days were excluded, to account for the possibility that long-term survival is disproportionally influenced by perioperative mortality which was significantly lower in the MIS group (7.2 vs. 3.4%). The MIS group had a lower incidence of positive surgical margins, higher lymph node retrieval, and a higher proportion of adjuvant chemotherapy use. These factors could be contributing to the survival advantage seen in patients undergoing MIS versus OS. It is not possible to fully explain the reasons for better margins, LN retrieval and adjuvant chemotherapy use after MIS using retrospective data: possible explanations include patient selection but inherit benefits of MIS such as improved visualization and postoperative recovery of patients could be important determinants and directly related to improved oncological outcomes. In previously published cohorts of T4 colon cancer, the incidence of positive margins, lymph node retrieval, postoperative mortality, and chemotherapy use was similar between MIS and OS, likely due to insufficient power. This could in part explain why the long-term survival outcomes were not different between MIS and OS in previous studies. [16–19,21-23,29].

OS was more frequently associated with contiguous organ resection (19.2% vs. 13.2%) and positive surgical resection margins (22.3% vs. 18.6%) compared to MIS. This finding is interesting and it could be a result of technical advantages gained by MIS approach in certain clinical situations. However we hypothesize it may also reflect patient selection favoring OS in cases of more locally advanced tumors where invasion of surrounding organs is suspected preoperatively. The finding of pathologic stage T4b which occurred more frequently in patients treated with OS compared to MIS (39.5% vs. 28.8%) is a possible indirect confirmation of preoperative decision-making. The exact role and possible advantages of MIS compared to OS for patient with a clinically staged T4b tumor cannot be clearly stated from our results and should be evaluated with a prospective clinical trial.[30-32].

Intraoperative conversion rates from an MIS to OS approach are approximately 7%–21% in previous studies on T4 colon cancer. [16–19,21,23,29,33] The conversion rate in the present study was 22.3%, which is higher than had been reported previously. However, data analyzed in this study are likely more representative of the majority of surgical practices treating colon cancer in the US. Overall survival at 5-years in the MISCO (45.1%) group was slightly lower compared to non-converted MIS group (46.2%) however, still longer than OS. This suggests with appropriate preoperative patient selection, an attempt at MIS is not detrimental even if conversion to OS is ultimately needed.

Limitations

Our analysis is limited by the variables available within the NCDB. The NCDB lacks several important variables (such as body mass index, patient's performance status, type of clinical staging evaluation, diagnostic procedures, prior surgical history, emergency surgery (i.e. due to perforation or obstruction), complications, date of recurrence, site of recurrence, or cause of death. Many of these variables are likely to be associated with choice of surgical approach and may also independently influence survival. [34] In addition, surgical volume is also an important factor when discussing outcomes related to surgical procedures that we could not directly evaluate. Another important development in the current understanding of the biology of colon cancer is the role of sidedness however information on tumor side is not available in NCDB [35]. Some of these unaccounted limitations could have influenced the difference in survival favoring MIS.

Conclusions

This study, the largest thus far, comparing MIS to OS for pT4 colon cancer shows that current criteria used by practicing surgeons were effective at selecting patients and led to favorable outcomes of MIS compared to OS including longer overall survival.

The advantages of MIS among patients with T4a appear similar to those seen in T1-T3 tumors and therefore MIS appears to be the optimal approach when feasible in T4a tumors. T4b cancers constitute a challenging subgroup where a prospective randomized comparison of OS and MIS would be needed to determine the optimal approach.

Synopsis

This is a NCDB analysis of short and long term surgical outcomes of patients with pT4 colon cancer treated with minimally invasive versus open approach. We minimized the influence of confounders using multivariate analysis and propensity score matching. Results indicate that minimally invasive surgery is associated with favorable outcomes and should not be contraindicated in T4 cancers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary tables

Supplementary Table 1
– Summary of clinical factors of matched and unmatched cohorts for the "as treated" analysis (MISCO patients are included in the Open group)

	Unmatched Cohort				Matched Cohort			
	MIS (n = 5851)	Open (n = 16147)	P	SMD	MIS (n = 4582)	Open (n = 4582)	P	SMD
Clinical T stage								
cTX	3147 (57.6)	8181 (54.8)	<0.001	<0.001	2485 (57.9)	2420 (56.5)	<0.001	<0.001
cT1-cT3	872 (16)	1716 (11.5)			706 (16.4)	539 (12.6)		
cT4	1444 (26.4)	5037 (33.7)			1101 (25.7)	1324 (30.9)		
Clinical stage group								
cStage II	763 (49.3)	2656 (51.3)	0.184	0.039	581 (48.6)	697 (50.3)	0.42	0.033
cStage III	785 (50.7)	2526 (48.7)			614 (51.4)	689 (49.7)		
Pathologic T stage								
pT4a	4260 (75.7)	9195 (59.9)	<0.001	0.343	3481 (76)	3037 (66.3)	<0.001	0.215
pT4b	1365 (24.3)	6150 (40.1)			1101 (24)	1545 (33.7)		
Pathologic stage group								
pStage II	2282 (39)	6683 (41.4)	0.002	0.049	1788 (39)	1863 (40.7)	0.114	0.033
pStage III	3569 (61)	9464 (58.6)			2794 (61)	2719 (59.3)		
Charlson-Deyo score								
0	4043 (69.1)	11103 (68.8)	0.881	<0.001	3153 (68.8)	3169 (69.2)	0.905	<0.001
1	1314 (22.5)	3656 (22.6)			1060 (23.1)	1042 (22.7)		
≥2	494 (8.4)	1388 (8.6)			369 (8.1)	371 (8.1)		
Chemotherapy								
None	2471 (42.2)	7755 (48)	<0.001	<0.001	1960 (42.8)	2207 (48.2)	<0.001	<0.001
Before surgery	45 (0.8)	234 (1.4)			30 (0.7)	53 (1.2)		
After surgery	3231 (55.2)	7823 (48.4)			2521 (55)	2239 (48.9)		
Other	104 (1.8)	335 (2.1)			71 (1.5)	83 (1.8)		
Radiotherapy								
None	5565 (95.1)	15004 (92.9)	<0.001	<0.001	4371 (95.4)	4294 (93.7)	<0.001	<0.001
Before surgery	9 (0.2)	66 (0.4)			6 (0.1)	11 (0.2)		
After surgery	154 (2.6)	776 (4.8)			119 (2.6)	200 (4.4)		
Other	123 (2.1)	301 (1.9)			86 (1.9)	77 (1.7)		
Lymph nodes sampled								
<12	514 (8.8)	2069 (12.9)	<0.001	0.13	341 (7.4)	532 (11.6)	<0.001	0.142
≥12	5317 (91.2)	14024 (87.1)			4241 (92.6)	4050 (88.4)		
Pathologic N stage								
PN0	2292 (39.4)	6793 (42.3)	0.001	<0.001	1821 (39.7)	1910 (41.7)	0.07	<0.001
PN1	1942 (33.4)	5052 (31.4)			1497 (32.7)	1401 (30.6)		
PN2	1576 (27.1)	4228 (26.3)			1264 (27.6)	1271 (27.7)		
Surgery extent								
Colectomy	5177 (89.3)	12788 (79.9)	<0.001	<0.001	4132 (90.2)	4112 (89.7)	0.84	<0.001
Colectomy + Contiguous Organ	554 (9.6)	2864 (17.9)			415 (9.1)	431 (9.4)		
Proctocolectomy	20 (0.3)	44 (0.3)			8 (0.2)	7 (0.2)		
Proctocolectomy + Contiguous Organ	49 (0.8)	301 (1.9)			27 (0.6)	32 (0.7)		
Surgical resection margins								
Negative	4798 (82.9)	12341 (77.5)	<0.001	0.135	3809 (83.1)	3620 (79)	<0.001	0.105
Positive	991 (17.1)	3578 (22.5)			773 (16.9)	962 (21)		
Tumor size								
<50 mm	2669 (46.8)	5803 (37)	<0.001	0.2	2043 (44.6)	2043 (44.6)	10000	<0.001
≥50 mm	3032 (53.2)	9876 (63)			2539 (55.4)	2539 (55.4)		
Multi-organ resection								
No	5197 (89.6)	12832 (80.2)	<0.001	0.265	4140 (90.4)	4119 (89.9)	0.484	0.015
Yes	603 (10.4)	3165 (19.8)			442 (9.6)	463 (10.1)		

Supplementary Table 2
– Results of multivariable Cox proportional hazard model for overall survival for the "intention to treat" analysis (MISCO included in the MIS group) and the "as treated" analysis (MISCO included in the OS group).

		MIS + MISCO vs Open			MIS vs Open + MISCO		
		HR	95% CI	P	HR	95% CI	P
Approach	MIS	0.8	0.75–0.85	<0.001	0.74	0.69–0.79	<0.001
Age	≥65	1.47	1.32–1.65	<0.001	1.57	1.38–1.79	<0.001
Gender	Female	0.99	0.93–1.05	0.72	0.97	0.91–1.03	0.336
Race	Black	0.98	0.88–1.09	0.692	1.02	0.9–1.16	0.762
	Asian	0.65	0.51–0.84	0.001	0.65	0.5–0.85	0.001
	Other	1.19	0.77–1.86	0.433	0.87	0.57–1.35	0.54
Insurance	Not Insured	0.76	0.6–0.95	0.019	0.89	0.68–1.18	0.427
	Private Insurance	0.75	0.67–0.83	<0.001	0.74	0.65–0.83	<0.001
	Medicaid	1.13	0.95–1.36	0.167	1.2	0.98–1.46	0.081
	Other Government	1.06	0.67–1.7	0.796	0.96	0.57–1.6	0.865
Education	20–28.9%	1.05	0.94–1.18	0.375	1.06	0.93–1.2	0.406
	14–19.9%	1.18	1.05–1.33	0.006	1.16	1.01–1.33	0.031
	<14%	1.2	1.06–1.37	0.004	1.29	1.12–1.49	<0.001
Income	$30,000 - $35,999	0.98	0.86–1.1	0.711	1.01	0.88–1.16	0.907
	$36,000 - $45,999	0.89	0.78–1	0.057	0.91	0.79–1.05	0.19
	$46,000+	0.82	0.72–0.94	0.004	0.8	0.69–0.93	0.004
Facility	Comprehensive Community Cancer Program	0.98	0.88–1.08	0.628	1.01	0.91–1.14	0.81
	Academic/Research Program	0.87	0.78–0.97	0.014	0.95	0.84–1.07	0.418
	Integrated Network Cancer Program	0.89	0.78–1.01	0.064	0.95	0.82–1.1	0.473
Pathologic Stage	Stage III	1.12	0.86–1.46	0.415	1.24	0.91–1.68	0.173
Chemotherapy	Before Surgery	0.41	0.28–0.59	<0.001	0.35	0.22–0.56	<0.001
	After Surgery	0.36	0.34–0.39	<0.001	0.36	0.33–0.38	<0.001
	Other	0.68	0.55–0.86	0.001	0.69	0.53–0.89	0.004
Radiotherapy	Before Surgery	0.97	0.45–2.08	0.937	1.06	0.38–2.93	0.908
	After Surgery	1.08	0.9–1.29	0.415	0.99	0.8–1.23	0.953
	Other	1.1	0.88–1.37	0.401	1.14	0.89–1.46	0.303
Charlson-Deyo score	1	1.13	1.05–1.21	0.001	1.08	1–1.17	0.059
	≥2	1.62	1.47–1.78	<0.001	1.5	1.35–1.67	<0.001
Surgery extent	Colectomy + Contiguous Organ	1.01	0.92–1.11	0.838	0.99	0.87–1.11	0.81
	Proctocolectomy	0.34	0.05–2.45	0.287	0.51	0.16–1.58	0.244
	Proctocolectomy + Contiguous Organ	1.05	0.72–1.52	0.817	0.59	0.34–1.03	0.061
Surgical margins	Positive	1.59	1.49–1.7	<0.001	1.56	1.45–1.69	<0.001
Lymph node sampled	≥12	0.65	0.6–0.71	<0.001	0.62	0.56–0.68	<0.001
Pathologic N stage	PN1	1.61	1.23–2.11	<0.001	1.44	1.06–1.96	0.021
	PN2	2.92	2.23–3.82	<0.001	2.56	1.88–3.49	<0.001
Pathological T stage	pT4b	1.11	1.04–1.19	0.003	1.1	1.02–1.19	0.016
Tumor size	≥50 mm	1.16	1.09–1.24	<0.001	1.15	1.07–1.23	<0.001

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