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Minimally invasive surgery for stage III colon adenocarcinoma is associated with less delay to initiation of adjuvant systemic therapy and improved survival

Lawrence Lee[1,2,3] · Nathalie Wong-Chong[2,3] · Justin J. Kelly[1] · George J. Nassif[1] · Matthew R. Albert[1] · John R. T. Monson[1]

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Abstract

Background Minimally invasive surgery (MIS) may improve surgical recovery and reduce time to adjuvant systemic therapy after colon cancer resection. The objective of this study was to determine the effect of MIS on the initiation of adjuvant systemic therapy and survival in patients with stage III colon cancer.

Methods The 2010–2014 National Cancer Database was queried for patients with resected stage III colon adenocarcinoma, and divided into MIS, which included laparoscopic and robotic approaches, and open surgery. Propensity-score matching was used to balanced open and MIS groups. The main outcome measures were delayed initiation of adjuvant systemic therapy (defined as > 8 weeks after surgery) and 5-year overall survival (OS). Multiple Cox regression was performed to identify independent predictors for 5-year OS, including an interaction between delayed systemic therapy and MIS, and adjusted for clustering at the hospital level.

Results There were 86,680 patients that were included in this study. Overall, 45% (38,713) underwent MIS colectomy, of which 93% underwent laparoscopic and 7% robotic surgery. After matching, 33,183 open patients were balanced to 33,183 MIS patients. Patient, tumor, and facility characteristics were similar in the matched cohort. More patients in the MIS group received adjuvant therapy within 8 weeks of surgery (49% vs. 42%, $p < 0.001$), and fewer MIS patients did not receive any systemic therapy (30% vs. 35%, $p < 0.001$). Delayed initiation of systemic therapy > 8 weeks was associated with worse 5-year OS (HR 1.27, 95%CI 1.19–1.36). MIS was independently associated with improved survival (HR 0.92, 95%CI 0.86–0.97). This relationship remained even if 90-day mortality was excluded.

Conclusions MIS approaches are associated with less delay to the initiation of adjuvant systemic therapy and improved survival in patients with stage III colon adenocarcinoma. Surgeons should favor MIS approaches for the treatment of stage III colon adenocarcinoma whenever possible.

Keywords Colon cancer · Adjuvant systemic therapy · Minimally invasive surgery · Laparoscopy · Robotics

Surgical resection is a key element in the management of colon cancer [1]. For patients with stage III colon adenocarcinoma, adjuvant systemic therapy is also the mainstay of treatment to minimize risk of recurrence and improve overall survival [2, 3]. While there are no clear guidelines on the

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✉ Lawrence Lee
larry.lee@mcgill.ca

[1] Center for Colon and Rectal Surgery, Florida Hospital, Orlando, FL, USA

[2] Department of Surgery, McGill University Health Centre, Montreal, QC, Canada

[3] Colon and Rectal Surgery, McGill University Health Centre, 1001 Decarie Blvd, DS1-3310, Montreal, QC H4A 3J1, Canada

appropriate time to initiation of adjuvant systemic therapy, its maximal benefit is obtained if started within 4–8 weeks of surgical resection. There are many data demonstrating that a longer time to adjuvant systemic therapy are associated with worse survival [4]. However, despite advances in the surgical technique, perioperative management strategies, and quality of care initiatives, more than 20% of patients with stage III colon cancer are not considered or offered adjuvant systemic therapy [5].

There are many reasons for the failure of delivery of appropriate systemic treatment for stage III colon cancer. Recovery after surgery can be prolonged [6], and the occurrence of surgical complications may also delay the initiation of systemic therapy [7]. It is in this context that minimally invasive surgery (MIS) for colon cancer resection may potentially provide long-term benefits. Short-term outcomes after MIS colectomy are superior to the open approach. High-quality evidence demonstrate reductions in blood loss, wound complications, return to bowel function, postoperative pain and length of hospitalization with the MIS approach for colon cancer [8]. Furthermore, there may be improved quality of life and performance status with the MIS approach in the early postoperative period compared to open surgery [9]. These improvements in postoperative recovery may allow for earlier initiation of adjuvant chemotherapy.

Retrospective, single institution data report a shorter time to initiation of adjuvant chemotherapy after laparoscopic and robotic colectomies for colon cancer [10]. A meta-analysis of observational studies of stage II/III colon or rectal cancer identified laparoscopy as a significant predictor of earlier adjuvant chemotherapy initiation compared to open surgery [11]. However, the studies comparing surgical approach were mostly of single-center design with small sample sizes and heterogeneous patient populations [11]. As such, the effect of MIS on the timing of adjuvant systemic therapy and consequently, long-term survival, remains unclear. Therefore, the objective of this study was to determine the effect of MIS on the initiation of adjuvant chemotherapy and survival in patients with stage III colon cancer.

Materials and methods

Data source and study subjects

The National Cancer Database (NCDB) is a cancer registry sponsored by the American College of Surgeons, the Commission on Cancer (CoC), and the American Cancer Society. It includes approximately 70% of all new cancer diagnoses in the United States consisting of over 1 million new cases per year from 1500 hospitals [12]. For this study, the 2010–2014 colon and rectosigmoid junction cancer participant user file (PUF) was used. These PUFs do not include rectal cancer. Patients were further excluded if they had metastatic disease at diagnosis, neoadjuvant therapy, no surgery was performed, or for histology other than colonic adenocarcinoma. Variable definitions can be found at http://ncdbpuf.facs.org/node/259. Patient characteristics included age, gender, race/ethnicity, comorbidities, insurance status, median household income, population density and education distribution of the patient's zip code, and distance traveled to the reporting institution. Patient comorbidities were defined according to the Deyo classification of the Charlson Comorbidity Index [13]. The NCDB does not provide more detailed information on specific comorbidities or body mass index. Hospital characteristics included hospital type and facility location. Facility is defined as per CoC accreditation criteria, based on total number of new cancer diagnoses, diagnostic and treatment services, research participation, and resident training. Hospital location is based on US census information. Annual hospital volume was divided based on the median number of colon cancer cases per year (90 resections) and divided into low- (fewer than 90 cases) and high-volume (90 or more cases) status. Tumor-related variables included tumor size, grade, location, lymphovascular, and perineural invasion. Treatment-related variables included primary surgical procedure and approach, lymph node yield, margin status, length of primary inpatient stay, 30-day readmissions, 30- and 90-day mortality, and vital status at last contact. Surgical approach was only included in the NCDB after 2010. Patients were divided into two groups based on their treatment: MIS or open. The MIS group included patients undergoing laparoscopic or robotic colectomy. Patients that were converted to open surgery were included in the MIS group. Cases where the surgical approach was not recorded were included in the open group, as per the NCDB variable definition.

Statistical analysis

The main outcome measures were time to initiation of adjuvant systemic therapy and 5-year overall survival (OS). Time to adjuvant therapy was categorized into three levels: ≤ 56 days, > 56 days, or no adjuvant systemic therapy delivery. The 56-day cut-point was chosen based on other data demonstrating worse oncologic outcomes with an 8-week or longer delay to the initiation of adjuvant systemic therapy after resected stage II and III colon cancer [4, 14–16]. Oncologic outcomes were defined using OS as the NCDB does not record local recurrence or metastatic disease, and therefore, disease-free survival could not be reported [17]. Propensity score matching was performed to minimize selection bias given the observational study design. A multiple logistic regression model is fitted using the intervention as the dependent variable, and calculates the probability

(logit score) of receiving a MIS colectomy based on the characteristics of each patient (age, gender, Charlson-Deyo score, insurance status, ethnicity, education, income, facility type, location within the colon, hospital volume, tumor size, T-stage, number of nodal metastases, total lymph node harvest, grade, margin status, and lymphovascular and perineural invasion). Nearest neighbor, 1-to-1 matching without replacement and within 0.2 of the standard deviation of the logit of the propensity score was performed to create balanced groups of open and MIS colectomy [18, 19]. Iterative balance checking after matching verified that the standardized difference (mean difference divided by the standard deviation of the mean difference) was less than 10% [20, 21]. Patients in either group who did not have any suitable matches were removed from the analysis.

Data are represented as *n* (%) for categorical variables and mean (standard deviation, SD) for continuous variables. Univariate analyses were performed using Student's *t* test for continuous variables and χ^2 test for categorical variables. Kaplan–Meier curves were used to describe OS and log-rank tests were used to compare the cumulative survival distributions. Multilevel regression analyses were performed using Cox proportional hazard models for OS using unique hospital identifier as the higher-level variable. The interaction between time to initiation of adjuvant systemic therapy and surgical approach was also tested. A subgroup analysis excluding patients that died within 90 days of surgery was also performed to account for potential delayed operative mortality. The NCDB does not contain information on postoperative complications, but these may affect delivery of adjuvant systemic therapy [7]. In order to account for this potential effect, a proxy variable for complications was defined as patients with length of stay greater than the median (6 days in this dataset). The specific effect of each 4-week delay in adjuvant therapy was also tested, adjusting for the same confounders as the main multivariate model. Multiple regression analyses were only performed using the propensity-matched cohort to further minimize bias [22]. Statistical significance was defined as $p < 0.05$. All analyses were performed using STATA 15.1 (StataCorp, College Station, TX).

Results

A total of 86,680 patients were eligible and were included in the analysis, of which 47,967 (55.3%) underwent an open procedure and 38,713 (44.7%) underwent an MIS procedure. There were 2856 robotic procedures (7.4% of all MIS procedures) and 35,857 laparoscopic procedures. Overall conversion rate was 14.7% amongst MIS procedures: 8.6% for robotic versus 15.2% for laparoscopic colectomies ($p < 0.001$). There were significant differences in patient, facility, tumor, and operative characteristics between patients undergoing open versus MIS procedures (Tables 1, Supplemental Table 1). In the unmatched cohort, patients undergoing MIS colectomy were more likely to receive adjuvant systemic therapy as well as initiate within 56 days of surgical resection. Patients undergoing MIS procedures had a significantly higher 5-year cumulative OS compared to those undergoing open procedures (61.4% vs. 51.1%, log-rank $p < 0.001$).

After the propensity score matching, 33,183 patients with open procedures were matched to 33,183 patients undergoing MIS colectomy, of which 2384 (7.2%) were robotic and 92.8% 30,799 (92.8) were laparoscopic. In the MIS group, the incidence of conversion to open surgery was 15.2% overall, including 9.4% for robotic and 15.6% for laparoscopic procedures ($p < 0.001$). There were no differences in patient, facility, tumor, and operative characteristics between open and MIS colectomy in the matched cohort (Table 1 and Supplemental Table 1). More patients in the MIS group received adjuvant systemic therapy as well as initiated it within 56 days of surgery (Table 1). Amongst patients that received adjuvant therapy, there were fewer patients in the MIS group that experienced a prolonged delay (31% (7146/23337) versus 35% (7587/21634), $p < 0.001$). MIS procedures were also associated with higher 5-year cumulative OS (Fig. 1A, B) compared to open (58.6% vs. 54.5%, log-rank $p < 0.001$). When stratified by interval to systemic therapy, MIS was associated with a statistically significant improved survival compared to open if adjuvant therapy was delivered within 56 days (70% vs. 68%, $p = 0.014$), beyond 56 days (61% vs. 60%, $p = 0.009$), and if no adjuvant therapy was administered (37% vs. 31%, $p < 0.001$). Patients in the MIS group had lower 5-year cumulative OS if they experienced a conversion (52.7% converted vs. 59.7%, $p < 0.001$) and similar OS compared to the open group ($p = 0.896$). In the subgroup analysis excluding 90-day mortality (Fig. 2A, B), MIS was still associated with a higher proportion of patients initiating adjuvant systemic therapy within 56 days (50.8% vs. 45.5%, $p < 0.001$), as well as higher 5-year OS (61.9% vs. 58.5%, $p < 0.001$).

Differences in patient, tumor, facility, and operative characteristics between patients that initiated adjuvant systemic therapy within 56 days of surgery versus those that had delayed initiation or no adjuvant systemic therapy are shown in Table 2. Due to the large sample size, almost all variables were statistically different, but clinically important differences (defined as ≥ 5%) were seen in surgical approach, age, comorbidities, insurance status, tumor location, and length of postoperative stay. The results of the different multiple regression models are shown in Table 3. In the main model, MIS and initiation of adjuvant systemic therapy ≤ 56 days were associated with improved survival, and the interaction between MIS and time to initiation of adjuvant therapy was significant. In

Table 1 Operative and pathologic details, and short-term outcomes

	Unmatched cohort			Matched cohort		
	Open $N=47,967$	MIS $N=38,713$	p	Open $N=33,183$	MIS $N=33,183$	p
Procedure performed			< 0.001			0.943
Partial colectomy	41,649 (87%)	35,274 (91%)		30,155 (91%)	30,118 (91%)	
Total (procto)colectomy	1536 (3%)	798 (2%)		676 (2%)	683 (2%)	
Colectomy with resection of contiguous organ	4189 (9%)	2354 (6%)		2145 (6%)	2165 (6%)	
Colectomy, NOS	593 (1%)	287 (1%)		207 (1%)	217 (1%)	
Tumor location			< 0.001			0.956
Ascending colon	22,153 (46%)	18,917 (49%)		16,270 (49%)	16,200 (49%)	
Transverse colon	4472 (9%)	2879 (7%)		2647 (8%)	2647 (8%)	
Left colon	15,987 (33%)	12,765 (33%)		10,807 (33%)	10,858 (33%)	
Rectosigmoid	5355 (11%)	4152 (11%)		3459 (10%)	3478 (10%)	
Mean total number of lymph nodes (SD)	20.9 (11.5)	21.4 (11.0)	< 0.001	20.9 (11.0)	20.8 (10.5)	0.764
Mean number of positive lymph nodes (SD)	3.9 (6.3)	3.5 (5.6)	< 0.001	3.6 (5.0)	3.6 (5.6)	0.618
Mean tumor size, cm (SD)	5.3 (4.1)	4.8 (3.9)	< 0.001	5.4 (4.4)	5.4 (4.5)	0.396
Pathologic T-stage			< 0.001			0.399
0	1059 (2%)	614 (2%)		241 (1%)	247 (1%)	
1	1403 (3%)	1991 (5%)		1271 (4%)	1191 (4%)	
2	3762 (8%)	4299 (11%)		3239 (10%)	3183 (10%)	
3	29,565 (62%)	24,734 (64%)		21,870 (66%)	21,892 (66%)	
4	12,178 (25%)	7075 (18%)		6562 (20%)	6670 (20%)	
Grade			< 0.001			0.552
Well/moderate diff	33,291 (69%)	27,595 (71%)		23,602 (71%)	23,516 (71%)	
Poor diff	13,280 (28%)	10,035 (26%)		8724 (26%)	8770 (26%)	
Unknown	1396 (3%)	1083 (3%)		857 (3%)	897 (3%)	
Lymphovascular invasion			< 0.001			0.499
Yes	22,109 (46%)	17,779 (46%)		15,442 (47%)	15,493 (47%)	
No	21,404 (45%)	17,709 (46%)		15,059 (45%)	15,090 (45%)	
Missing	4454 (9%)	3225 (8%)		2682 (8%)	2600 (8%)	
Perineural invasion			< 0.001			0.064
Yes	8375 (17%)	6221 (16%)		5386 (16%)	5451 (16%)	
No	34,242 (71%)	28,707 (74%)		24,272 (73%)	24,389 (74%)	
Missing	5350 (11%)	3785 (10%)		3525 (11%)	3443 (10%)	
Margin status			< 0.001			0.458
Negative	42,744 (89%)	36,004 (93%)		30,709 (92%)	30,646 (92%)	
Positive	47,528 (10%)	2510 (6%)		2275 (7%)	2349 (7%)	
Unknown/missing	465 (1%)	199 (1%)		199 (1%)	188 (1%)	
Mean length of stay, days (SD)	7.8 (7.2)	6.0 (5.8)	< 0.001	7.6 (6.9)	6.1 (5.8)	< 0.001
30-day readmission			< 0.001			0.334
No	43,492 (91%)	35,215 (91%)		30,187 (91%)	30,134 (91%)	
Yes	4260 (8%)	3355 (9%)		2860 (9%)	2931 (9%)	
Missing	215 (1%)	143 (0.4%)		136 (0.4%)	118 (0.4%)	
30-day mortality	1868 (5%)	567 (2%)	< 0.001	1120 (4%)	532 (2%)	< 0.001
90-day mortality	3196 (8%)	1071 (4%)	< 0.001	1923 (7%)	1000 (4%)	< 0.001
Adjuvant systemic therapy			< 0.001			< 0.001
≤ 56 days	19,625 (41%)	19,532 (51%)		14,047 (42%)	16,191 (49%)	
> 56 days	10,874 (23%)	82,86 (21%)		7587 (23%)	7146 (22%)	
No adjuvant therapy	17,391 (36%)	10,864 (28%)		11,549 (35%)	9846 (30%)	
Mean follow-up, months (SD)	29.5 (18.3)	30.6 (16.6)	< 0.001	30.5 (18.1)	30.4 (16.6)	0.511

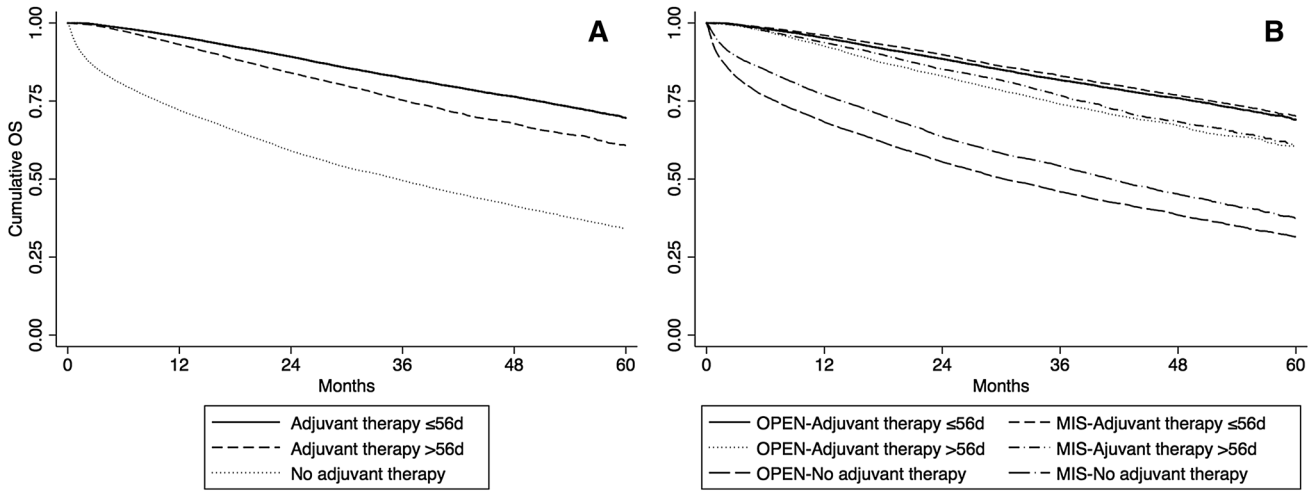

Fig. 1 5-year overall survival in the overall matched cohort based on **A** time to initiation of adjuvant therapy; **B** effect of surgical approach and time to initiation of adjuvant therapy

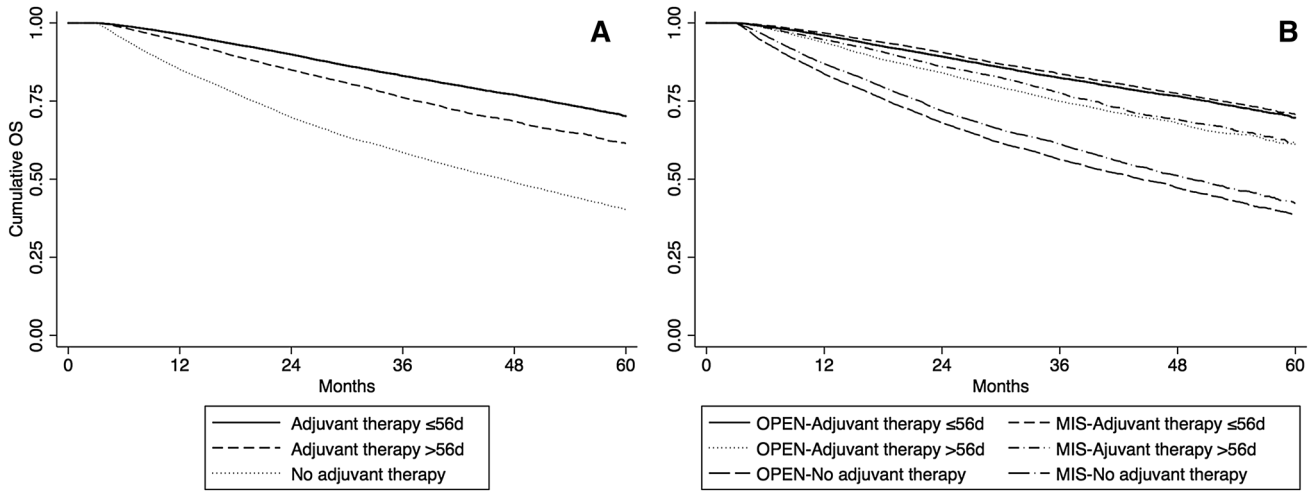

Fig. 2 Subgroup analysis of 5-year overall survival (excluding 90-day mortality) based on **A** time to initiation of adjuvant therapy; **B** effect of surgical approach and time to initiation of adjuvant therapy

all models, delayed initiation of adjuvant systemic therapy or no adjuvant therapy was independently associated with worse OS. Robotic colectomy was not independently associated with 5-year OS compared to the laparoscopic approach on sensitivity analysis using the multiple regression models without the interaction terms (HR 0.95, 95% CI 0.83, 1.07), as well as the model excluding 90-day mortality (HR 0.94, 95% CI 0.82, 1.09). Figure 3 demonstrates the adjusted effect of each 4-week delay in the initiation of adjuvant therapy.

Discussion

The administration of adjuvant systemic therapy for non-metastatic node-positive colon cancer significantly reduces disease recurrence and improves survival. Yet, a significant proportion of patients with stage III resected colon adenocarcinoma experience delays to the initiation of adjuvant systemic therapy, or do not receive it at all [5].

Table 2 Predictors of delayed initiation of chemotherapy (matched cohort only)

	No delay in adjuvant therapy (< 8 weeks) $N = 30,238$	Delayed adjuvant therapy (> 8 weeks) or No adjuvant therapy $N = 36,128$	Absolute difference[b]	p value
MIS approach	16,191 (54%)	16,992 (47%)	−7%	< 0.001
Conversion to open surgery[a]	2242 (14%)	2792 (16%)	+2%	< 0.001
Age, years (SD)	63.5 (11.2)	72.1 (12.6)	+8.6	< 0.001
Male gender	15,336 (51%)	17,183 (48%)	−3%	< 0.001
Charlson-Deyo score				< 0.001
0	21,976 (73%)	23,239 (64%)	−9%	
1	6523 (21%)	8960 (25%)	+4%	
2	1739 (6%)	3929 (11%)	+5%	
High volume hospital	15,652 (52%)	18,723 (52%)	0%	0.875
Race/ethnicity				< 0.001
White	25,133 (83%)	29,532 (82%)	−1%	
Black	3551 (12%)	4620 (13%)	+1%	
Hispanic	1026 (3%)	1355 (4%)	+1%	
Other/unknown	528 (2%)	621 (2%)	0%	
Insurance				< 0.001
No insurance	915 (3%)	972 (3%)	0%	
Private insurance	13,899 (46%)	8941 (25%)	−21%	
Medicare/Medicaid	15,086 (50%)	25,842 (71%)	+21%	
Unknown/missing	338 (1%)	373 (1%)	0%	
Procedure performed				< 0.001
Partial colectomy	27,662 (91%)	32,611 (90%)	−1%	
Total (procto)colectomy	539 (2%)	820 (2%)	0%	
Colectomy with resection of contiguous organ	1826 (6%)	2484 (7%)	+1%	
Colectomy, NOS	211 (1%)	213 (1%)	0%	
Tumor location				< 0.001
Ascending colon	13,900 (46%)	18,570 (51%)	+5%	
Transverse colon	2261 (7%)	3033 (8%)	+1%	
Left colon	10,664 (35%)	11,001 (30%)	−5%	
Rectosigmoid	3413 (11%)	3524 (10%)	−1%	
Mean total number of lymph nodes (SD)	21.4 (10.6)	20.3 (10.2)	−1.1	< 0.001
Mean number of positive lymph nodes (SD)	3.7 (4.1)	3.3 (3.9)	−0.4	< 0.001
Mean tumor size, cm (SD)	2.3 (0.7)	2.4 (0.7)	+0.1	< 0.001
Pathologic T-stage				
0	221 (1%)	267 (1%)	0%	
1	1149 (4%)	1313 (4%)	0%	
2	2984 (10%)	3438 (10%)	0%	
3	20,120 (67%)	23,642 (65%)	−2%	
4	5764 (19%)	7468 (21%)	+2%	
Grade				< 0.001
Well/moderate diff	21,760 (72%)	25,358 (70%)	−2%	
Poor diff	7738 (26%)	9756 (27%)	+1%	
Unknown	740 (2%)	1014 (3%)	+1%	
Lymphovascular invasion				< 0.001
Yes	14,148 (47%)	16,787 (46%)	−1%	
No	13,853 (46%)	16,296 (45%)	−1%	
Missing	2237 (7%)	3045 (8%)	+1%	
Perineural invasion				< 0.001
Yes	5021 (17%)	5816 (16%)	−1%	
No	22,471 (74%)	26,090 (72%)	−2%	

Table 2 (continued)

	No delay in adjuvant therapy (< 8 weeks) $N = 30,238$	Delayed adjuvant therapy (> 8 weeks) or No adjuvant therapy $N = 36,128$	Absolute difference[b]	p value
Missing	2746 (9%)	4222 (12%)	+3%	
Margin status				0.001
Negative	28,078 (93%)	33,277 (92%)	−1%	
Positive	1997 (7%)	2627 (7%)	0%	
Unknown/missing	163 (1%)	224 (1%)	0%	
Mean length of stay, days (SD)	5.5 (4.2)	8.0 (7.6)		< 0.001
30-day readmission				< 0.001
No	27,690 (92%)	32,631 (90%)	−2%	
Yes	2445 (8%)	3346 (9%)	+1%	
Missing	103 (0.3%)	151 (0.4%)	0%	

[a]Only amongst patients in the MIS group (no delay, $n = 16,191$; and delay > 8 weeks or no adjuvant therapy, $n = 16,992$)

[b]Represented as absolute difference in percentage or mean

Therefore, there exists an important need to identify potential methods to improve the delivery of adjuvant therapy. In this study, MIS colectomy for stage III colon adenocarcinoma was associated with fewer delays to adjuvant systemic therapy and increased 5-year survival compared to the open approach.

There are few guidelines on the optimal timing for the initiation of adjuvant systemic therapy after resected stage III colon cancer. It is generally assumed adjuvant therapy should be administrated as soon as possible after surgery, especially in light of data reporting worse oncologic outcomes with longer intervals. In the landmark paper by Biagi et al., each 4-week delay was associated with a 14% decrease in OS [4]. However, this risk relationship is not linear, as Sun et al. demonstrated that the risk significantly increases with any delay only beyond 44 days [15]. Other studies have reported optimal timing within 8 weeks after surgical resection [14, 16, 23, 24]. However, patients must have recovered enough after surgical resection in order to tolerate systemic therapy. It is in this context that MIS colectomy may offer a survival advantage by minimizing the physiologic impact of surgery and allowing for a shorter time to the initiation of adjuvant therapy.

A systematic review including 67,537 patients reported older age, martial status, low socioeconomic status, comorbid status, prolonged length of stay, and readmissions as significant predictors of a delay in adjuvant chemotherapy in colorectal cancer [11]. Many of these factors were also identified as significant predictors of delayed initiation in the present study. We accounted for most of these factors, amongst others, in our propensity score matching to create balanced cohorts of MIS and open procedures in order to isolate the effect of surgical approach on timing of adjuvant therapy. Even in the matched cohort, surgical approach was associated with fewer delays to adjuvant systemic therapy. There are several hypotheses for this finding. It is well demonstrated that laparoscopic colectomy has lower postoperative morbidity compared to open surgery [8], which will delay chemotherapy [24]. Laparoscopic colectomy is also associated with a decreased surgical stress response [25, 26] and improved functional recovery [27, 28] compared to open surgery, which may also result in increased ability to commence and tolerate adjuvant systemic therapy. However, there were still a significant proportion (30%) of patients in the MIS group that did not receive any adjuvant systemic therapy. A significant limitation of the NCDB is that the reason for delayed initiation or non-administration of adjuvant systemic therapy is not recorded. It can be hypothesized that these patients may be older, have more comorbidities, or experienced complications (which were all significant predictors in the present study). While the exact timing of systemic therapy after surgery may be up for debate, omission of adjuvant therapy is clearly associated with worse OS, regardless of approach. The timing of administration of adjuvant systemic therapy is affected by both patient and system factors [24]—although improvements in perioperative care and surgical techniques may lessen the impact of surgery and allow for more timely initiation of adjuvant therapy [29, 30].

In the present study, MIS was also independently associated higher 5-year OS compared to open surgery. However, it is unclear whether the survival advantage is uniquely related to the improved delivery of adjuvant systemic therapy or if there is an inherent benefit to MIS. These data do not demonstrate a clinically significant difference in 5-year OS for MIS versus open procedures if adjuvant therapy was initiated within 56 days or if it was delayed beyond 56 days. There was a 5% absolute difference amongst patients that did not receive any adjuvant therapy in favor of MIS, which was also seen in the interaction terms of the multiple regression survival model. The reasons for these findings are unclear

Table 3 Multiple regression analysis on 5-year overall survival

	Total cohort HR (95% CI)	Subgroup analysis excluding patients with 90-day mortality, HR (95%CI)
Delay in adjuvant systemic therapy		
≤ 56 days (ref.)	–	–
> 56 days	1.27 (1.19, 1.36)	1.28 (1.20, 1.38)
No adjuvant therapy	2.79 (2.63, 2.96)	2.07 (1.94, 2.19)
MIS approach	0.92 (0.86, 0.97)	0.91 (0.86, 0.97)
Interaction term		
MIS × ≤56 days delay (ref.)	–	–
MIS × > 56 days delay	1.16 (1.08, 1.27)	0.96 (0.87, 1.08)
MIS × no adjuvant therapy	0.96 (0.87, 1.16)	0.96 (0.88, 1.05)
Age, per year increase	1.02 (1.01, 1.03)	1.03 (1.02, 1.03)
Male gender	1.18 (1.07, 1.26)	1.16 (0.95, 1.13)
Charlson-Deyo score		
0 (ref.)	–	–
1	1.14 (1.10, 1.20)	1.13 (1.08, 1.18)
2+	1.52 (1.44, 1.60)	1.54 (1.45, 1.64)
Tumor location		
Ascending colon (ref.)	–	–
Transverse colon	1.01 (0.95, 1.07)	1.00 (0.93, 1.07)
Left colon	0.90 (0.86, 0.93)	0.87 (0.83, 0.91)
Rectosigmoid	0.86 (0.81, 0.97)	0.89 (0.83, 0.95)
Lymphovascular invasion		
Negative (ref.)	–	–
Positive	1.27 (1.22, 1.32)	1.28 (1.23, 1.33)
Unknown/missing	1.06 (0.99, 1.13)	1.05 (0.98, 1.12)
Perineural invasion		
Negative (ref.)	–	–
Positive	1.24 (1.19, 1.30)	1.28 (1.22, 1.34)
Unknown/missing	0.97 (0.91, 1.03)	0.95 (0.89, 1.02)
Margin status		
Negative (ref.)	–	–
Positive	1.56 (1.46, 1.66)	1.55 (1.45, 1.66)
Unknown/missing	1.48 (1.18, 1.84)	1.46 (1.17, 1.83)
Grade		
Well/moderate diff (ref.)	–	–
Poor diff	1.34 (1.30, 1.40)	1.37 (1.32, 1.43)
Unknown	1.08 (0.97, 1.20)	1.14 (1.01, 1.29)
LN harvest, per LN increase	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)
Involved LNs, per LN increase	1.03 (1.02, 1.03)	1.03 (1.02, 1.03)
Pathologic T-stage		
0/1 (ref.)	–	–
2	1.09 (0.95, 1.23)	1.09 (0.95, 1.27)
3	1.57 (1.40, 1.77)	1.66 (1.46, 1.89)
4	2.47 (2.18, 2.79)	2.77 (2.42, 3.17)
Tumor size, per cm increase	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
High volume hospital	0.96 (0.92, 0.99)	0.96 (0.91, 1.01)
Race/ethnicity		
White (ref.)	–	–
Black	1.03 (0.97, 1.10)	1.08 (1.01, 1.16)
Hispanic	0.89 (0.80, 0.99)	0.89 (0.79, 0.99)

Table 3 (continued)

	Total cohort HR (95% CI)	Subgroup analysis excluding patients with 90-day mortality, HR (95%CI)
Other/unknown	0.87 (0.75, 1.02)	0.80 (0.67, 0.95)
Insurance		
No insurance (ref.)	–	–
Private insurance	0.80 (0.72, 0.90)	0.76 (0.68, 0.86)
Medicare/Medicaid	0.94 (0.84, 1.06)	0.92 (0.82, 1.04)
Unknown/missing	0.77 (0.62, 0.97)	0.67 (0.53, 0.84)
Length of stay > 6 days	1.47 (1.42, 1.53)	1.42 (1.37, 1.48)

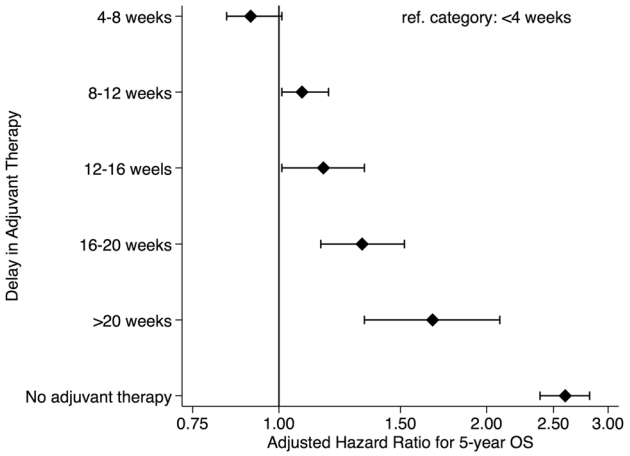

Fig. 3 Adjusted effect of each 4-week delay in the initiation of adjuvant systemic therapy on 5-year overall survival

as the NCDB does not record the reason why adjuvant systemic therapy was delayed or not administered. One of the main hypotheses again relates to lower incidence of surgical complications after MIS colectomy. Patients who experience a complication are also less likely to receive adjuvant therapy [7], which will affect long-term outcomes [5]. The specific type of surgical complication may also affect survival. Infectious complications, which have been implicated in the promotion of cancer metastases [31], are specifically associated with lower disease-free and overall survival [32, 33]. However, postoperative morbidity is not recorded in the NCDB therefore this specific hypothesis cannot be investigated using these data. Length of postoperative stay was significantly higher after open procedures, which is a surrogate measure of postoperative course and recovery. We performed a subgroup analysis by excluding patients who experienced a 90-day mortality to account for the potential difference in delayed operative mortality due to surgical approach. Even in this analysis, MIS was associated with fewer delays to systemic therapy and improved 5-year OS.

One of important questions raised by this study was the difference in OS in favor of MIS, which was not demonstrated by the large randomized trials comparing open and laparoscopic colectomy for colon adenocarcinoma [34, 35]. There may be several reasons for this discrepancy. The most obvious is that the present study is based on observational data, albeit from a highly inclusive national cancer registry. We attempted to create balanced cohorts of MIS and open procedures; however, there remains the possible of residual bias from unmeasured confounders [36]. Beyond methodological differences, several other factors should be considered. There have not been any new randomized trials comparing laparoscopic and open colectomy for colon cancer since the publication of the large trials in 2002–2004 [37]. MIS training, techniques, and equipment have evolved significantly over time, especially given that only patients operated on from 2010 to 2014 were included in the present study. There may have also been a learning curve effect early in the laparoscopic colectomy era (many of the trials had a minimum number of 20 laparoscopic colectomies performed to be eligible to participate) that could have affected both short- and long-term outcomes [38, 39]. Chemotherapy regimens have also changed over time, especially with the addition of oxaliplatin for stage III adenocarcinoma and other targeted agents for metastatic disease. These randomized trials also did not report time to adjuvant therapy.

The results of this study should be interpreted in view of other limitations. The NCDB does not include more granular data on the specific chemotherapy regimen or systemic therapy compliance. There may also be important variations in the delivery of appropriate systemic therapy in addition to the timeliness, which may affect oncologic outcomes [40]. Completion of the full-course of adjuvant therapy will also affect survival [41]. The comorbidity score in the NCDB is relatively imprecise, which will affect the decision to deliver adjuvant therapy and survival itself, although this was one of the matching covariates and was well balanced between the MIS and open groups. There are also other unmeasured variables such as operative complexity and perioperative management that may affect the ability to undergo adjuvant therapy [29, 42, 43]. The NCDB also does not include an emergency surgery variable, which could potentially explain the high incidence of margin involvement. These results may also not be widely generalizable, as the NCDB only includes

data from CoC accredited hospitals, and may have underrepresentation of certain ethnicities. However, the NCDB includes a diverse patient population that represents real-world practice, which may improve the generalizability of these data compared to randomized trials that have strict patient selection criteria.

In summary, an MIS approach in patients with stage III colon cancer is associated with fewer delays to adjuvant systemic therapy compared to an open procedure. This was associated with an important survival advantage for stage III colon cancer in favor of MIS. However, a significant proportion of patients in both groups did not receive adjuvant therapy at all. These data suggest that patients with non-metastatic colon cancer should undergo an MIS procedure whenever possible, but also further investigation into the reasons why so many patients are not administered adjuvant therapy in a timely fashion.

Compliance with ethical standards

Disclosure Dr. Albert reports consultant's fees from Applied Medical, Stryker, and Conmed, and stock options from Applied Medical. Drs. Lee, Wong-Chong Kelly, Nassif, and Monson have no conflicts of interest or financial ties to disclose.

References

1. Brenner H, Kloor M, Pox CP (2014) Colorectal cancer. Lancet 383:1490–1502
2. Boland GM, Chang GJ, Haynes AB, Chiang YJ, Chagpar R, Xing Y, Hu CY, Feig BW, You YN, Cormier JN (2013) Association between adherence to National Comprehensive Cancer Network treatment guidelines and improved survival in patients with colon cancer. Cancer 119:1593–1601
3. Booth CM, Nanji S, Wei X, Peng Y, Biagi JJ, Hanna TP, Krzyzanowska MK, Mackillop WJ (2016) Use and effectiveness of adjuvant chemotherapy for stage III colon cancer: a population-based study. J Natl Compr Canc Netw 14:47–56
4. Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM (2011) Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA 305:2335–2342
5. Becerra AZ, Probst CP, Tejani MA, Aquina CT, Gonzalez MG, Hensley BJ, Noyes K, Monson JR, Fleming FJ (2015) Opportunity lost: adjuvant chemotherapy in patients with stage III colon cancer remains underused. Surgery 158:692–699
6. Lee L, Tran T, Mayo NE, Carli F, Feldman LS (2014) What does it really mean to "recover" from an operation? Surgery 155:211–216
7. Jin LX, Sanford DE, Squires MH, Moses LE, Yan Y, Poultsides GA, Votanopoulos KI, Weber SM, Bloomston M, Pawlik TM, Hawkins WG, Linehan DC, Schmidt C, Worhunsky DJ, Acher AW, Cardona K, Cho CS, Kooby DA, Levine EA, Winslow E, Saunders N, Spolverato G, Colditz GA, Maithel SK, Fields RC (2016) Interaction of postoperative morbidity and receipt of adjuvant therapy on long-term survival after resection for gastric adenocarcinoma: results from the U.S. Gastric Cancer Collaborative. Ann Surg Oncol 23:2398–2408
8. Schwenk W, Haase O, Neudecker J, Muller JM (2005) Short term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev 3::CD003145
9. Dowson HM, Cowie AS, Ballard K, Gage H, Rockall TA (2008) Systematic review of quality of life following laparoscopic and open colorectal surgery. Colorectal Dis 10:757–768
10. Jung YB, Kang J, Park EJ, Baik SH, Lee KY (2016) Time to initiation of adjuvant chemotherapy in colon cancer: comparison of open, laparoscopic, and robotic surgery. J Laparoendosc Adv Surg Tech A 26:799–805
11. Malietzis G, Mughal A, Currie AC, Anyamene N, Kennedy RH, Athanasiou T, Jenkins JT (2015) Factors implicated for delay of adjuvant chemotherapy in colorectal cancer: a meta-analysis of observational studies. Ann Surg Oncol 22:3793–3802
12. Bilimoria KY, Stewart AK, Winchester DP, Ko CY (2008) The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol 15:683–690
13. Deyo RA, Cherkin DC, Ciol MA (1992) Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 45:613–619
14. Bos AC, van Erning FN, van Gestel YR, Creemers GJ, Punt CJ, van Oijen MG, Lemmens VE (2015) Timing of adjuvant chemotherapy and its relation to survival among patients with stage III colon cancer. Eur J Cancer 51:2553–2561
15. Sun Z, Adam MA, Kim J, Nussbaum DP, Benrashid E, Mantyh CR, Migaly J (2016) Determining the optimal timing for initiation of adjuvant chemotherapy after resection for stage II and III colon cancer. Dis Colon Rectum 59:87–93
16. Des Guetz G, Nicolas P, Perret GY, Morere JF, Uzzan B (2010) Does delaying adjuvant chemotherapy after curative surgery for colorectal cancer impair survival? A meta-analysis. Eur J Cancer 46:1049–1055
17. In H, Bilimoria KY, Stewart AK, Wroblewski KE, Posner MC, Talamonti MS, Winchester DP (2014) Cancer recurrence: an important but missing variable in national cancer registries. Ann Surg Oncol 21:1520–1529
18. Dehejia RH, S W (1999) Causal effects in nonexperimental studies: reevaluating the evaluation of training programs. J Am Stat Assoc 94:1053–1062
19. Austin PC (2009) Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biom J Biom Z 51:171–184
20. Flury BK, Reidwyl H (1986) Standard distance in univariate and multivariate analysis. Am Stat 40:249–251
21. Austin PC (2009) Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simul Comput 38:1228–1234
22. Linden A (2017) Improving causal inference with a doubly robust estimator that combines propensity score stratification and weighting. J Eval Clin Pract 23:697–702
23. Kim YW, Choi EH, Kim BR, Ko WA, Do YM, Kim IY (2017) The impact of delayed commencement of adjuvant chemotherapy (eight or more weeks) on survival in stage II and III colon cancer: a national population-based cohort study. Oncotarget 8:80061–80072
24. Becerra AZ, Aquina CT, Mohile SG, Tejani MA, Schymura MJ, Boscoe FP, Xu Z, Justiniano CF, Boodry CI, Swanger AA, Noyes K, Monson JR, Fleming FJ (2017) Variation in delayed time to adjuvant chemotherapy and disease-specific survival in stage III colon cancer patients. Ann Surg Oncol 24:1610–1617
25. Veenhof AA, Vlug MS, van der Pas MH, Sietses C, van der Peet DL, de Lange-de Klerk ES, Bonjer HJ, Bemelman WA, Cuesta MA (2012) Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. Ann Surg 255:216–221

26. Xu D, Li J, Song Y, Zhou J, Sun F, Wang J, Duan Y, Hu Y, Liu Y, Wang X, Sun L, Wu L, Ding K (2015) Laparoscopic surgery contributes more to nutritional and immunologic recovery than fast-track care in colorectal cancer. World J Surg Oncol 13::18
27. King PM, Blazeby JM, Ewings P, Kennedy RH (2008) Detailed evaluation of functional recovery following laparoscopic or open surgery for colorectal cancer within an enhanced recovery programme. Int J Colorectal Dis 23:795–800
28. Pecorelli N, Fiore JF Jr, Gillis C, Awasthi R, Mappin-Kasirer B, Niculiseanu P, Fried GM, Carli F, Feldman LS (2016) The six-minute walk test as a measure of postoperative recovery after colorectal resection: further examination of its measurement properties. Surg Endosc 30:2199–2206
29. Aloia TA, Zimmitti G, Conrad C, Gottumukalla V, Kopetz S, Vauthey JN (2014) Return to intended oncologic treatment (RIOT): a novel metric for evaluating the quality of oncosurgical therapy for malignancy. J Surg Oncol 110:107–114
30. Kim BJ, Caudle AS, Gottumukkala V, Aloia TA (2016) The impact of postoperative complications on a timely return to intended oncologic therapy (RIOT): the role of enhanced recovery in the cancer journey. Int Anesthesiol Clin 54:e33–e46
31. Cools-Lartigue J, Spicer J, McDonald B, Gowing S, Chow S, Giannias B, Bourdeau F, Kubes P, Ferri L (2013) Neutrophil extracellular traps sequester circulating tumor cells and promote metastasis. J Clin Invest. https://doi.org/10.1172/JCI67484
32. Artinyan A, Orcutt ST, Anaya DA, Richardson P, Chen GJ, Berger DH (2015) Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer: a study of 12,075 patients. Ann Surg 261:497–505
33. McSorley ST, Horgan PG, McMillan DC (2016) The impact of the type and severity of postoperative complications on long-term outcomes following surgery for colorectal cancer: a systematic review and meta-analysis. Crit Rev Oncol Hematol 97:168–177
34. Di B, Li Y, Wei K, Xiao X, Shi J, Zhang Y, Yang X, Gao P, Zhang K, Yuan Y, Zhang D, Wei X, Liu S, Wang J, Wang X, Zhang Y, Cai H (2013) Laparoscopic versus open surgery for colon cancer: a meta-analysis of 5-year follow-up outcomes. Surg Oncol 22:e39–e43
35. Kuhry E, Schwenk WF, Gaupset R, Romild U, Bonjer HJ (2008) Long-term results of laparoscopic colorectal cancer resection. Cochrane Database Syst Rev 2::CD003432
36. Brooks JM, Ohsfeldt RL (2013) Squeezing the balloon: propensity scores and unmeasured covariate balance. Health Serv Res 48:1487–1507
37. Martel G, Crawford A, Barkun JS, Boushey RP, Ramsay CR, Fergusson DA (2012) Expert opinion on laparoscopic surgery for colorectal cancer parallels evidence from a cumulative meta-analysis of randomized controlled trials. PLoS ONE 7:e35292
38. Akmal Y, Bailey C, Baek JH, Metchikian M, Pigazzi A (2011) Oncological outcomes of laparoscopic colon resection for cancer after implementation of a full-time preceptorship. Surg Endosc 25:2967–2971
39. Park EJ, Kim MS, Kim G, Kim CH, Hur H, Min BS, Baik SH, Lee KY, Kim NK (2015) Long-term oncologic outcomes of laparoscopic right hemicolectomy during the learning curve period: comparative study with cases after the learning curve period. Surg Laparosc Endosc Percutan Tech 25:52–58
40. Panchal JM, Lairson DR, Chan W, Du XL (2016) Geographic variation in oxaliplatin chemotherapy and survival in patients with colon cancer. Am J Ther 23:e720–e729
41. Morris M, Platell C, Fritschi L, Iacopetta B (2007) Failure to complete adjuvant chemotherapy is associated with adverse survival in stage III colon cancer patients. Br J Cancer 96:701–707
42. Bailey MB, Davenport DL, Vargas HD, Evers BM, McKenzie SP (2014) Longer operative time: deterioration of clinical outcomes of laparoscopic colectomy versus open colectomy. Dis Colon Rectum 57:616–622
43. Curtis NJ, Taylor M, Fraser L, Salib E, Noble E, Hipkiss R, Allison AS, Dalton R, Ockrim JB, Francis NK (2017) Can the combination of laparoscopy and enhanced recovery improve long-term survival after elective colorectal cancer surgery? Int J Colorectal Dis 33(2):231–234