Colon cancer surgery following emergency presentation: effects on admission and stage-adjusted outcomes.

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Colon cancer is a malignancy where outcomes are strongly related to the stage of disease on presentation. Timely detection leads to 5-year survival rates that can be as high as 97.4% for early stage disease.¹ Conversely, late detection with widespread metastatic disease can lower this survival rate to 8.1% at 5 years.² Screening initiatives are currently being assessed and implemented worldwide to lower the disease burden and to stimulate early detection.³ On the other side of the spectrum, research has also focused on factors that predict delayed presentation, worse staging at baseline, and thus poorer outcomes. Emerging evidence has already shown that certain symptoms on presentation predict advanced disease and poorer outcomes.⁴ Higher risk of advanced disease on presentation has also been identified in certain demographic groups, including underprivileged socioeconomic groups,⁵ and especially ethnic minorities.^{6,7}

Intuitively, emergency presentation is expected to be an unequivocally poor prognostic factor in patients with colon cancer, as the symptoms that lead patients to present at an emergency department (ED), including intestinal bleeding, perforation, or obstruction, are usually attributable to advanced disease.

This article analyzes colon cancer patients who are admitted after emergency presentation and eventually undergo surgical resection for colon cancer. It assesses the magnitude of the effects associated with emergency presentation on staging, surgical stay, and cancer-related outcomes.

Methods

Patient population

All colon cancer patients surgically treated at Massachusetts General Hospital in the 2004 to 2011 timespan were included for analysis. Data on all cases were collected from prospectively maintained internal data repositories or accrued from patient records under an institutional review board-approved protocol.

Definitions and objectives

Emergency presentation is defined as presentation or referral to our center through the ED with symptoms and clinical findings requiring admission and urgent surgical treatment within the index admission. All cases had a working diagnosis of colon cancer, or at least colonic malignancy as part of the differential diagnosis

before operation, which was in all cases followed by subsequent confirmation of malignancy through surgical pathology. Cases where the presence of colonic adenocarcinoma was never confirmed pathologically were not part of the included sample.

Differences between emergency admissions and the remainder of patients were assessed on 4 main levels: presentation characteristics, surgical pathology, surgical stay outcomes, and long-term outcomes. Presentation characteristics included general demographics (age, sex, ethnicity), lifestyle (alcohol and tobacco consumption, body habitus), comorbidity (expressed through a colon cancer-adjusted Charlson comorbidity score as well as type 2 diabetes, separately), and finally symptoms present at baseline presentation. The pathological characteristics compared included the TNM classification, as well as pathological characteristics with prognostic significance. Poor prognostic factors compared included positive resection margins (expressed as R+), tumor grade (expressed as high-grade disease), extramural vascular invasion (EMVI),⁸ perineural invasion,⁹ infiltrating tumor border configuration¹⁰ and absence of peritumoral lymphocytic response.¹¹

Inpatient characteristics which were analyzed included surgical duration, rates of laparoscopic surgery and conversion to open surgery, rates of multivisceral resection, and characteristics of the surgical admission including length of stay, rates of major surgical complications, and 30-day rates of readmission, reoperation, and death. Finally, the long-term outcomes compared were the need for postoperative chemotherapy as well as survival and disease-free survival, both expressed as duration and dichotomized as death, colon cancer-related death, overall metastatic disease, and metastatic recurrence. These end outcomes were also analyzed in multivariate models controlling for any significant covariates encountered during baseline analysis, as well as staging, expressed in the American Joint Committee on Cancer (AJCC) 7th edition classification (i.e., subdividing disease in stages 0, I, IIA, IIB, IIC, IIIA, IIIB, IIIC, and IV)¹²

Statistical analysis

A 2-tailed P value below 0.05 was considered statistically significant. We compared dichotomous outcomes among emergency and elective patients using the chi-square test and a relative risk (RR) calculation, while a 1-way analysis of

variance or a univariate linear regression, with the unstandardized B regression coefficient as a point estimate, was used for continuous outcomes. Multivariate analysis was performed to control the findings for any potentially significant confounders found during univariate analysis. The Cox proportional hazards model was used for time-related outcomes, while binary logistic regression was used for dichotomous outcomes.

Results

We included 1,071 patients, of whom 102 were emergency admissions, 83 of which came directly from our ED.

Baseline characteristics

Baseline characteristics are displayed in Table 1. There were nonsignificant differences in general characteristics, with patients with emergency presentation being slightly older, with lower body mass index, more ethnic minority patients, and a relative overrepresentation of women. Emergency patients had lower but nonsignificant rates of polyposis, a previous history of colorectal carcinoma, and inflammatory bowel disease and otherwise comparable rates of type 2 diabetes and overall comorbidity burden. There were no differences in regards to a history of smoking, but emergency presentations had higher rates of current smokers (17.6% vs. 11.4%; $P=0.062$) and a history of alcohol abuse (12.7% vs. 7.4%; $P=0.059$).

Patients diagnosed and treated in an emergency setting have different symptomatology on presentation than those treated electively. Most notably, patients presented to the emergency room (ER) with higher rates of abdominal pain or bloating (56.9% vs. 24.5%; $P<0.001$) and constipation (13.7% vs. 5.3%; $P<0.001$). In addition, unsurprisingly, ER patients presented with higher rates of intestinal obstruction (30.4% vs. 2.7%; $P<0.001$), perforation (15.7% vs. 0.8%; $P<0.001$), and bleeding (15.7% vs. 1.4%; $P<0.001$). These severe symptoms were also sporadically present in elective cases, which were either admitted in a subacute setting or had the symptoms incidentally detected during the baseline workup of their elective admission.

The advanced symptomatology of urgent cases is echoed by a more than doubled rate of perioperative metastatic disease, with 28.4% of emergency

admissions having metastatic disease established within 30 days of admission, compared with 13.3% in other patients (RR=2.13, 95% CI: 1.51-3.02; P<0.001).

Table 1. Baseline characteristics at presentation

	Emergency	Elective	P value
N (%)	102 (9.5%)	969 (90.5%)	-
Age (median, IQR)	69 (19)	67 (22)	0.24
Gender (% male)	48.0%	51.5%	0.51
Ethnic minority (%)	13.7%	9.9%	0.23
BMI (mean, $\pm$ SD)	26.9 (7.3)	27.7 (6.3)	0.29
History			
Charlson score (mean, $\pm$ SD)	0.78 (1.24)	0.72 (1.18)	0.62
Comorbid DM2 (%)	17.6%	17.9%	0.96
Comorbid IBD (%)	2.0%	3.7%	0.36
History of CRC (%)	1.0%	2.7%	0.30
History of polyps (%)	6.9%	13.5%	0.056
Lifestyle			
Current smoking (%)	17.6%	11.4%	0.062
Ever smoking (%)	50.0%	52.8%	0.59
Ever alcohol abuse	12.7%	7.4%	0.059
Symptoms			
Anemia	16.7%	23.9%	0.098
Abdominal pain/bloating	56.9%	24.5%	<0.001
Bright Red Blood Per Rectum	9.8%	15.6%	0.12
Bloody stools	6.9%	7.8%	0.73
Constipation	13.7%	5.3%	0.001
Diarrhea	9.8%	6.9%	0.28
Obstruction	30.4%	2.7%	<0.001
Perforation	15.7%	0.8%	<0.001
Gastrointestinal bleed	15.7%	1.4%	<0.001
Constipation	13.7%	5.3%	0.001
Metastatic presentation* (%)	28.4%	13.3%	<0.001

* Metastatic disease established within 30 days of initial presentation IQR: interquartile range. SD: Standard Deviation.

Surgical pathology

Pathological characteristics indicate considerably more advanced and aggressive disease, with worse staging in all levels, including tumor invasion (45.1% T4 disease vs. 20.9%; P<0.001), node-positive disease (56.6% vs. 38.6%; P<0.001), and metastatic disease (19.6% vs. 8%; P<0.001). Resections of emergency admissions had higher rates of margin positivity (15.7% vs. 9.7%; P=0.054), chiefly because of radial margin positivity (9.8% vs. 5.1%; P=0.045). Other pathological factors included higher rates of extramural vascular invasion (39.6% vs. 29.1%; P=0.021), perineural invasion (33.7% vs. 21.8%; P=0.005), absence of peritumoral lymphocytic response (86.8% vs. 72.2%; P<0.001), and infiltrating tumor border configuration (73.7% vs. 61.1%; P=0.004).

Table 2. Surgical pathology

	Emergency	Elective	RR (95% CI)	P value
T-stage=4	45.1%	20.9%	2.15 (1.68-2.75)	<0.001
N-stage ≥1	56.6%	38.6%	1.46 (1.21-1.77)	<0.001
M-stage=1	19.6%	8.0 %	2.44 (1.56-3.81)	<0.001
High grade	25.8%	19.2%	1.34 (0.93-1.94)	0.12
R+ resection	15.7%	9.7%	1.62 (0.99-2.63)	0.054
Proximal margin +	2%	0.5%	3.81 (0.75-19.4)	0.1
Distal margin +	1%	0.1%	9.52 (0.6-151.1)	0.11
Radial margin +	9.8%	5.1%	1.94 (1.01-3.70)	0.045
EMVI	39.6%	29.1%	1.35 (1.05-1.76)	0.021
Perineural invasion	33.7%	21.8%	1.54 (1.15-2.08)	0.005
No peritumoral lymphocytic response	86.8%	72.7%	1.19 (1.09-1.31)	<0.001
Infiltrating tumor border configuration	73.7%	61.1%	1.21 (1.06-1.37)	0.004

EMVI: extramural vascular invasion.

Surgical stay outcomes

Emergency patients required longer surgeries (median duration 141 vs. 124 minutes; $P=0.040$). This may in part be explained by higher rates of multivisceral resections (21.6% vs. 13%; $P=0.014$), and lower rates of laparoscopic surgery ($RR=0.44$; $P=0.014$) and segmental resections (69.6% vs. 79.7%; $P=0.045$), as well as a nonsignificant trend toward lower rates of specialized colorectal surgeons as the operating attending for emergency procedures (17.6% vs. 25.5%; $P=0.096$). In addition, emergency patients who underwent the procedure laparoscopically had a far higher conversion rate (44.4% vs. 12.5%; $P=0.002$) (Table 3).

Table 3. Surgical stay characteristics

	Emergency	Elective	RR (95% CI)	P value
Procedure type				
Segmental	69.6%	79.7%	0.87 (0.77-0.99)	0.045
Extended segmental	18.6%	12.8%	1.45 (0.94-2.25)	0.093
Total colectomy	8.8%	6.3%	1.40 (0.72-2.74)	0.32
By colorectal attending*	17.6%	25.5%	0.69 (0.45-1.07)	0.096
Laparoscopic resection	8.8%	27.2%	0.44 (0.24-0.85)	0.013
Conversion	44.4%	12.5%	3.55 (1.60-7.89)	0.002
Multivisceral resection	21.6%	13.0%	1.65 (1.11-2.49)	0.014
30-day readmission	12.7%	7.1%	1.79 (1.03-3.12)	0.040
30-day reoperation	2.9%	2.7%	1.09 (0.33-3.56)	0.88
30-day death rate	7.8%	0.8%	9.50 (3.64-24.8)	<0.001
	Emergency	Elective	B coefficient**	P value
Duration of surgery (mn, IQR)	124 (101)	141 (117)	17.6 (0.78-34.40)	0.040
Duration of stay (dys, IQR)	8 (6)	5 (4)	2.95 (1.59-4.32)	<0.001

* Reflects procedures led by specialized colorectal surgeons. All procedures are led by an attending surgeon.

** The unadjusted B regression coefficient provides an estimate of the difference between both groups in the units of the compared variables (for duration of surgery and stay: minutes and days, respectively)

Table 3. Surgical stay characteristics (continued)

Complications	Emergency	Elective	RR (95% CI)	P value
Anastomotic leak	2.9%	1.8%	1.68 (0.50-5.62)	0.40
Prolonged ileus	11.8%	10.2%	1.15 (0.65-2.02)	0.62
Delirium	4.9%	1.4%	3.39 (1.25-9.23)	0.017
Myocardial infarction	2.0%	0.5%	3.80 (0.75-19.3)	0.11
Cardiac arrest	2.0%	0.8%	2.38 (0.51-11.0)	0.27
Pneumonia	4.9%	2.6%	1.90 (0.74-4.86)	0.18
Surgical site infection	4.9%	7.1%	0.69 (0.28-1.66)	0.41
Urinary tract infection	4.9%	3.4%	1.43 (0.57-3.61)	0.43
Sepsis	4.9%	1.1%	4.31 (1.53-12.1)	0.006
Vasopressor need	8.8%	2.8%	3.17 (1.53-6.54)	0.002
ICU transfer	6.9%	2.9%	2.38 (1.06-5.30)	0.035
Total in-stay morbidity***	16.7%	13.8%	1.20 (0.76-1.91)	0.43

*** Total morbidity is any detected morbidity during admission from any of these:

Anastomotic leak, fascial dehiscence, intestinal bleeding, intestinal perforation, colonic obstruction, surgical site infection, urinary tract infection, delirium, pneumonia, sepsis, myocardial infarction, and cardiac arrest.

During surgical stay, complication rates of patients admitted after emergency presentation did not differ significantly when compared with elective colon cancer resections, with nonsignificant but higher rates of anastomotic leak, prolonged ileus, and lower rates of surgical site infection. Significantly higher risks were however measured for the occurrence of delirium (RR=3.39; P=0.017), sepsis (RR=4.32; P=0.006), as well as intensive care unit transfer (RR=2.38; P=0.035) and vasopressor necessity (RR=3.17; P=0.002). This led a median admission that was 3 days longer than for the remainder of the population (8 vs. 5 days; P <0.001) and near 10-fold increase of 30-day death rate (7.8% vs. 0.8%; P<0.001). Post discharge, patients admitted in an emergency setting also had a considerably higher 30-day readmission rates (12.7% vs. 7.1%; P=0.040).

Long-term outcomes

Echoing the worse baseline staging, emergency presentation cases had a shorter median disease-free survival (30 vs. 92 weeks; P=0.008). In addition, in patients without metastatic disease on presentation, ED presentations were also more likely to develop metastatic disease during follow-up (21.9% vs. 12.9%; P=0.025). This led to a higher death rate during follow-up (54.9% vs. 30%; P<0.001), with an even larger difference in colon cancer-related mortality surplus (39.2% vs. 15.8%; P<0.001). Not surprisingly, median survival duration was also significantly shorter (90 vs. 187 weeks; P<0.001) (Table 4).

Table 4. Long-term outcomes

	Emergency	Elective	RR (95% CI)	P value
Postoperative chemotherapy	38.2%	36.0%	1.06 (0.81-1.38)	0.65
New metastatic disease*	21.9%	12.9%	1.70 (1.07-2.72)	0.025
Overall metastatic rate	44.1%	24.5%	1.80 (1.41-2.30)	<0.001
Death rate	54.9%	30.0%	1.82 (1.50-2.23)	<0.001
Cancer-related death rate	39.2%	15.8%	2.48 (1.87-3.29)	<0.001
	Emergency	Elective	B coefficient*	P value
Disease-free survival (wks, IQR)	30 (181)	92 (184)	-32.5 (-56.3, -8.7)	0.008
Recurrence-free survival (wks, IQR)	68 (188)	111.5 (160)	-16.2 (-43.7, 11.3)	0.25
Survival duration (wks, IQR)	90 (232)	187 (194)	-53.3 (-79.2, -27.4)	<0.001

* In those without metastatic disease on presentation (n=913, including 73 ED admissions)

** unadjusted B regression coefficient providing an estimate of the difference between both groups in the units

Multivariate analysis

Table 5 shows the outcomes of multivariate analysis. After adjusting the survival curves for AJCC staging, age at surgery and comorbidity in multivariate Cox regression still indicated a clear increase in risk of death and shorter survival (hazard ratio=2.18; $P<0.001$). Similarly, adjusting disease-free survival for baseline AJCC staging still indicated a significantly higher hazard for recurrence and hence shorter disease-free survival (hazard ratio= 1.39; $P=0.042$). Logistic regression reiterates these findings after adjustment for the same covariates for odds ratios (ORs) of death and metastatic disease, while metastatic recurrence (in patients without metastatic disease on presentation), which was significant on univariate analysis (OR=1.9; $P=0.033$), was no longer significant after adjustment for baseline staging (OR=1.55; $P=0.17$). These survival characteristics are also shown in survival curves with and without adjustment of covariates, in Kaplan–Meier survival curves, and Cox proportional hazards survival estimates, respectively, as displayed in Figure 1.

Table 5. Multivariate assessment of outcomes

Cox regression	Univariate		Multivariate		
	HR (95% CI)	P value	Covariates	HR (95% CI)	P value
Survival	2.44 (1.83-3.25)	<0.001	AJCC, Age, ChC	2.18 (1.63-2.91)	<0.001
Disease-free survival	2.09 (1.52-2.87)	<0.001	AJCC	1.39 (1.01-1.93)	0.042
Logistic regression	OR (95% CI)				
	OR (95% CI)	P value	Covariates	OR (95% CI)	P value
Death	2.84 (1.88-4.29)	<0.001	AJCC, Age, ChC	2.07 (1.29-3.33)	0.003
Metastatic disease	2.44 (1.61-3.70)	<0.001	AJCC	1.61 (0.95-2.74)	0.080
Met post presentation*	1.90 (1.05-3.43)	0.033	AJCC	1.55 (0.83-2.92)	0.17

AJCC: 8-stage AJCC classification (7th edition) ChC: Charlson comorbidity score, disregarding colon cancer

* In those without metastatic disease on presentation (n=913, including 73 ED admissions)

Hazard ratios (HR) and odds ratios (OR) show relative odds or hazards of the negative events (death and recurrence) occurring in emergency admissions. All covariates shown have a significance of $P < 0.001$ as a variable in the model

Figure 1. Univariate and multivariate survival and disease-free survival models

The red lines depict patients admitted in an emergency setting, while the blue lines show the same outcome for the remainder of the population. (For interpretation of the references to color in this Figure, the reader is referred to the web version of this article.)

Comments

The aim of this study was to verify whether patients diagnosed with colon cancer in an emergency setting with admission and subsequent surgical treatment differed in presentation characteristics and had more advanced staging and worse outcomes, both during and after surgical admission.

The current literature supporting this hypothesis is scarce and crippled by applicability issues for the current colon cancer population. Some papers have produced valid points that echo the intuitive assumptions many clinicians have on the topic, but many of the papers laying the foundation for this work are outdated as they are from the prescreening era: a 1995 study by Scott et al ¹³ gave some of the first evidence pointing at more advanced disease and worse perioperative outcomes for emergency colorectal cancer patients, underlining the importance of screening initiatives, and a 1998 study by Porta et al. ¹⁴ demonstrated shorter survival rates for patients admitted through the ED in a small set of 80 colon cancer patients. Finally, with data from the same decade, Biondo et al. ¹⁵ confirmed differences in recurrence and survival in a prospective cohort (1996 to 1998), although not in all stages of disease.

In a more recent work, a British pilot study indicated a dramatic decrease in emergency admissions for colorectal cancer by virtue of fecal occult blood test screening, ¹⁶ although later reports of a local study in Canada ¹⁷ and an audit in England ¹⁸ showed that rates of emergency admissions for colon cancer remained alarmingly high, despite both areas providing universal health care with a colorectal screening program. A second issue that makes the findings of previous work hard to interpret specifically for colon cancer is the lack of differentiation that all but 2 ^{14,15} of the discussed articles make between colon and rectal disease - an issue shared with many publications on the matter. ¹⁹⁻²¹ Malignancies of the colon and rectum have been shown to be quite different in tumor biology ²² and subsequent prognosis ²³ and arguments to split both are a recurring issue in outcome studies. ²⁴

Our work is therefore the first to review a large cohort of colon cancer-specific patients in a single center. This population also has the heterogeneous composition of a large urban public hospital in the screening era, with on one side of the spectrum a significant portion benefitting from early detection through screening ²⁵ and on the other side patients who present through the ED and require emergency admission and surgery. We aimed to provide a comprehensive overview of the impact of these emergency presentations on all aspects of their subsequent care, including the course of the index admission, pathological characteristics, and both short- and long-term outcomes.

We found that patients admitted in an emergency setting largely had the same general characteristics as the remainder of the population, except for having a slightly worse lifestyle. These patients did of course present with far higher rates of symptoms that are prodromal of complicated and advanced disease, likely contributing to longer surgeries, higher complication rates, and a longer surgical stay. Surgical pathology subsequently showed far more advanced and aggressive disease on pathology, which in the long term led to shorter survival and disease-free survival, which was not identified in previous studies using smaller populations.^{19,26} This difference in long-term outcomes was significant and of considerable magnitude.

Our findings show that emergency presentation predicts more advanced disease and far worse outcomes, even after adjusting for staging at diagnosis. The detailed pathological characteristics of tumors of emergency admission patients hint at a possible explanation for this stage-independent disparity. Aside from classical TNM staging, many histopathological indicators of aggressive tumor behavior were far more common in emergency presentation patients. These included high-grade disease, lymphovascular and perineural invasion, transmural growth, and margin positivity; all these factors are likely to shorten the time interval between onset of disease and appearance of (serious) symptoms, and are independent predictors of poor outcomes in their own right.

Another potential explanation lies in the baseline lifestyle characteristics: emergency presentations had higher smoking and alcohol abuse rates. Aside from intrinsically adding even more risk and disease burden, these characteristics are also associated with low socioeconomic status,^{27,28} low health literacy,²⁹ and poor access to health care,³⁰ which may explain in part why emergency presentations come with more serious disease: for these underprivileged patients, often reluctant to seek medical attention until their symptoms become too severe to ignore, the ED is often the primary presentation site. In that sense, it is hardly a surprise to see these patients with both more advanced and more aggressive disease.

Conclusion

An ED presentation is related to a multifactorial high-risk profile, making it a stage-independent prognostic factor. The longer surgeries, surgical stays, and

higher readmission rates means these emergency presentations will also lead to significantly higher healthcare costs. Previously published literature confirms the higher cost of an emergency admission for colon cancer surgery, both inside ³¹ and outside the United States. ³² Considering the more advanced disease and the stage-independent disadvantage in outcomes and its implications for the chance of cure and need for adjuvant treatment and more intensive follow-up and surveillance, the costs are likely to remain higher in this patient population long after discharge. This provides yet another strong argument for preventive care and screening to detect disease early, especially when cost-effectiveness of screening initiatives is at the heart of the discussion. The ER provides an excellent starting point to find those patient groups who have the biggest potential for improvement and who carry the greatest challenges to achieve equal outcomes.

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