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The Conundrum of the Young Colon Cancer Patient

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Abstract:

Background: Colonoscopy has had a major impact on colon cancer incidence and survival for patients who are screened, usually beginning at the age of 50. Meanwhile, the incidence rate of colon cancer is actually increasing in the patients under 50, while no routine screening is implemented for this age group.

Methods: All patients surgically treated for colon cancer (2004-2011) without preexisting high-risk characteristics (HNPCC, IBD) were included (n=1015). Age-related disparities in baseline disease and outcomes were reviewed.

Results: Patients under 50 (n=108; 10.6%) had the highest baseline rates of metastatic (20.4% vs. 8.0%; $P<0.001$), node-positive disease (54.6% vs. 39.4%; $P=0.002$), and higher rates of extramural vascular invasion (38.9 vs. 29.4%; $P=0.043$). Cancer related mortality was also highest in this group (28.7 vs. 18.4%; $P=0.011$). Multivariable Cox regression shows that patients under 50 are still at significantly higher risk of mortality after adjustment for effects of age, baseline AJCC staging, smoking, and comorbidity (HR: 1.57, 95%CI 1.01-2.45; $P=0.049$).

Discussion: Patients under 50 present with the most advanced and aggressive disease, giving them the worst stage-independent prognosis of all age groups. Potential causes include age-related differences in tumor biology and underdetection by current screening efforts. This raises the question of how to address the conundrum of the young colon cancer patient, who often is the proverbial needle in a haystack of young patients with non-specific gastrointestinal symptoms, but would benefit considerably from early detection.

The introduction of large scale screening initiatives have played an essential role in the prevention and early detection of colorectal cancer and would have led to dramatic drops in incidence and mortality had they not been offset by population aging¹ through a combination of cumulative prevalence and age-related risk.² As age cut-offs are deemed unavoidable to make population-based screening financially and logistically viable, these initiatives have historically focused on the older, high-prevalence population segments.^{3,4} Colorectal screening programs put a lower age boundary for enrollment at 50 years or higher.^{3,5} However, in the last decade the proportion of new colon cancer cases that are diagnosed in patients under 50 years of age grew from about 8%⁶ to an estimate of over 10% in 2014.⁷ In fact, patients under 50 are the only demographic with increasing incidence while the overall trend for colon cancer incidence had been showing a steady decrease since the introduction of screening.^{7,8} Recently published data now also project that this age-related disparity is expected to increase further in the future.⁹ Since younger patients usually do not partake in screening initiatives, their diagnosis is reliant on symptomatic presentation, which often leads to delays and misdiagnosis.

This article aims to illustrate and discuss age-related disparities in surgically treated colon cancer patients; an emerging issue that seemingly will continue to grow in magnitude in the coming years. In this paper, we illustrate these disparities through our institution's surgically treated colon cancer cohort and discuss the implications for the treatment of colon cancer.

Methods:

Patients

A cohort that included all surgically treated colon cancer patients at Massachusetts General Hospital (MGH) from 2004 through 2011 (n=1071) was extracted from the MGH cancer registry and included in a data repository after institutional review board approval, using

data from the Research Patient Data Repository, complemented by review of patient records. This data repository was maintained prospectively starting 2011. Due to the significant differences in treatment approach and tumor biology, we exclusively focused on colon cancer and did not include patients with tumors of the rectum. Tumors of the colon were defined as any tumor proximal to the rectosigmoid junction.¹⁰ Data on long-term outcomes is periodically updated by reviewing patient follow-up records and the social security death index. The last status review of survival and follow-up was on April 1st 2014.

For the purposes of this research, we excluded 56 patients with concomitant high-risk diagnoses of hereditary nonpolyposis colon cancer or comorbid inflammatory bowel disease. The included population (n=1015) was subdivided into age categories meant to form subgroups matching the US screening upper and lower age thresholds. Thus, the groups were under 50 (n=108), 50 to 75 (n=590), and over 75 (n=317). Comparisons were made to show overall variations between age groups, as well as relative differences of every age group compared to the remainder of the population.

Statistical analysis

All statistical analysis was performed using SPSS statistical software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The threshold for statistical significance was set at a two-sided P-value of 0.05. Differences in dichotomous variables were assessed using a chi-square (χ^2) test. Significance of the differences in continuous variables over all four age groups was performed using a Kruskal-Wallis H test, while any comparison between a single subgroup and the remainder of the population was performed through a Mann-Whitney U test. Lastly, significant differences with a likely multifactorial origin will be assessed in

multivariable analysis using Cox proportional hazards models, which would allow to compare univariate hazard ratio (HR) and 95% CI of the events occurring to the multivariable HR after adjustment for age and stage where relevant, in addition to any relevant covariates encountered that may act as confounders.

Results:

Presentation characteristics

A total of 108 patients (10.6% of the included group) were under 50 years of age when operated on for colon cancer at our center. These patients presented with lower smoking rates and less comorbidity. Patients under 50 were diagnosed through screening in 9.3% of cases. The 10 screened young patients were almost exclusively screened either a positive family history (1st-degree: 4, 2nd-degree: 3). This screening rate was far lower than the 34.7% diagnosed through screening in patients aged 50-75 ($P<0.001$). Previous polyp detection or colorectal cancer diagnoses lowest in patients <50 and clearly subject to an age-dependent cumulative effect with the number of patients with a history of polyps more than quadrupling from 3.7% in patients under 50 to 16.7% in patients >75 ($P<0.001$), and the number of patients with a history of colorectal cancer growing from 0 in <50 to 4.4% in >75 ($P=0.002$). Further details on baseline characteristics can be found in **Table 1**.

Surgical admission and pathology

Median delay between diagnosis and treatment was shortest in patients <50 (18 days, others: 23 days, $P=0.088$), a factor that was demonstrated to be associated with more serious disease in previous work.¹¹ Patients <50 also had the longest median duration of surgery (<50 : 144 minutes vs. others: 124 minutes; $P=0.003$) while length of stay incrementally increased by age

groups ($P<0.001$). Readmission, reoperation and perioperative mortality rates did not differ significantly. All admission characteristics are shown in **Table 2**.

On surgical pathology, as shown in **Table 3**, a predominance of sigmoid tumors was witnessed in younger patients, which made up 39.8% of all tumors in patients under 50, compared to 23.8% in patients older than 50 ($P<0.001$). Statistically significant decreasing trends were noted in age group-specific rates of node-positive disease ($P=0.009$), metastatic disease ($P<0.001$), and microsatellite instability ($P<0.001$). 30-day metastasis rates also were lower in older age groups ($P<0.001$). Compared to the remainder of the population, patients <50 fared the worst in all of the above-mentioned pathological characteristics, with more cases with tumor-positive nodes (54.6 vs. 39.4%; $RR=1.39$, 95%CI 1.15-1.68; $P=0.002$), far more metastatic cases (20.4 vs. 8.0%; $RR=2.53$, 95%CI 1.64-3.90; $P<0.001$) as well as higher rates of established metastatic disease within 30 days of the index surgery (31.4 vs. 15.7%; $RR=2.01$; 95%CI 1.47-2.76; $P<0.001$). The pathological characteristics in patients under 50 were also reflected in their rates of extramural vascular invasion (38.9 vs. 29.4%; $RR=1.32$, 95%CI 1.02-1.71; $P=0.043$) and rates of microsatellite instability (11.1 vs. 2.4%; $RR=4.57$; 2.32-8.97; $P<0.001$).

Long-term outcomes and multivariable analysis

In follow-up, significant differences existed in rates of metastatic disease, being significantly higher in patients <50 (43.5%; $HR=1.80$; $P<0.001$), and significantly lower in patients >75 (19.9%; $HR=0.62$; $P=0.001$), whereas overall mortality was unsurprisingly highest in patients >75 (45.7%; $P<0.001$). However, colon cancer specific mortality was in fact highest in patients <50 (28.7%, $HR=1.55$; $P=0.025$). More details on long-term outcomes are shown in **Table 4**.

Figure 1 demonstrates differences in outcomes between patients under and over 50 in the shape of Cox proportional hazards survival curves. The curves show a univariate increase in hazard ratio (HR) for shorter disease-free survival of 1.80 (95%CI 1.31-2.46) $P < 0.001$. For mortality, when adjusting for age in order to correct for age-related causes of mortality, the HR of death for patients under 50 is 2.05 (95%CI 1.31-3.20; $P = 0.002$). Interestingly, when adjusting further for baseline AJCC staging, current smoking status and colon cancer-adjusted Charlson comorbidity score, the survival difference remains significant (HR: 1.57, 95% CI 1.001-2.44; $P = 0.049$)

Discussion

Recent evidence from 35 years of data from the Surveillance, Epidemiology and End Results (SEER) colorectal cancer registry confirms that despite a decreasing trend in the general population, incidence rates are increasing in patients under 50, and are expected to grow even further in the future.⁹ Evidence from our cohort forecasts a scenario where, along with a growth in numbers, patients under 50 will also form a subset with more advanced and more aggressive disease on presentation and subsequently will have the worst outcomes of any age group. If more generalized data confirms what our data illustrates, which is that that young colon cancer patients have an over 50% relative risk increase of developing metastatic disease and twice the relative hazards of age-standardized mortality, maybe the prevailing approach to forego routine screening of any form for patients under 50 should be re-addressed. If an interplay of advanced and aggressive disease is in fact to blame for the age-related disparities, a combination of late detection and fast progression will need to be addressed in unison. The assumption that early identification and enrollment in screening could solve this issue for certain at-risk groups will also have to be validated in further research as this means

A challenge to healthcare: further research and policy changes

The true challenge faced in current as well as future treatment approaches for colon cancer may well lie in the younger tier of the patient population: The young colon cancer patients' age excludes them from routine screening, and unless they are among the small subset of patients identified and screened because of pre-existent high-risk characteristics, their diagnosis will almost invariably be made symptomatically. Worse yet, colon cancer signs and symptoms are mimicked by a spectrum of other gastrointestinal conditions ubiquitous in their age category, ranging from constipation, hemorrhoids and irritable bowel syndrome¹² to inflammatory bowel disease without concurrent malignancy.¹³ This diagnostic ambiguity is a likely contributor to the more advanced disease younger colon cancer patients presented with.

For evident reasons, it is neither feasible nor desirable to include younger patients indiscriminately in screening initiatives. However, the alarming age-related gap in colon cancer survival between patients over or under 50 years of age shows that a considerable subset of younger patients is still missing out on the benefits of screening. Patients with hereditary colon cancer genotypes,¹⁴ inflammatory bowel disease,¹⁵ or primary sclerosing cholangitis¹⁶ are clear and well-established choices for earlier and more rigorous surveillance that cross age boundaries, and fortunately, in many cases, these patients are shown to be under adequate care and to have reaped the benefit of screening^{16,17} and show that identifying the right subset of patients and enrolling them in screening initiative can level the playing field and give them equivalent survival and quality of life.

The issue now lies in the patients currently identified as sporadic—those that do not fall in any of the known high-risk categories, and thus begin screening when they reach 50 years of age. Unfortunately, these sporadic cases form the majority of colon cancer patients under 50 and are

the core of the issue at hand. Far more effort is needed to find new targets for earlier screening. Ethnicity could potentially be an important starting point. The American College of Gastroenterologists has already called for a lowering of the recommended screening age in African-Americans to 45 in 2005,¹⁸ and recent cohort data from our center still shows that despite universal access to care in Massachusetts, ethnic minorities are still less likely to get screened and still present with more advanced disease at a younger age.¹⁹

Additionally, as current efforts to identify high-risk genetic profiles for colon cancer are getting more concrete and provide reproducible and clinically meaningful results,²⁰ a translational effort towards genetic profiling could also play an important role in the future to identify younger high-risk patients who would benefit the most from screening. Subsequently, tailored interventions currently used to increase screening compliance in carriers of high-risk genetic profiles may also be used to achieve timely enrollment.²¹

Relevance, limitations and counterarguments

The preexisting body of work on age disparities highlighted many facets of the issue of young-onset colon cancer, most often separately focusing on either incidence,^{8,9} stage,²² or overtreatment.²³ These works usually use population data like NCI SEER, which doesn't provide the same level of detail that a cohort study can provide on baseline characteristics, more subtle pathologic and admission characteristics and disease-specific mortality. To our knowledge, this is the first paper that comprehensively covers the full scope of the various issues related to young-onset surgically treated colon cancer in a single cohort from baseline presentation and admission characteristics to surgical pathology and long-term outcomes. Selecting a large, complete and unbiased population sample, careful evaluation of baseline characteristics during the

interpretation of results, and focusing on cancer-specific outcomes were important ways to keep bias and risk of erroneous interpretation to a minimum. However these points remain based on a single cohort and will need conformation in larger population-based studies. Some of the contrast shown may also be inherent to age itself as a factor: For example, lower cancer-related death rates with age could be in part due to older patients dying from other reasons or from co-morbid disease where colon cancer is not the sole culprit. Similarly, it is quite possible that higher mortality in younger patients is really in some aspects due to lower mortality in older patients, who may have slower-growing tumors.

A central element of any discussion about the expansion of screening initiatives is costs. If the routine screening age would be lowered, the cost would be substantial. Cost-effectiveness analysis specifically focused on younger patients will need to evaluate the relative merits of screening modalities in various combinations and time intervals, as was done initially for the current screening age range. Research on cost-estimates for colorectal has historically been focused on patients over 50 and have presented a cost of about US\$10.000 to 25.000 per life year saved.²⁴ More recent studies have focused mostly on reviewing the cost effectiveness of current screening standards,²⁵ making these cost models are hard to extrapolate to younger patients. Although in general, it follows to assume the relative low a priori odds of finding a tumor will put pressure on cost-effectiveness and increase chances of false positives. On the other hand, these factors may be offset by the potential gain in life-years and working years. With this in mind, the younger population may be an adequate target to test and validate novel cost-effective low-threshold mass screening modalities, the most important of which may be the fecal immunochemical tests (FIT)²⁶ and, provided it eventually becomes considerably more affordable, multi-target stool DNA testing.²⁷ Another rapid and noninvasive possibility would be to use CT colonography as a screening method, but this raises the issue of radiation exposure, which potentially has more consequences in younger patients.²⁸ With

the predominance of distal tumors witnessed in younger patients, and considering the higher rates of metastasis and mortality in sigmoid tumors previously demonstrated,²⁹ there may be a role for recommending sigmoidoscopy in this age group which would clearly be significantly less costly than recommending a full colonoscopy.

Conclusions

With current practice identifying only some of the younger at-risk future colon cancer patients and screening them adequately, the conundrum of the young colon cancer patient lies in those patients that currently do not have an evident risk factor. These young patients are not routinely screened and subsequently present far later, with symptomatic and often advanced and aggressive disease, leading to poorer outcomes. These patients are inherently hard to recognize due to the low à priori odds of their eventual diagnosis. The challenge lies in finding new ways to identify those young at risk patients. Cost-effectiveness needs to be kept in mind, and is most likely achievable if larger population studies identify factors distinguishing those at risk for young-onset colon cancer out of a vast number of patients with similar symptoms who do not harbor a malignancy. As long as we are not able to timely identify and screen them, younger colon cancer patients are likely to remain at a disadvantage.

Table 1. Baseline characteristics at presentation

	Age Categories				P
	Overall <i>N=1015</i>	<50 <i>N=108</i>	50-75 <i>N=590</i>	>75 <i>N=317</i>	
General					
Age (median, IQR)	67 (21)	44 (8)***	64 (12)***	82 (8)***	<0.001
BMI (median, IQR)	26.6 (7.7)	26.8 (7.9)	27.8 (8)***	24.9 (5.7)***	<0.001
Male (%)	50.6	48.1	53.7*	45.7*	0.062
Minority patients (%)	10.4	13.0	12.4*	6.0**	0.007
Comorbidity, Lifestyle and History					
History of Polyps (%)	12.5	3.7**	11.9	16.7**	0.001
Personal history of CRC (%)	2.5	0	1.4*	4.4**	0.003
First-degree relative CRC (%)	11.4	9.3	11.4	12.3	0.69
ASA (mean, SD)	2.37 ±0.60	2.06 ±0.54***	2.32 ±0.59**	2.57 ±0.57***	<0.001
Charlson (mean, SD)	0.73 ±1.20	0.26 ±0.74***	0.68 ±1.21**	1.00 ±1.22***	<0.001
Alcohol – social (%)	55.9	62.0	58.8*	48.3**	0.004
Alcohol – ever abuse (%)	7.9	4.6	9.8**	5.4*	0.024
Smoking – ever (%)	53.2	28.7***	58.0***	52.7	<0.001
Smoking – current (%)	12.2	11.1	14.4**	7.6**	0.005
Inflammatory bowel disease (%)	3.5	8.8**	3.9	0.9**	<0.001
HNPPCC (%) ^a	1.8	5.6**	1.4	0.9	0.002
Cancer presentation					
Screening diagnosis (%)	26.5	9.3***	34.7***	17.0***	<0.001
Emergency presentation (%)	9.9	7.4	10.6	10.4	0.653
CEA measured	58.0	67.6*	56.6	58.0	0.104
CEA (median, IQR) ^a	3.3 (8.7)	2.7 (10.9)	3.1 (9.0)	3.6 (7.7)	0.405
Neoadjuvant chemo (%)	3.3	10.2***	3.6	0.6**	<0.001

Abbreviations: IQR= Interquartile range; SD= Standard Deviation.
Charlson: Charlson comorbidity score, not accounting for colon cancer
a: in patients with preoperatively measured CEA (n=621)
*/**/***: Denotes values significantly different from remaining population with *: P<0.05; **: P<0.01***: P<0.001

Dichotomous outcomes expressed as percentages were compared using a chi-square coefficient. Difference of continuous values expressed as means or medians were compared using a Kruskal-Wallis test to assess for statistical significance between the three age categories, and using a Mann-Whitney U test to compare an age category with the remainder of the population.

Table 2. Admission characteristics

	Age Categories				P
	Overall	<50	50-75	>75	
Diagnosis-to-treatment, days (median, IQR)	22 (27)	18 (21)	24 (28)**	21 (30)	0.021
Stay duration, days (median, IQR)	5 (4)	4 (3)	4 (4)***	6 (5)***	<0.001
Surgery duration, minutes (median, IQR)	126 (101)	144 (93)**	130 (110)	110 (84)***	<0.001
Laparoscopic procedure (%)	26.0	33.3	28.0	19.9**	0.006
Conversion rate (%) ^a	13.8	10.3	15.4	11.6	0.70
30-day readmission (%)	7.6	6.5	7.6	7.9	0.89
30-day reoperation (%)	2.9	3.7	3.2	1.9	0.45
30-day death rate (%)	1.6	0.9	1.2	2.5	0.26

^a in laparoscopic procedures (n=195)
 /: Denotes values significantly different from remaining population with *: P<0.05; **: P<0.01***: P<0.001: (in bold)

Table 3. Surgical pathology

	Overall	Age Categories						P
		<50	RR (95%CI)	50-75	RR (95%CI)	>75	RR (95%CI)	
Primary disease site								
Left colon	12.0	15.7	1.36 (0.85-2.18)	13.2	1.28 (0.90-1.81)	8.5*	0.63 (0.42-0.94)	0.052
Right colon	52.9	35.2***	0.64 (0.49-0.83)	49.5*	0.86 (0.77-0.96)	65.3***	1.38 (1.24-1.55)	<0.001
Sigmoid	25.5	39.8***	1.67 (1.29-2.17)	28.1*	1.29 (1.03-1.60)	15.8***	0.53 (0.40-0.70)	<0.001
N+ disease (%)	41.0	54.6**	1.39 (1.15-1.68)	40.0	0.94 (0.81-1.09)	38.3	0.91 (0.77-1.07)	0.009
M+ disease (%)	9.4	20.4***	2.53 (1.64-3.90)	9.0	0.91 (0.62-1.34)	6.3*	0.59 (0.37-0.94)	<0.001
30-day metastasis (%)	17.3	31.5***	2.01 (1.47-2.76)	18.1	1.12 (0.85-1.47)	11.0***	0.55 (0.39-0.77)	<0.001
High-grade (%)	18.9	16.2	0.84 (0.53-1.33)	18.0	0.89 (0.68-1.17)	21.5	1.22 (0.92-1.60)	0.35
EMVI (%)	30.4	38.9*	1.32 (1.02-1.71)	28.7	0.88 (0.73-1.06)	30.6	1.01 (0.83-1.23)	0.11
MSI (%)	3.4	11.1***	4.57 (2.32-8.97)	2.4*	0.51 (0.26-0.99)	2.5	0.68 (0.31-1.48)	<0.001

*/**/***: Denotes values significantly different from remaining population with *: P<0.05; **: P<0.01***: P<0.001:

EMVI: Extramural Vascular Invasion

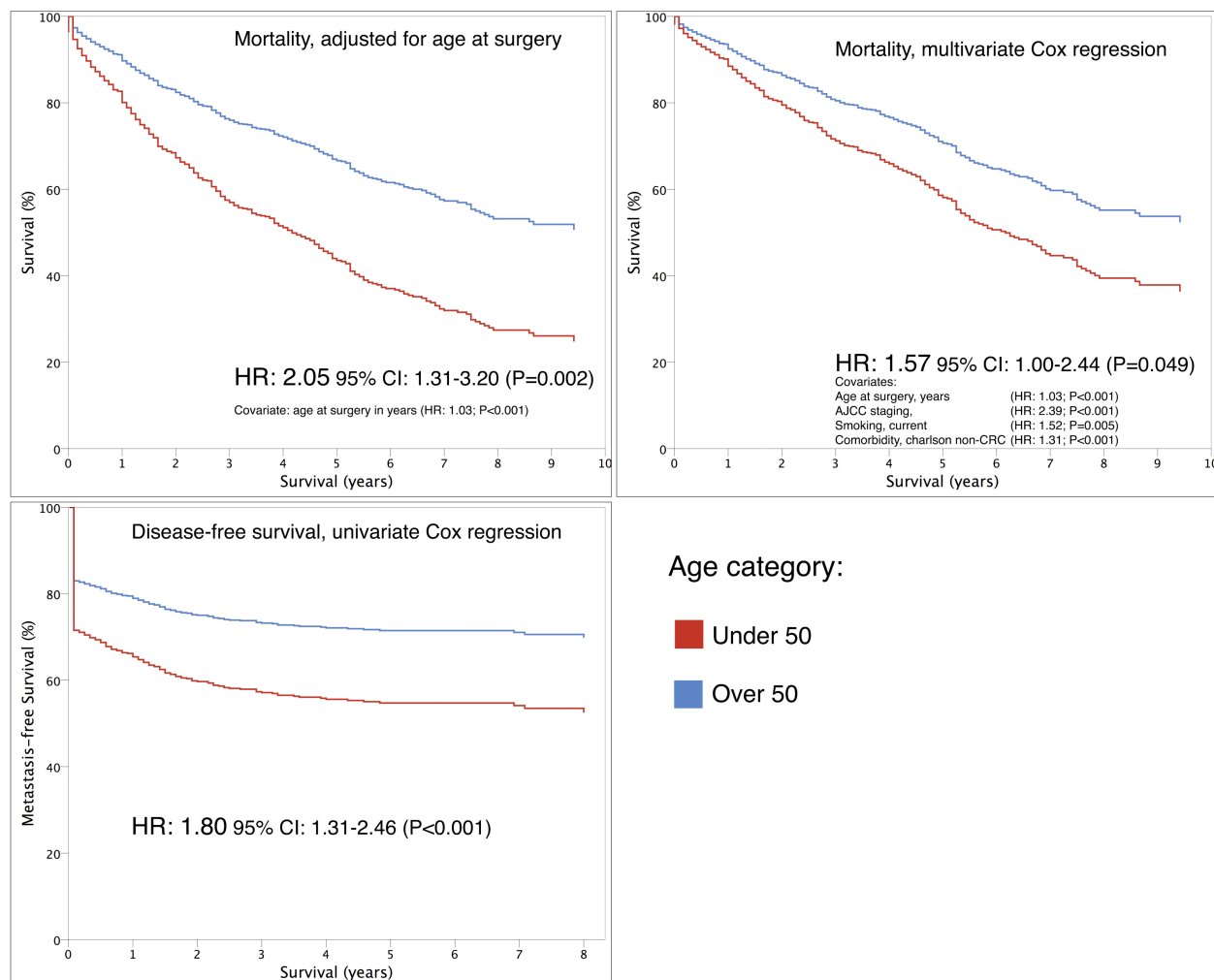
MSI: Microsatellite instability

Table 4. Long-term outcomes

	All	Age Categories						P
		<50	HR (95%CI)	50-75	HR (95%CI)	>75	HR (95%CI)	
Metastasis in follow-up(%)	10.7	12.0	1.41(0.79-2.52)	11.5	1.16(0.78-1.71)	8.8	0.72(0.47-1.11)	0.41
All metastatic disease(%)	28.1	43.5***	1.80(1.31-2.46)	29.7	1.13(0.89-1.44)	19.9**	0.62(0.46-0.81)	<0.001
All death(%)	36.3	33.3	0.91(0.64-1.28)	31.7***	0.67(0.54-0.82)	45.7***	1.63(1.32-2.01)	<0.001
Colon cancer death(%)	19.5	28.7**	1.55(1.06-2.27)	21.4.	1.15(0.86-1.54)	12.9**	0.64(0.45-0.90)	<0.001

*/**/***: Denotes values significantly different from remaining population with *: P<0.05; **: P<0.01***: P<0.001:
HR: hazard ratio, calculated using a time-standardized Cox proportional hazards model

Figure 1. Cox proportional hazards models comparing survival and disease-free survival for patients over and under 50 years



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