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Interval Colorectal Cancers at Ochsner Medical Center: Where Do We Stand?

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Background: An interval colorectal cancer is a cancer diagnosed prior to the recommended follow-up time from a previously negative colonoscopy. These cancers are thought to arise from a rapidly growing cancer, missed cancer, or incompletely resected adenomas. Our study aimed to identify interval cancers diagnosed during a 4-year period and to identify any potential risk factors associated with these cancers. Secondly, we compared our interval colorectal cancer rate with other published rates.
Methods: Our population included all patients who underwent colonoscopy for any indication between August 1, 2010 and July 31, 2014 (n=28,794), excluding individuals <18 years and patients with a history of inflammatory bowel disease, previously diagnosed colorectal cancer, or known hereditary cancer syndrome. Using a retrospective review of our institution's electronic medical record and data from the Louisiana Tumor Registry, we identified patients who were diagnosed with colorectal cancer. From these individuals, we reviewed and selected those who met the criteria for interval cancers.
Results: We identified 20 interval cancers during the 4-year study period. Based on the total number of index colonoscopies performed during the time period, our overall incidence rate was 0.07%. Approximately 1 interval cancer was diagnosed per 1,400 colonoscopy examinations. Our occurrence rate of 0.28 cases per 1,000 person-years of observation was less than or similar to the rates reported in other studies.
Conclusion: Our study demonstrated that our institution has a low incidence of interval cancers, supporting the effectiveness of our cancer screening program. To further minimize interval colorectal cancers, we recommend the documentation and reporting of endoscopy quality measures, as well as close follow-up intervals or alternate examinations for patients who have poor bowel preparation or incomplete/difficult examinations.

Keywords: *Colonoscopy, colorectal neoplasms, early detection of cancer, time factors*

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INTRODUCTION

Colorectal cancer is the third most common cancer and the second leading cause of death from cancer in the United States.[1] The overall lifetime risk of developing colorectal cancer in men and women is approximately 1 in 21 (4.7%) and 1 in 23 (4.4%), respectively.[1] Colonoscopy is considered the gold standard for screening and diagnosing colorectal cancers.[2] However, the literature suggests that colonoscopy fails to detect cancer approximately 5% of the time.[3,4] Therefore, high-quality screening colonoscopies by skilled endoscopists are necessary for cancer prevention and early detection.

Various medical societies have proposed colorectal screening guidelines utilizing mass screening strategies to reduce cancer rates and mortality.[2]

The reduction of interval cancers is considered a benchmark for the success of a screening protocol. However, prior to 2015, no universally accepted definition of interval cancer was available. Much of the previous literature used a 3- to 5-year cutoff to define interval colorectal cancers.[4-6] In 2015, an Expert Working Group of the Colorectal Cancer Screening Committee developed a standard definition for interval colorectal cancers with the goal of being able to compare rates across studies. They define an interval cancer as "a colorectal cancer diagnosed after a screening or surveillance exam in which no cancer is detected and before the date of the next recommended exam."[5]

Determining the exact cause of an interval cancer is difficult, but several factors have been proposed, including previously missed adenomas or cancers; incompletely

resected adenomas; or genetically predisposed, rapidly growing adenomas/tumors.

Because colonoscopy is a completely operator-dependent examination, in 2006, the American Society for Gastrointestinal Endoscopy (ASGE) and the American College of Gastroenterology (ACG) Task Force on Quality Endoscopy developed several quality indicators based on current evidence to help improve and standardize colonoscopy examinations.[7] These indicators include adenoma detection rate, colonoscopy withdrawal time, cecal intubation rate, and colonoscopy preparation documentation. Studies have shown that adenoma detection rates (adenoma detected on a screening colonoscopy) $<$20% are associated with a greater risk of interval cancer.[7,8] The ASGE/ACG Task Force on Quality Endoscopy initially devised an adenoma detection rate benchmark recommendation of $\geq$25% for men and $\geq$15% for women $>$50 years.[7] Newer recommendations published in 2014 suggest adenoma detection rate targets of $\geq$30% for men and $\geq$20% for women to decrease the risk of interval cancers.[8] The task force recommends a mean withdrawal time of $\geq$6 minutes to increase the detection of lesions.[7,8] Cecal intubation, with photo documentation, should be achieved in $\geq$95% of screening examinations to ensure the entire colon has been examined.[7] Colonoscopy preparation should be documented in every procedure note. Inadequate bowel preparation increases the likelihood of missing colon lesions; therefore, repeat colonoscopy should be offered to patients within the year.[9]

The aim of our study was to identify the interval colorectal cancers during a 4-year period at our institution and to determine if our interval cancer rate was similar to other published rates. Our study also aimed to identify any risk factors or associations to improve our understanding of interval cancers, to potentially improve the quality of colonoscopy examinations, and to minimize future cancers.

METHODS

Our study population included patients who underwent colonoscopy for any indication between August 1, 2010 and July 31, 2014, at Ochsner Medical Center main campus in the gastroenterology and colorectal surgery departments. These dates were chosen based on ease of data acquisition from our electronic medical record database. Individuals $<$18 years, patients with a history of inflammatory bowel disease, and patients with a history of previously diagnosed colorectal cancer or known hereditary cancer syndrome were excluded from analysis.

Through a retrospective review of our institution's electronic medical records and using data from the Louisiana Tumor Registry, we identified patients who were diagnosed with colorectal cancer during the defined time interval.

From these individuals, we reviewed and selected patients whose cancer was diagnosed prior to the recommended follow-up interval from a previous normal (no cancer detected) colonoscopy. If no previous colonoscopy was performed, the patient was excluded from the interval cancer population.

We adopted or developed the following standard terminology:

- Interval colorectal cancers – cancers diagnosed after a screening or surveillance examination (index colonoscopy) in which no cancer was detected and before the date of the next recommended examination
- Sporadic colorectal cancers – colorectal cancers found during the study period that did not meet the criteria for interval colorectal cancers

We defined colonoscopy groups as follows:

- Reference group – patients who had colonoscopies performed for any indication during the study period
- Interval group – patients whose index colonoscopy was negative (no cancer detected) but who received a follow-up colonoscopy in which the interval colorectal cancer was diagnosed

To calculate an overall and yearly interval colorectal cancer rate, we divided the total number of interval cancers by the total number of colonoscopies performed during the time period. Because of the wide range of recommended follow-up times after the index colonoscopy, we were unable to use these colonoscopies as an accurate measure of the colonoscopies performed during the time period. Therefore, we used the number of colonoscopies performed annually during our study period (2010-2014) as a surrogate number for the number of colonoscopies performed each year.

We also calculated our data in per-person years of observation. For interval cancers, if a person was diagnosed with interval colorectal cancer in the fortieth month after his/her initial colonoscopy, the patient contributed 3.33 person-years during which he/she was at risk of developing interval colorectal cancer. For reference group colonoscopies, person-year contributions were calculated by multiplying the number of reference group colonoscopies in a given year times the number of years in the follow-up period. For example, 7,340 reference group colonoscopies were performed in 2010-2011; therefore, the contribution was 7,340 $\times$ 4 years of follow-up $=$ 29,360 person-years). The total person-years at risk is the summation of all interval and reference contributions.

The occurrence rate, based on person-time, was calculated by dividing the number of new interval cancers identified during the study period by the sum of the time each person was observed, totaled for all persons. This denominator represents the total time the population was at risk for and being watched for interval cancer.

In addition to providing descriptive statistics, we used *t* tests for group comparison of normally distributed variables and chi-square or Fisher exact tests to compare proportions between the groups. Group comparisons included interval vs all sporadic cancers. Significance was set at $P<0.05$. We used SAS v.9.3 for data management and analysis.

RESULTS

A total of 28,794 reference group colonoscopies were performed during the 4-year study period. The mean age of patients receiving reference group colonoscopies was 59.9 $\pm$11.9 years.

From these 28,794 reference colonoscopies, 20 interval cancers were identified, for an incidence rate of 0.07% (Table 1). Approximately 1 interval cancer was diagnosed per 1,400 colonoscopy examinations. In terms of per-person years of observation, the 28,794 total examinations with 20 interval cancers diagnosed corresponded to 71,931

Table 1. Annual and Total Interval Colorectal Cancer Rates, 2010-2014

Date Range	Number of Interval Cancers	Number of Reference Colonoscopies	Interval Colorectal Cancer Rate[a]
8/1/2010 – 7/31/2011	4	7,340	0.05%
8/1/2011 – 7/31/2012	5	7,130	0.07%
8/1/2012 – 7/31/2013	6	6,790	0.09%
8/1/2013 – 7/31/2014	5	7,534	0.07%
4-year incidence, 2010 – 2014	20	28,794	0.07%

[a]Interval colorectal cancer rate = total interval cancers ÷ total reference colonoscopies.

per-person years, representing an occurrence of 0.28 cases/1,000 person-years of observation. The mean time to interval cancer diagnosis was 40.2 months; 50% (n=10) of interval cancers occurred in men and 50% (n=10) in women.

Table 2 provides details about the index colonoscopy for the 20 patients who developed interval cancers. Five patients had documented inadequate bowel preparation, 1 patient had an incomplete colonoscopy (the endoscopist failed to reach the cecum because of patient combativeness and the examination was terminated early), and 5 patients had documented difficult examinations because of patient combativeness (n=1), restricted mobility (n=1), or tortuous colons or looping of the endoscope (n=3).

As shown in Table 3, the most frequent indication for the index colonoscopy in the interval group was screening (85%). The most common reasons for the interval (follow-up) colonoscopy (when the interval cancer was diagnosed) were abnormal computed tomography (CT) scan (25%) and hematochezia (25%).

As shown in Table 4, interval cancers were most common in the right colon (55%) followed by the sigmoid colon (30%). The largest percentage of interval cancers was stage 4 (32%) at the time of diagnosis.

We found a significant difference in the mean age at diagnosis between the interval colorectal cancer group (71.35 ± 9.72 years) and the sporadic colorectal cancer group (63.22 ± 13.16 years) (P=0.0064).

No significant difference was detected between the sexes in interval cancers vs sporadic cancers (P=0.741). A significant difference was found in cancer location between the interval cancer group and the sporadic cancer group, with interval cancers more predominant in the right colon 55% (n=11) and sporadic cancers more common in the rectum 39% (n=241) (P=0.027).

Table 2. Details of Index Colonoscopies for Patients Who Developed Interval Cancers (n=20)

Variable	n (%)
Bowel preparation	
Inadequate	4 (20)
Adequate	13 (65)
Not specified	3 (15)
Completeness of procedure	
Incomplete	1 (5)
Complete	19 (95)
Documentation (picture on report)	12 (60)
Documentation of procedural difficulty	
Difficult	5 (25)
Not specified	15 (75)

DISCUSSION

We judged our interval colorectal cancer rate (0.07%) during the 4-year study period to be low, and we attempted to compare our rate to published studies. We encountered limitations with making such comparisons because of the lack of a standard rate calculation for interval colorectal cancers in the past. For example, some series estimated rates by dividing the total number of interval cancers by the total number of colorectal cancers diagnosed during a specified time period. These rates varied considerably, depending on the time factored for interval cancer diagnosis (eg, 6-36 months, 6-60 months, or based on previous 3-year to 5-year cutoffs).

To help with this problem, the Expert Working Group of the Colorectal Cancer Screening Committee recommended using person-years of observation as an alternative way to calculate rates. This measurement reflects the observed person-time at risk and allows for more accurate comparisons among studies.[5]

Table 3. Indications for Index and Follow-up Colonoscopies for Patients Who Developed Interval Cancers (n=20)

Indication	Index Colonoscopy n (%)	Follow-up Colonoscopy n (%)
Anemia	1 (5)	4 (20)
Positive fecal occult blood test	1 (5)	
Hematochezia	1 (5)	5 (25)
Screening	17 (85)	
Abdominal pain		1 (5)
Abnormal computed tomography scan		5 (25)
Constipation		1 (5)
Surveillance[a]		1 (5)
Unspecified		3 (15)

[a]Incorrect indication listed on the endoscopy report; history revealed that indication was iron deficiency anemia.

Table 4. Comparison of Interval Colorectal Cancers and Sporadic Colorectal Cancers Identified During the Study Period, 2010-2014

Variable	Interval Cancers n=20	Sporadic Cancers n=618	*P* Value
Mean age at diagnosis, years ± SD	71.35 ± 9.72	63.22 ± 13.16	0.0064
Cancer location, n (%)			0.027
Right colon	11 (55)	158 (26)	
Left colon		26 (4)	
Transverse colon	1 (5)	41 (7)	
Sigmoid colon	6 (30)	133 (22)	
Rectum	2 (10)	241 (39)	
Not specified		19 (3)	
Cancer stage, n (%)[a]			0.841
0		25 (4)	
1	5 (26)	181 (30)	
2	4 (21)	109 (18)	
3	4 (21)	153 (26)	
4	6 (32)	130 (22)	

[a]For interval cancers, n=19 and for sporadic cancers, n=598; stage was omitted in 21 histories.

A clinical review of interval colorectal cancers by Adler et al suggests that a conservative estimate of interval colorectal cancers is 1 case per 1,000 colonoscopy examinations.[3] They derived this rate from 2 large studies (the Nurses' Health Study and the Health Professionals Follow-up Study), producing upper and lower limit boundaries. From these data, Adler et al determined that within 10 years of a negative colonoscopy, 198 cancers were diagnosed during 285,717 person-years of follow-up, yielding a rate of 0.7 cases per 1,000 person-years of follow-up.[3]

A large prospective study assessing the interval cancer rate among patients with adenomas discovered on an interval colonoscopy found an incidence rate of 1.7 cases per 1,000 person-years of follow-up.[6] These cancers were diagnosed at a median follow-up of approximately 4 years.

In comparison with these rates, our study showed an occurrence rate of 0.28 cases per 1,000 person-years of observation. However, despite the conversion of data to person-years, a head-to-head comparison of published rates with our study cannot easily be made because the recommended follow-up time in our study was based on findings from a previous colonoscopy and ranged from 3-10 years. We found no studies in the literature similar to ours for direct comparison, and that is one of our study limitations.

Similar to other studies on interval colorectal cancers, we found that most interval cancers were in the right colon 55% (n=11). Some proposed explanations are the difficulty of visualizing flat and sessile polyps in the proximal colon and possible differences in tumor biology, predisposing to more aggressive, rapidly growing tumors.[4,7] Sporadic cancers in our study were found more frequently within the rectum (39%; n=241) followed by the right colon (26%; n=158). However, national data published in 2014 report the proximal colon (42%) followed by the rectum (28%) as the most common sites for colorectal cancers.[10] The difference between our findings and the 2014 report may be attributable to our referral patterns and/or population demographics, as cancer location differs in frequency with age and sex (ie, more rectal cancers are found in younger males).[10] More investigation into our sporadic cancer demographics would have to be performed to fully evaluate this difference.

In our study, interval cancers were diagnosed in older patients compared to sporadic cancers. This finding is supported by several studies that show age >65-70 years is a risk factor for interval cancers.[11] The most common indication for the index colonoscopy in the interval group was screening (85%), but the most common indications for follow-up colonoscopy in this group were hematochezia (25%) and abnormal CT scan (25%). Thirty-two percent of the interval cancers were stage 4, and the advanced stage likely explains the symptomatic presentation (gastrointestinal bleeding, need for CT scan) that prompted the diagnostic colonoscopy.

An important point to emphasize is that the bowel preparation for the index colonoscopy was inadequate for 20% of the patients who developed interval cancers. The recommended follow-up for these examinations was 3-5 years based on findings (ie, polyps) during the index examinations. However, inadequate preparation can make visualization of the colonic mucosa and detection of polyps or cancer extremely difficult. Shorter recommended follow-up intervals with adequate bowel cleansing may have prevented these cancers or detected them earlier. Since 2015, the ASGE guidelines for bowel preparation recommend repeating the examination within 1 year for patients with inadequate bowel preparation.[9]

One of the patients who developed interval cancer had an incomplete index colonoscopy in which the endoscopist failed to reach the cecum because of patient combativeness. The examination was aborted within the descending colon, and a follow-up air contrast barium enema was

unremarkable. Thirty-one months later, a stage 2 interval cancer was diagnosed in the patient's sigmoid colon, an area that had been reached during the index colonoscopy, suggesting the possibility of a missed adenomatous polyp that advanced during the time period between colonoscopies.

As previously noted, 25% of the index colonoscopies for the interval cancer group were documented as difficult. All 5 patients with difficult index examinations were diagnosed within 31-40 months after their index colonoscopy and thus before the recommended follow-up period. Difficult examinations can potentially increase the risk of missing lesions—whether adenomas or cancers—so we question whether we should be following these high-risk examinations with CT colonography or fecal immunochemical test, and if positive, determining if screening or surveillance colonoscopy is warranted earlier than previously recommended.

One patient excluded from our analysis was an 82-year-old male diagnosed with a 10-mm ascending colon polyp identified on colonoscopy for melena. The polyp was not removed because the patient was on dabigatran for atrial fibrillation at the time of the procedure. He was advised to return for polyp removal when he was off anticoagulation, but no definitive time frame was mentioned. The patient was lost to follow-up but presented 13 months later with anemia. At that time, his cardiologist safely took him off anticoagulation, and a stage 2 colon cancer at the site of the previous polyp was identified during colonoscopy. We did not include this patient in our data analysis because he was given a recommendation to follow up; however, we are using it as a learning example because if a definitive time frame had been mentioned, the outcome may have been different.

Limitations of our study include patients who were lost to follow-up after the index colonoscopy and perhaps had cancers diagnosed outside of our institution. As stated earlier, rate calculation is possibly another study limitation. We calculated our rate by dividing the total number of interval cancers diagnosed by the total number colonoscopies performed during that time period. Because of the wide range of recommended follow-up times after the index colonoscopy, we were unable to accurately calculate the total colonoscopies performed at that time. Therefore, we took the total number of colonoscopies performed annually during our study period from 2010-2014 and used it as a surrogate number for the amount of colonoscopies performed each year.

We were unable to adequately compare our interval cancer rate to others given the lack of standards for the definition of interval cancer and for rate calculations in previous studies. We believe as more institutions and studies adhere to the new standardized definitions developed by the Expert Working Group of the Colorectal Cancer Screening Committee, we will have a better basis to make comparisons.

Finally, including all adults $\geq$18 years could have falsely lowered our interval rate by increasing the total number of colonoscopies performed. However, it is noteworthy to mention that most of the patients in the reference group were within screening age (mean age of 59.9 $\pm$ 11.9 years). An alternative approach would have been to only include individuals of screening age in the analysis.

At the time of our study, we were not documenting quality measures such as adenoma detection rate, withdrawal time, cecal intubation rate, and quality of colonoscopy preparation. In February 2013, we began documenting these quality measures at our institution. These data are presented at performance improvement and quality meetings on a quarterly basis. The cumulative data are shared publicly through our annual reports of the gastroenterology and hepatology department. Moving forward, these measures will add to the performance of high-quality colonoscopies, helping to further decrease our interval colorectal cancers.

CONCLUSION

Our study demonstrated a very low incidence of interval cancers (0.07% during a 4-year period) with an occurrence rate of 0.28 cases per 1,000 person-years of observation, supporting the effectiveness of our cancer screening program. Furthermore, our data show that we are performing better than or similar to published studies. Based on our data, we recommend that endoscopists pay close attention to the right side of the colon and consider close follow-up intervals or alternate examinations in the setting of poor bowel preparation, incomplete colonoscopies, or difficult examinations to further minimize interval cancers.

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