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Retrospective Analysis of Site and Pathological Characteristics of Recurrence in Patients with Adenomatous Colonic Polyps

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Authors' contributions

This work was carried out in collaboration between all authors. Author EJC designed the study, wrote the protocol, performed data collection, wrote the initial manuscript and revisions, and is the article guarantor. Author ARC performed the literature review, data analysis and processing, manuscript writing, edition and revisions, author MBH helped with the writing of the manuscript. Author KC helped with the statistical analysis. Author CH edited the manuscript and revisions. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The benefits of colonoscopy surveillance in reducing the incidence and mortality of colorectal cancer are known. However, benefit may be driven by early detection of left side colon lesions to a greater extent than right side counterparts. The correlation between initial ("index") adenoma(s) location, recurrent polyp(s) and their respective pathologic grade is not well understood. The

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purpose of this study was to determine if index colonic adenoma polypectomy location (right vs. left) correlated with recurrent adenoma location and polyp pathology.
Methodology: Retrospective review of patient medical records including all cases of completely resected adenomatous polyp(s) without evidence of dysplasia at initial colonoscopy with repeat follow-up study between November 1998 and August 2009 was performed at a tertiary level academic hospital. The splenic flexure was used to discriminate right vs. left side colon polyps.
Results: Records of 112 patients (53.6% males) with index adenomatous colonic polyps who had follow-up complete colonoscopy with polypectomy were reviewed. Mean (SD) time of follow-up colonoscopy was 43.3 (22.6) months. The mean age at presentation was 59.5 years. Initial polyp site was found on the right in 46 patients (41.1%), left in 38 (33.9%), and both right and left in 28 patients (25.0%). Patients with right side index adenomas were significantly older compared to those with left side lesions, with a mean (SD) age of 61.2 (9.9) vs. 55.6 (7.3) years respectively ($p=0.008$). Polyp pathology on follow-up colonoscopy revealed 16 (14.3%) hyperplastic, 84 (75.0%) adenomatous, 6 (5.4%) tubulovillous, 5 (4.5%) high grade dysplasia (HGD), and 1 (0.9%) cancer case. 28 of 39 right side index adenomas (71.8%), and 24 of 33 left side index adenomas (72.7%) had same side adenomatous or higher grade pathologic recurrence. Ipsilateral recurrence proved to be statistically significant ($p<0.001$). In addition, right side index adenomatous polyps had higher rates of adenomatous polyp recurrence (44/46, 95.7%) compared to left side index ones (26/38, 68.4%), independent of recurrence site ($p<0.001$).
Conclusion: Initial adenomatous polyp side may predict recurrent adenomatous location and polyp pathologic grade. Follow-up endoscopic surveillance methods and intervals should consider side of previous adenomatous polyp location.

Keywords: Colonoscopy; polyp; recurrence.

1. INTRODUCTION

The burden of cancer is increasing as a result of population aging and growth. Colorectal cancer (CRC) is the third leading cause of cancer-related death in the United States, with an estimated 136,830 new cases and 50,310 deaths for 2014 alone [1,2]. However, CRC death rates have continuously decreased over the past decade [3], largely due to increased awareness, early detection, and new available treatments [4-6].

Most CRCs are believed to develop through a complex multistep process which involves transformation of normal mucosa to adenomatous lesions and subsequent carcinomas through a progressive cascade of genetic mutations characterized by excessive activation of oncogenes and inactivation of tumor suppressor genes. Interruption of the adenoma-carcinoma sequence by screening colonoscopy and polypectomy is key for CRC prevention. It is well known that patients with a history of adenomatous polyps have a higher risk of recurrence compared to non-polyp carriers [7]. Thus, closer surveillance is essential [8]. CRC however may less frequently develop from serrated lesions (sessile serrated adenomas and traditional serrated adenomas), which may account for up to 10% of CRCs. In addition, recurrent polyps and cancer may originate from various sources including previously missed lesions (6%-29%, primarily polyp size related), recrudescence of (incompletely) removed polyps, or de novo development [9-11].

Adenoma recurrence rates vary significantly between studies (20-50% within 3-5 years), probably due to differences in patient characteristics, compliance, follow-up interval duration, and endoscopic quality [12,13]. Professional groups have consequently developed guidelines for post-polypectomy surveillance intervals based on risk stratification to increase efficiency in detection of advanced adenomas and early cancers [14].

Many CRC screening tools have been proposed, but colonoscopy, although never tested by randomized trials, is advocated by most specialty societies as the preferred screening method [15-17]. Colonoscopy with polypectomy has proven to be a powerful tool in the reduction of CRC incidence and mortality [18,19]. Screening colonoscopy rates have rapidly increased in the United States, with a corresponding expected decline in CRC incidence [3,4,20,21]. Unfortunately, colorectal cancer occurs after complete colonoscopy more frequently than may be generally appreciated [22]. This has led to increasing controversy regarding follow-up intervals, efficacy and cost-effectiveness of current surveillance guidelines [23].

Previous studies have suggested proximal CRC presents different clinical and pathological features which may impact progression, recurrence, and long-term survival [24-26]. Some propose CRC should be studied as three distinct entities: right, left, and rectal cancer [27]. The pathophysiologic basis underlying this topographic difference is unclear. On a basic level, the proximal or right colon (cecum, ascending colon, and proximal two thirds of transverse colon) is derived from the embryonic midgut, whereas the distal or left colon (distal one third of the transverse colon, descending colon, sigmoid colon, and rectum) is derived from the embryonic hindgut [28]. Molecular analysis has shown topographic differences in field mucosal baseline oncogenes when comparing proximal and distal colonic mucosa [28,29]. In addition, regional variations in local microbiota, mucin chemotypes among other molecular elements, and their respective interactions within the mucosal surface may play a role in right vs. left sided colon cancer characteristics [30].

It has been proposed that colonoscopic surveillance methods be modified on the basis of initial ("index") polyp location. Observed benefit from frequent surveillance may be driven by early detection of left side pathology to a greater extent than the right side disease [31]. Our study aims to further evaluate differences in index adenomatous polyp characteristics and recurrence. Better understanding of factors that influence polyp recurrence rates may impact CRC screening, surveillance methods, timing and costs.

2. METHODOLOGY

Retrospective medical record review using endoscopy software (ProVation MD, 2013) was performed. All colonoscopy and corresponding pathology reports between 11/1998 and 8/2009 were studied. Patients with completely resected adenomatous lesion(s) without evidence of dysplasia at baseline colonoscopy and follow-up colonoscopy with recurrent polypectomy during the above time period were identified. Cases were divided into three groups according to index polyp(s) location: 1. Right only (R), 2. Right and left (R+L), and 3. Left only (L). The splenic flexure was used to discriminate right side vs. left side lesions. Eligibility criteria included patients age 18 to 90 years old that had at least two colonoscopies with polypectomies. Only patients with one or more adenomatous lesions on initial colonoscopy were studied. Time between colonoscopies, location, number, size (mm), and pathologic grade of polyps were recorded. Exclusion criteria involved: hyperplastic / non-adenomatous or dysplastic index polyps, pathology not available or polyp not retrieved, inadequate preparation, interval colonic resection independent of indication, short-term colonoscopy interval of less than six months (i.e. missed lesions, same polyp intervention), or suspected polyposis syndrome.

Data was analyzed using statistical software (SPSS Statistics Standard v22, 2013). Statistical significance was determined using Mantel-Haenszel χ^2, Fisher Exact, and ANOVA testing.

3. RESULTS

A total of 112 patients were identified (53.6% males), with mean age (SD) at presentation of 59.5 (9.6) years, and interval mean (SD) follow-up colonoscopy of 43.3 (22.6) months. 46 (41.1%), 38 (33.9%), and 28 (25.0%), had index adenomatous polyps on the right, left, or simultaneously right and left side respectively. Patients with right side index lesions were significantly older compared to those with left side ones, with a mean (SD) age of 61.2 (9.9) vs. 55.6 (7.3) years (p=0.008). Mean interval time (months) between colonoscopies did not differ between index right side (42.5) and index left side (43.6) adenoma surveillance (p=0.17) (Table 1).

Table 1. Baseline characteristics of patients with adenomatous colonic polyps at index colonoscopy (n=112)

	Index adenoma location			***P-value (R vs L)***
	Right	**Left**	**Right and left**	
Number (%)	46 (41.1)	38 (33.9)	28 (25.0)	
Age - mean (SD), years	61.2 (9.9)	55.6 (7.3)	61.7 (11.6)	**0.008*
Gender - n (%)				
Male	24 (40.0)	21 (35.0)	15 (25.0)	*0.770*
Female	22 (42.3)	17 (32.7)	13 (25.0)	*0.522*
Interval follow-up colonoscopy-mean (SD), months	42.5 (18.3)	43.6 (20.1)	43.8 (29.4)	*0.170*

Right side index adenomas and their left side counterparts had 71.8% (28/39) and 72.7% (24/33) same side adenomatous or higher pathologic grade recurrence on follow-up colonoscopy respectively (Table 2, Fig. 1). Ipsilateral recurrence proved to be statistically significant (p<0.001). Polyp pathology on follow-up colonoscopy revealed 16 (14.3%) hyperplastic, 84 (75.0%) adenomatous, 6 (5.4%) tubulovillous, 5 (4.5%) high grade dysplasia (HGD), and 1 (0.9%) cancerous lesion. When comparing index polyp location vs. recurrent polyp pathology irrespective of location, right side index lesions were more likely to have adenomatous or higher grade pathologic recurrences (44/46, 95.7%) compared to left side index ones (26/38, 68.4%), (p<0.001) (Table 2, Fig. 2).

4. DISCUSSION

Screening, detection and treatment of colorectal polyps have considerable implications for public health. In 2006, the United States Multi-Society Task Force (USMSTF) on CRC issued guideline recommendations on post-polypectomy surveillance based on a risk stratification approach. High risk criteria per baseline

Table 2. Correlation between index adenomatous colonic polyp location, recurrence location and pathology

		Index adenoma location			Total adenoma recurrence (n)	*P-value (R vs L)*
		Right	**Left**	**Right + Left**		
Recurrent adenoma location (n)	Right	28	6	11	45	
	Left	10	24	9	43	
	Right + Left	1	3	4	8	
Ipsilateral adenoma recurrence (%)		71.8	72.7	16.7		**0.001*
Recurrent polyp pathology independent of recurrence location - n (%)	Hyperplastic	2 (12.5)	12 (75.0)	2 (12.5)		**0.012*
	Adenoma†	44 (45.8)	26 (27.1)	26 (27.1)		**0.041*
						**0.001δ*
	TAD	38 (45.2)	22 (26.2)	24 (28.6)		
	TVAD	3 (50.0)	2 (33.3)	1 (16.7)		
	HGD	2 (40.0)	2 (40.0)	1 (20.0)		
	Cancer	1 (100)	0 (0)	0 (0)		

†: Adenoma, Tubular adenoma (TAD), Tubulovillous adenoma (TVAD), High grade dysplasia (HGD), Cancer.
δ: Hyperplastic vs Adenomatous† recurrence based on index adenoma location

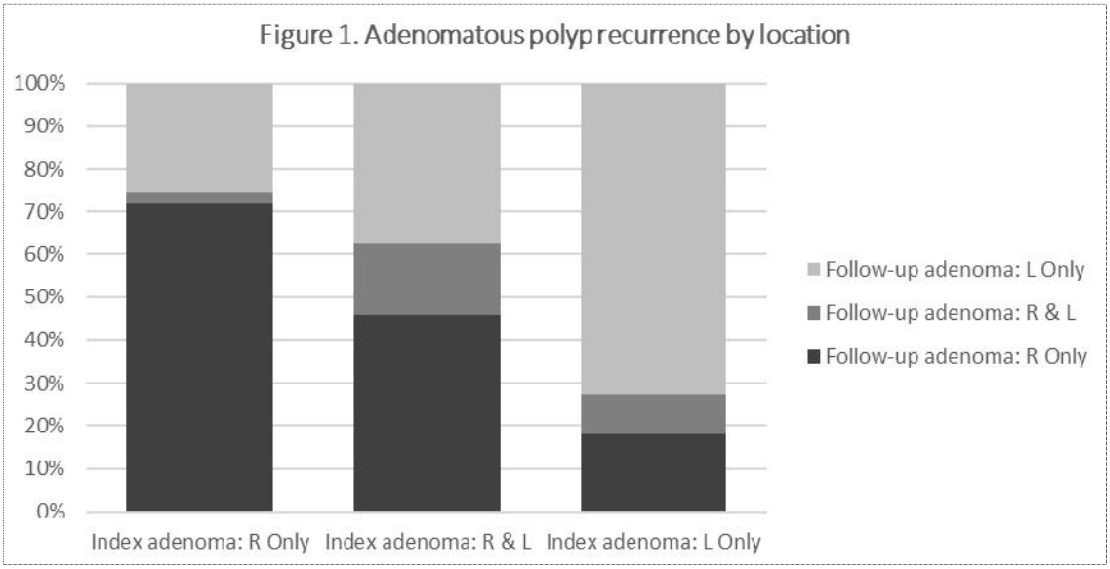

Fig. 1. Adenomatous polyp recurrence by location (Left vs. Right): Same side recurrence proved to be statistically significant (p<0.001).

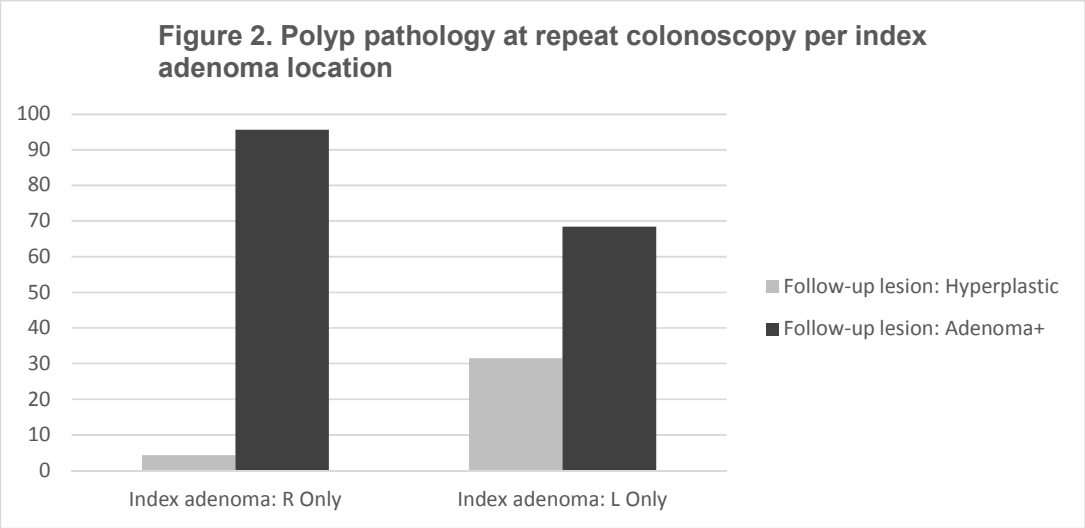

Fig. 2. Polyp pathology at repeat colonoscopy per index adenoma location (Left vs. Right): Right side index polyps were more likely to have adenomatous or higher grade pathologic recurrence (p<0.001)

†: Adenoma, Tubular adenoma, Tubulovillous adenoma, High grade dysplasia, Cancer

colonoscopy included presence of 3 or more adenomas, polyp size greater than 1 cm, high grade dysplasia, and villous features [13]. Recent evidence has raised concerns about index polyp location as a risk modifier. Small number of studies suggest a higher risk of recurrence and worse outcome related to right side colon lesions [32-34]. It has been hypothesized that technical difficulties related to right side polyp detection and suspected underlying biologic differences of proximal colon lesions play a role. A recent analysis of the Polyp Prevention Trial, estimated a 4-year risk for adenomatous polyp recurrence of 9% for proximal vs. 5% for distal index adenomatous polyps [13].

Our data showed a statistically significant association between index adenoma location and ipsilateral recurrence. Same side recurrence may be related to a process of topographic-specific field carcinogenesis which may suggest the need for novel techniques and patient-specific surveillance strategies [28,29]. In addition, as has been previously described, our study showed right side index adenomatous polyps were associated with more advanced pathologic grade of recurrent lesions. Based on such findings, right side index adenomatous polyps may require shorter surveillance intervals.

Our study has several limitations, data was collected from a single referral center with high adenoma detection rates which may differ from community-based settings. In addition, index adenoma size and resection technique, potential risk factors for recrudescence of incompletely removed polyps, were not considered. Our study focused on recurrence of adenomatous polyps, which are well known to account for over 90% of CRCs, serrated lesions which may account for the remaining 10% were not included. Prospective studies should ideally include index colonoscopy with short-term repeat colonoscopy after one year to exclude missed lesions, and subsequent colonoscopies at previously planned intervals. Large sized well controlled prospective studies are needed to assess the potential benefits and risks of modification to current post-polypectomy surveillance strategies.

5. CONCLUSION

Colorectal adenomatous polyps are more likely to recur on the same side (right vs. left). Index right side adenomas are associated with more advanced pathologic grade of recurrent lesions. These findings suggest further evaluation of current post-polypectomy screening guidelines based on location of index adenomatous polyp.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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