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Polyp size and advanced histology in patients undergoing colonoscopy screening: Implications for CT Colonography

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Abstract

Background & Aims—Colorectal cancer (CRC) screening with diagnostic imaging can detect polyps. The management of patients whose largest polyp is less than 10mm is uncertain. The primary aim of this study was to determine rates of advanced histology in patients undergoing CRC screening whose largest polyp is 9mm or less.

Methods—Subjects include all asymptomatic adults receiving colonoscopy for screening during 2005 from 17 practice sites, which provide both colonoscopy and pathology reports to the Clinical Outcomes Research Initiative repository. Patients were classified by size of largest polyp. Advanced histology was defined as an adenoma with villous or serrated histology, high-grade dysplasia or an invasive cancer. Risk factors for advanced histology were determined using Pearson chi-square and Fisher's Exact tests.

Results—13,992 asymptomatic patients had screening with colonoscopy; 6360 patients (45%) had polyps, with complete histology available in 5977 (94%). The proportion with advanced histology was 1.7% in the 1–5mm group; 6.6% in the 6–9mm group; 30.6% in the greater than 10mm group; 72.1% in the tumor group. Distal location was associated with advanced histology in the 6–9mm group ($p = 0.04$) and the greater than 10mm group ($p = 0.002$).

Conclusions—One in 15 asymptomatic patients whose largest polyp is 6 to 9mm will have advanced histology and would undergo surveillance at 3 years based on current guidelines. Since histology is necessary for this decision, most of these patients should be offered colonoscopy. Further study should determine if patients whose largest polyp is 1–5mm, can be safely followed without polypectomy.

Keywords

Colonoscopy; colon neoplasia; colorectal cancer

Introduction

New colon screening methods such as computer tomographic colonography (CTC), capsule colonoscopy and self-propelling endoscopes can detect, but not remove polyps. If these devices are used in clinical practice, clinicians will need to make decisions about which patients with polyps should be referred for optical colonoscopy and polypectomy. Currently, the images can estimate polyp size and morphology. There is consensus that patients with one or more polyps

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≥ 10 mm should all be referred for colonoscopy (1). In clinical studies, this will represent 5–10% of patients undergoing screening examinations (2–7). Management decisions for patients with smaller polyps are uncertain, particularly if the largest polyp is 6 to 9mm (1). Recommendations after CTC include offering patients a choice of colonoscopy or repeat CTC in 2–3 years if polyp(s) 6–9mm are detected at CTC. Many radiologists suggest that diminutive polyps (1–5mm) not be reported because polyps of this size fall below the threshold for accurate detection with CTC.

Ideally, decisions to proceed to colonoscopy should be made, based on the likelihood that small polyps (<10mm) will harbor neoplasia likely to progress to malignancy. However, the natural history of polyps is uncertain, because most detected polyps are removed during colonoscopy. However, in surveillance studies after polyps are removed, patients with advanced neoplasia (tubular adenoma ≥ 10 mm, adenoma with villous histology or high-grade dysplasia or invasive cancer) are more likely to develop interval advanced lesions and cancer compared to patients who did not have advanced lesions at baseline colonoscopy (8,9). Current surveillance guidelines (10) call for a shorter interval for surveillance for polyps < 10mm with advanced histology (3 years) compared to those patients who have 1–2 non-advanced adenomas <10mm (5–10 years). Detection and removal of polyps for histologic examination is required to risk-stratify patients for surveillance.

Few studies have been conducted in screening cohorts to examine rates of advanced histology based on the size of the largest polyp. Kim et al (11) reported that only 3% of polyps 6–9mm had advanced histologic features. However, other studies in non-screening cohorts (12–15), have found that polyps which are 6–9mm in size, may have villous histology (4–15%), high-grade dysplasia (4.3–5.8%) or invasive cancer (up to 1.5%). In these studies, patients with 6–9mm polyps may have also had larger polyps, creating potential bias toward finding more advanced lesions.

The likelihood of advanced neoplasia in a patient whose largest polyp is < 10mm remains uncertain in asymptomatic patients undergoing screening. We performed an analysis of colonoscopy outcomes during 2005 from a consortium of 17 practices which participate in the Clinical Outcomes Research Initiative (CORI). The primary aim of the current study was to determine the prevalence of advanced histologic features in polyps removed from asymptomatic patients who were receiving screening with colonoscopy. Patients were divided into groups, based on the size of the largest polyp(s): 1–5mm; 6–9mm; ≥ 10 mm; or description of lesion as a “tumor or mass”. We compared proportions of advanced histologic features in each group. Secondary aims were to determine if there were any risk factors for advanced histology in each patient group.

Methods

Clinical Outcomes Research Initiative (CORI)

During the study period, the CORI consortium included 65 practice sites in 25 states. Participating physicians use a structured, computerized endoscopic report generator to produce their endoscopic reports. The data file from that report is transmitted electronically to a central data repository. Sites were selected based on geographic and practice diversity. 17 practice sites transmit complete histology results to the repository, and represent the study sites for this analysis. These sites represent 24% of colonoscopy reports received during 2005. We compared demographic characteristics and procedure indications to determine if the histology cohort was representative of the CORI consortium. 10 sites contributed more than 500 reports, 6 sites contributed 100–500 reports, and one site contributed less than 100 reports.

Patients

Patients were included in this analysis if they were over age 20, and were undergoing a screening exam and had no other symptoms of lower gastrointestinal (GI) pathology. Three asymptomatic groups were included: average-risk, family history of CRC or adenoma and patients receiving colonoscopy for a positive fecal occult blood test or polyp found at screening sigmoidoscopy. Patients were stratified by indication group. Patients with any other indications for colonoscopy were excluded. Patients were assigned to groups, based on the size of the largest polyp(s) found at colonoscopy: 1–5mm; 6–9mm; ≥ 10 mm; description of “tumor or mass”. Histology for each polyp was reviewed.

Patients were excluded if polyp size was missing or if there was no way to link the histology result to the endoscopy report, such as when a polyp was seen but not removed, or the polyp was removed, but not retrieved. When polyp size was not provided, the patient was excluded.

Analysis

Each group was analyzed to determine the distribution of characteristics, based on the prevalence of advanced histology. The proximal colon was defined as all segments proximal to and including the splenic flexure. For patients with polyp(s) ≥ 10 mm, the proportion of polyps with advanced histology based on polyp size (5mm increments) was determined. Pearson's chi-square test was used to compare proportions. In instances with small cell sizes, Fisher's Exact Test was used for comparison. All analyses were performed using SAS v 9.1 software (SAS Institute, Inc., Cary, NC). A sensitivity analysis was performed to determine the impact of misclassification based on polyp size. In this analysis, we determined the rates of advanced neoplasia if there was a 1mm change in either direction for all polyps

Results

17 practice sites which provided both colonoscopy reports and pathology participated in this study. During 2005, 13,992 asymptomatic patients from these sites had a colonoscopy. Demographic characteristics are described in Table 1. We compared the study cohort to patients from 52 non-study CORI sites who were receiving screening colonoscopy exams to determine if they were representative of the consortium. Age, gender and race were similar. Non-study sites had a slightly lower proportion of non-white minorities compared to the study sites (14.1% vs 15.1%; $p = .003$).

6360 asymptomatic patients had one or more polyps found at colonoscopy and are the subjects of this analysis. 383 patients (6.0%) of patients were excluded because pathology was not available because the polyp was either not removed or not retrieved from the colon. The final groups are described in Table 2. The largest polyp was 1–5mm in 28.5%; 6–9mm in 9.1%; >10 mm in 7.2%; and described as tumor in 0.65%.

The overall rate of any adenoma was 26.0% (3541 of 13,605 patients with available pathology). The rates of advanced neoplasia are shown for each screening indication in Table 1. Among patients with available histology, the proportion with advanced neoplasia was 7.3%. Advanced neoplasia was significantly more common with increasing age ($p < 0.001$), male sex (OR 1.68; 95% CI 1.43, 1.96) and African American race (OR 1.35; 95% CI 1.04, 1.75) and in patients with positive FOBT.

The histology of the most advanced polyp in each patient is presented in Table 3a. Among 3744 patients whose largest polyp was 1–5mm, the polyp histology was neoplastic in 50.2%, and advanced in 1.7%. 1 patient (0.03%) had cancer and one (0.03%) had adenoma with high-grade dysplasia. The remaining patients with advanced histology had adenoma with villous histology or serrated adenoma.

Among 1198 patients whose largest polyp was 6–9mm, histology of most advanced polyp was neoplastic in 67.7%, and advanced in 6.6%. 0.92% had either cancer or adenoma with high-grade dysplasia..

Among 949 patients who largest polyp was ≥ 10 mm, polyp histology was neoplastic in 82.0%, with advanced histology in 30.6%. There was a progressive increase in the proportion of polyps with advanced histology with increasing size above 10mm (Table 3b; per polyp analysis). The proportion of polyps with advanced histology was 18.9% in 10–14mm polyps, 31.7% in polyps 15–19mm, 42.3% in polyps 20–24 mm and 75% in polyps ≥ 25 mm.

86 patients whose lesions were described as "tumors" in the endoscopic report are included for comparison. Advanced histology was found in 72.1%, including cancer (53.5%) and adenoma with high-grade dysplasia (7.0%). Despite the endoscopic description of tumor, 16.3% did not have a neoplastic lesion based on the histologic evaluation.

We performed a sensitivity analysis to determine how misclassification of polyp size would impact the outcome (Table 4). The analysis assumes that polyps were either overestimated in size by 1mm (for example, a 10mm polyp is reclassified as 9mm) or underestimated (a 9mm polyp is reclassified as 10mm). Using these assumptions, the base prevalence of advanced neoplasia in 6–9mm polyps is 6.6%, with a range of 4.6–11.7%. The base prevalence of advanced neoplasia in 1–5mm polyps is 1.7% with a range of 1.2–2.0%.

We examined risk factors associated with advanced histology within each group (Table 5). Age, gender and race were not associated with advanced histology within any of the groups. The prevalence of advanced histology was similar for each of the screening indications. Among patients with polyps ≥ 10 mm, distal location of the polyp was associated with a higher likelihood of advanced histology compared to proximal location ($p < 0.002$). Among patients whose largest polyp was 6–9mm, distal location was associated with a higher likelihood of advanced histology ($p < 0.04$).

Discussion

A primary goal of colorectal cancer screening is the identification and removal of pre-malignant colon polyps, which may lead to cancer prevention (8,16). Patients with neoplasia are enrolled into surveillance, based largely on the size and histology of the lesions. Recommended surveillance intervals are based on these findings (10). With the advent of new diagnostic screening tests which may image, but not remove polyps, clinicians must decide if patients should be referred for colonoscopy with polypectomy. Our study focused on an asymptomatic population receiving screening colonoscopy in diverse practice settings to determine the likelihood that patients would have adenomas with advanced histology. The overall rate for advanced neoplasia was 7.3%. Rates were higher with increasing age, male sex and African American race, and positive FOBT, consistent with other studies.

Patients with polyps ≥ 10 mm represented 7.2% of the screening cohort, consistent with prior studies (2–6). 7.4% had either cancer or adenoma with high-grade dysplasia. 23.2% had adenoma with villous histology or serrated adenoma and 51.4% had tubular adenomas. Our results confirm that there is a progressive increase in the proportion of advanced histologic features with increasing polyp size above 9mm (Table 3b). There is consensus that these patients should all be referred for colonoscopy.

Patients whose largest polyp is 6–9mm represented 9.1% of the screening cohort. This rate is consistent with other studies (2–7) in screening populations. The rate of advanced neoplasia was 6.6%, with variation of 4.6–11.7% in a sensitivity analysis Table 4). Cancer or high-grade dysplasia was found in 0.92%, and villous histology or serrated adenoma in 5.68%. The overall

prevalence of advanced histology is somewhat lower than some prior reports, which included patients with larger polyps and with symptoms (9–12). The natural history of these advanced lesions is uncertain, although it is likely that some will progress to malignancy. There is limited clinical experience with passive observation. Observation and repeat imaging could delay the diagnosis of cancer, which could result in development of a more advanced stage of cancer. If observation with imaging were to be recommended, the appropriate interval for repeat examination remains uncertain. Based on the observed prevalence of advanced histology in our study, approximately 15 patients whose largest polyp is 6 to 9mm would be referred to colonoscopy to identify one with advanced histology who will need more intensive surveillance. In addition, 61% of patients had non-advanced neoplastic polyps (tubular adenomas) and may benefit from polypectomy. In addition, 32.3% of patients whose largest polyp was 6–9mm had non-neoplastic lesions. If CTC was used for follow-up every three years, many of these patients would receive multiple unnecessary imaging studies. New colon screening guidelines now recommend that colonoscopy should be offered to all patients whose largest polyp is 6–9mm on imaging studies ().

Patients whose largest polyp is 1–5 mm represented 28.5% of the screening cohort. In prior studies which include patients with larger polyps, patients with 1 to 5mm polyps had villous histology in 0.7–6.5% or high-grade dysplasia in 1.1–2.3% (9–11). In our study, about 50% of these polyps are non-neoplastic. Few (1.7%) have advanced histology, and in most cases, this was an adenoma with villous histology. Cancer or high-grade dysplasia was rare (0.06%). In these patients, the risk of invasive colonoscopy and polypectomy may exceed the risk of progression to invasive cancer. Further study is needed to help define the natural history of diminutive (1–5mm) adenomas. Based on epidemiologic data, the likelihood of progression is small. If non-invasive imaging accurately detects polyp growth, then periodic imaging could be used to follow patients whose largest polyp is <6mm, and reduce the burden of colonoscopy. If imaging were to be used in this manner, radiologists would need to report the finding of 1–5mm polyps when they are the largest polyp. Further study is needed to determine if this is a rational approach. Some patients may prefer immediate referral to colonoscopy. Finally, we observe that the endoscopic description of “tumor” may not necessarily reflect the presence of cancer. Although most patients had lesions with advanced histology (72.1%), including cancer or high-grade dysplasia in 60.5%, we note that 16.3% did not have neoplastic lesions. Clearly, large hyperplastic polyps and other mucosal lesions such as ischemia, can appear to be malignant at endoscopy.

Rates of advanced neoplasia did vary based on age, gender, race and screening indication as expected (Table 1). However, when patients were stratified based on size of largest polyp, there were no differences in the rates of advanced histology within each size group (Table 5). Therefore, an average-risk patient with a 6–9mm polyp had a similar likelihood of advanced histology as a patient with positive FOBT whose largest polyp was 6 to 9mm.

This study has several limitations. The determination of polyp size was performed by the endoscopist, and prior work has suggested that size estimates may not be accurate (17–20). We performed a sensitivity analysis to account for this uncertainty (Table 4). Histology was performed by local pathologists, and not subject to central review. Prior work has found inter-observer variability among pathologists interpreting polyp histology. Systematic over-reading or under-reading of advanced histology could introduce bias. In our prior studies using central pathology review of local pathology interpretation, we did not detect any systematic bias (2). It is possible that patients had prior screening examinations which could have affected the overall rate of polyps. However, there is no reason to believe that a prior negative screening exam would have an impact on the histology of polyps found on the study examination.

In summary, our analysis of asymptomatic patients undergoing colonoscopy screening in diverse clinical settings, demonstrates that patients whose largest polyp is 1–5mm have a very low risk of advanced neoplasia (1.7%), with only rare cases of cancer or high-grade dysplasia. Most of these patients can be safely observed with periodic imaging, assuming that accurate imaging is available. Our study confirms that patients whose largest polyp is ≥ 10 mm have a high proportion of advanced histology (30.6%). Patients whose largest polyp is 6–9mm have an intermediate risk of advanced histology (6.6%; range 4.6–11.7%) including cancer or high-grade dysplasia in 0.92%. Based on these data, all patients with polyps >10 mm, and most patients whose largest polyp is 6–9mm should receive colonoscopy and polypectomy. This recommendation is now embedded into new colon cancer screening guidelines (21). Based on our data, 15–20% of asymptomatic patients would require colonoscopy after imaging studies. These data have important implications for CTC. If large proportions of patients will require colonoscopy after CTC, patients will need to understand the likelihood of requiring colonoscopy and the possible need for two bowel preparations. Further study is needed to examine the cost-effectiveness of CTC, if 20% of patients will require colonoscopy.

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Table 1

Patient Demographics (n = 13,992)

Age group:	n (%)	% with Advanced Neoplasia*
< 50	1,075 (7.7)	4.8
50–59	6,770 (48.4)	5.5
60–69	3,877 (27.7)	8.6
70–79	1,884 (13.5)	9.2
80+	386 (2.8)	12.4
<u>Gender</u>		
Female	6,594 (47.1)	4.9
Male	7,398 (52.9)	8.9
<u>Race/Ethnicity</u>		
White, non-Hispanic	11,869 (84.8)	7.0
Black, non-Hispanic	1,308 (9.4)	7.3
Asian-PI	375 (2.7)	5.1
Hispanic	322 (2.3)	5.9
Other	102 (0.7)	12.7
Missing	16 (0.1)	6.3
<u>Indication for Screening:</u>		
Average-risk	8,795 (62.9)	5.9
Family history of CRC or Adenoma	3,059 (21.9)	5.7
(+) fecal occult blood test or polyp found at sigmoidoscopy	2,138 (15.3)	13.7

* Advanced neoplasia defined as: tubular adenoma ≥ 10 mm; villous adenoma, adenoma with high-grade dysplasia or invasive cancer.

Table 2

Study Groups

Largest Polyp	Total	Missing Pathology	Final Study Group
1–5mm	3989	245 (6.1%)	3744
6–9mm	1275	77 (6.0%)	1198
≥10mm	1005	56 (5.6%)	949
Tumor	91	5 (5.5%)	86

Table 3**Table 3a: Most advanced Histology by Group**

Histology Category	Groups based on Largest Polyp			Tumor n = 86
	1–5mm n = 3744	6–9mm n = 1198	≥10mm n = 949	
Cancer	1 (0.0)	2 (0.2)	25 (2.6)	46 (53.5)
High-grade dysplasia	1 (0.0)	9 (0.8)	45 (4.7)	6 (7.0)
Villous/Tubulo-villous	44 (1.2)	53 (4.4)	204 (21.5)	10 (11.6)
Serrated Adenoma	17 (0.5)	15 (1.3)	16 (1.7)	0 (0)
Total Advanced Histology	63(1.7%)	79 (6.6%)	290 (30.6%)	62 (72.1%)
Tubular Adenoma	1817 (48.5)	732 (61.1)	488 (51.4)	10 (11.6)
Hyperplastic	1544 (41.2)	334 (27.9)	130 (13.7)	2 (2.3)
Inflammatory	67 (1.8)	12 (1.0)	14 (1.5)	1 (1.2)
Lymphoid aggregate	47 (1.3)	1 (0.1)	3 (0.3)	0 (0)
Non-adenoma/normal	206 (5.5)	40 (3.3)	24 (2.5)	11 (12.8)
Total Non-Neoplastic	1864(49.8%)	387(32.3%)	171(18.0%)	14 (16.3%)

Table 3b: Polyps ≥10mm: Most advanced Histology– Per Polyp Analysis (n=1241 polyps)

Histology Category	Groups based on Polyp Size			
	10–14mm n = 764 n (%)	15–20mm n = 199 n (%)	20–24mm n = 111 n (%)	≥25mm n = 80 n (%)
Cancer	12 (1.6)	4 (2.0)	1 (0.9)	8 (10.0)
High-grade dysplasia	17 (2.2)	11 (5.5)	9 (8.1)	10 (12.5)
Villous/Tubulo-villous	103 (13.5)	45 (22.6)	35 (31.5)	41 (51.3)
Serrated Adenoma	12 (1.6)	3 (1.5)	2 (1.8)	1 (1.3)
Total Advanced Histology	144 (18.9%)	63 (31.7%)	47 (42.3%)	60 (75.0%)
Tubular Adenoma	442 (57.9)	103 (51.8)	54 (48.7)	20 (25.00)
Hyperplastic	146 (19.1)	22 (11.1)	7 (6.3)	0 (0)
Inflammatory	12 (1.6)	3 (1.5)	1 (0.9)	0 (0)
Lymphoid aggregate	2 (0.3)	2 (1.0)	0 (0)	0 (0)
Non-adenoma/normal	18 (2.4)	6 (3.0)	2 (1.8)	0 (0)
Total Non-Neoplastic	178 (23.3%)	33 (16.6%)	10 (9.0%)	0

Table 4**Prevalence of Advanced Neoplasia – Sensitivity Analysis**

Group	Original Analysis	Overestimate (10mm now 9mm; 6mm now 5mm)	Underestimate (9mm now 10mm; 5mm now 6mm)
	N / total group N (%)	N / total group N (%)	N / total group N (%)
<6mm	63 / 3744 1.7 %	83 / 4213 2.0 %	34 / 2774 1.2 %
6 – 9mm	79 / 1198 6.6 %	132 / 1131 11.7 %	96 / 2074 4.6 %
> 9mm	290 / 949 30.6 %	218 / 545 40.0 %	301 / 1032 29.2 %
Tumor	62 / 86 72.1 %	62 / 86 72.1 %	62 / 86 72.1 %

Table 5
Risk Factors for Advanced Neoplasia; Groups stratified by size of largest polyp

	1-5mm n	Adv-Hist %	6-9mm n	Adv-Hist %	≥10mm n	Adv-Hist %	Tumor n	Adv-Hist %
Age								
<50	255	1.2	73	5.5	54	31.5	3	66.7
50-59	1800	1.5	542	5.7	397	30.0	23	56.5
60-69	1090	1.5	343	8.2	311	29.9	31	74.2
70-79	504	2.8	198	6.6	150	32.7	19	89.5
80+	95	3.2	42	7.1	37	32.4	10	70.0
p-value	.20		.70		.97		.18*	
Gender								
Female	1544	1.5	458	5.7	314	34.4	34	67.7
Male	2200	1.8	740	7.2	635	28.7	52	75.0
p-value	.44		.31		.07		.46	
Race								
White	3260	1.8	1049	6.6	799	30.3	75	73.3
Black	292	1.4	80	5.0	99	32.3	11	63.6
Hispanic	73	1.4	21	4.8	20	55.0	0	0
p-value	.85		.82		.06		.49*	
Location of largest polyp								
Distal	1985	1.6	580	8.4	522	33.9	38	86.8
Proximal	1376	2.1	558	5.0	383	28.2	48	60.4
Both Distal and Proximal	380	0.5	58	3.4	41	9.8	0	0
p-value	0.10		0.04		0.002		0.007	
Screening Indication								
Average-risk	2333	1.6	732	5.7	517	31.0	38	60.5
Family history	813	1.4	257	8.2	159	30.2	16	81.3
(+) FOBT/polyp SIG	598	2.3	209	7.7	273	30.0	32	81.3
p-value	.34		.32		.96		.10	

* Fisher's Exact test used to calculate p-value due to small cell sizes