Characteristics of Advanced Adenomas Detected at CT Colonographic Screening: Implications for Appropriate Polyp Size Thresholds for Polypectomy Versus Surveillance

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OBJECTIVE. Advanced adenomas are the primary target in colorectal screening. The purpose of this study was to delineate the prevalence and imaging characteristics of advanced adenomas detected at screening CT colonography (CTC) and the rates of invasive carcinoma and high-grade dysplasia for various polyp size categories. These observations may be a basis for formulation of polypectomy thresholds and CTC surveillance strategies.

MATERIALS AND METHODS. The imaging and pathologic findings for polyps measuring 6 mm or more obtained from a CTC screening population of 3,536 persons during a 32-month period were retrospectively reviewed. From this group, prevalence, size, histologic features, morphologic features, and location of advanced adenomas were tabulated. Advanced adenomas were defined by size (≥ 10 mm) and/or histologic findings (prominent villous component or high-grade dysplasia).

RESULTS. A total of 123 (38.3%) of 321 adenomas measuring 6 mm or more were classified as advanced, the overall prevalence being 3.1% (111 of 3,536 patients). The mean size of advanced adenomas was 16.6 ± 11.6 mm; most of the lesions (116/123, 94.3%) qualified as advanced on the basis of the size criterion alone. The seven lesions measuring 6–9 mm constituted 3.4% (7/205) of all medium-sized adenomas. The largest percentage (65/123, 52.8%) of the advanced adenomas had tubular histologic features, followed by tubulovillous (50/123, 40.6%), villous (5/123, 4.1%), and serrated (3/123, 2.4%) histologic features. High-grade dysplasia was uncommon (6/123, 4.9%), typically occurring in large lesions. Seven cases of cancer were detected, all lesions measuring 10 mm or more in size. The majority of advanced adenomas were classified as sessile (57/123, 46.3%) or pedunculated (57/123, 46.3%); a small percentage were flat (9/123, 7.3%). Advanced adenomas were located in the proximal colon in 43.9% (54/123) and distal colon in 56.1% (69/123) of the cases.

CONCLUSION. Advanced adenomas were generally large (≥ 10 mm in size); only a small percentage were medium sized (6–9 mm). There was a very low prevalence of high-grade dysplasia and invasive carcinoma in this series, particularly in the medium-sized group of lesions. These findings lend support to the practice of CTC screening in which large polyp size is used as a surrogate measure for the possible presence of advanced histologic features and medium-sized lesions are followed with noninvasive surveillance protocols.

Keywords: CT colonography, screening

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The advanced adenoma is an important concept in screening for colorectal carcinoma. It is defined as an adenoma that measures 10 mm or more in size, contains a substantial villous component, or exhibits high-grade dysplasia [1, 2]. The importance of an advanced adenoma is underscored by the fact that it represents the small subpopulation of adenomas considered most likely to progress to carcinoma. Progression typically occurs over many years with successive accumulation of genetic abnormalities. With detection and removal of advanced adenomas in the majority of the screening population, the incidence of colorectal carcinoma could be dramatically reduced. The purpose of this study was to delineate the prevalence and imaging characteristics of advanced adenomas detected at screening CT colonography (CTC) and the rates of invasive carcinoma and high-grade dysplasia for the various size categories of polyps. These observations may be a basis for formulation of polypectomy thresholds and CTC surveillance strategies.

Materials and Methods

Study Design

Retrospective review of the CTC databases encompassing the colorectal screening experience of four institutions was undertaken. Each institution functioned under an institutional review board–approved protocol governing the CTC program. The combined database comprises 3,536 patients who underwent imaging over a 32-month period. Most of the patients had no symptoms, were at average risk for colorectal cancer, and were referred for routine screening. Fewer than 3% of the patients reported concerning signs or symptoms, such as heme-positive stool, change in bowel habits, weight loss, or anemia. Average risk was defined as no history of adenomatous polyps, colorectal cancer, inflammatory bowel disease, or polyposis syndromes and a negative family history (first-degree relatives) [3]. Patient demographic characteristics of age and sex were compiled.

Records of all pathologically proven adenomas measuring 6 mm or more were extracted from the database. From this group, advanced adenomas—defined as any adenoma measuring 10 mm or more, containing a substantial (> 25%) villous component, or exhibiting high-grade dysplasia [1, 2]—were identified. Polyp characteristics of histologic features (tubular, tubulovillous, or villous), morphologic features (sessile, pedunculated, or flat), and anatomic location (proximal or distal with respect to the splenic flexure) were tabulated for all advanced adenomas. The presence of high-grade dysplasia and invasive carcinoma was recorded. For the purposes of this study, large polyps were defined as lesions measuring 10 mm or more and medium-sized polyps were defined as lesions measuring 6–9 mm in greatest dimension. Sessile lesions were defined as polypoid structures with a broad base of attachment, and pedunculated lesions as polyps with a defined stalk. Flat lesions were defined as a subset of sessile lesions with a plaquelike appearance and a height generally much less than half of the base (typically raised < 3 mm from the colonic mucosa) [4]. There was a subjective component to the morphologic classification of polyps.

A group of 112 patients with 120 medium-sized (6–9 mm) polyps with unknown histologic features were excluded from analysis. These patients were enrolled in a CTC surveillance arm of an institutional review board–approved protocol offered at a single institution. Three of the four institutions used a universal polypectomy strategy whereby all detected polyps, including all 6- to 9-mm polyps, were endoscopically removed.

CT Colonography Protocol

Each patient was limited to a liquid diet beginning 1 day before the scheduled morning CTC examination. Colonic catharsis was achieved with sodium phosphate (one or two 45-mL doses). Magnesium citrate or, in rare instances, polyethylene glycol was substituted for patients with renal or cardiac insufficiency. The patients ingested 250–500 mL of a dilute 2% barium mixture to tag residual stool and 60–120 mL of water-soluble iodinated contrast medium to tag residual fluid. On the morning of the examination, the colon was distended with gas immediately before imaging. Colonic distention was achieved either by patient-controlled insufflation with room air or by automated CO_2 delivery (ProtoCO_2L, E-Z-EM). Examinations were performed in both supine and prone positions on a 4-, 8-, or 16-MDCT scanner (LightSpeed series, GE Healthcare). CT technique consisted of 1.25- to 2.50-mm collimation, 1-mm reconstruction interval, 120 kVp, and 25–100 mAs. The DICOM CT images were sent to a dedicated CTC workstation for postprocessing and interpretation. All studies were interpreted on the day of the examination by radiologists experienced in CTC.

For detected polyps measuring 6 mm or more, the typical protocol for measurement included evaluation of both the 3D endoluminal view and the 2D multiplanar reformation view that best paralleled the long axis of the polyp. The multiple measurements were taken into account, and a final value was assigned that corresponded with the radiologist's best estimation of the true value [5]. For pedunculated polyps, the long axis of the polyp head was measured with exclusion of the polyp stalk.

Results

The mean age of all 3,536 patients was 57.3 ± 7.7 years; 50.3% (1,777/3,536) of the patients were men, and 49.7% (1,759/3,536) were women. A total of 321 adenomas 6 mm or larger were identified from the combined database (116 adenomas measuring ≥ 10 mm and 205 adenomas measuring 6–9 mm). From this group, 123 adenomas from 111 patients, constituting 38.3% of all pathologically proven adenomas measuring 6 mm or larger, met the criteria for advanced pathology (Fig. 1).

The mean size of advanced adenomas was 16.6 ± 11.6 mm. Most (94.3%, 116/123) of these lesions qualified as advanced according to the size criterion alone. Of the seven medium-sized advanced adenomas (in five patients), six qualified by the presence of a prominent villous component (tubulovillous or villous histology) and only one by the presence of high-grade dysplasia. Medium-sized (6–9 mm) advanced lesions constituted 5.7% (7/123) of the advanced adenomas seen. The mean age of patients with advanced adenoma was 60.1 ± 10.3 years, which was statistically significantly greater than that of the screening population as a whole ($p < 0.005$). Men were at significantly increased risk of harboring advanced adenoma compared with women, comprising 62.1% (69/111) of cases ($p < 0.01$).

A total of 205 pathologically proven adenomas measured 6–9 mm and thus were in the medium size category. An additional 120 polyps were of similar size but unknown histologic features, and all of the patients were enrolled within a surveillance arm at a single institution. This institution also accounted for 64 of the 205 endoscopically resected adenomas and two of the seven medium-sized advanced adenomas. Therefore, the advanced adenoma rate for 6- to 9-mm adenomas at the other three centers was 3.5% (five of 141), similar to that for resected 6- to 9-mm adenomas at the center with the surveillance arm (3.1%, 2/64). There was one case of high-grade dyplasia, and there were no cases of invasive carcinoma from these 205 6- to 9-mm adenomas. Because approximately 60% (72), of the 120 unresected 6- to 9-mm lesions would be expected to be adenomatous [6], we would anticipate that perhaps two or three would harbor advanced histology based on the data from the resected lesions.

The estimated prevalence of advanced adenoma in this largely healthy screening population was 3.1% (111/3,536), which would not be noticeably altered by inclusion of the two or three expected additional cases from the 6- to 9-mm surveillance group. The prevalence of large (≥ 10 mm) advanced adenoma was 3.0% (106/3,536), and the prevalence of medium-sized (6–9 mm) advanced lesions was 0.1% (5/3,536). Medium-sized advanced adenomas constituted 3.4% (7/205) of all pathologically proven medium-sized adenomas from this cohort. Seven cases of cancer were detected, all in lesions larger than 10 mm, giving a prevalence of 0.2% (7/3,536). No malignant polyps were found among 6- to 9-mm adenomas. The prevalence of high-grade dysplasia was 0.17% (6/3,536), five of six lesions measuring 10 mm or more and only one lesion in the 6–9 mm category.

Most of the advanced adenomas had tubular (65/123, 52.8%) or tubulovillous (50/123, 40.6%) histologic features. Only a small percentage (5/123, 4.1%) had a purely villous nature. A small percentage (3/123, 2.4%) of advanced adenomas were classified as serrated. Most of the lesions were classified as sessile (57/123, 46.3%) or pedunculated (57/123, 46.3%). A small percentage (9/123, 7.3%) of advanced adenomas were flat; none of the flat

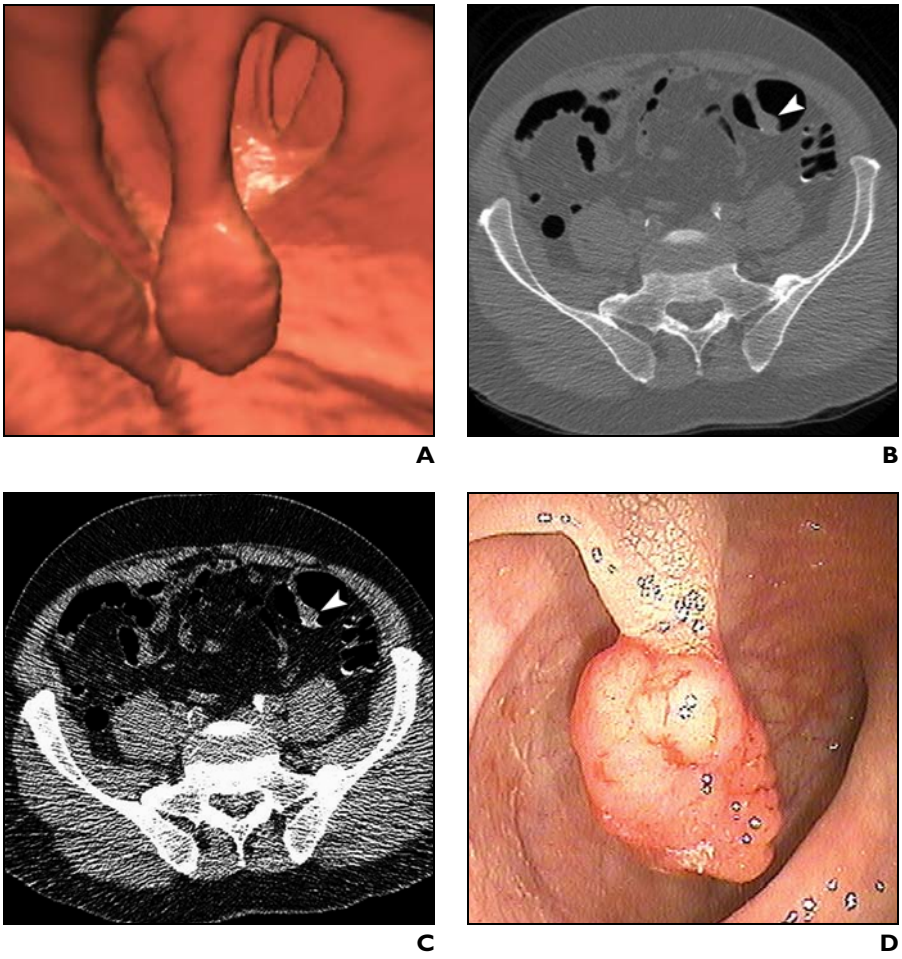

Fig. 1—63-year-old man at average risk who underwent screening CT colonography (CTC).
A, Endoluminal 3D colonographic image shows large (22-mm) pedunculated polyp in sigmoid colon. In general, large polyps are readily detected on CTC.
B, Transverse 2D image with CTC polyp windows shows large polyp (*arrowhead*).
C, Transverse CTC image with standard abdominal windows shows soft-tissue composition of sigmoid polyp (*arrowhead*).
D, Digital photograph from same-day optical colonoscopy shows polyp before endoscopic resection. Pathologic evaluation revealed advanced adenoma characterized by tubulovillous histologic features without high-grade dysplasia or malignant focus.

advanced lesions exhibited high-grade dysplasia. Two of the seven carcinomas were characterized as relatively flat, but these tumors were very large at 42 and 60 mm. With respect to anatomic location, 54 (43.9%) of the 123 advanced adenomas were found proximal to the splenic flexure, and 69 (56.1%) were in the distal colon.

Discussion

Colorectal carcinoma accounts for approximately 55,000 deaths per year in the United States yet is largely preventable through effective routine screening [7]. Most carcinomas are believed to arise over several years from adenomas that undergo a series of specific genetic perturbations [8]. Removal of adenomas has been shown to significantly decrease the expected incidence of colorectal carcinoma [9].

The current colonoscopic approach to screening for colorectal carcinoma involves removal of all polyps seen at optical colonoscopy with the true purpose of removing an adenoma. However, an all-inclusive approach to colorectal polypectomy is rather inefficient and leads to a large number of polypectomies. Not only are a large proportion of subcentimeter polyps nonadenomatous nonneoplastic lesions with no malignant potential [6], but also small tubular adenomas themselves represent a very dilute marker for colorectal carcinoma. It is well accepted [1, 2, 10–12] that most adenomas never transform to carcinoma. Prevalence data alone point to this fact: Adenoma prevalence in the United States ranges from 25% to 47% among persons 50 years old and older at average risk, yet the incidence of new carcinoma cases is only approximately 150,000 among approximately 80 million adults over this age cutoff [7, 8, 13].

Advanced adenomas are believed to represent the small subpopulation of adenomas at risk for carcinoma development and thus represent a focused target for cancer prevention. In this study, we examined the prevalence and characteristics of advanced adenomas detected in a large screening CTC population to determine whether certain imaging features and strategies exist to better filter this precursor target from the larger population of colorectal polyps.

Advanced adenomas constituted nearly 40% of adenomas 6 mm or larger in our series, for an overall prevalence of approximately 3%. Large polyp size (mean size, > 1.5 cm) was the defining characteristic for advanced adenomas in our screening population. It is important to note that nearly 95% of advanced adenomas in our series met the criteria for advanced status on the size criterion alone. Of the seven advanced lesions of medium size (6–9 mm), only one lesion exhibited high-grade dysplasia, and none exhibited malignancy. Overall, the prevalence for both high-grade dysplasia and invasive carcinoma was very low at 1.7 and 2.0 individuals, respectively, per 1,000 patients screened. Again, the size criterion alone would identify all such cases with the one exception of a medium-sized polyp with high-grade dysplasia, representing a negative predictive value well over 99%.

The prevalence and rates of advanced adenoma as well as high-grade dysplasia and carcinoma in our series were a marked departure from the results in other series, which have shown a much higher presence of advanced adenoma, high-grade dysplasia, and invasive carcinoma in both medium and large polyp categories [14–17]. We believe these differences largely involve differences in patient population characteristics and differences in definitions of polyp categories. Older optical colonoscopy and surgical series typically comprised older patients with symptoms [14, 15], factors shown to increase adenoma prevalence and the finding of risk of significant dysplasia [18]. More recent studies [16, 17] also have not represented true screening populations. In addition, polyp definitions in the more recent studies differ when 10-mm le-

sions are included in the small and medium category. These lesions would be in the large category in our series. Not all other series have demonstrated high cancer rates. Odom et al. [19] reported an invasive carcinoma rate of 0.07% for subcentimeter adenomas and 2.4% for 1- to 2-cm adenomas in a large asymptomatic screening series (n = 4,443 polyps), mirroring our results.

It can be argued that the low rates found in our series are spuriously low because of the group of 120 medium polyps with unknown histologic features that were excluded from analysis. Although the presence of this unknown-histologic-feature group is a limitation of our study that unfortunately could not be avoided, we believe that the stated prevalence rates are representative of this series. Three of the four institutions used a universal polypectomy practice resulting in removal of all of the 6- to 9-mm polyps. The 120 medium polyps with unknown histologic features are part of a surveillance protocol conducted at a single institution. If we extrapolate the rates from results of the resected 6- to 9-mm polyps, the number of additional advanced adenomas in the follow-up group is likely small, perhaps two or three additional lesions. Even in the unlikely worst-case scenario in which all 120 polyps are adenomas, we would expect approximately four or five additional advanced adenomas (3.5% of 120 polyps). The overall rate of advanced adenomas in the medium size group in our series would then be 3.7% (12/325), and the worst-case prevalence would be 3.3% (116/3,536). Similarly, there could conceivably be one additional adenoma with high-grade dysplasia, giving a rate of 0.6% (2/325) for medium-sized adenomas. Even in this proposed worst-case scenario, these rates and prevalences are much lower than reported in most other series. It is likely that these numbers would actually be lower because a significant proportion of the 120 polyps would be nonadenomatous lesions or false-positive CTC findings [6].

Results for this series indicate that size appears to be a valid surrogate marker for identifying advanced adenomas because the majority of these lesions measured 10 mm or more. If a 10-mm threshold for optical colonoscopic referral for polypectomy were used, a small minority of at-risk 6- to 9-mm adenomas would be missed. However, the feasibility of surveillance strategies to capture these smaller advanced adenomas increases given the low presence of invasive carcinoma (and high-grade dyplasia) in this group. The low prevalence of malignancy in 6- to 9-mm lesions in our series suggests that advanced adenomas can grow and cross the 10-mm threshold before malignant transformation occurs. Although the natural history of medium-sized adenomas is not known, it can be argued that these adenomas can be observed safely with CTC given the available data from barium enema and endoscopic surveillance [11, 20]. The benefits of such strategies for identifying a more efficient precursor target would likely include a significant decrease in the number of optical colonoscopic studies and polypectomies, which may translate into a decreased rate of complications and lower costs.

Other than size, the imaging characteristics of advanced adenoma examined in this series did not allow delineation of advanced adenoma from other polyps. The findings, however, do support the notion of CTC screening. For example, most advanced adenomas were sessile or pedunculated, only a small percentage appearing flat. Although we have not found flat polyps to be a substantial limitation in CTC screening in our population [4], these lesions are generally difficult to detect with any imaging technique. There were no instances of subcentimeter flat lesions with high-grade dysplasia or invasive carcinoma among this large cohort. Two adenocarcinomas were characterized as relatively flat, but these lesions were obvious large lesions measuring 42 and 60 mm. With regard to anatomic location, that nearly one half of all advanced adenomas were proximal to the splenic flexure is an argument for performing total colonic examination rather than flexible sigmoidoscopy. Not unexpectedly, the mean age of patients with advanced adenoma was greater than that of the screening population as a whole. This finding correlates with National Polyp Study [18] data showing advanced patient age, increased adenoma size, and villous histologic features were predictive of the presence of high-grade dyplasia.

The advent of effective colorectal cancer screening with CTC allows a less invasive, accurate evaluation of the entire colon [3, 21, 22]. CTC with state-of-the-art technique, including 3D polyp detection and tagging with oral contrast agents, has been shown to be as effective as optical colonoscopy in the detection of advanced neoplasia, which manifests predominately as large polyps and masses [3, 23]. Along with optical colonoscopy, CTC should increase the current dismal rates of compliance with colorectal screening [24]. In addition, screening with CTC may ultimately liberate optical colonoscopy screening resources for more polypectomy procedures. By focusing on detection and removal of large lesions, optical colonoscopy could be used more effectively as a therapeutic procedure.

In conclusion, advanced adenomas constitute a relatively small proportion of colorectal adenomas in a screening population, the overall prevalence being approximately 3%. These target lesions are generally large, measuring 10 mm or more in size. Only a small minority of advanced adenomas are in the medium size range (6–9 mm), with a very low prevalence of high-grade dysplasia or invasive carcinoma. The observations in this asymptomatic screening population lend support to the practice of CTC screening in which large polyp size is used as a surrogate measure for possible advanced histologic features and medium-sized lesions are followed with noninvasive surveillance protocols.

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