Longitudinal Ultrasound Assessment of Changes in Size and Number of Incidentally Detected Gallbladder Polyps

Andrew J. Walsh, MD, PhD[1], David B. Bingham, MD[2], Aya Kamaya, MD[1]

Gastrointestinal Imaging · Original Research

AJR JOURNAL CLUB

The Study Guide accompanying this Journal Club article can be found after the article's last page.

Keywords

cholesterol polyp, gallbladder polyp, intracholecystic papillary-tubular neoplasm, polyp growth, surveillance ultrasound

Submitted: Jul 21, 2021
Revision requested: Aug 5, 2021
Revision received: Aug 30, 2021
Accepted: Sep 14, 2021
First published online: Sep 22, 2021

The authors declare that they have no disclosures relevant to the subject matter of this article.

BACKGROUND. Previous European multisociety guidelines recommend routine follow-up imaging of gallbladder polyps (including polyps < 6 mm in patients without risk factors) and cholecystectomy for polyp size changes of 2 mm or more.

OBJECTIVE. The purpose of this study was to assess longitudinal changes in the number and size of gallbladder polyps on serial ultrasound examinations.

METHODS. This retrospective study included patients who underwent at least one ultrasound examination between January 1, 2010, and December 31, 2020 (as part of a hepatocellular carcinoma screening and surveillance program) that showed a gallbladder polyp. Number of polyps and size of largest polyp were recorded based primarily on review of examination reports. Longitudinal changes on serial examinations were summarized. Pathologic findings from cholecystectomy were reviewed.

RESULTS. Among 9683 patients, 759 (8%) had at least one ultrasound examination showing a polyp. Of these, 434 patients (248 men, 186 women; mean age, 50.6 years) had multiple examinations (range, 2–19 examinations; mean, 4.8 examinations per patient; mean interval between first and last examinations, 3.6 ± 3.1 [SD] years; maximum interval, 11.0 years). Among these 434 patients, 257 had one polyp, 40 had two polyps, and 137 had more than two polyps. Polyp size was 6 mm or less in 368 patients, 7–9 mm in 52 patients, and 10 mm or more in 14 patients. Number of polyps increased in 9% of patients, decreased in 14%, both increased and decreased on serial examinations in 22%, and showed no change in 55%. Polyp size increased in 10% of patients, decreased in 16%, both increased and decreased on serial examinations in 18%, and showed no change in 56%. In 9% of patients, gallbladder polyps were not detected on follow-up imaging; in 6% of patients, gallbladder polyps were not detected on a follow-up examination but were then detected on later studies. No gallbladder carcinoma was identified in 19 patients who underwent cholecystectomy.

CONCLUSION. Gallbladder polyps fluctuate in size, number, and visibility over serial examinations. Using a 2-mm threshold for growth, 10% increased in size. No carcinoma was identified.

CLINICAL IMPACT. European multisociety guidelines that propose surveillance of essentially all polyps and a 2-mm size change as the basis for cholecystectomy are likely too conservative for clinical application.

Gallbladder polyps are a common incidental finding that are estimated to occur in approximately 4–12% of the population [1–3]. Gallbladder polyps may be neoplastic or nonneoplastic, though the vast majority are nonneoplastic cholesterol polyps. A small subset of sonographically detected polyps are intracholecystic papillary-tubular neoplasms, which include adenomatous polyps and are considered neoplastic despite typically not harboring true malignancy [4]. The adenoma-carcinoma pathway of adenomatous gallbladder polyps is unclear compared with the colonic polyp pathway [5], yet all such polyps are presumed to have a theoretic risk of malignancy. The exact risk is uncertain but likely low, leading to controversy in the management of sonographically detected polyps. Indeed, gallbladder polyps are relatively common, whereas gallbladder carcinoma is relatively rare, with an incidence of only 1.5–12.8 per 100,000 [6]. Further, most gallbladder carcinomas do not arise from adenomatous polyps, as only approximately 6% of gallbladder carcinomas are associated with neoplastic polyps [4]. Given the relative rarity and unclear nature of the development of gallbladder carcinoma, it is difficult to prospectively

[1]Stanford Hospital and Clinics, 300 Pasteur Dr, H1307, Stanford, CA 94305. Address correspondence to A. Kamaya (kamaya@stanford.edu).

[2]Department of Pathology, Stanford Hospital and Clinics, Stanford, CA.

doi.org/10.2214/AJR.21.26614
AJR 2022; 218:472–483
ISSN-L 0361–803X/22/2183–472

study gallbladder polyps and determine appropriate clinical follow-up regimens.

Gallbladder polyps that measure 6 mm or less have historically been considered highly likely to be benign, and the American College of Radiology (ACR) in 2013 [7] and the Canadian Association of Radiologists (CAR) in 2020 [8] recommended no follow-up for such polyps. Both the ACR and CAR recommend yearly follow-up for polyps that measure 7–9 mm, though neither set of recommendations define thresholds regarding growth. However, a joint statement by four major European societies in 2017 recommended that polyps smaller than 6 mm in patients with no risk factors undergo 5 years of follow-up with imaging at 1, 3, and 5 years, whereas polyps smaller than 6 mm in patients with risk factors (including age > 50 years, primary sclerosing cholangitis, Indian ethnicity, or sessile polyp configuration) undergo 5 years of follow-up with imaging at 6 months and at 1, 2, 3, 4, and 5 years. In this statement, growth of 2 mm or more and size of 10 mm or greater are defined as thresholds for a surgical resection recommendation [9]. The time period during which the 2 mm of growth must occur is not defined in this statement. Management of incidentally detected gallbladder polyps is thus uncertain given the conflicting society management recommendations, particularly for incidental polyps measuring 6 mm or less. Further, the benefit of surveillance in the large population of patients with small gallbladder polyps has yet to be proven.

The purpose of this study was to assess longitudinal changes in the number and size of gallbladder polyps in patients undergoing serial ultrasound examinations for hepatocellular carcinoma (HCC) screening and surveillance and to correlate such changes with pathologic findings from cholecystectomy. The periodic repeat ultrasound examinations in these patients provides an opportunity to observe the natural history of gallbladder polyps, including those measuring 6 mm or less.

Methods

Study Design

This HIPAA-compliant retrospective study was approved by the institutional review board; informed consent was waived. Patients who underwent at least one ultrasound examination between January 1, 2010, and December 31, 2020, as part of the HCC screening and surveillance program at Stanford University Medical Center were identified. Of these patients, a database search was conducted for ultrasound reports containing the phrase "gallbladder polyp" or "gallbladder polyps," providing the initial set of ultrasound reports for subsequent manual review.

Ultrasound Examinations

Examinations were performed using a GE Logiq E9 or E10 (GE Healthcare), Acuson S2000 (Siemens Healthineers), or Aplio i900 (Canon Medical Systems) ultrasound machine. Each examination was performed by a sonographer certified by the American Registry for Diagnostic Medical Sonography and checked at the time of the examination by one of a group of 16 board-certified radiologists specializing in abdominal radiology (with experience ranging 2–40 years). Patients were instructed to fast for 6 hours before the examination to minimize bowel gas, which may negatively affect visualization of intraabdominal contents.

HIGHLIGHTS

Key Finding

- *Among 434 patients with incidental gallbladder polyps who underwent serial ultrasound examinations for HCC surveillance (range, 2–19 examinations; mean interval between first and last examinations, 3.6 ± 3.1 years), polyps fluctuated (i.e., increased and decreased on serial examinations) in number and size in 22% and 18% of patients, respectively.*

Importance

- *Previous European multisociety guidelines that propose routine polyp surveillance with 2-mm size change as the basis for cholecystectomy are likely too conservative for clinical application.*

Images of the gallbladder were obtained with gray scale in transverse and longitudinal views using an intercostal or subcostal approach and with curved-array, vector, or linear transducers with frequency ranging between 3.5 and 11 MHz. Sonographers and radiologists at our institution deem any protuberance from the endoluminal surface of the gallbladder wall that is nonmobile and nonshadowing to represent a gallbladder polyp. Further, color Doppler evaluation of gallbladder findings is used at the discretion of the sonographer but is typically performed for any detected abnormality, including gallbladder polyps. A description of polyp vascularity in the report is at the discretion of the interpreting radiologist but is typically included if present. Internal vascularity is not required for the sonographic diagnosis of a gallbladder polyp because many polyps lack detectable vascularity. Examinations include assessment of abnormalities reported on prior studies, even if the current examination is obtained for another reason. Standard institutional practice is to obtain cine images of any detected abnormalities, including cine images documenting resolution of previously reported abnormalities (e.g., resolution of a previously reported gallbladder polyp in an ultrasound examination being performed for HCC screening or surveillance).

Examination Analysis

An abdominal imaging fellow (A.J.W.) manually reviewed the ultrasound reports from the previously described search to confirm that the reports described the presence of a gallbladder polyp. For reports with a polyp, the investigator reviewed the report to determine the number and size of gallbladder polyps. The number of polyps was recorded as zero, one, two, or more than two. If the report did not indicate the number of polyps but rather described the polyps as multiple (or used a similar expression), then the number of polyps was recorded as more than two. Polyp size was defined as the largest single dimension of the polyp in the report. If multiple polyps were identified, then the size of the largest polyp was recorded. If the presence, number, or size of polyps was ambiguous or if it was uncertain whether the serial studies measured the same polyp, then the images were retrospectively reviewed by the investigator, and polyp size was measured manually on an independent PACS workstation (Sectra AB).

Patients were excluded if no gallbladder polyps were shown in at least one ultrasound examination after a review of reports and retrospective review of images for ambiguous reports.

Reports for patients with more than one ultrasound examination were assessed to determine whether the number of reported polyps changed on serial examinations and to categorize the largest reported polyp as showing one of the following four courses: an increase in size on at least one examination (without a size decrease), a decrease in size on at least one examination (without a size increase), both an increase in size on at least one examination and a decrease in size on at least one examination, or no change in size. An increase or decrease in size was defined as a change in the measured maximum polyp size of 2 mm or more. Additionally, reports were reviewed to determine whether the previously reported polyp was reported on a subsequent examination and, if it was not reported, whether the polyp remained unreported or was again reported on a later examination.

Pathologic and Clinical Follow-Up

Patients who underwent cholecystectomy were identified through review of the electronic medical record system. Indications for cholecystectomy were recorded. The pathology reports were reviewed to determine whether a polyp (either cholesterol polyp or intracholecystic papillary-tubular neoplasm) corresponding to the sonographically detected polyp was described pathologically and, if so, whether the polyp was malignant based on the pathology report. Pathology slides were not rereviewed for this assessment. In addition, electronic medical records were reviewed to identify clinical outcomes in patients with a polyp size of 10 mm or more.

Statistical Analysis

Data were presented using summary statistics, including the mean ± SD for continuous variables and counts and percentages for categoric variables. Polyp size and number were summarized at the patient level; in patients with multiple examinations, the ultrasound examination that showed the largest polyp was used for polyp size and the first ultrasound examination was used for polyp number. Change in number, change in size (among the four previously noted courses), additional events regarding nonvisualization, and mean change in size (computed for polyps showing an increase, decrease, or both increase and decrease in size on serial studies) were calculated for all polyps and for polyps measuring 6 mm or less, 7–9 mm, and 10 mm or more using the ultrasound examination that showed the largest polyp size. These outcomes were compared among the three polyp size groups using the chi-square test for categoric variables and one-way ANOVA for continuous variables. The polyp size thresholds were based on the 2013 ACR white paper on managing incidental gallbladder and biliary findings [7]. Values of $p < .05$ were considered statistically significant. Statistical analysis was performed using Excel for Mac (version 16.6.7, Microsoft).

Results

Patient and Polyp Characteristics

During the study period, 9683 patients in the HCC screening and surveillance program underwent at least one ultrasound examination. The database search identified 783 patients with at least one report that commented on a gallbladder polyp. Of these patients, 24 were excluded because the report was ambiguous, and subsequent manual review of the images identified no polyp. This exclusion resulted in a final study cohort of 759 patients who had at least one gallbladder polyp identified on at least one ultrasound examination (8% of the patients in the HCC screening and surveillance program who underwent at least one ultrasound examination). HCC risk factors for inclusion in the ultrasound screening and surveillance program among these 759 patients with at least one polyp included chronic hepatitis B (506 patients), chronic hepatitis C with stage III fibrosis or cirrhosis (170 patients), nonalcoholic steatohepatitis and/or nonalcoholic steatohepatitis–induced cirrhosis (21 patients), alcoholic cirrhosis (16 patients), and other causes of cirrhosis (46 patients).

A total of 325 patients had only one ultrasound examination, and 434 patients had multiple examinations (Fig. 1). The mean number of examinations among the 434 patients with more than one examination was 4.8 (range, 2–19; two examinations in 156 patients, three or more examinations in 278 patients; total of 2069 examinations in these 434 patients). The mean time between the first and last examinations in patients with multiple examinations was 3.6 ± 3.1 years, and the maximum time was 11.0 years.

Among the 759 patients with at least one ultrasound examination, 434 were men, and 325 were women; the mean age was 51.5 ± 13.2 years. Among the 434 patients with multiple ultrasound examinations, 248 were men, and 186 were women; the mean age was 50.6 ± 13.0 years.

Of the 759 patients, 466 (61%) had one polyp, 83 (11%) had two polyps, and 210 (28%) had more than two polyps (based on the first ultrasound in those with multiple examinations). In these 759 patients, the mean size of the largest polyp was 5 ± 2 mm, with a maximum size of 19 mm; 670 (88%) patients had a largest polyp size of 6 mm or less, 70 (9%) patients had a largest polyp size of 7–9 mm, and 19 (3%) patients had a largest polyp size of 10 mm or more (based on the ultrasound with the largest polyp size in those

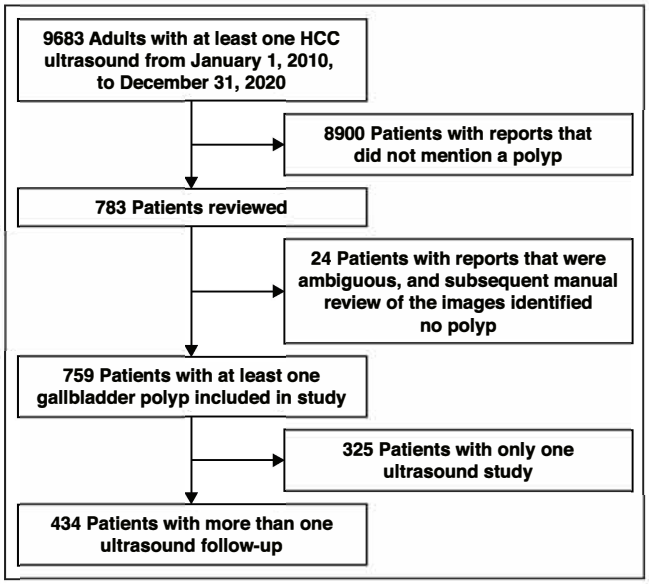

Fig. 1—Flowchart shows selection of patients included in study. HCC = hepatocellular carcinoma.

TABLE 1: Longitudinal Polyp Changes in 434 Patients With Gallbladder Polyps and Multiple Ultrasound Examinations Among All Patients and Stratified by Size of Largest Polyp

Event	All (n = 434)	Size ≤ 6 mm (n = 368)	Size 7–9 mm (n = 52)	Size ≥ 10 mm (n = 14)	p[a]
Change in number of polyps[b]					
Increase only	41 (9)	34 (9)	5 (10)	2 (14)	.83
Decrease only	59 (14)	52 (14)	6 (12)	1 (7)	.72
Increase and decrease	97 (22)	89 (24)	6 (12)	2 (14)	.16
No change	237 (55)	193 (52)	35 (67)	9 (64)	.35
Change in size of polyps[c]					
Increase only	42 (10)	25 (7)	15 (29)	2 (14)	< .001
Decrease only	71 (16)	54 (15)	14 (27)	3 (21)	.11
Increase and decrease	80 (18)	65 (18)	11 (21)	4 (29)	.57
No change	241 (56)	224 (61)	12 (23)	5 (36)	.002
Additional events					
Polyps not detected at follow-up					
No subsequent visualization	40 (9)	37 (10)	3 (6)	0 (0)	.33
Detected at subsequent visualization	27 (6)	24 (7)	3 (6)	0 (0)	.62
Mean change in polyp size (mm)					
Increase	2.6 ± 1.2	2.3 ± 0.5	2.9 ± 1.7	3.0 ± 1.0	.26
Decrease	−3.0 ± 1.5	−2.8 ± 1.1	−3.4 ± 2.5	−3.0 ± 0.8	.10
Increase and decrease	−0.3 ± 1.8	−0.3 ± 1.6	0.3 ± 1.5	−2.0 ± 3.7	.10

Note—Values are the number of patients with percentage in parentheses or mean ± SD.
[a]Chi-square test for categoric variables, one-way ANOVA for continuous variables.
[b]Number of polyps was categorized as zero, one, two, or more than two.
[c]Defined as difference of 2 mm or more between examinations.

with multiple examinations). Of the 434 patients with multiple ultrasound examinations, 257 (59%) had one polyp, 40 (9%) had two polyps, and 137 (32%) had more than two polyps on the first examination. Among these 434 patients, the mean size of the largest polyp on the examination showing the largest polyp was 5 ± 2 mm, with a maximum size of 12 mm. On the examination with the largest polyp, 368 (85%) patients had a largest polyp size of 6 mm or less, 52 (12%) patients had a largest polyp size of 7–9 mm, and 14 (3%) patients had a largest polyp size of 10 mm or less.

Longitudinal Changes in Polyps

In the 434 patients with multiple examinations, the polyps increased in number in 41 (9%) patients, decreased in number in 59 (14%), both increased and decreased in number in 97 (22%), and showed no change in number in 237 (55%). The largest polyp increased in size in 42 (10%) patients, decreased in size in 71 (16%), showed both an increase and a decrease in size in 80 (18%), and showed no change in size in 241 (56%). A total of 40 (9%) polyps were not detected on follow-up examinations, and 27 (6%) were not detected on an initial follow-up examination but were then detected on later studies. The mean change in size was 2.6 ± 1.2 mm in polyps that increased in size, −3.0 ± 1.5 mm in those that decreased in size, and −0.3 ± 1.8 mm in those showing both an increase and decrease in size. Table 1 shows the distribution of all of these events among polyps 6 mm or less, 7–9 mm, and 10 mm or more, and Figures 2–6 show examples of these polyp changes. An increase in size was significantly most common (p < .001) in polyps measuring 7–9 mm (29%); no change in size was significantly most common (p = .002) in polyps measuring 6 mm or less (61%). The remaining comparisons were not significantly different among the three groups (p > .05).

Pathologic and Clinical Follow-Up

Nineteen of the 759 patients underwent cholecystectomy. The cholecystectomy pathology report in 11 (58%) of these cases described a polyp corresponding with the sonographically detected polyp (cholesterol polyp in 10 and intracholecystic papillary-tubular neoplasm in 1). The mean size of the largest polyp reported on the most recent ultrasound examination before cholecystectomy was 6 mm (range, 2–11 mm). In all eight (42%) patients with no polyp described in the pathology report, the sonographically detected polyp measured 6 mm or less. No pathology report described the presence of gallbladder carcinoma (Table 2 and Fig. 7).

Of the 19 patients (from the 759 included in the study) with a largest polyp size of 10 mm or more, five underwent cholecystectomy; nine underwent follow-up ultrasound examinations through the end of the study period that showed a decrease in polyp size (maximum follow-up polyp size in these nine patients, 12 mm) and did not undergo cholecystectomy; two had inten-

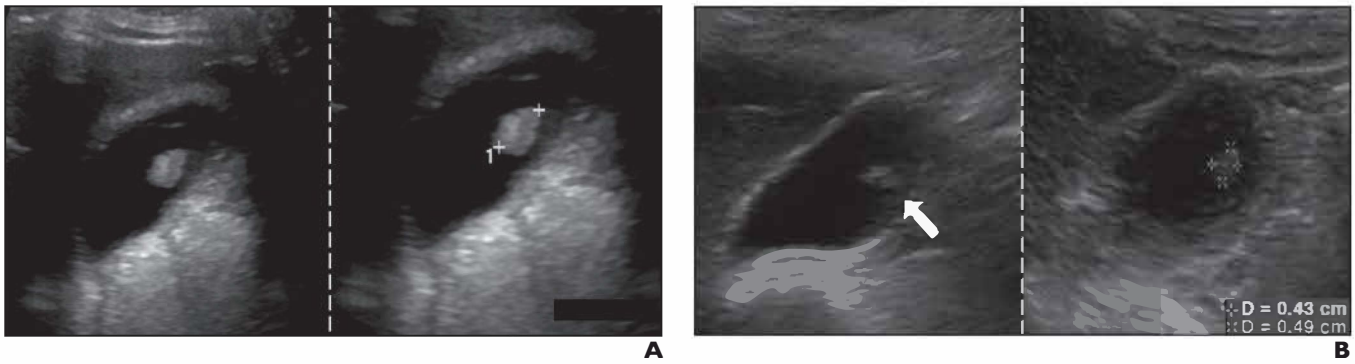

Fig. 2—38-year-old woman with chronic hepatitis B.
A, Longitudinal gray-scale ultrasound images show hyperechoic nonshadowing polyp (*no measurement, left; measurement with calipers, right*) measuring 8 mm.
B, Ultrasound images obtained 24 months later show decrease in size of polyp (*arrow, no measurement, left; measurement with calipers, right*), now measuring 5 mm. D = distance.

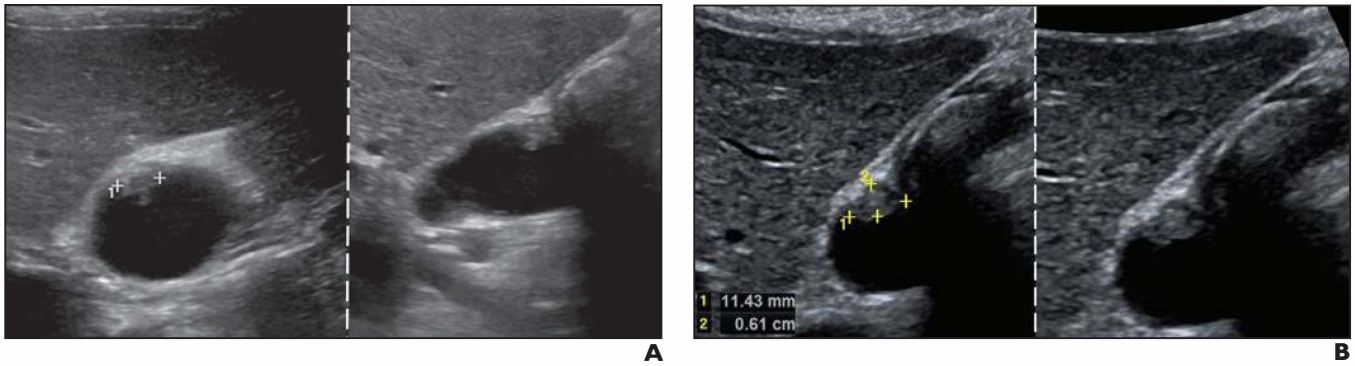

Fig. 3—60-year-old woman with chronic hepatitis B.
A, Transverse gray-scale ultrasound images show lobulated nondependent 9-mm polyp (*measurement with calipers, left; no measurement, right*).
B, Ultrasound images obtained 12 months later show polyp (*measurement with calipers, left; no measurement, right*) has increased in size to 11 mm.

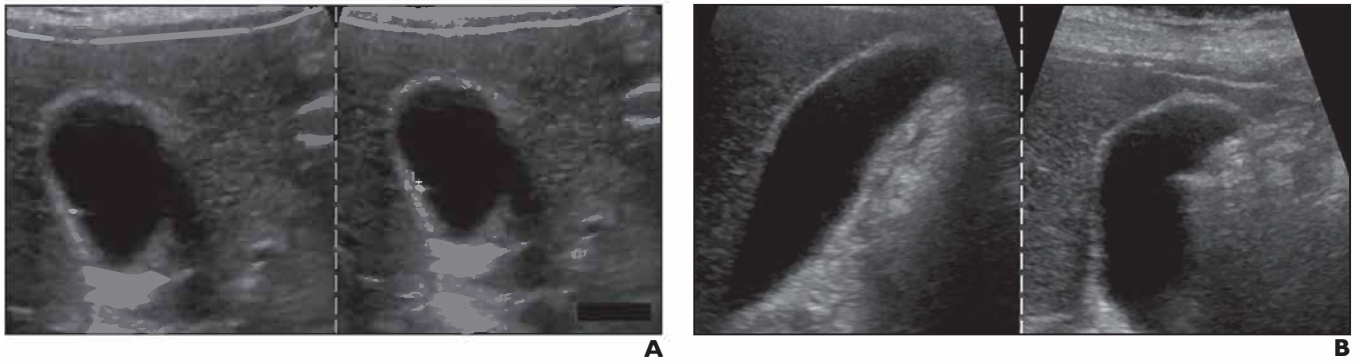

Fig. 4—76-year-old woman with chronic hepatitis B.
A, Initial gray-scale ultrasound images show 2-mm polyp (*no measurement, left; measurement with calipers, right*).
B, On ultrasound images obtained 5 months later, polyp is not visualized (*cranial, left; caudal, right*).

tional discontinuation of ultrasound follow-up; and three were lost to follow-up, with no subsequent ultrasound or clinical follow-up performed at our institution. In one patient with intentional discontinuation of ultrasound follow-up, the ultrasound examination showed a 19-mm polyp that was nonenhancing on follow-up contrast-enhanced MRI and appeared to represent sludge or stone; in the other patient, the ultrasound examination showed a 10-mm polyp that decreased to 8 mm on a follow-up ultrasound examination, though no further examinations were performed because the patient was treated for hepatitis C and did not require further HCC screening and surveillance.

Discussion

In our study, gallbladder polyps were incidentally identified on sonography in 8% of patients undergoing HCC screening and surveillance. Only 55% of polyps were unchanged in number on follow-up examinations, and only 56% were unchanged in size. The gallbladder polyps commonly varied (potentially both increasing

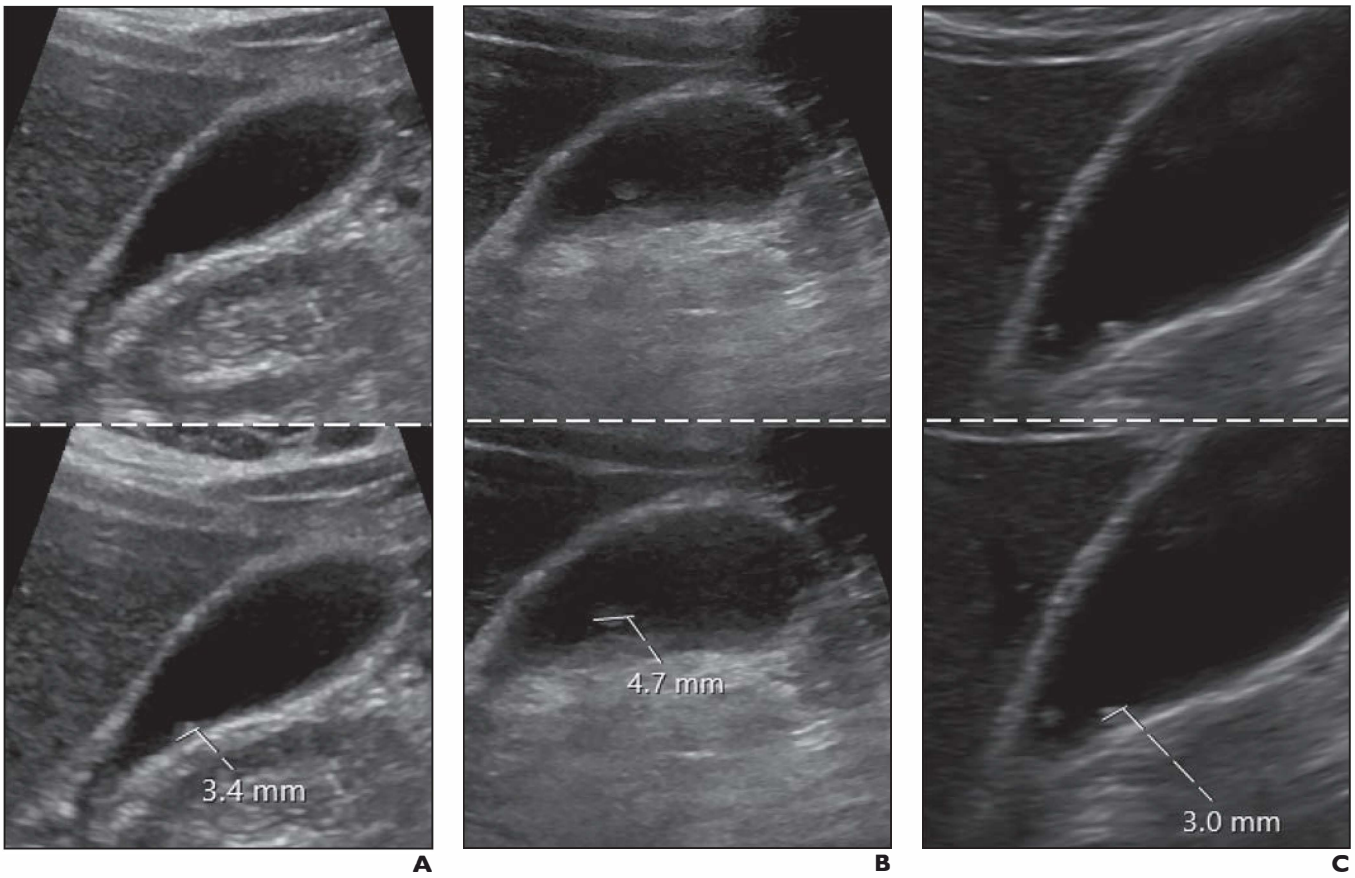

Fig. 5—45-year-old man with chronic hepatitis B.
A, Initial ultrasound images show 3-mm polyp (*no measurement, top; measurement with solid line, bottom*).
B, Ultrasound images obtained 6 months later show polyp (*no measurement, top; measurement with solid line, bottom*) increased in size to 5 mm.
C, Subsequent ultrasound images obtained 12 months after initial ultrasound show polyp (*no measurement, top; measurement with solid line, bottom*) decreased in size to 3 mm.

and decreasing) in size and number over multiple examinations. When using a 2-mm threshold for defining growth, 10% of polyps increased in size. No gallbladder carcinoma was found in the 19 of 759 patients who underwent cholecystectomy. European multisociety guidelines recommend that essentially all gallbladder polyps undergo surveillance imaging and that an increase in size of at least 2 mm should prompt cholecystectomy; however, such recommendations are too conservative according to our findings.

Earlier studies have also reported that benign gallbladder polyps often change in size and number over time [10, 11]. However, the proportion of patients with polyps that decreased in size over time in our study (16%) is greater than that reported in prior studies. Pedersen et al. [12] and Kratzer et al. [13] found that 3.9% and 4.5% of polyps, respectively, decreased in size. On the other hand, the proportion of patients with polyps that increased in size over time (10%) in our study is within a wide range reported in prior studies. Pederson et al., Kratzer et al., and Chou et al. [14] found that 6.2%, 0%, and 28% of polyps, respectively, increased in size.

We found that polyps are occasionally not visualized on follow-up studies, as previously described [11–13], but they may be subsequently visualized again on later studies. To our knowledge, this intermittent visualization and the size increase and decrease over serial examinations have not been previously described, perhaps because other studies compared only first and last ultrasound examinations whereas we assessed multiple longitudinal follow-up examinations performed as serial surveillance examinations in patients at risk for HCC.

Of the patients who underwent cholecystectomy, sonographically detected polyps were not present in 42% of pathology specimens. Although this number may seem high, it is less than other studies that found 69% [11] and 68% [15] of ultrasound-detected polyps were not present at pathology. Polyps not reported at pathology in our study all measured 6 mm or less.

Though the reason for the fluctuation in size and number of polyps is unclear, we hypothesize that these changes could be due to a number of reasons. First, cholesterol polyps are composed of cholesterol and macrophages. If the epithelial lining is disrupted, then the cholesterol in the polyps may dissolve into and precipitate out of solution in bile, which is a detergent salt, leading to fluctuation in the size of polyps [16, 17]. Second, macrophages may phagocytize cholesterol, leading to changes in size [18]. Third, cholesterol polyps may be loosely attached to the gallbladder wall by a thin tenuous stalk, leading to periodic sloughing of the polyp and subsequent nonvisualization on follow-up imaging [11, 19]. A tiny remnant at the point of the polyp attachment may remain, acting as a nidus for cholesterol polyp

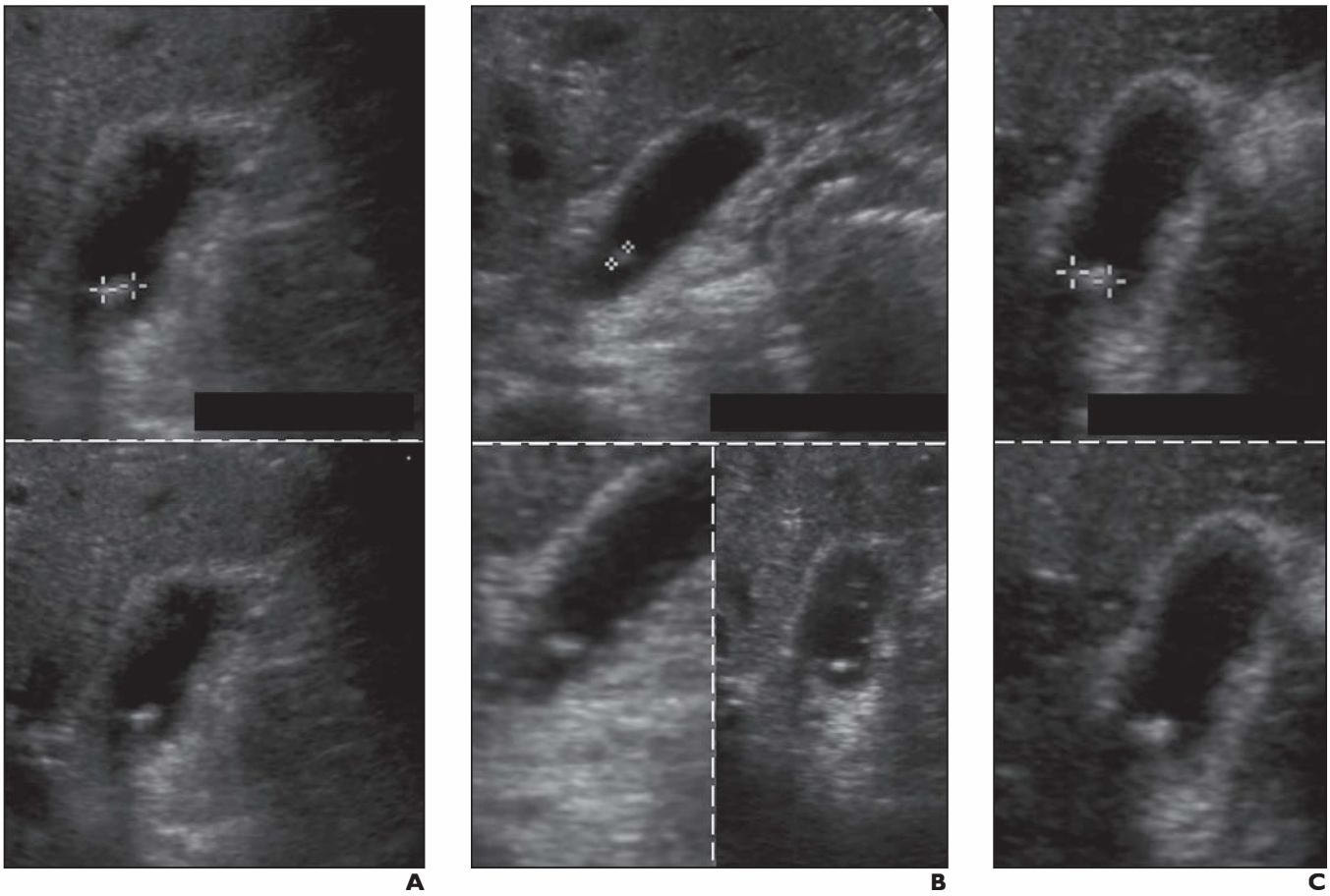

Fig. 6—53-year-old man with chronic hepatitis B.
A, Initial ultrasound images show solitary 5-mm polyp (*measurement with calipers, top; no measurement, bottom*).
B, Routine surveillance ultrasound images obtained 7 months later show no significant change in size of polyp (*measurement with calipers, top; no measurement in longitudinal plane, bottom left; no measurement in transverse plane, bottom right*). However, at least two additional 1-mm polyps are now seen (*bottom left and bottom right*).
C, Ultrasound images obtained 27 months after initial ultrasound show stability of larger polyp (*measurement with calipers, top; no measurement, bottom*) and resolution of smaller polyps.

regrowth. Fourth, tiny adherent nonshadowing stones or sludge may mimic gallbladder polyps [3, 11, 20] but change in configuration. Finally, technical differences such as transducer frequency, machine settings, and patient differences in fasting or degree of gallbladder distention may affect visibility of gallbladder polyps.

Gallbladder polyps can be classified as nonneoplastic or neoplastic, the latter having a small theoretic risk of carcinoma or malignant transformation. Because of this theoretic risk and the challenge of differentiating the two entities by imaging, all gallbladder polyps are typically regarded with some degree of suspicion. If neoplastic polyps could be differentiated from nonneoplastic polyps, then only those deemed more likely to represent neoplastic polyps could be targeted for surveillance, whereas nonneoplastic polyps could be spared follow-up imaging. This topic has received significant interest. Previous studies have found that neoplastic polyps are typically larger in size (most commonly > 15 mm) [21], hypo- or isoechoic [22], single in number [23], and sessile in configuration [24]. However, no single feature has been found to have a high PPV for neoplastic polyps or to be a statistically significant predictor in multivariable analysis [22].

Most guidelines use an absolute size or change in size overtime as the primary sonographic feature for determining risk stratification and management of gallbladder polyps [7–9]. Therefore, understanding the natural history of change in size and number of sonographically detected polypoid gallbladder lesions over time is critical in informing future guidelines. We acknowledge that as imaging technology and resolution of ultrasound images improve, size may become less of an important distinguishing feature of gallbladder polyps. Advanced techniques such as contrast-enhanced ultrasound have recently been shown to hold promise in differentiating nonneoplastic from neoplastic polyps and/or malignancies for larger (i.e., > 10 mm) polypoid gallbladder lesions. It is unclear whether such promising findings can be applied to subcentimeter gallbladder polyps, but as adoption of these advanced techniques increases and evidence accrues, further delineation between the two broad categories of polyps may be possible [25].

A limited number of studies have found an association between polyp growth and polyp neoplasia at pathology [26, 27], and recent studies show that growth may be part of the natural

TABLE 2: Summary of 19 Patients Who Underwent Cholecystectomy

Indication for Cholecystectomy	Polyp Reported on Pathology	Polyp Description	Largest Polyp Size on Pathology (mm)	Additional Pathology Findings	Largest Polyp Size on US[a] (mm)	No. of Polyps on US[a]
Biliary colic	No	NA	NA	Chronic cholecystitis and cholelithiasis	4	1
Liver transplant for HCC	Yes	Cholesterolosis	NR	NA	5	> 2
Left hepatectomy for HCC[b]	No	NA	NA	NA	4	1
Gallbladder polyp (10 mm)	Yes	Cholesterol polyp	NR	Cholelithiasis	10	> 2
Biliary colic	No	NA	NA	Chronic cholecystitis and cholelithiasis	5	2
Partial hepatectomy for HCC	No	NA	NA	Chronic cholecystitis and cholelithiasis	6	1
Biliary colic and enlarging polyp[c]	Yes	Cholesterolosis	6	Chronic cholecystitis, cholelithiasis, and adenomyoma	11	1
Pancreatic adenocarcinoma	No	NA	NA	Fundal adenomyosis and mild chronic cholecystitis	5	1
Gallbladder polyp on US	Yes	Multiple cholesterol polyps	NR	NA	10	> 2
Gallbladder polyp on US[d]	Yes	Multiple cholesterol polyps	7	Minimal chronic cholecystitis	11	> 2
HCC liver wedge resection	Yes	Cholesterolosis	NR	NA	4	> 2
Cholelithiasis	Yes	Cholesterolosis	NR	Mild chronic cholecystitis and cholelithiasis	4	> 2
Liver transplant for HCC and cholangiocarcinoma	Yes	Cholesterolosis	NR	Chronic cholecystitis	6	1
Gallbladder dyskinesia	Yes	Cholesterolosis	NR	Mild chronic cholecystitis	4	> 2
Liver transplant for HCC	No	NA	NA	Chronic cholecystitis	2	1
Gastric adenocarcinoma	Yes	Intracholecystic papillary neoplasm	3	High-grade and low-grade dysplasia	4	1
Liver transplant for HCC	Yes	Multiple polypoid areas	3	Chronic cholecystitis with mucosal edema	10	> 2
Liver transplant for HCC	No	NA	NA	Mild chronic cholecystitis	3	1
Wedge resection for HCC	No	NA	NA	NA	5	> 2

Note—US = ultrasound, NA = not applicable, HCC = hepatocellular carcinoma, NR = not reported.
[a]Most recent US before cholecystectomy.
[b]Normal gallbladder on pathology.
[c]Same patient as in Figure 3.
[d]Same patient as in Figure 7.

history of small gallbladder polyps [10, 28]. In 2020, Szpakowski and Tucker [10] reported the largest series to date, to our knowledge, of outcomes of sonographically detected gallbladder polyps. In their analysis of 35,856 patients with gallbladder polyps observed over a 20-year period, gallbladder polyp growth of 2 mm or more was found to be part of the natural history of benign polyps, similar to our observations. However, unlike our study, only 9.6% of the study cohort had two or more repeated ultrasound examinations. Further, they found that growth to 10 mm was not associated with increased risk of gallbladder cancer. In another study from 2020 by Rafaelsen et al. [28], 154 patients with gallbladder polyps smaller than 6 mm underwent reimaging by ultrasound 12 years later, and 15 patients (approximately 10%) had polyp growth of 2 mm or more; no patient developed cancer.

Our study has several strengths compared with prior studies. First, to our knowledge, our study is the first conducted in the United States to longitudinally evaluate gallbladder polyps exclusively in patients with underlying liver disease. Because these patients are recommended to undergo biannual serial ultrasound examinations for HCC surveillance, we were able to serially follow the natural history of gallbladder polyps over many examinations. This would not be possible otherwise in most patients with small polyps less than 7 mm as the ACR and CAR recommendations do not advocate follow-up of small gallbladder polyps. Though the European multisociety guidelines recommend follow-up of polyps smaller than 6 mm, these guidelines were released in 2017 and lack widespread adoption in the United States. Second, prior longitudinal studies have evaluated polyp growth

Fig. 7—43-year-old man with chronic hepatitis B.
A, Gray-scale ultrasound images show 11-mm nonmobile hyperechoic polypoid lesion (*measurement with calipers, left; no measurement, right*), which had increased in size from 9 mm 2 years earlier (not shown).
B, Patient underwent cholecystectomy given increase in polyp size. Photomicrograph (H and E, ×100) shows portion of cholesterol polyp. Epithelial lining (*arrowhead*), abundant cholesterol-filled macrophages (*short arrow*), and small vessel (*long arrow*) are also seen.

based on two [11, 26, 28] or three [12, 13] time points, whereas our study evaluated polyps at more numerous time points, allowing periodic monitoring of polyp size and number on the basis of a follow-up regimen similar to the European multisociety guidelines. Third, whereas earlier studies included large samples of patients with a single examination, we included a relatively large number of patients compared with other studies reporting longitudinal evaluation of gallbladder polyps on serial examinations [13, 19, 28]. Finally, ultrasound technology and image resolution during the period of our study (2010–2020) were substantially improved compared with the quality of the equipment during the period of previous studies, ensuring that our findings are applicable to current diagnostic imaging standards.

There are several limitations of our study. First, all patients were at risk for HCC. It is unclear whether patients with underlying liver disease may have a different susceptibility to development of gallbladder polyps or natural history of gallbladder polyps compared with other populations. Several studies suggest that chronic liver disease and chronic hepatitis B may increase the risk of gallstones and subsequent inflammation and polyp formation [29, 30]; however, other studies indicate that chronic liver disease is not a risk factor for polyps [31, 32]. Despite the recommendation for surveillance imaging every 6 months for at-risk patients, many patients in our study did not strictly follow this schedule, likely because of multiple factors including noncompliance (a well-known issue in surveillance imaging), changes in health insurance, and a relatively dynamic population within our geographic area due to employment changes within Silicon Valley.

Second, the ultrasound examinations were not performed specifically for follow-up of gallbladder polyps but rather for HCC surveillance, which may have contributed to the variability in reported polyp size and visibility. However, this design reflects standard ultrasound evaluation of gallbladder polyps, and thus our findings may be applied more broadly.

Third, a small proportion of polyps measured 10 mm or more; therefore, conclusions about polyps of this size are limited. Similarly, risk factors for gallbladder cancer could not be evaluated because no carcinomas were identified despite the large number of patients with gallbladder polyps.

Finally, only a small number of the 434 patients had a pathologic correlate. Thus, the pathologic correlate of most of the polyps is unknown. A cohort with a pathologic reference standard for all patients would be prone to substantial patient selection bias because small gallbladder polyps are only resected in the presence of a specific clinical reason. This selection bias may account for the higher malignancy rates reported by prior studies that included a pathologic reference standard for all polyps compared with malignancy rates encountered in clinical practice [26, 33]. This limitation is unavoidable when investigating gallbladder polyps because the vast majority are benign. Further, it would not be possible to assess the natural history of gallbladder polyps in terms of number and size (as per our study aim) if only resected polyps are included.

In conclusion, gallbladder polyps fluctuate in both size and number over serial examinations and may fluctuate in visibility. Using a 2-mm threshold for growth, 10% increased in size. No gallbladder carcinoma was identified in the small number of patients who underwent cholecystectomy. European multisociety guidelines that propose surveillance of essentially all polyps and a 2-mm change in size as a basis for cholecystectomy are likely too conservative for clinical application.

References

1. Jørgensen T, Jensen KH. Polyps in the gallbladder: a prevalence study. *Scand J Gastroenterol* 1990; 25:281–286
2. Heitz L, Kratzer W, Gräter T, Schmidberger J; EMIL study group. Gallbladder polyps: a follow-up study after 11 years. *BMC Gastroenterol* 2019; 19:42
3. Cha BH, Hwang JH, Lee SH, et al. Pre-operative factors that can predict neoplastic polypoid lesions of the gallbladder. *World J Gastroenterol* 2011; 17:2216–2222
4. Adsay V, Jang KT, Roa JC, et al. Intracholecystic papillary-tubular neoplasms (ICPN) of the gallbladder (neoplastic polyps, adenomas, and papillary neoplasms that are ≥1.0 cm): clinicopathologic and immunohistochemical analysis of 123 cases. *Am J Surg Pathol* 2012; 36:1279–1301
5. Roa I, de Aretxabala X, Araya JC, Roa J. Preneoplastic lesions in gallbladder cancer. *J Surg Oncol* 2006; 93:615–623
6. McCain RS, Diamond A, Jones C, Coleman HG. Current practices and future prospects for the management of gallbladder polyps: a topical review. *World J Gastroenterol* 2018; 24:2844–2852
7. Sebastian S, Araujo C, Neitlich JD, Berland LL. Managing incidental findings on abdominal and pelvic CT and MRI. Part 4. White paper of the ACR Incidental Findings Committee II on gallbladder and biliary findings. *J Am Coll Radiol* 2013; 10:953–956

8. Bird JR, Brahm GL, Fung C, Sebastian S, Kirkpatrick IDC. Recommendations for the management of incidental hepatobiliary findings in adults: endorsement and adaptation of the 2017 and 2013 ACR Incidental Findings Committee white papers by the Canadian Association of Radiologists Incidental Findings Working Group. *Can Assoc Radiol J* 2020; 71:437–447
9. Wiles R, Thoeni RF, Barbu ST, et al. Management and follow-up of gallbladder polyps: joint guidelines between the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), European Association for Endoscopic Surgery and Other Interventional Techniques (EAES), International Society of Digestive Surgery–European Federation (EFISDS) and European Society of Gastrointestinal Endoscopy (ESGE). *Eur Radiol* 2017; 27:3856–3866
10. Szpakowski JL, Tucker LY. Outcomes of gallbladder polyps and their association with gallbladder cancer in a 20-year cohort. *JAMA Netw Open* 2020; 3:e205143
11. Corwin MT, Siewert B, Sheiman RG, Kane RA. Incidentally detected gallbladder polyps: is follow-up necessary? Long-term clinical and US analysis of 346 patients. *Radiology* 2011; 258:277–282
12. Pedersen MR, Dam C, Rafaelsen SR. Ultrasound follow-up for gallbladder polyps less than 6 mm may not be necessary. *Dan Med J* 2012; 59:A4503
13. Kratzer W, Haenle MM, Voegtle A, et al.; Roemerstein Study Group. Ultrasonographically detected gallbladder polyps: a reason for concern? A seven-year follow-up study. *BMC Gastroenterol* 2008; 8:41
14. Chou SC, Chen SC, Shyr YM, Wang SE. Polypoid lesions of the gallbladder: analysis of 1204 patients with long-term follow-up. *Surg Endosc* 2017; 31:2776–2782
15. Mainprize KS, Gould SW, Gilbert JM. Surgical management of polypoid lesions of the gallbladder. *Br J Surg* 2000; 87:414–417
16. Jones MW, Deppen JG. *Gallbladder polyp*. StatPearls, 2021
17. Yao G, Bai X, Yang C, et al. Analysis of risk factors for gallbladder polyp formation: a retrospective study based on serial ultrasounds. *Eur J Gastroenterol Hepatol* 2020; 32:1154–1159
18. Kim EY, Hong TH. Bile cholesterol and viscosity, the keys to discriminating adenomatous polyps from cholesterol polyps by a novel predictive scoring model. *BMC Gastroenterol* 2020; 20:268
19. Csendes A, Burgos AM, Csendes P, Smok G, Rojas J. Late follow-up of polypoid lesions of the gallbladder smaller than 10 mm. *Ann Surg* 2001; 234:657–660
20. Akyürek N, Salman B, Irkörücü O, Sare M, Tatlicioğlu E. Ultrasonography in the diagnosis of true gallbladder polyps: the contradiction in the literature. *HPB (Oxford)* 2005; 7:155–158
21. Liu K, Lin N, You Y, et al. Risk factors to discriminate neoplastic polypoid lesions of gallbladder: a large scale, case-series study. *Asian J Surg* 2021 Mar 24 [published online]
22. Choi TW, Kim JH, Park SJ, Ahn SJ, Joo I, Han JK. Risk stratification of gallbladder polyps larger than 10 mm using high-resolution ultrasonography and texture analysis. *Eur Radiol* 2018; 28:196–205
23. Bhatt NR, Gillis A, Smoothey CO, Awan FN, Ridgway PF. Evidence based management of polyps of the gall bladder: a systematic review of the risk factors of malignancy. *Surgeon* 2016; 14:278–286
24. Kubota K, Bandai Y, Noie T, Ishizaki Y, Teruya M, Makuuchi M. How should polypoid lesions of the gallbladder be treated in the era of laparoscopic cholecystectomy? *Surgery* 1995; 117:481–487
25. Fei X, Lu WP, Luo YK, et al. Contrast-enhanced ultrasound may distinguish gallbladder adenoma from cholesterol polyps: a prospective case-control study. *Abdom Imaging* 2015; 40:2355–2363
26. Shin SR, Lee JK, Lee KH, et al. Can the growth rate of a gallbladder polyp predict a neoplastic polyp? *J Clin Gastroenterol* 2009; 43:865–868
27. Park JY, Hong SP, Kim YJ, et al. Long-term follow up of gallbladder polyps. *J Gastroenterol Hepatol* 2009; 24:219–222
28. Rafaelsen SR, Otto PO, Pedersen MRV. Long-term ultrasound follow-up in patients with small gallbladder polyps. *Dan Med J* 2020; 67:A06200414
29. Liew PL, Wang W, Lee YC, Huang MT, Lin YC, Lee WJ. Gallbladder disease among obese patients in Taiwan. *Obes Surg* 2007; 17:383–390
30. Xu Q, Tao LY, Wu Q, et al. Prevalences of and risk factors for biliary stones and gallbladder polyps in a large Chinese population. *HPB (Oxford)* 2012; 14:373–381
31. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. *Clin Epidemiol* 2014; 6:99–109
32. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. *Gut Liver* 2012; 6:172–187
33. Terzi C, Sökmen S, Seçkin S, Albayrak L, Uğurlu M. Polypoid lesions of the gallbladder: report of 100 cases with special reference to operative indications. *Surgery* 2000; 127:622–627

(Editorial Comment starts on next page)

Editorial Comment: The Gallbladder Polyp—Growth Happens

The heart of science is measurement.
—Erik Brynjolfsson [1]

We radiologists live in a world of measurements. In many instances, they are important in determining disease progression; however, at times, exclusive focus on size and growth can be misleading, resulting in overtreatment.

Nowhere is this truer than with the gallbladder polyp. Here, growth on the order of millimeters may prompt invasive surgery. Indeed, European Society of Gastrointestinal and Abdominal Radiology (ESGAR) guidelines stringently recommend follow-up of virtually all polyps, with cholecystectomy prompted by growth of 2 mm or more [2]. Central to this discussion are two questions that undergird the recommendation: What is the natural history of gallbladder polyp growth, and does growth truly suggest the possibility of malignancy?

This study adds to the sparse literature on the natural history of polyp growth and number, particularly in subcentimeter polyps. The sample consisted of patients with gallbladder polyps who underwent ultrasound every 6 months for hepatocellular carcinoma surveillance. This targeted combination provided the authors with unique data to longitudinally evaluate polyp growth and number. They found that benign polyps may grow. In polyps measuring 6 mm or less, 7% grew a mean of 2.3 mm, 15% decreased in size, and 18% showed variable size increase and decrease on serial studies. Thus, polyp size changed in 39% of patients with polyps measuring 6 mm or less. Polyp number similarly fluctuated. No patients with an increase in polyp size had cancer on pathology or further follow-up. This study supports earlier works showing similar findings [3, 4].

The study has a significant impact. Given the mean growth of 2.6 mm in nonmalignant polyps, adhering to the strict 2-mm threshold would cause many patients to undergo cholecystectomy, with attendant risks, for benign lesions. This study questions the ESGAR guidelines and suggests a less rigid approach to cholecystectomy, which could minimize unnecessary surgery.

Helena Gabriel, MD
Northwestern University
Chicago, IL
hgabriel@nm.org

The author declares that there are no disclosures relevant to the subject matter of this article.

doi.org/10.2214/AJR.21.26968

References

1. Lohr S. Big data, trying to build better workers. The New York Times. www.nytimes.com/2013/04/21/technology/big-data-trying-to-build-better-workers.html
2. Wiles R, Thoeni RF, Barbu ST, et al. Management and follow-up of gallbladder polyps: joint guidelines between the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), European Association for Endoscopic Surgery and other Interventional Techniques (EAES), International Society of Digestive Surgery-European Federation (EFISDS) and European Society of Gastrointestinal Endoscopy (ESGE). *Eur Radiol* 2017; 27:3856–3866
3. Szpakowski JL, Tucker LY. Outcomes of gallbladder polyps and their association with gallbladder cancer in a 20-year cohort. *JAMA Netw Open* 2020; 3:e205143
4. Shin SR, Lee JK, Lee KH, et al. Can the growth rate of a gallbladder polyp predict a neoplastic polyp? *J Clin Gastroenterol* 2009; 43:865–868

STUDY GUIDE

Longitudinal Ultrasound Assessment of Changes in Size and Number of Incidentally Detected Gallbladder Polyps

Alan Mautz, MD[1], Joseph J. Budovec, MD[2]

[1]Northern Light AR Gould Hospital, Presque Isle, ME.

[2]Medical College of Wisconsin, Milwaukee, WI.

*amautz@emhs.org, jbudovec@mcw.edu**

Introduction

1. How common are gallbladder polyps? How common is gallbladder carcinoma?
2. What are the American College of Radiology's and Canadian Association of Radiologists' recommendations for follow-up of gallbladder polyps? How do these recommendations vary from those provided in a joint statement from the four European societies mentioned in the article?
3. What is the stated objective of this study?

Methods

4. What study design was used? What were the inclusion criteria? What were the exclusion criteria?
5. How were data gathered for this study? How was ambiguity regarding size, number, or presence of polyps resolved? What relevant data regarding gallbladder polyps were used in this study?
6. What was the source of the polyp size thresholds mentioned in the statistical analysis?

Results

7. How common were gallbladder polyps in the studied population? How common were multiple polyps?
8. How often was gallbladder carcinoma diagnosed among the patients who were included in the study?

Discussion

9. What are the limitations of this study? Are these adequately discussed? What does the study state are its strengths with respect to past studies?
10. How variable are the presence and size of gallbladder polyps over time, according to the data used in this study? What explanations for this variability are given in this study?
11. How do you currently recommend follow-up of gallbladder polyps detected incidentally? What guidelines does your practice or institution use? Do you ever make recommendations that differ from the guidelines? If so, why?
12. How might you design a follow-up study?

Background Reading

1. Choi TW, Kim JH, Park SJ, Ahn SJ, Joo I, Han JK. Risk stratification of gallbladder polyps larger than 10 mm using high-resolution ultrasonography and texture analysis. *Eur Radiol* 2018; 28:196–205
2. Corwin MT, Siewert B, Sheiman RG, Kane RA. Incidentally detected gallbladder polyps: is follow-up necessary? Long-term clinical and US analysis of 346 patients. *Radiology* 2011; 258:277–282

*Please note that the authors of the Study Guide are distinct from those of the companion article.