Original Article

Dan Med J 2020;67(10):A06200414

Long-term ultrasound follow-up in patients with small gallbladder polyps

Søren Rafael Rafaelsen[1, 2], Peter Obel Otto[2] & Malene Roland V. Pedersen[1, 2]

1) University of Southern Denmark, Faculty of Health Sciences, Institute of Regional Health Research, 2) Department of Radiology, Vejle Hospital, Denmark

Dan Med J 2020;67(10):A06200414

ABSTRACT

INTRODUCTION: Gallbladder polyps often have a benign appearance by ultrasonography. Even so, the current guideline recommends follow-up in gallbladder polyps < 6 mm. The aim of this study was to investigate long-term follow-up growth of polyps in patients with a polyp size < 6 mm in a ten-year cohort.

METHODS: Abdominal ultrasonography reports from 2007 to 2009 were reviewed, including reports on patients diagnosed with a gallbladder polyp (polyp size < 6 mm) during the 2007-2009 period. The patients were invited to a final follow-up ultrasonography of the gallbladder conducted during October 2019 to February 2020. A total of 154 patients were included (100 women and 54 men).

RESULTS: In 53 patients (34.4%), the polyp was not visible at the ultrasonography follow-up. Gallbladder polyps were confirmed in 101 (65.6%) patients. A total of 49 patients had a single polyp (31.8%) and 52 (33.8%) patients had multiple polyps. The median size of the gallbladder polyp was 4 mm (range: 2.0-5.9 mm) at baseline compared with 4 mm (range: 1.7-15.0 mm) at the follow-up. A total of 15 patients experienced polyp growth of 2 mm or more. None developed gallbladder cancer.

CONCLUSIONS: Our study showed that gallbladder polyps < 6 mm has a low probability of increasing in size. None of the patients with small polyps developed gallbladder cancer.

FUNDING: none.

TRIAL REGISTRATION: not relevant.

Gallbladder polyps are lesions that protrude from the inside of the gallbladder wall into the cavity and are generally detected by abdominal ultrasonography. The reported prevalence in the healthy general population is approximately 5% [1, 2] but has recently been reported up to 12% [3]. Gallbladder polyps are typically asymptomatic with a benign appearance. Inflammation, adenomyomatosis, skinfolds and cholecystolithiasis may be misinterpreted as polyps during ultrasonography. To limit false positive outcomes, new scan methods have been suggested, such as elastography and use of contrast-enhanced ultrasound [4, 5]. Furthermore, ultrasonography of gallbladder polyps has been shown to be reproducible [6].

Current guidelines [7] recommend surgical removal of gallbladder polyps if > 10 mm because of malignancy risk and long-time follow-up ultrasonography of polyps between 6-9 mm. For gallbladder polyps < 6 mm, follow-up is also recommended at one, three and five years independently of risk factors. The knowledge about the growth rate of gallbladder polyps < 6 mm is limited, especially in patients without risk factors.

The aim of this study was to examine long-term follow-up growth in gallbladder polyps < 6 mm in size and to explore the risk of developing gallbladder cancer.

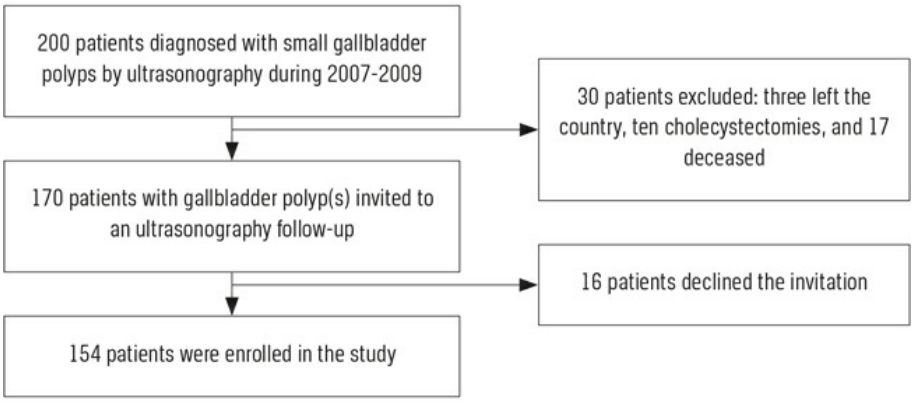
METHODS

This cohort study was approved by the Institutional Review Board (September 2019) of the University Hospital of Southern Denmark and the local Danish Data Protection Agency.

Study population

Retrospective ultrasonography reports between 2007 and 2009 were reviewed, including all abdominal ultrasonographies registered at the Radiology Department, Vejle Hospital. All patients diagnosed with a gallbladder polyp < 6 mm in size diagnosed at our department from 2007 to 2009 were invited to attend a ten-year follow-up ultrasonography examination. We identified 200 patients (**Figure 1**) who all received an electronic invitation to undergo ultrasonography. Patients who accepted the invitation were offered abdominal ultrasonography at the Radiology Department, Vejle Hospital, in the period from October 2019 to February 2020. Participation was voluntary and informed consent was mandatory. In total, 154 patients had a ten-year follow-up examination.

FIGURE 1 / Patient flow chart.



Ultrasonography image acquisition

Follow-up ultrasound examinations were performed using one of two identical ultrasound machines with convex transducers using a broadband operating frequency range of 1-5 MHz.

All patients fasted for a minimum of four hours prior to the examination. All procedures were performed with the patient placed in the supine position and, when needed, in the lateral decubitus position. Gallbladders were scanned in both longitudinal and transverse planes using the intercostal or subcostal method.

All technical parameters such as gain and focus were adjusted individually. Polyps were identified if the lesion was immobile without acoustic shadowing. Its largest diameter was measured in mm using an electronic ruler. An increase of polyp size of 2 mm was considered a significant growth. If potential gallstones were detected, this was documented by the presence or absence of acoustic shadowing. A picture archive communication system was used to store all imaging and ultrasonography reports. **Figure 2** shows ultrasonography of an echogenic gallbladder polyp approximately 7 mm in size without acoustic shadowing.

FIGURE 2 / Ultrasonography of an echogenic gallbladder polyp approximately 7 mm in size adherent to the gallbladder wall without acoustic shadowing. No gallstone was detected.

Data

Age and sex were recorded at the time of the abdominal follow-up scan. Polyp size was measured during the follow-up ultrasonography. The number of polyps and cholecystolithiasis or other findings were noted. A true growth of a polyp was defined as 2 mm. For deceased patients, the national pathology database was checked to rule out gallbladder cancer. All examinations were performed by either sonographers (99%) or radiologists (1%) with 1-20 years of ultrasonography experience.

The pathology reports were reviewed for all eligible patients to investigate if they had previously undergone cholecystectomy and to register any histopathological findings.

Statistical analysis

A statistical analysis was performed, and descriptive statistics were calculated using the Mann-Whitney U test. A p-value < 0.05 was considered statistically significant. The data were not normally distributed, and measurements are summarised as median values.

Trial registration: not relevant.

RESULTS

The clinical characteristics of the included 154 patients, 54 (35%) men and 100 (65%) women, are provided below. The median age was 62 years (range: 22-89 years); for women was 62 years (range: 22-89 years) and for men 61 years (range: 31-89 years).

Gallbladder polyps were confirmed in 101 (65.6%) patients. A total of 53 (34.4%) patients did not have a gallbladder polyp diagnosed at the ten-year follow-up scan. Based on the ultrasonography findings, the median size of gallbladder polyps was 4.0 mm (range: 2-6 mm) at baseline compared with 4.0 mm (range: 1.7-15 mm) at follow-up (p = 0.0524). Gallstones were detected in one (0.7%) patient at baseline and in 21 (13.6%) patients during follow-up.

A total of 49 patients had a single polyp (31.8%); 52 (33.8%) had multiple polyps. A total of 15 patients experienced a polyp growth of 2 mm or more (range: 2-10 mm). Their median age was 54 years (range: 31-76 years). **Table 1** presents an overview of polyp growth.

TABLE 1 / Visualisation of gallbladder polyp growth from baseline to ten-year follow-up. The values are number of patients.

	Baseline			Follow-up		
	0 polyps	1 polyp	⟩1 polyp	0 polyps	1 polyp	⟩1 polyp
⟨6 mm	-	83	71	53	47	40
6-9	-	-	-	-	2	10
≥10	-	-	-	-	-	2

We excluded a total of 17 deceased patients, none of whom had been diagnosed with gallbladder cancer.

Cholecystectomies were performed in ten patients with reported gallbladder polyps. The cholecystectomies were carried out for a variety of reasons not necessarily related to the presence of gallbladder polyps. None of the patients' pathology reports showed gallbladder malignancy. An overview of the findings is shown in **Table 2**.

TABLE 2 / Excluded patients with gallbladder polyps undergoing cholecystectomy.

Patient: sex, yrs of age, year	Follow-up ultrasonographies, n	Polyp size, mm	Polyps, n	Polyp growth, mm	Year of cholecystectomy	Cholecystectomy findings
Male, 40, 2008	1	4	3	0	2009	Inflammation, gallstone
Female, 39, 2009	1	5.7	2	-	2010	Inflammation, fibrosis
Female, 29, 2008	1	4	2	0	2010	2 polyps
Female, 43, 2007	5	4	2	0.8	2016	Inflammation, polyp
Male, 56, 2009	1	6	1	0	2011	Inflammation, fibrosis
Female, 44, 2010	0	4-5	3	-	2010	Inflammation, fibrosis
Female, 54, 2010	0	2.5	2	-	2010	Inflammation, fibrosis, polyp
Female, 62, 2006	4	3.0	1	2-3	2012	Inflammation, fibrosis
Female, 40, 2011	1	4	5	0	2011	Inflammation, fibrosis, gallstones
Female, 29, 2015	0	4	1	-	2015	Inflammation, fibrosis, gallstones

Gallstones were observed in 13.6% of the patients (n = 21; nine men, 12 women). Hence, the risk of gallstone was 16.7% in men and 12.0% in women with gallbladder polyps. In total, 53 (35.5%) of the patients had no polyps detected, 11 (7.1%) experienced no polyp growth, 39 (25.3%) had a decrease in polyp size and 51 (33.3%) had an increase in polyp size.

The polyps varied significantly in size in three patients. In one male patient aged 66 years, the polyp had increased by 10 mm at follow-up. The patient went from 5 mm in 2008 to 15 mm in the autumn of 2019. The second largest polyp was 4.7 mm, and gallstone was also detected in this patient who was recommended a cholecystectomy. The patient was diagnosed with prostate cancer in 2018 and declined cholecystectomy.

We recommended that the patient receive an additional ultrasound follow-up and encouraged him to reconsider the cholecystectomy, but he declined both.

A 43-year old woman experienced a polyp growth of 5.4 mm. In 2008, a total of six gallbladder polyps were detected, the largest measuring 5.9 mm. In 2019, she had multiple polyps, the largest measuring 11 mm. The second largest measured 9 mm, and no gallstones were detected. She was recommended surgery and underwent a CT of the thorax and abdomen to evaluate the polyps. The CT was performed three months after the ultrasound examination, and the polyp size was only 4-5 mm at the CT. The patient did not undergo cholecystectomy and concluded ultrasonography follow-up.

A 36-year old male patient experienced a growth rate of 5.4 mm (from 3.6 to 9.0 mm at follow-up in 2019). The patient had > 10 polyps and the second largest polyp measured 7 mm. No gallstones were detected. The patient underwent an additional ultrasonography four months later, and the gallbladder polyp then measured up to 12 mm in size. The patient was recommended surgery. He was not interested in having a cholecystectomy or enter ultrasonography follow-up and went travelling abroad. He was living in good health eight months after the latest follow-up ultrasonography.

DISCUSSION

The present study supports the hypothesis that small gallbladder polyps measuring < 6 mm carry a very low risk of malignancy development. Few studies have explored the growth of small gallbladder polyps over time. This study provided clinical insight into how the growth of small gallbladder polyps may develop over a very long period of time. Our results are in line with the 20-year cohort study published recently, showing that the risk of gallbladder cancer is the same in patients with and without gallbladder polyps [8]. Other studies investigating growth in small gallbladder polyps have been published. A systematic review including studies from 1996 to 2011 reported small gallbladder polyps growth to vary from 1% to 23% during follow-up [9]. In 2012, a two-year follow-up study suggested limited follow-up in patients with polyps < 6 mm, based on findings with polyps having remained stable in 100 patients, decreased in five patients, increased in eight patients and resolved in 15 patients [10]. A review found an increase in 6.9% of polyps and calculated the probability of malignancy to be zero in polyps < 4.15 mm [11]. A recent 20-year cohort study including 35,856 patients found 6% with gallbladder polyps and concluded that a growth of 2 mm or more appears to be part of the polyp's natural history [8].

Size measurement is important in polyp management. Few polyps will grow significantly during a follow-up period. In total, we found 15 polyps to increase by 2 mm or more during the ten-year follow-up. A systematic review found that 6.9% of polyps increased in size during follow-up [11]. Choi et al found a mean growth of 0.9 mm during 62.7 months of follow-up [12] and Collett et al reported a 1.5-mm growth at the two-year follow-up and 1.1 mm at the five-year follow-up [13]. A large 20-year study found growth of gallbladder polyps to be common, with growth in 66% of polyps sized < 6 mm, and growth in 53% of polyps sized 6-10 mm [8]. A two-year follow-up study found that a total of eight out of 203 patients experienced growth of their gallbladder polyps [10]. It is evident that few polyps will increase in size over a long period of time. Malignancy is more common in polyps > 10 mm in size and differentiation by ultrasound examination between benign and malignant lesions is a challenge [7].

In 53 (34.5%) patients, the polyps had dissolved and were no longer present in the gallbladder. It is possible that polyps detected a decade ago during baseline were skinfolds, gallstones or mis-interpretations not representing a true polyp. A true polyp is a sessile lesion of the gallbladder wall compared to a pseudo polyp that typically appears more pedunculated and is often named a cholesterol polyp. However, it is often difficult to distinguish between true and pseudo polyps in clinical practice, e.g. it is common to find cholesterol polyps after cholectomy and not true polyps. Pseudo polyps may also

appear as multiple polyps in the gallbladder. A recent review from 2018 investigated differentiation between true and pseudo gallbladder polyps and found a risk of misclassification; e.g., in a population of 1,000 patients, a total of 32 with true polyps could be misclassified as pseudo polyps [14].

Similar to our findings, Heitz et al performed a polyp follow-up study after 11 years and found polyps confirmed in 51.9% of the patients and missing in 48.1% [3]. Corwin et al found that in 34%, the polyp had resolved [15]. Presence of cholelithiasis may often be misinterpreted as gallbladder polyps. However, it is possible that patients had developed cholelithiasis during the observations period as we found one patient with gallbladder stones at baseline versus 21 patients at the ten-year follow-up. Also, the cholelithiasis could have been falsely reported at baseline.

Gallbladder cancer varies significantly between ethnic groups, and has been reported at an incidence of up to 27/100,000 in American indigenous populations [16], whereas in Denmark the reported incidence is up to 7/100,000 [17]. With this low risk of gallbladder cancer, we did not expect to find any cancers in our population of patients with small gallbladder polyps. Consequently, it may be justified to omit the ultrasound follow-up in patents with small gallbladder polyps, as gallbladder cancer is an extremely rare form of cancer and almost no polyps will progress to cancer. Otherwise, patients with small gallbladder polyps will have a large number of unnecessary follow-up ultrasound examinations. As the risk of malignant transformation of small gallbladder polyps (2-6 mm) is very low, we propose that no further follow-up is warranted.

Limitations and strengths

One limitation of this study is its small study size. Another limitation is that we did not implement a ten-year follow-up of the group of patients with a gallbladder polyp size of 6-10 mm.

A strength of this single-centre cohort study was the cohort design; however, a multicentre study is required to validate our findings. Furthermore, all patients were asymptomatic at the time of the follow-up examination, and it is possible that results may be different in a population with symptomatic patients. Even so, it is important to keep in mind that abdominal ultrasonography is a non-invasive, non-radiation and non-contrast examination that is very quick, simple to perform and comes at a low cost. Most of the examinations were performed by highly experienced sonographers with up to 20 years of experience with gallbladder examinations. The sonographers perform ultrasonography of gallbladder polyps daily and are highly skilled.

CONCLUSIONS

Our study showed that gallbladder polyps < 6 mm had a low probability of increasing in size. No cases of gallbladder cancer were observed among the patients. The need for follow-up in patients with small gallbladder polyps is questionable.

Correspondence: *Malene Roland V. Pedersen*. E-mail: malene.roland.vils.pedersen@rsyd.dk

Accepted: 11 August 2020

Conflicts of interest: none. Disclosure forms provided by the authors are available with the full text of this article at Ugeskriftet.dk/dmj

Acknowledgements: The authors wish to extend their gratitude to *Karl Erik Stovgaard, Mads Fredslund* and *Claus Smedegaard* for their commitment to this project.

LITERATURE

1. Afzal A, Kristiansen VB, Rosenberg J. Gall bladder polyps. Ugeskr Læger 2001;163:5003-6.
2. Jørgensen T, Jensen KH. Polyps in the gallbladder. A prevalence study. Scand J Gastroenterol 1990;25:281-6.
3. Heitz L, Kratzer W, Gräter T et al. Gallbladder polyps - a follow-up study after 11 years. BMC Gastroenterol 2019;19:42.
4. Teber MA, Tan S, Dönmez U et al. The use of real-time elastography in the assessment of gallbladder polyps: preliminary observations. Med Ultrason 2014;16:304-8.
5. Bae JS, Kim SH, Kang HJ et al. Quantitative contrast-enhanced US helps differentiating neoplastic vs non-neoplastic gallbladder polyps. Eur Radiol 2019;7:3772-81.
6. Lee SB, Lee Y, Kim SJ et al. Intraobserver and interobserver reliability in sonographic size measurements of gallbladder polyps. Eur Radiol 2020;30:206-12.
7. Wiles R, Thoeni RF, Barbu ST et al. Managenemt and follow-up of gallbladder polyps. Eur Radiol 2017;27:3856-66.
8. Szpakowski J, Tucker L. Outcomes of gallbladder polyps and their association with gallbladder cancer in a 20-year cohort. JAMA Netw Open 2020;3:e205143.
9. Wiles R, Varadpande M, Muly S et al. Growth rate and malignant potential of small gallbladder polyps - systematic review of evidence. Surg 2014;12:221-6.
10. 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(10):A4503.
11. Bhatt NR, Gilis A, Smmothey CO et al. Evidence based management of polyps of the gall bladder: A systematic review of the risk factors of malignancy. Surg 2016;14:278-86.
12. Choi SY, Kim TS, Kim HJ et al. Is it necessary to perform prophylactic cholecystectomy for asymptomatic subjects with gallbladder polyps and gallstones? J Gastroenterol Hepatol 2010;25:1099-104.
13. Collett JA, Allan RB, Chrisholm RJ. Gallbladder polyps: Prospective study. J Ultrasound Med 1998;17:207-11.
14. Wennmacker SZ, Lamberts MP, Martino MD et al. Transabdominal ultrasound and endoscopic ultrasound for diagnosis of gallbladder polyps. Cochrame Database Syst Rev 2018;8:CD012233.
15. Corwin MT, Siewert B, Sheiman RG et al. Incidentially detected gallbladder polyps: is follow-up necessary? Long-term clinical and US analysis of 346 patients. Radiology 2011;258:277-82.
16. Hundal R, Shaffer E. Gallbladder cancer: epidemiology and outcome. Clin Epidemiol 2014;7:99-109.
17. NORDCAN Association of the Nordic Cancer Registries. Nordcan kræftstatistik: Nøgletal: galdeblære og galdeveje. 2012-2016. www-dep.iarc.fr/NORDCAN/DK/frame.asp (25 Jun 2020).