Review

Growth rate and malignant potential of small gallbladder polyps – Systematic review of evidence

Rebecca Wiles, Mandar Varadpande, Sudha Muly, Jolanta Webb*

Radiology Dept, Aintree University Hospital NHS Trust, United Kingdom

A R T I C L E  I N F O

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A B S T R A C T

The background and purpose: The overall aim of this systematic review was to determine whether ultrasound (US) follow up for gallbladder polyps (GBPs) measuring less than 10 mms is necessary.

Methods: A search was performed in MEDLINE and EMBASE between January 1976 and January 2012 using keywords: gallbladder, polyps, neoplasm, cancer, tumour, carcinoma, malignant, adenoma. Included were studies involving adult patients, examined with transabdominal US at least twice. The outcomes of included studies were gallbladder polyp growth as demonstrated on US over time, followed where available by histological examination of cholecystectomy specimens.

Main findings: Ten studies met the inclusion criteria for the review. Altogether 1958 subjects with mean age between 41.5 and 59 years were followed up with US. The percentage of GBPs which showed growth over the follow up period ranged from 1% to 23%. 43 neoplastic polyps were found in total irrespective of size, 20 of which were malignant and at least 7 of those were >10 mms. At least 7 malignancies were present in polyps <10 mms but it was unknown if they had undergone growth on follow up.

Conclusions: Level II-2 and below evidence on rate of growth of small GBPs <10 mms exists in the literature. It indicates that growth does occur in a significant minority of small GBPs, but it is slow. Due to deficient reporting and small numbers of cases, the correlation between growth of GBP and development of malignancy cannot be established using currently available evidence. Malignancy can be present in polyps <10 mms although it is significantly more frequent in polyps >10 mms. Cholecystectomy for symptomatic GBPs irrespective of their size, alongside the current practice for removal of gall bladders containing asymptomatic polyps >10 mms, is proposed. No evidence based US follow up schedule can be recommended at present for asymptomatic polyps <10 mms, and in its absence an intuitive follow up with US is likely to continue.

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* Corresponding author. Radiology Dept, Aintree University Hospital NHS Trust, Longmoor Lane, Liverpool L9 7AL, United Kingdom. Tel.: +44 (0) 151 529 6376. E-mail addresses: jolanta.webb@aintree.nhs.uk, jolantawebb@hotmail.co.uk (J. Webb).

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Introduction

Gallbladder polyp (GBP) is a growth protruding into its lumen from the inner gall bladder wall. Standard ultrasound (US) features of a GBP are: protrusion of internal gall bladder wall of similar echogenicity as that of the gall bladder wall and hyperechoic compared with the surrounding bile, lack of mobility, and no associated acoustic shadowing.¹

An appreciable number are actually pseudopolyps, representing focal accumulation of cholesterol or adherent calculi, but whilst US features suggestive of a pseudopolyp have been described, an overlap of pseudopolyps with both true polyps and gallstones is common, making US differentiation difficult.²

GBPs are reportedly diagnosed in up to 5% of the general population, with frequency increasing due to more patients having US scans and a better US technology.³

True GBPs can be non-neoplastic or neoplastic. Non-neoplastic polyps comprise hyperplastic and inflammatory polyps. Neoplastic polyps can be benign or malignant; the benign ones being adenomas, adenomyomas, leiomyomas, fibromas, and lipomas, whilst malignant tumours being adenocarcinoma, squamous cell carcinoma, and mucinous cystadenoma.

Although adenomas are benign, they are seen as being premalignant, with an adenoma-carcinoma sequence proposed.⁴ Four out of five cases of gall bladder cancer (GBC) are diagnosed at an advanced stage, with 5-year survival rates being <15% for tumours invading muscularis mucosae or beyond.⁵ It is not known how many GBCs are preceded by a GBP, but clearly differentiating the non-neoplastic from malignant or premalignant polyp is extremely important. This distinction, however, constitutes a major diagnostic challenge. Malignancy is more frequent in polyps with diameters of 10 mm or greater, presence of coexisting gall stones, solitary and symptomatic polyps, congenital and some acquired biliary anomalies, in females and with increasing patient age.⁶–⁹ Some studies have shown an increase in prevalence of GBPs in certain ethnicity.¹⁰ Of these factors, size of at least 10 mm is the predictor of malignancy in pre-existing GBPs. Majority of incidentally detected GBPs, however, are less than 10 mm in size and are often too small to allow accurate characterisation.

Current practice regarding the management of GBPs consists of cholecystectomy for lesions with a diameter of 10 mm or greater, and US follow-up for lesions smaller than 10 mm.

However, the threshold size above which polyps should be followed, the interval of follow-up, and its overall duration remain controversial. The knowledge about the long-term natural history of smaller than 10 mms GBPs is limited and there is no evidence based guidelines.¹¹

The primary aims of this systematic review were to identify, appraise and synthesise the evidence on whether:

- GBPs smaller than 10 mms grow over time when followed up
- growth of a GBP smaller than 10 mms, as identified on US, is an indicator of malignancy.

Methods and materials

Inclusion and exclusion criteria

The inclusion and exclusion criteria used for studies is outlined below (Table 1).

Study identification

We searched Medline and Embase via the Evidence Search databases. Papers published between January 1976 and January 2012 were included. The references for all included articles were reviewed and any relevant abstracts and full text articles were obtained and included in the review. Full search strategy is available from the authors.

Study selection

The initial list of titles followed by the abstracts for those studies which met the inclusion and exclusion criteria was reviewed independently by at least two reviewers.

For those papers whose abstracts met the inclusion criteria, the full text articles were obtained.

Data extraction

Data was extracted independently by two reviewers using the Strengthening the Reporting Skills in Epidemiology (STROBE) checklist.¹²

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Table 1 – Inclusion and exclusion criteria.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Only studies involving adult patients were included. Papers which dealt with other than transabdominal US imaging modalities were excluded.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Studies in which the patient has had at least one follow up US scan of the gallbladder were included.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Studies were included in which the outcomes were:</td>
</tr>
<tr>
<td></td>
<td>- gallbladder polyp growth as demonstrated on US over time, or</td>
</tr>
<tr>
<td></td>
<td>- gallbladder polyp growth as demonstrated on US followed by histological examination of cholecystectomy specimens.</td>
</tr>
<tr>
<td>Study design</td>
<td>Randomised controlled trials, cohort studies and case control studies were included. Case studies were excluded. Both retrospective and prospective studies were included.</td>
</tr>
<tr>
<td>Additional criteria</td>
<td>Studies were excluded if a reasonable effort to procure a copy of the paper either in print or online failed.</td>
</tr>
<tr>
<td>Language</td>
<td>English and Polish language papers were included.</td>
</tr>
</tbody>
</table>
Data synthesis

The studies included were heterogeneous in their methods and outcomes. As such a narrative approach was taken to data synthesis.

Quality assessment

Each article was assessed independently for quality by two reviewers using the Critical Appraisal Skills Programme (CASP) assessment tool. The two reviewers then discussed the papers together to come to a consensus about the overall paper quality.

Results

Search results

The database search returned 478 studies (Medline search identified 376 studies and Embase search identified 102 studies). 56 were duplicates.

On the basis of screening of titles 299 articles were deemed not relevant and thus excluded.

123 remaining abstracts were reviewed. On the basis of screening of the abstracts 112 papers were excluded as not fulfilling the inclusion criteria. Full text of 11 studies was obtained.

One study which used endoscopic US follow up of GBPs detected on transabdominal US was then excluded. Ten studies met the inclusion criteria for the review.

Characteristics of included studies

Ten studies reported on the primary outcome of growth of GBPs over time assessed by transabdominal US. Four were prospective cohort studies, five were retrospective cohort studies and one was a prospective cohort study with a control group. Table 2 summarises the main characteristics of the included studies.

Papers were published between 1996 and 2011 and used data collected since 1988 in seven countries (five from Australasia and Far East, two from Europe, one from North America and one from South America).

Raw data on the growth of GBP over time were provided in seven studies.

Raw data on the presence of gall bladder neoplasm in the removed GBPs were given in eight studies.

Participants

Altogether 1958 subjects were followed up with US. Mean age was between 41.5 and 59 years. There were approximately 52% males and 48% females. Studies used a variety of inclusion and exclusion criteria. Importantly, there was a mixture of asymptomatic and symptomatic patients.

Intervention

Follow up with US ranged from a mean of 17 months to 71 months duration. All studies had at least a proportion of patients with one follow-up US scan. In some studies patients had more than one follow-up US scan.

Table 2 – Main characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study, country, year and design</th>
<th>Percentage of polyps which grew</th>
<th>Growth rate</th>
<th>Total number of neoplastic polyps (number of malignant ones in brackets)</th>
<th>Was the malignant neoplasm in a polyp which grew on follow up?</th>
<th>Malignant polyp size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moriguchi et al., Japan, 1996</td>
<td>11.7%</td>
<td>Not reported</td>
<td>1 (1)</td>
<td>No</td>
<td>Not reported</td>
</tr>
<tr>
<td>Collet et al., New Zealand, 1998</td>
<td>Not reported</td>
<td>1.5 mms at 2 years, 1.1 mms at 5 years</td>
<td>0 (0)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Csendes et al., Chile, 2001</td>
<td>8% at 48 months, 3% at 96 months, 14% at 144 months</td>
<td>Not reported</td>
<td>0 (0)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Kratzer et al., Germany, 2008</td>
<td>23%</td>
<td>Mean 3.3 mms</td>
<td>0 (0)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Colechia et al., Italy, 2009</td>
<td>5.7%</td>
<td>Mean 2 mms</td>
<td>0 (0)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Ito et al., USA, 2009</td>
<td>6%</td>
<td>Mean 3.5 mms</td>
<td>8 (1)</td>
<td>Not reported</td>
<td>14 mms</td>
</tr>
<tr>
<td>Choi et al., South Korea, 2010</td>
<td>Not reported</td>
<td>0.9 mms over 62.7 months</td>
<td>2 (0)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Park et al., South Korea, 2010</td>
<td>3.5%</td>
<td>Not reported</td>
<td>9 (9)</td>
<td>Not reported</td>
<td>Mean 11.2 ± 4.9 mms</td>
</tr>
<tr>
<td>Shin et al., South Korea, 2010</td>
<td>Not reported</td>
<td>0.23 mms per month</td>
<td>20 (6)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Corwin et al., USA, 2011</td>
<td>1%</td>
<td>Mean 2 mms</td>
<td>3 (3)</td>
<td>No</td>
<td>2 polyps &gt;10 mms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 polyp 7–9 mms</td>
</tr>
</tbody>
</table>
Outcomes

All 10 studies reported both on the primary outcome of growth rate of GBPs over time and relationship between GBPs growth rate and neoplasia. Histological examinations of some or all polyps were available in 8 of those 10 studies.

Quality assessment

Table 3 summarises the quality assessment of the included studies.

All 10 studies had a protocol and specified their inclusion criteria. All ten studies reported on their pre-specified outcomes.

Study findings

Seven studies reported on the primary outcome by measuring the size of GBP at baseline and at follow up. The percentage of GBPs which showed growth over the follow up period carried out in these studies ranged from 1% to 23%. Four studies reported growth in <10% of GBPs and two studies reported growth in >10% but <15% of GBPs.

The mean size by which the polyps grew during the follow up period was reported in four out of these 7 studies, and ranged between 2 mms and 3.5 mms. No growth (either static size or decrease in size) was reported in between 78% and 99% of followed up GBPs.

Three studies reported on the primary outcome by measuring the change in size of GBP over time. Choi et al. showed the mean change in size of 0.9 mms over 62.7 months follow up. Shin et al. reported growth of 0.23 mms/month in non-neoplastic GBPs and 0.37 mms/month in neoplastic polyps (p 0.031) but no association between polyp growth rate and neoplastic histology. Collett et al. reported growth of 1.5 mms at 12 months follow up and 1.1 mms at 60 months follow up.

In 8 studies histological findings in gall bladders diagnosed on US as containing GBPs and removed during cholecystectomy were reported. Cholecystectomies were performed for a variety of reasons, which were not necessarily related to the presence of GBPs. In one study (Shin et al.), histological result was available for all enrolled patients.

In one study (Park et al.) the number of performed cholecystectomies has not been given.

In the remaining 6 studies a proportion of patients, usually a minority, underwent cholecystectomy. In total 418 known cholecystectomies in presence of GBPs were performed in addition to an unknown number of cholecystectomies in the study by Park et al.

Forty-three neoplastic polyps were found in total, irrespective of size. Of these, 20 were malignant neoplasms (19 adenocarcinomas and 1 squamous cell carcinoma) and 23 were benign neoplasms (21 adenomas and 2 metaplastic adenomas).

The size of malignant neoplastic polyps was larger than 10 mms in at least 7 out 20 cases.

Two of these have arisen in polyps that were already >10 mms on the baseline scan. It was not reported if the remaining 5 malignant polyps grew to reach this size during follow up or if they were of such size at baseline study.

At least 7 malignancies were present in polyps smaller than 10 mms (but larger than 5 mms). It was not reported if these had undergone growth on follow up.

In 6 further cases it was not stated what the size of the malignant polyp was, neither was it reported if the polyp grew on follow up.

Discussion

Ten studies satisfied the inclusion criteria aiming to assess change in size of GBP over time.

They had variable design, follow up duration and reporting formats.

Nine studies concluded that the risk of development of malignancy in small polyps was low and that there was no correlation between growth and development of malignancy. One study cautioned that even small polyps can harbour malignancy, and indeed seven of 418 cholecystectomy specimens contained gallbladder malignancy in polyps <10 mm (but >5 mms).

It is noted that decrease in size or disappearance of some polyps during follow up was observed in most studies.

---

Table 3 - Quality assessment of included studies.

<table>
<thead>
<tr>
<th>Study author, date, country</th>
<th>Cohort recruited in acceptable way?</th>
<th>Outcome accurately measured to minimise bias?</th>
<th>Follow up complete enough?</th>
<th>Follow up long enough?</th>
<th>Results fit with other available evidence?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi et al., 2010, South Korea</td>
<td>Yes</td>
<td>Cannot tell</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ito et al., 2009, USA</td>
<td>Yes</td>
<td>Cannot tell</td>
<td>Cannot tell</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Park et al., 2009, South Korea</td>
<td>Yes</td>
<td>Yes</td>
<td>Cannot tell</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Kratzer et al., 2008, Germany</td>
<td>Yes</td>
<td>Yes</td>
<td>Cannot tell</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Colecchia et al., 2009, Italy</td>
<td>Yes</td>
<td>Cannot tell</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Corwin et al., 2011, USA</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Shin et al., 2009, South Korea</td>
<td>Yes</td>
<td>Cannot tell</td>
<td>Cannot tell</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Moriguchi et al., 1996, Japan</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Csendes et al., 2001, Chile</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Collett et al., 1998, New Zealand</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
It was clear that the risk of malignancy was significantly higher in polyps larger than 10 mms whether or not they were demonstrated to grow over time.

Of note was a slightly higher preponderance of GBPs in men in the reviewed studies, at odds with the known prevalence of GBC being more than twice as common in women. It could be hypothesised, therefore, that a GBP in a woman is more likely to be malignant than in a man.

**Summary of effectiveness of primary outcome**

**Quality of the evidence**

Studies showed variable design, concerning patient selection, follow up duration and frequency, measurement methodology, analysis of the obtained data and reporting.

Samples were mostly small and power calculations not performed, which in view of low prevalence of GBC was of importance. One study (Park et al.,¹⁸) followed up 1,027 patients for >12 months, but all the others were only following up between 31 (Kratzer et al.,¹⁶) and 176 (Choi et al.,²⁵) patients.

Patients’ ethnicity was not taken into account during selection of patients in any of the studies.

The stratification in size of the polyps into <10 mms and >10 mms was not reported in most of the studies.

Growth of polyps was inconsistently defined, varying between change of 2 mms or 3 mms when specified, but often the definition of growth was not specified.

In cases of multiple polyps only change in size of the largest polyp was usually reported so a smaller polyp may have grown without there being a documentation of this. Also in presence of multiple polyps histological correlation is more debatable.

The equipment used varied in quality, with older studies using ultrasound machines with lesser resolution than modern scanners, although still considered of diagnostic quality.

**Implications for practice and further research**

The review does answer the first primary objective which concerns the rate of growth of GBPs. It does not answer the second of the primary objectives regarding development of malignant neoplasms in growing small polyps <10 mms because the reporting did not include all the relevant information and incidence of GBC is very low. There were, however, malignant neoplasms present in smaller polyps measuring <10 mms.

The findings of this review have potentially significant implications for practice. Presence of malignant neoplasms in a small percentage of GBPs measuring below 10 mms challenges the current practice of only removing gall bladders containing polyps measuring >10 mms. No literature evidence for growth of a GBP being indicative of a developing malignancy leaves the question whether to serially follow up GBPs <10 mms unanswered. In the absence of evidence either supporting or disputing that the growth of a GBP is a sign of a GBC, two approaches could be taken. One would be a cholecystectomy for symptomatic GBPs irrespective of their size, perhaps considering the sex of the patient, in that a polyp in a woman may be more likely to be malignant. This would help to ensure that even small GBCs are removed in the process, but at a cost of a high number of unnecessary cholecystectomies.

Another approach would be continuation of the current practice of following up GBPs with serial US, perhaps at longer intervals in view of the proven slow growth rate, until they reach 10 mms, and then performing a cholecystectomy, at a cost of a high number of additional US examinations. Unfortunately there is also no evidence for a cut off point of size below which no action is necessary, however for pragmatic reasons the existing practice of not following up asymptomatic GBPs ≤5 mms is justified. In the economic reality and in view of low prevalence of GBC, neither of these approaches seems very practical.

Further shortcoming of these two approaches is the poor specificity of US. A recent study questioned the value of following GBPs up at all, in view of 50% of GBPs diagnosed in cholecystectomy specimens having been missed by transabdominal US.²⁴ Another one reported that 82% of US-diagnosed GBPs were not polyps on histology.²⁵

Future research into a technology allowing to distinguish pseudopolyps from true polyps based on their sonographic appearance would be very welcome.

Economic analysis of the cholecystectomy for symptomatic polyps <10 mms and of following up asymptomatic small polyps with serial US should be performed. In view of lack of evidence on growth-neoplasia link for GBPs, an economic model for the frequency of US follow up, based on prevalence of GBPs and GBC in general population, could be developed.

Future research could be more usefully concentrated on carrying out studies in the populations with high frequency of GBC.

**Conclusion**

Level II-2 and below evidence on rate of growth of small GBPs <10 mms exists in the literature. It indicates that growth does occur in a significant minority of small GBPs, but it is slow. Due to deficient reporting and small numbers of cases, the correlation between growth of GBP and development of malignancy cannot be established using currently available evidence. Malignancy can be present in polyps <10 mms although it is significantly more frequent in polyps >10 mms. Cholecystectomy for symptomatic GBPs irrespective of their size, alongside the current practice for removal of gall bladders containing asymptomatic polyps >10 mms, is proposed. No evidence based US follow up schedule can be recommended at present for asymptomatic polyps <10 mms, and in its absence an intuitive follow up with US is likely to continue.

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REFERENCES