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Review

The risk of malignancy in ultrasound detected gallbladder polyps: A systematic review☆

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HIGHLIGHTS

- The potential malignant risk of gallbladder polyps (GBPs) is low, but missing gallbladder cancer is potentially catastrophic.
- A cholecystectomy should be considered in any patient with a GBP of size of 10 mm or greater.
- For polyps of less than 10 mm, follow-up with Ultrasound imaging should be carried out until the stability of a GBP is firmly established.
- Where there is uncertainty, the patients should be managed within a recognised hepatobiliary centre.

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ABSTRACT

Introduction: Gallbladder polyps (GBPs) are a common incidental finding on ultrasound (US) examination. The malignant potential of GBPs is debated, and there is limited guidance on surveillance. This systematic review sought to assess the natural history of ultrasonographically diagnosed GBPs and their malignant potential.

Methods: The keywords: "Gallbladder" AND ("polyp" OR "polypoid lesion") were used to conduct a search in four reference libraries to identify studies which examined the natural history of GBPs diagnosed by US. Twelve studies were eligible for inclusion in this review.

Results: Of the 5482 GBPs reported, malignant GBPs had an incidence of just 0.57%. True GBPs had an incidence of 0.60%. Sixty four patients of adenomatous and malignant polyps were reported. Only in one patient was a malignant GBP reported to be <6mm. Risk factors associated with increased risk of malignancy were GBP >6mm, single GBPs, symptomatic GBPs, age >60 years, Indian ethnicity, gallstones and cholecystitis.

Conclusion: With the reported incidence of GBP malignancy at just 0.57%, a management approach based on risk assessment, clear surveillance planning, and multi disciplinary team (MDT) discussion should be adopted. The utilization of endoscopic ultrasound(EUS) should be Only considered on the grounds of its greater sensitivity and specificity when compared to US scans.

1. Introduction

The incidental detection of gallbladder polyps (GBPs) is more frequently being reported as the use and the quality of ultrasound (US) scanning increases [1–4]. The term GBPs or polypoid lesions of the gallbladder refers to any elevated lesion of the mucosal surface of the gallbladder wall. These polyps have been classified into adenomatous polyps, pseudotumours and malignant polyps [5–7].Evidence suggests that adenomas (an example of a "true tumours") have malignant potential, though this is a subject of debate, with conflicting opinions on the validity of an adenoma-adenocarcinoma pathway [8–11].

Polyps are incidentally detected in 0.3–12.3% of patients who undergo ultrasonography (US) of the gallbladder, or

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cholecystectomy [12–25]. The malignant potential of these lesions is small but significant, with previous studies suggesting between 3 and 8% of all GBPs are malignant [26,27]. Studies investigating the malignant potential of GBPs are however often limited by numbers with the majority including less than 100 patients [1,28,29].

Factors associated with an increased risk of malignancy are the subject of debate, and a number have been proposed to be significant including; increasing age, the presence of gallstones, gallbladder wall thickening, rapid polyp growth, a sessile polyp on US, smoking, Indian ethnicity, and symptomatic polyps [11,30–32]. Studies tend to agree that the larger the polyp the higher the risk of malignancy, with some studies reporting a malignant risk of between 45 and 67% in polyps measuring between 10 and 15 mm [2,7,14,30,31,33–48]. Studies are unclear whether gender is a risk factor for malignancy [16,17,44,49,50].

Current literature advise that all GBPs greater than 10 mm in diameter and/or causing symptoms should be surgically removed [49]. There is no clear guidance on how best to manage those patients not offered surgery at the outset. It has been suggested GBPs less than 10 mm may be safely followed conservatively, yet the frequency, duration and mode of surveillance remain unclear [40]. The aim of current practice is to promote early detection and treatment of potential or actual malignant polyps, as detection of gallbladder carcinoma (GBC) at either stage 1 or 2 carries 95–99% and 70% 5-year survival rates respectively [51]. In contrast GBC discovered at stage 3 or 4 has only a 5–12% 5-year survival rate [52].

Given the advances in radiological imaging, and the absence of evidence-based guidance on follow-up surveillance protocols for those patients not offered surgery at diagnosis, this review has sought to further investigate evidence to inform practice. This systematic review seeks to summarise the available literature and provide guidance on the risk of an ultrasound detected gallbladder polyp being either a true polyp or a gallbladder malignancy, and the relevant risk factors to consider in such patients.

2. Methods

2.1. Study protocol

A search of PubMed, DISCOVER (University of Liverpool), Scopus and ScienceDirect was conducted using the keywords:

"Gallbladder" AND ("polyp" OR "polypoid lesion")

The titles and abstracts were reviewed to establish potential eligibility, based on the criteria listed in Table 1. Duplicate references were excluded. All potentially relevant studies were retrieved and assessed for eligibility and data quality by two reviewers. The bibliographies of each included study were searched for other potentially relevant studies. Studies were assessed for both relevance and study quality.

Table 1
Review inclusion criteria.

Inclusion criteria
• Papers including the keywords: *"Gallbladder" AND ("polyp" OR "polypoid lesion")*
• Language of paper: English
• Study subject: Human
• Publish date: Post 1950
• Studies assessing the risk of malignancy in cases of gallbladder polyps
• Studies assessing the natural history of gallbladder polyps when followed up using Ultrasound.

2.2. Study selection

Studies that were included described patients who had GBPs detected by US. Studies were only included if they followed up the natural history of GBPs, or assessed their risk of malignancy.

2.3. Data extraction

Data extraction was performed using a standardised data extraction form. Information collected included the year of publication, country of origin, prevalence of GBPs, patients' demographics, size and distribution of GBPs, indications for cholecystectomy, histological results and follow up.

3. Results

3.1. Search results

The search identified 3744 references; following title review 474 abstracts were retrieved. Following dual author review 80 abstracts were deemed potentially relevant and retrieved for full paper review. Twelve papers were selected for inclusion in this systematic review, ten from the initial search and two from a search of the bibliographies of the eighty papers included for a full article review (Fig. 1).

3.2. Descriptive analysis of included studies

3.2.1. Quality of studies and risk of bias

Only twelve papers met inclusion criteria. Follow-up varied from eighteen months to eight years. Study group size varied from 34 to 18,610 patients. There was marked variance in study designs, five were retrospective [27,32,40,48,53] and seven were prospective [1,22,28,29,54–56].

A diagnosis of GBP is subject to a degree of observer bias, and all studies attempted to minimise observer bias by implementing standardised criteria for the diagnosis of GBPs. Ansari et al. had four sonographers/radiologists independently review patient US images and combine the radiology reports [28]. Kratzer et al. had eight trained assistants perform the US examinations [29].

Five studies retrospectively reviewed radiological reports to assess patients followed-up by ultrasound [27,32,40,48,53]. Corwin et al. reviewed the reports alongside the US images, with two authors assessing each image, whilst in the four other studies radiological reports were reviewed in isolation. The studies comment on the difficulties of reviewing reports retrospectively, as the quality of images is significantly lower than those during live imaging.

Aldouri et al. did not specifically study GBPs [32]. They studied the significance of ethnicity with regards to a patient's risk of gallbladder malignancy. As a result, there was some difficulty relating their data to GBPs.

3.2.2. Prevalence of gallbladder polyps

Two of twelve studies were able to calculate the prevalence of GBPs in their population. In a population of diabetic and non-diabetic out-patients the prevalence was calculated as 6.7% [1]. In a population of a rural German community the prevalence was significantly lower at 1.4% [29]. Both studies reported a higher prevalence of GBPs in males.

3.2.3. Demographics of patients with gallbladder polyps

Ten of twelve studies reported the age range of their populations. In nine studies the youngest patient was aged 14–25 years, and the oldest 74–94 [1,22,27,29,32,40,48,53,56]. The one remaining study had a narrower age range, 35–63 years of age [54].

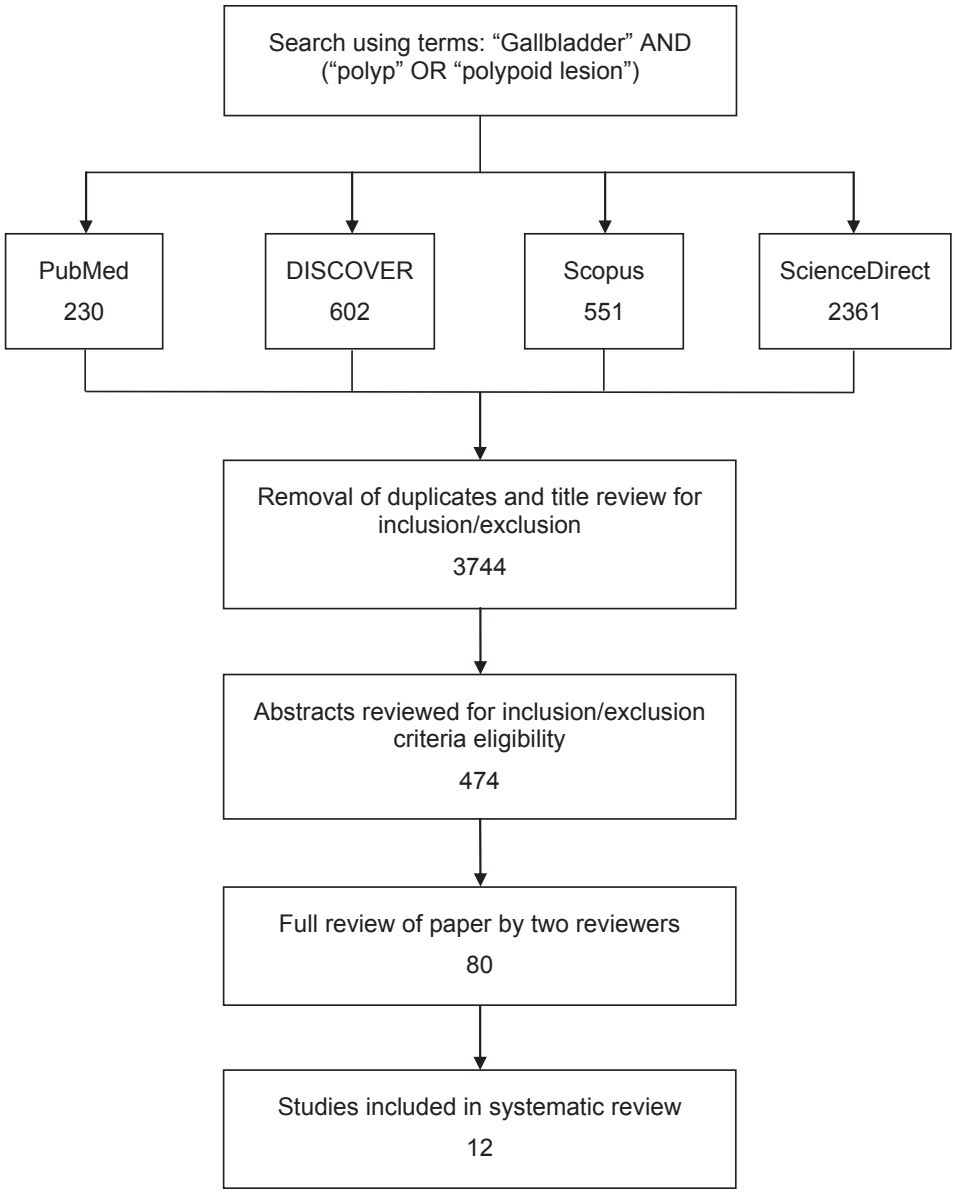

Fig. 1. Consort diagram showing systematic search process.

Ten of the twelve studies reported the gender distribution. Seven studies had a female predominance [22,27,32,40,48,53,56]; three studies had a male predominance [1,29,54]. The ratio of male to female varies from 1:1.28 to 1.92:1. Collett et al. reported the highest difference, though it should be noted this is in a study population of only 38 [1].

3.2.4. Gallbladder polyp description

Eleven of twelve studies reported the distribution of single and multiple polyps. Nine initially reported between 50.7 and 89.5% were single. One study reported that 59% of GBPs were multiple at 5 years follow-up [1].

Eleven of twelve studies reported the size distribution of GBPs. In eight studies, GBPs<5 mm accounted for over 50% of polyps. GBPs >10 mm accounting for 0–12.3% of GBPs in ten studies and 44.8% in the last study. GBPs measuring 6–10 mm accounted for 16.4–42.1% of polyps.

3.2.5. Follow-up

All twelve studies reported length of follow-up. Median follow-up length varied from 1.4 to 5.9 years. The greatest range of follow-up length in one study was 1.75–12 years, a similar range was reported in a second study [40,53].

Ten of twelve studies reported the follow-up rate over the study period. Four studies reported follow-up rates of 91.9–100% at the end of the study period [22,28,54,55]. Three studies reported follow-up rates of <50% by the end of the study period [40,53,56].

Nine of twelve studies recorded the appearance of GBPs on follow-up, with 50.0–94.3% of GBPs were stable or decreased in size on follow-up GBPs increasing in size on follow-up ranged from 5.0 to 26.5%. Seven of nine studies reported a significant proportion of GBPs, between 1.6 and 40.9%, were not visualised on follow-up [22,29,48,53,55,56].

3.2.6. Indications for cholecystectomy

Five of twelve studies reported indications for cholecystectomy

Table 2
Summary of histological results post-cholecystectomy.

Study	Number of cholecystectomies	Pseudopolyps[a]	True GBPs[a]	Malignant GBPs[a]	No GBPs[b]
Pedersen et al.	13	7 (53.8%)	0 (0%)	0 (0%)	6 (46.2%)
Csendes et al.	27	24 (88.9%)	0 (0%)	0 (0%)	3 (11.1%)
Corwin et al.	42	10 (23.8%)	2 (4.8%)	0 (0%)	30[c] (71.4%)
Ansari et al.	31	24 (77.4%)	0 (0%)	2 (6.5%)	5 (16.1%)
Kratzer et al.	0				
Ito et al.	80	46 (57.5%)	8 (10.0%)	0 (0%)	26 (32.5%)
Park et al.	172	139[d] (80.8%)	19 (11.0%)	14 (8.1%)	0 (0%)
Aldouri et al.	Unclear			4	
Collett et al.	0				
Moriguchi et al.	4	4 (100%)	0 (0%)	0 (0%)	0 (0%)
Colecchia et al.	0				
Sugiyama et al.	58	43 (74.1%)	4 (6.9%)	11 (19.0%)	0 (0%)
Total	427 (100%)	297 (69.6%)	33 (7.7%)	31 (7.3%)	70 (16.4%)

[a] As classified by Christensen and Ishak [5].
[b] Patients referred for cholecystectomy in which on histological examination no polyp was present.
[c] In one patient, polyp was seen at surgery but not at pathological examination.
[d] Park et al. did not specifically report the histological results of all cholecystectomies, for the sake of analysis, the results unaccounted for were presumed to be pseudopolyps.

[28,29,48,53,56], four studies did not report indications [27,32,40,55], and in two studies no patient underwent cholecystectomy [1,54].

GBP >10 mm and increase in GBP size on follow-up accounted for over 50% of indications in three studies (51.9–66.0%) [28,29,56].

3.2.7. Histological results

Eight of twelve studies reported patients undergoing cholecystectomy and recorded histological results (Table 2). Number of cholecystectomies ranged from 4 to 169.

Adenocarcinomas were the only malignant GBPs, and with 31 patients accounting for 7.3% of histological diagnoses. The only True GBPs reported were adenomas, and 33 patients were reported, accounting for 7.7% of histological diagnoses.

Four of the eight studies reported adenomas, 2–19 patients (1–11.0%) [27,48,53,55]. Four studies reported adenocarcinomas, 2–14 patients (6.5–19%) [27,28,32,55].

Seven studies reported Pseudopolyps, accounting for 69.6% of all GBPs seen at histology (n = 297). Five studies reported cases of no GBP seen at histology, accounting for 16.4% of all cholecystectomies. 368 of 427(86.2%) cholecystectomies showed pseudopolyps or no GBP.

3.3. Risk factors associated with true benign and malignant gallbladder polyps

3.3.1. Size

The size of GBPs was the most commonly assessed risk factor. Of 64 patients of true and malignant polyps in this review, only one patient was reported to be < 6 mm. This was a 4 mm adenocarcinoma in a patient of Indian ethnic background [32].

The size of the reported malignant polyps was assessed where possible (16 of 31 patients). Of these, just one (6.3%) patient was <6 mm in size, three (18.8%) patients were between 6 and 10 mm in size and twelve (75.0%) patients were ≥10 mm in size.

The size of the reported true polyps was assessed where possible (14 out of 33 patients). No true polyps were reported to be < 6 mm, six (42.9%) were 6–10 mm in size and eight (57.1%) were ≥10 mm in size.

Of the 5482 GBPs diagnosed in across these twelve studies, just 31 patients of malignant GBPs were reported, an incidence of 0.57%. Patients with true GBPs accounted for an incidence of 0.60% (n = 33). Meaning that in patients with an ultrasound diagnosis of GBPs and an indication for surgery, the actual incidence of either a true or malignant GBP is just over 1%.

3.3.2. Single and multiple GBPs

Park et al. reported no significant difference in risk of malignant polyps in either single or multiple polyps(P value = 0.64, 95% CI 0.425–1.692) [27]. Aldouri et al. concluded single GBPs above the size of 10 mm were a significant risk factor for gallbladder malignancy [32]. Both adenomas reported by Corwin et al. were single polyps [53]. Other studies within the review did not report whether true and malignant polyps were single or multiple GBPs.

3.3.3. Growth of GBPs on follow-up

The growth of GBP on follow-up was a recognised risk factor for malignancy within the studies, and was an indicator for cholecystectomy in three studies, however, none of such polyps turned out to be malignant [28,40,56]. Park et al. reported that 15 of 33 patients of true and malignant GBPs were <10 mm, and their growth on follow-up was an indicator of potential malignancy [27].

3.3.4. Other potential risk factors

Aldouri et al. concluded that age >60 years, gallstones, gallbladder wall thickening and Indian ethnicity were factors associated with increased risk of gallbladder malignancy, but due to the study design, the factors strongly associated with GBP malignancy could not be assessed [32].

In contrast Park et al. reported that increasing age was not a risk factor, though they concurred that gallstones significantly increased risk of malignant GBPs(P value = 0.001, 95% CI 1.849–9.854) [27]. They also concluded that none of sex, diabetes or other malignant diseases increased risk of malignant GBPs.

3.3.5. Risk factors

Established risk factors for true and malignant GBPs that are considered proven in the studies included are:

- Size greater than 6 mm, with risk increasing with size.
- Growth of polyp during follow-up [27].
- Single polyp [27,32,53].
- Indian ethnic background.

Risk factors for true and malignant GBPs that may be significant but not yet firmly established are:

- Gallstones.

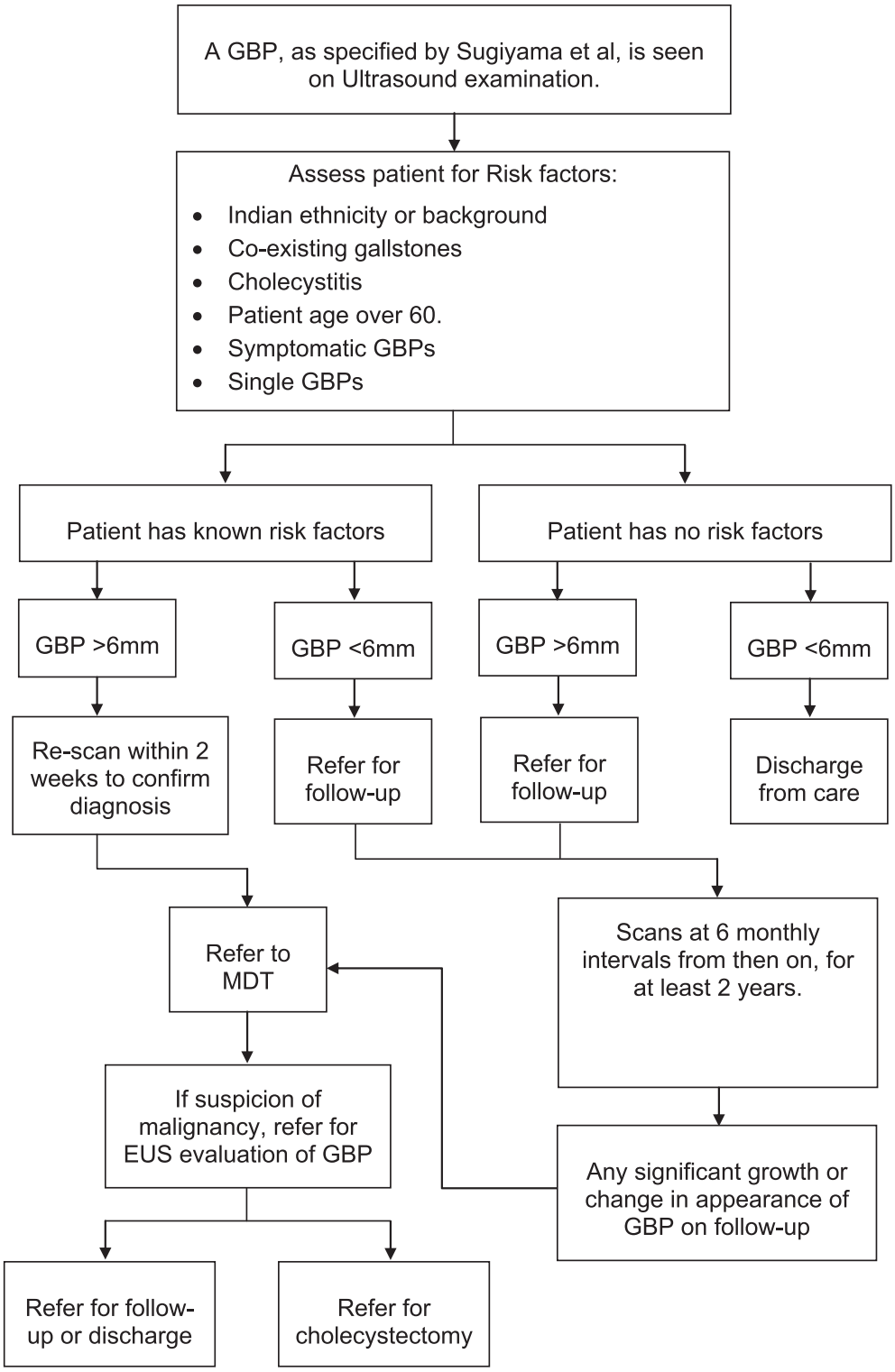

Fig. 2. Recommended guidelines for management of GBPs.

- Gallbladder wall thickening.
- Cholecystitis or other persistent symptoms (abdominal pain).
- Age above 60 years

None of the included studies has discussed the risk of malignant GBPs associated with primary sclerosing cholanigitis (PSC).

4. Discussion

The twelve studies included in this systematic review, indicate that the incidence of a true or malignant GBP is low, with GBPs <6 mm not posing significant malignant risk unless associated with known risk factors. Prevalence of GBPs is low, reported at 1.4–6.7% in this review. Subsequently, any study assessing GBPs must deal

with the difficulties associated with limited study populations.

Included studies focused largely on the size and number of polyps, and how this alters over follow-up. This approach, inadvertently, has made it difficult to identify other significant risk factors associated with malignant GBPs. Furthermore; several studies fail to fully report histological results, or even analyse the size of true and malignant polyps.

The size of a GBP is largely regarded as the most significant indicator of potential malignancy, with studies concurring that GBPs >10 mm in size warrant cholecystectomy [7,26,30,43,57–59]. Kubota et al. found that 88% of malignant polyps were over 10 mm, and within this review, 75% of reported patients of adenocarcinomas were over 10 mm at diagnosis [30].

The prevalence of GBPs is estimated to be between 0.3 and 12.3% based on a combination of surgical and population studies [1,12–17,29]. Within this study, prevalence was reported to be within this range (1.4% and 6.7%), though the figures differed by 5.3% [1,29]. With such a wide range in reported prevalence, it is likely that population demographics have a largely unappreciated impact on prevalence.

All studies in this review implemented standardised criteria for diagnosis of GBPs, whether from the Author's experience or as specified in previous studies [49,60–63]. Despite criteria, this review indicates a significant number of GBPs are not seen at histological examination post-cholecystectomy, with the incidence of no GBP at histology accounting for 16.4% of all reported histological results within this review. This concurs with findings of previous studies, with author's theorising that a significant number of GBPs seen on US are in fact gallstones, adherent sludge or cholesterol polyps that slough off prior to surgery [14,26,28,40,44,48,54,56].

Of patients where a GBP seen at US examination was present at histology, 83.2% of GBPs were diagnosed as Pseudopolyps. The most common of which were cholesterol polyps (114 cases). This concurs with previous studies that indicate cholesterol polyps may account for over 70% of all GBPs seen on US examination [26,33,63,64].

Previous studies have reported high incidences of malignancy in GBPs >10 mm, yet this review reported malignancy in just 7.55% of all GBPs >10 mm [65,66]. With this review reporting that GBPs>10 mm have a very low incidence, just 4.17% of GBPs, indicating that the risk of malignancy in incidentally US detected GBPs could be potentially overestimated.

Current literature advise cholecystectomy for all GBPs >10 mm and US follow-up for GBPs <10 mm [15,26,44,67,68]. Length of follow-up is ill-defined, with current evidence only indicating it should be 'lengthy', commonly at 6 or 12 month intervals [15,26,44,67,68]. This review demonstrated median follow-up of 1.4–5.9 years. Park et al. reported a patient in which it took seven years for the growth of a neoplastic GBP to be recognised, though the majority of neoplastic GBPs reported were detected much earlier, either at baseline or in early follow-up [27]. A recent report concluded that dysplasia to adenocarcinoma transformation may take over ten years, supporting long periods of follow-up for GBPs [69].

GBPs are almost exclusively diagnosed and followed-up by ultrasonography, despite multiple studies challenging its ability to do so accurately, as it remains the most appropriate and cost-effective method of screening [25,70,71]. Sugiyama et al. reported that US correctly diagnosed GBPs prior to cholecystectomy in 76% of 58 cases, though endoscopic ultrasound (EUS) demonstrated greater accuracy and was correct in 97% of cases [55]. Higher accuracies of US have been recorded; Yang et al. reported false positives in just 6% of their patient population [7]. Conversely other studies have reported US accuracy to be as low as 47% [13,49].

With the accuracy of US in assessment of GBPs being questioned, confirmed by failure to find the GBPs reported by US at a significant number of histological examinations, it seems prudent to suggest utilization of other imaging modalities such as Magnetic Resonance Cholangio-Pancreatography (MRCP), Positron Emission Tomography -Computed Tomography (PET-CT), or the reportedly higher accuracy of EUS in assessment of GBPs, especially where cholecystectomy is being considered. EUS may be invasive but does not carry the same risks as cholecystectomy [72]. In contrast, whilst risks of cholecystectomy are small, they are significant, including mortality resulting from vessel, bowel a bile duct injuries (reported incidence 0.3–1%) [73–75].

The major limitation of this review was the confidence with which data from the twelve studies could be comparatively analysed. A lack of uniform reporting of data hampered inter-study comparison, which made it difficult to assess GBP demographics, and more importantly to accurately assess the size range within which true and malignant GBPs were measured. The retrospective design of five of the studies also limits this review, as all, or a number of, patients with GBPs were reviewed/followed-up with sole use of radiological reports, without US images [27,32,48,53,56]. Though even in cases where US images were reviewed, it is noted they have suboptimal quality compared to those during live-imaging [56].

On the basis of the current evidence obtained from the available literature, it is very difficult to design a robust, evidence based management and follow-up plan for patients with US detected GBPs. Nevertheless, a proposed flowchart for management of GBPs has been designed to aid in the future management of this topical, yet controversial pathology (Fig. 2).

Despite the limitations of the available literature, this is the largest review of studies examining the natural history of ultrasonographically diagnosed GBPs to date.

5. Conclusion

The potential malignant risk of GBPs is low, but missing a GBC is potentially catastrophic. By applying the known predictors of malignancy, and utilising advanced methods of assessment, such as EUS, it should be possible to more effectively inform the management of patients with GBPs. Based on this review of the evidence, and recent recommendations by similar review [76], the authors recommend that a cholecystectomy should be considered in any patient with a GBP of size of 10 mm or greater. For polyps of less than 10 mm, follow-up with Ultrasound imaging should be carried out on a six monthly basis, for at least 2 years until the stability of a GBP is firmly established (Fig. 2). If there is evidence of growth, the option of cholecystectomy should be discussed with the patient. Ideally, where there is uncertainty, the patients should be managed within a recognised hepatobiliary centre with expertise in the management of biliary tract malignancy.

Ethical approval

Not applicable.

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Author contribution

Mohamed Elmasry: Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing and Manuscript review.

Don Lindop: Study concepts, Study design, Data acquisition,

Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing and Manuscript review.

Declan Dunne: Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Manuscript preparation, Manuscript editing and Manuscript review.

Graeme Poston: Manuscript editing and Manuscript review.

Hassan Malik: Manuscript editing and Manuscript review.

Stephen Fenwick: Study concepts, Study design, Manuscript preparation, Manuscript editing and Manuscript review.

Conflict of interest

The authors declare no conflict of interest.

Trial registry number

Not applicable.

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Mohamed Elmasry.
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