

Gallbladder Polyps—A Review

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ABSTRACT

Gallbladder polyps are being increasingly detected due to availability and widespread use of advanced imaging modalities for evaluation of abdominal lesions. Hence, physicians should know about the course of these polyps so that the patients are treated

in light of the best clinical evidence. This article reviews various aspects of gallbladder polyp development and management in the light of recent literature.

Keywords: Gallbladder polyp (GBPs); Cholecystectomy; Risk factors, Imaging, Malignancy; Follow up

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INTRODUCTION

Gallbladder polyps (GBPs) are lesions that protrude from the mucosal lining of the gallbladder wall into the gallbladder interior. With the widespread use of abdominal imaging, GBPs are becoming an increasingly common incidental finding [1-4] and are reported in as many as 7% ultrasonographic images of gallbladder [2].

The differential diagnosis for the GBPs is wide and includes benign and malignant lesions. Benign polyps include pseudotumors (cholesterol polyps, inflammatory polyps, cholesterosis and hyperplasia), epithelial tumors (adenomas) and mesenchymatous tumors (fibroma, lipoma and haemangioma), whereas malignant GBPs are generally adenocarcinomas [3]. On one hand, the benign lesions may either need no active management or can be cured by cholecystectomy. While on the other hand prognosis of gallbladder carcinoma is poor; meaning thereby that it is important to accurately differentiate between benign polyps and malignant or premalignant polyps [3].

The present review summarizes various factors related to GBPs, including the prevalence, risk factors, clinical presentation, diagnostic modalities and the current trends in management in light of the current literature.

A simple review of the evidence related to GBPs was performed after deriving references from PubMed Central, Medline, Cochrane Database, HINARI, AJOL, Scopus, Bioline International, Cogprints, Open-med, MD Links and IndMed. The search /MeSH terms included gallbladder

polyps, polypoid lesions of gallbladder, multiple gall bladder polyps, gallbladder cancer, epidemiology and management of gallbladder polyps. References published in the last decade were preferred. Older references were cited only when no appropriate reference was available from the recent literature.

PREVALENCE

The prevalence of GBPs in normal adults varies from 0.3% to 9.5 % in different regions and population groups. A study from India found prevalence of 0.32 % [5] whereas studies from Europe found prevalence of around 4.5% in Denmark [6] and 1.5% in Germany [7]. In Chinese population, the overall prevalence of GBPs was 9.5% [8] in one study and 6.9% in another study [9]. In the Japanese adult population, polyps were found in 5.6% [10].

RISK FACTORS

Various factors have been postulated to be associated with the occurrence of GBPs. These factors include:

1. **Age:** Studies have generally reported a predilection of GBPs in the fourth and fifth decades of life although this is not generally agreed upon [6, 11]. For example, middle age was associated with GBPs in one study from Chinese population [8] while another study from the same population could not find such an association [12]. However, GBPs are reported rarely in children [13].

2. **Gender:** Multiple studies have found that polyps are more prevalent among males with odds ratios ranging from 1.7 to 2.3 [12-18]. Adenomatous and adenocarcinomatous polyps are however more prevalent in females [19].
3. **Ethnic Background:** Different population groups have widely variable prevalence of GBPs. The reported prevalence in Chinese population is 9.5%, in Indians living in India it is 0.32%, in Indians living in the United Kingdom it is 3.3%, and in German population, the prevalence is 1.5% [5, 8, 12, 17, 20]. Different factors have been pointed out for high prevalence of GBPs in particular ethnic groups. Chen Y et al [12] found glucose intolerance to be a risk factor in Chinese population but a wide range of demographic characteristics and biochemical parameters, such as age, body mass index, cigarette smoking, alcohol consumption, blood pressure, lipid profile, hepatitis B virus carrier, liver function, and parity, were not proven to exhibit any correlation to GBPs. Lin WR et al [8] found the Chinese males with chronic hepatitis B viral infections to have a high risk for developing GB polyps. Lee YJ et al [21] noticed a shift in risk factor for GBP over the last decade, from HBsAg positivity to lipid profile abnormalities.
4. **Hereditary:** There are no clearly defined genetic links proven in literature. However, few recent reports suggest the possibility of familial links in malignant GBPs. RNA-Seq, functional enrichment analysis and protein-protein interaction (PPI) networks analysis differentially expressed genes in GBP samples have suggested some putative genes that express the significant hub proteins containing S100A9 (S100 calcium binding protein A9) and CR2 (complement component receptor 2) [22].
5. **Cholelithiasis:** There is no well-defined relationship between cholelithiasis and GBPs. In fact, studies have raised the possibility of an inverse association where presence of GBP decreases the risk of cholelithiasis [23, 24]. However, such studies may be prone to various selection biases. At least one study has reported a higher incidence of cholelithiasis in individuals with GBPs [6].
6. **Metabolic Disorder:** Multiple metabolic disorders have been associated with development of GBPs. These include glucose syndrome [16], low levels of high-density lipoprotein [25] and obesity [26].
7. **Intestinal Polyposis:** Several studies have found significant association of GBPs with intestinal polyposis syndromes such as Peutz Jeghers and Gardner's Syndromes [27-29].
8. **Miscellaneous Factors:** Yang HL found that chronic hepatitis B confers increased risk for development of GBPs [15]. In one series, increased incidence of polyps was seen in HIV patients who underwent endoscopic retrograde cholangiopancreatography for study of cholestasis [30].

HISTOPATHOLOGY

On the basis of histopathology, GBPs can be categorized as benign or malignant.

Benign Polyps:

1. **Cholesterol polyps:** This group is the commonest variant and represents 60-90% of all the GBPs. Cholesterol polyps are often multiple and are smaller than 10 mm. These polyps are often associated with vesicular cholesterosis which results from an abnormal accumulation of cholesterol esters and triglycerides in the macrophages in epithelial and sub-epithelial tissues of the gallbladder wall [32].
2. **Adenomyomatosis:** This is a non-inflammatory lesion, occurring in the middle age and predominantly female patients, accounting for about 25% of GBPs and seen in about 8% of cholecystectomy specimens. The lesion may diffusely involve the gallbladder or involve only a particular segment. The latter variant generally affects the fundus of the gallbladder and appears as a solitary polyp and is regarded as a high-risk condition for development of gallbladder carcinoma, especially in elderly patients [33-35].
3. **Inflammatory polyps:** The inflammatory polyps account for about 10% of polyps. They are typically less than 10 mm [36] and result from granulation and fibrous tissue arising in response to chronic inflammation of gallbladder wall [37].
4. **Adenoma:** Adenomas are uncommon lesions [37] and occur primarily in women.

These are found in 0.5% of cholecystectomy specimens and are associated with gallstones, chronic cholecystitis, familial adenomatous polyposis and Peutz-Jegher's syndrome. Adenomas may be sessile or pedunculated and can be classified histologically as tubular, papillary, or tubulo-papillary. The tubular adenoma is the commonest type and is covered by simple columnar epithelium and is composed of pyloric or intestinal-type glands. Papillary adenomas are less common and are composed of papillary structures lined by cuboidal or columnar cells. The term tubulo-papillary is used when the contribution of tubular glands and papillary structures each is more than 20% of the lesion. Very rarely villous adenoma may develop in gallbladder [38]. The adenomas, particularly pyloric gland adenomas, are believed to play a role in the development of gallbladder carcinogenesis [39-40].

Malignant polyps

The malignant polyps are rare and include adenocarcinoma, mucinous cystadenoma, squamous cell carcinoma and adenoacanthoma [37].

1. **Adenocarcinoma:** Adenocarcinoma of gallbladder, though generally considered rare, is the most common malignancy of biliary tract (accounting for 80%-95%) [41-42]. This tumor is a highly lethal disease with an overall 5-year survival of less than 5% and mean survival of than 6 months. Age, female gender, congenital biliary tract anomalies, and a genetic predisposition represent important risk factors and environmental triggers play a critical role in cancer development, best exemplified by cholelithiasis and chronic inflammation from biliary tract, and parasitic infections [43]. Histopathological analysis reveal infiltrative (diffuse thickening and induration of wall with possible fistula formation due to deep ulceration) or exophytic (irregular, cauliflower mass that grows into lumen and invades wall)
2. **Cystadenocarcinomas:** Cystadenocarcinomas arising from the gallbladder are extremely rare. They are unilocular or multilocular cystic neoplasm containing septations and need to be differentiated from other more common cystic lesions of the liver such as simple cysts, parasitic cysts and abscesses [44-45].

3. **Squamous cell carcinoma:** Squamous cell carcinoma is rare and constitutes only 0.5-3% of all malignancies of gallbladder and most of the reported cases have had a component of adenocarcinoma. Pure squamous cell carcinoma of the gallbladder grows slowly, is usually localized and rarely metastasizes. Two important causative possibilities proposed in literature include gallstones and parasitic infestation. Another important pathogenetic theory for squamous cell carcinoma is the metaplasia-dysplasia-carcinoma sequence and most of the specimens show some degrees of atypical epithelial change adjacent to the invasive tumor [46].

CLINICAL PRESENTATION

Most cases are asymptomatic and are detected incidentally by abdominal imaging for unrelated reason [37, 47-49] or else on histopathological analysis of gallbladder specimen retrieved by cholecystectomy for other indications like cholelithiasis. In symptomatic cases, the symptoms are nonspecific including vague abdominal discomfort and dyspepsia. The fragments of polyps might fall off and lead to episodes of biliary pain, nausea and vomiting [50]. Complications such as acute cholecystitis [50], mucocele, pyocele, obstructive jaundice, cholangitis and pancreatitis due to cystic/biliary duct obstruction by dislodged polyps are reported in the literature [51-52]. In rare instances, hemobilia due to polyp fragmentation may be the presenting feature [53-54].

IMAGING MODALITIES

Ultrasound (US): Abdominal ultrasound is the first line imaging modality due to its low cost, non-invasiveness, repeatability and accessibility [54-55]. The polyps appear as fixed hypo-echoic masses protruding into gallbladder lumen with or without acoustic shadow. However, this modality lacks sensitivity and is limited by operator skills and body habitus of patient [55]. Chattopadhyay et al [56] found that Abdominal US has 66.66% sensitivity and 100% specificity in the pre-operative suspicion of malignancy. Kwon et al [57] found the sensitivity to range from 36% to 90%. Three dimensional ultrasound (3DUS) is a recent advance in radio-diagnosis and studies have shown that 3DUS diagnosis correlates well with 2DUS with regard to most gallbladder problems including polyps and hence does not

offer any specific advantage [58]. Endoscopic ultrasound (EUS) is more accurate than abdominal US in diagnosis of GBPs but its accuracy for differentiating malignant from benign lesions of less than 1.0 cm has been found to be low [59]. Besides, EUS is associated with discomfort and requires sedation during procedure.

A scoring system has been developed to predict the neoplastic potential of the polyps termed as EUS scoring system [60-61]. The scoring system is based upon significant EUS variables including tumor maximum size, internal echo pattern, and hyperechoic spotting. Higher the EUS score, higher is the probability for the polyp to be of neoplastic nature. Choi WB et al [60] found that the risk of neoplastic polyp was significantly higher for polyps with a score of 6 or greater compared with those with a score of less than 6 ($p < 0.01$) and Sadamoto Y et al found the sensitivity, specificity and accuracy of this scoring system for determining the presence of neoplasia in polyps scoring 12 or higher is 78%, 83% and 83% respectively [61].

Contrast enhanced ultrasonography have been found to be an effective adjunct in the diagnosis of GBPs and differentiation of malignant from benign polyps [52]. In a series from USA, galactose-based contrast agent was used for evaluation of GBPs and the technique was found to be 100% sensitive and 77% specific in differentiating malignant from benign lesions [62].

Harmonic endoscopic ultrasonography (H-EUS): Harmonic imaging is a new greyscale imaging technique that works on the principle of harmonics [63]. Harmonics are the frequencies occurring at multiples of the fundamental transmitted sonographic frequency. In conventional US, the same frequency spectrum that is transmitted by the transducer into the patient are subsequently received to produce an image. In H-EUS, higher harmonic frequencies generated by propagation of the ultrasound beam through tissue are used to produce the sonographic image. Harmonic imaging offers better quality of images due to several potential advantages, including improved lateral resolution, reduced side-lobe artefacts, reduced noise and clutter, reduced slice thickness, and increased contrast resolution due to improved signal-to noise ratio [64]. The contrast-enhanced version of this modality termed as contrast-enhanced harmonic EUS (CH-EUS) uses additional techniques such as quantitative perfusion analysis for objective assessment of

images and has the potential to improve the preoperative diagnostic accuracy. In a series by Imazu H et al [65], the overall sensitivity, specificity and accuracy for diagnosing malignant GB polyp of H-EUS and CH-EUS were 83.3 versus 89.6, 65 versus 98% ($p < 0.001$) and 73.1 versus 94.4% ($p < 0.001$).

CT Scan: Abdominal CT scan is often incapable of detecting polyps smaller than 10 mm; larger polyps appear as soft tissue density projections into the lumen of the bladder, and demonstrate enhancement similar to that of the rest of the gallbladder. More intense enhancement should be viewed with suspicion, as it is more commonly associated with malignant lesions [66-67]. Jang JY et al [68] found the diagnostic sensitivity and specificity for malignant polyp was 72% and 44.4% respectively for conventional CT scan. Recently, multi-detector CT (MDCT) [69], and advanced versions of two –phase spiral / helical CT have been found to be effective in evaluation of smaller sized GBPs and in differentiation of benign from malignant lesions by precise characterization of gallbladder wall thickening [70]. In the series by Kim SJ et al [69], MDCT was found to provide 83.9% accuracy in the diagnosis of the local extent of gallbladder carcinomas.

Magnetic resonance imaging (MRI): Magnetic resonance imaging (MRI) has not been widely used to evaluate gallbladder diseases, due to the disadvantages of poor spatial and contrast resolution. However, dynamic MRI with a spoiled gradient pulse sequence (SPGR) has been found to be useful in differentiating benign from malignant lesions as malignant lesions demonstrate early and prolonged enhancements, while benign lesions show early enhancement with subsequent washout [71-72]. Similarly several recent studies have reported the effectiveness of diffusion-weighted MR imaging (DWI) in the gallbladder studies, and have found that malignant tumors may show high signal intensity on DWI, reflecting their high cellularity and/or their long relaxation time [73]. Eaton JE et al [74] found that the sensitivity and specificity of MRI for a gallbladder lesion of 0.8 cm size and for the presence of gallbladder neoplasia was 100% (95% confidence interval [CI], 77% - 100%) and 70% (95% CI, 35%–93%), respectively.

Positron emission tomography (PET): Studies have shown fluorine -18-fluorodeoxyglucose

(FDG)-Positron emission tomography (PET) to distinguish between benign and malignant gallbladder wall thickening [75]. Delayed 18F-FDG PET may be more helpful than early 18F-FDG PET for detecting malignant changes in polyps because of increased uptake and increased lesion-to-background contrast. However, the diagnostic performance of 18F-FDG PET may decrease significantly with increasing levels of C-reactive protein [76].

DETERMINATION OF MALIGNANT POTENTIAL

The most important prognostic factor in the management of GBPs is the determination of the malignant potential of these polyps as prognosis of gallbladder cancer is poor with a 5-year survival rate of approximately 10%. Numerous studies have attempted to define characteristics, listed below, that increase the likelihood that a given gallbladder polyp is malignant.

Polyp size greater than 10 mm: Most case series in the literature have postulated that the likelihood of malignant transformation in GBP increases as the size increases, especially if size is greater than 10 mm [77-79]. Pedersen et al [80] did not detect malignant change in any of the 203 GBPs that were less than 6mm in size. Nonetheless, there are some case series that support a more aggressive approach towards smaller polyps after detecting cancer in smaller polyps. Kubota K et al. [81] discovered 13% of gallbladder carcinomas in polyps smaller than 10 mm. Shinkai et al. [82] also found that 6% of the cancers in his series of 74 polyps were detected in lesions that were smaller than 5mm in diameter. Park et al. [83] found that polyps greater than 10 mm had a 24.2 times higher risk of malignancy than polyps smaller than 10 mm although malignant potential was also detected in smaller polyps.

Solitary lesions: Sarkut P et al. [78] after analysis of records of cholecystectomies conducted for 99 GBPs found histopathologically confirmed adenocarcinoma in 21 lesions that were solitary. Similarly, Shinkai et al. [82] in their series of 74 GBPs found that neoplastic polyps tended to be solitary (number of polyps when histopathological diagnosis was adenoma, $n = 1.40 \pm 0.89$ and when diagnosis was cancer, $n = 1.16 \pm 0.40$). However, when there were fewer than 3 lesions, the incidence of neoplasm was 37% among polyps 5 to 10 mm in diameter.

Age of the patient: In most studies, the risk of malignancy in GBP was greater in the patients older than 50 years than younger patients [48, 77-79]. Park et al. [84] considered age above 57 years as a risk factor whereas in series of Kwon et al. [57] and Tezki C et al. [85], the age of 60 years was found to be a significant risk factor for malignancy.

Growth in size over time: The increase in size of the GBPs during follow-up has been considered as a risk factor [80, 86]. Nevertheless, the precise definition of increase in size has not been clearly established in the literature. Cairns et al. [87] after studying the risks and cost-effectiveness of surveillance followed by cholecystectomy for gallbladder polyps concluded that increase in size during surveillance predicted neoplastic potential. In their series, they found that only 6.6% of polyps exhibited an increase in size over time and the polyps that subsequently progressed in size had a significantly greater diameter at first presentation than those polyps that remained static (7 mm vs 5 mm, respectively). Shin et al. [86] reported the rapid growth rate of greater than 0.6 mm/month to be a risk factor.

Concurrent cholelithiasis: Cholelithiasis associated with GBP has been mentioned as a risk factor by some workers [48, 80, 85]. But in many other studies, no definite relationship was found between the malignant potential of GBPs and concurrent cholelithiasis. Kwon et al. [57] studied 291 patients who underwent cholecystectomy with confirmation of GBP on histopathological analysis of the specimen; benign GBPs were found in 256 patients (88.0%) and malignant GBPs in 35 patients (12.0%) and no statistically significant difference was found when polyps were related to concurrent cholelithiasis (21.5% in benign [55/256]; 17.1% in malignant [6/35], $P=0.554$).

Adenomatous nature: Adenomatous nature of the GBPs has been inconsistently linked to cancer development in many studies. Kozuku et al. [88] found the adenomatous residue in 15 (19.0%) out of 79 cases of invasive carcinoma and suggested that the transition of benign adenoma into carcinoma was histologically traceable. Lee et al. [89] noticed malignant transformation in 23.5% of adenomas and inferred that the adenoma is a precancerous lesion and the adenoma-carcinoma sequence is one of the pathways for gallbladder cancer carcinogenesis. However, Roa et al. [90] found

no adenomatous residue in specimen of 196 early-stage gallbladder carcinomas, arguing against an adenoma-carcinoma sequence. Furthermore, molecular studies have shown that the genetic mutations frequently seen in GB cancer are absent in adenomas [91].

Sessile morphology: Sessile morphology of polyps is a factor that has been shown to increase the probability of malignancy [18,92]. One of the possible explanations for frequent sessile morphology in malignant GBPs is that most gallbladder cancers arise in situ from flat, dysplastic epithelium, present in sessile lesions [84].

Indian ethnic origin: Aldouri AQ et al. [20] found the Indian ethnic origin of the patient to be an independent risk factor for neoplastic transformation irrespective of size of GBP.

MANAGEMENT

After the review of current literature, the recommendations for management of gallbladder polyps can be summarized as following:

Symptomatic: In symptomatic GBPs, cholecystectomy is recommended and laparoscopic approach is routinely adopted [93-94]. However, when there is a preoperative suspicion for malignancy, the general recommendations are to use an open approach [95]. The surgical approach remains controversial and more studies are needed to examine the pros and cons of each approach to facilitate evidence-based standardization [79]. Asymptomatic but size greater than 10 mm: Cholecystectomy is indicated in patients with large gallbladder polyps size over 10 mm, irrespective of symptomatology. The approach is laparoscopic if no other risk factors are present otherwise open cholecystectomy is preferred [79, 95-96].

Asymptomatic but size between 6 and 10 mm: Cholecystectomy is recommended if lesions are associated with risk factors of malignancy such as age greater than 50 years [18] or high scores with EUS [54]. In the absence of risk factors and when EUS scores are low, regular follow-up is needed [18]. However, clear guidelines on a screening interval are not available, even though screening by ultrasound at intervals of every 6–12 months has been recommended [18]. Guruswamy et al. [97] has recommended a need

for randomized clinical trials with low bias -risk to address the question of whether cholecystectomy is indicated in gallbladder polyps smaller than 10 mm.

Asymptomatic but size less than 6 mm : Multiple case-series have proven that no treatment or active follow-up is required [70]. However, if the lesions are sessile or the patient is above 50 years, some investigators recommend laparoscopic cholecystectomy due to higher risk of malignancy or regular follow up by ultrasonography at least every six months [18]. If after laparoscopic cholecystectomy, histopathological examination shows the presence of malignancy, than the procedure is considered curative for cancers confined to the gallbladder mucosa (T1a), while cancers that invade the muscularis (T1b) have higher probability of lymph node metastases or lymphatic invasion due to which many workers recommend laparotomy , re-exploration and hepatoduodenal lymph node dissection [98-99]. However, an initial open versus laparoscopic approach has not been found to influence long term survival of the patient [100-101]. Inadvertent opening of cancerous gallbladders during laparoscopic cholecystectomy has been documented to increase the likelihood of recurrence and port site metastases [102].

CONCLUSION

GBPs are being increasingly diagnosed due to wide availability and use of imaging modalities for the work-up of various symptoms. GBPs remain a concern for both healthcare providers as well as patients due to the risk of malignancy requiring a comprehensive understanding of natural course of gallbladder polyp and risk factors of malignancy by the treating physician. The imaging GBP should evaluate its size, shape and number so that the malignancy risks can be estimated. Most polyps are small, benign and remain static for a long period. When the polyps are symptomatic, cholecystectomy should be offered as treatment. GBPs smaller than 10 mm detected in patients younger than 50 years have a minimal probability of malignancy. Such patients may be reassured and can be safely offered follow-up. The presence of multiple lesions in a young patient suggests benign nature. In patients with polyps larger than 10 mm, cholecystectomy is recommended. Laparoscopic approach is recommended for cholecystectomy unless there are factors suggestive of malignancy are present.

In patients with smaller polyps but with suspicious characteristics (like sessile nature) seen on ultrasound particularly when the patient is older than 50 years, surgery should be recommended even though the probability of malignancy remains low.

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