Diagnostic and Therapeutic Algorithm: Polypoid Lesions of the Gallbladder

Woojin Lee

Introduction

The term gallbladder polyp generally refers to any mucosal projection into the gallbladder lumen regardless of whether it is neoplasm or not [1]. Compared with'gallbladder polyps' or other terms, the morphological term 'polypoid lesions of the gallbladder' could be more comprehensive and clinically useful for this heterogeneous group of diseases, among which true gallbladder polyps are relatively rare.

Most gallbladder polyps are not neoplastic lesions. Actually, 70% of these elevated lesions are pseudopolyps, which include cholesterol polyps, cholesterol stones (crystal), cholesterolosis, or adenomyomatosis. Pseudopolyps do not in themselves have malignant potential. True gallbladder polyps can be benign or malignant. Benign true gallbladder polyps are most commonly adenomas while malignant polyps are usually adenocarcinomas.

Clinically, diagnosis, routine medical check-up, and follow-up of these elevated lesions are almost always performed by ultrasonography (US). Despite gallbladder polyps being common, only a few develop to carcinoma, which usually presents late in diagnosis and carries a poor prognosis. Prognosis of advanced gallbladder cancer is dismal (5-year survival rate less than 5%), but 5-year survival rate of T1 gallbladder cancer is reported 71–100%.

Although it is ideal to treat true gallbladder polyps early, after histological diagnosis, clinicians must decide to recommend cholecystectomy based on indirect information such as the radiographic appearance of the polyp, patient demographics, and symptoms. It may be difficult, therefore, for the practicing radiologist or clinician to know what to recommend when they encounter a gallbladder polyp. This was also suggested by the results from a survey that there is inhomogeneity of surgical practice in the management of gallbladder polyps [2].

The current literature lacks uniformity and a single consensus on gallbladder polyps because a majority of data was acquired by individual, observational, and retrospective studies which involved limited numbers of participants and might have been biased. Currently, larger gallbladder polyps, for example, larger than 1 cm, are recommended for surgical removal in view of the higher chance of malignancy. On the other hand, patients with smaller polyps usually require repeated US and follow-up. This policy not only imposes a certain degree of anxiety on the part of patients, but also carries with it significant economic cost to the health care system.

W. Lee (✉)
Department of Internal Medicine, National Cancer Center, Goyang-si, Gyeonggi-do, Korea
e-mail: lwj@ncc.re.kr

J. B. Chung and K. Okazaki (eds.), *Diseases of the Gallbladder*,
https://doi.org/10.1007/978-981-15-6010-1_26

Epidemiology

Due to the rising prevalence of gallbladder polyp and more frequent use of abdominal imaging modalities, the detection of gallbladder polyps has been increasing in past decades, affecting approximately 5–10% of the global adult population [3–6]. However, only 5% of these are considered to be "true" gallbladder polyps [7].

Most of the cases are diagnosed by abdominal US especially for periodic health examination. Otherwise, gallbladder polyps are often found incidentally during cholecystectomy. The frequency of resected gallbladder polyps in cholecystectomy specimens ranges from 2.6 to 12.1%; it seems to vary widely among reports and appears to be related to the indications for cholecystectomy, as well as to the study design [8].

Although the detection of gallbladder polyps has been increasing, the risk factors and natural history remain unclear. In contrast to the well-known risk factors for gallstones, no consistent relationship has been found between the formation of gallbladder polyps and sex, age, or medical conditions, such as diabetes, hyperlipidemia, and metabolic syndrome.

Histologic Type

Nonneoplastic polyps account for 95% and most of the neoplastic polyps are adenoma. Histological diagnostic terms are more scientific and accurate for each subtype of these lesions, but they could only be obtained postoperatively and therefore are difficult to be commonly used in clinical application and with imaging modalities. A worldwide, uniformly accepted classification is still lacking.

Cholesterol Polyps

Cholesterol polyps are the most common type (60%) of gallbladder polyp. Usually they are multiple, pedunculated, and less than 10 mm in diameter (Fig. 1) [9]. However, the sizes of these polyps vary quite widely, in some cases measuring over a centimeter. About 20% may be single lesions. They are not neoplastic polyps, but variants of cholesterolosis resulting from infiltration of lipid-laden foamy macrophages in the lamina propria.

The cholesterol in bile is absorbed by the gallbladder epithelium and taken up by macrophages and accumulates in the lamina propria. Cholesterol deposition within the lamina propria creates a mass and protrudes out of the mucosa into the lumen, and these masses are called cholesterol polyps. They are surrounded by vascular connective tissue and attached to the fibromuscular layer of the gallbladder wall protruding into the gallbladder lumen. They are covered with a single layer of epithelium enveloping a core of cholesterol filled macrophages. In cases where cholesterol deposits are tiny and diffuse, creating tiny, yellow excrescences on the surface of the gallbladder mucosa, having an almost strawberry-like appearance, the condition is referred to as cholesterolosis.

Diagnosis is easier in cases when there are multiple polyps. When there is one large cholesterol polyp, differentiation from the far less common adenoma is difficult (Fig. 2). Rarely, they may detach and behave clinically as gallstones, causing biliary colic, bile duct obstruction, or pancreatitis [10]. Cholesterol polyps have no malignant potential and no proven relation to gallstones. Surgery is not required unless the patient is symptomatic.

Adenomyoma

Adenomyomatosis of the gallbladder is characterized by excessive proliferation of the epithelium and hypertrophy of the muscle. This proliferation is associated with invagination of the proliferated epithelium into the muscularis propria. The invaginated epithelium forms an intramural diverticulum referred to as Rokitansky–Aschoff sinuses. In addition to mucosal hyperplasia, the smooth muscle layer is hypertrophied, both of these pathologic processes causing marked thickening of the

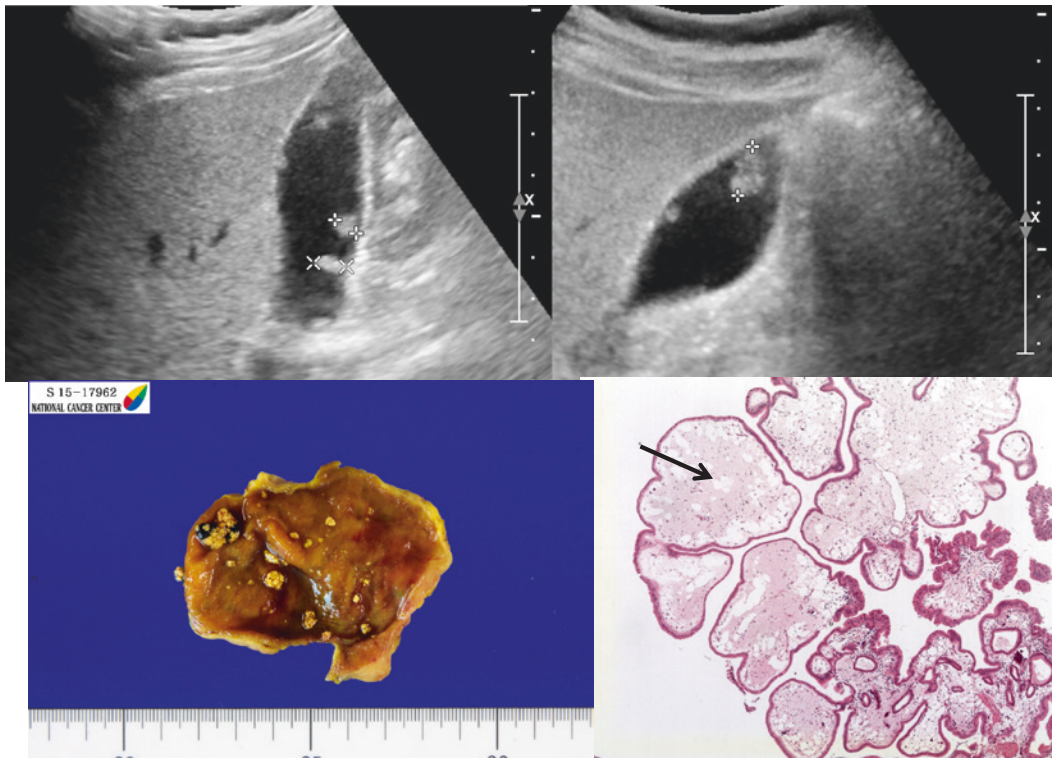

Fig. 1 Cholesterol polyp. **a** Sonographic view of multiple gallbladder polyps (0.8 cm, 0.6 cm size). **b** Sonographic view of another 1.1 cm-sized polyp. **c** Photograph of the gross pathologic specimen after cholecystectomy shows multiple yellowish cholesterol polyps. **d** H-E stain of the specimen demonstrating lipid-laden macrophages (arrow)

gallbladder wall. The Rokitansky–Aschoff sinus is usually confined to the thickened muscle, but in some cases, the sinus extends into the perimuscular connective tissue like a colonic diverticulum. Occasionally, Rokitansky–Aschoff sinuses are impacted with cholesterol crystals, debris, or fragments of stone.

There are three different types: the localized type, the segmental type, and the diffuse type. The focal type, the most common form, is referred to as adenomyoma. In the segmental type, there is a focal circumferential thickening of the gallbladder wall, often at the fundus or body. When it occurs at the body, there is a segmental narrowing of the gallbladder, dividing the gallbladder lumen into two separate compartments, mimicking an hour-glass. Segmental adenomyomatosis commonly occurs in the Phrygian cap and also gallstones are frequently entrapped in the cap. The diffuse form of adenomyomatosis causes diffuse thickening of the gallbladder wall and it may be difficult to distinguish adenomyomatosis from acute or chronic cholecystitis.

Localized form of gallbladder adenomyomatosis, confined to the fundus, may resemble a polyp. It is not neoplastic and confined to the gallbladder muscle layer. The average size is about 10–20 mm. Focal or segmental adenomyomatosis of the gallbladder fundus may be difficult to distinguish from intraluminal polyps or small carcinomas (Fig. 3). Surgery is not required unless it is symptomatic or indistinguishable from a tumor.

Inflammatory Polyps

Inflammatory polyps are small, sessile lesions, and the average size is about 5–10 mm, although

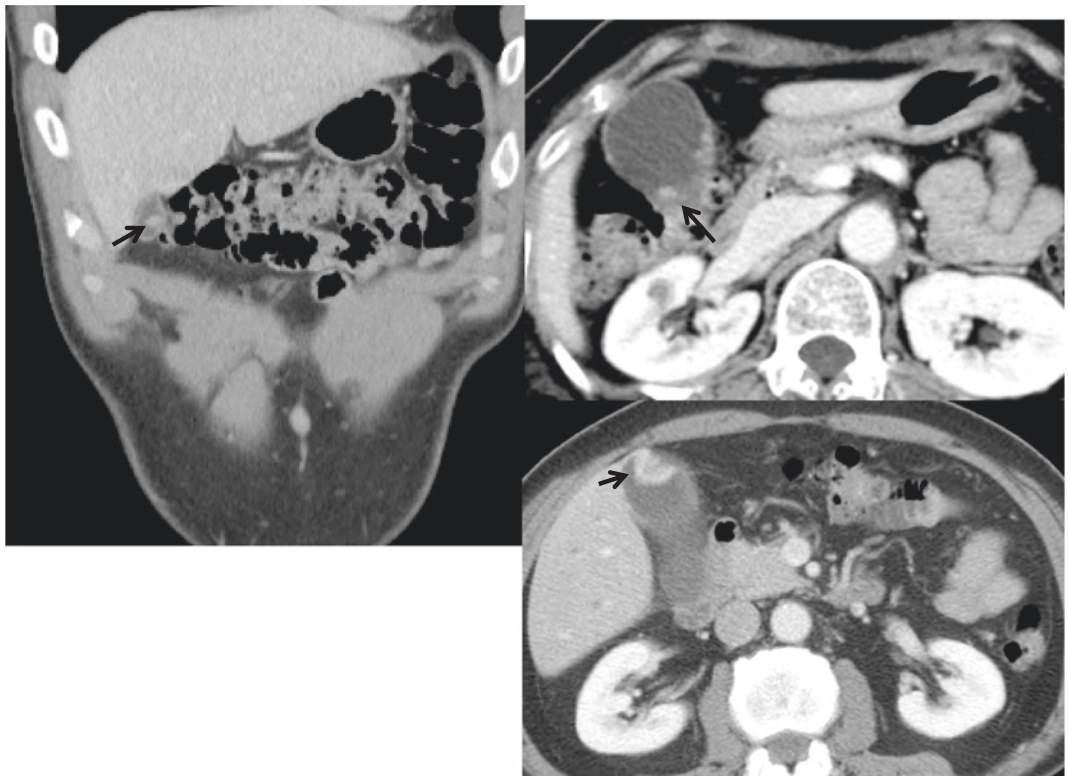

Fig. 2 CT view of single, large gallbladder polyp. **a** 1.4 cm-sized cholesterol polyp (after cholecystectomy). **b** 1.1 cm-sized gallbladder adenoma (after cholecystectomy). **c** 2.1 cm-sized gallbladder adenocarcinoma (after cholecystectomy)

inflammatory polyps larger than 1 cm have been described. These large polyps can be confused with gallbladder carcinoma [11]. About 50% may be single lesions. In about half, 2–5 lesions are observed. Surgery is not required and most are found incidentally during cholecystectomy.

Adenomas

Unlike other gastrointestinal adenomatous polyps, gallbladder adenoma is a rare lesion, found in only 0.15% of resected gallbladders [12]. Adenoma is characteristically a single lesion with a diameter of 5–20 mm (Fig. 4). Commonly, adenoma appears as sessile or pedunculated polypoid nodules. It can occur anywhere in the gallbladder. When multiple, as they are in approximately one-third of cases, 2–5 polyps are usually present. Adenomas may cause symptoms but are typically incidentally found. They are most frequently seen in patients with primary sclerosing cholangitis (PSC) and gastrointestinal polyposis syndromes, such as Peutz–Jegher and Gardner syndromes.

Histopathologically, adenomas are classified into tubular, papillary, and tubulopapillary types. Tubular adenomas are the most common and appear lobular, possessing smooth contours, while papillary adenomas appear cauliflower-like.

It is the only polyp in the gallbladder that has a premalignant potential. Several studies do support this potential progression [13, 14]. However, the frequency of progression from adenoma to carcinoma is much lower than that for colon polyps. Gallbladder cancer is 4 times more common than gallbladder adenoma. Furthermore, adenomas are rarely found around invasive gallbladder cancers, and adenomas are less frequently associated with gallstones than

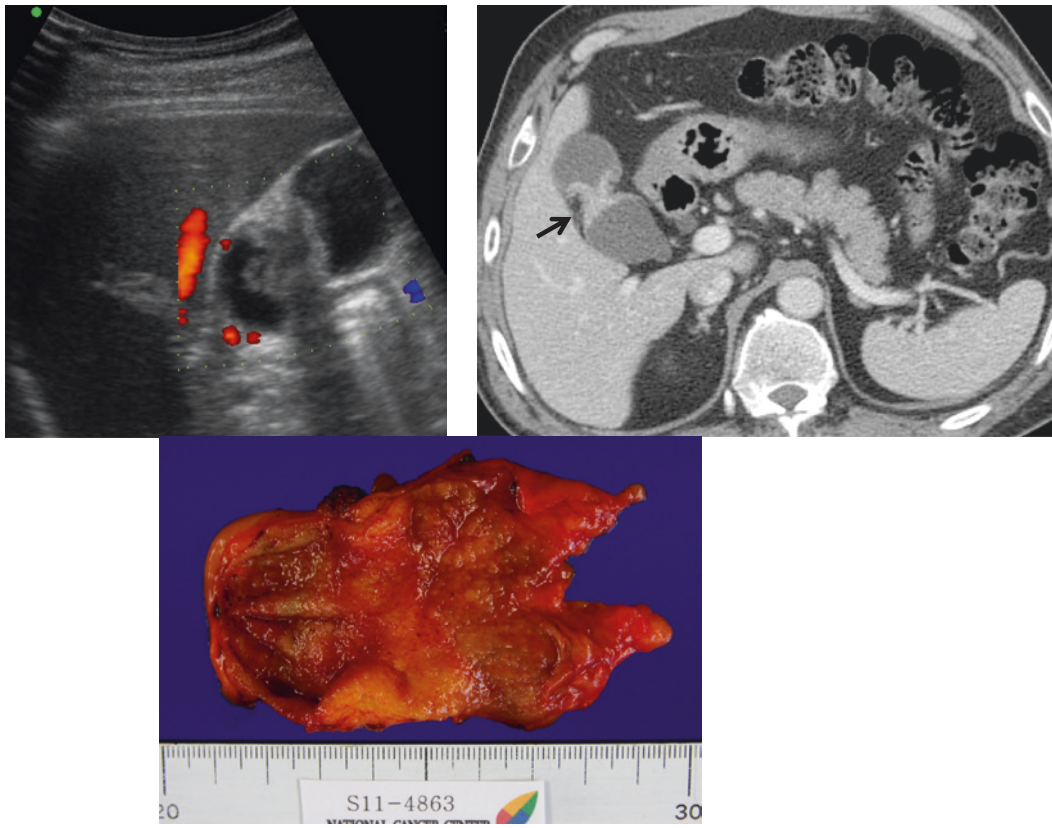

Fig. 3 Gallbladder cancer that mimicks segmental adenomyomatosis. **a**, **b** Sonographic and CT view of annular wall thickening of the gallbladder body. **c** Photograph of the gross pathologic specimen after cholecystectomy shows irregular wall thickening of the gallbladder body

gallbladder cancers. Therefore, this progression is not felt to be the predominant pathway of carcinogenesis in the gallbladder, and K-*ras* mutations have not been detected in gallbladder carcinomas associated with an adenoma. The frequency of transition from adenoma to cancer is unclear [13].

The pathologic diagnosis of adenoma or adenocarcinoma can only be made after cholecystectomy. In general, malignant tumors account for 3–8% of the gallbladder polyps. Virtually all adenomas with a focus of carcinoma are >12 mm in diameter; lesions <10 mm can be monitored with US. For lesions 10–18 mm in size, laparoscopic cholecystectomy should be considered in good surgical candidates. For lesions >18 mm in size, open rather than laparoscopic cholecystectomy should be considered because invasive cancer is more likely and extended resection may be required.

Other Polyps

Fibromas, leiomyomas, neurofibromas, carcinoids, and lipomas of the gallbladder have been reported, but are less than 0.1%. Pathology cannot be diagnosed before resection.

Clinical Features and Diagnosis

Because clinical findings alone cannot distinguish the histological types of gallbladder polyps, surgery is determined based on symptoms and image findings.

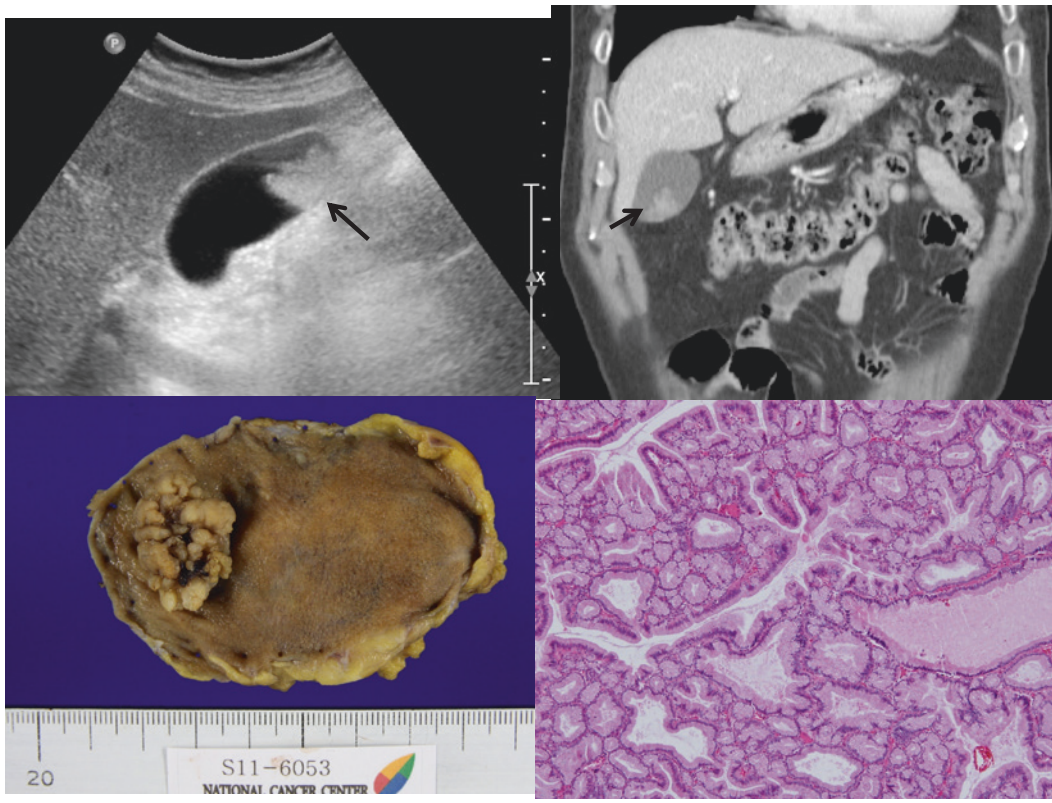

Fig. 4 Gallbladder adenoma. **a**, **b** Sonographic and CT view of 2.4 cm-sized solitary polypoid mass (arrow). **c** Photograph of the gross pathologic specimen after cholecystectomy shows lobulated polypoid mass. **d** H-E stain of the specimen demonstrating tubular adenoma, pyloric gland type

Most gallbladder polyps do not cause symptoms. Polyps can be found incidentally after cholecystectomy for the treatment of gallstone or by imaging studies performed for periodic health exams or other indications. Rarely, biliary pain may appear [15, 16]. Rare cases of acute acalculous cholecystitis and even hemobilia have been reported [17]. It is unclear whether the polyps primarily drive the symptoms, and it is difficult to distinguish the symptoms from those associated with gallstones. There is no sufficient evidence to show that tumor markers will assist in the decision-making process for gallbladder polyps.

Although imaging features of gallbladder polyps may, at times, indicate a specific diagnosis, there is a large degree of overlap in the appearances of benign and potentially malignant gallbladder lesions. About 85% of the polyps found by US are less than 5 mm in size. Only 2% are more than 10 mm in size.

Radiologic findings can be used to stratify gallbladder polyps into three groups: those that need no further follow-up, those that require follow-up, and those that should undergo cholecystectomy. In addition to the likelihood of malignancy on the basis of imaging findings, a surgeon's judgment on whether to perform cholecystectomy relies on clinical factors, such as patient age, medical comorbidities, and the presence of symptoms that are attributable to gallbladder disease.

US is the most commonly used and best available imaging modality because it is the simplest and sensitive diagnostic methods for the detection of gallbladder polyps. However, US is often limited by the body habitus of the patient, and technical limitations can lead

to intraobserver variability in interpretation. It cannot reliably distinguish between non-neoplastic and neoplastic polyps (see chapter "Differential Diagnosis of Benign and Malignant Lesions with Imaging") [18]. On US, a gallbladder polyp is seen as an elevation of the gallbladder wall that protrudes into the lumen. It should not be mobile or demonstrate posterior acoustic shadowing (which would suggest it is more likely a calculus). It may be sessile or pedunculated. A clearly infiltrating or large mass should be treated as a gallbladder cancer rather than a polyp (Fig. 5). If there is clear reverberation or "comet tail" artifact present posterior to the lesion, this should be identified as a focal adenomyomatosis [19, 20]. The general sensitivity of US in detecting gallbladder polyp ranges from 36 to 90%, reaching 99% in patients without gallstones [21]. It was noted that gallstones mask the presence of polyps [22–24]. Besides, small polyps can also be obscured on US by thickened gallbladder wall [25].

Endoscopic ultrasound (EUS) is a more sensitive and specific method for diagnosing gallbladder polyps because of its use of high-frequency probes, which provide better resolution of small lesions (see chapter "Role of EUS"). EUS may be useful for identifying benign features of a polyp—such as cystic spaces or comet-tail artifact, which is associated with adenomyomatosis—that may not be visible with a transabdominal approach [26]. An EUS scoring system to predict malignancy in a gallbladder polyp on the basis of its size, its internal echo pattern, and the presence of hyperechoic spotting has been suggested, with sensitivity and specificity of 78% and 83%, respectively [20, 27, 28]. One study comparing

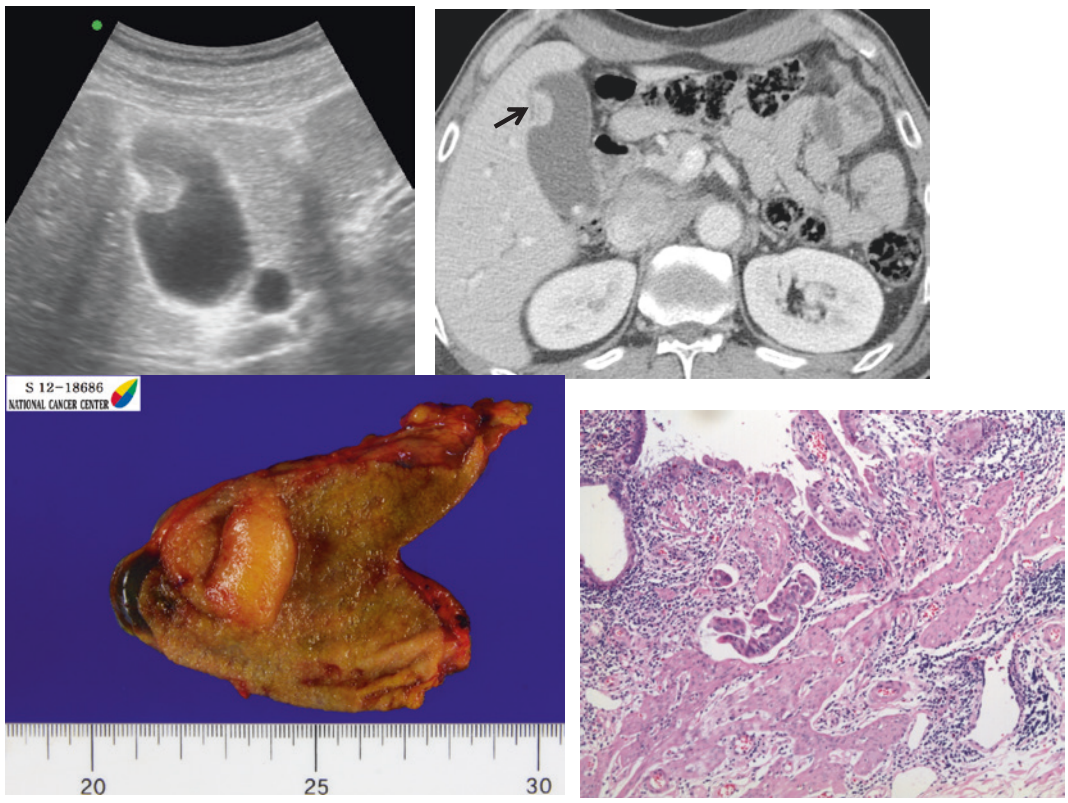

Fig. 5 Gallbladder adenocarcinoma. **a**, **b** Sonographic and CT view of 1.9 cm-sized, solitary polypoid mass (arrow). **c** Photograph of the gross pathologic specimen after cholecystectomy shows large, solid mass. **d** H-E stain of the specimen demonstrating adenocarcinoma

transabdominal US and EUS found that the diagnostic accuracy of EUS for differentiating polyp types exceeded 90% [20]. However, EUS alone is not sufficient to determine treatment plan in many cases. Also, it is limited due to the need for equipment and skilled endosonographers and the risk of adverse events.

High-resolution ultrasound (HRUS) operates at a higher frequency than conventional US (5–7 MHz) but a lower frequency than EUS (5–12 MHz) and therefore theoretically has a better diagnostic accuracy than US but is less accurate than EUS [29]. However, it does have the benefit over EUS, in that it is a noninvasive procedure. The diagnostic accuracy of HRUS has been shown to be comparable with EUS for the differential diagnosis of gallbladder polyps [30]. Perhaps most importantly, considering patient comfort and the lack of requirement for sedation, HRUS has real potential as an important diagnostic modality for the differential diagnosis and staging of malignant gallbladder polyps and early gallbladder cancer.

Contrast-enhanced ultrasound (CE-US) has also been used to assess gallbladder polyps. It was reported that CE-US may facilitate the detection of gallbladder polyps by helping to distinguish them from mural folds, gallbladder contents, or sludge and also to detect invasion into the liver and metastasis [31, 32]. Moreover, it may offer more useful information for distinguishing adenoma from cholesterol polyps compared with conventional US, especially in cases in which the polyp was larger than 1 cm [33, 34].

Computed tomography (CT) or magnetic resonance imaging (MRI) has been reported to be less sensitive than ultrasound and it has limitation in differential diagnosis of small gallbladder polyps (see chapter "Differential Diagnosis of Benign and Malignant Lesions with Imaging"). Enhanced helical CT could reveal gallbladder polyps larger than 5 mm and could differentiate neoplastic or nonneoplastic lesions [35, 36]. Attempts have also been made to predict the malignant potential of gallbladder polyps using MRI with diffusion weighted imaging [37]. If malignant polyps are suspected by abdominal US, additional abdominal CT or MRI is performed to detect the invasion into surrounding tissue, presence of lymphadenopathy, or distant metastasis.

Several cases in which preoperative 18-fluorodeoxyglucose positron emission tomography (PET) accurately predicted the presence of malignant tumor of the gallbladder in patients with gallbladder polyps have been reported (Fig. 6) [38]. However, it was applicable for the assessment of 1–2 cm gallbladder polyps and false-positive results may occur in the presence of acute cholecystitis, a limitation of FDG PET.

In summary, alternative imaging modalities, particularly EUS, may provide additional information in the diagnosis of gallbladder polyps. At present, however, there is insufficient data to suggest that they should be used ahead of conventional US in the investigation of gallbladder polyps. In addition, transabdominal US is a relatively low cost, low risk, and widely available technique. Some specific centers with sufficient resources and expertise may find the additional information available useful, especially in patients for whom cholecystectomy may have additional risk.

When gallbladder polyps are detected by imaging, such as US, they are sometimes not found in cholecystectomy specimen. Such false positive finding of gallbladder polyps on US ranges from 6 to 43% [22, 25, 39, 40]. Normal mucosal folds, sludge, or small stones impacted in the gallbladder wall can be misinterpreted as polyps. In addition, small polyps may fall off during processing of surgical specimens. Thus, patients should be informed before operation of the possibility of negative findings or of finding a gallstone instead.

Treatment

When a gallbladder polyp is identified on abdominal US, the two major questions are (1) is this causing any symptoms and (2) does this need to be removed? As discussed above, most polyps are generally thought to be asymptomatic. Therefore, the main role for the clinician in managing these polyps is recommending when to proceed with surgery and

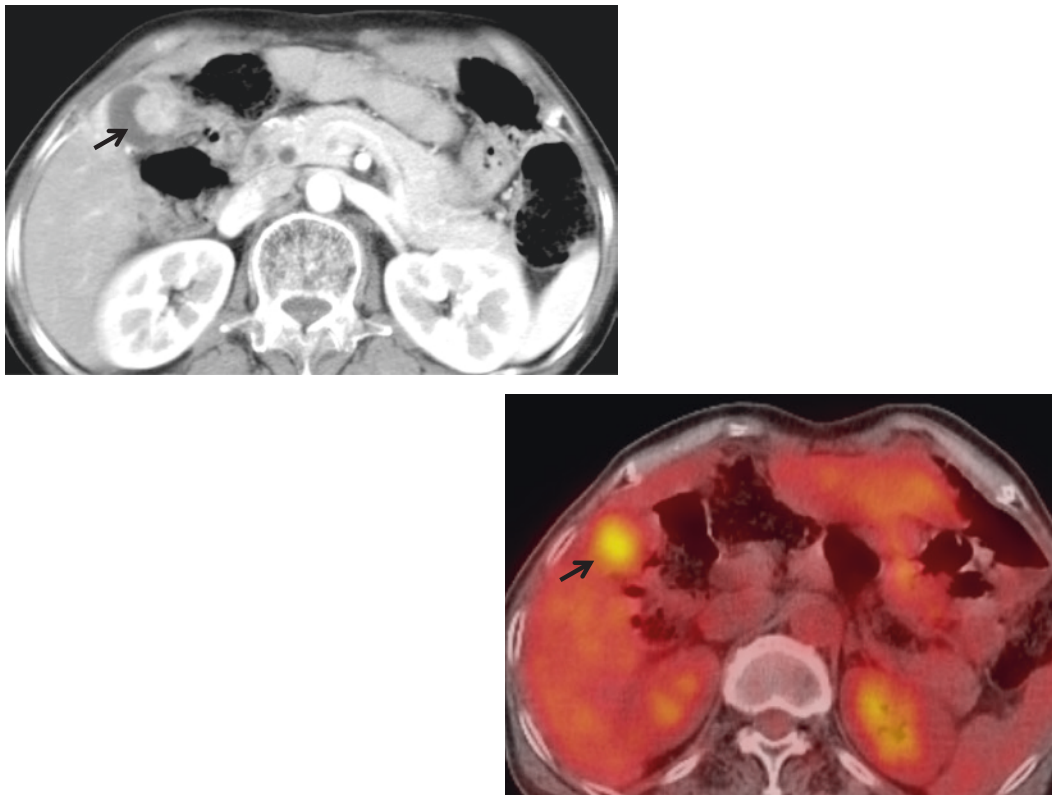

Fig. 6 Gallbladder adenocarcinoma. **a** CT view of 2 cm-sized, enhancing gallbladder polypoid mass (arrow). **b** PET view of the increased FDG-uptaken mass (arrow)

when to take a watchful waiting approach, recognizing that gallbladder cancer, while quite rare, carries a poor prognosis. The main concern in the management of gallbladder polyps is to identify and treat malignant lesions that are usually still at a relatively early stage and amendable to surgical cure. Currently, there remain controversies and challenges in many aspects of gallbladder polyps. It is difficult to differentiate benign lesions from malignant gallbladder polyps based on available diagnostic modalities. Prophylactic cholecystectomy is sometimes performed too early or is even absolutely unnecessary for well-functioning gallbladders with some subtypes of gallbladder polyps.

As mentioned earlier, the commonly reported rate of malignancy in gallbladder polyps is around 3 to 8%. Obviously, operation will be overdone if cholecystectomy is offered to every patient with gallbladder polyps. The issue is further complicated by the reliability of US which is usually the diagnostic tool used. The reported sensitivity and specificity of US in diagnosing gallbladder polyps is widely variable. Unnecessary operations would occur in case of false positive findings. The risks associated with surgery include damage to intra-abdominal structures during port insertion, bile duct injury (between 0.3 and 1%), and bile leak [41, 42]. Furthermore, endoscopic retrograde cholangio-pancreatography (ERCP) to manage a bile leak and bile duct injury are associated with significant adverse events [43, 44].

It is unlikely that small gallbladder polyps themselves cause patient's symptoms. There is evidence, however, that gallbladder polyps may be indicative of underlying inflammation or stone disease that may not have been detected on US [45]. The relationship between symptoms and risk of malignancy is not established.

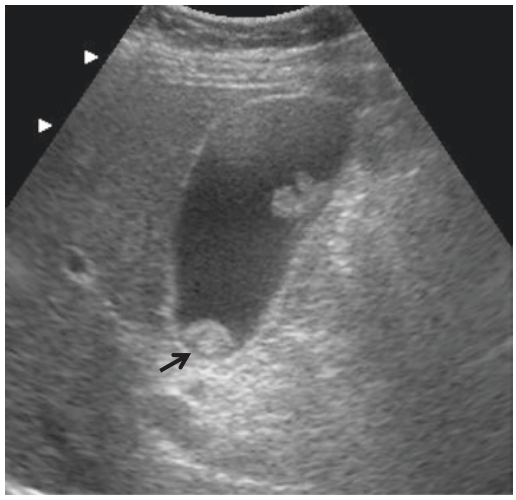

Fig. 7 Sonographic view of gallbladder polyp and gallbladder stone (arrow). After laparoscopic cholecystectomy, the diagnosis of the polyp reveals cholesterol polyp

Patients with biliary pain and US evidence of both polyps and stones in the gallbladder should undergo elective cholecystectomy (Fig. 7). The decision is more complicated for patients in whom gallbladder polyps without concurrent gallstones are discovered. For these patients, the decision to operate depends on the severity of symptoms, confidence of the clinician that the symptoms are biliary in origin, and US features (particularly the size) of the polyp.

Most polyps do not grow over time. About 7% of the polyps increase in size during follow-up (Fig. 8). Polyps less than 5 mm rarely grow. Sometimes (7–34%) polyps are reported to disappear [46–51].

Because polyps 10 mm in size or larger have a greater likelihood of being cancerous, elective laparoscopic cholecystectomy should be considered in acceptable surgical candidates with asymptomatic polyps of this size [45, 52, 53]. In a patient who is a poor surgical risk with a polyp that is 10 mm or larger, periodic monitoring for polyp growth (perhaps every 6 months) with US or additional characterization with EUS may be reasonable.

Polyps larger than 18 mm in diameter pose a significant risk of malignancy and should prompt cholecystectomy if possible. One study found that lesions of this size often contain advanced, invasive cancer that involves the serosal surface of the gallbladder and requires a more extensive dissection than can be accomplished by laparoscopy [54]. As a result, the investigators advocate open cholecystectomy for these large polypoid lesions of the gallbladder. Unfortunately, trials comparing these surgical approaches are not available. Thus, the ideal surgical approach for gallbladder polyps with suspicion of malignancy is unsettled.

How best to manage patients with polyps that are 6–9 mm in size is debated. Multiple polyps, pedunculated polyps, and those that are hyperechoic compared with the liver are usually cholesterol polyps, while solitary and sessile polyps that are isoechoic with the liver are more likely to be neoplastic. In this generally low-risk population, periodic surveillance for polyp growth or change may be prudent. One group of investigators has recommended transabdominal US evaluation 3–6 months after the initial discovery of such polyps to exclude a rapidly growing tumor, followed by ongoing surveillance at 6–12-month intervals. The optimal duration of surveillance is unknown. Two studies have suggested that the 10-mm cut-off value for cholecystectomy may be too high, as premalignant or malignant gallbladder lesions were found in persons with polyps that were initially 6–9 mm in size [49, 55]. So, some other investigators have advocated aggressive approach of performing cholecystectomy for polyps of this size given the small but possible risk of neoplasia such as increased size of polyp (>2 mm) [20], single [48, 56], sessile polyp (including focal gallbladder wall thickening >4 mm) [48, 57–68], Indian ethnicity [58] or old age [46, 56, 57, 60, 61]. As with most other cancers, the risk of a gallbladder polyp being malignant increases with increasing patient age. Currently, there is insufficient data to determine what the most appropriate threshold is. Also, there was insufficient evidence to include gallstones as a strong risk factor, but some of these patients are likely to be symptomatic and as such will undergo cholecystectomy anyway.

The best practice for gallbladder polyp surveillance needs clarification. Given the rarity of

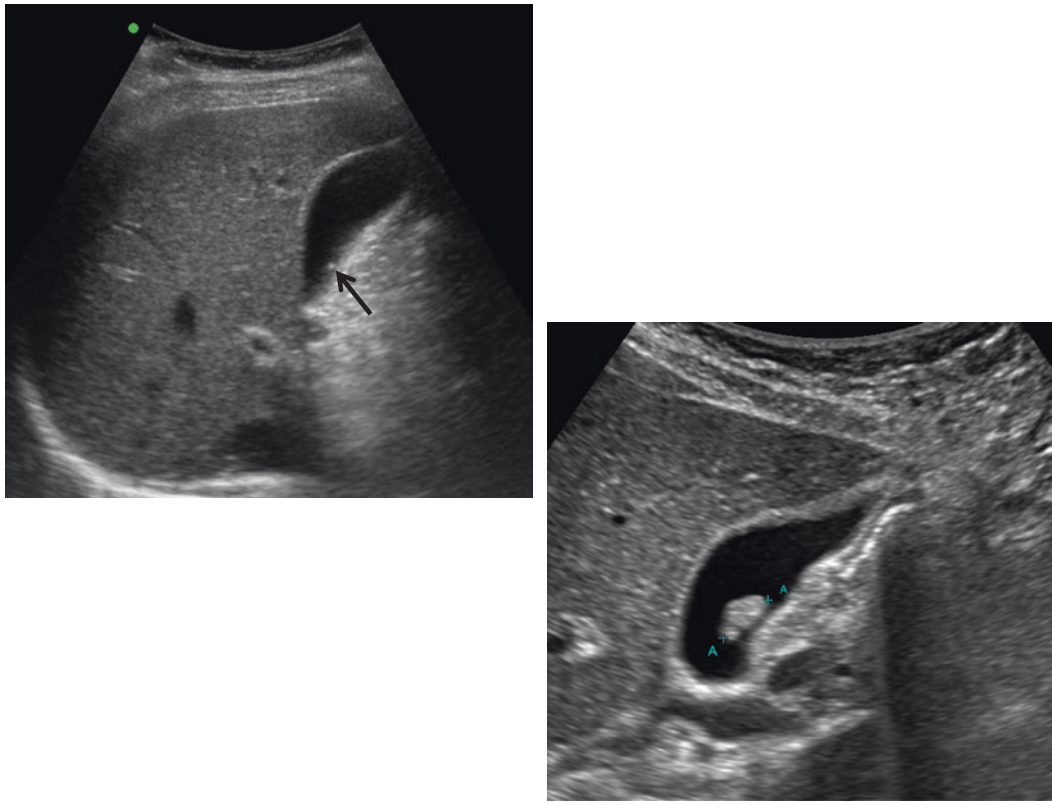

Fig. 8 **a**, **b** Sonographic view of increasing single gallbladder polyp (from 0.3 cm (arrow) to 1.1 cm) over 10 years. After laparoscopic cholecystectomy, the diagnosis reveals cholesterol polyp

gallbladder cancer, the cost of universal gallbladder polyp surveillance may not be justifiable; the cost-effectiveness might be improved by limiting surveillance to polyps between 5 and 10 mm in size because no study has reported neoplasia in an asymptomatic polyp less than 6 mm in size [50]. Polyps less than 6 mm in size are usually benign and most frequently represent cholesterolosis. However, although no malignant polyps have been shown to be below 4 mm, there is still a risk of adenomas and these polyps therefore would still require follow up but on a less frequent basis [46]. If the gallbladder polyp disappears, then it was likely a pseudopolyp and does not require further follow-up.

The recommendations for following small gallbladder polyps expectantly may not apply to patients with PSC, in whom the risk of malignancy in polypoid lesions of the gallbladder may be as high as 60% [62–65]. These patients should undergo a more intensive follow-up and have a lower threshold for cholecystectomy than non-PSC patients. In this high-risk population, cholecystectomy for polyps smaller than 10 mm should be considered. This, however, is challenged by observations that gallbladder cancer is seen only in polyps greater than 8 mm and that cholecystectomy in patients with PSC and cirrhosis is associated with high morbidity [65–67]. There was insufficient data to support cholecystectomy in all patients with PSC and a gallbladder polyp, because of the potential increased morbidity.

Recently, the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) developed a consensus-based guideline. A summary of the recommendations is described in the algorithm (Fig. 9) [68].

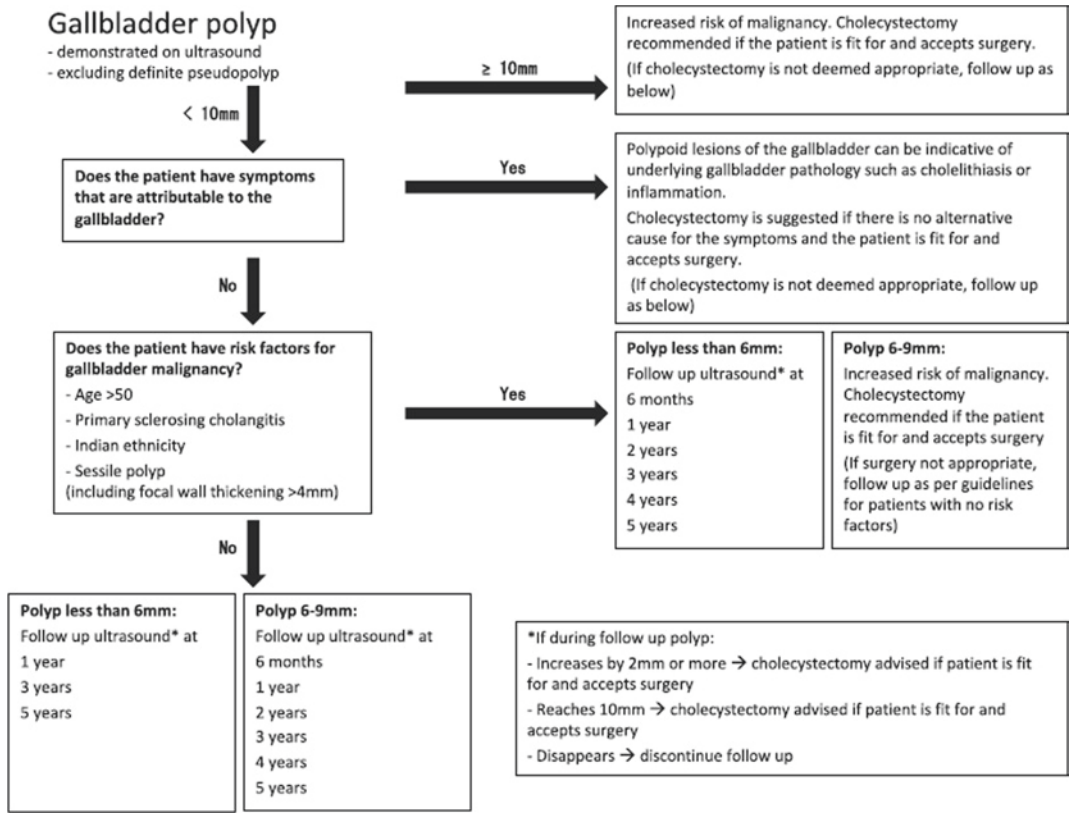

Fig. 9 Management algorithm of gallbladder polyp (Reproduced from Wiles et al. [68])

Conclusion

Currently, there remain controversies and challenges in many aspects of gallbladder polyps. It is difficult to differentiate benign lesions from malignant gallbladder polyps based on available diagnostic modalities. Patients with gallbladder polyps should be treated with personalized and differentiated strategies. Better understanding of the clinicopathologic characteristics, risk factors, classification and natural history of gallbladder polyps are necessary and larger prospective trials involving multiple centers should be conducted.

References

1. Okamoto M, Okamoto H, Kitahara F, Kobayashi K, Karikome K, Miura K, et al. Ultrasonographic evidence of association of polyps and stones with gallbladder cancer. Am J Gastroenterol. 1999;94:446–50.
2. Marangoni G, Hakeem A, Toogood GJ, Lodge JP, Prasad KR. Treatment and surveillance of polypoid lesions of the gallbladder in the United Kingdom. HPB (Oxford). 2012;14:435–40.
3. Lee YJ, Park KS, Cho KB, Kim ES, Jang BK, Chung WJ, et al. Shifting prevalence of gallbladder polyps in Korea. J Korean Med Sci. 2014;29:1247–52.
4. Choi YS, Do JH, Seo SW, Lee SE, Oh HC, Min YJ, et al. Prevalence and risk factors of gallbladder polypoid lesions in a healthy population. Yonsei Med J. 2016;57:1370–5.
5. Kratzer W, Schmid A, Akinli AS, Thiel R, Mason RA, Schuler A, et al. Gallbladder polyps: prevalence and risk factors. Ultraschall Med. 2011;32(Suppl 1):68–73.
6. Jørgensen T, Jensen K. Polyps in the gallbladder: a prevalence study. Scand J Gastroenterol. 1990;25:281–6.
7. Lin WR, Lin DY, Tai DI, Hsieh SY, Lin CY, Sheen IS, et al. Prevalence of and risk factors for gallbladder polyps detected by ultrasonography

among healthy Chinese: analysis of 34,669 cases. J Gastroenterol Hepatol. 2008;23:965–9.
8. Terzi C, Sökmen S, Seçkin S, Albayrak L, Uğurlu M. Polypoid lesions of the gallbladder: report of 100 cases with special reference to operative indications. Surgery. 2000;127:622–7.
9. Selzer DW, Dockerty MB, Stauffer MH, Priestley JT. Papillomas (so-called) in the non-calculous gallbladder. Am J Surg. 1962;103:472–6.
10. Parrilla Paricio P. Garcia Olmo D, Pellicer Franco E, Prieto González A, Carrasco González L, Bermejo López J. Gallbladder cholesterolosis: an aetioloaical factor in acute pancreatitis of uncertain origin. Br J Surg. 1990;77:735–6.
11. Maevama R, Yamaguchi K, Noshiro H, Takashima M, Chijiiwa K, Tanaka M. A large inflammatory polyp of the gallbladder masquerading as gallbladder carcinoma. J Gastroenterol. 1998;33:770–4.
12. Swinton N, Becker W. Tumors of the gallbladder. Surg Clin North Am. 1948;28:669–72.
13. Kozuka S, Tsubone N, Yasui A, Hachisuka K. Relation of adenoma to carcinoma in the gallbladder. Cancer. 1982;50:2226–34.
14. Farinon AM, Pacella A, Cetta F, Sianesi M. "Adenomatous polyps of the gallbladder" adenomas of the gallbladder. HPB Surg. 1991;3:251–8.
15. Mitty WF Jr, Rousselot LM. Cholesterosis of the gallbladder. Gastroenterology. 1957;32:910–6.
16. Kmiot WA, Perry EP, Donovan IA, Lee MJ, Wolverson RF, Harding LK, et al. Cholesterolosis in patients with chronic acalculous biliary pain. Br J Surg. 1994;81:112–5.
17. Cappell MS, Marks M, Kirschenbaum H. Massive hemobilia and acalculous cholecystitis due to benign gallbladder polyp. Dig Dis Sci. 1993;38:1156–61.
18. Akyürek N, Salman B, Irkörücü O, Sare M, Tatlicioğlu E. Ultrasonography in the diagnosis of true gallbladder polyps: the contradiction in the literature. HPB (Oxford). 2005;7:155–8.
19. Shapiro RS, Winsberg F. Comet-tail artifact from cholesterol crystals: observations in the postlithotripsy gallbladder and an in vitro model. Radiology. 1990;177:153–6.
20. Sugiyama M, Atomi Y, Yamato T. Endoscopic ultrasonography for differential diagnosis of polypoid gall bladder lesions: analysis in surgical and follow up series. Gut. 2000;46:250–4.
21. Chattopadhyay D1, Lochan R, Balupuri S, Gopinath BR, Wynne KS. Outcome of gall bladder polypoidal lesions detected by transabdominal ultrasound scanning: a nine year experience. World J Gastroenterol. 2005;11:2171–3.
22. Yang HL, Sun YG, Wang Z. Polypoid lesions of the gallbladder: diagnosis and indications for surgery. Br J Surg. 1992;79:227–9.
23. Rodríguez-Fernández A, Gómez-Río M, Medina-Benítez A, Moral JV, Ramos-Font C, Ramia-Angel JM, et al. Application of modern imaging methods in diagnosis of gallbladder cancer. J Surg Oncol. 2006;93:650–64.
24. Koga A, Watanabe K, Fukuyama T, Takiguchi S, Nakayama F. Diagnosis and operative indications for polypoid lesions of the gallbladder. Arch Surg. 1988;123:26–9.
25. Jones-Monahan KS, Gruenberg JC, Finger JE, Tong GK. Isolated small gallbladder polyps: an indication for cholecystectomy in symptomatic patients. Am Surg. 2000;66:716–9.
26. Sugiyama M, Xie XY, Atomi Y, Saito M. Differential diagnosis of small polypoid lesions of the gallbladder: the value of endoscopic ultrasonography. Ann Surg. 1999;229:498–504.
27. Sadamoto Y, Oda S, Tanaka M, Harada N, Kubo H, Eguchi T, et al. A useful approach to the differential diagnosis of small polypoid lesions of the gallbladder, utilizing an endoscopic ultrasound scoring system. Endoscopy. 2002;34:959–65.
28. Cheon YK, Cho WY, Lee TH, Cho YD, Moon JH, Lee JS, et al. Endoscopic ultrasonography does not differentiate neoplastic from non-neoplastic small gallbladder polyps. World J Gastroenterol. 2009;15:2361–6.
29. Kim JH, Lee JY, Baek JH, Eun HW, Kim YJ, Han JK, et al. High-resolution sonography for distinguishing neoplastic gallbladder polyps and staging gallbladder cancer. AJR Am J Roentgenol. 2015;204:W150–9.
30. Jang JY, Kim SW, Lee SE, Hwang DW, Kim EJ, Lee JY, et al. Differential diagnostic and staging accuracies of high resolution ultrasonography, endoscopic ultrasonography, and multidetector computed tomography for gallbladder polypoid lesions and gallbladder cancer. Ann Surg. 2009;250:943–9.
31. Meacock LM, Sellars ME, Sidhu PS. Evaluation of gallbladder and biliary duct disease using microbubble contrast-enhanced ultrasound. Br J Radiol. 2010;83:615–27.
32. Liu XS, Gu LH, Du J, Li FH, Wang J, Chen T, et al. Differential diagnosis of polypoid lesions of the gallbladder using contrast-enhanced sonography. J Ultrasound Med. 2015;34:1061–9.
33. Yuan HX, Cao JY, Kong WT, Xia HS, Wang X, Wang WP. Contrast-enhanced ultrasound in diagnosis of gallbladder adenoma. Hepatobiliary Pancreat Dis Int. 2015;14:201–7.
34. Choi JH, Seo DW, Choi JH, Park DH, Lee SS, Lee SK, et al. Utility of contrast-enhanced harmonic EUS in the diagnosis of malignant gallbladder polyps (with videos). Gastrointest Endosc. 2013;78:484–93.
35. Furukawa H, Kosuge T, Shimada K, Yamamoto J, Kanai Y, Mukai K, et al. Small polypoid lesions of the gallbladder: differential diagnosis and surgical indications by helical computed tomography. Arch Surg. 1998;133:735–9.
36. Lou MW, Hu WD, Fan Y, Chen JH, E ZS, Yang GF. CT biliary cystoscopy of gallbladder polyps. World J Gastroenterol. 2004;10:1204–7.
37. Irie H, Kamochi N, Nojiri J, Egashira Y, Sasaguri K, Kudo S. High b-value diffusion-weighted MRI in

differentiation between benign and malignant polypoid gallbladder lesions. Acta Radiol. 2011;52:236–40.
38. Koh T, Taniguchi H, Kunishima S, Yamagishi H. Possibility of differential diagnosis of small polypoid lesions in the gallbladder using FDG-PET. Clin Positron Imaging. 2000;3:213–8.
39. Ozdemir A, Ozenc A, Bozoklu S, Coskun T. Ultrasonography in the diagnosis of gallbladder polyps. Br J Surg. 1993;80:345.
40. Csendes A, Burgos AM, Csendes P, Smok G, Rojas J. Late follow-up of polypoid lesions of the gallbladder smaller than 10mm. Ann Surg. 2001;234:657–60.
41. Gurusamy KS, Koti R, Fusai G, Davidson BR. Early versus delayed laparoscopic cholecystectomy for uncomplicated biliary colic. Cochrane Database Syst Rev. 2013;(6):CD007196.
42. Krähenbühl L, Sclabas G, Wente MN, Schäfer M, Schlumpf R, Büchler MW. Incidence, risk factors, and prevention of biliary tract injuries during laparoscopic cholecystectomy in Switzerland. World J Surg. 2001;25:1325–30.
43. Gurusamy KS, Abu-Amara M, Farouk M, Davidson BR. Cholecystectomy for gallbladder polyp. Cochrane Database Syst Rev. 2009;(1):CD007052.
44. Christensen M, Matzen P, Schulze S, Rosenberg J. Complications of ERCP: a prospective study. Gastrointest Endosc. 2004;60:721–31.
45. Mainprize KS, Gould SW, Gilbert JM. Surgical management of polypoid lesions of the gallbladder. Br J Surg. 2000;87:414–7.
46. Babu BI, Dennison AR, Garcea G. Management and diagnosis of gallbladder polyps: a systematic review. Langenbecks Arch Surg. 2015;400:455–62.
47. Wiles R, Varadpande M, Muly S, Webb J. Growth rate and malignant potential of small gallbladder polyps–systematic review of evidence. Surgeon. 2014;12:221–6.
48. Bhatt NR, Gillis A, Smoothey CO, Awan FN, Ridgway PF. Evidence based management of polyps of the gall bladder: a systematic review of the risk factors of malignancy. Surgeon. 2016;14:278–86.
49. Park JY, Hong SP, Kim YJ, Kim HJ, Kim HM, Cho JH, et al. Long-term follow up of gallbladder polyps. J Gastroenterol Hepatol. 2009;24:219–22.
50. Cairns V, Neal CP, Dennison AR, Garcea G. Risk and cost-effectiveness of surveillance followed by cholecystectomy for gallbladder polyps. Arch Surg. 2012;147:1078–83.
51. Shin SR, Lee JK, Lee KH, Lee KT, Rhee JC, Jang KT, et al. Can the growth rate of a gallbladder polyp predict a neoplastic polyp? J Clin Gastroenterol. 2009;43:865–8.
52. Kubota K, Bandai Y, Otomo Y, Ito A, Watanabe M, Toyoda H, et al. Role of laparoscopic cholecystectomy in treating gallbladder polyps. Surg Endosc. 1994;8:42–6.
53. Sheth S, Bedford A, Chopra S. Primary gallbladder cancer: recognition of risk factors and the role of prophylactic cholecystectomy. Am J Gastroenterol. 2000;95:1402–10.
54. Kubota K, Bandai Y, Noie T, Ishizaki Y, Teruya M, Makuuchi M. How should polypoid lesions of the gallbladder be treated in the era of laparoscopic cholecystectomy? Surgery. 1995;117:481–7.
55. Zielinski MD, Atwell TD, Davis PW, Kendrick ML, Que FG. Comparison of surgically resected polypoid lesions of the gallbladder to their pre-operative ultrasound characteristics. J Gastrointest Surg. 2009;13:19–25.
56. Elmasry M, Lindop D, Dunne DF, Malik H, Poston GJ, Fenwick SW. The risk of malignancy in ultrasound detected gallbladder polyps: a systematic review. Int J Surg. 2016;33:28–35.
57. Park JK, Yoon YB, Kim Y-T, Ryu JK, Yoon WJ, Lee SH, et al. Management strategies for gallbladder polyps: is it possible to predict malignant gallbladder polyps? Gut Liver. 2008;2:88–94.
58. Aldouri AQ, Malik HZ, Waytt J, Khan S, Ranganathan K, Kummaraganti S, et al. The risk of gallbladder cancer from polyps in a large multiethnic series. Eur J Surg Oncol. 2009;35:48–51.
59. Choi SY, Kim TS, Kim HJ, Park JH, Park DI, Cho YK, et al. Is it necessary to perform prophylactic cholecystectomy for asymptomatic subjects with gallbladder polyps and gallstones? J Gastroenterol Hepatol. 2010;25:1099–104.
60. Gallahan WC, Conway JD. Diagnosis and management of gallbladder polyps. Gastroenterol Clin North Am. 2010;39:359–67.
61. Corwin MT, Siewert B, Sheiman RG, Kane RA. Incidentally detected gallbladder polyps: is follow-up necessary–Long-term clinical and US analysis of 346 patients. Radiology. 2011;258:277–82.
62. Karlsen T, Schrumpf E, Boberg K. Gallbladder polyps in primary sclerosing cholangitis: not so benign. Curr Opin Gastroenterol. 2008;24:395–9.
63. Said K, Glaumann H, Bergquist A. Gallbladder disease in patients with primary sclerosing cholangitis. J Hepatol. 2008;48:598–605.
64. Buckles DC, Lindor KD, Larusso NF, Petrovic LM, Gores GJ. In primary sclerosing cholangitis, gallbladder polyps are frequently malignant. Am J Gastroenterol. 2002;97:1138–42.
65. Eaton JE, Thackeray EW, Lindor KD. Likelihood of malignancy in gallbladder polyps and outcomes following cholecystectomy in primary sclerosing cholangitis. Am J Gastroenterol. 2012;107:431–9.
66. Razumilava N, Gores GJ, Lindor KD. Cancer surveillance in patients with primary sclerosing cholangitis. Hepatology. 2011;54:1842–52.
67. Schramm C, Lohse AW. Gallbladder polyps in primary sclerosing cholangitis: indication for early intervention. Hepatology. 2012;56:396.
68. Wiles R, Thoeni RF, Barbu ST, Vashist YK, Rafaelsen SR, Dewhurst C, et al. Management and follow-up of gallbladder polyps: Joint guidelines between the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), European Association for Endoscopic Surgery and other Interventional Techniques (EAES), International Society of Digestive Surgery- European Federation (EFISDS) and European Society of Gastrointestinal Endoscopy (ESGE). Eur Radiol. 2017;27:3856–66.