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World J Gastrointest Surg 2024 June 27; 16(6): 1507-1512

ISSN 1948-9366 (online) DOI: 10.4240/wjgs.v16.i6.1507

EDITORIAL

Current considerations for the surgical management of gallbladder adenomas

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Specialty type: Gastroenterology and hepatology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B Scientific Significance: Grade B

P-Reviewer: McFadden N, Canada

Received: February 23, 2024 Revised: April 29, 2024 **Accepted:** May 16, 2024 Published online: June 27, 2024 Processing time: 128 Days and 0.3

Hours



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Abstract

Gallbladder adenomas are rare lesions (0.5%) associated with potential malignant transformation, particularly with gallbladder adenomas that are ≥ 1 cm in size. Early detection and management are crucial for preventing lethal carcinoma development. These polyps can often be distinguished from the more often nonneoplastic cholesterol pseudopolyps (5%-10%), which are benign. Ultrasonography is the first-line tool for initial diagnosis and follow-up when indicated. The question is whether cholecystectomy is always necessary for all adenomas. The management of gallbladder adenomas is determined according to the size of the tumor, the growth rate of the tumor, the patient's symptoms and whether risk factors for malignancy are present. Adenomas ≥ 1 cm in size, an age > 50 years and a familial history of gallbladder carcinoma are indications for immediate laparoscopic cholecystectomy. Otherwise, ultrasound follow-up is indicated. For adenomas 6-9 mm in size, the absence of ≥ 2 mm growth at 6 months, one year, and two years, as well as an adenoma sized < 5 mm without existing risk factors indicates that no further surveillance is required. However, it would be preferable to individualize the management in doubtful cases. Novel interventional modalities for preserving the gallbladder need further evaluation, especially to determine the long-term outcomes.

Key Words: Biliary diseases; True neoplastic polyps; Gallbladder adenomas; Benign biliary tumors; Gallbladder polyps; Extrahepatic biliary neoplasms

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Core Tip: Gallbladder adenomas are rare benign neoplastic lesions associated with malignant potential. Thus, early management is essential to prevent transformation. They are usually detected incidentally by imaging. Current imaging modalities can ensure a reliable diagnosis in vague cases. The management includes either laparoscopic cholecystectomy or ultrasound surveillance.

Citation: Pavlidis ET, Galanis IN, Pavlidis TE. Current considerations for the surgical management of gallbladder adenomas. World J Gastrointest Surg 2024; 16(6): 1507-1512

URL: https://www.wjgnet.com/1948-9366/full/v16/i6/1507.htm

DOI: https://dx.doi.org/10.4240/wjgs.v16.i6.1507

INTRODUCTION

Gallbladder polyps affecting 5%-10% of the adult population, consist of nonneoplastic cholesterol pseudopolyps in the vast majority of cases and they are usually discovered incidentally [1]. Adenomas or true neoplastic polyps are rare benign lesions that represent 0.5% of gallbladder neoplasms and 3%-9% of gallbladder polyps[2-5]. However, they can have malignant potential according to their size, which leads to gallbladder cancer with poor prognosis (a 5-year overall survival of 5%-8%)[6]. The malignant transformation process follows the dysplasia-carcinoma in situ-invasive carcinoma sequence[7]. The transformation is related to the adenoma's size, and the transformation rate can be as high as 5% when the size of the adenoma is ≥ 10 mm and is up to 40% when the size of the adenoma is ≥ 20 mm[2,6,8]. The early-stage diagnosis of gallbladder cancer is important for optimizing therapeutic management [9,10]. It is obvious that timely cholecystectomy prevents the progression of any adenoma, but whether timely cholecystectomy is necessary in all patients or constitutes overtreatment in some patients remains unclear [11]. Indications for immediate laparoscopic cholecystectomy include an adenoma size ≥ 10 mm or the presence of specific imaging findings, an age > 50 years and a familial history of GB carcinoma[11-15]. Otherwise, ultrasound follow-up is indicated in patients under 50 years of age who have adenomas that are < 10 mm in size and who do not have any predisposing genetic factors [7,16-19]. A follow-up is not considered necessary for patients who have an adenoma that is < 5 mm in size and who do not have any significant family history[16-19].

The initial diagnostic approach is based on plain abdominal ultrasound. The distinction of adenomas from cholesterol pseudopolyps is a challenging task. The use of computed tomography (CT), magnetic resonance imaging (MRI), and current ultrasonic modalities, including simple endoscopic or enhanced contrast endoscopic, high resolution, and novel of three dimensions ultrasound, increase the diagnostic accuracy [6,15,18]. Various scoring system models can accurately predict true adenomas and should be developed[20-24].

The risk of malignant transformation of adenomas is correlated with age > 60 years; the presence of gallstones ≥ 3 cm for at least twenty years; a polyp size equal to or greater than 10 mm; patient origin from Asia, mainly India[25]; chronic infection by Salmonella[7] or Helicobacter pylori (H. pylori)[26]; a body mass index greater than 30 kg/m²; a diagnosis of schistosomiasis[27]; a diagnosis of primary sclerosing cholangitis; a polyp with a broad basis; and a thickened gallbladder wall greater than 4 mm and/or the presence of an abnormal gallbladder wall layer [7,15,18,28]. H. pylori may not be associated with gallbladder adenoma or gallstone formation[29]. However, the most reliable risk factor for malignant transformation of gallbladder adenomas is size, regardless of the presence or absence of other factors[30].

Minimally invasive procedures for polypectomy alone, in which the gallbladder is preserved and is functional, have recently gained increasing interest[31]. These methods include: (1) Ultrasound-guided radiofrequency for adenoma ablation[32-34]; (2) endoscopic cholecystostomy under ultrasound guidance, which serves as a bridging procedure to endoscopic polypectomy through the gallbladder wall[35,36]; (3) laparoscopic-assisted transumbilical gastroscopy for gallbladder-preserving adenoma resection[37-39]; (4) peroral choledochoscopic gallbladder-preserving adenoma resection[40, 41]; and (5) transgastric endoscopic gallbladder preserving surgery[42]. However, there are still no adequate data available, and these novel approaches require expertise and further evaluation, including further evaluation of the long-term outcomes. Additionally, some skepticism exists about the use of these methods in the current era of laparoscopic cholecystectomy, which is a minimally invasive procedure.

DIAGNOSIS

For gallbladder pathology assessment and differentiation of malignant from benign lesions, the most applicable diagnostic technique worldwide in clinical practice is ultrasound[43-45], and CT[46] and MRI are the second most applicable diagnostic techniques[6,47,48]. However, ultrasound alone is not accurate enough[49]. Further reliability can be obtained with additional CT scans, or better yet, MRI, and this highlights the misdiagnosis bias and can prevent unnecessary operations and thus overtreatment[50]. When a strong possibility of malignancy exists clinically, MRI should be the firstline imaging modality. Contrast-enhanced or endoscopic ultrasound (EUS) is valuable when the equipment is available [28]. High-frequency ultrasound in combination with color Doppler ultrasound constitutes a valuable diagnostic modality with high diagnostic accuracy for gallbladder adenomas (sensitivity of over 90% and specificity of 100%)[51]. Highresolution ultrasound is considered particularly reliable for the assessment of the gallbladder wall layering [49]. In sus-

picious cases, EUS provides high-resolution images, and the combination of EUS with fine needle aspiration ensures the safe diagnosis of malignant transformation of adenomas[52].

During the recommended ultrasound follow-up of small gallbladder adenomas, a growth rate ≥ 2 mm is considered a risk factor for malignant transformation, indicating that there should be no delay in pursuing cholecystectomy[53,54]. In general, a size of 10 mm is considered the limit for operative intervention, while a size of 7 mm is an indication for waiting and ultrasound follow-up[55]

The tumor markers CA19-9, CEA, CA125, and CA242 may be elevated in patients with gallbladder carcinoma, and measurements of these markers can contribute to the early diagnosis of gallbladder carcinoma [56]. In patients with an adenoma ≥ 11 mm in size, increased CA19-9, CEA, and CA72-4 levels constitute strong indications of malignant transformation[57].

SURGICAL MANAGEMENT

The therapeutic management of gallbladder adenomas remains somewhat debated. The European Association for Endoscopic Surgery and other Interventional Techniques, the European Society of Gastrointestinal Endoscopy, the International Society of Digestive Surgery - European Federation and the European Society of Gastrointestinal and Abdominal Radiology have set guidelines[58], and these guidelines have recently been updated[15]. The recommended management depends on whether symptoms are present and the size and the rate of adenoma growth [28]. However, due to the rarity of gallbladder adenomas, there are few large studies, and the current studies have provided low-quality data and thus somewhat unreliable recommendations. In addition, obtaining new knowledge and following the current guidelines are crucial for the correct treatment of gallbladder adenomas[28].

Cholecystectomy is strongly recom-mended for adenomas ≥ 10 mm in size, those that are associated with symptoms, regardless of size, and those with a growth rate of ≥ 2 mm within two years. Monitoring is recommended for patients with smaller lesions, regardless of whether the patient is or without risk factors[15,28,58]. The assessment and definition of risk factors is a multidisciplinary task[20,37,58].

For patients with adenomas 6-9 mm in size without growth or a small size increase ≤ 2 mm during the scheduled follow-up at 6 months, one year, and two years, follow-up should be terminated [8,15,28,58]. Cholecystectomy is recommended for patients who are fit for surgery if any risk factor for malignancy is found at the initial diagnosis of adenomas that are 6-9 mm in size, and surgery should be performed after patients are reassured and consent is obtained [6,15,28,58].

For patients with adenomas ≤ 5 mm in size without risk factors, no follow-up is necessary. Otherwise, follow-up lasting two years is recommended [11,15,19,58]. These small adenomas have a low risk of size increase, and there are no reports of malignant transformation in these types of tumors according to long-term (up to 10 years) ultrasound follow-up[59]. Subsequently, small adenoma surveillance has limited benefit and is not recommended [16]. However, when a risk factor coexists, ultrasound surveillance lasting at least 5 years is recommended, and for any 2 mm increase in the adenoma's size, imperative cholecystectomy is recommended[60].

Laparoscopic cholecystectomy is currently the gold standard for gallbladder adenomas that require interventional procedures[6,15,61]. However, if a gallbladder adenoma ≥ 20 mm in size exists, a surgical plan similar to that of gallbladder carcinoma will be drawn up, as long as there are not any preoperative evidence or even an indication of malignancy[62]. Laparoscopic cholecystectomy is not recommended for such patients since there is a strong possibility of malignant transformation[63]. Thus, an open surgery should preferably be carried out by a surgeon experienced in hepatobiliary surgery, who should keep in mind the following cancer management strategy.

For patients with adenomas 10-15 mm in size or with gallbladder wall thickening, it is recommended that an experienced general surgeon safely perform laparoscopic cholecystectomy, as long as there is not any preoperative evidence or even an indication of malignancy. It is of the utmost importance to avoid gallbladder perforation in any case to prevent the possible intraperitoneal spread of cancer cells in cases of initially hidden malignancy, which will eventually be discovered via specimen biopsy. This obligation may necessitate the conversion of laparoscopic surgery to open surgery without any hesitation due to the possible operative difficulties encountered[60,64].

In cases where a cholecystectomy specimen biopsy is used to diagnose gallbladder adenocarcinoma, the extent of subsequent surgical resection depends on the disease stage. An already performed simple cholecystectomy is an adequate treatment for stage T1a disease, and no further treatment is needed. Otherwise, for more advanced disease, an additional operation will be needed. Some of the additional operations include wide lymphadenectomy in every case, accompanied by complementary gallbladder bed hepatic resection, in patient with T1b stage; resection of the IV and V hepatic segments for patients with T2 stage; hepatic trisegmentectomy or major hepatectomy with Roux-Y hepaticojejunostomy and, if needed, adjacent organ resection for patients with T3 stage[9,65].

CONCLUSION

Gallbladder adenomas have a low incidence but have a risk of malignancy. These patients are usually asymptomatic, and these tumors are usually detected incidentally by imaging. The management policy must be planned according to whether symptoms are present as well as the size and the rate of adenoma growth. Gallbladder removal is needed for all patients with tumors sized ≥ 10 mm, those patients who have a tumor 6-9 mm in size with a coexisting malignancy risk factor, those who have symptoms, those who have gallstones, and those who have had an adenoma growth rate ≥ 2 mm during the regular two-year ultrasound follow-up. For small adenomas ≤ 5 mm in size without risk factors, no follow-up.



is needed. The management of gallbladder adenomas should be individualized in ambiguous cases.

FOOTNOTES

Author contributions: Pavlidis TE designed research, contributed new analytic tools, analyzed data and review; Galanis IN analyzed data and review; Pavlidis ET performed research, analyzed data, review and wrote the article.

Conflict-of-interest statement: Dr. Pavlidis has nothing to disclose.

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S-Editor: Lin C L-Editor: A P-Editor: Xu ZH

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