Diagnosis of Gallbladder Tumors

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Abstract

Gallbladder cancer is among the organs examined in mass screening for cancer using ultrasonography; the reported prevalence of gallbladder cancer in such screening of a general population was 0.011%, while the prevalence of gallbladder polyps was reported as 4.3 to 6.9%. Endoscopic ultrasonography is useful for the differential diagnosis of gallbladder tumors detected by mass screening, as well as for estimating the depth of tumor invasion and detecting abnormal connections between pancreatobiliary ducts. While a systematic approach leading to diagnosis by endoscopic ultrasonography is useful, recent advances of contrast-enhanced ultrasonography are expected to establish it as a new modality for early detection. At our hospital, 7 of 26 patients with abnormal connections between pancreatobiliary ducts developed gallbladder carcinoma (23.1%), and 7 of 48 patients with gallbladder carcinoma had abnormal connections between pancreatobiliary ducts (12.5%). Serial observation in patients with gallstones and prophylactic surgery in patients with abnormal connections between pancreatobiliary ducts are necessary.

Key words: gallbladder carcinoma, polypoid gallbladder lesions, endoscopic ultrasonography, contrast-enhanced ultrasonography, anomalous connections between pancreatobiliary ducts, gallstones

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Introduction

Gallbladder tumors may be detected incidentally during routine ultrasonography in patients with or without symptoms. These tumors include a variety of histologic types, such as adenocarcinoma, adenoma, hyperplasia, cholesterol polyp, inflammatory polyp, and adenomyomatosis. Accurate diagnosis is important for avoiding unnecessary surgery. Advances in imaging modalities include endoscopic ultrasonography, multi-detector-row computed tomography, magnetic resonance imaging, contrast-enhanced ultrasonography, and endoscopic retrograde cholecystography. This review provides an update on diagnosis of gallbladder tumors.

Incidence of Gallbladder Carcinoma

In Japan, gastric cancer was the leading cause of cancer-related deaths until 1999, when lung cancer took the lead. Biliary tract cancer has been reported by the Ministry of Health, Labor and Welfare (1) to be the sixth leading cause of cancer-related deaths in Japan, where 16,841 people died

of biliary tract cancer in 2007. Deaths per year from biliary tract cancer are increasing steadily, now numbering 3.8 times higher than in 1975, when 4,484 people died of biliary tract cancer. Early detection of gallbladder cancer is an urgent goal.

Gallbladder Tumors in Mass Screening

In Japan, mass screening for digestive cancer using ultrasonography has been provided through-out the country. The gallbladder is one of the organs examined. Mihara et al (2) reported the detection rate for gallbladder cancer in mass screening of 1,306,947 persons as 0.011% (143 cases); bile duct cancer, 0.003% (39 cases); and pancreatic cancer, 0.008% (114 cases). In a mass survey by our affiliated institution, detection rates of gallbladder carcinoma, gallstone, and cholesterol polyp of the gallbladder were 0.01%, 4.1%, and 9.1% respectively among 43,348 persons (unpublished data). The detection rate of gallbladder carcinoma was similar in both studies.

In healthy populations, the prevalence of gallbladder polyps was reported as 4.3% in Denmark (3); 5.9% in Ja-

pan (4); and 6.9% in Taiwan (5). Polypoid gallbladder lesions include a variety of pathologic types. Benign lesions are divided into two types, true tumors and pseudotumors. Pseudotumors include cholesterol polyps, inflammatory polyps, and hyperplasia. True tumors, which include adenomas and malignant lesions, should be treated by surgical resection, while pseudotumors can be observed serially. Kubota et al. (6) reported that 57% of cholesterol polyps measured less than 10 mm, but 75% of adenomas and 13% of cancers were smaller than 10 mm. Those authors concluded that the lesion number or size alone failed to predict histologic nature of polyps detected by ultrasonography.

High Risk for Gallbladder Carcinoma

Early detection prior to symptoms is the most important step in improving the prognosis of gallbladder carcinoma. One approach is to use certain modalities in all patients, as in mass screening. Another method is to perform periodic evaluations in patients with factors indicating a high risk of gallbladder cancer. Identification of individuals at high risk for gallbladder cancer thus is necessary to perform efficient screening.

High-risk individuals for gallbladder carcinoma have been identified as those with congenital dilation of the common bile duct, abnormal connections between pancreatobiliary ducts, reflux of pancreatic juice into the bile duct, or gallstones, as well as persons belonging to a familial gallbladder cancer kindred (7-9). Gallstones and abnormal connections between pancreatobiliary ducts and gallstones are two very important risk factors for gallbladder cancer. At our hospital, 7 of 26 patients with abnormal connections between pancreatobiliary ducts developed gallbladder cancer (23.1%), while 7 of 48 patients with gallbladder carcinoma had an abnormal connection between pancreatobiliary ducts (12.5%).

Differential Diagnosis of Gallbladder Tumors

1. Multi-detector-row computed tomography

Contrast-enhanced computed tomography can disclose the hemodynamics of gallbladder carcinoma, and it is a useful method for differential diagnosis in cases where a mass has replaced the gallbladder or thickened the gallbladder wall (10). Recently, the usefulness of multi-detector-row computed tomography was reported for tumor staging in gallbladder carcinomas (11). Although conventional computed tomography was not helpful in the differentiation when gallbladder polyps were smaller than 10 mm in diameter, recent advances in multi-detector-row computed tomography have increased its accuracy rate for the differential diagnosis of gallbladder polyps. Furukawa et al (12) reported that computed tomography generally shows polypoid gallbladder carcinoma as an enhancing, intraluminal tissue mass denser than surrounding bile. These authors also re-

ported sensitivity, specificity, positive predictive value, negative predictive value, and the overall accuracy in computed tomographic diagnosis of neoplastic lesions to be 88%, 87%, 88%, 87%, and 87%, respectively. The report concluded that computed tomography can reliably identify neoplastic lesions that should be resected.

2. Magnetic resonance imaging

Magnetic resonance imaging has not been widely used to evaluate gallbladder diseases, having the disadvantages of poor spatial and contrast resolution. However, recent advances in instrumentation have improved the spatial and contrast resolution and also the signal-to-noise ratio (13). Yoshimitsu et al (14) reported the usefulness of dynamic magnetic resonance imaging for differentiating benign from malignant gallbladder lesions. Among polypoid masses, malignant lesions (n=9) demonstrated early and prolonged enhancements, while benign lesions (n=14) showed early enhancement with subsequent washout.

Development of magnetic resonance cholangiopancreatography promises easy delineation of pancreatobiliary ducts and thereby detection of abnormal connections between pancreatobiliary ducts (15) which is an important risk factor for gallbladder carcinoma.

3. Transpapillary approach

Percutaneous transhepatic fine-needle aspiration (16) and percutaneous transhepatic cholecystoscopy have been reported as precise diagnostic techniques in the evaluation of gallbladder polyps. In 1989, we reported the usefulness of percutaneous transhepatic cholecystoscopy for diagnostic evaluation of gallbladder polyps (17). This procedure is the most reliable method for the diagnosis of gallbladder polyps, but it is time consuming and poorly tolerated by patients.

The diagnostic accuracy of endoscopic retrograde cholangiopancreatography is not satisfactory, because this method can only show a filling defect in the gallbladder without delineating the surface of polypoid lesions. Endoscopic retrograde cholangiopancreatography usually is used for the diagnosis of tumor extension to the bile duct or for demonstrating abnormal connections of pancreatobiliary ducts, an abnormality closely linked with gallbladder carcinoma. Several efforts have been made to improve the diagnosis using the transpapillary approach. Fujita et al (18) and Foerester et al (19) reported successful cases, with the expectation that this technique would expand diagnostic and therapeutic possibilities in diseases of the gallbladder. Diagnostic endoscopic inspection and biopsy would involve a slender endoscope into the gallbladder.

Watanabe et al (20) reported the clinical usefulness and problems associated with transpapillary gallbladder biopsy and obtained specimens sufficient for histologic diagnosis in 8 of 9 cases (88.9%). Diagnostic accuracy for malignant and benign diseases was 100% and 83.3%, respectively. Inserting a sheath through the cystic duct into the gallbladder is

difficult, and obtaining biopsy specimens is more difficult on the peritoneal side than on the hepatic side of the gallbladder. Using an improved technique, Itoi et al (21) successfully cannulated the gallbladder for biopsy via the cystic duct in 71 of 85 (83%). This procedure should be accepted as a precise diagnostic modality once it can be performed more easily and safely.

4. Endoscopic ultrasonography

Endoscopic ultrasonography is recommended for further examination after conventional ultrasonography, because images obtained are more distinct than with conventional ultrasonography. Several studies have evaluated endoscopic ultrasonography for polypoid gallbladder lesions (22-24). Such images appear promising for distinguishing cholesterol polyps from other polyps, and the overall accuracy for differentiating neoplastic from non-neoplastic masses was reported as 91.1% (22). Endoscopic ultrasonography is highly accurate in the diagnosis of cholesterol polyp and adenomyomatosis, which represent the most common types of gallbladder polyps. This ultrasonographic method can delineate cholesterol polyps, which have a thin stalk and show homogeneous echoes (except for punctuate, highly echogenic areas) from early gallbladder carcinoma, which has a thick stalk and shows heterogeneous echoes.

Mitake et al (23) reported the effectiveness of endoscopic ultrasonography in the diagnosis of gallbladder carcinoma and determination of the extent of tumor invasion; differential diagnosis between early and advanced-stage tumors was 79.5% accurate, and the overall accuracy for tumor invasion depth was 76.9%. Tumor infiltration can be detected as hypoechoic tumor invading the layers of the gallbladder wall. In patients with an adenocarcinoma, characterized as T2 by the tumor node metastasis classification, endoscopic ultrasonography demonstrates a hypoechoic lesion at the base of tan essentially sessile polyp invading only as deeply as the second or third hyperechoic layer of the gallbladder wall (24).

Developments of contrast agents may increase the usefulness of endoscopic ultrasonography. In 1998, Hirooka et al (25) reported that in contrast-enhanced endosonography, enhancement was observed in 11 of 12 adenocarcinoma (91.7%) but not in adenosquamous carcinoma or cholesterol polyps. Depth of tumor invasion was assessed accurately in 11 of 14 cases (78.6%) by conventional endoscopic ultrasonography, and in 13 of 14 cases (92.9%) by contrast-enhanced endosonography.

Endoscopic ultrasonography demonstrates connections between pancreatobiliary ducts in the parenchyma of the pancreas as clearly as endoscopic retrograde cholangiopancreatography (26). As abnormal connections between pancreatobiliary ducts are closely associated with gallbladder carcinoma, identifying these is very important for early diagnosis of cancer.

5. Contrast-enhanced ultrasonography

Advances in conventional ultrasonography, such as high-resolution ultrasonography, have contributed to improved detection of polypoid gallbladder lesions. Accuracy of ultrasonography for diagnosis of polypoid gallbladder lesions was reported as 70 to 90%. Malignancy should be considered when polypoid lesions exceed 20 mm in diameter, are solitary, sessile or associated with gallstones. Color Doppler ultrasonography has been reported to be useful in the evaluation of malignant lesions. Hirooka et al (27) reported that in cancerous gallbladder polyps, the color signal pattern was diffuse, becoming linear at the base. Velocity and the resistance index were 39.0 ± 12.4 cm/s and 0.62 ± 0.12 , respectively, which was significantly different from control measurements. In combination with conventional ultrasonography, color Doppler ultrasonography could be useful in distinguishing benign from malignant gallbladder masses.

Recently developed contrast agents may refine diagnosis by this technique. In 2007, Hattori et al (28) reported the usefulness of contrast-enhanced ultrasonography using a galactose-based contrast agent (Levovist, Nippon Schering, Japan) for differential diagnosis of polypoid gallbladder lesions. They examined contrast-enhancement patterns and time-intensity curves. Contrast enhancement patterns were classified as linear, scattered, diffuse, or branched. When diffuse and branched types were considered indicative of cancer, accuracy was 84.5%, sensitivity 100%, and specificity 76.9%. In gallbladder carcinoma, the time-intensity curve rose sooner than in other diseases as time progressed from no contrast to early-phase. In adenocarcinoma, high-intensity values persisted at 120 s. With an intensity of 90 or greater at 120 s taken to indicate cancer, accuracy was 89.7%, sensitivity 89.5%, and specificity 89.7%. The report concluded that ultrasonographic contrast-enhancement patterns show characteristic associations with pathologic findings, serving as a valuable adjunct in diagnosis of gallbladder diseases.

Recently, another new contrast agent has become available (29). Contrast-enhanced ultrasonography using perflubutane (Sonazoid, Daiichi-Sankyo, Tokyo) has been investigated in the differential diagnosis of polypoid gallbladder lesions. In gallbladder cancer, staining throughout the tumor was continuous, consistent with diffuse hypervascularity. Differences between lesion types in flow image size and convection of blood flow were observed. Flowing images, designated as an irregular rolling sign or eruption sign, appeared to be characteristic of gallbladder cancer. On the other hand, in benign gallbladder polyps, staining was scattered with the flow image being uniform and small. Therefore, contrast-enhanced ultrasonography using perflubutane should be useful in the differential diagnosis of gallbladder tumors (29).

Conclusion

Mass screening by using ultrasonography can detect gall-

bladder abnormalities, among which early gallbladder carcinoma should be distinguished from other diseases. Further evaluation using endoscopic ultrasonography is useful, but recent advances in contrast-enhanced ultrasonography are expected to increase capabilities for early diagnosis.

Serial observation of patients with gallstones, as well as prophylactic surgery for patients with abnormal connections between pancreatobiliary ducts, are necessary.

The authors state that they have no Conflict of Interest (COI).

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