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Optimal Indication of Prophylactic Cholecystectomy for Gallbladder Stones and Polyps in terms of Risk Factors of Gallbladder Cancer

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Till now, two distinct epithelial lesions, dysplasia and adenoma, are currently recognized as premalignant stages of gallbladder (GB) carcinogenesis. In these two carcinogenesis pathways, GB stones and polyps are regarded as one of the most important risk factors of GB carcinoma respectively. Although there still remain controversies for the indication of prophylactic cholecystectomy for GB stones and polyps due to lack of high-level evidence, the present review demonstrated that patients who have GB stones with more than 3 cm size, chronic typhoid carriers, porcelain GB, or anomalous pancreaticobiliary ductal union and patients with more than 1 cm sized GB polyp would be recommended prophylactic cholecystectomy.

Key Words: Gallbladder; Stone, Polyp; Carcinoma; Cholecystectomy

INTRODUCTION

Two distinct epithelial lesions, dysplasia and adenoma, are currently recognized as premalignant stages of gallbladder (GB) carcinogenesis. Some authors have claimed that the adenoma-carcinoma sequence is the usual route for the development of invasive carcinomas of the GB, based on the findings that remnants of adenomas have been found within or adjacent to invasive carcinomas.[1,2] However, others believe that the vast majority of GB carcinomas evolve from flat dysplasia-carcinoma in situ lesions.[3,4] Although there still remain controversies for the exact role of GB stones and polyps in these two carcinogenesis pathways, they are regarded as one of the most important risk factors of GB carcinoma. However, due to the lack of high-level evidence, there is a paucity of evidence-guidelines for the treatment and surveillance of GB stones and polyps.

The purpose of this systematic review is to review the articles for the role of GB stones and GB polyps as risk factors of GB cancer and to suggest the optimal indication of prophylactic cholecystectomy.

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1. GB Stones

In 1999, Dr. Wistuba[3] provided first image of the dysplasia-carcinoma cascade and in 2004, improved this and provided diagrammatic representation of the multistep pathogenetic sequence[5]. And Dr. Castillo[6] provided genetic alterations in GB cancer on the template of metaplasia-carcinoma sequence. In this sequence, chronic inflammation is currently thought to be key underlying cause for the development of cancer and gallstone is the main cause of GB inflammation. There are several characteristics of gallstones that could develop GB cancer. They are stones with more than 3 cm size, long standing gallstones, many numbers of stones, stones with heavier weight & larger volume, cholesterol stones, chronic typhoid carrier, porcelain GB, and associated anomalous pancreaticobiliary duct union.

1) More Than 3 cm Sized Large Stones

Stone size is known as one of the most potent risk factor of gallbladder cancer. In 1983, Diehl[7] demonstrated that more than 3 cm sized stone carry a tenfold increased risk of developing gallbladder cancer when compared with smaller stones. After Diehl's study, many articles[8-10] showed the same results as Diehl's (Table 1). Till now, although whether 3 cm size is real risk factor or larger size might be a surrogate marker for long duration of gallstones and chronic inflammation should be elucidated, large size is always firstly mentioned risk factor and indication of prophylactic cholecystectomy.

Table 1. Large size gallstones as a risk factor of gallbladder cancer

Author (publication year)	Number of population	Stone size	Risk of Cancer development
Diehl[7] (1983)	81 Case, 146 Controls	2.0-2.9 cm	OR 2.4
		>3.0 cm	OR 10.1
Lowenfels[8] (1989)	1,676 patients	>3.0 cm	RR 9.2 (2.3-37)
Lowenfels[9] (1992)	73 Case, 186 Controls	>3.0 cm	RR 8.1 (1.7-29)
Csendes[10] (2000)	592 Case, 98 Controls	Large stone	p<0.001

OR, odds ratio; RR, relative risk

Table 2. Duration of gallbladder stone as a risk factor of gallbladder

Author (publication year)	Number of population	Duration	Cancer development
Zatonski[11] (1992)	73 cases, 186 controls	>20 yrs	OR 12.1
Zatonski[12] (1997)	196 cases, 1,515 controls	>20 yrs	OR 6.2
Serra[13] (2002)	114 cases, 114 controls	>24 yrs	OR 11.02
Hsing[14] (2007)	1,037 cases, 959 controls	<1 yr	OR 25.4
		>6 yrs	OR 16.8

OR, odds ratio

2) Long standing Stones

Gallstones present for more than 20 years have been shown to be associated with an increased risk for gallbladder cancer.[11-13] This result seems to be related to the cumulative effect of inflammation. However, large population based study from China showed that the duration of the presence of stone did not alter the risk of GB cancer already associated with gallstones (Table 2).[14]

3) Number or Weight/volume of Stones

There are a few reports that more stones[10,15] and heavier stones[14,15] are associated with increased risk of cancer. Maybe a greater risk of trauma caused by such stones might be linked to the hypothesis of chronic inflammation to carcinoma.

4) Type of Stones: Cholesterol Stones

There are a few reports[14,16] that the cholesterol stones are more prevalent in GB cancer. However, Srivastava[17] reported that quantity of cholesterol was significantly less in GBC (GB cancer?) than in benign GB diseases. It sho- uld be elucidated that whether this is only because cholesterol stone is the commonest stone or whether cholesterol stone really cause more inflammation than pigment stones or metabolites of cholesterol stones influence more potently the carcinogenesis of GB cancer.

5) Chronic Typhoid Carrier

Numerous reports proposed an association between chronic carriage and elevated risk of GB cancer.[18-27] Most of the studies were from south Asia especially India and Chile. Recently published systematic review[28] showed that typhoid chronic carriers had 4.28 of odds ratio and prophylactic cholecystectomy could be recommended for these carriers. However, we don't know the role of bacteria as a carcinogen and also should be elucidated whether careful monitoring or prophylactic cholecystectomy might be done.

6) Porcelain Gallbladder

Since in 1967 Etala[29] reported that the 62% of porcelain GB patients were associated with GB cancer, porcelain GB had been thought as one of the most potent malignant risk factor of GB cancer. However, after then, other studies didn't demonstrated such a high association between porcelain GB and GB cancer.[30-34] However, based on recently published systemic review[35], the risk of GB cancer was lower than anticipated and the rate was only 6%. But it is significantly higher than reference group. Therefore, in the absence of better risk stratification, non-operative approach would not be reasonable for porcelain GB.

7) Anomalous Pancreaticobiliary Duct Union (APBDU)

In fact, APBDU is regarded as an independent risk factor of GB cancer regardless of the presence of gallstone. This anatomy cause reflux of pancreatic juice into the bile duct and would lead to malignant change in the mucosa via epithelial hyperplasia, metaplasia, and dysplasia. APBDU is most prevalent in Asia, especially in Japan. And the most frequently referred study is by Japanese study group on PBM (pancrea-

ticobiliary maljunction).[36,37] About 30% of the patients with PBM has biliary malignancy and among them GB cancer is significantly more predominant than bile duct cancer.[37] Therefore, now there is consensus that prophylactic cholecystectomy for APBDU is needed.

8) Indication of Prophylactic Cholecystectomy for GB Stones

Chronic inflammation is currently though to be a key underlying cause for development of GB cancer. And in this concept, gallstone is one of the most potent co-factor or causal agent of GB cancer. Till now, gallstone patients with more than 3 cm sized large stone, chronic typhoid carriers, porcelain GB, or APBDU anomalous pancreaticobiliary ductal union would be recommended prophylactic cholecystectomy.

2. GB Polyps

Although the role of GB adenoma in the pathogenesis of GB carcinoma is not so much as GB inflammation, as other digestive tract, the transformation from adenoma to carcinoma has been demonstrated in GB.[1,2] There are various GB polyps and only less than 5% of polyps are potentially malignant adenomatous polyp. And theoretically, we should find these polyps and perform prophylactic cholecystectomy. Till now, preoperative diagnosis of adenomatous polyp is impossible. Therefore, we are trying to find malignant predicting factors pf GB polyps.

1) More Than 1 cm Size

Recently, two systematic reviews[38,39] on GB polyp were published. They showed pathologically, more than half of the polyps were cholesterol polyp and around 10% were adenoma and adenocarcinoma. In the distribution of pathology according to size, there was no cancer with less than 5 mm sized polyp and most of cancer were more than 1 cm. Therefore, prophylactic cholecystectomy could not be considered less than 1cm sized polyp.

2) Increase of Size during Follow-up

Increase of polyp size is considered as one of malignant predicting factors. There are many studies that to investigate natural history of GB polyp, followed growth of small polyps during relatively long-term period prospectively[40-44] and retrospectively.[45-49] According to these studies, growing polyps are less than 10% and among growing polyps, neoplastic polyps are only 3% (Table 3). Therefore, in small polyps, an increase in size does not necessarily correlate with development of malignancy.

3) Age and Solitary/sessile Polyps

In general, mean age of patients with malignant lesion is greater than that of patients in preneoplastic or benign group. And in GB, risk of malignancy is also higher in old patients than young patients. And solitary polyps and sessile polyps are thought to be more prevalent in malignant polyp. Recently reported systematic review[50] demonstrated the relationship between these factors and malignancy. Optimal cut-off polyp size for cholecystectomy is 10 mm. Through risk assessment, they suggested that cholecystectomy should be done for polyps greater than 10 mm and for polyps measuring 4 to 10 mm can be guided by the risk stratification algorithm, recommending cholecystectomy for over 50 years old, or sessile and

Table 3. Natural history of gallbladder polyps

Series (publication year)	Number of Patients	F/U (mo)	Growing polyp (%)	Growth rate (mm)	Neoplastic polyp (malignant)	Growing malignant polyp	Malignant polyp size (mm)
Moriguchi[40] (1996)	109	72	11.7	n/a	1(1)	No	n/a
Collett[41] (1998)	38	60	n/a	1.5/2 yr	0(0)	n/a	n/a
Csendes[42] (2001)	111	36	8	n/a	0(0)	n/a	n/a
Kratzer[43] (2008)	34	84	23	Mean 3.3	0(0)	n/a	n/a
Colechia[44] (2009)	56	60	5.7	2/5 yr	0(0)	n/a	n/a
Ito[45] (2009)	143		6	Mean 3.5	8(1)	No	14
Park[46] (2009)	1,558	37	3.5	n/a	33(8)	No	Mean 11.2
Shin[47] (2009)	145	12	n/a	0.23/mo	20(6)	No	n/a
Choi[48] (2010)	185	57	n/a	0.9	2(0)	n/a	n/a
Corwin[49] (2011)	149	60	1	Mean 2	3(0)	n/a	n/a
Total	2,428		7.0%		2.7% (0.7%)		

n/a, not available; F/U, follow up

single polyp.

4) Concurrent GB Stones

The prevalence of GB polyp with concurrent gallstones is very lower than anticipated.[48,51] Several articles demonstrated malignant GB polyps were more frequently associated with gallstones than benign polyps[52,53], and Boulton[54] suggested treatment algorithm of GB polyp including concurrent gallstones as a risk factor. However, after then no further studies exist and the evidence is very insufficient.

5) Indication of Prophylactic Cholecystectomy for GB Polyps

For GB polyp, potential malignant risk is low, but missing GB cancer is potentially catastrophic. The size of a GB polyp is largely regarded as the most significant indicator of potential malignancy, and more than 1 cm in size warrant prophylactic cholecystectomy. And for increase of size, age more than 50 years, concurrent GB stones, although there is lack of evidence, close follow-up and careful monitoring should be needed.

CONCLUSION

Although there still remain controversies for the indication of prophylactic cholecystectomy for GB stones and polyps because of lack of high-level evidence, patients who have GB stones with more than 3cm size, chronic typhoid carriers, porcelain GB, or APBDU and patients with more than 1 cm sized GB polyp would be recommended prophylactic cholecystectomy.

Conflict of Interest

There is no conflict of interest to be disclosed.

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