

## Clinical characteristics of incidental or unsuspected gallbladder cancers diagnosed during or after cholecystectomy: A systematic review and meta-analysis

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Library were reviewed and 26 publications were included in the meta-analysis. The inclusion criterion for incidental GB cancer was GB cancer diagnosed during or after cholecystectomy that was not suspected at a preoperative stage. Pooled proportions of the incidence, distribution of T stage, and revisional surgery of incidental GB cancer were analyzed.

**RESULTS:** The final pooled population comprised 2145 patients with incidental GB cancers. Incidental GB cancers were found in 0.7% of cholecystectomies performed for benign gallbladder diseases on preoperative diagnosis (95%CI: 0.004-0.012). Nearly 50% of the incidental GB cancers were stage T2 with a pooled proportion of 47.0% (95%CI: 0.421-0.519). T1 and T3 GB cancers were found at a similar frequency, with pooled proportions of 23.0% (95%CI: 0.178-0.291) and 25.1% (95%CI: 0.195-0.317), respectively. The pooled proportion that completed revisional surgery for curative intent was 40.9% (95%CI: 0.329-0.494). The proportion of patients with unresectable disease upon revisional surgery was 23.0% (95%CI: 0.177-0.294).

**CONCLUSION:** A large proportion of incidental GB cancers were T2 and T3 lesions. Revisional surgery for radical cholecystectomy is warranted in T2 and more advanced cancers.

**Key words:** Gallbladder cancer; Laparoscopic surgery; Cholecystectomy; Revisional surgery; Incidental diagnosis

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### Abstract

**AIM:** To perform a systematic review of incidental or unsuspected gallbladder (GB) cancer diagnosed during or after cholecystectomy.

**METHODS:** Data in PubMed, EMBASE, and Cochrane

**Core tip:** A low incidence of gallbladder (GB) cancer was diagnosed incidentally during or after cholecystectomy. In incidental GB cancers, revisional surgery for radical resection is inevitable. This systematic review provides clinical information of incidental GB cancers based on

a relatively large number of patients. Approximately three-quarters of incidental GB cancers were T2 and more advanced cancers. Therefore, a large proportion of the patients with incidental GB cancers required revisional surgery to achieve R0 resection. However, more than 20% of patients demonstrated unresectable disease when revisional surgery was attempted. Therefore, additional imaging studies are necessary in patients with GB cancers diagnosed following cholecystectomy.

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## INTRODUCTION

The prognosis of gallbladder (GB) cancer is poor, and a high proportion of patients are diagnosed at an advanced stage<sup>[1,2]</sup>. Laparoscopic cholecystectomy (LC) is the gold standard for the surgical treatment of benign GB diseases. Although benign GB disease can be diagnosed preoperatively, GB cancer is diagnosed during or after cholecystectomy at a low incidence. If GB cancer is suspected during LC, conversion to open surgery to perform radical resection after confirmation of the cancer by intraoperative frozen biopsy is considered. When GB cancer is diagnosed after cholecystectomy, reoperation for radical resection according to the depth of invasion of the cancer (T stage) is inevitable<sup>[3]</sup>. However, reoperation with radical surgery is not performed in all patients for several reasons including refusal to undergo radical surgery, poor medical condition, or cancer progression suggesting unresectability.

The diagnosis of advanced GB cancer by computed tomography (CT) is accurate and reliable, but the ability to identify early-stage cancer on CT remains disappointing. Therefore, preoperative staging using CT has an overall accuracy ranging from 83%-86%<sup>[4]</sup>. Diagnostic features of GB include wall thickening suggesting that the GB cancer area is heterogeneously enhanced, a thick one-layer pattern or a strongly enhanced thick inner layer with a weakly enhanced (or non-enhanced) thin outer layer; these features were found to be highly sensitive and specific for GB cancer in one study<sup>[5]</sup>. The diagnosis (or suspicion) of cancer can be missed preoperatively when combined with cholecystitis. Although cholecystectomy is a suitable treatment for early GB cancer, the diagnostic rate is low<sup>[6]</sup>. Most published studies on incidentally diagnosed GB cancer are based on a single-center experience with

a relatively small number of patients compared with the clinical significance of incidental GB cancer. The aim of this study was to perform a systematic review of incidental or unsuspected GB cancer diagnosed during or after cholecystectomy (laparoscopic or open). The incidence and clinical characteristics of the incidentally found GB cancers were investigated.

## MATERIALS AND METHODS

### Search strategy

Published literature in PubMed, EMBASE, and the Cochrane Library was searched using the following keywords and MeSH terms: "gallbladder neoplasm(s)", "gallbladder cancer(s)", "unsuspected", "incidental", "cholecystectomy", "laparoscopic". Language limitation was not applied during the initial search, but was restricted to English language literature in the last step of the selection process. Studies were limited to those on humans. All retrieved articles were manually screened to ensure a satisfactory study design.

### Selection and exclusion criteria

The inclusion criterion for incidental GB cancer was GB cancer diagnosed during or after cholecystectomy that was not suspected at the preoperative stage. Therefore, studies including patients who had suspected GB cancer at preoperative evaluation were excluded, even if laparoscopic cholecystectomy was performed. Studies that included patients with both suspected and unsuspected GB cancers were enrolled in this study if the clinicopathologic characteristics of the unsuspected (incidental) GB cancers were available exclusively. If data on the incidental GB cancer were insufficient, the study was excluded. Case series and studies that included fewer than 20 patients with incidental GB cancers were excluded from this systematic review.

### Data extraction

Two authors (CSB, CKS) independently extracted information using retrieved abstracts. After determining inclusion of the studies, the following details were investigated: study period, country of the study, number of patients with incidental GB cancer, overall number of patients who underwent cholecystectomy during the same period, number of reoperations for radical surgery, reason not to perform reoperation, operative procedures, pathologic characteristics focusing on the depth of invasion (T stage) and lymph node metastasis, and residual disease after revisional surgery. Any discrepancies in data collection between the two authors were solved by consensus.

We focused on the incidence of incidentally diagnosed GB cancer and the clinical characteristics associated with reoperation for radical surgery by pooled analysis. The primary outcomes were

**Table 1** Summary of the publications included

Ref.	Year	Study period	Country	Study setting	No. of IGC	Revisional surgery	T stage					Study quality
							Tis	T1	T2	T3	T4	
Z'graggen <i>et al</i> <sup>[8]</sup>	1998	1992-1995	Swiss	Swiss registry	37	6	0	9	16	8	4	4
Sarli <i>et al</i> <sup>[9]</sup>	2000	1986-1995	Italy	Single center	20	6	1	6	4	9	0	5
Suzuki <i>et al</i> <sup>[10]</sup>	2000	1992-1998	Japan	Multicenter	41	11	1	25	14	1	0	5
Wakai <i>et al</i> <sup>[11]</sup>	2002	1992-1999	Japan	Single center	28	10	0	15	13	0	0	5
Toyonaga <i>et al</i> <sup>[12]</sup>	2003	1982-2000	Japan	Multicenter	73	21	0	23	43	7	0	6
de Aretxabala <i>et al</i> <sup>[13]</sup>	2004	Unavailable	Chile	Single center	64	26	2	5	39	18	0	4
Yildirim <i>et al</i> <sup>[14]</sup>	2005	1990-2003	Turkey	Single center	65	28	0	13	34	18	0	4
Lam <i>et al</i> <sup>[15]</sup>	2005	1998-2002	Hong Kong	Multicenter	63	4	1	4	23	26	7	6
Xu <i>et al</i> <sup>[16]</sup>	2007	1990-2005	China	Single center	23	6	0	11	7	5	0	3
Pawlik <i>et al</i> <sup>[17]</sup>	2007	1984-2006	United States, Brazil, Italy, Germany	Multicenter	148	109	0	18	85	41	4	5
Shih <i>et al</i> <sup>[18]</sup>	2007	1995-2004	United States	Single center	53 <sup>5</sup>	39						5
Shukla <i>et al</i> <sup>[19]</sup>	2008	2003-2007	India	Single center	90 (76 <sup>1</sup> )	54	0	23	33	20	0	4
Kwon <i>et al</i> <sup>[20]</sup>	2008	1992-2004	Japan	Single center	38	14	0	20	17	1	0	5
Zhang <i>et al</i> <sup>[21]</sup>	2009	1999-2007	China	Single center	20	7	4	4	6	4	2	5
Choi <i>et al</i> <sup>[22]</sup>	2009	2002-2007	Korea	Single center	33	7	2	10	17	4	0	5
Butte <i>et al</i> <sup>[23]</sup>	2010	2000-2008	Chile	Single center	49	20	0	8	32	9	0	4
Glauser <i>et al</i> <sup>[24]</sup>	2010	1994-2004	Swiss	Swiss registry	89 (69 <sup>1</sup> )	19	2	14	34	14	5	6
Kim <i>et al</i> <sup>[25]</sup>	2010	1997-2008	Korea	Single center	26	2	1	6	17	2	0	4
de Aretxabala <i>et al</i> <sup>[26]</sup>	2010	2005-2009	Chile	Single center	23	15	0	3	15	5	0	3
Goetze <i>et al</i> <sup>[27]</sup>	2010	1997-	German	German registry	624 <sup>2</sup>	231	22	118	300	143	30	6
Fuks <i>et al</i> <sup>[28]</sup>	2011	1998-2008	France	Multicenter	218	148	0	24	84	81	29	6
Clemente <i>et al</i> <sup>[29]</sup>	2012	1998-2009	Italy	Single center	44 <sup>3</sup>	34	0	5	19	10	0	4
Maker <i>et al</i> <sup>[30]</sup>	2012	1992-2009	United States	Single center	162 <sup>6</sup>	162	0	12	71	79	0	5
Lendoire <i>et al</i> <sup>[31]</sup>	2012	1999-2010	Argentina	Single center	40 <sup>4</sup>	24	0	1	12	11	0	4
Yi <i>et al</i> <sup>[32]</sup>	2013	1992-2009	China	Single center	38	10	0	14	4	12	8	6
Xu <i>et al</i> <sup>[33]</sup>	2013	1993-2011	China	Single center	36	20	0	16	11	9	0	5

<sup>1</sup>Number of available data; <sup>2</sup>11 patients were Tx (unknown T stage); <sup>3</sup>The exact T stages of 10 patients were not described; <sup>4</sup>The exact T stages of 16 patients were not described; <sup>5</sup>Exact T stages were not described. Instead, AJCC TNM stages were shown; <sup>6</sup>All patients included in this publication received revisional surgery. IGC: Incidental gallbladder cancer.

the incidence of incidental GB cancers following cholecystectomy and the distribution of T stage (depth of invasion) of the GB cancers. Secondary outcomes were the proportion of patients who underwent reoperation after cholecystectomy or conversion to open surgery during operation for radical surgery, the proportion of patients with unresectable disease even though radical surgery was attempted, and the proportion of patients with residual malignant disease after radical surgery for GB cancers. The quality of all publications was assessed using the Newcastle-Ottawa Scale<sup>[7]</sup>. Of the three categories used in the Newcastle-Ottawa Scale (Selection, Comparability, and Outcome), we used the following for study assessment: "Selection," (1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; and (3) ascertainment of exposure; and "Outcome" (1) assessment of outcome; (2) sufficiency of length of follow up; and (3) adequacy of follow-up of cohorts. A study was given one star for each question. The numbers of stars and characteristics of the included studies are presented in Table 1.

### Statistical analysis

Data and outcomes extracted from each study were pooled and analyzed using Comprehensive

Meta-Analysis software Version 2 (Biostat, New Jersey, United States). A single weight-adjusted proportion for each variable was computed for each study. The random effect model was used to derive pooled estimates of proportion with 95%CI for the outcomes explored.

## RESULTS

### Study characteristics and incidence of incidental (unsuspected) GB cancers

A total of 986 publications were initially identified and 26 were finally included in this systematic review (Figure 1). These 26 studies<sup>[8-33]</sup> were observational cohort studies based on data from national registries ( $n = 3$ ), multicenter studies ( $n = 5$ ), and single center surgical experiences ( $n = 18$ ). In total, 2145 patients with incidental GB cancers (diagnosed during or after cholecystectomy) were included in this systematic review. The characteristics of the publications are shown in Table 1. Ten publications<sup>[8-10,15,20-22,24,25,33]</sup> reported the incidence of incidentally found GB cancers and the total number of cholecystectomies performed during the same study period. Among the ten publications<sup>[8-10,15,20-22,24,25,33]</sup>, 403 incidental GB cancers were detected in the 80228 cholecystectomies. The pooled proportion of incidental

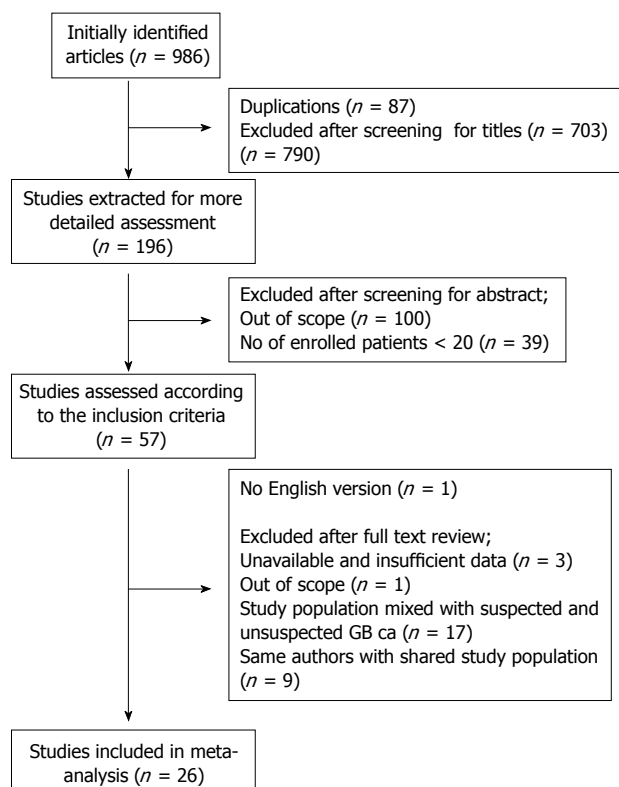


Figure 1 Selection of the publications.

GB cancers among the cholecystectomies performed for benign gallbladder diseases was 0.7% (95%CI: 0.004-0.012).

### Distribution of T stage and presence of lymph node metastasis in incidental GB cancers

The versions of cancer stage according to the American Joint Committee on Cancer (AJCC) used were different according to the study period: 3rd edition<sup>[8,34]</sup>, 4<sup>th</sup> edition<sup>[13,35]</sup>, 5<sup>th</sup> edition<sup>[10-12,36]</sup>, 6<sup>th</sup> edition<sup>[14,15,17,18,20-23,25,27,37]</sup>, 7<sup>th</sup> edition<sup>[24,28,29,31,32,38]</sup>, and Nevin staging<sup>[16,39]</sup>. In five studies<sup>[8,16,19,26,30]</sup>, the exact version of the staging system used was not clearly defined. For T stage, Tis, T1, and T2 are the same in the 3<sup>rd</sup> to 7<sup>th</sup> editions of AJCC stage. Tis is carcinoma in situ. T1a tumor invades mucosa and T1b invades muscle layer. T2 invades perimuscular connective tissue, without extension beyond the serosa or into the liver<sup>[34-38]</sup>. T3 tumors are those that perforate the serosa, or directly invade one adjacent organ, or both (extension 2 cm or less into the liver), whereas T4 tumors extend more than 2 cm into the liver and/or into two or more adjacent organs in the 4<sup>th</sup> and 5<sup>th</sup> editions<sup>[35,36]</sup>. In the 6<sup>th</sup> and 7<sup>th</sup> editions of AJCC<sup>[37,38]</sup>, T3 tumors perforate the serosa or directly invade the liver and/or one other adjacent organ or structure, and T4 tumors invade the main portal vein or hepatic artery, or two or more extrahepatic structures. Although T3 and T4 stage are somewhat different among the versions of AJCC stage, we regarded T3, T4 in each edition as the same T3, and

Table 2 Distribution of T stage in incidental gallbladder cancer in 25 studies<sup>[8-17,19-33]</sup>

T stage	Range of proportion reported by primary studies	Pooled proportion	95%CI
Tis	0%-20.0%	2.4%	1.5%-3.8%
T1	4.2%-61.0%	23.0%	17.8%-29.1%
T2	13.2%-75.0%	47.0%	42.1%-51.9%
T3	0.0%-69.8%	25.1%	19.5%-31.7%
T4	0.0%-21.1%	4.2%	2.6%-6.5%

T4, respectively, throughout the editions.

Table 2 shows the pooled proportion of T stages among the incidental GB cancers in 25 studies<sup>[8-17,19-33]</sup>. Nearly 50% of the incidental GB cancers were T2 stage, with a pooled proportion of 47.0% (95%CI: 0.421-0.519). T1 and T3 GB cancers were found at a similar frequency, with pooled proportions of 23.0% (95%CI: 0.178-0.291%) and 25.1% (95%CI: 0.195-0.317), respectively.

Patients with incidental GB cancers tended to undergo less aggressive surgery than those with suspected (diagnosed preoperatively) GB cancers as some patients did not undergo revisional surgery for incidental GB cancer. Therefore, information on the lymph node status of incidental GB cancers was limited as not all patients underwent lymph node dissection. Thirteen publications<sup>[11,14-17,20,22,23,25,28-31]</sup> reported the presence of lymph node metastasis. In principle, lymph node status is confirmed by pathologic examination after lymph node dissection. However, a review of the publications revealed that lymph node dissection was not performed for GB cancers, but was usually performed at the discretion of the surgeon according to the T stage. Moreover, the extent of dissection was not homogeneous. Considering this limitation, the reported rate of lymph node metastasis might be underestimated compared with the actual lymph node status. Nonetheless, the pooled proportion of detected lymph node metastasis among the patients with incidental GB cancers was 14.2% (95%CI: 0.107-0.185) with a range of 7.9%-26.5%.

### Revisional surgery for radical cholecystectomy

If the GB cancer is found during or after operation, proceeding with revisional surgery for R0 resection is necessary. Twenty-four publications reported performing revisional surgery for curative intent<sup>[8-29,31-33]</sup>. We analyzed the proportion of patients in which the revisional surgery was completed, excluding patients who underwent only exploration. The pooled proportion that had complete revisional surgery was 40.9% (95%CI: 0.329-0.494) (Figure 2). The revisional surgery consisted of liver resection and/or bile duct resection and/or lymph node dissection. The extent of liver resection was somewhat different among the studies; however, most of the liver resection procedures involved wedge resection of the



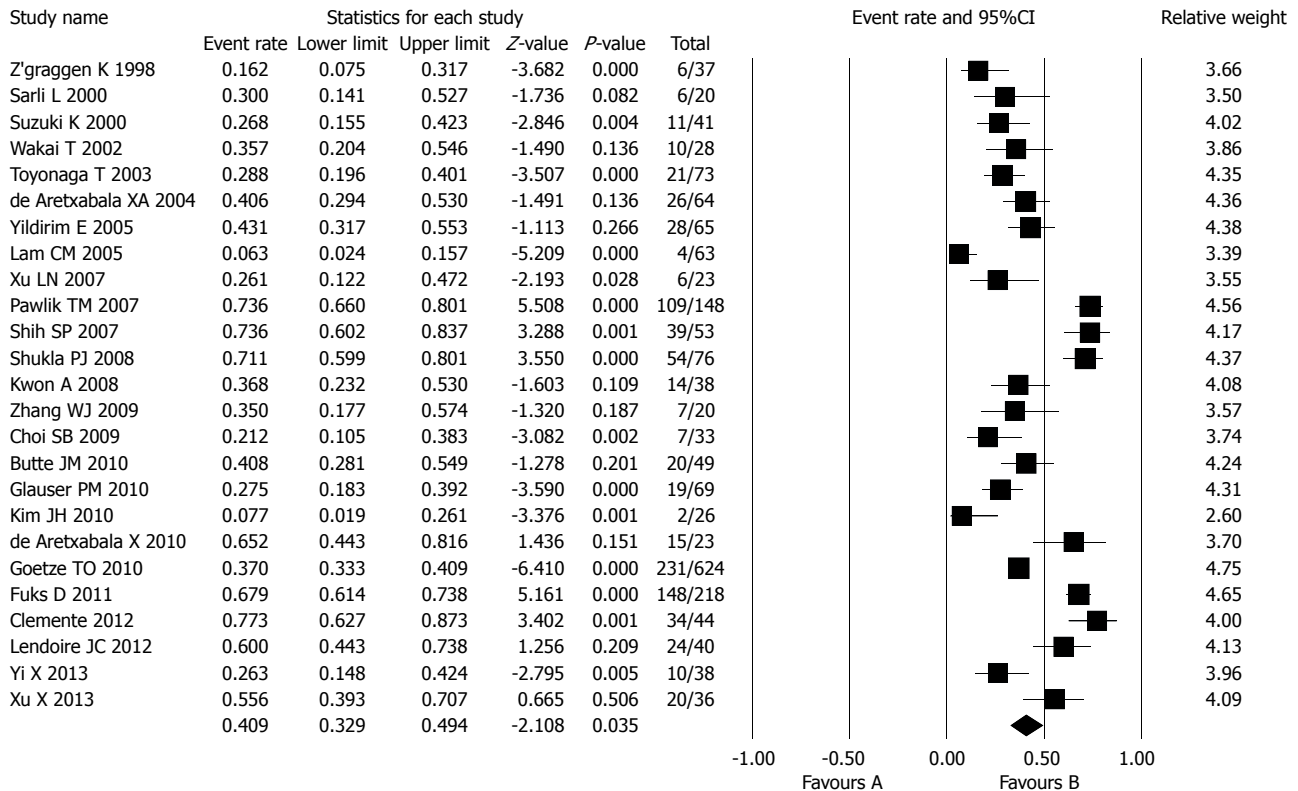


Figure 2 Pooled proportion to complete revisional surgery.

liver and bisegmentectomy of segment IVB and V.

Another clinical problem in patients who undergo laparoscopic cholecystectomy for incidental GB cancer is whether port site resection should be included in the revisional surgery. Nine publications<sup>[10,11,17,19,28-31,33]</sup> discussed whether port site excision should be performed. Two studies<sup>[19,33]</sup> did not report the total number of patients who underwent port site excision; however, two patients in each study demonstrated a residual cancerous lesion in the pathologic exam after revisional surgery. Two studies<sup>[10,11]</sup> included whether port site excision was performed and five studies<sup>[17,28-31]</sup> reported the total number of port site excisions and the positive rate for cancer cells in pathologic examination of the port site. The pooled proportion of patients with positive cancer cells at the port site was 8.1% (95%CI: 0.03-0.202).

#### **Proportion of unresectable GB cancers when revisional surgery was attempted and the presence of residual cancerous lesions after revisional surgery**

Although the failure to detect incidental GB cancers at preoperative evaluation infers the presence of early cancers that might be missed, the proportion of advanced incidental cancers is too serious to be ignored. When revisional surgery was attempted (intraoperative conversion or reoperation after initial surgery) some patients were confirmed to have unresectable/inoperable diseases and underwent only exploration. Twenty-one publications<sup>[8-13,15,17-26,28,31-33]</sup>

reported the proportion of unresectable disease when revisional surgery was attempted, and the pooled proportion of patients with unresectable disease was 23.0% (95%CI: 0.177-0.294) (Figure 3).

The aim of revisional surgery is to achieve an adequate resection margin and to perform lymph node dissection for locoregional control. The proportion of patients in which residual cancerous lesions were found after revisional surgery was reported in 14 publications<sup>[9-12,14,17,19,20,22,23,25,28,29,31]</sup> and the pooled proportion with residual disease was 38.7% (95%CI: 0.316-0.462). The most common locations of residual disease were the liver (GB bed) and lymph nodes; less common sites were the bile duct and port site. Two studies<sup>[22,31]</sup> did not report the location of residual disease in detail.

## **DISCUSSION**

From a prognostic point of view, R0 resection is the most important positive factor for overall survival of GB cancers<sup>[1,2]</sup>. The extent of surgery is different according to the depth of invasion (T stage) of the tumors. For a T1a tumor, cholecystectomy is the standard procedure, whereas for a T1b tumor, cholecystectomy with lymph node dissection has been performed<sup>[40]</sup>. For T2 and more advanced tumors, liver resection including the gallbladder bed and lymph node dissection are recommended. Extrahepatic bile duct resection is not performed uniformly, and is

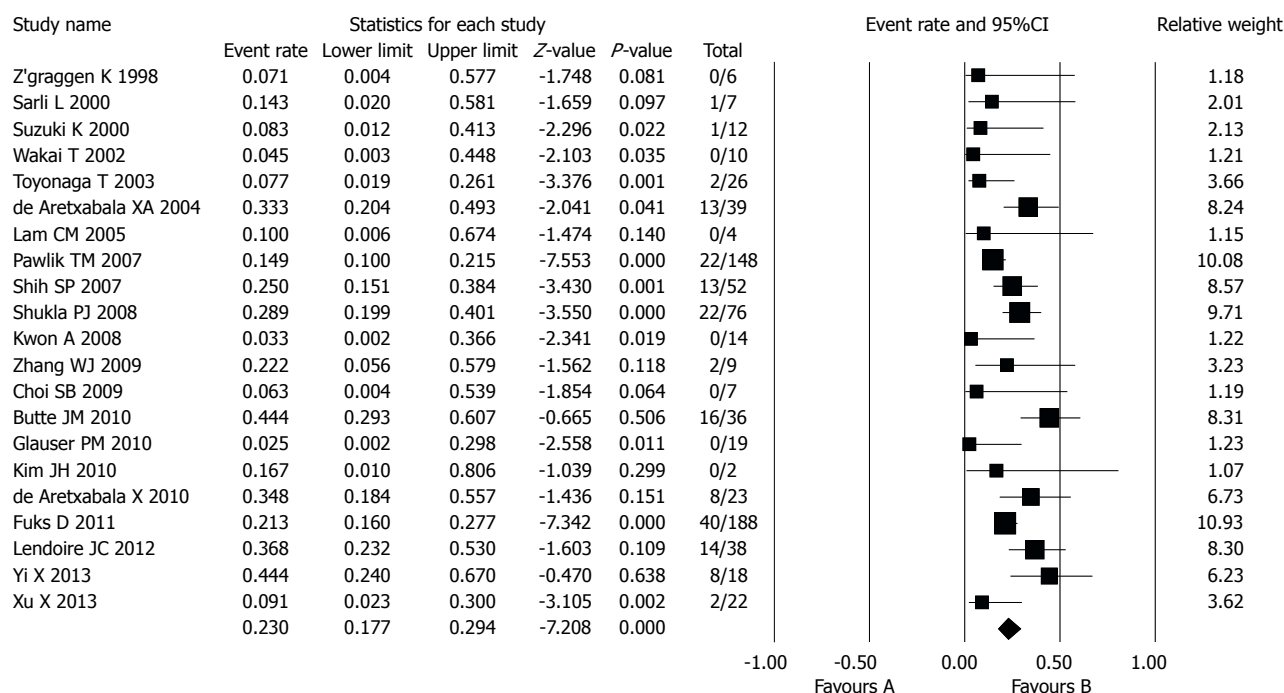


Figure 3 Pooled proportion of patients with unresectable disease when revisional surgery attempted.

somewhat controversial in the surgical treatment of GB cancers<sup>[41,42]</sup>. According to our study, approximately one-quarter of the patients did not require revisional surgery because they presented with Tis or T1 disease. Therefore, approximately three-quarters of patients with incidental GB cancers were ultimately candidates for revisional surgery.

The most important clinical problem related to incidentally found GB cancers is the decision of whether to proceed with revisional surgery for radical cholecystectomy. If the GB cancer is found during the operation, conversion to radical surgery is relatively easy. However, if GB cancers are found after the operation, reoperation for revisional surgery is both necessary and critical. Although R0 resection is the treatment of choice, some patients with incidental GB cancers diagnosed following cholecystectomy refused reoperation for revisional surgery. As most of the publications were based on the retrospective review of medical records, the exact proportion of patients who refused revisional surgery is not described in all studies. Several publications reported the number of patients who refused revisional surgery even though it was indicated due to advanced tumor stage<sup>[18,21,23,32,33]</sup>. Refusal of radical cholecystectomy is one of the more difficult issues encountered in clinical practice. As described before, because R0 resection is the most important factor determining prognosis, reoperation for revisional surgery should be strongly recommended.

In this systematic review, the pooled proportion of patients with unresectable disease when attempting revisional surgery was 23.0% (95%CI:

0.177-0.294). Even though GB cancer was not suspected before surgery, the disease was too advanced to perform radical surgery. Therefore, precise preoperative evaluation is necessary to assess the extent of disease before revisional surgery, especially in patients who undergo reoperation after a relatively long time interval from the first operation. For preoperative diagnosis of GB cancers, multidetector computed tomography (MDCT) is now widely available and has a reported accuracy of up to 84% for determining local extent or the T stage of primary gallbladder carcinoma<sup>[43]</sup> and 85% for predicting resectability<sup>[44]</sup>. Positron emission tomography (PET)-CT scanning might also be an option, and has been reported to have value for the detection of regional lymph node metastasis and distant metastases that are not diagnosed by MDCT<sup>[45,46]</sup>. Biliary magnetic resonance imaging is also useful for the detection of GB cancer<sup>[47]</sup>. However, considering the impact of postoperative change, it is not possible to draw conclusions about the efficacy of CT, PET, or MR to detect residual cancerous lesions or metastatic disease after cholecystectomy, and there was a lack of evidence on this issue in our review of the literature for incidentally found GB cancers. Further preoperative evaluation might be necessary taking into consideration the relatively significant proportion of patients who had unresectable disease when attempting revisional surgery.

The prognostic impact of incidentally diagnosed GB cancer on survival compared with preoperatively suspected GB cancer has not been widely studied. It is not clear whether incidental GB cancer has the same prognosis, or poorer prognosis, compared

with the same stage of non-incidental GB cancer. For incidental GB cancers, it is likely that the combined presence of cholecystitis complicates the diagnosis of GB cancer. Several studies have reported the negative impact of cholecystitis on survival<sup>[22,29,48]</sup> although the exact mechanism has not been investigated. Incomplete en bloc resection during cholecystectomy that causes spillage of cancer cells might affect the prognosis of GB cancer considering the relatively high pooled proportion of patients with residual cancerous lesions after revisional surgery in this study. However, the results of most of the studies warrant radical resection to improve survival<sup>[3,24,27,28]</sup>. In contrast, one study reported that the tumor characteristics differed between suspected and incidental GB cancer, and suggested that incidental GB cancer has a significant better median survival<sup>[49]</sup>.

When comparing the survival impact of laparoscopic versus open procedures for the treatment of GB cancer, several studies reported no significant prognostic difference between the two procedures, suggesting that laparoscopic cholecystectomy does not decrease survival<sup>[9,13,50-52]</sup>. However, another study showed that laparoscopic cholecystectomy had an increased risk of disseminating tumor cells, suggesting that open surgery is warranted in cases of known or suspected GB cancer<sup>[53]</sup>. However, more recently, several authors have reported that early lesions of GB cancer can be managed successfully using laparoscopic cholecystectomy, achieving a satisfactory survival result and a low rate of port-site recurrence<sup>[54,55]</sup>.

Whether port site resection should be performed is one of the major issues in revisional surgery after laparoscopic cholecystectomy. In our review, not all of the centers adopted port site resection as part of revisional surgery, and the pooled proportion in which cancer cells were detected in the port site was low. Maker *et al.*<sup>[30]</sup> focused on the necessity for port site resection in the surgical management of incidental GB cancer. They concluded that port site metastases were associated with poorer survival. However, port site resection was not associated with improved survival and should not be considered mandatory during definite surgical treatment for incidental GB cancer. In the early laparoscopic era, many authors reported that laparoscopic surgery might promote peritoneal seeding during the surgical treatment of cancer patients<sup>[56,57]</sup>. However, there was no definite difference in the oncologic outcome between the two procedures in more recent studies<sup>[9,13]</sup>.

In conclusion, incidental (unsuspected) GB cancers were not all early lesions; in fact, T2 and T3 lesions accounted for a large proportion of these cancers. Our data indicated that revisional surgery for radical cholecystectomy is warranted to gain a survival benefit in T2 and more advanced cancers, although surgical procedures were not homogeneous and

were determined according to the extent of disease. Furthermore, even though these GB cancers were found incidentally, some incidental GB cancers were unresectable when attempting revisional surgery. Therefore, additional imaging studies to determine the extent of disease and resectability are necessary before performing revisional surgery.

## COMMENTS

### Background

Laparoscopic cholecystectomy (LC) is the gold standard for surgical treatment of benign GB diseases. Gallbladder (GB) cancer is diagnosed during or after cholecystectomy at a low incidence. The aim of this study was to perform a systematic review of incidental or unsuspected GB cancer diagnosed during or after cholecystectomy (laparoscopic or open). The incidence and clinical characteristics of the incidentally found GB cancers were investigated.

### Research frontiers

R0 resection is the treatment of choice for GB cancers. Although the incidence of GB cancers diagnosed during or after cholecystectomy, is low, incidental GB cancers can cause difficult problems in clinical practice. In this study a systematic review of incidental GB cancer was performed, based on a relatively large number of patients with incidental GB cancers, focusing on the clinical characteristics and significance of incidental GB cancers; incidence, T stage, revisional surgery, and proportion of unresectable disease.

### Innovations and breakthroughs

The prognosis of GB cancer is poor, and a high proportion of patients are diagnosed at an advanced stage. LC is the gold standard for surgical treatment of benign GB diseases. Although benign GB disease was diagnosed preoperatively, GB cancer can be diagnosed during or after cholecystectomy at a low incidence. If GB cancer is suspected during LC, conversion to open surgery to perform radical resection after confirmation of the cancer by intraoperative frozen biopsy is considered. When GB cancer is diagnosed after cholecystectomy, reoperation for radical resection according to the depth of invasion of the cancer (T stage) is inevitable. However, reoperation with radical surgery is not performed for all patients for several reasons including refusal to undergo radical surgery, poor medical condition, or cancer progression suggesting unresectability. This study is based on the systematic review of incidental GB cancers. Most published studies on incidentally diagnosed GB cancer are based on a single-center experience with a relatively small number of patients comparing the clinical significance of incidental GB cancer. Therefore, this study provides clinical information on incidental GB cancers diagnosed during or after cholecystectomy based on a relatively large number of patients.

### Applications

The results of this study suggest that approximately three-quarters of incidental GB cancers were T2 and more advanced GB cancers. Therefore, a large proportion of patients with incidental GB cancers required revisional surgery. However, more than 20% of patients had unresectable disease when revisional surgery was attempted. Therefore, additional imaging studies are necessary in patients with GB cancers diagnosed following cholecystectomy.

### Terminology

Revisional surgery is radical cholecystectomy including liver resection and/or extrahepatic bile duct resection and lymph node dissection. Although the extent of revisional surgery is different according to the stage of tumor, the aim of revisional surgery is to perform R0 resection.

### Peer review

A large proportion of incidental GB cancers were T2 and T3 lesions. Revisional surgery for radical cholecystectomy is warranted to gain a survival benefit in T2 and more advanced cancers. Some incidental GB cancers were unresectable when attempting revisional surgery; therefore, additional imaging studies for revisional surgery are necessary to determine the extent of disease.

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