

Systematic review on the surgical treatment for T1 gallbladder cancer

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Abstract

AIM: To evaluate the efficacy of simple and extended cholecystectomy for mucosa (T1a) or muscularis (T1b) gallbladder (GB) cancer.

METHODS: Original studies on simple and extended cholecystectomy for T1a or T1b GB cancer were searched from MEDLINE (PubMed), Cochrane Library, EMBase, and CancerLit using the search terms of GB, cancer/carcinoma/tumor/neoplasm.

RESULTS: Twenty-nine out of the 2312 potentially relevant publications met the eligibility criteria. Of the 1266 patients with GB cancer included in the publications, 706 (55.8%) and 560 (44.2%) had T1a and T1b GB cancer, respectively. Simple cholecystectomy for T1a and T1b GB cancer was performed in 590 (83.6%) and 375 (67.0%) patients, respectively ($P < 0.01$). In most series, the treatment of choice was simple cholecystectomy for T1a GB cancer patients with a 5-year survival rate of 100%. Lymph node metastasis was detected in 10.9% of the T1b GB cancer patients and in 1.8% of the T1a GB cancer patients, respectively ($P < 0.01$).

Eight patients (1.1%) with T1a GB cancer and 52 patients (9.3%) with T1b GB cancer died of recurrent GB cancer ($P < 0.01$).

CONCLUSION: Simple cholecystectomy represents the adequate treatment of T1a GB cancer. There is no definite evidence that extended cholecystectomy is advantageous over simple cholecystectomy for T1b GB cancer.

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Key words: Gallbladder; Cancer; Cholecystectomy; Simple; Extended

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INTRODUCTION

Gallbladder (GB) cancer confined to mucosa (T1a) or muscularis (T1b) is classified as an early cancer. Because of the high prevalence of advanced stage GB cancer at presentation, early GB cancer has been less studied among all GB cancers. However, on the basis of studies performed on GB cancer, less than 10% are early GB cancers and the proportion is growing because they tend to be diagnosed after laparoscopic cholecystectomy.

Most authors would agree that T1a GB cancer is a local disease and simple cholecystectomy represents its adequate treatment, provided that the resection margin is not involved. It was reported that the incidence of lymph node metastasis of GB cancer is less than 5%^[1-9].

Recurrent GB cancer has been reported only in the form of case reports^[2-4,10-12] and the 5-year survival rate of most GB cancer patients is approaching 100%^[1,3,13-21]. Particularly, laparoscopic cholecystectomy is believed to be the adequate treatment of T1a GB cancer^[4,12,14,16-20,22,23]. Although port site recurrence^[24] and possible tumor seeding caused by pneumoperitoneum^[25] are concerned, few cases have been reported^[10,24].

It has been argued that T1b GB cancer may have spread regionally or systematically at presentation. Therefore, whether T1b GB cancer should be treated with simple cholecystectomy or extended cholecystectomy still remains debatable. Some authors believe that T1b GB cancer should be considered simply as a local disease with the following reasons. First, lymphovascular and perineural invasion and lymph node metastasis are rarely found in patients with pT1b GB cancer^[26]. Second, the outcome of patients with pT1b GB cancer in terms of survival after simple cholecystectomy is excellent and similar to that of patients with pT1a GB cancer when the resection margins are not invaded^[10,17]. Third, extended cholecystectomy does not increase the long-term survival rate of patients with pT1b GB cancer^[15,17]. Fourth, no difference has been observed in survival rates between patients who underwent subsequent laparotomy with additional resection and those who did not^[7,15,17]. On the other hand, others believe that lymphovascular and perineural invasion and lymph node metastasis are more frequently found in patients with pT1b GB cancer^[11,13,14], and pT1b GB cancer recurs more frequently than pT1a GB cancer^[7,11,18]. Extended cholecystectomy increases the long-term survival rate of patients with pT1b GB cancer^[5,11,27].

Few early GB cancer cases are available and randomized trials are difficult to conduct for the assessment of appropriate surgical procedures. Therefore, a pooled systematic analysis of the efficacy of each surgical procedure for early GB cancer is essential to establish the appropriate management of T1a and T1b GB cancer. This study was to evaluate the efficacy of simple and extended cholecystectomy for T1a or T1b GB cancer.

MATERIALS AND METHODS

Search strategy

Original studies on surgery for T1 GB cancer were searched from MEDLINE (PubMed, 1966-2008), Cochrane Library (1996-2008), EMBase (1970-2008), and CancerLit (1970-2008) using the search terms of GB, cancer/carcinoma/tumor/neoplasm.

Selection criteria

Of the identified studies, only publications in the English language were included. Selection was confined to peer-reviewed articles. Unpublished data, abstracts, case reports and case series containing less than 5 patients were excluded. Studies in which the T stage was inadequately assessed and diagnosis was other than adenocarcinoma were excluded. All surgical studies on histologically proven

T1a and T1b GB cancer were included. T1a and T1b GB cancer was defined as a cancer confined to the mucosa to muscularis, respectively. Only studies describing surgical intervention (simple cholecystectomy or extended cholecystectomy, *etc.*) for T1a and T1b GB cancer were included. Only the most recent publications were included when the selected articles included the same or overlapping data in multiple publications.

Data extraction

Two authors (Lee SE and Kang MJ) reviewed each article and performed data extraction independently according to the predefined inclusion criteria. General information pertaining to the study design, patient number and follow-up length were recorded. Types of intervention were classified into simple cholecystectomy and extended cholecystectomy, respectively. Because the extent of extended cholecystectomy varied in each article, we defined it as cholecystectomy, regional lymph node dissection, liver resection beyond wedge resection and/or resection of other organs, respectively. The overall 5-year survival rate of patients with GB cancer was defined as the primary outcome. Secondary outcomes included mortality, morbidity, and recurrence of GB cancer. The extracted data were then cross-checked by the two authors to eliminate the discrepancy.

Statistical analysis

Data are presented as median (range) unless otherwise stated. Interpretative analyses were performed based on pooled as opposed to individuals. Since patient data could not account for censored, missing or incomplete follow-up, survival analyses could not be conducted based on these data.

RESULTS

Search results

Overall, the search identified 2312 potentially relevant publications. After the titles and abstracts were reviewed, 252 publications were potentially eligible and full text reviews were conducted. Finally, 29 studies^[1,3-22,24,26-32] that specifically assessed the surgical outcomes of patients with T1a and T1b GB cancer met the eligible criteria (Figure 1). There were no randomized studies and all studies were retrospective in nature. Furthermore, the majority of studies involved a small number of patients (median 15, range 5-89) except for nation-wide surveys^[1,5,7,16] (Table 1).

Characteristics of the study population

Twenty-nine publications included 1266 patients with T1 GB cancer. Of these 1266 patients, 706 (55.8%) and 560 patients (44.2%) had T1a and T1b GB cancer, respectively.

Types of surgical intervention

The operative procedures performed in the 1266 patients are summarized in Table 2. Simple cholecystectomy for T1a and T1b GB cancer was performed in 590 (83.6%) and 375 (67.0%) patients, respectively ($P < 0.01$). Ex-

Table 1 Characteristics of included studies on surgical treatment of patients with T1 gallbladder cancer

Authors	Yr	No. of patients	Primary outcome		Secondary outcome		
			3 YSR	5 YSR	Morbidity	Mortality	Recurrence
Ogura <i>et al</i> ^[13]	1991	366 ¹					NS
Shirai <i>et al</i> ^[26]	1992	89	NS	NS	NS		
Ouchi <i>et al</i> ^[11]	1994	15	NS		NS		
Chijiwa <i>et al</i> ^[28]	1994	5	NS		NS		
de Aretxabala <i>et al</i> ^[14]	1997	24	NS		NS		NS
Mori <i>et al</i> ^[22]	1997	9	NS	NS	NS		
Benoist <i>et al</i> ^[1]	1998	36 ²					
Z'graggen <i>et al</i> ^[29]	1998	9		NS	NS		
Shimada <i>et al</i> ^[9]	2000	17			NS		
Suzuki <i>et al</i> ^[30]	2000	25	NS		NS		
Wakai <i>et al</i> ^[6]	2001	25	NS		NS		
Puhalla <i>et al</i> ^[24]	2002	9		NS			
Wagholikar <i>et al</i> ^[7]	2002	14	NS		NS		
Kim <i>et al</i> ^[17]	2002	19	NS		NS		
Ouchi <i>et al</i> ^[18]	2002	234 ³	NS		NS		
Wakai <i>et al</i> ^[10]	2002	15	NS		NS		
Cucinotta <i>et al</i> ^[4]	2005	12	NS	NS	NS		
Yildirim <i>et al</i> ^[15]	2005	13					
Eguchi <i>et al</i> ^[31]	2005	12	NS	NS	NS		
Sun <i>et al</i> ^[19]	2005	15	NS		NS		
Otero <i>et al</i> ^[32]	2006	51	NS		NS		
Yagi <i>et al</i> ^[8]	2006	13	NS		NS		
Chan <i>et al</i> ^[12]	2006	33	NS	NS	NS		
Cangemi <i>et al</i> ^[27]	2006	15	NS				
Kang <i>et al</i> ^[16]	2007	11	NS				
You <i>et al</i> ^[3]	2008	52	NS				
Kwon <i>et al</i> ^[20]	2008	20	NS		NS		
Kohya <i>et al</i> ^[21]	2008	15	NS		NS		NS
Goetze <i>et al</i> ^[5]	2008	93 ⁴	NS		NS		

¹Japan survey from 172 major hospitals; ²French cooperative group AURC (Association Universitaire de Recherche en Chirurgie); ³Japan nationwide survey on laparoscopic cholecystectomy from 253 hospitals; ⁴German Registry of Incidental Gallbladder Carcinoma of the German Society of Surgery. NS: Not stated.

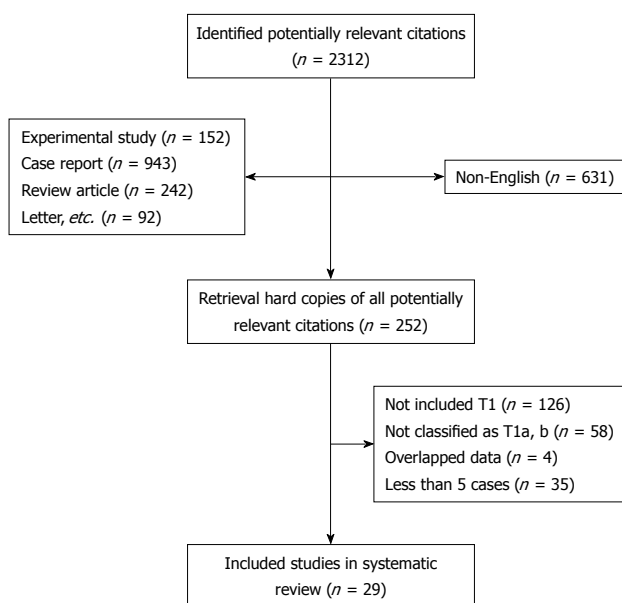


Figure 1 Flowchart of included articles.

tended cholecystectomy for T1a and T1b GB cancer was performed in 110 (15.6%) and 168 (30.0%) patients, respectively ($P < 0.01$).

Postoperative morbidity and mortality

Five articles (17.2%)^[1,3,15,16,24] discussed the postoperative morbidity related to the operative procedure. Complications occurred in 11 patients (11/52, 21.2%) following simple cholecystectomy, and in 21 patients (21/75, 28%) after extended cholecystectomy. Five postoperative deaths (1.0%)^[1,24] occurred after simple cholecystectomy and the causes of death included acute myocardial infarction and pulmonary embolism. Seven postoperative deaths (1.5%)^[1,10,11,24] occurred after extended cholecystectomy. Three patients died of co-morbidities of the disease, two patients died of hemorrhage, one patient died of peritonitis and one died of liver failure.

Lymph node metastasis

Of the 29 reviewed articles, information on lymph node metastasis was available from 17 publications (58.6%)^[3,5-7,10,11,13-18,24,26-28,31] (Table 3). Lymph node metastasis was found in 1.8% and 10.9% of T1a and T1b GB cancer patients, respectively ($P < 0.01$). Of the 17 publications, only 5 included lymph node metastasis cases^[3,5,13,15,17] (Table 4).

Recurrence

Information pertaining GB cancer recurrence was available from 26 out of 29 articles (89.76%)^[1,3,5-8,10-13,15-22,24,26-30,32].

Table 2 Surgical procedures for mucosa and T1b gallbladder cancer *n* (%)

	T1a (<i>n</i> = 706)	T1b (<i>n</i> = 560)	<i>P</i> value	Total (<i>n</i> = 1266)
Simple cholecystectomy	590 (83.6)	375 (67.0)	< 0.01	965 (76.2)
Open cholecystectomy	321 (54.4)	286 (76.3)	< 0.01	607 (62.9)
Laparoscopic cholecystectomy	269 (45.6)	89 (23.7)		358 (37.1)
Extended cholecystectomy	110 (15.6)	168 (30.0)	< 0.01	278 (22.0)
2nd operation	16 (14.5)	43 (25.6)		59 (21.2)
Major hepatectomy	6 (0.8)	16 (2.9)	NS	22 (1.7)
Pancreatoduodenectomy	0	1 (0.2)	NS	1

NS: Not stated.

Table 3 Lymph node metastasis of T1 gallbladder cancer *n* (%)

	T1a (<i>n</i> = 280)	T1b (<i>n</i> = 276)	<i>P</i> value	Total (<i>n</i> = 556)
Lymphovascular invasion	7 (2.5)	33 (12.0)	< 0.01	40 (7.2)
Perineural invasion	1 (0.4)	7 (2.5)	NS	8 (1.4)
Lymph node metastasis	5 (1.8)	30 (10.9)	< 0.01	35 (6.3)

NS: Not stated.

Table 4 Studies reporting lymph node metastasis of T1 gallbladder cancer *n* (%)

	T1a	T1b	Odds ratio	95% CI
Goetze <i>et al</i> ^[5]	0/21	1/72 (1.4)	1.296	1.159-1.448
Yildirim <i>et al</i> ^[13]	0/5	1/8 (12.5)	1.714	1.063-2.765
You <i>et al</i> ^[3]	0/27	2/25 (8.0)	2.174	1.610-2.935
Kim <i>et al</i> ^[17]	0/10	1/9 (11.1)	2.250	1.342-3.771
Ogura <i>et al</i> ^[13]	5/201 (2.5)	25/165 (15.2)	7.000	2.616-18.733

Eight patients (1.1%) with T1a GB cancer^[3,4,10-12,18,26] and 52 patients (9.3%) with T1b GB cancer^[4-7,11,12,17-19,27,32] died of recurrent GB cancer (*P* < 0.01). The studies reporting recurrent GB cancer are listed in Table 5. Cases of T1a GB cancer recurrence and the recurrence pattern of T1b GB cancer are summarized in Tables 6 and 7, respectively.

Survival rate

Twenty-one publications^[1,3,5-11,13-21,27,30,32] described the 5-year survival rate of GB cancer patients. The 5-year survival rate of patients with T1a and T1b GB cancer is 45%-100% and 37.5%-100%, respectively (Table 8).

Only 6 publications^[5,6,11,15,17,27] compared the survival rates of patients after simple cholecystectomy or extended cholecystectomy. No significant difference was observed in the survival rate of patients with T1a GB cancer after different operative procedures. However, 3 publications^[5,11,27] showed a significantly longer survival time of patients with T1b GB cancer after extended cholecystectomy (Table 9).

Outcome of patients after laparoscopic cholecystectomy and open cholecystectomy

Only two studies^[4,12] compared the survival rates of patients with T1 GB cancer after laparoscopic cholecystectomy and open cholecystectomy. No significant difference

Table 5 Studies reporting recurrence cases of T1 gallbladder cancer *n* (%)

	T1a	T1b	Odds ratio	95% CI
You <i>et al</i> ^[3]	1/27 (3.7)	0/25	0.510	0.39-0.67
Shirai <i>et al</i> ^[26]	2/78 (2.6)	0/11	0.874	0.81-0.95
Wakai <i>et al</i> ^[10]	1/13 (7.7)	0/2	0.923	0.79-1.08
Z'graggen <i>et al</i> ^[29]	0/3	1/6 (16.7)	1.200	0.84-1.72
Waghlikar <i>et al</i> ^[7]	0/2	5/12 (41.7)	1.286	0.91-1.82
Goetze <i>et al</i> ^[5]	0/21	14/72 (19.4)	1.362	1.19-1.56
Cangemi <i>et al</i> ^[27]	0/4	5/11 (45.4)	1.667	1.01-2.77
Kim <i>et al</i> ^[17]	0/10	1/9 (11.1)	2.250	1.34-3.77
Chan <i>et al</i> ^[12]	1/14 (7.1)	3/19 (15.8)	2.438	0.23-26.29
Otero <i>et al</i> ^[32]	0/25	9/26 (34.6)	2.471	1.71-3.57
Ouchi <i>et al</i> ^[11]	1/8 (12.5)	3/7 (42.9)	5.250	0.40-68.94
Ouchi <i>et al</i> ^[18]	1/167 (0.6)	3/67 (4.5)	7.781	0.79-76.19
Cucinotta <i>et al</i> ^[4]	1/5 (20)	6/7 (85.7)	24.000	1.14-505.2
Wakai <i>et al</i> ^[6]	0	2/25 (8.0)		

was observed in the survival rate of patients after the two operative procedures. However, it must be emphasized that the total number of patients included was small. In addition, 6 studies^[17-20,22,30] evaluated the safety of laparoscopic cholecystectomy on the basis of recurrent GB cancer and survival rate of GB cancer patients, showing a low recurrence rate and a high survival rate (Table 10). Meta-analysis could not be performed because no studies reported the hazard ratio for overall survival rate according to the surgical procedure.

DISCUSSION

This review evaluated the surgical outcomes of patients with T1 GB cancer. The evidence was of low quality, because it was obtained from the reviewed articles, and most studies were case series. No study was controlled, and all reviewed articles were retrospective in nature. Furthermore, such studies usually involved a small number

Table 6 Recurrence cases of T1a gallbladder cancer after surgical treatment (*n* = 8)

	Operation	Time of recurrence (mo)/site	Survival after op (mo)
Shirai <i>et al</i> ^[26]	NA ¹	NA/CBD	76
	NA ¹	NA/CBD	66
Ouchi <i>et al</i> ^[11]	Simple cholecystectomy	NA/CBD	45
Ouchi <i>et al</i> ^[18]	Laparoscopic cholecystectomy ²	NA/NA	NA
Wakai <i>et al</i> ^[10]	Laparoscopic cholecystectomy	NA/P. seeding	52
Cucinotta <i>et al</i> ^[4]	Laparoscopic cholecystectomy	7/Port site	20
Chan <i>et al</i> ^[12]	Laparoscopic cholecystectomy	48.3/liver, lung	51
You <i>et al</i> ^[3]	Laparoscopic cholecystectomy	3/CBD	19

¹Cystic duct margin (+) patients; ²Gallbladder perforation during laparoscopic cholecystectomy. CBD: Common bile duct; NA: Not available.

Table 7 Recurrence pattern of T1b gallbladder cancer after surgical treatment *n* (%)

	Simple cholecystectomy (<i>n</i> = 375)	Extended cholecystectomy (<i>n</i> = 185)
Loco-regional recurrence	12 (50.0)	
CBD	3 (6.4)	
Lymph node	5 (10.6)	
Port site	4 (8.5)	
Systemic recurrence	12 (50.0)	3 (60)
Liver	7 (14.9)	2 (40)
Peritoneal seeding	4 (8.5)	
Lung	1 (2.0)	1 (20)
Unknown	23 (48.9)	2 (40)
Total ^b	47 (12.5)	5 (2.7)

^b*P* < 0.01. CBD: Common bile duct.

Table 8 Five-year survival rates of patients with T1a and T1b gallbladder cancer after surgical treatment

	N	5 YSR (%)		
		T1 (T1a/T1b)	T1a (SC/EC)	T1b (SC/EC)
Benoist <i>et al</i> ^[1]	36 ¹ (13/23)		45	44
You <i>et al</i> ^[3]	52 (27/25)		96.3	96
de Aretxabala <i>et al</i> ^[14]	24 (11/13)		100	75
Kang <i>et al</i> ^[16]	11 (3/8)		100	100
Sun <i>et al</i> ^[19]	15 (10/5)		100	100
Kwon <i>et al</i> ^[20]	20 (18/2)		100	100
Kohya <i>et al</i> ^[21]	15 (8/7)		100	100
Yildirim <i>et al</i> ^[15]	13 (5/8)		100	80
			(100/100)	(50/100)
Kim <i>et al</i> ^[17]	19 (10/9)		100	100
			(100/100)	(100/100)
Ouchi <i>et al</i> ^[11]	15 (8/7)		(71/100)	(42/100)
Cangemi <i>et al</i> ^[27]	15 (4/11)		100	(37.5/100)
Ogura <i>et al</i> ^[13]	366 (201/165)		82.6	72.5
Ouchi <i>et al</i> ^[18]	234 (167/67)		99	95
Otero <i>et al</i> ^[32]	51 (25/26)		70	
Goetze <i>et al</i> ^[5]	93 (21/72)			(42/79)
Wakai <i>et al</i> ^[6]	25 (0/25)			87 (100/75)
Waghlikar <i>et al</i> ^[7]	14 (2/12)			68
Shimada <i>et al</i> ^[9]	17 (10/7)			86.7
Eguchi <i>et al</i> ^[31]	25 (19/6)			92
Wakai <i>et al</i> ^[10]	15 (13/2)			(90/100)
Yagi <i>et al</i> ^[8]	13 (12/1)			100

¹All patients underwent simple cholecystectomy. SC: Simple cholecystectomy; EC: Extended cholecystectomy.

Table 9 Five-year survival rates of patients with T1b gallbladder cancer after different surgical procedures

	N (SC/EC)	5 YSR (%)		<i>P</i> value
		SC	EC	
Wakai <i>et al</i> ^[6]	25 (17/8)	100	75	NS
Kim <i>et al</i> ^[17]	9 (6/3)	100	100	NS
Yildirim <i>et al</i> ^[15]	8 (5/3)	50	100	NS
Ouchi <i>et al</i> ^[11]	7 (5/2)	42	100	< 0.05
Cangemi <i>et al</i> ^[27]	11 (8/3)	37.5	100	< 0.01
Goetze <i>et al</i> ^[5]	72 (49/23)	42	79	0.03

NS: Not significant; SC: Simple cholecystectomy; EC: Extended cholecystectomy.

Table 10 Clinical outcome of laparoscopic cholecystectomy for T1a and T1b gallbladder cancer

	N		Recurrence		5 YSR (%)	
	T1a	T1b	T1a	T1b	T1a	T1b
Mori <i>et al</i> ^[22]	7	2	0	0		
Kim <i>et al</i> ^[17]	9	6	0	1 (port site)	100	100
Sun <i>et al</i> ^[19]	10	5	0	0	100	100
Eguchi <i>et al</i> ^[31]	13	5	0	0	100	100
Kwon <i>et al</i> ^[20]	18	2	0	0	100	100
Ouchi <i>et al</i> ^[18]	167	67	1 ¹	3 ¹	99	95

¹Site was not described.

of patients, making it difficult to draw a statistically sound conclusion. The inclusion of heterogeneous groups of patients who underwent surgery at different centers by different specialists also made interpretation of results challenging. However, the relatively low incidence of this condition makes it impractical to conduct adequately powered randomized controlled trials to compare different surgical and/or nonsurgical interventions. Therefore, a systematic review of evidence despite a lower scientific level was needed.

Simple cholecystectomy for T1a GB cancer was performed in 84% of patients. Of these patients, 46% underwent laparoscopic cholecystectomy. Lymph node metastasis was found only in 1.8% GB cancer patients with a recurrence rate of 1.1%. Because 50% of the recurrence occurred in the common bile duct, pathological confirmation of cystic duct margin would be important. If cystic duct margin was proved to be positive for GB cancer,

resection of the common bile duct should be performed. Although the 5-year survival rate of patients with T1a GB cancer was 45%-100%, the publications^[1,11,32] showing a low survival rate did clarify that most deaths were not related to GB cancer. The remaining publications reported a 5-year survival rate of over 90%, indicating that simple cholecystectomy is the adequate surgical treatment of T1a GB cancer. In particular, recent reports^[17-20,30] showed a 100% 5-year survival rate of patients with GB cancer following laparoscopic cholecystectomy, indicating that laparoscopic cholecystectomy is a safe procedure for GB cancer. However, because a report^[10] on peritoneal seeding due to GB perforation during laparoscopic cholecystectomy and a report^[4] on port site recurrence following laparoscopic cholecystectomy, careful dissection to avoid perforation of GB should be performed and GB should be retrieved using a plastic bag.

Simple cholecystectomy and extended cholecystectomy for T1b GB cancer were performed in 67% and 30% patients, respectively. More patients with T1b GB cancer underwent extended cholecystectomy ($P < 0.01$). Despite a lack of evidence, many authors agreed that aggressive approach would be needed for T1b GB cancer. This review validated the rationale behind this approach to a certain extent. Lymph node metastasis of T1b GB cancer was 11%, which was significantly higher than that (2%) of T1a GB cancer ($P < 0.01$). The publications^[3,5,13,15,17] reporting lymph node metastasis of T1a and T1b GB cancer showed that the incidence of lymph node metastasis of T1b GB cancer is 1.3-7 times higher than that of T1a GB cancer (Table 4). The recurrence rate of T1b GB cancer was 9%, which was significantly higher than that (1%) of T1a GB cancer ($P < 0.01$). The publications^[3-7,10-12,17,18,26,27,29,32] reporting the recurrence rate of T1a and T1b GB cancer showed that the recurrence rate of T1b GB cancer is 1.3-24 times higher than that of T1a GB cancer (Table 7). In addition, the recurrence rate of GB cancer was higher after simple cholecystectomy than after extended cholecystectomy (12.5% *vs* 2.7%, $P < 0.01$). Although the recurrence sites were not available in 50% of the cases reviewed, no patient showed loco-regional recurrence after extended cholecystectomy in the remaining cases. The 5-year survival rate of patients with T1b GB cancer was 37.5%-100%. Studies^[1,5,11,15,27] showing a 5-year survival rate of less than 50% discussed simple cholecystectomy cases. Of these publications, 3^[5,11,27] showed a significantly higher survival rate after extended cholecystectomy than after simple cholecystectomy. However, the total number of patients included was too small to comment on statistical significance. Except for these studies, the rest showed a 5-year survival rate of over 80% for patients with GB cancer irrespective of surgical procedure. Although there was no definite evidence that extended cholecystectomy was advantageous over simple cholecystectomy in this review, regional lymph node dissection should be included in any surgical procedure for T1b GB cancer considering that the lymph node metastasis rate was relatively high. Although the recurrence rate of GB cancer was high and the survival rate of GB cancer

patients was low after simple cholecystectomy, extended cholecystectomy was recommended for T1b GB cancer in several guidelines^[33,34]. In view of the inconclusive results obtained from this review, multicenter prospective studies should be performed to clarify the surgical strategy for T1b GB cancer.

In conclusion, T1 GB cancer should be treated based on the outcomes of this review. Simple cholecystectomy for T1a GB cancer is the adequate treatment and laparoscopic cholecystectomy is a safe procedure for T1b GB cancer, provided the port site recurrence is considered. Careful dissection should be conducted considering that the peritoneal seeding is associated with bile spillage. Resection margin of cystic duct should be confirmed histopathologically with possible common bile duct resection in mind. There is no definite evidence that extended cholecystectomy is advantageous over simple cholecystectomy for T1b GB cancer. Because lymph node metastasis is considerable, regional lymphadenectomy should be performed for the treatment and staging of GB cancer.

COMMENTS

Background

Most authors agree that mucosa (T1a) gallbladder (GB) cancer is a local disease and simple cholecystectomy represents its adequate treatment provided that the resection margin is not involved. It has been argued that muscularis (T1b) GB cancers may have spread regionally or systematically at presentation. Therefore, whether T1b cancers should be treated with simple cholecystectomy or extended cholecystectomy still remains debatable.

Research frontiers

Few early GB cancer cases are available and randomized trials are difficult to conduct for the assessment of appropriate surgical procedures. Therefore, a pooled systematic analysis of the efficacy of each surgical procedure for early GB cancer is essential to establish the appropriate management of T1a and T1b GB cancer.

Innovations and breakthroughs

Original published studies on surgery for T1 GB cancer were searched from MEDLINE (PubMed, 1966-2008), Cochrane Library (1996-2008), EMBase (1970-2008), and CancerLit (1970-2008).

Applications

Simple cholecystectomy for T1a GB cancer is its adequate treatment and laparoscopic cholecystectomy is safe procedure for T1b GB cancer provided the port site recurrence is considered. There is no definite evidence that extended cholecystectomy is advantageous over simple cholecystectomy for T1b GB cancer.

Terminology

GB cancer confined to T1a or T1b is as an early cancer.

Peer review

This review evaluated the surgical outcomes of T1 GB cancer. The evidence is of low quality, because it was obtained from the reviewed articles, and most studies were case series. No study was controlled and all reviewed articles were retrospective in nature. Furthermore, such studies usually involved a small number of patients, making it difficult to draw a statistically sound conclusion. The inclusion of heterogeneous groups of patients who underwent surgery at different centers by different specialists also made interpretation of results challenging. However, the relatively low incidence of GB cancer makes it impractical to conduct adequately powered randomized controlled trials comparing different surgical and/or nonsurgical interventions. Therefore, systematic review of evidence despite a lower scientific level is needed.

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