### **Original Research Article**

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# Simple cholecystectomy versus radical resection for stage I gallbladder cancer: a meta-analysis

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#### **ABSTRACT**

**Background:** GBC was first reported more than two hundred years ago, but the poor therapeutic effect for GBC patients is still frustrating now, the 5-year survival rate is no more than 5%, and the mean survival time is only about half a year. The objective of this study was to evaluate the importance of radical resection in the treatment of Nevin II and T1b stage gallbladder cancer (stage II GBC) by analyzing the survival rate and tumor recurrence rate after accepting simple cholecystectomy (SC) and radical resection (RR).

**Methods:** PubMed, Embase, Chinese National Knowledge Infrastructure and Wanfang databases was searched from inception to February 2016. Quality assessment was conducted in each of the available studies by using the validated Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort and case-control studies. Publication bias was also assessed by using a funnel plot. The odds ratio (OR) and its 95% confidence interval (95% CI) were employed to estimated effect size. All statistical analyses were carried out using Rev Man 5.2 software.

**Results:** A total of fifteen studies encompassing 424 patients meeting the search criteria were included. Pooled analyses revealed that comparing to simple cholecystectomy, radical resection can significantly increase the 1-, 3- and 5-year survival rate of patients with stage II GBC (OR = 3.28, 95% CI: 1.83-5.89, P < 0.0001; OR = 2.52, 95% CI: 1.49-4.28, P = 0.0006; OR = 3.19, 95% CI: 1.85-5.51, P < 0.0001), and patients after radical resection have a significant lower tumor recurrence rate (OR = 0.30, 95% CI: 0.11-0.80, P = 0.02).

**Conclusions:** The short- and long-term survival rate of patients with stage II GBC following radical resection is obviously higher than that of patients receiving simple cholecystectomy, and the tumor recurrence rate is obviously lower. Radical resection would be a better choice for stage II GBC.

Keywords: Gallbladder cancer, Meta-analysis, Radical resection, Simple cholecystectomy

#### **INTRODUCTION**

GBC was first reported more than two hundred years ago, but the poor therapeutic effect for GBC patients is still frustrating now, the 5-year survival rate is no more than 5%, and the mean survival time is only about half a year. It still relies on surgical method to treat and provide the

possibilities of favorable prognosis, while auxiliary methods like radiotherapy and chemotherapy are likely to reduce the chance of tumor relapse and improve the long-term survival of GBC patients.<sup>2</sup>

GBC patients' survival time - one of the major indicators for prognosis judgment isn't affected by sexuality, age or

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biochemical criterions but has a strong correlation with the extent of GBC. The later clinical stage tumor stays, the worse prognosis tends to arrival. Nevin staging and AJCC staging are the most frequent staging system in clinical practice, appropriately guiding the choice of surgical method.<sup>3,4</sup> T1a and T1b GBC are respectively confined to mucosa and muscularis, collectively called early stage of GBC. Tis and T1a stage GBC has an encouraging probability of getting radical cure by simply cholecystectomy, and patients with these stages of GBC may not benefit from a radical resection.<sup>5</sup> But it is noteworthy that gallbladder rupturing or bile leaking during the cholecystectomy may bring about tumor cells metastasis, for cases like these, a re-resection shall be taken into consideration.<sup>6</sup> Unlike the consensus on T1a GBC, whether T1b GBC needs radical resection is still controversial. Some militant views considered that GBC was highly malignant and early metastasizing, radical surgeries should be carried out regardless of tumor staging.7 However, some believed T1b GBC hadn't invaded beyond muscular layer, simple cholecystectomy was enough to get a satisfactory survival time allowing for the low risk of lymph node metastasis at this early stage, and some others thought there was no differences between two kinds of surgical procedure.<sup>8,9</sup>

Although surgery is admittedly the best choice, controversy is hard to settle unless it's proved by large sample and high quality clinical trials. The stage of Nevin II and T1bN0M0 equally refer to the time when GBC only invades muscularis. In this study, we named these two stages as stage II GBC, and performed meta-analysis to discuss the status of radical resection in the treatment of stage II GBC via comparing GBC patients' survival time and tumor recurrence rate following simple cholecystectomy and radical resection.

#### **METHODS**

#### Retrieval strategy

A systematic literature search was performed in PubMed, Cochrane Library, Web of science, date from database creation to February 2016. Titles and abstracts were retrieved and screened by two independent reviewers. The search strategy used consisted of a combination of database-specific MeSH terms, free text words and Boolean operators. Filters were used in PubMed to exclude animal studies. The following key words were searched in each database: "gallbladder cancer", "cholecystectomy" and "radical resection". Appropriate adjustments were made according to the database. References of the articles acquired were also searched manually.

#### Inclusion criteria

Randomized controlled trials studies and non-randomized controlled trials were all appreciated, only if covering T1b or Nevin II GBC patients and comparing the postoperative survival rate after accepting simple cholecystectomy and radical resection (cholecystectomy, wedge resection of the gallbladder bed and regional lymph nodes dissection). Language of study is limited to English and Chinese. Patients with GBC should be suitable for surgery treatment and there was explicit evidence of pathological diagnosis, and no local invasion or distant metastasis. No adjuvant therapy was performed before or after operation.

#### Exclusion criteria

Articles were excluded if

- The GBC staging was unknown, tumors stay at advanced stage or combined with liver or biliary tumors
- There exist no control group, or it's not about the two surgical methods mentioned above
- Follow-up time was less than one year, or the time nodes weren't the 1st, 3rd or 5th year
- Case reports, reviews, meta-analysis, systematic review, animal studies, etc.
- Replicated published researches
- No adequate information and data can be extracted, or data can't be utilized.

#### Data extraction

Two authors independently scrutinized all articles and decided which trials were to be included. A data extraction form was developed and used to extract and record information on included studies. The following information from each trial was extracted: Study and patient characteristics, staging of disease, surgical method, corresponding survival rate and tumor recurrence rate. Results will be compared between reviewers; any disagreement about data extraction was resolved by discussion among the authors.

#### Assessment of study quality

Two reviewers independently assessed the methodological quality of each trial by Newcastle-Ottawa Scale (NOS). NOS include three parts: selection, comparability and outcome. The total score ranges from 0 to 9, and studies with more than six points belong to high quality research. Disagreement was resolved by discussion. In case of no identical conclusion, a third reviewer was contacted.

#### Statistical analysis

When data were available for a pooled estimate of the impact of intervention, it was intended that meta-analyses would be conducted for direct comparisons. When data were not available for pooling, we performed a descriptive analysis. Data were analyzed by Review Manager 5.2. The main assessment criteria are 1-, 3- and 5-year survival rate and tumor recurrence rate. The

comparison of post-operative effect was denoted by odds ratio (OR) and 95% confidence interval (95% CI). We examined intervention effects with the two-sided significance set at P<0.05. We explored the presence of statistical heterogeneity by  $x^2$  test with significance set at P<0.10 and measured the quantities of heterogeneity by  $I^2$ . When high heterogeneity didn't exist, fixed-effect model was used. On the contrary, random-effect model would be used, and in addition, subgroup analysis or sensitivity analysis would be made to seek sources of heterogeneity. The result of meta-analysis and larvaceous publication bias will be exhibit as forest plot and funnel plot respectively.

#### **RESULTS**

## Characteristics of included literatures and quality assessment

Fifty studies were finally extracted from 408 publications identified from databases and other sources, the flowing chart is showed in Figure 1.<sup>5,11-24</sup> All the studies were non-randomized control trials. Table 1 and 2 respectively show the character of included literatures and NOS quality assessment scale. In the fifty researches, five of them used Nevin staging, and 424 cases were contained in total.

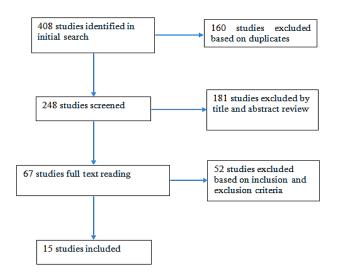


Figure 1: Electronic search flow chart.

#### Effects of interventions

Survival rate analysis

Twelve of the fifty retrospective studies recorded 1-year survival rate.  $^{5,11-14,16-19,21,23,24}$  Data of 1-year survival rate from nine studies can be pooled (Figure 2). Heterogeneity exists ( $\chi 2 = 11.54$ , P = 0.17, I2 = 31%), hence random model was used, and the result shows RR is obviously

better than SC in increasing 1-year survival rate (OR=3.28, 95% CI: 1.83-5.89, P<0.0001). In addition, in the study of Kim et al, Cavallaro et al and Ke et al. <sup>14,16,19</sup> 1-year survival rate of stage II GBC were all 100%.

	RR		SC			Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% (	1
Cangemi 2006	3	3	6	8	3.5%	2.69 [0.10, 73.20]		<del>-   •</del>	
Goetze 2008	22	23	38	49	7.5%	6.37 [0.77, 52.71]		+	
Jiang 2013	18	20	14	20	9.9%	3.86 [0.67, 22.11]		+-	_
Sun 2011	6	7	8	9	7.1%	0.75 [0.04, 14.58]			_
Tashiro 1982	16	17	62	69	10.2%	1.81 [0.21, 15.76]		<del></del>	_
Wagholikar 2002	0	1	11	11	17.5%	0.01 [0.00, 1.04]	-		
Xu 2010	16	21	3	17	5.6%	14.93 [3.01, 74.04]		-	•
Yi 2013	3	3	7	8	4.1%	1.40 [0.04, 43.79]		<del></del>	
Zhang 2014	33	43	21	43	34.6%	3.46 [1.37, 8.73]		-	-
Total (95% CI)		138		234	100.0%	3.28 [1.83, 5.89]		•	
Total events	117		170						
Heterogeneity: Chi <sup>2</sup> = 11.54, df = 8 (P = 0.17); i <sup>2</sup> = 31%								N1 1	40 400
Tect for overall effect 7 = 3.00 /P < 0.0001)								Favours SC Favour	10 100 s RR

Figure 2: Analysis of the 1-year survival rate after simple cholecystectomy and radical resection.

	RR		SC			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cangemi 2006	3	3	4	8	1.9%	7.00 [0.27, 178.47]	<del></del>
Goetze 2008	18	23	32	49	23.9%	1.91 [0.60, 6.05]	+
Ke 2011	1	1	1	2	1.6%	3.00 [0.06, 151.19]	<del></del>
Ren 2011	4	8	3	5	9.9%	0.67 [0.07, 6.41]	
Sun 2011	6	7	6	9	4.0%	3.00 [0.24, 37.67]	
Tashiro 1982	12	17	46	69	28.8%	1.20 [0.38, 3.82]	-
Xu 2010	9	21	1	17	3.4%	12.00 [1.33, 108.02]	<del></del>
Yi 2013	3	3	3	8	1.4%	11.00 [0.43, 284.30]	<del>                                     </del>
Zhang 2014	18	43	8	43	25.0%	3.15 [1.18, 8.38]	-
Total (95% CI)		126		210	100.0%	2.52 [1.49, 4.28]	•
Total events	74		104				
Heterogeneity: Chi² = 6.46, df = 8 (P = 0.60); I² = 0%							0.01 0.1 1 10 100
Test for overall effect. Z = 3.44 (P = 0.0006)							

Figure 3: Analysis of the 3-year survival rate after simple cholecystectomy and radical resection.

	RR		SC			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cangemi 2006	3	3	3	8	1.7%	11.00 [0.43, 284.30]	+
Goetze 2008	18	23	21	49	18.3%	4.80 [1.53, 15.02]	
Ke 2011	1	1	0	2	0.6%	15.00 [0.18, 1236.18]	<del>-   · -  </del>
Ouchi 1999	2	2	0	2	0.5%	25.00 [0.34, 1831.59]	+
Ren 2011	1	8	2	5	13.5%	0.21 [0.01, 3.37]	
Sun 2011	5	7	5	9	7.9%	2.00 [0.24, 16.36]	<del></del>
Tashiro 1982	10	17	40	69	41.0%	1.04 [0.35, 3.04]	-
Tian 2015	7	7	11	13	3.3%	3.26 [0.14, 77.84]	<del></del>
Xu 2010	5	21	0	17	2.6%	11.67 [0.60, 227.90]	+
Yi 2013	3	3	2	8	1.2%	18.20 [0.67, 494.80]	+
Zhang 2014	11	43	2	43	9.4%	7.05 [1.46, 34.07]	
Total (95% CI)		135		225	100.0%	3.19 [1.85, 5.51]	•
Total events	66		86				
Heterogeneity: Chi <sup>2</sup> =	: 13.24, df	= 10 (F	= 0.21);	l² = 24°	%		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Test for overall effect: Z = 4.17 (P < 0.0001)							0.01 0.1 1 10 10 Favours SC Favours RR

Figure 4: Analysis of the 5-year survival rate after simple cholecystectomy and radical resection.

Table 1: Summary of studies included in the meta-analysis.

Author	Stage	Case	1-year su rate	1-year survival rate		3-year survival rate		5-year survival rate		Recurrence rate (n)	
		(n)	Group SC	Group RR	Group SC	Group RR	Group SC	Group RR	Group SC	Group RR	
Yi et al	pT1b	11	7/8	3/3	3/8	3/3	2/8	3/3	3	0	
Cangemi et al	pT1b	11	6/8	3/3	4/8	3/3	3/8	3/3	5	0	
Tashiro et al	Nevin II	86	62/69	16/17	46/69	12/17	40/69	10/17	1	0	
Kim et al	pT1b	6	4/4	2/2	-	-	-	-	1	0	
Ouchi et al	pT1b	4	-	-	-	-	0/2	2/2	2	0	
Cavallaro et al	pT1b	6	1/1	5/5	1/1	5/5	-	-	0	1	
Wagholikar et a	pT1b	12	11/11	0/1	-	-	-	-	5	0	
Goetze et al	pT1b	72	38/49	22/23	32/49	18/23	21/49	18/23	12	2	
Zhang et al	Nevin II	86	21/43	33/43	8/43	18/43	2/43	11/43	-		
Jiang et al	Nevin II	40	14/20	18/20	-	-	-	-	-		
Tian et al	pT1b	20	-	-	-	-	11/13	7/7	-		
Ke et al	pT1b	3	2/2	1/1	1/2	1/1	0/2	1/1	-		
Sun et al	pT1b	16	8/9	6/7	6/9	6/7	5/9	5/7	-		
Ren et al	Nevin II	13	-	-	3/5	4/8	2/5	1/8	-		
Xu et al	Nevin II	38	3/17	16/21	1/17	9/21	0/17	5/21	-		

pT1a, pT1b: AJCC staging; SC: simple cholecystectomy; RR: radical resection; -: no data.

Ten studies recorded 3-year survival rate. $^{5,11,13,16-21,24}$  Figure 3 presents the pooled data of 3-year survival rate, the result shows there's no heterogeneity ( $\chi 2=6.46$ , P=0.60, I2=0%), fix model was used and it's obviously that RR contributes to higher survival rate for stage II GBC patients (OR = 2.52, 95% CI: 1.49-4.28, P=0.0006). Besides, 3-year survival rate of stage II GBC was 100% in the study of Cavallaro et al. $^{16}$ 

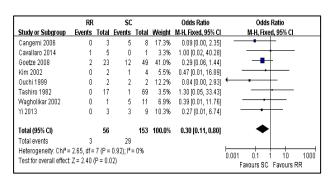


Figure 5: Analysis of the recurrence rate after simple cholecystectomy and radical resection.

Eleven studies recorded 5-year survival rate. $^{5,11,13,15,17-22,24}$  The result in Figure 4 shows low heterogeneity exists ( $\chi 2 = 13.24$ , P = 0.21, I2 = 24%), and RR is also superior to SC in terms of 5-year survival rate (OR = 3.19, 95% CI: 1.85-5.51, P<0.0001).

#### Tumor recurrence rate

Eight retrospective studies can be extracting the data of tumor recurrence rate, which shows in figure 3.

Heterogeneity didn't exist ( $\chi 2 = 2.65$ , P = 0.92, I2 = 0%), and fix model was used. It shows the recurrence rate is apparently higher in group SC (OR = 0.30, 95% CI: 0.11-0.80, P = 0.02).

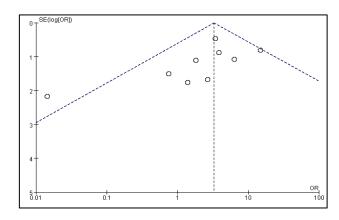


Figure 6: Funnel plot for detection of publication bias.

#### Sensitivity analysis and bias identify

In the meta-analysis of pooling data for the survival rate and recurrence rate, no significant clinical or methodological heterogeneity exist between each study after carefully read. We screened out studies one by one for sensitivity analysis, and the statistics had no significant change, which indicated the result of meta-analysis was steady and reliable. Funnel plot was used for detecting publication bias in figure 6, in which were essential symmetry on both sides and small possibility of publication bias.

Table 2: Quality of literatures included in the meta-analysis (NOS quality assessment scale).

Audhou	Selection	Comparability	Outcome	Total	
Author	(score)	(score)	(score)	Total	
Yi et al	3	2	3	8	
Cangemi et al	4	2	3	9	
Tashiro et al	3	2	3	8	
Kim et al	2	2	3	7	
Ouchi et al	4	2	3	9	
Cavallaro et al	4	2	3	9	
Wagholikar et al	3	2	3	8	
Goetze et al	4	2	3	9	
Zhang et al	4	2	3	9	
Jiang et al	4	2	2	8	
Tian et al	4	2	3	9	
Ke et al	4	2	3	9	
Sun et al	4	2	3	9	
Ren et al	4	2	3	9	
Xu et al	4	2	3	9	

#### **DISCUSSION**

Fifteen studies were included to evaluate the influence of post-operative survival rate and tumor recurrence rate after RR and SC in patients with stage II GBC. The result shows that, for tumors invading gallbladder muscularis, RR is superior to SC and benefits more.

GBC usually proceeds rapidly and has strong invasive ability and there're no specific symptoms at the beginning of the disease in most cases. Hence it's hard to detect early and always bring about high mortality when advanced stage set in. Surgical treatment is the major method to cure, especially for the early stage GBC. Inoperable GBC or tumors with distant metastasis might profit from adjuvant therapy and the survival time lengthen.<sup>2</sup>

Surgical procedures for GBC are mainly as follows: simple cholecystectomy, radical resection, extended radical resection and palliative operation, the selection of which is guided by the progress of tumor. Post-operative survival time of GBC patients is affected by T-stage, lymph node invasion, distant metastasis and jaundice, and at the meantime, tumor recurrence and metastasis may have a correlation with the degree of tumor invasion, the histological tumor site and grade.1 Simple cholecystectomy is acknowledged as the optimal choice when tumor is confined to the mucosal layer of gallbladder without breaking through the muscularis (Tis or T1a stage), because the invasive range of tumor at this stage is always smaller and the rate of lymph node metastasis is relatively lower. Yamaguchi et al.<sup>25</sup> found that patients with GBC of T1 stage following simple cholecystectomy can live more than 5 years. Similarly, in the included researches, Kim et al and Cavallaro et al. respectively compared the 1-and 3-year survival rate after two kinds of surgery, which was all up to 100%.<sup>14,16</sup> Also, few patients suffered from post-operative tumor recurrence in these studies. Lee et al carried out a systematic review for T1 stage GBC, in included researches of which 67% and 30% patients with T1b GBC respectively accepted simple cholecystectomy and radical resection.<sup>8</sup> The rate of lymph node metastasis can get as high as 11%. And the tumor recurrence rate after simple cholecystectomy and radical resection were 12.5% and 2.7% (P<0.01).

Lee considered simple cholecystectomy was safe for T1b GBC as long as performing "no tumor" procedure during operation and achieving R0 resection, there's no enough evidence to suggest radical resection had more advantages. It's also worth noting that lymph node excision is of the utmost importance to reduce post-operative tumor recurrence in each surgical method since the high possibility of lymph node metastasis of T1b GBC.

Tumors from the neck of gallbladder or cystic duct are more likely to appear intraluminal implantation metastasis, regional invasion or lymph node metastasis due to the short distance towards bile duct, hepatic portal and the first station of lymph nodes. The gallbladder wall is rich with lymphatic vessels which exist between muscularis and serosal layer; hence the possibility of early lymphatic metastasis cannot be ignored. Since there's no serosal layer on the side of gallbladder bed, post-operative residual tumor cells may get into portal system via cholecystic vein causing hard-to-find hematogenous or organ metastasis. Hence, from the anatomical point of view, radical resection is imperative for the treatment of stage II GBC, and sometimes extended lymphadenectomy and combined extra-hepatic bile ducts resection are also essential.<sup>26</sup>

#### **CONCLUSION**

This meta-analysis shows radical resection was superior to simple cholecystectomy on post-operative survival rate and tumor recurrence rate. However, whichever surgical procedure is conducted, "no tumor" procedure and R0 resection take a very high priority. It's difficult to carry out randomized controlled trials for the comparison of two surgical methods, mainly because it's hard to detect asymptomatic GBC at early stage. Studies about surgical treatment of GBC are mostly retrospective studies with small sample size. So it needs more clinical researches of high quality and large sample size to confirm the significance of radical resection for stage II GBC.

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Ethical approval: The study was approved by the

institutional ethics committee

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