RESEARCH ARTICLE

Factors for Postoperative Gallstone Occurrence in Patients with Gastric Cancer: a Meta-analysis

Xiang-Jun Chen, Nian Li, Ying-De Huang, Shuang Ren, Fang Liu, Lian Chen, Yong Wang, Min Chen*

Abstract

Objective: To evaluate risk factors for gallstones after gastrectomy. Methods: To identify documents published from 1990 to 2011 the Pubmed, Cochrane Library, Springer Link, CBM and WanFang databases were searched and a meta-analysis was performed with RevMan 5.2 software for odds ratios and 95%CIs. Results: Fifteen studies were selected for the meta-analysis. The pooled ORs [95%CIs] were 0.56 [0.43, 0.73], (*P*<0.0001) for digestive tract reconstruction, 0.80 [0.54, 1.17], (*P*=0.25) for pylorus preservation, 0.33[0.15, 0.75], (*P*=0.008) for resection scope of stomach, 0.33 [0.15, 0.75], (*P*=0.008) for lymphadenectomy, and 0.13 [0.05, 0.33], (*P*<0.0001) for vagotomy. Conclusions: Digestive tract physical reconstruction and vagus nerve preservation can reduce the morbidity of gallstones after gastrectomy. Total gastrectomy can add to the morbidity of galltones as does increasing the degree of lymph node dissection. There was no significant difference in gallstones with or without pylorus preservation.

Keywords: Gastric cancer - gastrectomy - gallstones - risk factors - meta-analysis

Asian Pac J Cancer Prev, **15 (2)**, 877-881

Introduction

The surgery is the preferred treatment method of gastric cancer. With the mature of surgical techniques and postoperative comprehensive treatment, the survival time of patients with gastric cancer was greatly extended after surgery; therefore, the postoperative complications have been paid more and more attention. In the follow-up, a portion of patients visited clinic again for gallstone, which seriously affected the life quality of patients (Segawa et al., 1991; Ikeda et al., 1995). In recent years, the gallstone occurrence after gastric cancer operation was extensively studied, researcher found that the gallstone occurrence was related to the following factors: whether cutting off vagus nerve, the dissection degree of lymph node, the scope of gastrectomy, the reconstruction way of digestive tract, whether pylorus-preserving, etc; however, some scholars still have different opinions. In our study, we used Meta-analysis to comprehensive quantitative analyze the research literature of postoperative gallstone of gastric cancer at home and abroad, explore their relationships and mechanisms, which provide a theoretical basis for the prevention and treatment of gallstones after gastric cancer operation.

Materials and Methods

Search strategy

We searched the clinical studies about postoperative gallstone occurrence of gastric cancer in the following database: Pubmed, Cochrane Library, Springer Link, Chinese Biomedical Literature and Wanfang database. The retrieval time was from 1990 to 2012. The key words were gastric cancer, gastrectomy, gastric resection, gallstones, gallbladder stone, cholecystolithiasis, digestive tract reconstruction, PPG, vagotomy and lymphadenectomy in Chinese and English.

Inclusion criteria

1) The clinical research on relationship of postoperative gallstone occurrence of gastric cancer and surgery method, and the gallstones were not detected pre-operation. 2) The researches are randomized controlled trials, cohort studies and case-control studies. 3) Literature data are accurate and reliable, and the number of cases or incidence which are associated with our study must be clearly recorded. 4) The follow-up time is at least one year.

Exclusion criteria

1) Animal experiments, review or case report. 2) If several articles are from the same institution or repetitive publication, we select the most detailed one. 3) The literatures which have little information, poor quality and lack of control group.

Data extraction

The data of included literatures were extracted by two independent reviewers: first author, published age,

*Department of Medical Quality Control, West China Hospital, Sichuan University, Chengdu, China *For correspondence: chenmin_hxyy@163.com*

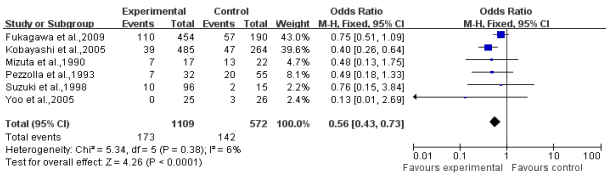

Figure 1. The Meta-analysis of Relation Between Postoperative Gallstone Occurrence and Digestive Tract Reconstruction

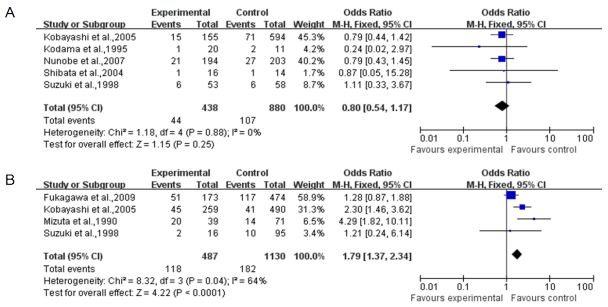

Figure 2. The Meta-analysis of Relation Between Pylorus-preserving or Gastrectomy Range and Postoperative Gallstone Occurrence. A.Pylorus-Preserving; B.Gastrectomy Range

research types, inclusion way (continuous inclusion or discontinuous inclusion), the number of cases and postoperative events (follow-up, etc.).

Quality assessment

According to Guyatt et al. (1994) and Maeso, et al. (2010) recommended evaluation method; we conducted quality assessment for included literatures.

Statistically analysis

The data were analyzed with RevMan 5.2 software. Firstly, the data were performed heterogeneity test, if the result was homogeneous, using the fixed effect model; if it was heterogeneity, using the random effect model. The evaluation indicators were analyzed with odds ratio (OR) and 95% confidence interval (CI). A *P* less than 0.05 was considered as statistically significant.

Results

Literature retrieval

According to the inclusion and exclusion criteria, we rejected the literature which didn't fit criterion, then 15 literatures (Mizuta et al., 1990; Pezzolla et al., 1993; Kodama et al., 1995; Wu et al., 1995; Hidetoshi et al., 1998; Furukawa et al., 1999; Shibata et al., 2004; Tomita et al., 2004; Akatsu et al., 2005; Kobayashi et al., 2005; Yoo et al., 2005; Nunobe et al., 2007; Kojima et al., 2008; Fukagawa et al., 2009; Sun et al., 2011) were included into this study, including 3 RCT articles, 5 cohort study articles and 7 case-control study articles. The number of cases is from 32 to 893 in the 15 articles.

Quality assessment of included literatures

All studies have raised a clear question; only three studies have pointed out randomized grouping, but no specific method; all studies have good follow-up, but the follow-up time was different, some patients exited the follow-up in some studies, but the proportion was in the range of error; only one study has clearly pointed out using blind method; 11 studies have compared the baseline characteristics in all groups, and the baseline characteristics of 2 studies was significantly different; the conventional treatment of 11 studies was similar except the interventions. Our evaluation showed that the included literatures had poor quality in general.

Digestive tract reconstruction

We divided the digestive tract reconstruction into physiological reconstruction group and non-physiological reconstruction group according to whether foods go through duodenal, including one RCT article (Yoo et al., 2005), one cohort study (Pezzolla et al., 1993) and four case-control studies (Mizuta et al., 1990; Hidetoshi et al., 1998; Kobayashi et al., 2005; Fukagawa et al., 2009) (Figure 1). We did heterogeneity tests for the included studies (P=0.38, I^2=6%), indicating that the homogeneity was excellent, then we analyzed the studies with fixed effect model, the pooled OR [95%CI] was 0.56 [0.43, 0.73], combined effect size had statistically significant (P<0.0001). The results showed that the incidence of postoperative gallstone in physiological reconstruction group was lower than that of non-physiological reconstruction.

Pylorus-preserving

We divided pylorus-preserving into two groups, including one RCT study (Kodama et al., 1995), two cohort studies (Shibata et al., 2004; Nunobe et al., 2007) and two case-control studies (Hidetoshi et al., 1998; Kobayashi et al., 2005) (Figure 2A). The heterogeneity test was (P=0.88, I^2=0%), indicating that the homogeneity was good, then we analyzed the studies with fixed effect model, the pooled OR [95%CI] was 0.80 [0.54, 1.17], combined effect size had statistically significant (P=0.01). The results showed that there was no significant difference between pylorus-preserving or not and incidence of postoperative gallstone.

Gastrectomy range

We analyzed the total gastrectomy and distal gastrectomy, a total of four case-control studies (Mizuta et al., 1990; Hidetoshi et al., 1998; Kobayashi et al., 2005; Fukagawa et al., 2009) were included in the analysis (Figure 2B). The heterogeneity test was (P=0.04, I^2=64%), there was heterogeneity, then we analyzed the studies with random effect model, the pooled OR [95%CI] was 2.0 [1.16, 3.45], there was significant different between combined effect size (P=0.25). The results showed that the incidence of postoperative gallstone in total gastrectomy was higher than that of distal gastrectomy.

Dissection degree of lymph node

We divided the dissection degree of lymph node into ≤D1 group and ≥D2 group, including three case-control studies (Wu et al., 1995; Akatsu et al., 2005; Fukagawa et al., 2009). The heterogeneity test was (P=0.001, I^2=85%),

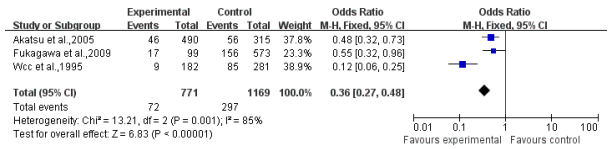

Figure 3. The Meta-analysis of Relation Between Dissection Degree of Lymph Node and Postoperative Gallstone Occurrence

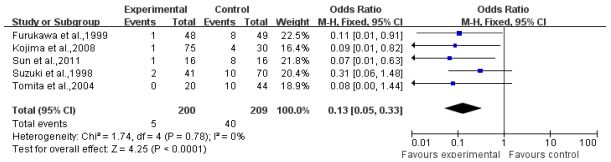

Figure 4. The Meta-analysis of Relation Between Vagus Nerve-Preserving and Postoperative Gallstone Occurrence

and there was greater heterogeneity, then we analyzed the studies with random effect model, the pooled OR [95%CI] was 0.33 [0.15, 0.75], and the combined effect size had statistically significant (P=0.008) (Figure 3). The results showed that the incidence of postoperative gallstone in dissection degree of lymph node ≤D1 group was lower than that of ≥D2 group.

Vagus nerve-preserving

We made grouping based on whether reserving vagus nerve, including one RCT study (Sun et al., 2011), two cohort studies (Furukawa et al., 1999; Tomita et al., 2004) and two case-control studies (Hidetoshi et al., 1999; Kojima et al., 2008) (Figure 4). The heterogeneity test was (P=0.78, I^2=0%), indicating that the homogeneity was good, then we analyzed the studies with fixed effect model, the pooled OR [95%CI] was 0.13 [0.05, 0.33], and the combined effect size had statistically significant (P<0.0001). The results showed that the incidence of postoperative gallstone in vagus nerve-preserving group was lower than that of vagus nerve-cutting off group.

Discussion

The physiological function of gallbladder is concentrating and storing bile from the liver. After eating, gallbladder does contractile activity through nerve and body fluid, discharge bile to duodenum, and participate in digestion. When the gallbladder function is affected and damaged, then intrahepatic cholestasis occurs, and it is prone to gallstone (Brix et al., 1998). Scholars detected the gallbladder motility function after gastrectomy, and measured the gallbladder volume in the fasting and fat meal with ultrasound scan, it was proved that the gallbladder systolic function was poorer in gastrectomy patients than that of normal control group, suggesting that gastrectomy can cause poor gallbladder function, cholestasis or even biliary sludge formation (Ao et al., 1990; Inoue et al., 1992; Hahm et al., 2000).

The motor function of gallbladder is regulated by a variety of humoral factors. Cholecystokinin (CCK) is a kind of peptide hormone released by intestinal mucosa typeI cells, secreted mainly by duodenum and jejunum andileum. CCK involves in gallbladder smooth muscle receptors to promote gallbladder discharge bile, and diastolic Oddis sphincter discharge bile into duodenum, participate in digestion. Bergh, et al showed that CCK secretion was significantly lower in gastrectomy patients than that of normal control group (Bergh and Meal 2003). Lu et al. (2003) made grouping in accordance with digestive tract reconstruction for gastrectomy patients, the authors gave test meal to patients and detected the gastrointestinal hormone levels, the results showed that CCK levels were significantly higher in patients of physiological reconstruction than that in patients of non-physiological reconstruction when the chyme passed duodenum. In our study, we also set up physiological reconstruction group and non-physiological reconstruction group and analyzed them with Meta software, the results showed that the incidence of postoperative gallstone in physiological reconstruction group was significantly lower than that of non-physiological reconstruction (P<0.0001), suggesting that physiological reconstruction method of digestive tract could reduce the incidence of postoperative gallstone. The mechanisms might be that when the digestive tract performed the non-physiological reconstruction, the chyme would directly go into the jejunum, which caused CCK secretion reduction, gallbladder dyskinesia, cholestasis and gallstone formation.

With the development of medical technology, the diagnosis rate of early gastric cancer has been greatly improved (Kodera et al., 2001; Moriwaki et al., 2003). How to reduce surgical trauma under the premise of removing tumor have attracted the attention, pylorus-preserving gastrectomy (PPG) has been widely applied (Morita et al., 2008). Pylorus-preserving could improve the postoperative life quality and reduce complications, which have been proved by clinical studies (Ikeguchi et al., 2010). It is usually considered that removing pylorus antrum could cause reduced gastric acid secretion and reduced gastrin levels, which affected bile secretion and resulted in change of bile composition, biliary salt precipitation, and it is prone to gallstone formation. Many studies indicated that the vagus nerve coeliac branch, hepatic branch and pyloric branch were easy to damage when removing pylorus, which might affect gallbladder function. In this study, we compared pylorus-preserving and pylorus-cutting off, the results showed that there was no significant difference between pylorus-preserving or not and the incidence of postoperative gallstone (P=0.25). Kodama, et al also showed that there was no significant difference of gallbladder motor function between pylorus-preserving group and traditional distal gastrectomy group (Kodama et al., 1995), suggesting that whether pylorus-preserving had no significant effect on the gallbladder motor function.

Our study retrieved one article about occurrence of gallstone after proximal gastrectomy (Fukagawa et al., 2009), but it can't be analyzed. So we only compared the total gastrectomy and distal gastrectomy, including four case-control studies, the pooled OR [95%CI] was 2.0 [1.16, 3.45], (P=0.01), indicating that the larger range of stomach resection, the more occurrence of postoperative gallstone. The reason might be that the residual stomach volume was decreased after gastrectomy, which reduced

the bile for digestion, so the excess bile formed siltation to form gallstone. In addition, in gastric cancer operation, the larger the scope of stomach resection, the greater damage to surrounding blood vessels, nerves and other tissues, which also might affect the postoperative gallbladder function. However, in our study, all the inclusion literatures were retrospective studies, their evidence was low level, and all studies only analyzed the total gastrectomy and distal gastrectomy, therefore, the conclusion still remains to be determined.

Wu, et al. (1995) reported that the higher the dissection degree of lymph node, the higher the incidence of gallstone]. In this study, only three case-control studies were included in the analysis, the results of Meta-analysis also showed that the dissection degree of lymph node was associated with postoperative gallstone. It is usually considered dissection of lymph node would damage surrounding nerves and blood vessels, especially the nerves which dominate biliary system, the higher dissection degree, the greater the damage; and this will affect the gallbladder motor function and cause gallstone. Some scholars believed that when the lymph node around gallbladder were dissected, it was easy to cause adhesions, resulting in influence on gallbladder evacuation motility. However, there was a high heterogeneity in combined analysis, and there were a few inclusion studies and all of them were retrospective analysis, the quality was poor.

Abdominal vagus nerves participate in the domination of abdominal organs, such as gallbladder, liver, pancreas and small intestine, etc. Vagus nerves dominate gallbladder movement and keep gallbladder tension. Stimulation of vagus nerve can promote gallbladder contraction and Oddis sphincter relaxation to excrete bile. Injury of vagus nerve in gastrectomy could cause Oddis sphincter tension increasing and gallbladder contraction weakness, therefore, the bile excretion was difficult, resulting in bile cholestasis and gallstone formation (Parkin et al., 1973; Ihasz M and Griffith, 2003). Which is consistent with our study, however, the heterogeneity of literatures was high, the reason is that the literatures are non-randomized and unblended studies, and the quality is poor.

In this study, the combined analysis showed that gastrointestinal physiological reconstruction and vagus nerve-preserving could reduce the incidence of postoperative gallstone; the total gastrectomy increased the incidence of gallstone; and the gallstone increased with the improvement of lymph node dissection. However, our study still has shortcomings: overall, the literatures were undergrade. In the 17 articles, although the follow-up was good, the follow-up time was not consistent; the majority adopted non-randomized and unblended study; half of the literatures didn't compare the baseline characteristics of each group, and another half of the literatures compared the baseline characteristics, but there were significant differences among groups; there were differences between clinical treatments. Therefore, the bias is inevitable, and the conclusion of our study will be restricted. It still needs more randomized controlled studies to evaluate comprehensively and objectively the related factors of gastrectomy and postoperative gallstone.

References

Akatsu T, Yoshida M, Kubota T, et al (2005). Gallstone disease after extended (D2) lymph node dissection for gastric cancer. *World J Surg*, **29**, 182-6.

Ao YF, Chen SJ, Zhang ZS (1990). The clinical investigation of the gallbladder contraction function after perioperative. *Chinese Journal of Surgery*, **28**, 386-9.

Bergh C, Meal S (2003). Satiety and cholecystokinin in gastrectomized humans . *Physiol behav*, **78**, 143-7.

Brix TH, Christensen K, Holm NV, Harvald B, Hegedüs L (1998). A population-based study of Graves' disease in Danish twins. *Clin Endocrinol (Oxf) JT*, **48**, 397-400.

Fukagawa T, Katai H, Saka M, et al (2009). Gallstone formation after gastric cancer surgery. *J Gastrointest Surg*, **13**, 886-9.

Furukawa H, Hiratsuka M, Imaoka S, et al (1999). Phase II study of limited surgery for early gastric cancer: segmental gastricresection. *Ann Surg Oncol*, **6**, 166-70.

Guyatt GH, Sackett DL, Cook DJ (1994). Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for mypatients? Evidence-Based Medicine Working Group. *JAMA*, **271**, 59-63.

Hahm J, Park J, Cho Y, et al (2000). Changes in gallbladder motility in gastrectomized patients. *Korean J Intern Med JT*, **15**, 19-24.

Hidetoshi S, Yasunori M, Kageyoshi S, et al (1998). Evaluation of the vagus preserving gastrectomy aiming at prevention of postgastrectomy gallstone formation. *Jpn J Gastroenterol Surg*, **31**, 813-8.

Ihasz M, Griffith CA (2003). Gallstones after vagotomy, *Am J Surg*, **141**, 246-7.

Ikeda Y, Shinchi K, Kono S, Tsuboi K, Sugimachi K (1995). Risk of gallstones following gastrectomy in Japanese men. *Surg Today*, **25**, 515-8.

Ikeguchi M, Hatada T, Yamamoto M, et al (2010). Evaluation of a pylorus-preserving gastrectomy for patients preoperatively diagnosed with early gastric cancer located in the middle third of the stomach. *Surg Today*, **40**, 228-33.

Inoue K, Fuchigami A, Higashide S, et al (1992). Gallbladder sludge and stone formation in relation to contractile function after gastrectomy. A prospective study. *Ann Surg*, **215**, 19-26.

Kobayashi T, Hisanaga M, Kanehiro H, et al (2005). Analysis of risk factors for the development of gallstones after gastrectomy. *Br J Surg*, **92**, 1399-403.

Kodama M, Koyama K, Chida T, Arakawa A, Tur G (1995). Early postoperative evaluation of pylorus-preserving gastrectomy for gastric cancer. *World J Surg*, **19**, 456-60; discussion 461.

Kodera Y, Yamamura Y, Kanemitsu Y , et al (2001). Lymph node Metastasis in cancer of the middle-third stomach: criteria for treatment with a pylorus-preserving gastrectomy.*Surg Today*, **31**, 196-203.

Kojima K, Yamada H, Inokuchi M, Kawano T, Sugihara K (2008). Functional evaluation after vagus-nerve-sparing laparoscopically assisted distal gastrectomy. *Surg Endosc*, **22**, 2003-8.

Lu HS, Zhang JZ, Wu XY (2003). A Prospective Randomized Study on the Method of Reconstruction after Total Gastrectomy.*Journal of Surgery Concepts and Practice*, **8**, 379-82.

Maeso S, Reza M, Mayol JA, et al (2010). Efficacy of the Da Vinci surgical system in abdominal surgery compared with that of laparoscopy: a systematic review and Meta-analysis. *Ann Surg*, **252**, 254-62.

Mizuta T, Ishihara Y, Saito A, et al (1990). The Includence and Clinical Significance of Cholelithiasis after Gastrectomy. *Japanese journal of gastroenterological surgery*, 23, 2232-7.

Morita S, Katai H, Saka M, et al (2008). Outcome of pylorus-preserving gastrectomy for early gastric cancer. *Br J Surg*, **95**, 1131-5.

Moriwaki Y, Kunisaki C, Kobayashi S, et al (2003). Progressive improvement of prognosis for patients with gastric cancer (dynamic stage grouping) with increasing survival interval from initial staging: how much longer can a given survivor expect to live? *Surgery*, **133**, 135-40.

Nunobe S, Sasako M, Saka M, et al (2007). Symptom evaluation of long-term postoperative outcomes after pylorus-preserving gastrectomy for early gastric cancer. *Gastric Cancer*, **10**, 167-72.

Parkin GJS, Smith RB, Johnston (1973). Gallbladder volume and contractility after truncal, selective and highly selective (parietal-cel1) vagotomy in man. *Ann Surg*, **178**, 581.

Pezzolla F, Lantone G, Guerra V, et al (1993). Influence of the method of digestive tract reconstruction on gallstone development after total gastrectomy for gastric cancer. *Am J Surg*, **166**, 6-10.

Segawa K, Niwa Y, Arisawa T, et al (1991). The prevalence of gallstones in gastrectomized patients: a comparative study in a large population. *Jpn J Med*, **30**, 424-9.

Shibata C, Shiiba KI, Funayama Y, et al (2004). Outcomes after pylorus-preserving gastrectomy for early gastric cancer: a prospective multicenter trial. *World J Surg*, **28**, 857-61.

Sun PD, Cao H, Zhu JM (2011). Value of radical dissection with vagus nerve preservation for proximal gastric cancer.*Chines Journal of Gastrointestinal Surgery*, **14**, 117-9.

Tomita R, Tanjoh K, Fujisaki S (2004).Total gastrectomy reconstructed by interposition of a jejunal J pouch with preservation of hepatic vagus branch and lower esophageal sphincter for T2 gastric cancer without lymph node Metastasis.*Hepatogastroenterology*, **51**, 1233-40.

Wu CC, Chen CY, Wu TC, Iiu TJ, P'eng PK (1995). Cholelithiasis and cholecystitis after gastrectomy for gastric carcinoma: acomparison of lymphadenectomy of varying extent. *Hepatogastroenterology*, **42**, 867-72.

Yoo CH, Sohn BH, Han WK, Pae WK (2005). Proximal gastrectomy reconstructed by jejunal pouch interposition for upper third gastric cancer: prospective randomized study. *World J Surg*, **29**, 1592-9.