Related factors of postoperative gallstone occurrence of gastric cancer-a Meta analysis

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Abstract: To investigate the risk factors of gallstone occurrence after gastrectomy in gastric cancer patients. PubMed, Web of Science, The Cochrane Library, EMBASE, and CINAHL and thewww.clinicaltrial.gov database on ongoing clinical trials were searched to identify all the RCTs investigating gallstone occurrence incidence in gastric cancer patients after gastrectomy. The risk of bias of the original studies was assessed. The data were analyzed using Review Manager 5.2 software. The meta analysis result shown that there was a significant difference between hysiological reconstruction group and non-physiological reconstruction group. (95%CI:0.53 [0.41, 0.68], *P*<0.0001), no significant difference between pylorus-preserving and no pylorus-preserving groups.(95%CI: 0.80 [0.54, 1.17], P=0.25). Moreover, the meta analysis shown incidence of gallstone in laparoscopy-assisted distal gastrectomy group was lower compare to total gastrectomy group. (95%CI: 2.00 [1.16, 3.45], P=0.01), and occurrence of gallstone after gactric operation in ≤D1 group was lower than that in ≥D2 group (95%CI: 0.33 [0.15, 0.75], P=0.008). The meta analysis result shown that the gallstone occurrence rate in vagus nerve-preserving group was lower than that in no-vagus nerve reservation group. (95%CI:0.13 [0.05, 0.33], P<0.0001). Threfore, our meta analysis shown that physiologic digestive tract reconstruction and vagus nerve preservation reduced gallstones occurrence after gastrectomy. Moreover, total gastrectomy and extensive lymph node dissection increased the occurrence. There was no significant difference in the occurrence of gallstones whether there was pylorus preservation or not.

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1. Introduction

As we know, the gallstone has been reported as one of the most common complications after gastrectomy. (Hauters et al.,1988;. Wu et al.,1995) The gallstone disease after gastrectomy may be relative to lithogenic change in bile juice and gallbladder physiological change, all which may be caused by lots of surgical procedures, including gastric resection, intestinal reconstruction and vagotomy.(Takeo et al., 2009) The patients with asymptomatic gallstones were advised to undergo cholecystectomy, but several long term researches changed this consensus. Asymptomatic gallstones patients have a low rate serious biliary symptoms.(Tomotaka et al.,2005)

Gastric cancer is an serious disease and threatens seriously people life health. For example, the incidence of early gastric cancer has been increasing for decades, reaching nearly 60% in Japan.(Souya et al., 2007). The prognosis of patients with gastric cancer is known to be excellent, with five years survival rates exceeding 90%.(Kazuyuki et al.,2008) The focus of interest in the treatment of gastric cancer has shifted to minimally invasive treatments and improvement in the quality of life after gastrectomy without impairment to the excellent prognosis. Lots of minimally invasive treatments recently introduced include endoscopic mucosal resection, endoscopic submucosal dissection,laparoscopic surgery and limited resection by open surgery.(Kazuyuki et al,2008)Therefore, the surgical resection is still the main treatment for it.

Gallstones are strongly associated with increased risk of biliary tract cancers, including gastric cancer. (World Cancer Research Fund, 2007; Hsing et al., 2007) However, the relationship between it and digestive system cancers outside of the biliary tract is not well established. As we know, gallstones is the second most common disease of gastrointestinal discharge diagnosis in USA in 2009, over 300,000 physician visits 2009 year. Gallstones is associated with the imflammation of gallbladder, liver, pancreas and other biliary tract system.(Fukuma et al.,1996) Although cholecystectomy can reduce the inflammatory status of gallstones, it may also increase the exposure of the stomach, which may be influence the digestive system cancer risk.

In this meta analysis, we evaluated the the association of gallstone with after gastrectomy in patients with gastric cancer.

2. Methods

2.1 Searching methods

A systematic search of articles published during 1990 to 2012 were performed in PubMed, Web of Science, The Cochrane Library, EMBASE, and

CINAHL and the www.clinicaltrial.gov database to identify relevant RCTs using the search teams of "gastric cancer", "gastric carcinoma', "gastrectomy", "gastric operation", "gastric resection", "galltones", "gallbladder stone", "digestive tract reconstruction", "vagotomy", "lymphadenectomy" and "cholecystolithiasis". After a article was found, we check the abstract, full text and all references, two reviews were hand searched for additional eligible studies. All references cited in the original studies or review articles concerning the relevant topic were retrieved to broaden the search for relevant publications. Literature screening was independently performed by two reviewers. The all included studies are no language restriction.

2.2Data extraction

Two authors independently extracted the following from the included studies: name of the first author, publication year of the article, country or area, number of patients and outcomes. In addition, the response taccording to researching type and the hazard ratios (HRs) for overall survival (OS) and their 95% confidence intervals (CIs) were collected for statistical analyses. Full-text versions of potentially relevant papers identified in the initial screening were retrieved. If multiple articles from the same study were found, only the article with the longest follow-up period was included. Data concerning study design, participant characteristics, interventions, and outcome measures were independently extracted. We contacted the authors of the primary reports to request any unpublished data. If the authors did not reply, we used the available data for our analyses. Any discrepancies were resolved through discussion or consultation with a third person.

2.3 Quality assessment

Quality assessment of included literatures was performed as follow: (Table 1).

Table 1. The quality assessment table of included literatures

(1) Objective: Is the study for answering a clear purpose question?
(2) Randomization: Are the patients randomly assigned to each group?
(3) Follow-up: Whether registering the number of patients in the beginning of the study? Is the end time of study clear?
(4) Blind method: Do the patients and researches know the therapeutic intervention program?
(5) Baseline characteristics: Are the general characteristics similar in each group at the beginning of the study?
(6) Intervention: In addition to the interventions, are the conventional treatments similar in each group?

2.4 Data analysis and statistical methods

Statistical analyses were performed with Review manager version 5.2 software (The Cochrane Collaboration). The heterogeneity of trail outcome among RCTs was assessed by $\chi 2$ test ($p< 0.1$ was defined as a significant heterogeneity) or I2 test. The publication bias was assessed by examining the funnel plot. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for all primary and secondary outcomes were calculated by Mantel-Haenszel fixed-effect model (FEM) if there was no statistical heterogeneity; otherwise, the DerSimonian-Laird random effects model (REM) was used. Each study was pooled with a fixed- or random-effect model based on heterogeneity.

3. Results

3.1 Literature characters

As shown in Figure 1, after searching, total 16 articles (Rezzolla et al.,1993;Kobayashi et al., 2005; Fukagawa et al.,2009; Yoo et al.,2005;Suzukin et al., 1998; Mizuta et al.,1990; Shibata et al.,2004; Kodama et al.,1995;Nunobe et al., 2007; Wcc et al.,1995; Akatsu et al.,2005; Sun et al., 2011; Tomita et al.,2004; Furukawa et al.,1999; Kojima et al.,2008; Zhang et al., 2011) involving in 4373 cases were included into this meta analysis.More details could be find Figure 1 and Table 2.

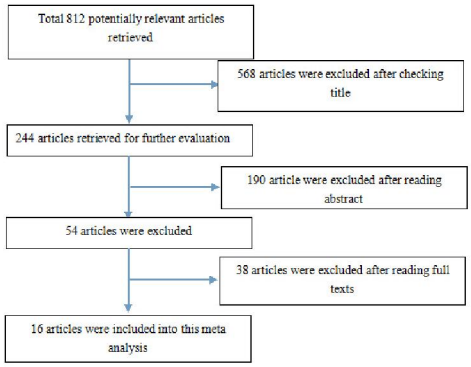

Fig 1. Flow diagram of the process of selecting RCTs reviewed.

Table 2. General data of inclusion articles.

Author	Published years	Research type	consecutive patients	cases	lost to follow up
Pezzolla F[(1993)]	1993	Cohort study	YES	102	YES
Kobayashi T[(2005)]	2005	case-control study	YES	749	NO
Fukagawa T[(2009)]	2009	case-control study	YES	893	YES
Yoo CH[(2005)]	2005	Randomized Controlled Trial	YES	51	NO
Suzuki Hidetoshi[(1998)]	1998	case-control study	YES	111	NO
Mizuta Tetsuaki[(1990)]	1990	case-control study	YES	110	NO
Shibata C[(2004)]	2004	Cohort study	YES	74	YES
Kodama M[(1995)]	1995	Randomized Controlled Trial	YES	64	YES
Nunobe S〔2007〕	2007	Cohort study	YES	441	YES
Wcc〔1995〕	1995	case-control study	YES	463	NO
Akatsu T〔2005〕	2005	case-control study	YES	805	NO
Sun DP〔2011〕	2011	Randomized Controlled Trial	YES	32	NO
Tomita R〔2004〕	2004	Cohort study	YES	64	NO
Furukawa H〔1999〕	1999	Cohort study	YES	97	NO
Kojima K〔2008〕	2008	case-control study	YES	105	NO
Zhang J[2011]	2011	Cohort study	YES	212	NO

3.2 Quality assessment of included articles

As shown in Table 3, we found that three included articles were randomization study, and all papers had follow-up results, most papers had baseline characteristics, however, only one paper was blind study. More details can be found in Table 3.

Table 3. Quality evaluation.

	AIM	randomization	Follow-up	blind	Baseline characteristics	intervene
Pezzolla F	+	—	+	—	+	+
Kobayashi T	+	—	+	—	—	—
Fukagawa T	+	—	+	—	—	—
Yoo CH	+	+	+	+	+	+
Suzuki Hidetoshi	+	—	+	—	—	—
Mizuta Tetsuaki	+	—	+	—	—	—
Shibata C	+	—	+	—	+	+
Kodama M	+	+	+	—	+	+
Nunobe S	+	—	+	—	+	+
Wcc	+	—	+	—	+	+
Akatsu T	+	—	+	—	+	+
Sun DP	+	+	+	—	+	+
Tomita R	+	—	+	—	+	+
Furukawa H	+	—	+	—	+	+
Kojima K	+	—	+	—	+	+
Zhang J	+	—	+	—	+	+

+: description in the articles;—: no description in the articles.

3.3 Meta analysis results

3.3.1 Gastrectomy region

Total gastrectomy and laparoscopy-assisted distal gastrectomy methods in relation to gallstone occurrence were performed in here.The heterogeneity test (I^2= 64%) shown that the random model should be used in here. The meta analysis shown incidence of gallstone in laparoscopy-assisted distal gastrectomy group was lower compare to total gastrectomy group.(95%CI: 2.00 [1.16, 3.45], P=0.01)(Fig 1)

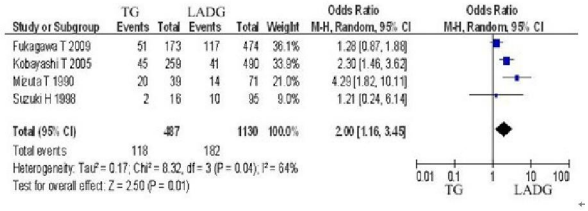

Fig 1. A meta-analysis of gallstone occurrence in total gastrectomy and laparoscopy-assisted distal gastrectomy groups. TG: total gastrectomy; LADG: laparoscopy-assisted distal gastrectomy.

3.3.2 Digestive tract reconstruction

As shown in Fig 2, theterogeneity tests (I^2=23%) indicated that Fixed effect model should be used in here. The meta analysis result shown that there was a significant difference between hysiological reconstruction group and non-physiological reconstruction group.(95%CI:0.53 [0.41, 0.68], *P*<0.0001). group was lower than that of non-physiological reconstruction.

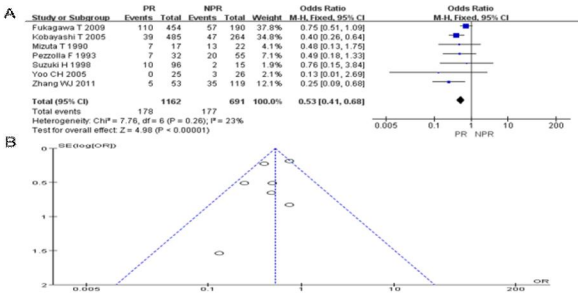

Fig 2. A. A meta-analysis of gallstone occurrence in physical reconstruction method and no physical reconstruction method groups. B. Funnel plot for gallstone occurrence in physical reconstruction method and no physical reconstruction method groups PR: physical reconstruction; NPR: no physical reconstruction.

3.3.3 Lymph node Dissection

As shown in Figure 3, the association of incidence of gallstone with ≤D1 group or ≥D2 group were evaluated in here. The heterogeneity test result(I^2=85%) shown that the random model was used in here. The meta analysis result indicated that occurrence of gallstone after gactric operation in ≤D1 group was lower than that in ≥D2 group (95%CI: 0.33 [0.15, 0.75],P=0.008).

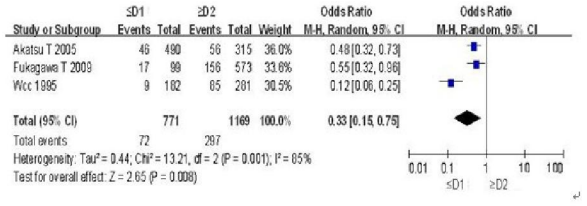

Fig 3. A meta-analysis of gallstone occurrence in different lymph node dissection degree.

3.3.4 Pylorus-preserving

As shown in Figure 4, five papers were included into here. The heterogeneity test(I^2= 0%) indicated that the fixed model was used in here. The meta analysis result showed that there was no significant difference between pylorus-preserving and no pylorus-preserving groups.(95%CI: 0.80 [0.54, 1.17], P=0.25).

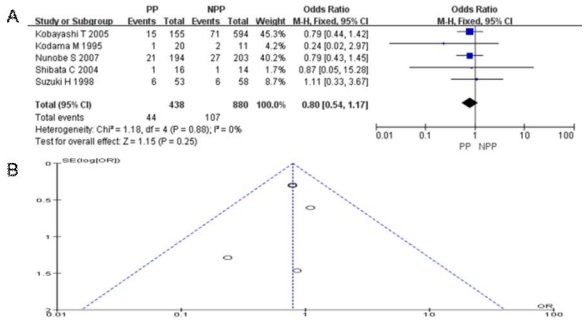

Fig 4. A meta-analysis of gallstone occurrence in pylorus-preserving and no pylorus-preserving groups. B. Funnel plot for gallstone occurrence in pylorus-preserving and no pylorus-preserving groups. PP: pylorus-preserving; NPP: no pylorus-preserving.

3.3.5 Vagus nerve-preserving

In here, we evaluated the relation of vagus nerve reservation with gallstone occurrence compared to no-vagus nerve reservation group. The heterogeneity test result(I^2=0%) shown that we should used the fixed model in here. The meta analysis result shown that the gallstone occurrence rate in vagus nerve-preserving group was lower than that in no-vagus nerve reservation group. (95%CI:0.13 [0.05, 0.33], P<0.0001).(Fig 5)

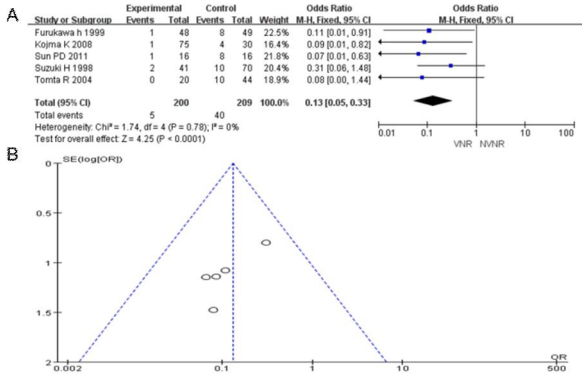

Fig 5. A meta-analysis of gallstone occurrence in vagus nerve reservation and no vagus nerve reservation groups. B.Funnel plot for gallstone occurrence in vagus nerve reservation and no vagus nerve reservation groups. VNR: vagus nerve reservation; NVNR: no vagus nerve reservation.

4. Discussion

In this meta analysis, we reported that there were significant differences in hysiological reconstruction group,aparoscopy-assisted distal gastrectomy, ≤D1 and vagus nerve-preserving groups, but no pylorus-preserving and total gastrectomy group.

The incidence of gallstones 5 and 10 years after gastrectomy was 13.6 and 22.1 per cent respectively in this study, compared with a 5-year incidence of 3.3 and 7.7 per cent in men and women respectively in a general population aged 60 years in Denmark7, and a 10-year incidence of 6.3 per cent in a general population of women in Italy. (Kobayashi et al., 2005. Jensen et al.,1991. Angelico et al.,1997; Turunen et al., 1964. Horwitz et al., 1965. Sapala et al., 1979). The incidence of gallstones depended on the extent of gastrectomy. It is speculated that complete amputation of the vagal trunk with dissection of the oesophagus (as in total gastrectomy) has a great influence on the contractile ability of the gallbladder.

To prevent these disorders, preservation of the autonomic nerves has been introduced in conventional open gastrectomy for early gastric cancer (Asao et al., 2004). Recently, this autonomic nerve preservation has been combined with laparoscopic gastrectomy because laparoscopic surgery has the advantage of a magnified view that allows clear identification of the nerve branches. However, increasing surgical experience and technical innovations have extended the indications for the laparoscopic approach. In the study by Kwon et al., the conversion rate from laparoscopic to open surgery was 10% and the overall complication rate was 14% in patients with a previous gastrectomy who underwent laparoscopic cholecystectomy. (Kwon et al., 2001). Thus, laparoscopic cholecystectomy is currently performed more frequently for gallstones after gastrectomy, provided that the patients are selected properly and appropriate caution is exercised.

Gallstone formation without any symptoms is often observed, but not treated by cholecystectomy. However, we always performed cholecystectomy simultaneously with gastric cancer surgery for existing gallstones even asymptomatic ones because of our concern with postoperative acute cholecystitis resulting from bile juice stagnation and infection. In contrast, many gallstones formed after gastrectomy do not cause severe symptoms requiring further surgery, as shown by the results of this study in which only 12 of 173 patients (6.9%) with gallstone formation underwent an operation for gallstones subsequent to gastric cancer surgery. Accordingly, prophylactic cholecystectomy is unnecessary for the large majority of patients who undergo gastric case surgery, but in cases of extended lymph-node dissection, such additional surgical treatment seem necessary, given the high frequency of gallstone formation following gastrectomy.

The types of gastrectomy and reconstruction did not significantly differ between the D1 and D2 dissection groups. In addition, none of the patients had a history of prolonged intake of certain medications such as oral contraceptives or aspirin. Csendes et al. prospectively evaluated the effect of selective hepatic vagotomy on the formation of gallstones, and reported that 41% of such cases developed gallstones 3 to 5 years after surgery (Csendes et al.,1978). Hepatic vagotomy has been believed to be an important cause of gallstone formation. However, in the present study, the hepatic vagal nerves were transected not only in the D2 dissection group but also in the D1 dissection group. Therefore, there may be other factors associated with an increased risk of gallstones after D2 dissection.llstones after D2 dissection.

Despite the location of tumors, D2 dissection requires removal of the lymph nodes around the common hepatic artery and the celiac artery (Japanese Gastric Cancer Association). This procedure is accompanied by transection of the retroperitoneal sympathetic and parasympathetic nerves from the celiac ganglion. Gallbladder function is regulated not only by the hepatic vagal nerves but also by the retroperitoneal sympathetic and parasympathetic nerves. Thus, destruction of the retroperitoneal sympathetic and parasympathetic nerves may, at least partially, facilitate gallstone formation after D2 dissection.

In this meta analysis, the results shown that there were significant differences in hysiological reconstruction group,aparoscopy-assisted distal gastrectomy, ≤D1 and vagus nerve-preserving groups, but no pylorus-preserving and total gastrectomy group.

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