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Application of laparoscopic surgery in gallbladder carcinoma

Laparoscopic surgery in GC

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Abstract

Gallbladder carcinoma is a rare type of cancer of the digestive system, with an incidence that varies by region. Surgery plays a primary role in the comprehensive treatment of gallbladder carcinoma and is the only known cure. Compared with traditional open surgery, laparoscopic surgery has the advantages of convenient operation and magnified field of view. Laparoscopic surgery has been successful in many fields, including gastrointestinal medicine and gynecology. The gallbladder was one of the first organs to be treated with laparoscopic surgery, and laparoscopic cholecystectomy has become the gold standard surgical treatment for benign gallbladder diseases. However, the safety and feasibility of laparoscopic surgery for patients with gallbladder carcinoma remain controversial. Over the past several decades, research has focused on laparoscopic surgery for gallbladder carcinoma. The disadvantages of laparoscopic surgery include a high incidence of gallbladder perforation, possible port site metastasis, and potential tumor seeding. The advantages of laparoscopic surgery include less intraoperative blood loss, shorter postoperative hospital stay, and fewer complications. Nevertheless, studies have provided contrasting conclusions over time. In general, recent research has tended to support laparoscopic surgery. However, the application of laparoscopic surgery in gallbladder carcinoma is still in the exploratory stage. Here, we provide an overview of previous studies, with the aim of introducing the application of laparoscopy in gallbladder carcinoma.

Key Words: Gallbladder carcinoma; Laparoscopic surgery; Open surgery; Gallbladder perforation; Port site metastases; Prognosis

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Core Tip: Gallbladder carcinoma is a rare cancer of the digestive system. Surgery is the main treatment strategy for this disease. The gallbladder was one of the first organs to

undergo laparoscopic surgery. However, the safety and feasibility of laparoscopic surgery in patients with gallbladder carcinoma remain controversial. The disadvantages and advantages of laparoscopic surgery have been reported by different studies. In general, recent studies have tended to support laparoscopic surgery by experienced surgeons in selected patients. Clinical research with high-level evidence is required to validate the existing conclusions.

INTRODUCTION

Since the second half of the last century, noncommunicable diseases have replaced infectious diseases as the main global health concern^[1]. Specifically, over 75% of premature deaths among individuals aged 30–70 years are caused by noncommunicable diseases^[1]; cardiovascular disease and cancer are the main culprits. Based on current trends, cancer is expected to surpass cardiovascular diseases and become the leading cause of premature death during this century^[2]. More than 80% of all countries have formulated cancer control plans; however, detailed evidence-based programs that are tailored to resource levels remain lacking^[3]. Digestive system tumors, such as gastric and colon cancer, account for a high proportion of the global cancer incidence and mortality rates^[4, 5]. Gallbladder carcinoma (GC) is a relatively rare gastrointestinal tumor. According to the 2018 global cancer estimates of incidence and mortality, its morbidity and mortality rates account for 1.2% and 1.7% of all tumors, ranking 22nd^[5]. In the 2020 edition, the incidence and mortality rate account for 0.6% and 0.9% of all tumors, ranking 25th^[4]. Furthermore, the incidence of GC varies greatly by country and region^[6]. For example, in China, where the incidence is high, an estimated 30–50 thousand new cases and 25–40 thousand deaths occur annually^[7, 8], while in the United States, where the incidence is low, an estimated 4–10 thousand new cases and 2–4 thousand deaths occur each year^[8, 9]. The therapeutic outcome of GC remains unsatisfactory, with a median survival time of approximately 25 mo after curative resection^[10, 11]. Surgery is the only potential cure for GC^[6, 11], and selecting a reasonable surgical extent and approach for individual patients is crucial. Moreover, laparoscopic

technology has developed rapidly since its application in the field of surgery^[12-15], and favorable outcomes of laparoscopic surgery for GC have been achieved^[16-18]. However, the safety and feasibility of laparoscopic surgery for patients with GC remain controversial^[19]. The present study aims to review the changes in tumor staging of GC, the application of laparoscopic techniques in surgery, and the advantages and disadvantages of laparoscopic surgery for GC, to analyze the safety and effectiveness of laparoscopic surgery for patients with GC.

TUMOR STAGING OF GC

Tumor staging is vital to determine the subsequent ⁷ treatment and prognosis. The American Joint Committee on Cancer (AJCC) cancer staging system is the most commonly used and widely accepted tumor staging system. The AJCC stages GC according to the depth of tumor invasion, lymph node status, and distant metastases^[20]. Specifically, T staging is based mainly on the depth of invasion of the gallbladder wall, as well as the direct invasion of the liver and other surrounding organs (Table 1). N staging is based primarily on the number of positive lymph nodes (Table 2), and M staging is based on the presence or absence of distant metastases. However, GC staging differs significantly between the 7th and 8th editions of the AJCC. The changes are based on the biological behavior and prognosis of different tumor stages. Identifying the stage of the tumor and the content of the stage change is crucial for the selection of appropriate treatment, especially when deciding whether the tumor is suitable for laparoscopic surgery.

Two main changes were made from the AJCC 7th edition to the AJCC 8th edition of GC tumor staging. First, the T2 stage has been further classified according to the tumor location as T2a (peritoneal side) and T2b (hepatic side). T2b exhibits a worse prognosis than T2a^[21]. Second, N staging is no longer based on the location of lymph node metastases, but rather on the number of lymph node metastases, which is correlated with the prognosis^[22]. These changes have practical implications for laparoscopic surgery in patients with GC. For example, no-touch radical excision is more feasible for

T2a tumors than T2b tumors. Moreover, at least six lymph nodes must be resected and evaluated^[23, 24], including in laparoscopic surgery.

APPLICATION OF LAPAROSCOPIC TECHNIQUE IN SURGERY

The advent of laparoscopy has revolutionized surgery. Compared with traditional open surgery, laparoscopic surgery has the advantages of convenient operation and a magnified field of view. It allows surgeons to see the details of the interior of the abdominal cavity, providing better operating conditions. Surgeons can perform a variety of complex operations by manipulating various movements of the sticks, avoiding blood stains on the gloves and direct contact of hands and organs. Additionally, for patients, the long scar on the abdomen from open surgery is replaced by a few small holes, which facilitates physical and psychological recovery. Laparoscopic techniques have been successful in most aspects of surgery. For example, for laparoscopic gastrectomy, numerous clinical studies have reported no differences from open surgery in postoperative complications, mortality, and oncological outcomes^[25-28]. Laparoscopic gastrectomy leads to less blood loss, shorter hospital stays, and faster return of bowel function, at the expense of longer operation times. Due to the short- and long-term advantages, laparoscopic gastrectomy has been recommended in many national guidelines^[29]. Moreover, laparoscopic liver resection has demonstrated better surgical outcomes, such as duration of hospitalization and postoperative complication rates, with similar overall survival and disease-free survival times, compared with open liver resection^[30]. Due to the widespread application of laparoscopic liver resection, the International Laparoscopic Liver Society was formed in 2016 by a group of experts^[31]. Single-incision and robot-assisted technology are also available for minimally invasive liver surgery^[32, 33]. Additionally, laparoscopic techniques have achieved great success in the treatment of adrenal, prostate, and rectal diseases, among others^[34-36]. For some established laparoscopic procedures, such as cholecystectomy, different methods and port numbers have been reported^[37]. Laparoscopic surgery has also been combined with endoscopic techniques to treat

concomitant gallstones and common bile duct stones, early gastric cancer, gastrointestinal stromal tumors, and other diseases^[38-40]. Compared with its relatively established application in gastrointestinal surgery, the application of laparoscopic surgery in GC is still in the exploratory stage.

LAPAROSCOPIC SURGERY FOR GC

The gallbladder was one of the first organs to undergo laparoscopic surgery. Mühe performed the first laparoscopic cholecystectomy (LC) in 1985, and Dubois began to regularly perform LC by 1988^[41]. Thereon, the application of laparoscopic techniques in benign diseases of the gallbladder developed quickly, and LC has become the gold standard treatment for gallstones, gallbladder polyps, and other benign diseases. However, the application of laparoscopy in GC is far inferior to that in gastrointestinal tumors. The limitations include the clarity of the endoscopic field of view, the convenience of operation, and most importantly, the principles of no-touch surgery. Nevertheless, research over the past several decades has focused on laparoscopic surgery for GC.

Research before 2000

Since the application of LC, the safety of this operation has gained attention. The two major risks of laparoscopy for GC include gallbladder perforation and port site metastasis. As the gallbladder serves as a temporary storage site for bile, intraoperative perforation must be avoided. Sarli *et al*^[42] performed a matched cohort analysis involving 1,127 patients who underwent LC. Intraoperative gallbladder perforation occurred in more than 10% of patients (131/1127), and the only risk factor associated with gallbladder perforation was the surgeon's experience. Moreover, a study in Italy of 350 consecutive patients who underwent LC at the authors' hospital revealed that chronic cholecystitis, gallbladder hydrops, and a history of previous laparotomies were risk factors for gallbladder perforation during surgery^[43]. Specifically, the probability of intraoperative gallbladder perforation was 3.5% among patients with no risk factors

and up to 25% among those with all risk factors. Accidental bile spillage induced by gallbladder perforation during surgery may result in tumor implantation and metastasis, which is one of the greatest concerns of laparoscopic surgery for GC. With the widespread application of laparoscopic technology in gastroenterology and gynecology, whether laparoscopic surgery could result in tumor seeding in patients with GC and other abdominal tumors has been studied. A questionnaire study from Germany, Switzerland, and Austria including 117,840 patients that underwent LC (including 409 cases of incidental GC) and 412 patients that underwent laparoscopic colorectal procedures found that 109 patients experienced tumor recurrence^[44]. Thus, laparoscopic surgery for cancer exhibited a higher rate of abdominal wall metastasis than that of open surgery, and the use of plastic retrieval bags and an intact tumor specimen did not eliminate the possibility of port site recurrence. Furthermore, Z'graggen *et al*^[45] studied 37 patients with preoperatively unknown gallbladder adenocarcinoma and found that these patients had a high rate of port site recurrence, which increased in cases of gallbladder perforation. Additionally, a national, multicenter study from Sweden involving data from 30 hospitals, including 11,976 LCs, found that, of 447 patients with GC, 270 had their gallbladder removed, 55 underwent laparoscopic surgery, and 9 exhibited port site metastasis^[46]. The researchers inferred that port site metastases are common and recommended open surgery in cases of suspected GC. In addition to gallbladder perforation and port site metastasis, pneumoperitoneum is also expected to be associated with poor prognosis^[44]. For these reasons, many researchers have proposed that laparoscopic surgery is more appropriate for patients with early-stage GC. In addition, Wibbenmeyer *et al*^[47] identified 9 patients with GC out of 928 patients who underwent cholecystectomy and reported that this procedure was suitable for patients with GC confined to the mucosa. Overall, early studies on laparoscopic surgery for GC focused primarily on the risks of laparoscopic technology.

Research from 2000 to 2010

After a period of application, the focus of research on laparoscopic surgery for GC shifted from the risks of surgery to the changes in the treatment of GC. However, intraoperative gallbladder perforation remained an issue. A Japanese survey of 498 patients with GC revealed that approximately 20% of patients who underwent LC experienced gallbladder perforation during surgery, and their survival rate was significantly lower than those without gallbladder perforation^[48]. Recommendations have also been made for unsuspected GC after LC. Steinert *et al*^[49] reviewed the studies regarding GC and LC and recommended a radical procedure and additional port site excision after a postoperative diagnosis of stage $\geq T2$ GC. A study from Japan identified 9 patients with unsuspected GC from a cohort of 1,663 patients who underwent LC^[50]. Five of the nine patients experienced tumor recurrence and died 4–37 mo after the initial operation. As a result, the authors emphasized the importance of preventing bile spillage. The widespread popularization of LC has also promoted the diagnosis and treatment of early-stage GC. Kokudo *et al*^[51] retrospectively studied 152 patients with GC and found that the preoperative diagnostic accuracy for T and N staging was 52.6% and 24.5%, respectively. These low rates of preoperative diagnosis hinder the selection of appropriate treatment options. Shih *et al*^[52] compared 53 patients with incidentally diagnosed GC and 54 patients with preoperatively diagnosed lesions. They found that LC could result in the early discovery of GC, likely improving patient prognosis. Moreover, Darabos *et al*^[53] reviewed 3,158 patients who underwent LC and 3,083 patients who underwent classic cholecystectomies. They reported that more early-stage GC could be diagnosed and treated due to the increased use of LC, highlighting the importance of LC for early-stage GC. Thus, advances in laparoscopic equipment and surgical techniques have played a distinct role in promoting the development of laparoscopic surgery for GC.

Research from 2010 to 2020

Research from 2010–2020 evaluated the relationship between bile spillage caused by intraoperative perforation and the prognosis of GC. In a Korean study, 12 patients with

GC with intraoperative bile spillage were compared with 16 patients without bile spillage^[54]. Both disease-free survival (71.4 vs. 20.9 mo) and overall survival (72.6 vs. 25.8 mo) were significantly shorter in the bile spillage group. The authors demonstrated that bile spillage was associated with incomplete resection and systemic recurrence, and they recommended that open surgery should be considered when GC is suspected. With the widespread use of retrieval bags, studies evaluated whether the routine use of retrieval bags would reduce the occurrence of port-site complications. A meta-analysis was performed to investigate the role of retrieval bags in LC, but no significant benefit in reducing the infection rate was found^[55]. Despite concerns of the risks of laparoscopic surgery, a growing number of studies began to suggest its advantages^[56-59]. For example, Goetze *et al*^[60] used the German Registry system and analyzed 837 patients with incidental GC. They divided the patients into three groups: a laparoscopic approach group, an open surgery group, and an initially laparoscopic approach but converted to open surgery group. The laparoscopic approach was associated with significantly better 5-year survival rates and had similar accidental intraoperative perforation rates and recurrence rates to those of open surgery. Moreover, Yoon *et al*^[61] performed a 10-year prospective cohort study, including 45 patients with GC (Tis, *n* = 2; T1a, *n* = 10; T1b, *n* = 8; T2, *n* = 25). The disease-specific survival rate was 92.3%, and the authors considered the long-term prognosis to be favorable and recommended laparoscopic surgery for selected patients. Furthermore, Jang *et al*^[62] studied 197 patients with stage T1 GC and reported that the 5-year disease-specific survival rates were similar in patients who underwent LC and open cholecystectomy, as well as in patients underwent extended and simple cholecystectomy. Due to the advantages of a shorter hospital stay, less blood loss, and better cosmetic outcomes, they recommended LC to be performed by highly experienced surgeons as standard treatment for stage T1 GC. Moreover, Itano *et al*^[63] studied 19 patients with suspected stage T2 GC and reported that the laparoscopic surgery group had lower intraoperative blood loss (104 vs. 584 mL), shorter postoperative hospital stays (9.1 vs. 21.6 days), and similar operative times (309 vs. 324 min) and numbers of harvested lymph nodes (12.6 vs. 10.2)

compared with the open surgery group. They also reported no cases of recurrence after a mean follow up time of 37 mo. Hence, the authors recommended laparoscopic surgery as the preferred strategy for suspected stage T2 GC. In a retrospective study from India, 24 patients who underwent radical LC were compared with 46 patients who underwent radical open cholecystectomy^[64]. Compared with the open group, the laparoscopic group had longer operating times (270 vs. 240 min), lower blood loss (200 vs. 275 mL), and similar mortality and lymph node yield. Thus, these authors also recommended radical LC for selected patients with GC. Shirobe *et al*^[65] reported a study on 11 patients with GC who underwent radical LC with lymph node dissection. The 5-year survival rates of patients with stage T1b and T2 GC were 100% and 83.3%, respectively. Therefore, the authors recommended exclusive laparoscopic surgery for patients with stage T1b and T2 GC. Due to the advances in laparoscopic technology, even reoperation for incidental GC can be completed laparoscopically^[66, 67]. Moreover, laparoscopic resection of the hepatoduodenal ligament and IVb-V segments could be performed appropriately and safely at experienced centers. Although controversy remains, laparoscopic surgery has become more common for GC due to its rapid development and proven efficacy for other types of abdominal tumors.

Research from 2020 and beyond

In recent years, more studies have been conducted on laparoscopic surgery for GC. Because of the development of high-definition display equipment, the refinement of surgical equipment, and the technical progress of surgeons, current research supports the application of laparoscopic surgery for GC. Kim *et al*^[68] performed a propensity analysis to compare the outcomes of pure extended LC and open extended cholecystectomy. They found that extended LC resulted in shorter postoperative hospital stays (7 vs. 12 days) and similar complication rates and disease-free survival rates compared with open surgery. Moreover, Navarro *et al*^[69] performed a propensity score-matched analysis of patients with stage T2 GC. They compared 43 patients who underwent radical LC with 43 patients who underwent open radical cholecystectomy

and found that the LC group had a shorter hospital stay, lesser blood loss, fewer complications, and similar 5-year overall and disease-free survival rates compared with open surgery group. Similarly, Wang *et al*^[18] retrospectively reviewed 106 patients with incidental GC after LC. All patients underwent reoperation, and radical laparoscopic reoperation resulted in better 1-year (95.56% vs. 86.89%) and 5-year (44.44% vs. 29.51%) survival rates, lesser blood loss (100 ± 25.4 vs. 200 ± 45.6 mL), shorter hospital stays (3.5 ± 1.9 vs. 5.6 ± 2.7 days), and lower complication rates (6.7% vs. 13.1%) compared with open surgery. In addition, a study from China included 50 patients with GC and found that laparoscopic surgery was associated with shorter postoperative hospital stay (6.2 ± 2.4 vs. 8.6 ± 2.3 days) and lesser intraoperative blood loss (242 ± 108.5 vs. 401 ± 130.3 mL)^[70]. Moreover, Bakos *et al* reported a study of 47 patients with GC and found that LC could diagnose GC at an early stage in some patients^[71]. Cho *et al*^[72] performed a propensity score-matched analysis to evaluate the effects of laparoscopic surgery on patients with stage T2 GC. Compared with the open surgery group, the laparoscopic surgery group showed significant advantages in terms of operation time (316.8 ± 80.3 vs. 218.9 ± 145.0 min) and postoperative hospital stay (14.4 ± 6.0 vs. 8.4 ± 5.9 days). However, the 3-year overall and disease-free survival rates were similar between the laparoscopic and open surgery groups. Hamad *et al*^[73] used the National Cancer Database to investigate the impact of different operative approaches on lymph nodes. They identified 2,014 patients and found that patients who underwent open and minimally invasive surgery had similar lymph node evaluation and yield rates. Due to the difficulty in diagnosing GC by only imaging tests before surgery, Tokumitsu *et al*^[74] reported and recommended their novel approach using whole-layer LC and gallbladder bed dissection, which could serve as an optimal treatment strategy. Imamura *et al*^[75] evaluated 13 patients who underwent whole-layer LC and 18 patients who underwent laparoscopic gallbladder bed resection, and reported that their surgical strategy was curative and safe.

Systematic reviews have also provided evidence supporting the use of laparoscopic surgery for GC. Liu *et al*^[76] systematically reviewed 24 studies of minimally invasive

surgery for GC and found that minimally invasive surgery for GC could be performed safely in selected patients by experienced surgeons. Feng ⁵*et al*^[77] performed a systematic review and meta-analysis of 15 studies with a total of 1,068 patients and found no significant differences in the 1-, 3-, and 5-year overall survival rates, intraoperative blood loss, operation time, number of harvested lymph nodes, and complication rates between laparoscopic and open surgery. However, the length of hospitalization was shorter in the laparoscopic group. This review revealed that laparoscopic surgery is as safe and feasible as open surgery in patients with early-stage GC.

With the advancement of laparoscopic technology, some complex operations can now be performed laparoscopically. For example, a patient with synchronous GC and extrahepatic cholangiocarcinoma underwent successful laparoscopic hepatopancreaticoduodenectomy^[78]. Additionally, a patient with postoperatively diagnosed GC underwent successful laparoscopic bile duct resection with lymph node dissection and was discharged on postoperative day 4^[17]. Nevertheless, although great care is taken to protect the port site, port site metastasis still occurs on occasion^[79, 80]. Moreover, the use of retrieval bags has been recommended as the gold standard^[80]. While recent studies focus on the advantages of laparoscopic surgery for GC, it still remains controversial. Finally, most existing studies have focused on early and mid-stage GC, recommending that laparoscopic surgery be performed by experienced surgeons.

CURRENT SITUATION AND DEVELOPING TREND

Although laparoscopic technique has been widely used in patients with GC and many studies have obtained positive results, it is not recommended by current guidelines. ³The Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) published their clinical practice guidelines for the management of biliary tract cancers in 2007, and updated them twice in 2015 and 2020^[19, 81]. As the only guidelines that provide the management of all biliary tract malignant diseases, JSHBPS recommend open cholecystectomy as a rule for patients with suspected GC. They suggested that laparoscopic surgery could be

performed as a clinical study with informed consent. Meanwhile, in the guideline for the diagnosis and treatment of GC (2019 edition), ⁸ Branch of Biliary Surgery, Chinese Surgical Society and Chinese Committee of Biliary Surgeons do not recommend laparoscopic surgery for patients with GC^[82]. Accumulation of evidence is awaited for the application of laparoscopic surgery in GC. In Table 3, we summarize the data of several existing studies in recent years. More researches are expected in the next few years.

The application of laparoscopic surgery in GC is in line with the concept of minimally invasive and Enhanced Recovery After Surgery (ERAS). Robotic surgery can be seen as an upgrade and advancement of laparoscopic surgery. It has also been used in patients with GC. Sucandy *et al*^[83] reported a study of 15 consecutive patients with GC who underwent robotic surgery. No intraoperative complications were observed, and the median hospital stay was 3 days. Byun *et al*^[84] reported 16 patients who underwent robotic extended cholecystectomy for suspected stage T2 or above GC. The mean operation time was 198 min, and the median hospital stay was 7 days. Robotic surgery has many advantages over open and laparoscopic surgery, especially regarding ergonomics^[85]. Its role in the treatment of GC should be complementary to laparoscopic techniques. ERAS is a multidisciplinary and comprehensive patient management model^[86-90]. This model aims to reduce the perioperative stress response, decrease complications, and shorten the length of hospitalization and has been proven effective for many types of surgery^[91-93]. However, ERAS study on patients with GC is rare^[94]. Laparoscopic surgery for GC can reduce trauma, accelerate patient recovery, and shorten the hospital stay, which satisfies the requirements of ERAS. The development trend of laparoscopic surgery in GC is bound to include robotic surgery and ERAS management.

CONCLUSION

Laparoscopic surgery for GC is feasible, and a considerable amount of research has been conducted on the safety of this surgical strategy. While gallbladder perforation

and port site metastasis are major concerns of laparoscopic surgery, many clinical studies have confirmed the advantages of laparoscopic surgery over open surgery in terms of operation time, intraoperative bleeding, and hospital stay, as well as their similarity regarding therapeutic efficacy. However, compared with its applications for gastrointestinal tumors, the application of laparoscopic surgery for GC is underdeveloped. Prospective, multicenter, randomized, and controlled clinical trials are required to further confirm the safety and feasibility of laparoscopic surgery for GC. Currently, laparoscopic surgery for GC should be conducted within reason, according to the tumor stage and experience of the surgeons.

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