



The Dilemma and the Latest Research Progress of Laparoscopic Gallbladder Cancer Radical Treatment

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Abstract: *In the context of minimally invasive surgery, laparoscopic technology has developed vigorously, and it has been maturely applied to the treatment of other malignant gastrointestinal tumors such as gastric cancer and colorectal cancer and has achieved good results, but its development in the treatment of gallbladder malignant tumors is extremely slow. At present, there is still controversy about whether laparoscopic technology is suitable for the treatment of gallbladder malignant tumors, and with the continuous exploration of minimally invasive treatment of gallbladder malignant tumors by some scholars, this view is gradually accepted and recognized. Based on the latest research results at home and abroad, this article discusses the latest research progress, difficulties and advantages of laparoscopic radical cholecystectomy.*

Keywords: Laparoscopic; Gallbladder cancer; Laparoscopic radical cholecystectomy.

1. Research Background

Gallbladder cancer (GBC) is a rare and highly malignant tumor of the digestive system. Although its incidence is low, its mortality is extremely high, with an average survival time of 6 months and a 5-year survival rate of only 5%. Gallstones are the most important risk factor for gallbladder cancer, and about 85% of GBC patients suffer from gallstones. Secondly, gallbladder polyps, chronic inflammation of gallbladder, biliary tract infection and obesity are also believed to be closely related to the pathogenesis of gallbladder cancer, but the pathogenesis of GBC is still unclear [1]. In China, gallbladder cancer is more common in women, and more than half of them are diagnosed at the age of 56-75 years old. Due to its hidden early onset, about 90.521% of patients lose the opportunity for surgery due to the initial failure to detect GBC [2]. Early diagnosis and treatment is the key to improve the therapeutic effect of GBC patients, and surgical treatment is the only possible way to cure GBC. At present, with the upgrading of medical equipment and the improvement of doctors' operation, problems such as laparoscopic lymph node dissection and laparoscopic gastroenterostomy have been overcome, and more and more research centers have turned their attention to LRC, but whether LRC can achieve radical resection (R0 resection) and peritoneal implantation metastasis is still controversial.

2. Current Dilemmas and Challenges of Laparoscopic Radical Cholecystectomy

2.1 Trocar Implant Metastasis

In the early understanding, the treatment of biliary malignancy was listed as a prohibited area of laparoscopic technique. The high probability of postoperative Trocar implantation metastasis is an important reason preventing the widespread use of laparoscopy in the diagnosis and treatment of GBC [3]. The early view was that LRC increased the risk of gallbladder rupture, allowing bili-carrying cancer cells to spread within the abdominal cavity, and contaminated instruments and tumor excision via Trocar further increased the risk of implant metastasis. In addition, the carbon dioxide in the pneumoperitoneum will reduce the body's immunity, resulting in gasification and the "chimney effect" will promote the spread of malignant tumors. In 1999, Paolucci V et al. found that 409 patients with unexpected gallbladder cancer were found after simple laparoscopic cholecystectomy, and the six-month postoperative follow-up showed that 70 patients had incision metastasis, with a metastasis rate of 17.1% [4]. A 2017 review of 27 articles showed that the rate of incision metastasis after GBC has decreased from 18.6% before 2000 to 10.3%, but the incidence is still higher than other primary tumors [5]. A 2014 meta-analysis using animal models showed that laparoscopic carbon dioxide pneumoperitoneum did not increase the rate of postoperative incision metastasis in tumor patients, and the duration of carbon dioxide pneumoperitoneum had no significant effect on incision metastasis, but it also pointed out its limitations such as uneven experimental parameters, small sample size, and short follow-up time [6]. An expert consensus meeting held in Seoul in 2016 pointed out that with improved preventive measures (such as the use of specimen bags to remove GBC specimens), Trocar implantation and peritoneal metastasis after LRC can be effectively reduced [7]. Data from the central register of "Accidental gallbladder cancer" of the German Surgical Association suggest that the incidence of postoperative Trocar implantation metastasis is lower in patients who use sample retrieval bag compared with those who do not use it. In the case of intraoperative perforation of accidental gallbladder cancer, the incidence of Trocar metastasis and peritoneal metastasis under the protection of sample bag tends to decrease [8]. In the past, it was believed that routine port resection after LRC could reduce the occurrence of Trocar metastasis. In 2017, the American Alliance for Extra-hepatic Biliary Malignancies reviewed the treatment of patients with unexpected gallbladder cancer in 10 institutions from 2000 to 2015, and proved that port resection was not associated with improved overall survival, and routine port resection was not recommended [9]. At present, with the use of a series of protective measures, the incidence of incision metastasis after LRC has decreased significantly, but the overall tumor recurrence rate is still high, and more clinical studies are still needed to solve this problem.

2.2 Whether Minimally Invasive Techniques Can Meet the Requirements of Radical Resection and Adequate Lymph Node Dissection

Another key point in the treatment of gallbladder cancer with minimally invasive technology is whether R0 resection can be achieved. R0 resection means that the tumor is completely removed and the incision margin is also negative under the microscope. It is generally believed that R0 resection can provide a higher survival rate for patients. Lymph nodes in the region of gallbladder cancer included duodenal ligament lymph nodes (12 groups), which could be subdivided into parahepatic proper artery (12a), paracommon bile duct (12b), paracholecystic duct (12c), and posterior portal vein (12p). Paraarterial lymph nodes along the proper liver (group 8) and posterior superior pancreatic lymph nodes (group 13a). Non-regional lymph nodes: abdominal trunk (9 groups); Mesentery (14 groups); Abdominal aorta (16 groups); Prepancreatic (group 17) and posterior inferior pancreas (13b). The guidelines for the diagnosis and treatment of biliary malignancies issued by the Chinese Society of Clinical Oncology in 2023 suggest that radical R0 resection is the only cure for gallbladder cancer, which should be performed by experienced hepatobiliary surgeons, and the number of lymph node dissection for gallbladder cancer should be > 6 (including groups 12, 8 and 13) [10]. In 2021, a meta analysis study showed that there was no significant difference in R0 removal rate between minimally invasive and traditional open surgery in the treatment of early and middle stage gallbladder cancer

patients, and there was no significant statistical significance in the number of lymph nodes obtained between the two groups [11]. A retrospective study conducted by Lee JW et al in 2022 showed that LRC had the same R0 resection rate and lymph node dissection as traditional open surgery [12]. At present, it is basically clear that minimally invasive surgery for early and middle gallbladder cancer can achieve the same R0 resection rate and the number of lymph nodes obtained as open surgery.

3. T Staging and Surgical Treatment of Gallbladder Cancer

3.1 Surgical Treatment of GBC in Stage T2 and Before T2

The best treatment for GBC before stage T1a is simple cholecystectomy. Studies have shown that there is no statistical significance in the five-year survival rate between patients undergoing laparoscopic surgery and those undergoing open surgery at stage T1a [13]. At this stage, the disease was hidden, and the tumor was only confined to the lamina propria of the gallbladder, and gallbladder R0 resection was considered to have achieved radical curative effect [14]. The latest (csc) guidelines for the diagnosis and treatment of biliary malignancies released in 2023 also agree with this view, and GBC patients before stage T1a can be treated with simple cholecystectomy [10]. Stage T1b GBC has invaded the muscle layer, and lymph node metastasis has been present at this stage. It is believed in the early stage that radical surgery and venous lymph node dissection are recommended for patients with stage T1b GBC [15]. However, with the deepening of LRC research, some scholars believe that simple cholecystectomy is enough. Lee H et al. conducted a meta-analysis of 22 articles, and the results showed that there was no significant difference in prognosis between simple cholecystectomy and radical cholecystectomy for gallbladder cancer [16]. At present, open or laparoscopic surgery for stage T1b GBC is controversial.

However, regardless of the surgical method, the survival rate after T1b GBC is very good, with a 5-year survival rate of 97% [17]. T2 stage GBC refers to malignant tumors that invade connective tissue but do not invade serosal layer, and the lymph node metastasis rate of T2 stage GBC is 46% [18]. The eighth edition of AJCC divided T2 stage GBC into peritoneal side (T2a) and hepatic side (T2b). At present, a general consensus has been reached on the surgical treatment of stage T2 GBC. Patients with stage T2a without liver invasion only undergo cholecystectomy plus lymph node dissection, without the need for hepatectomy, while patients with stage T2b require extensive radical gallbladder cancer resection (cholecystectomy + lymph node dissection + partial hepatectomy). In addition, the survival rate of patients with peritoneal tumors is significantly higher than that of patients with hepatic tumors [19]. In 2008, scholar Cho et al reported for the first time that 3 cases of occasional T2 GCB patients underwent complete laparoscopic resection, achieving 100%R0 resection, and believed that LRC was an effective treatment for selective T2 GCB patients [20]. Shirobe T et al. found that laparoscopic surgery had a good therapeutic effect on T2 GBC patients without liver invasion, with a 5-year survival rate of 83.3%[21]. Cho JK et al also reported in 2022 that endoscopic surgery for T2 GBC had a short-term prognosis and long-term oncology outcome that was no worse than open surgery, and recommended minimally invasive treatment for T2 GBC patients [22].

3.2 Surgical Treatment of Stage T3 GBC

Stage T3 GBC tumor has invaded the serosal layer and is prone to lymphatic metastasis. CSCO guidelines (2023) indicate that cholecystectomy, regional lymph node dissection and liver 4b+5 resection are sufficient for patients without hepatoduodenal ligament lymph node metastasis and liver bed involvement less than 2cm. Patients located in the neck of the gallbladder, invading the gallbladder triangle, or complicated with hepatoduodenal ligament lymph node metastasis, need to undergo

right half liver or right hepatic trilobectomy [10]. Chinese scholar He Hongying et al. believed that the surgical method and scope should be determined according to the pathological types of T3 gallbladder cancer, and the scope of liver resection and lymph node dissection are independent factors affecting the survival rate [23]. In 2018, Kim S et al. reported that a patient with stage T3 GBC accompanied by liver infiltration and lymph node metastasis underwent LRC, and no recurrence was observed at the postoperative follow-up of 14 months after 6 months of postoperative chemotherapy [24]. In 2022, Huang L et al. retrospectively analyzed 79 patients with stage T3 gallbladder cancer, and proved that LRC was basically similar to traditional open surgery in the number of lymph node dissection, complication rate and postoperative survival rate [25]. At present, there are few clinical reports on minimally invasive treatment of T3 GBC, and its feasibility needs to be supported by more research data.

3.3 Treatment of Stage T4 GBC

GBC tumors in stage T4 invade hepatic artery or portal vein, or infiltrate at least two surrounding organs, and patients in this stage are generally considered to have lost the opportunity for surgery, and palliative surgery combined with multidisciplinary treatment to improve patients' quality of life is the main method [1]. Some scholars also believe that as long as the lesions are limited, radical surgery can be performed if R0 is reached, and radical surgery plus adjuvant chemotherapy can significantly benefit the survival of patients [26]. According to the 2023 CSCO guidelines, right hemihepatic or right hepatic trilobectomy is feasible for patients with stage T4 GBC without distant metastasis, but the incisional margin must remain negative [10]. At present, there is no evidence that endoscopy is suitable for the treatment of T4 gallbladder cancer.

4. Advantages of Minimally Invasive Technique in the Treatment of Gallbladder Cancer

4.1 Advantages of LRC Over Traditional Open Surgery

Table 1: Data summary of partial LRC and traditional open surgery in recent 5 years

author	Case study	Operation time (minutes)	Intraoperative blood loss (ml)	Length of stay (days)	Complication rate (%)
Han Weiguang [31]	Group A:33	192.3±26.7	188.9±40.7	9.8±2.9	8 (24.2%)
	Group B:38	206.2±29.5	210.8±45.4	12.6±3.4	17 (44.7%)
Pan Debiao [32]	Group A:23	194.13±92.77	173.91±92.77	9.30±2.77	2 (8.7%)
	Group B:29	200.17±29.32	210.34±104.69	12.59±3.13	5(17.2%)
Nag HH [33]	Group A:30	286.5±71.6	158.6±85.7	6.4±3.1	5(16.6%)
	Group B:38	274.2±96.3	219.4±87.7	9±8.0	12(31.5%)
Guo Guoxiao [34]	Group A:48	190.06±27.43	169.80±91.14	9.05±2.57	4 (8.33%)
	Group B:48	204.19±26.81	211.82±101.37	13.18±2.96	11(22.92%)
Navarro JG [28]	Group A:30	274.2±96.3	158.6±85.7	6.4±3.1	5(16.6)
	Group B:38	286.5±71.6	219.4±87.7	9±8.0	12(31.5)
Cho JK [22]	Group A:37	165.8 ±128.8	-	6.8±4.9	5(13.5%)
	Group B:44	332.3±93.3	-	15±7.5	11(25%)
Lee JW [12]	Group A:20	186.60±88.14	320.00± 451.72	10.95±4.82	2(10.0%)
	Group B:24	231.67±82.97	593.75 ± 912.04	12.80±4.87	5(20.8%)

As a minimally invasive procedure, LRC means that the incision is smaller than that of open surgery, and laparoscopy can enlarge the surgical field of view for delicate operation. The author searched the reports in recent years and summarized them, as shown in Table 1. The results showed that the operation time and intraoperative blood loss of LRC were better than those of open surgery. The length

of hospital stay and postoperative complications of LRC were significantly lower than those of open surgery. Meta-analyses such as Lv TR in 2021 also proved that patients with LRC had faster postoperative recovery, less intraoperative blood loss, lower incidence of postoperative complications, and a survival period similar to that of open surgery [11]. In addition, laparoscopy can be used as a diagnostic means, and staging laparoscopy can avoid open surgical exploration for 55.9% of unresectable GBC patients [27]. Meanwhile, Navarro JG et al. found that patients undergoing laparoscopic surgery could start adjuvant chemotherapy earlier [28]. In 2019, Primrose JN et al reported that the use of capecitabine chemotherapy after GBC could improve the overall survival rate of patients [29]. Therefore, early adjuvant chemotherapy is a major advantage of LRC.

4.2 Whether You Can Achieve the Same Survival Rate as Open Surgery

Whether minimally invasive surgery can achieve the same survival rate as open surgery is a matter of great concern to everyone. Dou Changwei et al. studied the short-term efficacy and long-term prognosis of laparoscopic and open radical resection of gallbladder cancer and found that the postoperative follow-up found that the 1-year and 3-year overall survival rates were 79.4% and 54.1% in the endoscopic group, and 55.7% and 37.6% in the open group, respectively. The difference was statistically significant ($P<0.01$). The 1-year and 3-year progression-free survival rates were 63.6% and 49.6% in the laparoscopic group, and 37.7% and 12.9% in the open group, respectively, with statistical significance ($P<0.01$). In view of the high number of early cases in the endoscopic group, subgroup analysis found that endoscopic surgery could achieve long-term survival outcomes comparable to open surgery [30]. Cho JK et al also reported that there was no significant difference in 3-year disease-free survival rate and 3-year overall survival rate between minimally invasive surgery and open surgery [22]. Lee JW et al. 's retrospective study also confirmed this view. LRC and ORC can achieve similar 5-year survival rates. The team conducted subgroup analysis on T2 and N0 patients, and the results showed that the endoscopic group could achieve better postoperative survival rates [12].

5. Conclusion

Although there are still some doubts and challenges in LRC, throughout the development process of laparoscopic treatment of malignant tumors, it has been subjected to the interrogation of oncology efficacy in the early stage, and it is currently going through an early stage of exploration. Most scholars believe that endoscopic technology can achieve better therapeutic effects in gallbladder cancer patients before T2 stage. However, the number of relevant studies on T3 and T4 is small, the sample size is not large, and there is bias in surgical selection. Therefore, more surgical centers need to try to carry out LRC and provide high-quality mass cases for proof. With the continuous progress of medicine, a variety of minimally invasive surgery is gradually developing, I firmly believe that one day in the near future can usher in the minimally invasive era of gallbladder cancer treatment.

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References

- [1] Hundal R, Shaffer E A. Gallbladder cancer: epidemiology and outcome[J]. *Clinical epidemiology*, 2014: 99-109.

- [2] Epidemiological characteristics, diagnosis, treatment and prognosis of gallbladder cancer in China [J]. Chinese Journal of Digestive Surgery, 202,21(1):114-128.
- [3] Lundberg O, Kristoffersson A. Port site metastases from gallbladder cancer after laparoscopic cholecystectomy. Results of a Swedish survey and review of published reports[J]. European Journal of Surgery, 1999, 165(3): 215-222.
- [4] Paolucci V, Schaeff B, Schneider M, et al. Tumor Seeding following Laparoscopy: International Survey[J]. World Journal of Surgery, 1999, 23(10):989-997.
- [5] Berger-Richardson D, Chesney T R, Englesakis M, et al. Trends in port-site metastasis after laparoscopic resection of incidental gallbladder cancer: a systematic review[J]. Surgery, 2017, 161(3): 618-627.
- [6] Xianwei, Mo, Yang, et al. Does carbon dioxide pneumoperitoneum enhance wound metastases following laparoscopic abdominal tumor surgery? A meta-analysis of 20 randomized control studies[J]. Tumor Biology, 2014, 35(8):7351-7359.
- [7] Han H S, Yoon Y S, Agarwal A K, et al. Laparoscopic surgery for gallbladder cancer: an expert consensus statement[J]. Digestive surgery, 2018, 36(1): 1-6.
- [8] Goetze T O, Paolucci V. Use of retrieval bags in incidental gallbladder cancer cases[J]. World journal of surgery, 2009, 33: 2161-2165.
- [9] Ethun C G, Postlewait L M, Le N, et al. Routine port - site excision in incidentally discovered gallbladder cancer is not associated with improved survival: a multi - institution analysis from the US Extrahepatic Biliary Malignancy Consortium[J]. Journal of surgical oncology, 2017, 115(7): 805-811.
- [10] Chinese Society of Clinical Oncology Guidelines Working Committee, Chinese Society of Clinical Oncology (cSCO) Guidelines for the diagnosis and treatment of biliary malignancies [M]. Beijing: People's Health Publishing, 2023.
- [11] Lv T R, Yang C, Regmi P, et al. The role of laparoscopic surgery in the surgical management of gallbladder carcinoma: A systematic review and meta-analysis[J]. Asian Journal of Surgery, 2021, 44(12): 1493-1502.
- [12] Lee J W, Kwon J H, Lee J W. Oncologic and long-term outcomes of laparoscopic and open extended cholecystectomy for gallbladder cancer[J]. Journal of Clinical Medicine, 2022, 11(8): 2132.
- [13] Seung, Eun, Lee, et al. Practical guidelines for the surgical treatment of gallbladder cancer. [J]. Journal of Korean Medical Science, 2014; 29(10): 1333-1340.
- [14] Lundgren L, Muszynska C, Ros A, et al. Management of incidental gallbladder cancer in a national cohort[J]. Journal of British Surgery, 2019, 106(9): 1216-1227.
- [15] Do You D, Lee H G, Paik K Y, et al. What is an adequate extent of resection for T1 gallbladder cancers? [J]. Annals of surgery, 2008, 247(5): 835-838.
- [16] Lee H, Kwon W, Han Y, et al. Optimal extent of surgery for early gallbladder cancer with regard to long - term survival: a meta - analysis[J]. Journal of Hepato - Biliary - Pancreatic Sciences, 2018, 25(2): 131-141.
- [17] Yuza K, Sakata J, Prasoon P, et al. Long-term outcomes of surgical resection for T1b gallbladder cancer: an institutional evaluation[J]. BMC cancer, 2020, 20: 1-9.
- [18] Goetze T O. Gallbladder carcinoma: prognostic factors and therapeutic options[J]. World journal of gastroenterology, 2015, 21(43): 12211.
- [19] Lee W, Jeong C Y, Jang J Y, et al. Do hepatic-sided tumors require more extensive resection than peritoneal-sided tumors in patients with T2 gallbladder cancer? Results of a retrospective multicenter study[J]. Surgery, 2017, 162(3): 515-524.
- [20] Cho A, Yamamoto H, Nagata M, et al. Total laparoscopic resection of the gallbladder together with the gallbladder bed[J]. Journal of hepato-biliary-pancreatic surgery, 2008, 15: 585-588.
- [21] Shirobe T, Maruyama S. Laparoscopic radical cholecystectomy with lymph node dissection for gallbladder carcinoma[J]. Surgical endoscopy, 2015, 29: 2244-2250.

- [22] Cho J K, Kim J R, Jang J Y, et al. Comparison of the oncological outcomes of open versus laparoscopic surgery for T2 gallbladder cancer: a propensity-score-matched analysis[J]. *Journal of Clinical Medicine*, 2022, 11(9): 2644.
- [23] He Hongying, Li Guangtao, Li Qingli, et al. Clinical efficacy and prognosis analysis of stage T3 gallbladder carcinoma radical resection [J]. *Chinese Journal of Digestive Surgery*, 2019, 18(10): 966-978. (in Chinese)
- [24] Kim S, Yoon Y S, Han H S, et al. Laparoscopic extended cholecystectomy for T3 gallbladder cancer[J]. *Surgical Endoscopy*, 2018, 32: 2984-2985.
- [25] Huang L, Zhang C, Tian Y, et al. Laparoscopic segment 4b+ 5 liver resection for stage T3 gallbladder cancer[J]. *Surgical Endoscopy*, 2022, 36(12): 8893-8907.
- [26] Kang M J, Song Y, Jang J Y, et al. Role of radical surgery in patients with stage IV gallbladder cancer[J]. *HPB*, 2012, 14(12): 805-811.
- [27] Agarwal A K, Kalayarasan R, Javed A, et al. The role of staging laparoscopy in primary gall bladder cancer — an analysis of 409 patients: a prospective study to evaluate the role of staging laparoscopy in the management of gallbladder cancer[J]. *Annals of Surgery*, 2013, 258(2): 318-323.
- [28] Navarro J G, Kang I, Hwang H K, et al. Oncologic safety of laparoscopic radical cholecystectomy in pT2 gallbladder cancer: A propensity score matching analysis compared to open approach[J]. *Medicine*, 2020, 99(20).
- [29] Primrose J N, Fox R P, Palmer D H, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study[J]. *The Lancet Oncology*, 2019, 20(5).
- [30] Dou Changwei, Zhang Chunxu, Liu Jie, et al. Comparison of short-term efficacy and long-term prognosis of laparoscopic and open radical resection for gallbladder cancer [J]. *Chinese Journal of Surgery*, 2022, 60(2):8.
- [31] Han Weiguang, Xin Wei. Clinical study of laparoscopic and laparotomy for early gallbladder cancer [J]. *Chinese Oncology Clinic and Rehabilitation*, 2019,28(10):1153-1157.
- [32] Pan Debiao, Ye Guanxiong, Xu Shengqian, et al. Comparison of clinical efficacy of laparoscopic radical surgery and open radical surgery in the treatment of early gallbladder cancer [J]. *Journal of Hepatobiliary and Pancreatic Surgery*, 2019, 31(2):4.1007-1954.
- [33] Nag H H, Sachan A, Nekarakanti P K. Laparoscopic versus open extended cholecystectomy with bi-segmentectomy (s4b and s5) in patients with gallbladder cancer[J]. *Journal of Minimal Access Surgery*, 2021, 17(1): 21.
- [34] Guo G Z. Comparison of curative effect between laparotomy and laparoscopic radical cholecystectomy for early stage cholecystectomy [J]. *Journal of Clinical Medicine*, 2020, 40(9): 2.1003-3548.