ORIGINAL ARTICLE

Minimally invasive versus the conventional open surgical approach of a radical cholecystectomy for gallbladder cancer: a retrospective comparative study

Anil K. Agarwal[1], Amit Javed[1], Raja Kalayarasan[1] & Puja Sakhuja[2]

[1]Department of Gastrointestinal Surgery, and [2]Department of Pathology, GB Pant Hospital & MAM College, Delhi University, New Delhi, India

Abstract

Background: Laparoscopic surgery has traditionally been contraindicated for the management of gall bladder cancer (GBC). This study was undertaken to determine the safety and feasibility of a laparoscopic radical cholecystectomy (LRC) for GBC and compare it with an open radical cholecystectomy (ORC).

Methods: Retrospective analysis of primary GBC patients (with limited liver infiltration) and incidental GBC (IGBC) patients (detected after a laparoscopic cholecystectomy) who underwent LRC between June 2011 and October 2013. Patients who fulfilled the study criteria and underwent ORC during the same period formed the control group.

Results: During the study period, 147 patients with GBC underwent a radical cholecystectomy. Of these, 24 patients (primary GBC– 20, IGBC – 4) who underwent a LRC formed the study group (Group A). Of the remaining 123 patients who underwent ORC, 46 matched patients formed the control group (Group B). The median operating time was higher in Group A (270 versus 240 mins, $P = 0.021$) and the median blood loss (ml) was lower (200 versus 275 ml, $P = 0.034$). The post-operative morbidity and mortality were similar ($P = 1.0$). The pathological stage of the tumour in Group A was T_{1b} ($n = 1$), T_2 ($n = 11$) and T_3 ($n = 8$), respectively. The median lymph node yield was 10 (4–31) and was comparable between the two groups ($P = 0.642$). During a median follow-up of 18 (6–34) months, 1 patient in Group A and 3 in Group B developed recurrence. No patient developed a recurrence at a port site.

Conclusion: LRC is safe and feasible in selected patients with GBC, and the results were comparable to ORC in this retrospective comparison.

Correspondence

Anil K. Agarwal, Department of Gastrointestinal Surgery, GB Pant Hospital & MAM College, Delhi University, New Delhi 110002, India. Telefax: +91 11 23235702. E-mails: aka.hpb@gmail.com, anilagarwal@outlook.com

Introduction

Minimally invasive surgery in gall bladder cancer (GBC) has a potential role in staging of the disease (staging laparoscopy), palliative bypass in locally advanced or metastatic disease and radical surgery for potentially curable disease.[1–8] The benefits of a staging laparoscopy have previously been documented and been shown to prevent a non-therapeutic laparotomy in 23–62% of patients.[1] In patients with gastric outlet obstruction resulting from metastatic disease, a laparoscopic gastrojejunostomy has been shown to decrease post-operative hospital stay and time to resume oral intake.[2] Traditionally, curative laparoscopic surgery has been contraindicated in patients with suspected GBC.[9]

Reports of tumour implantation after a laparoscopic cholecystectomy for unsuspected GBC was the most important factor that precluded widespread employment of a laparoscopy in the treatment of GBC.[10,11] Recently, however, a few studies have advocated the use of a minimally invasive, laparoscopic approach.[3–8] The majority of these series have either a small number of patients or have included only early GBC.[3–7] In the largest feasibility study published to date, 18 patients with T_1 and T_2 GBC underwent a cholecystectomy along with resection of a small liver wedge and hepatoduodenal lymphadenectomy[7].

This present study was undertaken to determine the safety and feasibility of a laparoscopic radical cholecystectomy (LRC)

in patients with the T_{1-3} primary and incidental GBC (IGBC) and to compare the outcome with patients who underwent an open radical cholecystectomy (ORC).

Methods

In a retrospective analysis of GBC patients operated at a tertiary referral teaching hospital, (June 2011 and October 2013), all patients with suspected GBC, who did not have evidence of metastatic disease on clinical examination, underwent an ultrasound followed by dual phase computed tomography (CT) of the abdomen. Patients with primary GBC with either no or limited liver infiltration (on CT abdomen); and IGBC patients (Stage T_{1b}–T_3) after a laparoscopic cholecystectomy were considered for a LRC and or resection. Informed consent was obtained and those who refused a laparoscopic procedure were offered an open radical cholecystectomy. Other exclusion criteria for LRC included extensive liver infiltration on CT, extrahepatic adjacent organ involvement (biliary, duodenal, colonic, pancreatic), IGBC detected after an open cholecystectomy and any systemic illness which contraindicated a laparoscopic procedure.

A laparoscopic radical cholecystectomy was performed using five abdominal ports with the patient in a French (low lithotomy) position. The pneumoperitoneum was established using an infra-umbilical port and a staging laparoscopy was performed as previously described.[1] In patients with no evidence of disseminated disease on staging laparoscopy, additional ports were placed: 5 mm right pararectal port below the right subcostal region, 11 mm left pararectal port above the level of umbilicus, 5 mm left midclavicular port below the left subcostal region and a 5 mm epigastric port.

Surgical technique for LRC

The patient was placed in the reverse trendelenberg position with a left lateral tilt. Before proceeding with a radical resection, a routine sampling biopsy of the inter-aortocaval (IAC) 16b1 lymph nodes was done. For this sampling, duodenal kocherization was performed using two left-sided working ports to expose the IAC area adequately. Any enlarged lymph nodes in the IAC region below the level of left renal vein were excised and sent for frozen section examination. In the absence of grossly enlarged lymph nodes, fibrofatty tissue from the same anatomical location was excised and examined. The surgical resection was abandoned if metastatic disease was identified on the frozen section histopathological analysis.

In primary GBC patients with no IAC lymph node metastasis, further dissection was performed to expose structures in the hepatocystic triangle as is done during a standard laparoscopic cholecystectomy. The cystic artery was ligated and divided. The cystic duct was double clipped and divided, and the cystic duct margin was sent for the frozen section examination. The IGBC patients in whom the data on the cystic duct margin was not available, a dissection was performed to locate the cystic duct and the margin for the frozen section was sent for examination. To avoid slippage of the clips and subsequent bile spillage, Hem-o-lok clips® (Weck Closure System; Research Triangle Park, Durham, NC, USA) were preferred for the cystic duct. A wedge of segment IVb, V was marked using a hook cautery. To facilitate the marking and dissection at the inferior surface of segments IVb and V, the right lobe of the liver was retracted upwards without handling the tumour. The liver parenchymal transection was performed using a combination of a Harmonic Scalpel™ (Ethicon Endosurgery, Cincinnati, OH, USA), Ligasure™ (Valleylab, Boulder, CO, USA) and an ultrasonic aspirator (CUSA™; Valleylab). Superficial liver transection was performed using the Harmonic Scalpel™, whereas Ligasure™ and CUSA™ were preferred for the deeper liver transection. The middle hepatic vein in the superior aspect of the gall bladder bed was subsequently clipped and divided. The resected tumour specimen was placed in a specimen retrieval bag and was temporarily placed away from the operative field.

The extent of a lymphadenectomy included lymph nodal dissection along the entire length of the hepatic artery from the celiac axis to the level of its bifurcation into the right and left hepatic arteries; dissection of the retropancreatic lymph nodes, and lymph nodal clearance of the hepatoduodenal ligament including pericholedochal and peri/retroportal lymph nodes. A circumferential dissection of the hepatoduodenal ligament was completed, and the entire lymph nodal tissue was excised enbloc. In this fashion, a standard lymphadenectomy (which includes clearance of nodes from the hepatoduodenal ligament skeletonizing the vascular structures and the bile ducts with clearance of nodes anterior and posterior to the head of the pancreas and the hepatic artery till its origin from the celiac axis) was completed. The entire specimen was placed in a protective bag and was removed through a small periumbilical incision. After ensuring satisfactory hemostasis, a silastic drain was placed in the right subhepatic space and the wound was closed in layers. In patients who underwent an ORC, a right subcostal incision was used as previously described.[1] In patients with IGBC, in addition to the radical cholecystectomy, a full thickness excision of all port sites used for the initial laparoscopic cholecystectomy was added.

Post-operative management and follow up

The post-operative complications were documented and the bile leak was defined and graded according to the International study group of liver surgery guidelines.[12] The follow-up protocol included clinical examination, ultrasound abdomen and serum tumour marker levels (CEA and CA 19-9) every 3 months for the initial 2 years and then every 6 months for the next 3 years. A dual phase CT abdomen was performed in patients with suspicious findings on ultrasound abdomen.

Statisical analysis

Patients who underwent a laparoscopic radical cholecystectomy during the study period were analysed and compared with a select group of matched patients who underwent an open radical cholecystectomy during the same period. Statistical analysis was performed using statistical program GraphPad INSTAT version 4 (GraphPad Software, Inc., La Jolla, CA, USA). The mean and median values were compared using the Mann–Whitney test. Proportions were compared using Fischer's exact test. A P-value of < 0.05 was considered statistically significant.

Results

During the 28-month study period, 147 patients with GBC underwent a radical cholecystectomy. Of these, 24 patients (primary GBC – 20, IGBC – 4) who underwent a laparoscopic radical cholecystectomy formed the study group (Group A). Of the remaining 123 patients who underwent an ORC, 46 matched patients who fulfilled the criteria used for LRC were selected for comparison (Group B). The median age of patients undergoing a LRC was 44 (21–61) years with a female-to-male ratio of 2.6:1. Table 1 depicts the comparison of the two groups. The demographic characteristics (age and gender) were comparable between the two groups. The median operating time (min) was higher in Group A as compared with Group B (270 versus 240, $P = 0.021$), however, the median blood loss

(ml) was less (200 versus 275, $P = 0.034$). None of the patients in either group had perforation of the gallbladder or bile spillage during the radical cholecystectomy. There was no post-operative mortality in either group. The post-operative morbidity included Grade A (International study group of liver surgery) bile leak ($n = 5$, Group A – 1 and Group B – 4), sub-hepatic collection requiring single time aspiration ($n = 2$, Group A – 1, Group B – 1), minor chyle leak which settled with conservative treatment ($n = 1$, Group A), wound dehiscence requiring secondary suturing ($n = 1$, Group B) and post-operative pneumonia ($n = 2$, Group B). The incidence of morbidity in Group A (3/24, 12.5%) was similar to that in Group B (8/46, 17.4%; $P = 0.737$).

The pathological T stage of the resected specimen in primary GBC patients in Group A was T_{1b} in 1, T_2 in 11 and T_3 in 8 patients, respectively. The pathological T stage was comparable between the two groups (Table 2). Of the 13 IGBC patients, 9 (Group A – 3, Group B – 6) did not have any residual tumour in the GB fossa and 4 (Group A – 1, Group B – 3) had a residual tumor in the GB fossa. The excised port sites were free of tumour in all except 1 patient (Group B) who had tumour deposits in the epigastric port site. The median (range) number of IAC lymph nodes sampled in Group A and B were 2 (1–3) and 2 (1–4), respectively, and all the sampled nodes were negative for malignancy. The cystic duct margin was negative in all patients and all of them underwent a curative (R0)

Table 1 Comparison of clinicopathological features of patients who underwent a laparoscopic (Group A) and open (Group B) radical cholecystectomy

Parameter	Group A (n = 24)	Group B (n = 46)	P value
Demography			
Age, median (range)	44 (21–61)	49 (23–70)	0.281
Sex ratio, female: male	2.6:1	3:1	0.848
Operative data			
Duration of surgery in min, median (range)	270 (180–340)	240 (180–360)	0.021
Blood loss in ml, median (range)	200 (100–850)	275 (100–800)	0.034
Post-operative data			
Hospital stay in days, median (range)	5 (3–16)	5 (3–17)	0.111
Morbidity, n (%)	3 (12.5)	8 (17.4)	0.737
Histopathology			
Lymph node yield, median (range) [mean (± SD)]			
Overall	10 (4–31) [12.5 (± 5.4)]	11 (5–26) [12.9 (± 5.4)]	0.642
Primary GBC	12 (6–31) [13.6 (± 4.8)]	12.5 (5–26) [13.9 (±5.6)]	0.781
IGBC	5 (4–10) [5.5 (± 1.7)]	6 (5–10) [7.4 (± 1.9)]	0.146
Stage, n (%)			
I	3 (12.5)	5 (10.9)	1.000
II	10 (41.7)	10 (21.7)	0.099
IIIA	6 (25.0)	13 (28.3)	1.000
IIIB	5 (20.8)	18 (39.1)	0.181

Table 2 Studies on a laparoscopic radical cholecystectomy for gallbladder cancer

	Cho et al[7]	Gumbs et al[8]	Present series
Study period	2004–2007	2005–2011	2011–2013
No of patients	18	15	24
Inclusion criteria	Primary GBC (T1 and T2)	Primary GBC (T1–3) and IGBC	Primary GBC (T1–3)and IGBC
Inter-aorto caval node sampling biopsy	No	No	Yes
Extent of liver resection	GB with 2 mm liver wedge	Segment IVb & V	Segment IVb & V
Lymph node yield, median, range	8 (4–21)	4[a](1–11)	10 (4–31)
Port site recurrence	–	–	–

[a]Average lymph node yield.

resection. The median (range) [mean ($\pm$ SD)] lymph node yield in Group A: 10 (4–31) [12.5 ($\pm$ 5.4)] was comparable to Group B: 11 (5–26) [12.9 ($\pm$ 5.4)]. The mean and median lymph node yield was higher in primary GBC patients compared with IGBC patients in both groups. Five patients in Group A had a lymph node positive tumour. After a median (range) follow-up of 18 months (6–34), 23/24 patients in Group A and 43/46 patients in Group B were alive without any evidence of recurrence. One patient in Group A with T_3N_0 (14 nodes resected) disease developed jaundice owing to nodal recurrence at 14 months follow up. No patient developed recurrence at a port site. Three patients in Group B developed recurrence (nodal recurrence – 2, liver metastasis – 1) at 11, 13 and 16 months follow up, respectively. Of the 3 patients, 2 had T_3N_1 disease and 1 had T_2N_1 disease.

Discussion

The present series is one of the largest to report the safety, feasibility and outcomes after LRC for GBC. While a laparoscopic cholecystectomy is one of the most commonly performed minimally invasive procedures, laparoscopic management of GBC has been relatively slow to develop. Traditionally, a suspicion of GBC was considered a contraindication for the laparoscopic approach,[9] the main concern being the high incidence of reported port site recurrence (0–48%).[10,11] In these reports, published in late 90s and in the early 2000s, a laparoscopic cholecystectomy was done for suspected benign pathology, with the plane of transection breaching the cystic plate, and perhaps associated with GB perforation in a significant number of cases.

Before adopting the minimally invasive approach for surgical management of GBC, the important questions that need to be addressed include the technical feasibility of performing an adequate oncological resection, whether there is an increased incidence of port-site metastases after LRC and whether the long-term oncological outcomes are similar to that of an open procedure.

With regards to the technical feasibility, the major components of an LRC include a liver resection and lymphadenectomy. The feasibility of a laparoscopic liver resection (both major and minor hepatectomy) has been established.[13] Similarly, studies have demonstrated similar short- and long-term outcomes after open and laparoscopic D2 lymphadenectomy for gastric cancer.[14] In the present series, an R_0 resection with adequate lymphadenectomy could be accomplished in all the patients without any gall bladder perforation and bile spillage.

The proposed mechanisms of port site recurrence are direct and indirect implantation of tumour cells at the port sites, during the laparoscopic procedure.[15] Direct implantation of tumour cells may occur from seeding of exfoliated malignant cells during either forcible extraction of the tumor (specimen) without a protective bag, either through a small wound or by contact with instruments contaminated with tumour cells. Indirect contamination is usually secondary to the pneumoperitoneum and occurs either by an 'aerosol' effect wherein exfoliated tumour cells are disseminated to the port sites during the turbulence of insufflation or by a 'chimney' effect wherein the tumour cells are transferred to wound during episodes of desufflation.[16] The evidence favouring pneumoperitoneum (indirect implantation) as the cause of port site recurrence are occasional reports of port site recurrence in patients who underwent laparoscopic surgery without tumour manipulation and recurrence in ports other than the extraction port.[17–19] However, experimental studies using improved tumour models (solid tumour models instead of intraperitoneal cell culture lines) have shown that mechanical factors such as surgical manipulation and tumour rupture may play a more important role in the causation of port site recurrence and pneumoperitoneum alone (indirect implantation) has a negligible effect.[20] The experience with laparoscopic colorectal cancer surgery demonstrated that with the use of appropriate preventive measures the incidence of port site recurrence was approximately 1.1%, which was comparable to open surgery.[21,22] In the present series, during a median (range) follow-up of 18 (6–34) months, none of the patients who underwent a laparo-

scopic radical cholecystectomy developed a recurrence at the port site. Thus, with proper surgical techniques such as minimal tumour handling, avoidance of the bile spillage and use of a protective bag for specimen extraction, recurrence at the port site can be minimized.

The first prospective study on laparoscopic surgery for suspected GBC included 30 patients selected based on a pre-operative endoscopic ultrasound and intra-operative laparoscopic ultrasound done to rule out any liver invasion.[7] All patients underwent a laparoscopic cholecystectomy with a 2 mm liver wedge to avoid transecting through the cystic plate and avoid bile spillage. Hepatoduodenal with a hepatic artery lymphadenectomy was performed in 18 patients who had evidence of malignancy on frozen section examination of a cholecystectomy specimen (Table 2). No additional hepatic resection was performed in patients who had GBC on frozen section examination. A limitation of this study was that it included a very specific subgroup of patients with GBC with no liver infiltration. Also, although a laparoscopic hepatoduodenal and hepatic artery lymph node clearance was done, only a 2 mm liver wedge was resected along with the gall bladder. Recently, Gumbs et al.[8] reported their experience of minimally invasive surgery for an extrapancreatic cholangiocarcinoma performed over a period of 6 years in three different international centres. Of the 29 cases included in their multi-institutional study, 15 underwent an LRC for GBC. The average lymph node yield in their series was only four, which is less than what is recommended.[8] The present series wherein 24 patients underwent LRC with a median lymph node yield of 10 is one of the largest series to report the feasibility of LRC for early (T_1 and T_2) and select locally advanced (T_3) GBC. At a median (range) follow-up of 18 (6–34) months none of the patients developed a port site recurrence. Similarly in the series reported by Cho et al.[7] and Gumbs et al.[8], none of the patients had a port site recurrence during a median follow-up of 18 and 23 months, respectively. As the median reported time to port site recurrence is 6 months after the index cholecystectomy, it is reasonable to assume that LRC does not increase the incidence of port site recurrence, if adequate preventive measures are taken.[23] These reports also highlight the fact that port site recurrence after a laparoscopic cholecystectomy performed for unsuspected GBC cannot be extrapolated to LRC as there are critical technical differences between these two procedures. In the present series, none of the patients had a positive cystic duct margin. However, if the cystic duct margin is positive, a CBD excision should be performed. The feasibility of laparoscopic CBD excision in GBC has been reported in the literature.[4]

In the present series (and in the 2 previously reported series), all patients underwent an R_0 resection, and there was no bile spillage. The mean and median lymph node yield in the LRC group was 12.5 and 10, respectively, which was comparable to the lymph node yield in the ORC Group and those reported in the other major ORC series.[24,25] While one patient

(pT_3N_0) in the present series developed lymph nodal recurrence with jaundice at 14 months follow up, it does not appear related to the laparoscopic approach as an R_0 resection with adequate lymph node yield (14 nodes) was achieved in that patient. None of the patients with early GBC developed a recurrence. Similarly, in the other series, none of the early GBC patients developed a recurrence during a median follow-up of 18 months in one series; and 2 patients with stage IIIB disease developed recurrence at 3 and 20 months follow-up in the other series.[7,8] The reported recurrences after LRC were in patients with stage III disease suggesting that the tumour biology rather than the access route is the cause for recurrence.

The benefits of performing a laparoscopic resection include accomplishing the procedure with similar radicality both in terms of adequate liver resection and locoregional lymphadenectomy with all the benefits of the minimal access approach including less pain, early ambulation, decreased would-related complications and a cosmetic scar. From the present series, it is evident that with the careful patient selection and proper surgical techniques such as minimal tumour handling, avoidance of the bile spillage and the use of a protective bag for specimen extraction, early oncological outcomes comparable to the open procedure could be achieved and the benefits of a minimal invasive procedure could be provided to the patients. AS LRC is a technically complex procedure, it should be performed only in centres with sufficient experience in advanced laparoscopic hepatobiliary surgery. A limitation of the present study is that the groups are not randomized and the comparison is with a matched group, which may have a potential for a bias. While the present study has shown that early oncological outcomes of LRC and ORC are comparable, randomized trials with long-term follow up would be a definite answer to the question of oncological equivalence. The results of the present non-randomized retrospective comparative study will form the basis for a future randomized trial.

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