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Laparoscopic versus Open Approach in Gallbladder Cancer Treatment - 9-Year Experience in Fundeni Clinical Institute

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Abbreviations:
MIS: minimally invasive surgery;
US: ultrasound;
CT: computed tomography;
MRI: magnetic resonance imaging;
MRCP: magnetic resonance cholangiopancreatography;
PET-CT: positron emission computed tomography;
EUS: endoscopic ultrasonography.

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Rezumat

Abordul chirurgical laparoscopic versus abordul deschis în tratamentul cancerului de colecist - 9 ani de experiență în Institutul Clinic Fundeni

Introducere: Cancerul de colecist reprezintă cea mai frecventă malignitate a tractului biliar, frecvent asimptomatic şi diagnosticat incidental pe piesele de colecistectomie, dar cu prognostic slab. În cazurile confirmate histopatologic, tratamentul trebuie completat prin chirurgia radicală, iar abordul laparoscopic pare să fie sigur şi fezabil. Scopul studiului actual este de a prezenta experiența clinicii noastre chirurgicale în tratamentul a 83 de pacienți diagnosticați cu cancer de colecist între anii 2015 şi 2024 şi de a sublinia rolul abordului chirurgical laparoscopic. De asemenea, s-a efectuat un review al literaturii care analizează rolul actual al chirurgiei laparoscopice în tratamentul acestui tip de cancer.
Materiale şi Metode: Au fost efectuate 57 de rezecții radicale şi 26 rezecții în scop paliativ. Dintre rezecțiile radicale, 52 au fost realizate utilizând abordul deschis şi 5 utilizând abordul chirurgical laparoscopic. 14 cazuri din 57 au fost reprezentate de re-rezecții pentru cazuri confirmate histopatologic pe piese de colecistectomie simplă. În majoritatea cazurilor, colecistectomia simplă a fost efectuată prin abord laparoscopic. Abordul chirurgical laparoscopic a fost utilizat în 3 cazuri de re-rezecție după colecistectomie simplă laparoscopică şi 2 cazuri diagnosticate per-primam.
Rezultate: Vârsta medie a pacienților din grupul deschis a fost 64,21 ani, iar a celor din grupul laparoscopic a fost 67,2 ani. Sexul feminin a fost predominant. Majoritatea pacienților au avut una sau mai multe comorbidități cu un scor ASA 3 sau 4 în 52 de cazuri din 57. Pacienții incluşi în grupul laparoscopic au avut un scor ASA mai mic comparativ cu cei din grupul în care s-a optat pentru abordul chirurgical deschis. Durata intervenției chirurgicale a fost similară între cele două aborduri (308 minute laparoscopic versus 294 minute deschis). Rata complicațiilor postoperatorii a fost semnificativ mai mare în grupul deschis. Numărul de ganglioni limfatici recoltați a fost similar indiferent de abordul chirurgical. Grupul laparoscopic a beneficiat de o durere postoperatorie mai redusă, recuperare rapidă a mobilității şi a toleranței digestive per os, cu o durată a spitalizării semnificativ redusă față de grupul

deschis (6,2 zile versus 13 zile). Cancerul de colecist evoluează asimptomatic în stadiile precoce, iar diagnosticul în stadii avansate limitează opțiunile terapeutice. Totuşi, în cazurile depistate incidental pe piesele de colecistectomie pentru presupusă boală benignă (stadii T1-T3), re-rezecția poate fi realizată de cele mai multe ori prin abord laparoscopic. De asemenea, în cazuri selecționate, diagnosticate per-primar, acest abord poate fi optim în echipe experimentate.
Concluzii: Abordul chirurgical laparoscopic este o alternativă ideală la abordul deschis în tratamentul chirurgical al cancerului de colecist în stadii preoce. Acesta oferă siguranță din punct de vedere oncologic, rate similare de rezecție R0 şi număr similar de ganglioni limfatici recoltați. Beneficiul maxim al chirurgiei laparoscopice poate fi obținut în centre cu volum mare şi cu echipe chirurgicale experimentate.

Cuvinte cheie: cancer colecist, laparoscopie, chirurgia deschisă

Abstract

Introduction: Gallbladder cancer is the most common biliary malignancy frequently diagnosed incidentally on cholecystectomy specimens for presumed benign disease. Once the diagnosis is confirmed on histopathologically, the treatment must be completed by resecting the gallbladder liver bed and regional lymph nodes. The laparoscopic approach seems to be efficient and oncologically safe. The aim of our study was to present the 9-year experience in treating gallbladder cancer in our surgery clinic by both open and laparoscopic approach completed by a literature review with the latest updates regarding the state of the laparoscopic approach in treating this type of cancer.
Materials and Methods: Fifty-seven patients underwent radical surgery and 26 resections had a palliative purpose. Among radical resections, 52 were performed by using the open approach and 5 by using the laparoscopic approach. 14 cases out of 57 were completion procedures performed after a malignant histopathological finding was confirmed on a simple cholecystectomy specimen. In the majority of cases, the primary simple cholecystectomy was performed by laparoscopic approach. The laparoscopic approach was used in 3 cases of re-resection and 2 per-primam resections.
Results: The median age of the patients was 64.21 years in the open group and 67.2 years in the laparoscopic group. Most patients were females. All patients had one or more comorbidities with an ASA score of 3 or 4 in 52 patients out of 57. ASA score had lower values in the laparoscopic group. The average surgery time for the laparoscopic group was 308 minutes, similar to the one for the open group that was 294 minutes. The complication rate was higher in the open group. The number of harvested lymph nodes was similar between the groups. The laparoscopic group benefited of lower postoperative pain, faster recovery and shorter hospital stay (6.2 days versus 13 days). Gallbladder cancer evolves asymptomatic in early stages and the diagnosis in advanced stages limits the therapeutic options. Still, in cases incidentally diagnosed on cholecystectomy specimens for presumed benign disease (stages T1-T3), the re-resection might be performed by laparoscopic approach. Also, in per-primam diagnosed selected cases, the laparoscopic resection might be performed by experimented teams.
Conclusions: The laparoscopic approach is an ideal alternative to the open approach in treating early-stage gallbladder cancer. This surgical approach provides oncological safety, similar R0 resection rates and number of harvested lymph-nodes. The maximum benefit of this surgical approach is achieved in high-volume centers with experimented teams.

Keywords: gallbladder cancer, laparoscopy, open surgery

Introduction

Gallbladder cancer is the most common biliary malignancy, developed from the mucosal lining of the gallbladder, with a low global incidence, but with a poor prognosis. It accounts 1.2% of all cancers diagnosed annually and 1.7% of all cancer deaths, with a higher incidence in female population compared to male population (1-3).

Gallbladder cancer is usually asymptomatic for a long time and the diagnosis is made incidentally on routine cholecystectomy specimens in approximately 60-70% of the cases or in an advanced disease stage presenting with persistent abdominal pain, nausea, weight loss, and jaundice (4,5).

The highest incidence is reported in Latin America and Asia followed by Eastern and Central Europe. A low incidence is found in the United

States and Mediterranean European countries (6).

The female population is more often affected (almost six times) and median age is 67 years (6,7).

Routine histopathological examination of the cholecystectomy specimens is usually recommended even if there are studies suggesting a cost-effective strategy meaning evaluation only if there is a macroscopic suspicion of cancer especially in areas with very low incidence (8-14).

When the diagnosis is confirmed by the histopathological evaluation of the gallbladder, the surgical treatment must be completed depending on the stage of the disease. Radical surgery is represented by resection of the gallbladder liver bed and regional lymph nodes (8,9,13,15).

In T1a incidental gallbladder cancer, simple cholecystectomy is considered adequate if the cystic duct margins are free. In T1b tumors, the surgical treatment remains controversial, some studies reporting that an extended resection in this disease stage is not associated with a better prognosis, with no differences in overall survival between the patients treated by simple cholecystectomy and those receiving radical surgery (15-19).

Still, there are some studies reporting an increase in 5-year overall survival up to 30% after radical surgery in T1b stage (20,21).

The decision for radical surgery should be guided by the depth of invasion and the surgical margins. A simple cholecystectomy is considered proper by some authors when the parietal invasion is restricted to the muscular layer with free surgical margins (16,18).

Regarding T2 and T3 tumors, re-resection is firmly indicated, being associated with survival improvement. The extent of liver resection (wedge resection of the liver bed or an anatomical segmentectomy IVb and V) in these disease stages represents a controversial subject. Some studies (22) found that anatomical segmentectomy is associated with better disease-free survival for T2b tumors, but without difference in overall survival for T3 tumors, while others (23) did not find any long-term benefits of the extended resection. An extended resection is not indicated if the R0 resection cannot be achieved (15,24,25).

Primary cholecystectomy specimen may not be sufficient for disease staging and re-resection may be needed in order to properly stage the disease and establish the prognosis (26). Click or tap here to enter text. The risk for residual disease is correlated with a higher pT stage and it strongly influences the prognosis, patients with residual disease having worse survival. This may potentially explain why radical resection in T1b stage is not firmly indicated and does not have obvious benefits, the risk for residual disease being low and the spread being mostly local (17,27,28).

Common bile duct resection is not routinely recommended, not being associated with a higher lymph node count or with improved survival and the decision is guided by the status of the cystic duct margin. During surgery, the margins could be re-evaluated by fresh frozen sections taking into account that the bile duct resection has oncological benefits if the margins prove to be positive (15, 29-32).

As mentioned before, radical surgery for gallbladder cancer also involves regional lymphadenectomy including cystic duct, portal lymph nodes and Eastern countries recommend extended lymphadenectomy along the hepatic artery and in the posterosuperior pancreaticoduodenal region. Lymph node metastases beyond these regions limit the role of radical surgery and their removal increases the morbidity and the mortality rates without any oncological benefits. Even if the patients with only cystic duct positive nodes have similar disease-free survival with those having completely negative lymph nodes, the status of the cystic nodes has a predictive value for the status of the hepatic pedicle lymph nodes. The risk for lymph node involvement is correlated with the T stage and the minim number of lymph nodes required for optimal staging is considered 6 (15,33-36).

Before making the decision for radical surgery, a complete imagistic work-up must be achieved to assess the liver, lymph node or peritoneum involvement and also to detect metastatic disease in the abdomen or in the chest.

The primary imaging investigation in both per-primam diagnosed gallbladder cancer and incidentally diagnosed on cholecystectomy specimen is represented by computed tomography scan (CT) which provides information on the extent of the local disease, vascular invasion, the presence of portal lymphadenopathies or peritoneal implants. It has a sensitivity of 99% and specificity of 76% in determining disease resectability (37-39).

MRI (magnetic resonance imaging) is mostly dedicated to per-primam diagnosed unclear cases due to its increased accuracy in evaluating T-stage being able to differentiate between T1a and T1b lesions which is paramount in establishing the surgical procedure (simple cholecystectomy in T1a tumors versus cholecystectomy en bloc with the liver bed in T1b tumors). Also, by using contrast,

which is preferentially excreted in the bile, MRCP (magnetic resonance cholangiopancreatography) offers both anatomic and functional evaluation of the gallbladder and bile ducts (37,38,40-42).

EUS (endoscopic ultrasonography) is not routinely used in gallbladder cancer diagnosis, but it is extremely useful in cases when gallbladder disease presents just as wall thickening and a differential diagnosis with adenomyomatosis and various types of cholecystitis should be performed. This method can stratify the gallbladder wall and to evaluate the key points suggestive for gallbladder cancer: "discontinuity or irregular thickening of the innermost hyperechoic layer (mucosa), irregular thickening of the outermost hyperechoic layer (serosa), or loss of the multilayer pattern" (37,43-49).

Positron emission tomography (PET-CT) might be useful to find occult regional or distant disease (30,50-52).

The appropriate imaging evaluation and disease staging plays an important role in choosing the surgical approach considering that open surgery might be preferred when bile duct resection is necessary. Also, adequate imaging methods are important in radiological interventions in pre-operative setting such as: percutaneous fine needle aspiration cytology or biopsy under US or CT guidance; percutaneous transhepatic biliary drainage when the biliary obstruction involves the primary confluence; pre-operative percutaneous portal vein embolization in cases when the gallbladder tumor involves the right lobe artery or portal vein or primary or right secondary confluence and when right extended hepatectomy represents the curative surgical resection, determining hypertrophy of the contralateral lobe and decreasing the risk of post-hepatectomy liver failure; or with palliative purpose-biliary drainage to control the jaundice or celiac plexus neurolysis to alleviate the pain (53-58).

The surgical approach used in treating gallbladder cancer was a subject of controversy for many years, but given the advances obtained in minimally invasive surgery (MIS) techniques, well trained surgical teams that diminished the differences between the open and the minimally-invasive approach and its established role in treating other malignancies, this approach became very popular. The majority of the literature confirmed its feasibility and safety in treating gallbladder cancer and supported the development and improvement of this surgical approach.

Study Objectives

The aim of our study was to evaluate the state of current literature comparing the open approach with the MIS approach in gallbladder cancer treatment and also to present the experience of our clinic in treating this type of malignancy.

Method

We conducted a search in PubMed using mesh terms for gallbladder cancer AND MIS AND (overall survival OR disease-free survival OR recurrence rate) starting from 2018 to 2024. The inclusion criteria were represented by: year of publication-2018-2024, language-Romanian or English, type of article-observational, randomized controlled trial, systematic review, literature review, meta-analysis, cohort study, propensity score matched study. The exclusion criteria were represented by: missing data regarding the oncological safety of the minimally-invasive approach and other types of articles that were not excluded by checking the inclusion criteria. We retrieved 19 articles after the final review of our search that were read as full article and relevant data were extracted regarding the conclusions of each article, oncological outcomes, duration of surgery and blood loss (*Table 1*). Also, we discussed relevant literature involving the start of MIS in treating gallbladder cancer, the indications of this approach, its limitations, controversies and comments about this approach, its evolution over time and future perspectives. Finally, we presented the data obtained in our clinic treating 83 patients with gallbladder cancer by open and MIS approach between 2015 and 2024.

Results

Starting from 2018, E. Sinagra evaluated a small cohort of 6 patients who underwent MIS (laparoscopic and robotic surgery) radicalization for gallbladder cancer identified on cholecystectomy specimens and the results obtained were encouraging. In all cases an R0 resection was achieved, with a mean number of retrieved lymph nodes of 17.5 which assured optimal disease staging and no recurrences during the 16-32 months of follow-up (59).

Also, in 2018 Y. S. Yoona published the results of an expert survey regarding laparoscopic surgery in gallbladder cancer completed by data obtained in a literature review. The survey was conducted

Table 1. Literature review-conclusions

First Author	Year of Publication	Journal	Type of study	Comparative	Multicentric	Laparoscopic/ Robotic	Conclusions
Emanuele Sinagra	2018	Minimally Invasive Therapy & Allied Technologies	Observational	No	No	Both	Minimally-invasive approach can be done without compromising the oncological outcomes.
Yoo-Seok Yoon	2018	Digestive Surgery	Survey results of the expert meeting and literature review	Yes	Yes	Laparoscopic	Laparoscopic surgery for gallbladder cancer should be performed in highly selected cases and by experienced surgeons.
Mahesh Goel	2018	J Surg Oncol	Observational	Yes	No	Robotic	RRC is safe and feasible and the short- term results are compared with ORC.
Xabier de Aretxabala	2018	Surgical Endoscopy	Observational-Prospiective	No	No	Laparoscopic	Laparoscopic approach is safe and feasible for gallbladder cancer treatment.
E. A. Vega	2020	BJS Society	Observational	Yes	Yes	Laparoscopic	Laparoscopic approach is oncologically non-inferior to open approach.
Changwei Dou	2019	Surgical Endoscopy	Observational	Yes	No	Laparoscopic	Laparoscopic approach has comparable perioperative outcomes with open approach and improved 1-year survival.
Jae Yool Jang	2019	Surgical Oncology	Observational	Yes	No	Laparoscopic	For T2 gallbladder cancer, laparoscopic approach has similar disease-free survival and overall survival with open approach.
Jia-Wei Feng	2019	Journal of surgical research	Observational	Yes	No	Laparoscopic	Laparoscopic approach is feasible in Tis-T3 gallbladder cancer with similar survival rates with the open approach.
Samer AlMasri	2020	J Surg Oncol	Review	Yes	Yes	Both	Minimally-invasive approach is oncologically non-inferior to open approach.
Yoonhyeong Byun	2020	Surgical Endoscopy	Observational	No	No	Robotic	Robotic approach is adequate in advanced stage, with sufficient lymph node dissection and rapid recovery.
Ahmad Hamad	2020	Surgical Endoscopy	Observational	Yes	Yes	Robotic	Minimally-invasive approach is associated with similar rates of lymph node evaluation and yield.
Yoonhyeong Byun	2020	J Hepatobiliary Pancreat Sci.	Observational	Yes	No	Robotic	Long term survival studies are needed for the robotic approach.
Fei Liu	2021	ANZ J Surg	Systematic review	No	Yes	Both	Minimally-invasive surgery for gallbladder cancer is limited to highly selected patients and is considered to be technically feasible in experienced surgeons.
Tian-Run Lv	2021	Asian Journal of Surgery	Systematic review and Meta-analysis	Yes	Yes	Laparoscopic	Laparoscopic approach is safe and feasible for early- or middle-staged lesions.
Lyonell B. Kone	2022	Cancers	Systematic review	No	Yes	Robotic	Robotic approach is non-inferior to the open approach, but randomized studies are needed.
Jun Yang	2022	Frontiers in Surgery	Matched-Comparison	Yes	No	Robotic	Robotic approach is a safe and effective alternative to open approach in T1-T3 gallbladder cancer.
Weng Jiayi	2022	Journal of Clinical and Translational Research	Review	No	No	Robotic	Robotic approach is safe and feasible and selected patients with gallbladder cancer treated in experienced centers.
Jin-Kyu Cho	2022	J. Clin. Med	Propensity-Score-Matched-Analysis	Yes	No	Laparoscopic	Laparoscopic approach has long-term oncological outcomes and favorable short-term outcomes in comparison with open surgery
Xin Wu	2023	Clinical and Translational Oncology	Observational	Yes	No	Laparoscopic	The prognosis is similar for patients treated by laparoscopic approach and open approach.

online involving 9 surgeons with expertise in hepato-pancreato-biliary surgery from 5 countries. The majority of the surgeons responded that laparoscopic approach is comparable to open surgery in treating gallbladder cancer, but in selected patients taking into account that local invasion, cystic duct involvement or large tumors may compromise the MIS technique and consequently the oncological safety. The literature review found that laparoscopic surgery for gallbladder cancer was mostly used in early-stage disease, but the indication was extended

progressively as the surgeons' expertise increased obtaining similar oncological outcomes to open surgery (60-64).

The feasibility and safety of the laparoscopic approach in treating gallbladder cancer was also confirmed by the study of X. de Aretxabala published in 2018 mentioning that this technique allows complete exploration in order to find residual unidentified tumor while providing a similar lymph node yield to open approach with improved postoperative recovery (65).

The laparoscopic approach of gallbladder cancer incidentally detected on cholecystectomy specimens proved to be non-inferior to the open approach in the study published by E. A. Vega too. This multicentric, retrospective, observational study followed a number of 255 patients treated by open surgery (no. 190) and laparoscopic surgery (no. 65) and found similar overall survival between the two approaches with shorter hospital stay for the laparoscopic group, encouraging the rapid spread of the laparoscopic approach and early patient referral to expert centers (66).

In the study published by C. Dou in 2019, the laparoscopic approach seemed to improve the 1-year overall survival while being associated to reduced intraoperative blood loss, faster recovery, shorter hospital stay and similar lymph node yield and postoperative morbidity to the open approach (67).

The role of the laparoscopic surgery in T2 gallbladder tumors was evaluated in the 13-year, retrospective study published by J. Y. Jang who found that the complication rate and oncological outcomes were comparable to the open approach, but suggesting that future prospective studies are needed in order to properly establish the safety of this approach (68).

The feasibility of the laparoscopic approach in Tis-T3 gallbladder cancer with similar survival rates with the open approach was confirmed by the study of J. W. Feng who also underlined the need for future prospective, randomized studies (69).

The laparoscopic approach seemed to be non-inferior to the open approach, with short-term benefits, similar long-term results and maximized rewards in highly selected patients, in experienced surgeon's hands (70-74).

In 2019, M. Goel compared the early outcomes and the feasibility of robotic surgery in gallbladder cancer to open approach and found that even if the duration of surgery was longer in the robotic group, blood loss, postoperative morbidity, length of hospital stay were reduced. The number of retrieved lymph nodes was similar between the groups and no port-site recurrences were registered (52).

Also, Y. Byun studied a group of 16 patients who underwent robotic extended cholecystectomy for gallbladder cancer stage T2 or above and obtained optimal oncological results such as: free resection margins in all cases, more than 6 lymph nodes retrieved, no mortality or recurrence within 90 days of follow-up and quick recovery (75).

Moreover, several studies supported the feasibility and oncological safety of the robotic approach mentioning that it is an optimal alternative to the open approach in T1-T3 gallbladder cancer, associated with similar rates of lymph node evaluation and yield, beneficial especially in selected patients treated in experienced centers. Still, prospective randomized studies are needed in order to confirm these findings (76-79).

In our clinic, we studied 83 patients with gallbladder cancer treated between 2015 and 2024. 57 patients underwent radical surgery and 26 resections had a palliative purpose. In this study we will refer only to the radical group of patients treated in our institution.

The radical resection group of 57 patients included 52 patients operated using an open approach and 5 patients operated by laparoscopic approach.

The median age of the patients was 64.21 years in the open group (39 y.o. to 88 y.o) and 67.2 years in the laparoscopic group (59 y.o to 75 y.o). The majority of patients (63.15%) were females, 33 in the open group and 3 in the laparoscopic group.

All patients who underwent completion procedures were evaluated by whole body CT scan during the oncological assessment before the planned surgery. Five patients underwent pre-operative CT scan before the simple cholecystectomy for presumed acute cholecystitis, but without relevant oncological information at that moment. In the group of patients with per-primam diagnosed gallbladder cancer, all patients underwent whole body CT-scan, 8 patients were evaluated by PET-CT to detect suspected metastases, 9 patients were evaluated by MRI in suspected T1 stage, and 1 patient underwent EUS with fine needle biopsy. Simple abdominal ultrasound was performed in all cases, but without diagnosis value for gallbladder cancer. We followed the imagistic work-up recommendations by NCCN guidelines presented in *Table 2*. All patients had one or more comorbidities with an ASA score of 3 or 4 in 52 patients out of 57 (91.22%) (*Table 3*).

Table 2. NCCN Imaging Guidelines for Workup of GBC (38,148)

Presentation of GBC	Imaging workup
Incidental finding of GBC at surgery or pathologic review: T1a with negative margins	Observe clinically. No imaging.
Incidental finding of GBC at surgery or pathologic review: ≥T1b or cystic node positive	Multiphasic abdominal/pelvic CT/MRI with IV contrast, chest CT ± contrast.
GBC suspected on preoperative imaging	Multiphasic abdominal/pelvic CT/MRI with IV contrast, chest CT ± contrast. MRI is preferred for evaluating masses within the gallbladder and assessing bile duct involvement. Attention to nodal disease—porta hepatis, and left gastric and aortocaval basins.
Jaundice with clinical suspicion of GBC	Multiphasic abdominal/pelvic CT/MRI with IV contrast, chest CT ± contrast to assess resectability
Metastatic disease	Biopsy
Follow-up imaging	Multiphasic abdominal/pelvic CT/MRI with IV contrast, chest CT ± contrast.
Role of PET/CT	Limited sensitivity but high specificity in detection of nodal metastasis. Used when findings on CT/MRI are equivocal.

CA 19-9 levels ranged from 19 UI/ml in stage I disease to 202 UI/ml in stage IVb disease, the increase being correlated with disease stage as illustrated in *Table 4* and *Fig. 1*.

Fourteen cases (including T1a stage) out of 57 were completion procedures performed after a malignant histopathological finding was confirmed on a simple cholecystectomy specimen (11 patients in the open group and 3 patients from the laparoscopic group). In the majority of cases, the primary simple cholecystectomy (10 cases) was performed by laparoscopic approach.

The group that underwent completion procedures included 14 patients with the following histopathological stages on simple cholecystectomy specimens: T2a (no. 4), T2b (no.4), T3 (no. 5) and intracholecystic papillary neoplasm (ICPN), (no. 1). In T1a stage (no. 5) on cholecystectomy specimen, simple cholecystectomy was considered the final treatment.

In the rest of the cases, the completion proce-

Table 3. ASA Score

ASA Score	Open	Laparoscopic	Total
1	0	0	0
2	5	0	5
3	29	2	31
4	18	3	21

Table 4. CA 19-9 levels by disease stage

Disease stage	Minimum CA 19-9 serum levels	Maximum CA 19-9 serum levels	Medium CA 19-9 serum levels
I	1	54	19.45
IIA	2	26	12.20
IIB	43	282	162.50
IIIA	4	1000	182.16
IIIB	8	700	212.72
IVA	105	179	142.00
IVB	1	943	202.31

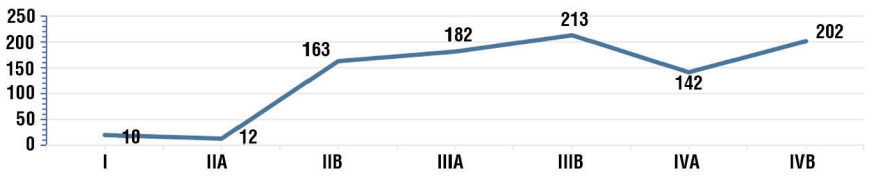

Figure 1. CA 19-9 levels by disease stage

dure included segments 4b-5 hepatectomy and regional lymph-node dissection. Five patients underwent laparoscopic resection: ICPN (no. 1), T2a (no. 1), T2b (no. 1) and T3 (no. 2). Nine cases underwent completion procedures by open approach: T2a (no. 3), T2b (no. 3), T3 (no. 3) due to severe comorbidities that did not permit effective pneumoperitoneum.

The group of patients with per-primam diagnosed gallbladder cancer included the following histopathological tumor stages: T1b (no. 4), T2 (no. 7), T3 (no. 20), T4 (no. 7). The surgical intervention included segments 4b-5 hepatectomy with regional lymph-node dissection and associated pancreaticoduodenectomy in 20 cases with D1, D2 tumor invasion or distal common biliary duct invasion and common biliary duct resection with hepaticojejunostomy in 16 cases with positive cystic duct stump on intraoperative fresh-frozen sections (no. 4) and invasion in the common biliary duct (no. 12). All patients underwent open resection due to preoperative disease staging indicating the need for an extended resection, excepting 2 cases of T1b stage overstaged on preoperative imaging.

Table 5 illustrates the types of surgical interventions performed and *Table 6* illustrates the preoperative staging for patients who were treated of per-primam diagnosed gallbladder cancer.

During the completion surgery, the trocar sites were resected in all cases due to possible trocar site metastases, no malignant confirmation on histopathological exam was found. The average surgery time for the laparoscopic group was 308 minutes, similar to the one for the open group that was 294 minutes. The histopathological findings are described for both groups in *Table 7* and *Table 8*.

Table 5. Types of surgical intervention performed in the open and laparoscopic group

Laparoscopic simple cholecystectomy	5
Laparoscopic 4b-5 hepatectomy + regional lymph-node dissection	5
Open 4b-5 hepatectomy + regional lymph-node dissection	2
Open 4b-5 hepatectomy + regional lymph-node dissection+ pancreaticoduodenectomy	20
Open 4b-5 hepatectomy+ regional lymph-node dissection + common biliary duct resection	16

Table 6. Preoperative disease staging

TNM stage	No. of patients
T1a	0
T1b	0
T2	10
T3	20
T4	5
N0	20
N1	4
N2	3
M1	1

In the open group the median size of the tumor was 3.65 centimeters compared to 2.6 centimeters in the laparoscopic group, only for patients who were operated on with a curative intent from the start.

The median postoperative stay was 13 days for the open group compared to 6.2 days in the laparoscopic group. Intensive care unit stay had a median of 4 days for the open group compared to 1.4 days in the laparoscopic one. Only one patient from the open group died due to pulmonary complications that occurred secondary to chronic

Table 7. Histopathological classification of patients from the open group

T	No. pts.	N	No. pts.	M	No. pts.	G stage	No. pts.
T1a	5	0	31	0	49	G1	24
T1b	4	1	8	1-liver	3	G2	19
T2a	8	2	13			G3	9
T2b	5						
T3	23						
T4	7						

Table 8. Histopathological classification of patients from the laparoscopic group.

T	No. Pts.	N	No. Pts.	M	No. Pts.	G	No. Pts.
ICPN	1	N0	4	M0	5	G1	1
T2	2	N1	1	M1	0	G2	3
T3	2	N2	0			G3	1

ICPN= Intracholecystic papillary neoplasm

fibrotic pulmonary disease without any surgical problems.

In the laparoscopic group, only one minor complication was found, small bile leak that was treated in a conservative manner – drainage tube was maintained in place for 14 days after the surgery.

In the open group, 25 patients did not present any postoperative complications. Sixteen patients presented Grade II Clavien-Dindo complication that were solved in a conservative manner.

Four patients had Grade III A Clavien-Dindo complication, developed intraabdominal collections secondary to small bile leaks at the site of the surgical resection and were drained under computed tomography guidance.

Grade III B Clavien-Dindo complication occurred in 4 patients, three patients were reoperated for bleeding and one for surgical drainage of an abdominal abscess and lavage of the abdominal cavity.

Grade IV A Clavien-Dindo – single organ disfunction (respiratory) occurred in 2 patients and after intensive care unit admission and proper treatment using antibiotics and non-invasive ventilation techniques such as C-pap the evolution was favorable

We summarized the complications of the open group in *Table 9*.

Even though our laparoscopic group is small, we note the clear benefits of the procedure in selected cases. We will emphasize this once we include more patients in the laparoscopic group.

Discussions

Gallbladder cancer is considered a public health concern due to its poor prognosis. The most recent epidemiological studies report 122,469 new cases and 89,045 deaths identified in 2022 with the highest incidence in South Central Asia and Eastern Asia (80,81). The most common risk factors for gallbladder cancer are represented by long-standing gallstones, obesity, and other metabolic disorders (81-83).

Table 9. Complications in the open group

No. of complications	No. pts.
0	23
1	19
2	5
≥ 3	5
Clavien-Dindo	**No. pts.**
Grade I	25
Grade II	16
Grade III a - radiologic	4
Grad III b - reintervention	4
Grad IV	2
Grad V – deceased	1

The evolution in early stages is asymptomatic and a diagnosis made in advanced stages, when the complications occur, limits the therapeutic options. Usually, the diagnosis in early-stage disease is made incidentally on cholecystectomy specimens for presumed benign gallbladder disease. Apart from the already established methods of diagnosis and disease staging, new diagnosis methods have arisen such as EUS-guided fine needle aspiration/biopsy with a positive predictive value for gallbladder malignancy of 100% and a negative predictive value of 83.3%, increasing the diagnostic rate and allowing the preparation of a more accurate treatment plan. Also, in gallbladder masses when the necrotic tissue is difficult to be differentiated of the space-occupying lesion, contrast-enhanced harmonic EUS is useful in locating the lesion (56,84-92).

Other methods such as liquid biopsy and biomarkers related to tumor cells offer information on protein expression and tumor genetic spectrum. The most common tumor markers studied are CEA and CA 19-9 with higher levels in patients with gallbladder cancer compared to those with benign disease or healthy, but without specificity or diagnostic value, and also with low sensitivity even when the two markers are combined. Still, increased levels associated with imaging confirmed diagnosis may serve as a prognostic factor. However, an independent prognostic factor for lymph-node metastasis is represented by CA-242 expression level (84,93-95).

More specific biomarkers studied are represented by CTCs (circulating tumor cells), ctDNA (circulating tumor DNA) and exosomes. CTCs arise from primary or secondary tumors, are found in peripheral blood, and might help the diagnosis, the evaluation of metastatic disease and the relapse follow-up. ctDNA is also a product of tumor cells found in peripheral blood holding information about genetic and epigenetic changes, being a potentially "novel diagnostic and non-invasive marker for gallbladder cancer". Other biomarkers which might serve the diagnosis and staging in gallbladder cancer are represented by proteins, micro-RNAs, and long noncoding RNAs. These methods represent new frontiers not

only in the diagnosis, staging, and follow-up in gallbladder cancer, but also in screening setting (84,96-109).

The optimal curative therapeutic option is represented by the R0 surgical resection, but it should be guided by the pathological T-stage in cholecystectomy specimens and by the imaging T-stage in per-primam diagnosed gallbladder cancer (110-114).

As we mentioned before, the extended liver resection along with extensive lymph node dissection is required to achieve R0 resection in disease stages over T1a on cholecystectomy specimens, considering the controversies regarding the therapeutic strategy in T1b stage.

Recently, a Hepato-Biliary-Pancreatic Surgery Division from the University of Tokyo published an algorithm to guide the decision-making process to achieve optimal oncological results avoiding unnecessary extended surgery. This algorithm is based on preoperative T-stage evaluation by imaging methods (CT/MRI) along with intraoperative lymph-node assessment by regional lymph node sampling and cystic duct stump rapid pathological analysis to guide the need for the bile duct resection and hepaticojejunostomy.

This strategy provides precious information for the surgical strategy. In image T1 with positive #12b or #12c lymph-node sampling, the gallbladder bed resection and N1 lymph-node dissection is required. In image T2 with negative #12b or #12c lymph-node dissection and negative #13 sampling, gallbladder bed resection and no further lymph-node dissection is recommended. In image T2 with positive #12b or #12c dissection and negative #13 sampling, gallbladder bed resection and N1 lymph-node dissection is indicated. In image T2 with negative #12b or #12c dissection and positive #13 sampling or imagine T2 with positive #12b or #12c dissection and positive #13 sampling, the strategy includes gallbladder bed resection/ hemi-hepatectomy which might associate pancreaticoduodenectomy and N2 lymph-node dissection. Finally, in image T3/T4 with negative #12b or #12c dissection and #13 sampling, gallbladder bed resection/ hemihepatectomy and N1 lymph-node dissection is needed. In image T3/T4 with positive #12b or #12c dissection and negative #13 sampling, gallbladder bed resection/ hemihepatectomy and N2 lymph-node dissection is appropriate. In image T3/T4 with negative #12b or #12c dissection and positive #13 sampling or both positive #12b or #12c dissection and #13 sampling, gallbladder bed resection/ hemihepatectomy which might associate pancreaticoduodenectomy, and N2 lymph-node dissection is recommended.

The authors report that this therapeutic decision-making algorithm is effective and does not compromise the oncological results, with no lymph-node recurrence in patients with image T1, T2 and with 1.4% bile duct recurrence in patients with intraoperative negative cystic duct stump. This strategy is considered optimal to tailor the extent of the liver resection and lymph-node dissection. Also, it provides the appropriate information regarding the need of bile duct resection by intraoperative pathological assessment of the cystic duct stump avoiding the complications related to empirical extrahepatic bile duct resection (110-112, 114-116).

In August 2024, in the article published by Y. Feng, a prognostic nomogram was proposed to help the medical practitioners follow patients who received extensive radical surgery for gallbladder carcinoma. The need for extensive radical surgery in stage II-III gallbladder cancer and in cases with positive lymph-nodes was emphasized with benefits regarding tumor-specific survival (117).

Still, there are studies supporting that patients with T2, T3 resected gallbladder cancer have a poor prognosis, and that the extent of surgical resection is not associated with overall survival, suggesting that a more specific patient selection should be performed in order to better select those who can benefit from radical surgery. The poor prognosis factors presented were the extent of the disease, tumor grade, and residual disease after resection. However, the use of adjuvant chemotherapy in this group of patients reduced the mortality (118).

Furthermore, in the study published by L. Nicolais in 2024, the benefit of extended surgical resection in all stages was reported with improved survival when using adjuvant chemotherapy in advanced disease stage. The improved prognosis was also supported by associated lymph-node dissection in T1b disease or over T1b disease stage (119).

The role of the perioperative chemotherapy in gallbladder cancer is considered insufficiently studied due to its inclusion between other biliary cancers (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, ampullary cancer) and lack of specific studies. A large systematic review and meta-analysis (on 1986 patients) was published in 2021 evaluating the oncological efficacy of chemotherapy in advanced gallbladder cancer. The

chemotherapy regimens used were represented by cisplatin and gemcitabine, gemcitabine and oxaliplatin or gemcitabine monotherapy. The conclusion, when comparing the results to chemotherapy in gallbladder cancer with the rest of the biliary tract cancers, was that patients with gallbladder cancer have higher overall radiological response rate, but shorter progression-free survival and overall survival (120).

The efficacy of neoadjuvant chemotherapy in gallbladder cancer is supported in the study published by S. Patkar in 2023 analyzing 1307 patients who received perioperative chemotherapy and its impact on survival outcomes. Neoadjuvant chemotherapy was used in 216 patients with stage III disease, 11 patients with stage IV disease, and 77 patients with inoperable disease upon surgical exploration. The best oncological result was achieved in patients who completed neoadjuvant chemotherapy and R0 resection, with superior overall survival compared to those who underwent neoadjuvant chemotherapy, but complete resection was not possible. Also, when comparing the patients operated after neoadjuvant chemotherapy with those who received adjuvant chemotherapy, the median overall survival was equivalent between groups, but the disease-free survival was higher in the group operated upfront with adjuvant chemotherapy regimen. Still, considering the results of this study, the role of neoadjuvant chemotherapy seems to be in selecting the patients with favorable tumor biology between those with locally advanced gallbladder cancer, while surgery followed by adjuvant chemotherapy might be considered the optimal strategy, but more studies are needed in order to firmly establish this therapeutic approach (121).

Even if the majority of literature supports the efficacy, feasibility, and oncological safety of MIS in treating T1-T3 gallbladder cancer, there are some controversies regarding the risk of port-site metastasis developed after using this surgical approach. In 2017, D. B. Richardson reported in a systematic review an incidence of 18.6% of port-site metastasis before 2000 decreasing to 10.3% between 2000-2014 as the experience of surgeons increased (122).

Rare cases of port-site metastasis occurring several years (12 years was the longest interval) after surgery were reported drawing the attention to the importance of peritoneal metastasis associated leading to poor prognosis. The risk is higher for the trocar hole from where the specimen is extracted (123-131). The risk is increased in cases with intraoperative perforation of the gallbladder and the use of the retrieval bag has a protective effect when the perforation does not occur (132). Therefore, the use of a protective measure for specimen extraction is essential along with avoiding the gallbladder perforation (133).

The risk factors for early recurrence of gallbladder cancer are represented by older age (over 60 years old), elevated levels of CEA and CA 19-9 (which were correlated with advanced tumor stages, lymph-node metastasis and perineural invasion), poor tumor differentiation, the presence of lymphovascular invasion, and perineural invasion. Also, liver involvement, higher T stage, and the presence of lymph-node metastasis are considered predictors of early recurrence after radical resection. Analyzing these factors is important in planning an effective oncological strategy depending on the individualized recurrence risk, the benefit of adjuvant chemotherapy being more evident in high-risk patients and in establishing a more aggressive follow-up regimen in patients with high risk of early recurrence (134-144).

Conclusions

MIS approach is a feasible and oncologically safe alternative to the open surgery in T1-T3 gallbladder cancer, with similar lymph node count and with maximum benefits and selected patients in experienced surgery teams.

We strongly recommend routine pathological specimen orientation in order toto differentiate between tumors involving the visceral gallbladder surface and those involving the liver bed of the gallbladder, therefore avoiding useless re-resection.

In confirmed cases, the distal margin of the cystic duct must be analyzed considering the difficulties encountered in re-resection, especially when a short duct is involved, in this manner avoiding useless resections of the common biliary duct (when the margin is negative) which are associated with high morbidity, but with no oncological benefits. Yet, even if on the extended resection specimen no residual cancer is found, the overall survival is reduced in patients with positive cystic duct margins so the common bile resection in these cases leads to improved survival (145-147).

In any case of suspected gallbladder cancer, a fresh frozen exam should be performed along with rigorous patient surveillance and urgent pathological examination in order to complete the

resection as soon as possible. However, fresh frozen sections are not the optimal method for tumor depth evaluation and, if the lesion is small, the specimen should be carefully used not to be compromised for the final pathological examination (116).

The strength of our study is represented by the comprehensive evaluation of the patients treated by open approach versus laparoscopic approach in incidentally diagnosed gallbladder cancer versus per-primam diagnosed gallbladder cancer. We emphasized the patients' characteristics included in each group and that the most aggressive tumors were diagnosed per-primam, in advanced stages, and required extensive resections, while early-stage disease was mostly incidentally diagnosed and allowed minimally invasive resection. Unfortunately, we did not include data regarding perioperative chemotherapy, but it will complete the data obtained in this study in the future. We believe that our study might present interest in developing more effective strategies in screening, diagnosing, and treating gallbladder cancer in our country.

Conflicts of Interests

The authors declared no potential conflicts of interest.

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