



## A Systematic Review on Gallbladder Cancer with Associated Case Vignette

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### Abstract

Gallbladder cancer is a rare malignancy with poor prognosis due to its aggressive biology and advanced stage at presentation. The ideal management of gallbladder cancer is highly variable and depends on mode of presentation: Incidental finding on post cholecystectomy specimen, mass on cross-sectional imaging, or jaundice from biliary obstruction. We present a systematic review of the literature regarding management of gallbladder cancer presenting as a histologically unconfirmed mass on imaging. A case vignette of a patient with gallbladder cancer presenting as cholelithiasis with associated mass and cholecystocolonic fistula will serve to highlight the management of gallbladder cancer with complicated features.

**Keywords:** Gallbladder; Adenocarcinoma; Treatment; Surgery; Clinical Trials

### Case Vignette

An 88-year-old woman presented to her local emergency department with a two-day history of general malaise and non-bloody emesis. She denied fevers, abdominal pain, weight loss, change in bowel habits, or prior episodes. Past medical history was significant for hypertension and Meniere's disease. She had no prior abdominal operations. Comprehensive physical examination was unremarkable, including no signs of jaundice, abdominal tenderness, organomegaly, or palpable lymphadenopathy. Ultrasound of the right upper quadrant demonstrated a heterogeneous, cystic and solid mass-like thickening of the gallbladder fundus along the visceral surface close to the right colon, with associated cholelithiasis (Figure 1). CT scan similarly revealed mass-like inflammatory changes of the gallbladder extending to the hepatic flexure of the colon (Figure 2). Differential diagnosis was broad, including: Primary gallbladder malignancy with colonic involvement, primary colonic malignancy with gallbladder involvement, perforated acute cholecystitis with abscess, and cholecysto-colonic fistula that could be benign or malignant.

Basic blood work revealed normocytic anemia with a hemoglobin of 10 g/dl. White blood cell count, platelets, INR, electrolytes, renal panel, and liver function tests were all within normal limits. CA 19-9 was elevated at 287 and CEA was normal at 1.5. MRI was recommended for further evaluation, but was contraindicated due to cochlear implants. A complete colonoscopy

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**Figure 1:** Heterogeneous cystic and solid mass like thickening of the gallbladder fundus with incidental cholelithiasis.



**Figure 2:** Axial and coronal CT images of the gallbladder demonstrating mass like inflammatory changes extending to the right hepatic flexure of the colon.

was unremarkable for hepatic flexure mass or right colon fistula but demonstrated left sided diverticulosis. A staging CT of the chest, abdomen, and pelvis were negative for metastatic disease. Given the complexity of her case, she was presented at multidisciplinary cancer conference where the consensus was to perform en bloc multivisceral resection.

Staging laparoscopy showed no evidence of liver, omental, or peritoneal implants (Figures 3A-3C). Open operative exploration was conducted via midline laparotomy and the final operative procedure included an en bloc segment 4b/5 liver resection, cholecystectomy with cholangiogram, right hemicolectomy with primary anastomosis, and hilar lymphadenectomy. Intra-operative analysis of cystic duct margin was negative and therefore, no bile duct resection was performed. Final pathology demonstrated poorly differentiated, multifocal gallbladder adenocarcinoma, with one focus in the fundus of the gallbladder and the other in the infundibulum near the cystic duct (Figure 4A, 4B). There were 2 positive hilar lymph nodes out of 22 regional lymph nodes including hilar, common hepatic artery, and pericolon nodes. All resection margins were negative. The cholecysto-colonic fistula was presumed to be secondary to chronic calculous cholecystitis with no evidence of direct malignant invasion. Therefore, the final stage was pT3N1M0, Stage IIIB by American Joint Committee on Cancer (AJCC) staging manual, 8<sup>th</sup> edition [1].

The patient recovered well from her operation and was discharged after a 10-days hospitalization without any major complications. She was presented once again at multidisciplinary cancer conference, which recommended adjuvant systemic chemotherapy with capecitabine for the gallbladder adenocarcinoma, given her advanced age. As margins were all negative on surgical resection, external beam radiation therapy was not advised. The patient has since completed her course of adjuvant therapy and remains on active surveillance.

## Introduction

Gallbladder cancer is a rare malignancy, with an incidence of 2.2 per 100,000 patients worldwide [2]. It tends to present with late stage and aggressive biology. Risk factors for gallbladder cancer include: Female sex, advanced age (median age of diagnosis 67 years) [3], ethnicity (American Indian, Indian, Chilean, Central and Northern European) [2,4,5], chronic cholecystitis of any etiology, and chronic bacterial infection, such as Salmonella [2,6-9]. Additional risk factors include: gallbladder adenoma/polyp  $\geq 1$  cm, porcelain gallbladder, hyalinizing cholecystitis, atrophic gallbladder, and anomalous pancreaticobiliary duct junction [2,6-9].

Preoperative diagnosis of GB cancer remains difficult. If a gallbladder mass is suspected on initial work-up, it is best further

evaluated by high-resolution CT with liver protocol or MRI with contrast [10]. Staging requires CT chest and pelvis, if not previously performed [10]. If there is suspicion for metastatic disease, which would preclude resection, histologic confirmation should be obtained prior to discussion of further treatment [10]. Obtaining a tissue biopsy may not be feasible, which further adds to the complexities of diagnosing gallbladder cancer prior to surgical resection. Options include less invasive methods such as Endoscopic Retrograde Cholangiopancreatography (ERCP) with cholangioscopy or ERCP with bile duct brushings [11,12]. When these methods fail to provide a tissue diagnosis, intraoperative ultrasound with biopsy or oncologic resection without preoperative diagnosis should be considered [13].

In the United States, 87% of gallbladder cancers present as an incidental finding following cholecystectomy for typical symptom-related indications [14]. In this circumstance, further surgical and medical therapy will be based upon the histologic T stage as well as clinical N and M stage, obtained by staging CT chest, abdomen, and pelvis [10]. Tumor markers such as CA 19-9 can be considered in the staging of any known or suspected gallbladder cancer [10]. Diagnostic laparoscopy with peritoneal washings also plays a role in determining candidacy for resection as well as prognosis [10]. For gallbladder cancer that presents without prior histologic diagnosis, such as a gallbladder mass, a similar approach to determining clinical T, N, and M stage is indicated in directing further oncologic management [10].

## Methods

A literature review was initiated using PubMed and Google Scholar to identify current evidence on gallbladder adenocarcinoma using the keywords “gallbladder” and “adenocarcinoma”, returning 4,053 articles. Non-human, non-English, and non-adult studies were excluded. The reference librarian at our institution filtered through the chosen titles selecting further relevant keywords such as “treatment”, “surgery”, “prognostic factors”, and “clinical trials”, returning 133 articles for which abstracts were reviewed. After abstract review, we excluded case studies, opinion pieces, other systematic reviews, and non-relevant articles yielding 56 articles for full text review. One additional article was included after reviewing relevant citations of the 56 articles under full text review. Of these articles, we further categorized them into pre-, intra-, and post-operative variables to allow for a comprehensive analysis. A total of 12 articles were ultimately chosen for inclusion that we found representative of each unique topic, based on quality of data and outcome reporting (Figure 5) [15].

## Results

We identified 12 unique studies for full text review focusing on

**Table 1:** Quality of Evidence was determined using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) [15].

Study	Design	Patients	N	Intervention	Control	Outcome	Quality of Evidence <sup>1</sup>
Chaudhari [16]	Retrospective	GBC T2-4	160	Neoadjuvant chemo followed by curative surgery	No curative surgery	Chemotherapy response rate 52.5%. Overall Survival after neoadjuvant chemotherapy: 49 mon (curative surgery) vs. 7 mon (control); p=0.0001	Moderate
Agarwal [17]	Prospective	Resectable GBC T1-4 via imaging	409	Staging Laparoscopy	None	Detecting unresectable tumor: 25.5% (T3/4) vs. 10.7% (T1/T2); p=0.02	Low
Ajki [18]	Prospective	Biliary cancers	41	Peritoneal cytology	None	Positive cytology: 0% (T1/T2), 6% (T3), 38% (T4); p=0.03	Low
Gani [19]	Retrospective	GBC T1-4	449	Common Bile Duct (CBD) resection	No CBD resection	34.2% underwent CBD resection: No benefit in overall survival (HR=1.40, 95% CI 0.87-2.27, p=0.170).	Low-Moderate
Fuks [20]	Retrospective	Incidental GBC	218	Surgical resection	No CBD resection	43% underwent CBD resection. Postoperative complications: 60% (CBD resection) vs. 23% (No CBD resection); p=0.0001	Low-Moderate
Ethun [21]	Retrospective	Incidental GBC	266	Port Site Excision (PSE)	No PSE	A 3-year OS: 65% (PSE) vs. 43% (no PSE); P=0.07 Distant disease recurrence-rate: 80% (PSE) and 81% (no PSE); P=1.0	Low-Moderate
Cho [22]	Retrospective	GBC T2a – T2b	81	Cholecystectomy with hepatic resection and lymph node removal	Cholecystectomy without hepatic resection	T2a: Median OS 94.1% (hepatic resection) vs. 100% (control) p=0.365 T2b: Median OS 70.9% (hepatic resection) vs. 100% (control) p=0.552 LN dissection: 3-year OS 100% (LN dissection w/o hepatic resection) vs. 94.1% and 70.6% (T2a and T2b LN dissection with hepatic resection)	Low
De Savornin Lohman [23]	Retrospective	Incidental GBC	463	Re-resection	Initial resection only	Re-resection vs. Single resection Median OS: 52.6 months vs. 13.7 months (p<0.001)	Low
Bergquist [24]	Retrospective (NCDB data)	GBC T2-4	4373	Curative intent resection and adjuvant chemotherapy	Surgery alone	T2N1: Overall survival (surg + adj) >overall survival (surgery alone); p<0.001 T3/4N1: Overall survival (surg + adj) >overall survival (surgery alone); p=0.002 Node negative did not show significant increase in OS.	Moderate
Sharma [25]	Randomized Controlled Study	Unresectable GBC	82	Chemotherapy: FU and Folinic Acid [FUFA] OR mGEMOX	Best Supportive Care (BSC)	Median OS: 4.5, 4.6, and 9.5 months (BSC, FUFA, and mGEMOX arms respectively) (P=0.039) Progression-free survival (PFS): 2.8, 3.5, and 8.5 months (BSC, FUFA, and mGEMOX arms respectively) (P=0.001).	Moderate
Singh [26]	Prospective Non-Randomized Controlled study	Metastatic/Unresectable GBC	65	Combination Chemotherapy OR Single Agent	Best Supportive Care	Chemotherapy vs. BSC: Median OS 35.6 vs. 13 weeks respectively (p value <0.001). Combo vs. Single Agent Chemo: Median OS 37 and 26.7 weeks respectively (p value- 0.002).	Low-Moderate
Tran [27]	Retrospective (NCDB data)	GBC T1-T3N1M0	1335	Resection + adjuvant therapy w/radiation	Surgery alone	Surgery + AT w/radiation: HR, 0.66; 95% CI, 0.52-0.84 (margin-negative resection) HR, 0.54; 95% CI, 0.39-0.75 (margin-positive resection)	Low-Moderate

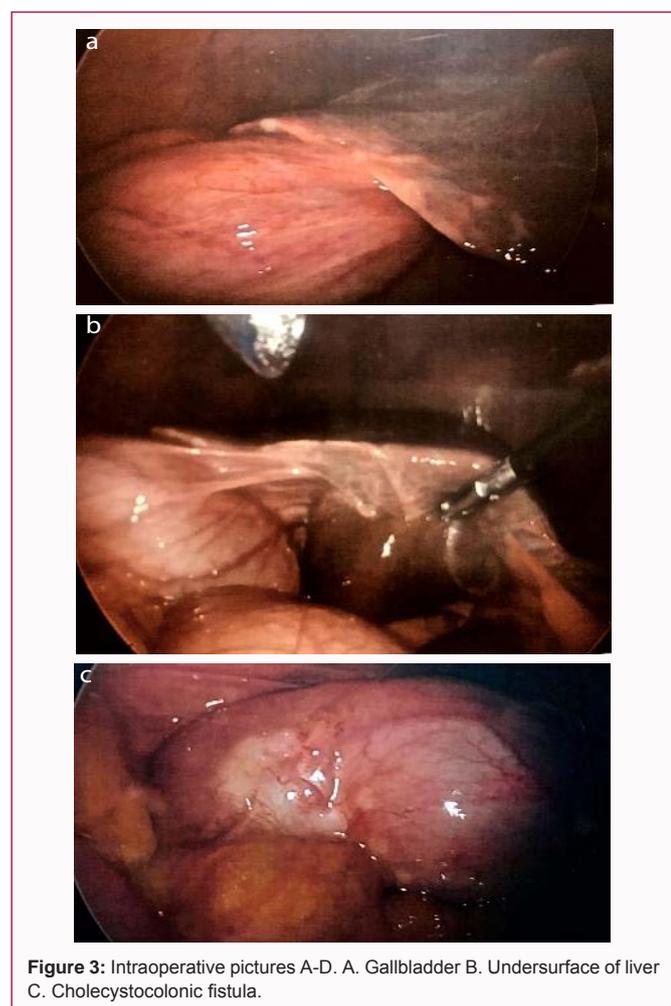
management of GB mass suggestive of GB cancer, distilled down from 4,053 articles found upon initial search [16-27]. These 12 studies were evaluated in their entirety for data extraction and interpretation [16-

27]. The key findings of these articles along with their corresponding quality of evidence are summarized in (Table 1) [16-27]. The quality of evidence was determined using the Grading of Recommendations,

**Table 2:** NCCN Guidelines for unresectable and metastatic disease.

Unresectable and Metastatic Therapy	Recommended Agents <sup>a</sup>
Preferred Chemotherapy	1 <sup>st</sup> Line- Gemcitabine & cisplatin (category 1)
	2 <sup>nd</sup> Line if disease progression- FOLFOX
NTRK gene fusion positive tumors	Entrectinib
	Larotrectinib
MSI-H/dMMR tumors	Pembrolizumab
Agents used with concurrent radiation	5-fluorouracil
	Capecitabine
Radiation therapy	CD-CRT
	IMRT
	SBRT
Symptom control/complication prevention radiation therapy	EBRT

<sup>a</sup>Therapy recommendations are category 2A unless specified otherwise [10]

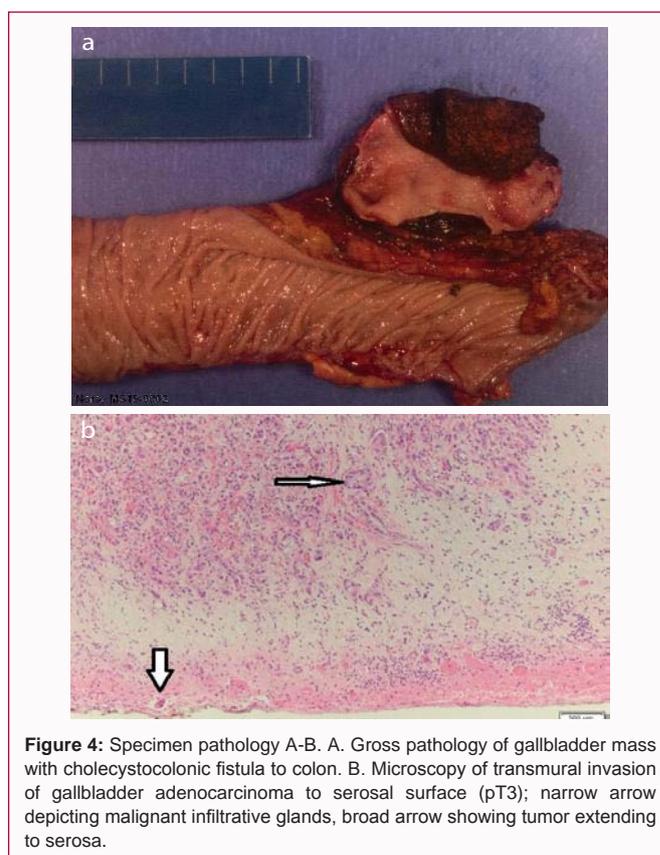


**Figure 3:** Intraoperative pictures A-D. A. Gallbladder B. Undersurface of liver C. Cholecystocolonic fistula.

Assessment, Development, and Evaluation (GRADE) criteria [15].

### Discussion

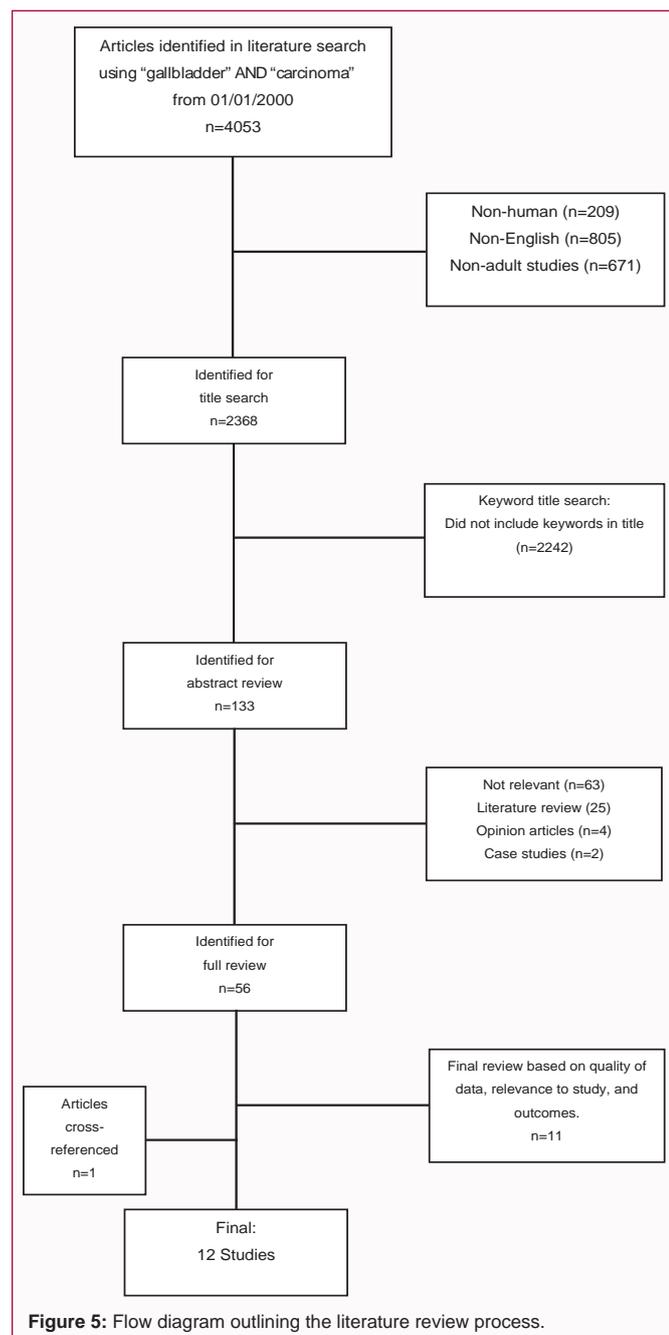
Surgical management of gallbladder cancer is dependent upon relative timing of presentation: preoperatively, intraoperatively, or postoperatively [10]. Postoperative management is largely dictated by histologic diagnosis of T stage: Any lesions T1b or greater have been found to benefit from further surgery [10]. If a gallbladder mass is diagnosed prior to operative intervention (such as preoperative



**Figure 4:** Specimen pathology A-B. A. Gross pathology of gallbladder mass with cholecystocolonic fistula to colon. B. Microscopy of transmural invasion of gallbladder adenocarcinoma to serosal surface (pT3); narrow arrow depicting malignant infiltrative glands, broad arrow showing tumor extending to serosa.

or intraoperative gallbladder mass), further imaging with high-resolution CT with liver protocol or MRI with contrast and staging CT of the chest, abdomen, and pelvis is indicated [10]. The clinical T, N, M stage of such investigations will determine further management, including any need for surgical resection [10]. The overall goal of curative resection is to achieve margin negative resection with adequate lymphadenectomy [10].

Tumor markers in the form of CA 19-9 are also useful in the absence of hyperbilirubinemia, which is a poor prognostic marker for biliary malignancies [28]. However, only patients with a positive Lewis antigen genotype are able to secrete CA 19-9 [29]. According to Vestergaard et al., it is estimated that 7% of the population lack this antigen and therefore, do not secrete detectable concentrations



of CA 19-9 regardless of tumor burden, limiting the utility of this test in such a population [29].

If uncertain of the extent of metastatic disease, staging laparoscopy may be considered to differentiate resectable from unresectable disease, but it is not required if there is high-resolution (preferably  $\leq 2$  mm thick cuts), preoperative, cross-sectional imaging available [10]. When staging laparoscopy was performed in patients initially deemed resectable on preoperative imaging, Agarwal et al. found the overall yield in detecting unresectable disease in locally advanced gallbladder cancer to be 25.2% vs. 10.7% in early T1/T2 gallbladder cancer [17]. This study suggests that the yield of staging laparoscopy is highest for advanced disease (clinical T3 or greater stage), which may mitigate the risk of nontherapeutic laparotomy [17].

If a mass is discovered intra-operatively during attempt at

laparoscopic cholecystectomy, it is recommended to perform peritoneal washings for cytology, staging laparoscopy of all 4 quadrants with particular attention to the liver, peritoneum, and omentum, biopsy of any suspicious lesions, and deferral of resection to allow complete staging workup [10]. Peritoneal cytology has been performed in various settings in the workup of biliary tract cancer, but it has only been shown to be positively associated with advanced disease with the prevalence of positive cytology of 6% and 38% in T3 and T4 biliary malignancies, respectively [18]. For patients who are found to have T3 and T4 lesions corresponding with stage 3 and stage 4 disease, respectively, the prognosis for each is universally poor [18]. Therefore, although overall survival was worse in patients with positive peritoneal cytology, when adjusting for TNM stage, the positive peritoneal cytology did not have significant prognostic value [18].

Instead, positive peritoneal cytology may detect occult metastatic disease that may preclude curative intent surgical resection. With this said, Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has been anecdotally shown to improve overall survival in patients with biliary tract cancers, including gallbladder cancer [30,31]. In a multi-institutional, prospective cohort study, median survival was 21.4 months in patients who underwent CRS/HIPEC compared to 9.3 months in patients who underwent surgical resection with systemic chemotherapy [30]. This study was limited by small sample size (34 CRS/HIPEC and 21 systemic chemotherapy following surgical resection) for which only 16 patients had primary gallbladder cancer [30]. Larger studies are necessary to support the utilization of CRS/HIPEC in gallbladder cancer with limited peritoneal disease, for which National Comprehensive Cancer Network (NCCN) guidelines currently do not recommend [10].

For Tis to T1a lesions with negative margins, typically detected incidentally following cholecystectomy for other indications, observation only is recommended [10]. For T1b or greater disease, further resection has been advocated from partial segment 4b/5 liver resection to formal hepatic lobectomy (depending on extent of involvement), resection of adjacent organs if involvement is suspected (e.g. colon), hilar lymphadenectomy, and possibly bile duct resection with reconstruction if there is bile duct involvement [10]. For patients with a histological diagnosis of T1b to T3 gallbladder cancer following cholecystectomy, 35% of patients had residual disease detected on re-resection, which was associated with improved median overall survival, compared to those without re-resection (52.6 months vs. 13.7 months,  $p < 0.001$ ) [30].

Although still recommended by NCCN guidelines, the need for hepatic resection for T1b and greater lesions has been debated [10]. In a 2019 retrospective study by Cho et al., no significant difference in Overall Survival (OS) was identified when hepatic resection was performed for T2a (94.1% vs. 100%,  $p = 0.552$ ;) or T2b lesions (70.9% vs. 100%,  $p = 0.365$ ) [22]. However, patients with more aggressive pathologic, clinical, or radiologic features were more likely to undergo hepatic resection, a selection bias that could explain the survival differences [22]. Moreover, the study had a small sample size of only 81 patients, and was likely inherently underpowered to detect any meaningful differences [22].

T3 and greater lesions (based upon clinical or pathological stage) that are resectable should be considered for neoadjuvant therapy prior to undergoing resection [16]. There is an emerging paradigm for neoadjuvant therapy in gallbladder cancer, as it is an

aggressive disease that is inherently systemic with curative surgery often associated with significant perioperative risk, as shown by Kneuert et al. [32] reporting an overall morbidity of 28% and a perioperative mortality rate of 2.7% in 13,558 patients undergoing major hepatobiliary surgery. Shen et al. found that bile duct resection yields an overall morbidity of 54% in hepatobiliary surgery [33]. In a study published by Chaudhari et al. in 2018, patients undergoing neoadjuvant chemotherapy and exhibiting over 50% response rate who then subsequently underwent curative resection, were found to have increased overall survival compared to those who did not receive neoadjuvant chemotherapy [OS 49 months vs. 7 months;  $p=0.0001$ ] [16].

The need for Common Bile Duct (CBD) resection and reconstruction should be considered only in instances when a negative cystic duct or biliary margin cannot be achieved. A multi-institutional review in which 32.4% of patients underwent concomitant CBD resection after surgical resection for curative intent found that CBD resection did not affect overall survival [19]. Concomitant CBD resection was actually associated with decreased survival [HR=1.40, 95% CI 0.87 to 2.27,  $P=0.170$ ] [19] and associated with an increased risk of postoperative complications [60% vs. 23%,  $p=0.0001$ ] [20]. Given the increased perioperative risks without associated survival benefit, bile duct resection should only be performed if required for margin negative resection.

Adjuvant chemotherapy in the treatment of gallbladder cancer is recommended for most stages [10]. Lymph node metastasis is considered a poor prognostic factor for gallbladder cancer and is frequently treated with adjuvant therapy, although the optimal management of these patients is unknown [10]. In 2018, Bergquist et al. evaluated the impact of adjuvant chemotherapy in patients with T2 or greater and node positive disease, finding an improved overall survival with adjuvant chemotherapy [24]. However, only 25 percent of patients included in the study were available for analysis of overall survival, as they were the only patients to receive the appropriately indicated adjuvant therapy after surgical resection, demonstrating the need for further trials [24]. As most gallbladder cancer recurrences are systemic rather than local, the benefit of adjuvant radiation is uncertain. In a recent study assessing combined adjuvant chemotherapy and radiation in patients with T1-T3/N1/M0 disease, there was an associated survival benefit with combined chemoradiation, regardless of margin status in comparison to adjuvant chemotherapy alone suggesting a potential role for adjuvant radiation in lymph node positive gallbladder cancer [27].

Although surgery provides the potential for durable cure, the majority of patients will present at an advanced stage and are considered to have unresectable disease at the time of diagnosis [13]. Unresectable disease precluding surgical resection may be classified as metastatic or locally advanced disease. This includes: Liver metastases; peritoneal metastases; malignant ascites; distant thoracic metastases; tumor involvement of para-aortic, para-caval, aorto-caval, and superior mesenteric artery, and/or celiac axis lymph nodes; extensive vascular involvement of the hepatoduodenal ligament without ability to perform resection and reconstruction; or encasement/occlusion of the hepatic artery or portal vein [1]. When assessing clinical N stage of patients, only hilar lymph nodes within the hepatoduodenal ligament are considered surgically resectable [1]. Such patients with unresectable disease due to advanced T or N stage or positive M stage are traditionally recommended to undergo palliative chemotherapy

with or without external beam radiation therapy with aims to control the disease and prolong survival, if appropriately fit [10]. Table 2 summarizes the NCCN guidelines currently recommended for optimal therapy for patients in this category [10].

In a prospective, non-randomized trial comparing chemotherapy to best supportive care in patients with unresectable gallbladder cancer, median overall survival with the use of chemotherapy was 36 weeks compared to 13 weeks with best supportive care ( $p<0.001$ ). When comparing chemotherapy regimens, a combination of either Gemcitabine-Cisplatin or Gemcitabine-Oxaliplatin therapy was superior to single agent chemotherapy with Gemcitabine or Capecitabine with median survival of 37 vs. 27 weeks ( $p<0.002$ ) [26]. These results further validate similar findings demonstrated by Sharma et al. in 2010, supporting the use of chemotherapy over best supportive care to prolong survival in unresectable disease [25]. Furthermore, Gemcitabine and Cisplatin was shown to be associated with a significant survival advantage without substantial toxicity compared to Gemcitabine alone, supporting the role of combination chemotherapy in advanced gallbladder disease [34].

## Conclusion

Gallbladder cancer remains a highly aggressive disease and should be included in the differential diagnosis among patients with a GB mass or mass-like thickening. While this presentation is less frequent, it remains a clinical challenge necessitating appropriate recognition and consideration. Despite its history of poor prognosis, there is emerging evidence to support multi-modal management [10,24,27]. Traditionally, for resectable disease, this has consisted of margin negative surgical resection followed by adjuvant systemic therapy. However, evolving evidence supports upfront neoadjuvant systemic therapy, particularly for more advanced disease [16]. In these situations, a neoadjuvant approach to gallbladder cancer has been shown to improve overall survival, compared to surgery first approach [16]. Moreover, a neoadjuvant approach in locally advanced gallbladder cancer may allow for down-staging for eventual surgical resection. In cases of metastatic disease (including lymph node metastases beyond the hepatoduodenal ligament), systemic chemotherapy has been shown to improve survival compared to best supportive care [25,26,34]. As a result, gallbladder cancer should be managed in a subspecialty referral center with a multidisciplinary approach to care.

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