Original Article

Role of chemoradiation in gallbladder cancer—a single institution retrospective analysis

Ravi Kumar Paluri[1,2#^], Hatic Haris[1#], Peng Li[1,3], Olumide Gbolahan[1], Rojymon Jacob[1], Upender Manne[1]

[1]Division of Hematology-Oncology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; [2]Atrium Health Wake Forest Baptist, Comprehensive Cancer Center, Winston-Salem, NC, USA; [3]Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL, USA

Contributions: (I) Conception and design: RK Paluri, H Haris; (II) Administrative support: U Manne, RK Paluri; (III) Provision of study materials or patients: RK Paluri, H Haris; (IV) Collection and assembly of data: RK Paluri, H Haris; (V) Data analysis and interpretation: P Li, RK Paluri, U Manne; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Ravi Kumar Paluri, MD, MPH, FACP. Associate Professor, Division of Hematology-Oncology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; Atrium Health Wake Forest Baptist, Comprehensive Cancer Center, 1 Medical Center Blvd., Winston-Salem, NC 27157, USA. Email: rpaluri@wakehealth.edu.

Background: Gallbladder cancer is one of the highest fatal malignancy. We conducted a retrospective analysis to study the outcomes of gallbladder malignancy in an academic care setting.

Methods: Data was collected retrospectively on patients treated at University of Alabama at Birmingham between January 2005 and June 2015 from the electronic medical record using a standardized data collection tool (Redcap). We evaluated for predictors of overall survival (OS) and progression-free survival (PFS).

Results: Of the 93 patients in this study, 66.7% were female. Adjuvant chemotherapy (CT) was given to 11% and adjuvant chemoradiation (CRT) to 14%. On multivariate analysis, albumin >3.5 g/dL, uninvolved margins, absence of lymphovascular invasion, and peri-neural invasion were independent predictors of OS and PFS. The overall median survival time was 24.3 months with a 5-year survival rate at 23.7%. Surgery with CRT for the full cohort had a median OS of 54.4 *vs.* 15.6 months (P=0.0048) compared to surgery CT alone. The OS in stage 3–4 patients with surgery alone *vs.* surgery & CT was 5.5 *vs.* 28.7 months, respectively (P=0.0061). The PFS for the same group was 4.6 *vs.* 17.5 months (P=0.0052).

Conclusions: The dismal survival rates of gallbladder cancer made adjuvant therapy (CT or CRT) critically important. Concurrent CRT needs to be evaluated in randomized clinical trials for potential improvement in clinical outcomes compared to currently approved standard of care, adjuvant CT alone.

Keywords: Gallbladder cancer; retrospective analysis; outcomes; single institution; adjuvant chemoradiation (adjuvant CRT)

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Introduction

Gallbladder cancer and cancers of the extrahepatic ducts account for approximately 12,200 cases annually in the United States, resulting in 3,700 deaths (1). The incidence rate is 1–2 cases per 100,000, signifying a gradual decline over the past 30 years (2). The disease is more prevalent in women, with shorter median survival, relapse time, and shorter recurrence after recurrence compared to hilar cholangiocarcinoma (3). Risk factors include

^ ORCID: 0000-0002-2317-7082.

cholelithiasis, porcelain gallbladder (7–15%), anomalous pancreaticobiliary duct junction, and primary sclerosing cholangitis.

Most patients remain asymptomatic, but symptoms such as pain, anorexia, nausea/vomiting, and obstructive jaundice may develop. In some cases, a palpable gallbladder in a jaundiced patient, known as the Courvoisier sign, can be identified (4). Adenocarcinoma is the most common histological feature, followed by squamous cell or adenosquamous carcinoma, similar to other gastrointestinal malignancies (5). The 5-year survival rate is about 10% (6), with the prognosis significantly influenced by the stage of the disease. Node-positive disease often results in dismal outcomes. Thus, most patients with muscle-invasive (T2) disease require interval portal lymphadenectomy for accurate staging (7).

Surgery remains the only curative treatment option for incidental gallbladder cancer with Tis or T1a staging (6). However, given the poor prognosis for patients with T stages equal to or greater than two and nodal disease, consideration of adjuvant therapy is crucial (3). According to the National Comprehensive Cancer Network (NCCN), standard options typically include adjuvant fluoropyrimidine chemoradiation (CRT), fluoropyrimidine, or gemcitabine chemotherapy (CT). A Surveillance, Epidemiology, and End Results (SEER) database revealed a nonsignificant improvement in survival when comparing adjuvant therapy with surgery, the most considerable survival benefit being in cases of nodal involvement (8). While adjuvant therapy in gallbladder cancer has shown improved outcomes, underpowered trials, and data dilution from including other biliary tract cancers make informed decision-making challenging.

The lack of high-quality, data-driven evidence often results in treatment regimens shaped by institutional protocols and personal preferences. This led to significant underutilization of adjuvant therapy approaches (9). To better comprehend the role of adjuvant CRT therapy in localized gallbladder cancer and patients with unresectable disease, we conducted a retrospective analysis to study the outcomes of gallbladder malignancy in patients at our institution. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-186/rc).

Highlight box

Key findings

- According to a retrospective study conducted at a single institution, the use of adjuvant chemoradiation (CRT) is linked to improved survival when compared to surgery as a standalone treatment.

What is known and what is new?

- Adjuvant chemotherapy (CT) is the established standard of care for biliary tract tumors. However, in certain cases, selected patients in the adjuvant setting might benefit from the inclusion of CRT.

What is the implication, and what should change now?

- The efficacy of CRT should be assessed through larger randomized clinical trials to determine whether it offers potential enhancements in clinical outcomes when compared to the currently approved standard of care, which involves only adjuvant CT.

Methods

We retrospectively collected data on patients with gall bladder cancer treated at tertiary-level cancer center, University of Alabama at Birmingham between January 2005 and June 2015 using a standardized data collection tool (Redcap). We obtained Institutional Review Board approval before conducting the study. To be included in the study, participants had to meet the following requirements: age >18 years, and their tumor had to be located in the gallbladder and undergo definitive surgery. There were also exclusion criteria: patients with multiple primary tumors, those diagnosed with carcinoma *in situ*, those with incomplete information regarding their cancer type, unknown surgical method, and those with incomplete follow-up information, and those who passed away within 30 days of diagnosis. Stage 4b patients were not included as they were deemed unresectable. The variables assessed included: basic demographics (age, race, insurance status, residence), symptoms at presentation, including imaging/laboratory data, functional status, stage at presentation, presence of biliary stents, histology of pathology, and CT used. The American Joint Committee on Cancer (AJCC), 2017, eighth edition, tumor-node-metastasis (TNM) staging for gallbladder cancer system was used.

Statistical analysis

Survival outcomes were compared between patients who received different treatments. We conducted all statistical analyses using SAS software version 8.2 (SAS Institute Inc., Cary, NC, USA) and generated survival curves with Prism 8 (GraphPad Software Inc., San Diego, CA, USA). Patient survival rates were evaluated using the Kaplan-

Meier method, and survival rate comparisons across two or more groups were analyzed using the log-rank test. During the development of the Cox regression model, we first performed univariate analysis to identify statistically significant variables suggesting predictors of overall survival (OS). Taking into account data integrity, we included some variables as continuous variables in the regression model. Variables that were significant in univariate analysis were then incorporated into the Cox regression model (using a backward method) for multivariate analysis, helping us to evaluate for any independent factors that influenced patient prognosis. OS was defined as the time between surgery and death or censored at the last follow-up date. Progression-free survival (PFS) was defined as the time to recurrence or death. All tests were two-sided, and we deemed a P value of less than 0.05 as statistically significant.

Ethical statement

The retrospective study conformed to the provisions of the Declaration of Helsinki (as revised in 2013) and was conducted in accordance with the standard research regulations. The study was approved by the Institutional Review Board of the University of Alabama at Birmingham (No. 151217003), and in alignment with institutional policies. The need for informed consent was waived due to the retrospective nature of this study. Patient data were de-identified and handled with confidentiality to ensure patient privacy and protection.

Results

Patient characteristics

In the evaluation of 93 patients diagnosed with gallbladder cancer: the median age was 65.6 years, with a majority of the patients (66.7%) being females. Most patients were Caucasians (67.7%), followed by African Americans (30.1%).

The most common type of tumor was adenocarcinoma. According to the AJCC 2017 staging, 30% of the patients were diagnosed at an early stage (stage I & II). The median time to start CT after surgery was 1.5 months. The treatment details were as follows: 10.8% of the patients received adjuvant CT with gemcitabine; 14.0% received both adjuvant CT and radiation; fluoropyrimidine was used as a radiation sensitizer; 2.2% received neoadjuvant CT (CT given before surgery to shrink the tumor); 1.1% received neoadjuvant CT and radiation; 5.4% received palliative CT. In 48.0% of the patients, no postoperative CT was administered. The treatment modality was unknown in 17.2% of the patients. These findings gave insights into the demographics of gallbladder cancer patients, the nature of the tumors, the stage at diagnosis, and the treatment approaches used at the tertiary-level cancer center (*Table 1*).

Survival analysis

On univariate analysis, albumin >3.5 g/dL, uninvolved margins, absence of lymphovascular invasion, and perineural invasion were favorable predictors of OS and PFS (*Table 2*). However, there was no statistical significance in multivariate analysis owing to the small sample size. The median follow-up was 20.2 months. The median survival for the study cohort of 93 patients was 19.1 months, with a 5-year survival rate of 20% (*Figure 1*). Stage-specific OS rates for early stages (1 & 2) at 5 years was 53.1% *vs.* 10.8% for late stages (3 & 4) (*Figure 2*). For the cohort assessment who underwent any form of adjuvant therapy (CT or CRT), the median survival with surgery alone was 27.4 *vs.* 24.3 months with no statistical significance (P=0.6429, *Figure 3*). Among the patients who received any adjuvant CT or CRT (n=31), the median survival was higher for the patients who received CRT compared to CT (54.4 *vs.* 15.6 months, P=0.0048; *Figure 4*). The median OS in stage 3–4 patients with surgery alone *vs.* adjuvant CT/CRT was 5.5 *vs.* 28.7 months, respectively (P=0.0061; *Figure 5*). The PFS for the same group was 4.6 *vs.* 17.5 months (P=0.0052; *Figure 6*).

Discussion

Patients diagnosed with gall bladder cancers frequently face a generally unfavorable prognosis. Treatment-wise survival analysis revealed that most patients underwent surgical procedures, as surgery is the definitive treatment for gallbladder cancers. Patients diagnosed at stage I are prime candidates for extensive surgery. Even though surgical resection is a commonly employed treatment approach for patients at higher stages, there is a significant risk of distant metastasis and a consequent decrease in the 5-year survival rate. As a result, additional or adjuvant therapy is strongly recommended for these patients (10,11). A comprehensive treatment plan that combines surgery and adjuvant therapy is adopted for those with stages III and IV. Even though the usage of adjuvant therapy in these patients remained low, there is a paradigm shift in incorporating adjuvant

Table 1 Demographical and oncological characteristics of patients (n=93)

Characteristics	Value
Age (years)	65.6 (11.9)
Gender (female)	62 (66.7)
Race	
Caucasians	63 (67.7)
AA	28 (30.1)
Other	2 (2.2)
Smoking (yes)	35 (37.6)
Alcohol (yes)	21 (22.6)
Albumin	
<2.0 g/dL	2 (2.2)
2.0–3.5 g/dL	22 (23.7)
>3.5 g/dL	48 (51.6)
Unknown	21 (22.6)
CA19-9 (U/mL)	950.0 (4,165.3)
Clinical stage	
1	7 (7.5)
2	35 (37.6)
3	27 (29.0)
4	24 (25.8)
Pathological staging	
1	9 (9.7)
2	19 (20.4)
3	28 (30.1)
4	37 (39.8)
Tumor histology	
Ductal adenocarcinoma	1 (1.1)
Signet-ring cell carcinoma	2 (2.2)
Adenosquamous	4 (4.3)
Papillary adenocarcinoma	3 (3.2)
Mucinous adenocarcinoma	2 (2.2)
Adenocarcinoma (not otherwise specified)	73 (78.5)
Neuroendocrine carcinoma	2 (2.2)
Small cell carcinoma	3 (3.2)
Other (any comments)	3 (3.2)
Margin status	
Involved	29 (31.2)
Uninvolved	45 (48.4)
Unknown	19 (20.4)
LVI	
Yes	17 (18.3)
No	28 (30.1)
NA	48 (51.6)
PNI	
Yes	19 (20.4)
No	20 (21.5)
Unknown	54 (58.1)
Total number of lymph nodes examined	1 [0–10]
Total number of positive lymph nodes	0 [0–4]
Positive lymph nodes	28 (30.1)
Treatment modality	
Adjuvant	32 (34.4)
CT	17 (18.3)
CRT	14 (15.1)
Radiation alone	1 (1.1)
Neoadjuvant	7 (7.5)
CRT	3 (3.2)
CT	4 (4.3)
Surgery alone	45 (48.4)
Unknown	9 (9.7)

Data are presented as mean (SD), n (%), or median [range]. AA, African Americans; CA19-9, carbohydrate antigen 19-9; LVI, lymphovascular invasion; NA, not available; PNI, peri-neural invasion; CT, chemotherapy; CRT, chemoradiation.

therapy routinely with recent data based on the BILCAP study. However, the role of chemoradiotherapy remains undefined, though some studies suggest that postoperative adjuvant radiotherapy could benefit selected patients.

After our retrospective analysis of patients with gallbladder malignancy, it was apparent how dismal the survival rates were in this group, while at the same time, it drove the

Table 2 Univariate analyses of OS

Characteristics	Hazard ratio (95% CI)	P
Age (>18 *vs.* ≤18 years)	1.01 (0.99, 1.04)	0.2099
Gender (female *vs.* male)	0.84 (0.51, 1.38)	0.4905
Race (AA *vs.* non-AA)	0.91 (0.53, 1.55)	0.7304
Smoking (yes *vs.* no)	1.21 (0.73, 2.03)	0.4608
Alcohol (yes *vs.* no)	1.16 (0.65, 2.08)	0.6120
Albumin (>3.5 *vs.* ≤3.5 g/dL)	0.41 (0.24, 0.71)	0.0016
Margin (uninvolved *vs.* involved)	0.32 (0.18, 0.58)	0.0001
LVI (yes *vs.* no)	5.15 (2.20, 12.07)	0.0002
LN (+ *vs.* –)	1.25 (0.74, 2.10)	0.4028
PNI (yes *vs.* no)	5.42 (2.09, 14.07)	0.0005
Time to treatment from surgery (1 month increase)	1.02 (1.00, 1.04)	0.0658

OS, overall survival; CI, confidence interval; AA, African Americans; LVI, lymphovascular invasion; LN, lymph node; PNI, peri-neural invasion.

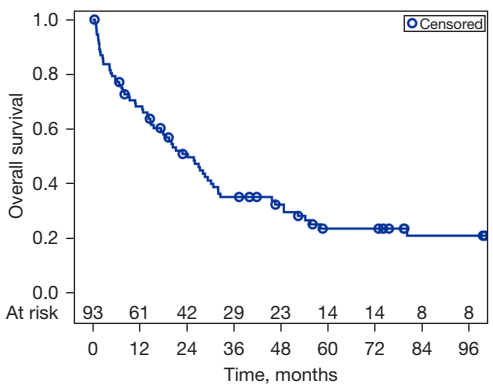
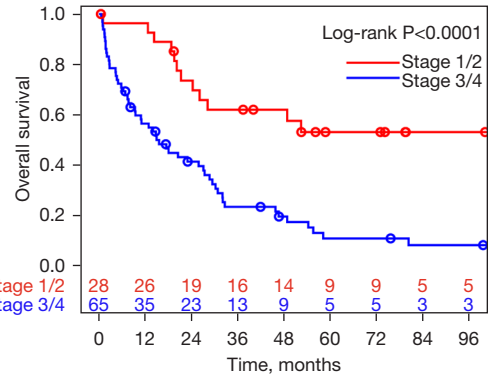


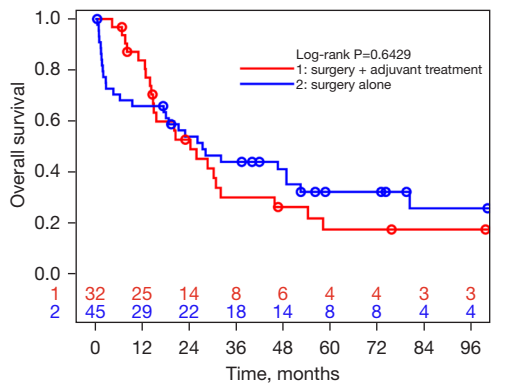
Figure 1 Median 5-year OS of study cohort. OS, overall survival.

impetus to explore potential treatment modalities to improve outcomes. Most patients presented with a clinical stage ≥3 which profoundly impacts the OS. The association of tobacco and alcohol on gallbladder cancer in our study showed no strong link, but this is certainly not the case for other biliary tract malignancies (12). The role of albumin as an independent risk factor of the OS in gallbladder patients stems from it being a barometer of inflammation and malnutrition (13). With increased lymphovascular/peri-neural invasion and surgical margins involved, there is an impact on PFS & OS and the treatment modalities that need to be utilized.



Group	Median survival (months)	1 year	2 years	3 years	5 years
1 & 2 (n=28)	NA	96.3%	73.6%	62.0%	53.1%
3 & 4 (n=65)	15.0	56.5%	41.4%	23.4%	10.8%

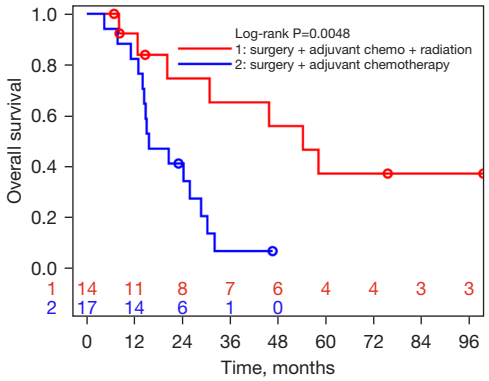
Figure 2 OS stage 1 & 2 *vs.* 3 & 4. NA, not available; OS, overall survival.



Group	Median survival (months)	1 year	2 years	3 years	5 years
+ adjuvant	24.3	83.8%	52.8%	30.2%	17.6%
Alone	27.4	65.9%	53.9%	44.1%	32.4%

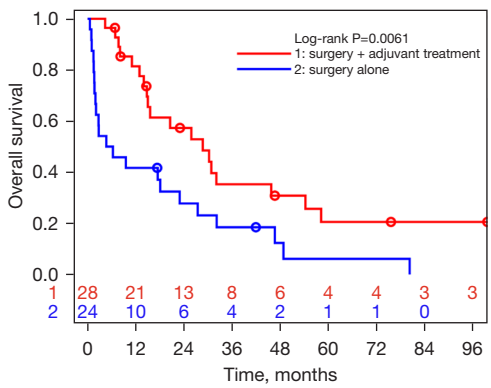
Figure 3 OS surgery alone *vs.* surgery plus adjuvant treatment (all stages). OS, overall survival.

For the whole cohort assessment (n=93) who underwent any form of adjuvant therapy (CT or CRT), there was no significant difference between surgery alone *vs.* adjuvant therapy (P=0.6429). Among the patients with all stages who received any adjuvant CT or CRT (n=31), the median survival was higher for those who received CRT compared to CT (54.4 *vs.* 15.6 months, P=0.0048). This group included high-risk stage 4a patients who had portal vein, hepatic vein, or local organ involvement. For stages 1–3,



Group	Median survival (months)	1 year	2 years	3 years	5 years
+ chemo	15.6	82.4%	41.2%	6.9%	
+ chemo + rad	54.4	92.3%	74.6%	65.3%	37.3%

Figure 4 OS of patients: surgery plus chemotherapy *vs.* surgery plus chemotherapy plus radiation. Chemo, chemotherapy; rad, radiation; OS, overall survival.

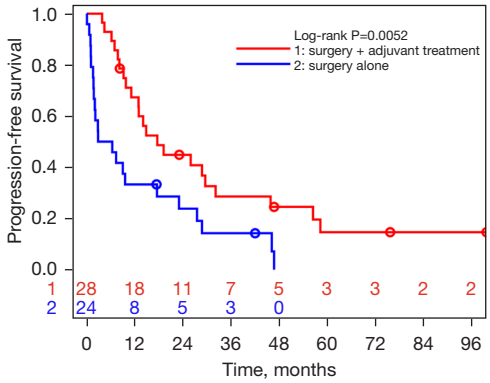


Group	Median survival (months)	1 year	2 years	3 years	5 years
+ adjuvant	28.7	81.4%	57.3%	35.3%	20.6%
Alone	5.5	41.7%	27.8%	18.5%	6.2%

Figure 5 OS of stage 3 & 4 patients: surgery alone *vs.* surgery plus adjuvant treatment. OS, overall survival.

surgery (n=16) with CRT had a median OS of 58.1 *vs.* 20.5 months (P=0.004) compared to surgery followed by CT. The median OS in stage 3–4 patients with surgery alone *vs.* adjuvant CT/CRT was 5.5 *vs.* 28.7 months, respectively (P=0.0061). This suggests the benefit of radiation in the adjuvant setting in selected high-risk patients.

The most critical factor predicting local recurrence and survival is the presence of residual cancer after surgical



Group	Median survival (months)	1 year	2 years	3 years	5 years
+ adjuvant	17.5	67.4%	44.9%	28.6%	14.7%
Alone	4.6	33.3%	23.8%	14.3%	0%

Figure 6 PFS of stage 3 & 4 patients: surgery alone *vs.* surgery plus adjuvant treatment. PFS, progression-free survival.

resection (14). Thus, the current standard of care is to undergo a secondary hepatic resection in patients diagnosed with incidental gallbladder cancer after cholecystectomy. This often leads to upstaging of disease by identification of liver invasion in a significant proportion of patients (15). In addition, the presence of lymph node metastasis also affects survival, as demonstrated by the inferior survival in our stage 3 and 4 patients. Extended cholecystectomy thus translates to a survival benefit by improving the accuracy of staging and also by resection of residual disease even in patients treated with CRT (16,17).

Adjuvant treatment with radiation has shown improvements in survival outcomes across multiple studies (18), likely due to improvement in local control, and the benefit appears limited to patients with regional lymph node, vascular or liver involvement. Adjuvant CRT with a 5-fluorouracil (5-FU)-based regimen has improved local control and survival (17,19). The meta-analysis by Wang *et al.* showed improvements mainly in patients with T2–4 or node-positive disease (20). An analysis of 5,029 patients with T1–3N0–1 gall bladder cancer from the National Cancer Data Base (NCDB) demonstrated improved 3-year OS with CRT with no benefit in node-negative patients (9). However, another analysis of the NCDB shows that the survival benefit with adjuvant therapy in T2–3 node-positive disease is not sustained at 5 years follow-up (21).

The benefit of adjuvant therapy, as evident in our analysis, appears most established in patients with locally

advanced disease who receive adjuvant CRT with a 5-FU-based regimen (10). Interestingly, node positivity seems to predict a better response to CRT compared to CT (22), suggesting that radiation continues to play a role in node-positive disease. This study also demonstrated that patients with T2 or T3 disease with unknown lymph node status had improved survival with CRT, highlighting the need to adopt intensification strategies, especially if lymph node status is unknown.

While adjuvant radiation-based approaches have demonstrable local control and a survival benefit, there continues to be a high distant failure rate, highlighting the need for a practical systemic treatment approach (23,24). The traditional gemcitabine and platinum-based regimen has improved OS and PFS across multiple randomized studies (25,26) in advanced gallbladder cancer. The study by Takada *et al.* (27) was one of the early studies to show the benefit of a maintenance CT regimen after surgical resection. Recently, adjuvant capecitabine for eight cycles in patients with completely resected gall bladder cancer demonstrated a significant improvement in OS (53 for capecitabine *vs.* 36 months for observation, P=0.028) (28). However, the dosing used in the study (1,250 mg/m^2 twice daily 14/21 days) may be intolerable for many patients and will likely require dose reductions.

Combining CT with CRT could improve distant and local recurrence rates. There appears to be a benefit of CT in addition to the CRT backbone in the retrospective study by Lim *et al.*, demonstrating improved disease-free survival and OS rates (29). The single-arm SWOG S0809 study, which treated patients with four cycles of gemcitabine plus Xeloda followed by concurrent capecitabine-based CRT, demonstrated promising efficacy and feasibility of sequential therapy, but 2-year recurrence rates remained close to 50% (30). Our study signaled a significant difference between CRT and CT alone that needs further validation in a larger cohort.

The retrospective nature of this study lends itself to several limitations—most significantly being the small sample size. This study relied on records, so they're dependent on the accuracy of those records while transitioning to an electronic medical record system (31). This study only shows associations, not cause-and-effect relationships. The treatment modality was unknown in 17.2% of the patients. The mean number of nodes included in lymphadenectomy needed to be improved, and there was the possibility of missing data with pathology reports. This variability is likely attributable to the lack of standardized guidelines concerning the number of lymph nodes to be removed during surgery.

Additionally, discrepancies in staging could stem from changes in staging criteria between 2010 and 2017. Moreover, the single-center studies may not represent the wider population, as they reflect the specific patient population and treatment practices at the tertiary-level cancer center. In addition, patients selected for intensive adjuvant strategies using CT with or without radiation are often in better overall health, which could have affected the survival benefit in our study due to selection bias.

Nevertheless, the strength of our study is that it provides important insights into the best treatment modality for an aggressive form of malignancy. This is valuable for generating hypotheses that can be tested in future prospective studies. The lack of high-quality randomized data on this rare malignancy remains a challenge. Still, our retrospective study with a larger population of 93 patients provides insight into CT or CRT's role. Also, examining our study cohort shows that the makeup is diverse. Further research on multidisciplinary approaches for gall bladder cancer management is needed, particularly at advanced stages.

Conclusions

The dismal relapse and survival rates of gallbladder cancer make adjuvant therapy critical in improving outcomes.

Adjuvant radiation or CRT can offer potential benefits in treating gallbladder cancer. However, its use is generally individualized based on factors such as the stage of the disease, the patient's overall health status, the risk of recurrence, and the potential benefits and risks of intensive CT. Patients should have a detailed discussion with their oncologist to make an informed decision about their treatment plan. We have examined different treatment modalities related to CT and CRT combined with surgery, demonstrating significant disease control. These results will require further validation in prospective cohort studies.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-186/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-186/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-186/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-186/coif). RKP serves as a consultant for Ipsen, Seagen, and Exelixis. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The retrospective study conformed to the provisions of the Declaration of Helsinki (as revised in 2013) and was conducted in accordance with the standard research regulations. The study was approved by the Institutional Review Board of the University of Alabama at Birmingham (No. 151217003), and in alignment with institutional policies. The need for informed consent was waived due to the retrospective nature of this study. Patient data were de-identified and handled with confidentiality to ensure patient privacy and protection.

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