Surgical treatment and Survival of Gallbladder Cancer Patients: A Systematic Review

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Received: January 2022; Accepted: February 2022; Published: March 1, 2022.
Citation: Ali Ibrahim A. Alshehri. Surgical treatment and Survival of Gallbladder Cancer Patients: A Systematic Review World Family Medicine. 2022; 20(3): 75-83. DOI: 10.5742/MEWFM.2022.9525019

Abstract

Objective: To assess the outcome and overall survival of surgery for gallbladder cancer.

Methods: A systematic literature search was performed in PubMed. The review question was structured in PICO format. Then, the search was conducted according to a certain research strategy and certain limitations. The titles and abstracts of all retrieved citations were assessed by two medical consultants, who decided which articles to read in full text. The selected full text articles were independently screened by the researcher and the two colleagues. In a consensus meeting, it was determined which articles fulfilled the pre-defined inclusion criteria and eligibility.

Results: A total of four citations were identified as fulfilling the predetermined eligibility criteria (two prospective cohort studies and two retrospective studies), while 630 studies which did not fulfill the inclusion criteria were excluded.

Conclusions: Optimal treatment of gallbladder cancer is still evolving. Radical surgery in combination with standardized lymph node dissection constitutes the cornerstone of the surgical treatment. Patients' overall survival depends upon their tumor stage, levels of CA199, and tumor location in gallbladder.

Key Words: Gallbladder cancer, Surgery, Survival, Systematic Review.

Introduction

Gallbladder cancer (GBC) is a rare cancer, where most patients are diagnosed at advanced stages, with an aggressive nature and subsequent high mortality. Its worldwide incidence is less than 2/100,000 (1). It has broad geographical and ethnic distributions, with low incidence in Saudi Arabia (2), and higher incidence among Mexican and Indian Americans, and Eastern Europeans. Well-established risk factors include age, obesity, cholelithiasis, female gender, positive family history, and anomalous junction of the pancreato-biliary duct (3).

Surgery for patients in early stages (i.e., pT1 and pT2) is the only chance for cure, while in advanced stages, radical surgery may be impossible, due to metastases into the liver hilum, other organs or lymph nodes (4). However, recurrence and mortality rates remain high in patients with advanced cancer stages after radical resections and the extensive surgery is associated with high morbidity (5).

Early stages of GBC are often diagnosed incidentally in conjunction with cholecystectomy due to gallstone disease, and an additional radical surgery is mostly needed (6). However, the extent of needed radical surgeries remains a matter of debate, according to several questions, regarding the extent of liver resection, lymph nodes dissection, and the need for bile duct resection and sometimes other organs (7).

The present systematic review aimed to assess the outcome and overall survival of surgery for gallbladder cancer.

Methods

In accordance with the PRISMA checklist, a systematic literature search was performed in PubMed by the researcher. The following review question was structured in PICO format (Table 1):

"In adult patients diagnosed with gallbladder cancer (P), liver resection, lymph node resection, common bile duct resection, or extensive surgery of adjacent structures (I), compared with cholecystectomy alone (C), what is their disease-free survival (O)?".

Then, a literature search was conducted according to the following research strategy:
("gallbladder neoplasms"[MeSH Terms] OR gallbladder cancers[Text Word]) AND "surg [Ti]*

The following search limitations were considered:
- Study design: Cohort, randomized controlled, or retrospective studies. All case reports, case series, and reviews were not included.
- Language: English
- Limits: Abstract, Full text, and Publication years 2020-Present.

The titles and abstracts of all retrieved citations were assessed by two medical consultants (OM and HA), who decided which articles to read in full text. The selected full text articles were independently screened by the researcher and the two colleagues. In a consensus meeting, it was determined which articles fulfilled the pre-defined inclusion criteria and eligibility (Table 1).

The included studies and their design and patient characteristics are presented in Table 2. The articles were critically appraised using the Systematic review - Critical Appraisal Skills (CASP) program. In most studies differences in the overall survival were compared. A graphic presentation of the selection process is presented in Diagram (1):

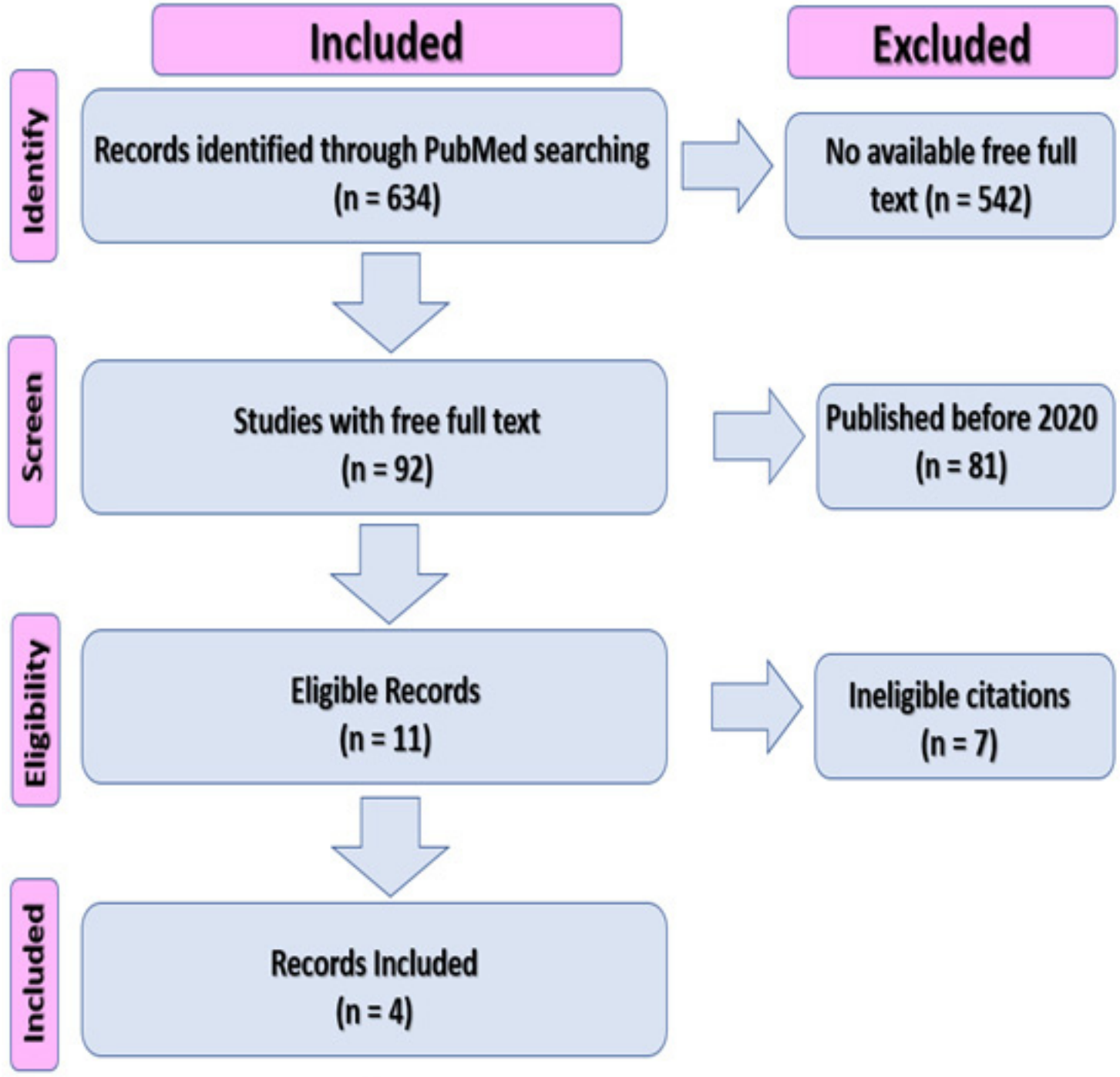
Table 1: The PICO list for the inclusion criteria and eligibility

Population (P)	• Adults • Preoperative diagnosis of gallbladder cancer. • Subgroup evaluation by T-stage or TNM-stage
Intervention (I)	• Liver resection, liver segments 4b & 5 or radical resection • Lymph node resection (standard or extended) • Resection of the common bile duct • Extensive surgery of adjacent structures or/and organs
Comparison (C)	• Cholecystectomy alone
Outcome (O)	• Disease-free survival

Table 2: Description of the studies included in the systematic review

Reference	Study design	Intervention	Outcome
Liu et al. [8]	Prospective Cohort	- 35 patients received hyperthermic intraperitoneal perfusion chemotherapy combined with radical surgery and Capecitabine. The study group induded43 patients received radical surgery and capecitabine	The 1-year survival rates of the study and control groups were 91.4% vs. 76.7% The 2-year survival rates were 26.3% vs. 17.5%, respectively (P<0.05)
Chang et al. [9]	Prospective Cohort	715 GBC cases were divided into three groups who received simple resection (full-thickness cholecystectomy for removal of primary tumor site, n=126), radical resection (gallbladder bed removal combined with partial hepatectomy, n=349), and palliative surgery (treatment at advanced stages, n=240).	Radical resection had best overall survival at clinical stage II, while simple resection had best overall survival at tumor clinical stage IV
Leigh et al. [10]	Retrospective	17 patients received cytoreductive surgery and hyperthermic intraperitoneal chemotherapy	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy may offer a survival benefit in selected hepatocellular carcinoma patients with peritoneal carcinomatosis
Yuza et al. [11]	Retrospective	47 patients with T1b GBC, 29 (62%) underwent simple cholecystectomy and 18 (38%) underwent radical resection with regional lymph node dissection	Most T1b GBCs had local disease. In T1b GBC patients, the decision of radical resection is justified. Additional radical resection is not required following simple cholecystectomy provided that the penetration depth is restricted toward the muscular layer and that surgical margins are uninvolved.

Diagram 1


Included
Excluded
Identify
Records identified through PubMed searching (n = 634)
No available free full text (n = 542)
Screen
Studies with free full text (n = 92)
Published before 2020 (n = 81)
Eligibility
Eligible Records (n = 11)
Ineligible citations (n = 7)
Included
Records Included (n = 4)

Results

A total of four citations were identified as fulfilling the predetermined eligibility criteria. We excluded 630 studies because they did not completely fulfill the inclusion criteria, having no available free full text (n=542), or being published before 2020 (n=81). The remaining 11 full-text articles were assessed for eligibility of which 7 were excluded. Therefore, we included four studies in the final synthesis (8); Chang et al. (9); Leigh et al. (10); and Yuza et al. (11), with a total number of 857 included patients.

The systematic review comprised two prospective cohort studies Liu et al (8) and Chang et al. (9) in addition to two retrospective studies Leigh et al. (10); and Yuza et al. (11). No randomized controlled trials were found. Outcome variable was mainly overall survival, but no studies described the quality of life of included patients. Prospective cohort studies were sub-grouped according to intervention and comparisons were performed for each intervention.

Management of GBC patients

The study of Liu et al. (8) explored the effect of hyperthermic intraperitoneal perfusion chemotherapy combined with radical surgery and capecitabine on gallbladder cancer. Surgical plans were based on patients' preoperative imaging, important organ functions, liver reserve functions, and resectability of the liver. Resection of the liver was according to the National Comprehensive Cancer Network guidelines (12), with routine liver S4b plus S5 resection at stage T2 and T3; right hepatectomy or enlarged right hepatectomy was performed for patients with liver bed involvement >2 cm, located in the neck of the gallbladder, invading the gallbladder triangle, or involving liver duodenal ligament lymph node metastasis; and according to the results of lymph node biopsy in groups 13a and 16 during the operation, hepatoduodenal ligament lymph node dissection or enlarged lymph node dissection was selected. Cystic duct biopsy was routinely performed during the operation, and the positive patients needed to be combined with extrahepatic bile duct resection, ranging from the upper back of the pancreatic head to the first hepatic hilum, and a Roux-en-Y bile duct jejunum anastomosis (10).

Chang et al. (9) studied the impact of surgical strategies on the survival of gallbladder cancer patients. According to the strategies of received surgical treatment, their patients were divided into: simple resection (i.e., partial or total resection of primary tumor site, n=126); radical resection (i.e., total resection of primary tumor site with other organs, n=349); and palliative surgery (n=240), which was performed in patients with distant metastases cancer, wide tumor invasion, and conditions wherein the patient cannot bear aggressive surgery or they refuse. Patients with tumor location not in gallbladder neck, earlier clinical staging (I/II), T1/T2 stage, normal level of tumor markers, and gallstone were more likely to undergo simple resection. Patients with young age, N1/N2 stage, and poorly differentiated tumor were more likely to receive radical resection. Patients with M1 stage, CA199 ≥ 27 U/ml, CA242 ≥ 20 IU/ml, and unreceived adjuvant therapy were more likely to receive palliative surgery.

The study of Leigh et al. (10) explored whether cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is indicated in hepatobiliary malignancies. Cytoreductive surgery/Hyperthermic intraperitoneal chemotherapy was performed in a standard fashion (13), with diagnostic laparoscopy in all cases to assess the feasibility of cytoreduction prior to hyperthermic intraperitoneal chemotherapy. However, the procedure was aborted at the discretion of the operating surgeon if the tumor burden was deemed too bulky to attempt cytoreduction. The peritoneal cancer index was calculated prior to operative debulking (14), and the completeness of cytoreduction score was recorded at the conclusion of the procedure. All patients who underwent hyperthermic intraperitoneal chemotherapy received 40 mg of mitomycin C at 42 °C for 90 minutes. Creation of anastomoses was performed after the completion of hyperthermic intraperitoneal chemotherapy. Major perioperative complications were graded according to the Clavien-Dindo classification system (III–V), as occurring within 30 days of cytoreductive surgery/hyperthermic intraperitoneal chemotherapy (15).

Yuza et al. (11) retrospectively investigated the long-term outcomes of surgical resection for GBC patients of whom 29 patients (62%) underwent simple cholecystectomy and 18 patients (38%) underwent radical resection with regional lymph node dissection.

Outcome and Survival

The study of Liu et al. (8) reported that GBC patients who underwent hyperthermic intraperitoneal perfusion chemotherapy had longer hospitalization time for patients needed to extend the extubation time of the abdominal drainage tube. Moreover, due to the complexity of gallbladder cancer surgery, the general operation time is long, so intraoperative hypothermia is prone to occur. Cisplatin applied to patients who received hyperthermic intraperitoneal perfusion chemotherapy did not cause significant liver and kidney damage, and only one patient with myelosuppression could be corrected after symptomatic treatment. The most common complication of hyperthermic intraperitoneal perfusion chemotherapy was gastrointestinal reactions, manifested as the discomfort of the abdomen and delayed defecation. However, there were no serious surgical-related complications, e.g., hepatic wound bleeding, bile leakage, and anastomotic leakage. Therefore, cytoreductive surgery/hyperthermic intraperitoneal chemotherapy is associated with improved cancer survival but an increased risk of infection, which was the most important cause of perioperative morbidity and death. The overall infection rate was 30% in the control group and 34% in the hyperthermic intraperitoneal perfusion chemotherapy group.

Moreover, Liu et al. (8) reported that the median survival of the surgery combined with the gemcitabine treatment group was 15.3 months. The median survival time of patients treated with hyperthermic intraperitoneal perfusion chemotherapy was 19.2 months, suggesting that hyperthermic intraperitoneal perfusion chemotherapy may significantly prolong the median survival time of patients. The one-year survival rates of the study groups were 91.43% vs. 76.71%, and the two-year survival rates were 26.29% vs. 17.53%, respectively. The median survival of the surgery combined with the gemcitabine treatment group was 15.3 months. The median survival time of patients treated with hyperthermic intraperitoneal perfusion chemotherapy was 19.2 months, suggesting that hyperthermic intraperitoneal perfusion chemotherapy may significantly prolong the median survival time of patients. The one-year survival rates of the study groups were 91.43% vs. 76.71%, and the two-year survival rates were 26.29% vs. 17.53%, respectively.

The study of Chang et al. (9) reported a high mortality rate within about 12 months after surgery as one of the primary limitations for the utilization of radical surgery at stage II. At advanced stages, compared with simple resection or palliative surgery, the effect of radical surgery on overall survival was significantly decreased. There was no significant difference in 5-year survival at stage III between radical resection and simple resection groups, but palliative surgery groups had the lowest overall survival. Thus, aggressive resection is still an effective therapy at stage III, even if it is only available in some individuals . The difference of overall survival at stage IV between radical resection and palliative surgery groups was not significant. Also, the simple resection groups had good performance for overall survival at stage IV. The median overall survival time of the 715 patients was 24 months. From stage I to IV cases, the survival rates were 85.71%, 64.63%, 36.08%, and 10.42%, respectively. Compared with the palliative surgery groups, patients with simple resection or radical resection had significant longer overall survival time ($p<0.0001$). Patients with simple resection had the best overall survival outcome, with a 47.62% of survival rate and 51 months of median overall survival time. The overall survival outcome of patients with radical resection was moderate, with a 39.83% survival rate and 34 months of median overall survival time. The palliative surgery patient group had the worst overall survival outcome, with an 8.75% of survival rate and 10 months of median overall survival time. The difference of overall survival between simple resection and radical resection in stage I patients was not significant ($p=0.934$). However, patients with radical resection had a better overall survival than patients with simple resection at stage II ($p = 0.042$). Compared with simple resection and radical resection groups, patients with palliative surgery had the worst overall survival at cancer stage III ($p=0.028$). At cancer stage IV, patients with simple resection had the best overall survival ($p = 0.0129$).

Moreover, Chang et al. (9) found that GBC patients from the countryside, those with tumor location of gallbladder body or neck, with increased TNM stages, with poorly differentiated of the tumor, with CA199 ≥ 27 U/mL, with CA242 ≥ 20 IU/mL, and with surgical treatment of radical resection or palliative surgery were related to a worse prognosis.

The study of Leigh et al. (10) reported that the median overall survival for their patients was 23 months with one-year and three-year survival rates of 73% and 41%, respectively, with a longer survival in the hepatocellular carcinoma cohort compared to the other cohorts. Of the pancreaticobiliary malignancies, the longest median survival was seen in patients with cholangiocarcinoma (19 months), though this was still considerably shorter than in hepatocellular carcinoma. The median progression-free survival for the entire cohort was 8 months, with no significant differences between the cohorts. All patients experienced tumor recurrence by 3 years postoperatively. The shortest median progression-free survival was in patients with GBC (2 months), and the longest was in patients with pancreatic cancer (15 months). Age at surgery (HR 1.13, $p = 0.027$) and peritoneal cancer index (HR 1.24, $p = 0.011$) were independent predictors of overall survival, while there were no independent predictors of progression-free survival.

Yuza et al. (11) reported that open surgical approach was more prevalent among patients who underwent open radical resection than among patients who underwent simple cholecystectomy (open in 21 patients; laparoscopic in 8 patients, $P=0.017$). The cumulative 10- and 20-year overall survival rates were 65% and 25%, respectively. The 10-year overall survival rate following simple cholecystectomy was akin to that following radical resection (66% and 64%, respectively, $P=0.618$). The outcome following simple cholecystectomy (10-year disease-specific survival rate of 100%) was equivalent to that following radical resection (that of 86%, $P=0.151$). While old age (> 70 years, hazard ratio: 5.285, $P = 0.003$) and gender (female, hazard ratio: 0.272, $P=0.007$) had a strong effect on patients' overall survival; surgical procedure (simple cholecystectomy vs. radical resection) and surgical approach (open vs. laparoscopic) did not did not affect inclusive survival in patients with T1b GBC.

Discussion

GBC is an uncommon cancer type with a high mortality rate and poor long-term survival outcomes (16). Surgical treatment is the most effective intervention for the cure of GBC patients (17); however, curative resection is feasible in a minority population of GBC patients (18). According to the Guidelines of the National Comprehensive Cancer Network, a radical resection is recommended for T1b and more advanced GBC (12).

Currently, there are no accepted, robust treatment guidelines for T1b GBC. The National Comprehensive Cancer Network guidelines endorsed radical resection along with portal lymph node dissection for T1b GBC (12), whereas the Japanese guidelines recommend simple cholecystectomy, provided that the depth of invasion is histologically restricted to the muscular layer (19).

The present systematic review has focused on surgical approaches for management of GBC. The lack of knowledge in this field highlights the importance of a structured care to centralize experience and to standardize both the surgical procedure and the documentation to gain more knowledge in the future. It is important to perform radical liver resection with tumor free margins, but the extent of liver resection for earlier stages has been insufficiently evaluated (6; 20).

The fact that lymph node metastases deteriorate survival after gallbladder cancer surgery is unquestionable. An adequate lymph node resection seems important not only for staging, but also for survival. Niu et al. (21) reported that, in patients with advanced lymph node infiltration (N2), no benefit was seen despite extended lymph node resection. Interestingly cases with skip lymph node metastases (N2 lymph node tumors despite no N1 tumors) have been described (22) and might explain conflicting data for N2-positive patients, as some report outcome comparable to N1- patients (23).

Eilard et al. (24) stated that the effect of direct radical surgery versus staged operations in a controlled setting where pathology reports are rap idly analyzed and the needed re-resections are scheduled within a very short time span, has not been studied. The current practice is based on the general oncologic principle to aim at direct radical resection. The low survival rate of patients with residual cancer at the time of re-resection supports this principle, though the time passed from the first to the second operation might influence the rate of residual disease.

Liver resection is related to a high mortality rate, while young age would play a protective role for patients with radical resection in the perioperative period. Patients with advanced tumor stages, high levels of tumor markers (CA199, CA242), metastatic cancer (M1), and unreceived adjuvant therapy, were more associated with palliative surgery.

For the metastatic cancer and surgery inoperable patient, palliative surgery would be the treatment for relieving the patient's pain and promoting the patients' quality of life (9).

Hyperthermic intraperitoneal perfusion chemotherapy has achieved unique effects in the treatment of peritoneal cancer. Moreover, cytoreductive surgery combined with hyperthermic intraperitoneal perfusion chemotherapy was applied for the treatment of advanced gallbladder cancer (25-26). Liu et al. (8) included patients with stage III GBC treated with operation and capecitabine or hyperthermic intraperitoneal perfusion chemotherapy combined operation and capecitabine were enrolled to identify the effect of hyperthermic intraperitoneal perfusion chemotherapy on stage III GBC.

Due to the complexity of GBC surgery, the general operation time is long, so intraoperative hypothermia is prone to occur. Compared with the control group, hyperthermic intraperitoneal perfusion chemotherapy has corrected the hypothermia caused by long-term surgery to a certain extent and promoted body temperature recovery. Cisplatin applied to hyperthermic intraperitoneal perfusion chemotherapy did not cause significant liver and kidney damage. After hyperthermic intraperitoneal perfusion chemotherapy treatment, there were no serious surgical-related complications such as hepatic wound bleeding, bile leakage, and anastomotic leakage. Also, there was no difference in the incidence of postoperative complications between the two groups (8).

Cytoreductive surgery/hyperthermic intraperitoneal perfusion chemotherapy is associated with improved cancer survival but an increased risk of infection in patients predominantly for colorectal cancer and pseudomyxoma peritonei. The overall infection rate is 43%, and the most common site of infection is surgical site infection accounting for 27% (27).

Hundal and Shaffer (28) stated that the 5-year survival rates were 8% for stage IIIa and 7% for stage IIIb. Mao et al. (29) showed that the median survival time of patients with advanced GBC was less than one year. The study of advanced cholangiocarcinoma with the value of adjuvant chemotherapy after surgery revealed that the median overall survival of stage III cholangiocarcinoma was about 20 months (30).

Therefore, radical surgery combined with postoperative capecitabine chemotherapy is one of the standard treatments for stage III GBC. Consequently, combined with hyperthermic intraperitoneal perfusion chemotherapy can effectively prolong survival time without increasing surgery-related complications.

Study limitations

This systematic review could not include any randomized controlled trials. In the included retrospective studies, there is always a risk for selection bias, mainly favoring the more extensive treatments, performed on the fittest patients in each subgroup or in the most experienced centers. Moreover, since all studies included in the present systematic review were either retrospective or prospective cohort studies there was an obvious risk for selection bias, more pronounced in more advanced stages. Especially for major interventions, there was a risk for confounding by indication with more extensive surgery in cases with large tumor burden.

Conclusion

Hyperthermic intraperitoneal perfusion chemotherapy combined with radical surgery and capecitabine on stage III gallbladder cancer could increase survival benefits without increasing surgery-related complications.

At tumor stage II GBC, radical resection is the most effective surgical therapy. However, the effect of radical resection at advanced stages could be restricted. Advanced tumor stages, high levels of CA199, and tumor location in

gallbladder body or neck would indicate a poor prognosis. Compared with aggressive resection, palliative surgery groups would have a significantly worse prognosis. The overall survival for GBC mainly depends on the stages of detected tumor; however, aggressive surgery could be the reasonable surgical therapy for patients with GBC, especially, and radical resection could be a most effective surgical strategy for patients with tumor at stage II to obtain a long-term survival. The role of radical resection in advanced stages is restricted, but, in early stages, the utilization of radical surgery should be further developed.

Hepatopancreaticobiliary malignancies with pancreatic adenocarcinoma have poor survival with current palliative systemic therapies. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy may offer a survival benefit for hepatocellular carcinoma with pancreatic adenocarcinoma. However, there does not appear to be any benefit for pancreaticobiliary malignancies.

Most T1b GBCs spread only locally. As pre-operative diagnosis, including tumor penetration of T1b GBC, is difficult, the decision of radical resection is justified. Radical resection may not be essential after simple cholecystectomy provided that the depth of invasion is restricted to the muscular layer and that surgical margins are uninvolved.

Therefore, optimal treatment of GBC is still evolving. Radical surgery in combination with standardized lymph node dissection constitute the cornerstone of the surgical treatment. Overall survival of patients with GBC depends upon tumor stage, levels of CA199, and tumor location in gallbladder. GBC should be rap idly managed.

Acknowledgements
The author would like to thank Dr. Ossama Mostafa and Dr. Hussein Assiri for their efforts and help in assessment of citations and their assistance in deciding which articles to include in the systematic review.

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