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ORIGINAL ARTICLE

Ten-year experience in the management of gallbladder cancer from a single hepatobiliary and pancreatic centre with review of the literature

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Abstract

Background. There is no consensus regarding the optimum surgical approach to gallbladder cancer. This study reviews the management of gallbladder cancer in a single unit. *Methods.* Retrospective study of 73 consecutive patients diagnosed with gallbladder cancer. Twenty-three patients underwent surgery with curative intent (surgical group), 28 patients underwent exploratory surgery but had inoperable disease (surgically inoperable group) and 22 patients had inoperable disease radiologically (radiologically inoperable group). Within the surgical group, nine patients (cholecystectomy group) were diagnosed with gallbladder cancer after routine cholecystectomy. *Results.* The inoperable groups had significantly higher bilirubin and alkaline phosphatase (ALP) than the surgical group ($p = 0.02$ and $p < 0.01$, respectively). Age >68, white cell count (WCC) $>7.6 \times 109$/L, platelet $>345 \times 109$/L, bilirubin >16 mol/L, ALP >124 iu/L and sodium ≤ 137 mmol/L were markers of inoperability. Age, haemoglobin and neutrophil:lymphocyte ratio (NLR) were predictors for survival following surgery ($p = 0.04$, $p = 0.01$ and $p < 0.01$, respectively). The surgical and cholecystectomy groups had significantly higher median survivals than the surgically and radiologically inoperable groups (18.97 and 26.17 months versus 5.03 and 12.20 months, $p = 0.04$). *Conclusion.* Curative surgical resection of gallbladder cancer improved survival. Exploratory laparotomy which revealed inoperable disease reduced survival. Preoperative WCC, platelet, bilirubin and ALP may be used as additional discriminators during the investigation and work up prior to surgery.

Key Words: *gallbladder, cancer, malignancy, survival*

Introduction

Carcinoma of the gallbladder is associated with a very poor prognosis. The overall five-year survival without aggressive surgical treatment is less than 5% [1,2]. Surgery remains the only curative treatment for gallbladder cancer. Unfortunately, the majority of patients have metastatic or locally advanced disease at presentation [3]. Less than 20% of cases have disease which is potentially curable by surgical resection at the time of diagnosis [4].

Surgical management for gallbladder cancer is variable and a range of different operations are undertaken for the disease in different centres. This varies from simple cholecystectomy to extended liver resection with resection of common bile duct and lymphadenectomy [5–7]. However, there is evidence of long-term survival following radical resection [8], although, this surgery is associated with significant morbidity and mortality [9].

Despite the advances in radiological assessment allowing more accurate preoperative staging of the disease, a significant proportion of gallbladder cancers are found to be unresectable at surgical exploration [4]. A thorough selection process is therefore critical to ensure that, as few patients are possible with incurable disease proceeding to surgery. Identification of factors which may predict tumour unresectability could prevent patients being subjected to unnecessary surgical exploration with no potential survival benefit.

This study reviewed the clinical practice in a single hepatobiliary and pancreatic unit over a 10-year period with the aim of identifying factors that

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correlate with improved outcome following surgical intervention for gallbladder cancer.

Methods

Patients

Seventy-three consecutive patients were referred to the Department of Hepatobiliary and Pancreatic Surgery at Leicester General Hospital with suspected gallbladder cancer between 1996 and 2006. We reviewed retrospectively collected data from medical records, and therefore, ethical approval is not required for the study.

Each patient underwent a rigorous assessment process in an attempt to determine tumour resectability prior to surgery. Patients with resectable disease radiologically underwent staging laparoscopy to identify metastatic and miliary disease below the resolution of conventional radiological imaging. All suspicious peritoneal and serosal deposits or lymph nodes were biopsied. Patients with tumour masses which had favourable anatomical characteristics for resection and no evidence of widespread disease or lymph node metastasis proceeded to an extended right liver resection (right trisegmentectomy), excision of the common bile ducts, radical lymphadenectomy (with skeletonisation of the left portal vein and left hepatic artery) and hepaticojejunostomy using a roux-en-Y configuration (radical resection). Patients in whom extended liver resection was deemed not feasible due to anaesthetic concerns proceeded to segmental liver resection (IVb/V) with excision of the common bile duct, radical lymphadenectomy and hepaticojejunostomy (segmental resection).

Comparison of groups

Comparisons between the groups were made in respect of the patients' demographics, socioeconomic status, tumour characteristics, disease staging, operative details and serological results. These factors were further analysed to identify predictors for operability and survival.

Statistical analysis

Student's *t*-, Fisher's exact and Chi-squared tests were applied to compare the groups on all variables. Receiver Operator Characteristics (ROC) curves were utilised for further analysis of factors that demonstrated significant differences between the groups. Survival functions were measured using Kaplan-Meier survival curves. All statistical analyses were carried out using SPSS 13.0® for Windows®. A value of $p < 0.05$ was considered statistically significant.

Results

Between 1996 and 2006, 73 patients were diagnosed with gallbladder cancer in this unit. The surgical group included 23 patients who underwent surgery with curative intent. Amongst the patients with inoperable disease, 28 patients were deemed inoperable only at surgical exploration (surgically inoperable group) and 22 were deemed to have inoperable disease based on radiological findings (radiologically inoperable group). Within the surgical group, nine of the 23 patients had the diagnosis of gallbladder cancer made following histological examination of the cholecystectomy specimen. These patients were further studied as a subgroup (cholecystectomy group) in this study.

The overall median survival for all patients in this study was 12.4 months. Figure 1 showed that the median survival were significantly higher for the surgical group (19.0 months) and the cholecystectomy group (26.2 months) as compared to the surgically inoperable group (5.0 months) and the radiologically inoperable group (12.2 months), with a p value of 0.04. It is worth noting that there are six patients who survived more than 36 months following surgery with curative intent. Five of these patients are still alive at the time of writing, with one patient remaining alive 81.9 months following their original resection. Overall operative mortality was 5.9%.

Demographics including gender, body mass index (BMI), socioeconomic status and racial origin, were comparable among the groups (Table I). The inoperable groups were found to be significantly older than the surgical group ($p = 0.03$). The surgically and radiologically inoperable groups had significantly higher serum white cell count (WCC), platelet count, bilirubin and alkaline phosphatase (ALP) levels but lower sodium concentration at presentation than the

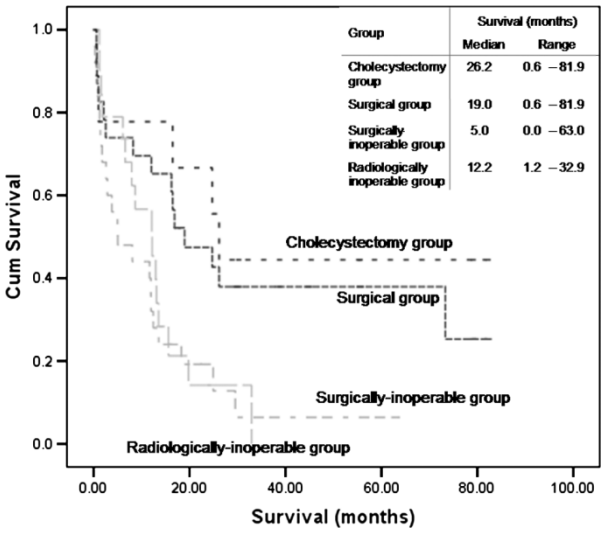

Figure 1. Comparison of survival among the groups ($p = 0.04$).

Table I. Comparison of variables between the groups.

Variables	Cholecystectomy group ($n=9$)	Surgical group ($n=23$)	Surgically inoperable group ($n=28$)	Radiologically inoperable group ($n=22$)
Demographics				
Female: male ratio	3.5	1.8	1.8	1.8
BMI (kg/m^2)	26 (23–32)	24 (18–32)	25 (19–36)	24 (17–26)
Age	66 (47–80)	65 (37–80)	65 (44–83)	75 (54–89)
Socioeconomic status				
Professional/managerial	4	11	10	8
Skilled non-manual	4	6	12	6
Skilled, manual	1	3	3	5
Not working	0	3	3	3
Racial origin				
White	8	16	25	18
White med	0	0	1	0
Asian	0	4	2	3
Black	1	2	0	1
Oriental	0	1	0	0
Preoperative stenting				
Percentage (%) stented	11.1%	13.0%	25.0%	4.6%
WCC ($\times 10^9$/l)	7.5 (4.8–11.6)	8.0 (4.5–16.9)	9.4 (3.7–20.9)	11.5 (6.7–23.7)
Neutrophil ($\times 10^9$/l)	4.9 (3.2–8.1)	5.2 (2.1–14.9)	6.3 (1.7–17.1)	8.3 (1.2–20.0)
Lymphocytes ($\times 10^9$/l)	1.8 (1.2–2.6)	1.9 (0.4–3)	1.8 (0.8–3.6)	1.7 (0.7–3.6)
Nl:LR	2.9 (1.4–4.5)	3.1 (1.1–24.3)	3.8 (1.0–19.2)	5.6 (0.5–26.2)
Haemoglobin (g/dl)	13.6 (12.2–16.5)	12.7 (9.1–16.5)	11.7 (8.9–16.5)	12.4 (7.9–14.5)
Platelet ($\times 10^9$/l)	260 (72–325)	251 (72–615)	326 (156–663)	421 (156–716)
Serology				
Sodium (mmol/l)	138 (136–141)	138 (133–143)	136 (127–141)	133 (127–140)
Potassium (mmol/l)	4.0 (3.5–4.3)	4.1 (3.4–4.7)	3.8 (3.2–5.2)	3.75 (3–5)
Urea (mmol/l)	4.6 (3.6–5.5)	5.15 (3.2–21.5)	4.3 (2.6–7.1)	5.1 (2.8–22.3)
Creatinine (μmol/l)	73 (64–100)	78 (60–309)	74 (56–137)	83 (72–152)
Albumin (g/l)	42 (34–47)	40 (18–47)	33 (17–135)	33 (21–47)
Bilirubin (μmol/l)	10 (5–16)	11 (4–193)	20 (4–398)	17 (5–514)
ALP (iu/l)	83 (36–158)	109 (36–324)	244 (56–1682)	281 (72–1187)
ALT (iu/l)	22 (16–87)	22 (7–159)	54 (11–223)	32 (9–970)
Tumour markers				
CA19.9 (Ku/l)	5 (4–6)	6 (4–23)	610 (3–51453)	152 (94–1280)
CEA (mg/l)	3 (2–4)	4 (2–169)	5 (2–53)	4 (3–82)
Survival				
Survival (months)	26.2 (0.6–81.9)	19.0 (0.6–81.9)	5.0 (0.0–63.0)	12.2 (1.2–32.9)

surgical group ($p=0.03$, $p=0.04$, $p=0.02$, $p<0.01$ and $p<0.01$, respectively).

On comparison of preoperative serological results between the surgical group and the surgically inoperable group, the latter had a significantly higher bilirubin, ALP, alanine transaminase (ALT) levels and a lower sodium concentration compared to the surgical group with p values of 0.02, 0.01, 0.04 and 0.01, respectively. Other serological studies, including full blood count, liver and renal function tests were not notably different between the two groups. There was no difference in the proportion of patients requiring biliary stenting to relieve jaundice preoperatively ($p=0.29$).

The ROC curve was utilised to analyse the value of age (>68), WCC ($>7.6\times10^9$/L), platelet count ($>345\times10^9$/L), bilirubin (>16 mol/L), ALP (>124 iu/L) and sodium concentration (≤137 mmol/L) in

Table II. ROC analysis for markers of resectability.

Variables	Criterion	Area under ROC curve	Sensitivity	95% CI	Specificity	95% CI	p-Value
Age	>68 years	0.638	56.0	41.3–70.0	69.6	47.1–86.7	0.041
WCC	$>7.6\times10^9$/l	0.638	74.4	57.9–86.9	50.0	28.2–71.8	0.564
Platelet	$>345\times10^9$/l	0.648	51.3	34.8–67.6	86.4	65.1–96.9	0.038
Bilirubin	>16 μmol/l	0.659	56.4	39.6–72.2	86.4	65.1–96.9	0.024
ALP	>124 iu/l	0.802	76.9	60.7–88.8	77.3	54.6–92.1	<0.001
Sodium	≤137 mmol/l	0.744	69.2	52.4–83.0	72.7	49.8–89.2	<0.001

Table III. Kaplan-Meier analysis for predictors of survival.

Variables	*p*-Values for surgery with curative intent group	*p*-Values for surgically inoperable group	*p*-Values for all surgical exploration
Age <50 years	0.04	ns	ns
21 ≥BMI <25	ns	ns	ns
Gender	ns	ns	ns
Preoperative stenting	ns	ns	0.03
WCC $<9.5 \times 10^9$/l 0.01	ns	ns	<0.01
Neutrophil $<0.6 \times 10^9$/l	0.01	ns	<0.01
Lymphocytes $>0.9 \times 10^9$/l	ns	ns	ns
NLR <3.75	<0.01	ns	0.02
Haemoglobin ≥11.7 g/dl	0.01	ns	<0.01
Platelet $\geq 325 \times 10^9$/l	ns	ns	<0.01
Albumin >35 g/dl	ns	ns	ns
Bilirubin <25 μmol/l	ns	ns	ns
ALP <110 iu/l	ns	ns	0.03
ALP <50 iu/l	ns	ns	ns
Histological grading of tumour	<0.01	na	<0.01
Clear resection margin (R0)	ns	na	na
Tumour size (≤25 mm)	ns	na	na
T stage	ns	na	na
N stage	<0.01	na	0.01
M stage	<0.01	na	<0.01
Overall TNM stage	0.03	na	0.03
Estimated blood loss ≤300 mls	ns	na	ns
Blood transfusion ≤1 unit	ns	na	ns

na, Not applicable; ns, Statistically not significant.

an attempt to predict patients who would have inoperable disease at surgical exploration. The chief outcome variable was tumour resectability. The areas under the ROC curves plotted were 0.64, 0.64, 0.65, 0.66, 0.80 and 0.74, respectively (Table II). Amongst the above markers, elevated ALP has the best predictive value for tumour unresectability.

Kaplan-Meier survival curves were used to further analyse factors that predict survival within the surgical group (Table III). The analysis showed that age (<50), haemoglobin concentration (≥11.7 g/dL), WCC ($<9.5 \times 10^9$/L), neutrophil ($<0.6 \times 10^9$/L), neutrophil:lymphocyte ratio (NLR) (<3.75) were predictors for survival in this group of patients with p values of 0.04, 0.01, 0.01, 0.01 and <0.01, respectively (Figures 2–6). The TNM (Tumour, Node, Metastasis) staging of disease was also predictive of survival ($p = 0.03$).

Within the surgical group, 10 patients underwent radical resection and the remaining 12 patients had segmental resection. The median survival for those who underwent radical resection was higher than those who had segmental resection but the difference was not statistically significant (24.7 months versus

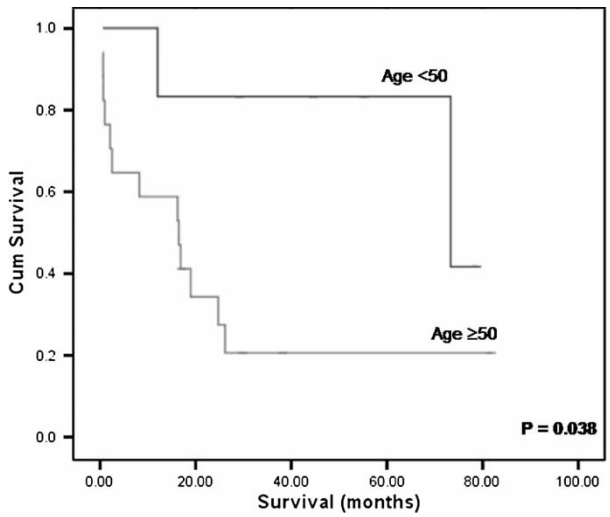

Figure 2. Influence of age on survival within the resection group ($p = 0.04$).

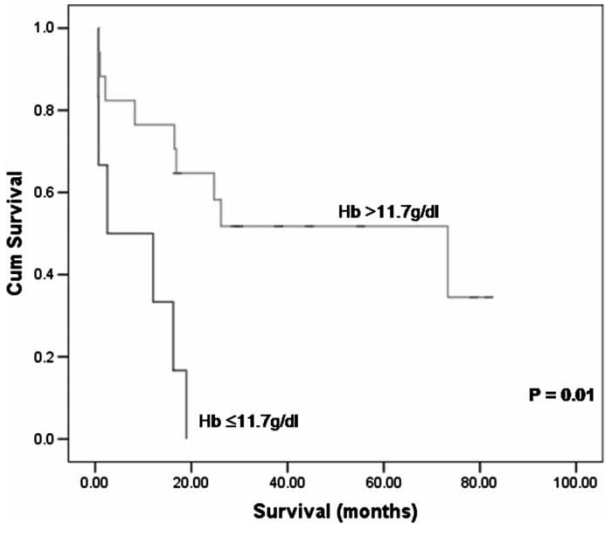

Figure 3. Preoperative haemoglobin level affects survival following resection ($p = 0.01$)

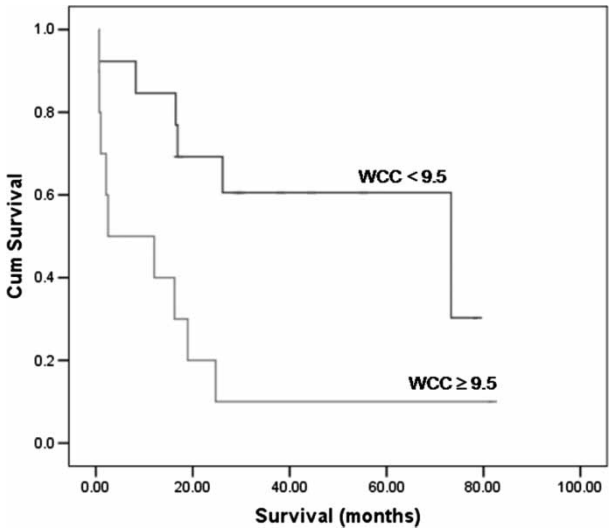

Figure 4. White cell count and survival within the resection group ($p = 0.01$).

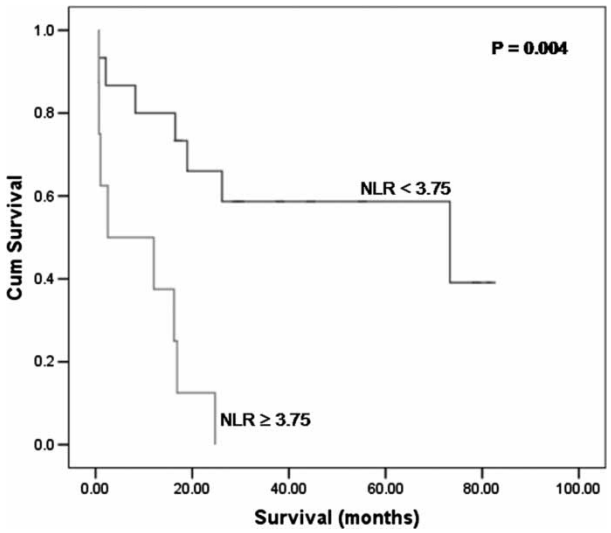

Figure 6. Neutrophil:lymphocyte ratio and survival within the resection group ($p < 0.01$).

16.5 months, $p = 0.326$). Adenocarcinoma was the most common histological type, present in 19 of the 22 patients who had surgery with curative intent.

Discussion

Overall five-year survival for patients with advanced carcinoma of the gallbladder is dismal [10–12]. Following complete surgical resection of early stage disease, the actuarial survival rate had been reported to be as high as 100% [13–15]. However, only a small proportion of patients have resectable disease at the time of diagnosis. Early detection of disease is therefore crucial to improve overall prognosis.

In this study, the survival following resection with curative intent is better than that reported in the literature [16–18]. The improved survival is likely to be due to the careful selection of patients for surgery.

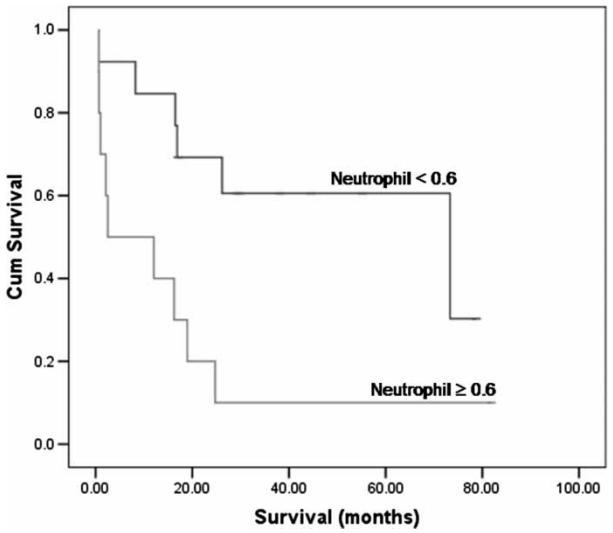

Figure 5. Neutrophil count and survival within the resection group ($p = 0.01$).

The overall operative mortality in our series is 5.9% and is comparable to other series [7,19]. Over the 10-year period, 25% of the gallbladder cancers treated in this unit were identified incidentally following histological examination of resected specimen from elective cholecystectomy. Furthermore, the median survival in this group of patients following curative resection is as high as 26.2 months. This highlights the importance of routine histological examination of all gallbladder specimens, in spite of reports suggesting otherwise [20].

This study also found that more than half of the patients selected for curative surgery for gallbladder cancer did not have resectable disease despite a rigorous preoperative assessment and staging process. The median survival for the surgically inoperable group is significantly lower than that of the radiologically inoperable group, suggesting that exploratory surgery has a negative impact on survival. Other studies have also reported a reduced survival in patients who underwent non-curative surgical exploration [4,21,22].

In comparing preoperative variables between the surgical group and the surgically inoperable group, this study has identified a number of factors which could be used to further predict resectability. The strongest of these factors was serum ALP. Elevated ALP level is a common finding in patients with gallbladder cancer [23]. ALP rises as a result of biliary obstruction due to extrinsic tumour compression upon the biliary tree. The presence of jaundice with associated derangement of biochemical markers may be representative of aggressiveness of the disease and have a role in predicting tumour unresectability and survival [24].

Kaplan-Meier survival curve, plotted for NLR, found it to be a predictor of survival for those who underwent surgery with curative intent. There is

Table IV. Summary of the literature on surgical management of gallbladder carcinoma.

Study	Year	Type of operation	*N*	Age	Mortality	Morbidity	Survival	Remarks
		Total	90					
		Cholecystectomy (excluding pT1 disease)	21					
Kai et al. [31]	2007	Extended cholecystectomy (resection of the gallbladder bed, excluding patient with pT1 disease)	34	Mean 65 (36–89)	NA	NA	Five-year survival rates with pT1, pT2, pT3 and pT4 were 100%, 58%, 23% and 12%, respectively.Five-year survival with pN0, pN1, pN2 and pN3 were 70%, 32%, 14% and 0%, respectively.Five-year survival with Stage I,II, III, Iva and IVb were 100%, 77%, 42%, 28% and 0%, respectively.	Improved survival with more aggressive surgical approach in pT2 gallbladder carcinoma.For pT3/4 patients, five-year survival despite curative resection only approached 30%.
		Resection of segment 4a and 5 (excluding pT1 disease)	20					
		Total	53					
Scheingraber et al. [19]	2007	Resection with curative intent (Individual approach =9; standardized approach =21)	21	Mean 67 (39–88)	9%	26.4%	Median survival following resection with curative intent =14 months (standardized approach) versus seven months (individual approach).	Anatomical liver resection, proof for bile duct infiltration, and in case of tumour invasion, radical resection and lymph dissection of the hepaticoduodenal ligament are essential to improve outcome of locally advanced gallbladder cancer.
		Palliative surgery	32					
		Total	65					
		Cholecystectomy+/– bile duct resection	17					
		Non-anatomical wedge resection +/– bile duct resection	19					
Sasaki et al. [8]	2006	Segment 4+5 resection +/– bile duct resection	11	Mean 64.3(8–80)	3.1%	29.2% overall; 47% with concomitant pancreatico duodenect-omy	Number of five-year survivors =26.	24.1% recurrence despite R0 resection.
		Extended right	1					
		Liver resection+ pancreaticoduodenectomy	17					
		Total	94					

Table IV (*Continued*)

Study	Year	Type of operation	*N*	Age	Mortality	Morbidity	Survival	Remarks
Yokomizo et al. [14]	2006	pN0	70	Mean 68.6 (48–91)	NA	NA	Overall five-year survival = 79.5%Five-year survival for pN0 = 87.1%five-year survival for pN1 = 55.7%.	All patients in this study had pT2 gallbladder carcinoma.
		pN1	24					
		Total (58 without EHBD infiltration, 29 with EHBD infiltration)	110					
		Simple cholecystectomy	11					
		Limited liver resection	24					
Sakamoto et al. [29]	2006	Segment 4+5 resection	15	Median 67(32–80)	11%	24% (for 58 patients without EHBD infiltration)	Five-year survival without biliary infiltration = 55%. Five-year survival with biliary infiltration = 10%.	Biliary infiltration is defined as cancer infiltration of the wall of the extra-hepatic bile duct, via the hepatoduodenal ligament.
		Extended right	29					
		Hepatectomy and pancreaticoduodenectomy	15					
		Hepatectomy combined with lymphadenectomy	8					
		Total	22		9%	46%		
Reddy [9]	2006	Extended hepatic resections	11	Median 54(45–80)	0%	45%	Actuarial three-year overall survival = 72% (median 62 months); Actuarial three-year recurrence-free survival = 68% (median 51months)Number of three-year survivors = 3.	Morbidity is significantly higher in those who underwent bile duct excision 67% versus 10% (in those without bile duct excisionAll R0 resection. fourpatients had portal vein embolisation preoperatively.
		Segment IVB/V hepatectomy	11		9%	27%		
Nagino et al. [34]	2006	Extended hepatic resections and extra-hepatic bile duct resection	61	NA	18%	NA	Number of three-year survivors = 10Number of five-year survivors = 5Three-year survival = 25.3%Five-year survival = 17.1%.	All curative resections, all had portal vein embolisation preoperatively.
		Total	64					
		Extended hepatic resections	19					

Table IV (*Continued*)

Study	Year	Type of operation	*N*	Age	Mortality	Morbidity	Survival	Remarks
Foster [16].	2006	Simple cholecystectomy	28	Median 64(34–82)	NA	NA	Overall median survival = 13 months Estimated five-year survival following extended hepatic resection = 42% Estimated five-year survival following simple cholecystectomy = 22% Estimated five-year survival following palliative resection = 0%.	Radical liver resection improves survival in T2-T3 disease as compared with simple cholecystectomy.
		Palliative resection	17					
		Total	6421					
Kiran [18]	2006	Radical resection	443	Median 73	NA	NA	Overall median survival = 8 months.	Surveillance, Epidemiology, and End Results (SEER) classified disease into localised, regional and distant stage.Median survival for localised stage = 22 monthsMedian survival for regional stage = 8 monthsMedian survival for distant stage = 3 months.
		Complete/partial cholecystectomy +/– lymph node dissection	3236					
		Others (including excision/ debulking)	2742					
		Total	70					
Xiao et al. [21]	2005	Radical resection	22	Mean 58 (26–84)	4.5%	36%	Median survival for radical versus palliative resection versus exploratory laparotomy = 28 months versus nine months versus three months.	22 patients had Nevin stage IV disease; 48 patients had Nevin stage V disease.
		Palliative resection	15					
		Exploratory laparotomy	33					
		Total	19		NA	NA		

Table IV (*Continued*)

Study	Year	Type of operation	*N*	Age	Mortality	Morbidity	Survival	Remarks
Lai [2]	2005	Resection with curative intent (1 had laparoscopic cholecystectomy, 14 had radical cholecystectomy)	15	NA	7.1%	31.6%	Overall five-year survival = 19.1% Median survival following radical resection = 24 months.Five-year survival following resection with curative intent = 57.1%Median survival of five months followingpalliative resection Median survival of three months following palliative medical treatment.	Aggressive resection improves survival results.
		Palliative surgical resection	4		0%	NA		
		Palliative medical treatment	28		NA	NA		
		Total	72					
Kondo et al. [35]	2003	Extended hepatic resections	51	Median 69.5(53–79)	19%	NA	Overall three-year survival = 19% three-year survival without portal vein involvement = 28%.	This study only included patients with Stage IV gallbladder cancer.
		Palliative surgery	21					
		Total number who had resection with curative intent	112					
Kondo [32]	2002	Extended hepatic resections	56	Median 64(33–82)	9%	46%	Overall median survival = 18 months five-year survival = 25%.	
		Other type of resections	56					
		Total	116		21%	44%		
Kondo*l* [30]	2002	Radical resection with curative intent	80	NA	15%	53%	Median survival for stage III = 22.2Median survival for stage IV (M0) = 12.1 monthsMedian survival for stage IV (M1) = 6.6 monthsMedian survival after palliative operation = 4.7 months.	Portal vein resection +/–pancreaticoduodenectomy did not contribute to long-term survival.
		Palliative operation	36		33%	42%		
		Total	68					
Yamaguchi et al. [36]	2002	Simple cholecystectomy	9	Mean 62.8(33–82)	10%	NA	Five-year survival with perineural invasion versus without perineural invasion = 7% versus 72%.	71% patients had perineural invasion.
		Wedge resection	10					
		Liver resection	47					

Table IV (*Continued*)

Study	Year	Type of operation	*N*	Age	Mortality	Morbidity	Survival	Remarks
		Total	28					
Chijiiwa [6]	2001	Extended cholecystectomy / radical resection	22	Mean 62.5	3.6%	14%	Five-year survival following extended cholecystectomy/ radical resection = 59%Five-year survival following simple cholecystectomy = 17%.	All patients in this study had pT2 gallbladder carcinoma.
		Simple cholecystectomy	6					
		Total	58		3.4%			
Endo et al. [37]	2001	Simple cholecystectomy	8	NA	0%	NA	Cumulative five-year survival rate following curative resection = 38.1%Number of three-year survivor = 2.	Hepatoduodenal ligament invasion predicts poor surgical outcome.
		Liver resection + bile duct resection	49		4.1%			
		Total resections with curative intent	100		3.9%			
Fong [22]	2000	Minor liver resection	58	Median 65	0%	48%	Median survival = 26 monthsActuarial five-year survival = 38%Median survival for those who had non-curative operation = 8 months, with actuarial five-year survival of 3%.	Preoperative jaundice and operative blood loss predicted mortality.
		Extended liver resection	42		10%			
		Total	86					
Benoist [7]	1998	Radical resection (partial hepatectomy, regional lymphadenectomy, common bile duct resection)	21	Median 65(42–93)	3.5%	6%	Actuarial overall five-year survival = 26% Median survival following radical resection = 8 monthsActuarial five-year survival following simple cholecystectomy = 44% (Stage I); 22% (Stage II); 0% (Stage III).	Amongst the radical group eight of 21 had nodal metastasis. Actuarial five-year survival = 0% with nodal metastasis and 43% without nodal metastasis.
		Simple cholecystectomy	65					
		Total	70					
		Cholecystectomy	35					
Yamaguchi [38]	1997	Extended cholecystectomy (cholecystectomy+liver bed resection)	23	Mean68.5(32–92)	5.7%	NA	Survival rate pT1 = 100% (five-year)Survival rate pT3 = 22% (three-year) Survival rate pT4 = 20% (one-year).	Cholecystectomy was adequate for pT1 gallbladder carcinoma. Extended cholecystectomy or hepatectomy with extrahepatic bile duct resection and lymph node dissection were justified for pT2 gallbladder carcinoma.

Table IV (*Continued*)

Study	Year	Type of operation	*N*	Age	Mortality	Morbidity	Survival	Remarks
		Extended liver resection	12					
		Total	58					
Bartlett [4]	1996	Resection for cure	23	Median 58(38–78)	0%	26%	Five-year actuarial survival for resection group =58%Median survival for those with unresectable disease =5.2 months.	13 of 17 patients had re-operation after simple cholecystectomy for T2-T3 tumour had residual disease. Therefore, re-resection after simple cholecystectomy is likely to include residual disease and should thus provide the only chance of long-term survival.
		Exploratory laparotomy but unresectable.	35					

NA, data not available.

evidence that NLR is a prognostic factor for colorectal cancer [25] and a predictor of postoperative complications [26]. It is possible that NLR acts as a marker of the tumour-induced systemic inflammatory response and hence is an indirect index of tumour burden. More recent reports suggest that NLR may be clinically valuable in a number of hepatobiliary malignancies, including the prediction of survival following resection of colorectal liver metastases [27] and resectability of pancreatic cancer [28].

A review of the existing literature on the surgical treatment of gallbladder cancer demonstrates that there is no consensus for the management or the surgical approach in those patients. Table IV shows the available literature on the surgical management of gallbladder cancer. Surgical options ranging from simple cholecystectomy to extended liver resection +/– bile duct resection +/– pancreaticoduodenectomy have been described and recommended for all stages of gallbladder cancer [8,18,29]. The literature consistently report an improved survival following radical resection with curative intent [2,30,31] despite the increased perioperative morbidity [9,32]. In spite of this, outcomes from centre to centre following surgery with curative intent were highly variable, with median survivals ranging from seven to 28 months [19,21].

Palliative surgery may carry the benefit of improving the quality of life in these patients. For example, segment III hepaticojejunostomy can be an effective and reliable means of palliation for those with hilar obstruction secondary to gallbladder carcinoma [33]. However, it is important to note that exploratory laparotomy where tumour resection was abandoned due to inoperability has been associated with extremely poor outcome. This is supported by a number of studies [4,21,22] and makes a search for preoperative markers that may indicate tumour unresectability even more important. Confidence in these predictive values would enable us to avoid subjecting patients to unnecessary surgical exploration which may have a negative impact on their survival.

Conclusion

A more standardised management approach for the early detection of gallbladder cancer and radical resection provides a better chance of cure for this disease. Radical resection offers the best probability of long-term survival but is associated with an increased morbidity and mortality. In patients, whose functional status precludes this type of surgery, a more conservative approach such as a segmental liver resection may be required. Surgical exploration where unresectable disease is encountered reduces survival significantly. Hence, diligent preoperative evaluation of all gallbladder cancers is essential to optimise the survival and quality of life in these patients. A more standardised approach in the

surgical management of gallbladder cancer would in addition facilitate the future comparisons between different series.

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