Gallbladder Cancer: Differences in Presentation, Surgical Treatment, and Survival in Patients Treated at Centers in Three Countries

Jean M Butte, MD, Kenichi Matsuo, MD, Mithat Gönen, PhD, Michael I D'Angelica, MD, FACS, Enrique Waugh, MD, Peter J Allen, MD, FACS, Yuman Fong, MD, FACS, Ronald P DeMatteo, MD, FACS, Leslie Blumgart, MD, FACS, Itaru Endo, MD, Hernán De La Fuente, MD, FACS, William R Jarnagin, MD, FACS

BACKGROUND: Gallbladder cancer (GBCA) is a rare malignancy with a variable incidence worldwide. This study analyzed GBCA patients treated at centers in 3 countries. The aim was to assess for location-specific differences in presentation and outcomes, which might suggest differences in pathogenesis or disease biology.

STUDY DESIGN: Data for consecutive patients submitted to operation at Instituto Oncológico Fundación Arturo López Pérez (FALP, Chile), Yokohama City University (YCU, Japan), and Memorial Sloan-Kettering Cancer Center (MSKCC, USA) between 1999 and 2007 were studied retrospectively. Patient demographics, disease- and treatment-related variables and outcomes were analyzed by chi-square, Kruskal-Wallis, and log-rank test.

RESULTS: Two hundred sixty-one patients (MSKCC, 130; FALP, 85; YCU, 46) underwent exploration, and 160 (MSKCC, 91; FALP, 33; YCU, 36) underwent R0 resection. Patients treated at FALP were younger (median 57 years, $p < 0.001$) and more often female (80%, $p < 0.005$); at YCU there were fewer patients with incidental tumors (19.5% compared with more than 60% at FALP and MSKCC, $p < 0.001$). En bloc liver and bile duct resections were performed more commonly at MSKCC and YCU ($p < 0.001$). Patients treated at FALP had more advanced tumor stage compared with those treated at MSKCC and YCU ($p < 0.001$). Disease-specific survival (DSS) was not different among the groups when patients submitted to an R0 resection were analyzed ($p = 0.12$). On multivariate analysis, T-stage, nodal involvement, and bile duct involvement were predictors of DSS; center was not significant.

CONCLUSIONS: Despite some differences in presentation, disease extent, and surgical treatment, DSS after curative intent resection was similar among all 3 groups. The most important predictors of outcomes were related to tumor extent rather than country of origin. (J Am Coll Surg 2011; 212:50–61. © 2011 by the American College of Surgeons)

Gallbladder cancer (GBCA) is an aggressive and highly lethal malignancy,[1] the most common cancer of the biliary tract and the sixth most common gastrointestinal cancer.[2]

Disclosure Information: Nothing to disclose.

Received August 14, 2010; Revised September 3, 2010; Accepted September 10, 2010.

From the Departments of Surgery (Butte, Matsuo, D'Angelica, Allen, Fong, DeMatteo, Blumgart, Jarnagin) and Epidemiology and Biostatistics (Gönen), Memorial Sloan-Kettering Cancer Center, New York, NY; and the Departments of Surgery, Yokohama City University, Yokohama, Japan (Matsuo, Endo) and Instituto Oncológico Fundación Arturo López Pérez, Santiago, Chile (Butte, Waugh, De La Fuente).

Correspondence address: William R Jarnagin, MD, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065. Email: jarnagiw@mskcc.org

Despite an increasing number of patients diagnosed incidentally, most are found with advanced disease, when potentially curative treatment is not feasible and palliative therapy is the only option.[3]

The incidence of GBCA worldwide follows a geographic pattern with considerable variability. The highest incidences are found in India, Asia, Eastern Europe, and South America.[1,4] In a recent world epidemiology report on GBCA, the highest mortality rate was seen in Chile, where GBCA is the primary cause of cancer death in women.[4,5] Japan is another country with a relatively high incidence, where GBCA is responsible for 3.5% of cancer deaths in women and 1.25% in men.[6] By contrast, North America is an area of low incidence, with approximately 1 to 2 new

ISSN 1072-7515/11/$36.00
doi:10.1016/j.jamcollsurg.2010.09.009

Abbreviations and Acronyms

DSS = disease-specific survival
FALP = Instituto Oncológico Fundación Arturo López Pérez
GBCA = gallbladder cancer
MSKCC = Memorial Sloan-Kettering Cancer Center
YCU = Yokohama City University

cases per 100,000 persons diagnosed annually; however, Native American populations, particularly in the Southwest, and immigrants from high-incidence areas have greater risk.[1] In different regions, factors associated with the development of GBCA and the clinical presentation at diagnosis may vary widely.[7,8] Although gallstones commonly coexist with GBCA and appear to play a role in carcinogenesis,[9] the nature of this relationship is ill-defined, and it is equally uncertain if this or other factors account for the marked differences in incidence rates in low and high risk areas around the globe.

Complete resection is the standard of care in patients with localized disease, and is potentially curative.[1,10,11] Despite this, controversy persists regarding the extent of liver resection and lymph node dissection and the benefit of empiric excision of the common bile duct and/or major hepatectomy, major vascular resection, and resection of adjacent organs.[1,10] Optimal resection extent is not well defined and tends to differ worldwide. A recent study from Asia showed that more aggressive surgical treatment is not necessarily better, with essentially the same long-term survival compared with less extensive resections;[12] we have reported similar results.[10]

This study analyzed 3 cohorts of GBCA patients treated at centers in 3 countries with different disease incident rates (Instituto Oncológico Fundación Arturo López Pérez [FALP, Santiago, Chile], Yokohama City University [YCU, Yokohama, Japan], and Memorial Sloan-Kettering Cancer Center [MSKCC, New York, NY]). Demographic, disease-, and treatment-related variables were examined for center-related differences in presentation and outcomes, which if present, might suggest location-dependent differences in disease biology.

METHODS

Subjects and data collection

After Institutional Review Board approval from all 3 institutions, records of patients with potentially resectable GBCA submitted to operation were identified and analyzed retrospectively. At each institution, data were obtained from departmental databases supplemented with review of the medical record. Recorded data included patient demographics, preoperative laboratory values, operative procedures, perioperative outcomes, tumor histopathology and staging, follow-up, and survival.

Preoperative assessment included physical examination and imaging studies (thoracic CT, abdominal CT or MRI, and ^{18}F-fluorodeoxyglucose positron emission tomography [^{18}FDG PET-CT] in selected patients). Postoperative follow-up included physical examination and CT, MRI, and/or ^{18}FDG PET-CT every 4 to 6 months. In patients with incidental tumors (ie, a previous noncurative cholecystectomy), review of the gallbladder specimen was performed in order to determine T stage, the results of which were used to select patients for further surgical therapy (see below).

Surgical mortality was defined as death resulting from postoperative complications at any time after surgery. At the time of last follow-up, patient status was categorized as follows: no evidence of disease, alive with disease, dead of disease, surgical mortality, or dead of other causes. The follow-up was the interval between the date of the definitive operation and the date of last follow-up or death. Only dead of disease was considered an event in the analysis of disease-specific survival (DSS).

Final disease staging was based on the 6th edition of the American Joint Committee on Cancer manual.[13] Curative intent treatment (R0 resection) was defined as a complete resection without microscopic involvement of any margins; R1 and R2 resections were defined as microscopic or macroscopic (or gross) disease, respectively, at 1 or more margin.

Operative details

Our operative approach to resection of GBCA has been documented previously.[10,14,15] There were no differences in indications for operation nor in the general operative strategy across centers. In patients with incidental gallbladder cancers, T1a lesions were considered cured by cholecystectomy alone; tumors with invasion deeper into the wall were selected for reoperation and definitive resection. The optimal management of T1b tumors remains controversial, but reoperation was generally recommended for these lesions as well. In this analysis, the small number of patients with incidental T1b and T2 tumors who refused or otherwise did not undergo reoperation were placed in the R0 resection group.

Staging laparoscopy was performed selectively just before laparotomy to exclude metastatic disease in patients with advanced disease or suspicious radiographic findings. The type of liver resection selected was based on the extent of disease and possible compromise of surgical margins. Major hepatectomy was defined as a right or left hepatectomy or extended hepatectomy. Extended right hepatec-

tomy included Couinaud's segments 4, 5, 6, 7, and 8. Extended left hepatectomy included resection of segments 2, 3, 4, 5, and 8. Right hepatectomy included resection of segments 5, 6, 7, and 8, and left hepatectomy included segments 2, 3, and 4. Minor hepatectomy was defined as resection of segments 4B and 5 or less. Common bile duct resection was typically performed when it was not possible to obtain a negative cyst duct margin or if there was clear or suspected ductal involvement; some patients underwent empiric bile duct resection in order to facilitate lymph node clearance. Lymph node dissection included resection of lymphatic tissue in the porta hepatis and portocaval areas, from the common hepatic artery on the left and the supraduodenal area on the right and extending up to the base of the liver. Vascular involvement (portal vein, hepatic artery) was generally indicative of advanced disease, but vascular resection and reconstruction were performed in selected patients.

Pathologic examination

Incidental GBCA was defined as a tumor identified in the final gallbladder specimen, typically removed for symptoms related to gallstones and not suspected during preoperative staging or during initial cholecystectomy. In these patients, a re-review of the specimen was carried out to confirm the final diagnosis and depth of tumor invasion. Primary tumor size was defined as the largest diameter axis through the sectioned specimen. In patients submitted to reoperation, the final disease stage was determined based on examination of all available specimens; in patients found to have unresectable disease, the final stage incorporated the intraoperative findings (ie, nodal involvement, peritoneal or liver metastases). Patients were staged according to the American Joint Committee on Cancer staging manual, 6th edition.[13] Histologic type, differentiation or grade (well, moderate, or poor), the presence of perineural invasion and/or vascular invasion, and bile duct involvement were determined. Bile duct involvement by tumor was based on histopathologic analysis in patients submitted to resection or clinical and/or intraoperative findings in patients who had unresectable disease. Lymph node involvement (N1 disease) was defined as tumor present in at least 1 lymph node. Staging was based on analysis of the resected specimens; however, in patients who did not undergo a resection, the final stage was based on operative findings combined with analysis of any available tissue.

Survival analysis

DSS information was obtained and compared among the 3 centers from 255 patients, after excluding 2 patients who died perioperatively and 4 patients with neuroendocrine tumors. Also, DSS was obtained and compared in patients treated with curative intent (R0 resection) after excluding patients with neuroendocrine tumor (n = 157).

Statistical analysis

Categorical variables were summarized using proportions and continuous variables were summarized using mean (± standard deviation) and median (range). Characteristics of patients were compared across centers using chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Survival curves were constructed by the Kaplan-Meier method and were compared using the log-rank test. Univariate Cox proportional hazards regression was used to identify factors individually predictive of DSS for the entire cohort and separately for patients who underwent an R0 resection; the small number of patients with T1a tumors treated at each center were included in the survival calculations. All variables significant at the 10% level in univariate analysis were considered for multivariate analysis on a Cox model with 2 exceptions: (1) Numbers of examined and positive nodes were not recorded for approximately 10% of the patients and we chose to use N stage in the multivariate analysis instead; (2) Incidental diagnosis, abdominal pain, and jaundice were highly correlated and only incidental diagnosis was considered in the Cox model, to avoid problems of colinearity. P values from the univariate and multivariate Cox models were from the score test. All tests were 2-sided and statistical significance was defined at $p < 0.05$. Statistical analysis was performed with SAS version 9.2 and R version 2.9.

RESULTS

Clinical presentation

Between 1999 and 2007, 261 patients underwent surgical treatment for GBCA: 130 from MSKCC, 85 from FALP, and 46 from YCU. There were 2 postoperative deaths (0.77%), leaving 259 evaluable patients. Women comprised 175 patients (67%) and median age was 63 years (range 28 to 91 years) (Table 1). The proportion of women was significantly higher at MSKCC (63.1%) and FALP (80%) compared with YCU (54.3%), where the ratio was closer to 1 ($p < 0.005$). Patient age was also notably different; those treated at FALP were significantly younger (median age 57 years, range 41 to 91 years) compared with those at MSKCC (median age 66 years, range 28 to 90 years) and YCU (median age 69 years, range 48 to 85 years) ($p < 0.001$). Not surprisingly, the ethnic distribution differed among centers. At MSKCC, there was greater heterogeneity, but Caucasians represented the large majority (n = 99, 76.2 %). By contrast, Hispanics accounted for nearly all patients at FALP (n = 81, 95.3%), and Asians comprised the entire group (n = 46, 100%) at YCU. The

Table 1. Clinical Presentation of 261 Patients with Gallbladder Cancer

Variable	Total 261	MSKCC n = 130	FALP n = 85	YCU n = 46	p Value
Sex, n (%)					<0.005
Female	175 (67)	82 (63.1)	68 (80)	25 (54.3)	
Male	86 (32.9)	48 (36.9)	17 (20)	21 (45.7)	
Age, y					<0.001
Mean ± SD	64 ± 10.7	65 ± 10.6	59 ± 9.9	68 ± 9	
Median	63	66	57	69	
Range	28–91	28–90	41–91	48–85	
Race, n (%)					<0.001
White	99 (37.9)	99 (76.2)	0	0	
Hispanic	86 (33)	5 (3.8)	81 (95.3)	0	
Asian-Japanese	46 (17.6)	0	0	46 (100)	
African-American	10 (3.8)	10 (7.7)	0	0	
Pacific-Islander	7 (2.7)	7 (5.4)	0	0	
Native-American	4 (1.5)	0	4 (4.7)	0	
No information	4 (1.5)	4 (3.1)	0	0	
Indian	3 (1.2)	3 (2.3)	0	0	
Asian-American	1 (0.4)	1 (0.8)	0	0	
Arabic	1 (0.4)	1 (0.8)	0	0	
Diagnosis, n (%)					<0.001
Incidental	152 (58.2)	88 (67.7)	55 (64.7)	9 (19.5)	
Pre-/intraoperative	109 (41.8)	42 (32.3)	30 (35.3)	37 (80.5)	
Jaundice	30	17	13	No information	
Weight loss	23	11	12	No information	
Gallstone associated					<0.001
Yes	215 (82.4)	106 (81.5)	85 (100)	24 (52.2)	
No	46 (17.6)	24 (18.5)	0	22 (47.8)	

FALP, Instituto Oncológico Fundación Arturo López Pérez; MSKCC, Memorial Sloan-Kettering Cancer Center; YCU, Yokohama City University.

majority of patients had undergone a previous noncurative cholecystectomy and incidental diagnosis before definitive surgery (n = 152, 58.2%); however, incidental tumors were far less common at YCU (19.5%) compared with the other 2 centers ($p < 0.001$) (Table 1).

Treatment

Details pertaining to operative intervention are outlined in Table 2. The majority of patients (61.3%) underwent a complete resection (ie, R0 or curative intent), although the proportion of such resections was higher at YCU (78.3%) and MSKCC (70%) compared with FALP (38.8%) ($p < 0.001$). Partial hepatectomy was part of the surgical treatment in nearly two-thirds of patients (n = 164, 61.5%), and a bile duct resection was carried out in one-third (n = 94, 36%). Differences were found in the extent of surgery among the 3 centers, with more liver and bile duct resections in MSKCC and YCU versus FALP (77.1% vs 68% vs. 33.7% and 43.8% vs 67.4% vs 7.1%, respectively) ($p < 0.001$). Likewise, although the majority of patients were treated with curative intent (n = 160, 61.3%), this occurred more frequently in MSKCC and YCU versus FALP, (70% vs 78.3% vs 38.8%, respectively) ($p < 0.001$).

In those treated with curative intent (n = 160), the primary resections were: 4B and 5 liver segmentectomy in 115 patients, extended hepatectomy in 20, hepatectomy in 5, pancreaticoduodenectomy combined with 4B and 5 liver segmentectomy in 3 patients, and cholecystectomy alone in 17 patients. These procedures were combined with porta hepatis lymphadenectomy (except in patients treated with cholecystectomy alone) and in selected patients, included bile duct resection, adjacent organ resection, or vascular reconstruction. The R0 resection group included 13 patients with T1 tumors (9 T1a and 4 T1b). Palliative cholecystectomy or exploration and biopsy were the most common procedures performed in patients with unresectable disease (Table 2).

Pathologic characteristics

Two hundred twenty-four patients presented with invasive disease at the time of diagnosis or re-exploration in those with incidental tumors (T2 in 124 [47.5%], T3 in 95

Table 2. Extent of Surgical Treatment

	Total (n = 261)		MSKCC (n = 130)		FALP (n = 85)		YCU (n = 46)		
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p Value**
Type of operation									<0.001
Curative intent (R0-resection)*	160	61.3	91	70	33	38.8	36	78.3	
R1/R2 resection	83	31.8	31	23.8	42	49.4	10	21.7	
No resection	18	6.9	8	6.2	10	11.6	0		
Type of resection									<0.001*
Segmentectomy 4b/5	134	50.2	77	58.8	29	33.7	28	56	<0.001
Extended hepatectomy	25	9.4	19	14.5	0		6	12	<0.001
Hepatectomy	5	1.9	5	3.8	0		0		
Pancreatoduodenectomy†	6	2.2	1	0.8	1	1.2	4	8	
Cholecystectomy‡	17	6.4	0		7	8.1	10	20	
Additional resection									
Bile duct	94	36	57	43.8	6	7.1	31	67.4	<0.001
Other organ	24	9.2	15	11.5	1	1.1	8	17.4	
Vascular (and reconstruction)	3	1.2	0		0		3	6.5	
Palliative resection/no resection§									
Cholecystectomy only	61	22.8	21	16	39	45.3	1	2	<0.001
No resection (biopsy only)	18	6.9	8	6.2	10	11.6	0		

*$p < 0.001$ when segmentectomy 4b/5+extended hepatectomy+pancreatoduodenectomy+hepatectomy vs cholecystectomy only+no resection were compared among the 3 institutions.
†Pancreatoduodenectomy+Segmentectomy 4b/5, 5 patients, pancreatoduodenectomy+cholecystectomy, 1 patient.
‡Including 17 patients treated with only cholecystectomy (T1a, 9; T1b, 4; T2,4).
§Does not include R1 resections.
FALP, Instituto Oncológico Fundación Arturo López Pérez; MSKCC, Memorial Sloan-Kettering Cancer Center; YCU, Yokohama City University.

[36.4%], and T4 in 5 [1.9%], [Tables 3 and 4]). There were more T1 and T2 tumors in patients from FALP and YCU compared with MSKCC (64.7% vs 60.9% vs 49.2%, respectively) ($p < 0.004$), and more T3 and T4 tumors in patients treated at MSKCC versus FALP and YCU (46.2% vs 25.9% vs 39.2%, respectively) ($p < 0.004$). In 14 patients (5.4%) the depth of tumor invasion was not obtained. The most frequent histologic tumor type was adenocarcinoma (n = 240, 91.5%), seen in nearly 90% or more of patients at all sites. Other less common types included adenosquamous (n = 13, 5%), squamous (n = 3, 1.5%), neuroendocrine (n = 4 [high grade in 3], 1.5%), and undifferentiated (n = 1, 0.4%) ($p < 0.04$). Two hundred eleven (81%) patients had at least 1 lymph node resected, and this was more common at MSKCC (86.9%) and YCU (95.7%) compared with FALP (63.5%) ($p < 0.001$) (Table 4). The median number of lymph nodes resected was 3 (range 0 to 94). One hundred (38.3%) patients had positive lymph nodes, 111 (42.5%) had negative lymph nodes, and 50 (19.2%) had none evaluated histologically. The median number of positive lymph nodes for all patients was 1 (range 1 to 43), and was higher in patients treated in YCU ($p < 0.001$).

For the entire cohort, liver involvement was seen in 104 patients (39.8%), the bile duct was involved in 49 (18.8%), and both the liver and bile duct in 33 (12.6%). Liver involvement was more common in patients treated at MSKCC (n = 69, 53.1%) versus FALP (n = 21, 24.7%) or YCU (n = 14, 30.4%) ($p < 0.001$), and there were no differences among the 3 groups in either bile duct (MSKCC [n = 27, 20.8%], FALP [n = 15, 17.6%], and YCU [n = 7, 15.2%] [p = 0.67]) or both liver and bile duct involvement (MSKCC [n = 20, 15.4%], FALP [n = 7, 8.2%], and YCU [n = 6, 13%] [p = 0.3]). Likewise, in patients with incidental tumors (n = 152), residual disease in the liver was more common at MSKCC (n = 30, 34.1%) versus FALP (n = 7, 12.3%) or YCU (n = 1,

Table 3. Site of Residual Disease after Re-exploration in Patients with Incidental Diagnosis

Site of disease involvement, n (%)	Total (n = 152)	MSKCC (n = 88)	FALP (n = 55)	YCU (n = 9)	p Value
Liver	38 (25)	30 (34.1)	7 (12.3)	1 (11.1)	<0.03
Bile duct	8 (5.3)	4 (4.6)	4 (7.3)	0	0.792
Both	10 (6.6)	7 (8)	3 (5.5)	0	0.792

FALP, Instituto Oncológico Fundación Arturo López Pérez; MSKCC, Memorial Sloan-Kettering Cancer Center; YCU, Yokohama City University.

Table 4. Histopathologic Characteristics and Disease Stage for All Patients

Variable	Total (n = 261)	MSKCC (n = 130)	FALP (n = 85)	YCU (n = 46)	p Value
Pathology, n (%)					
Adenocarcinoma	240 (91.5)	115 (88.4)	83 (97.6)	42 (91.3)	<0.04
Adenosquamous	13 (5)	9 (6.9)	2 (2.4)	2 (4.3)	
Squamous	3 (1.5)	3 (2.3)	0	0	
Endocrine*	4 (1.5)	3 (2.3)	0	1 (2.2)	
Undifferentiated	1 (0.4)	0	0	1 (2.2)	
Differentiation (n = 210), n (%)					0.242
Well	17 (8.1)	7	10	No information	
Moderated	114 (54.3)	68	46	No information	
Poor	79 (37.6)	50	29	No information	
T stage, n (%)					<0.004
T1a	9 (3.4)	0	4 (4.7)	5 (10.9)	
T1b	14 (5.4)	7 (5.4)	4 (4.7)	3 (6.5)	
T2	124 (47.5)	57 (43.8)	47 (55.3)	20 (43.5)	
T3	95 (36.4)	60 (46.2)	22 (25.9)	13 (28.3)	
T4	5 (1.9)	0	0	5 (10.9)	
Tx	14 (5.4)	6 (4.6)	8 (9.4)	0	
Lymph nodes (patients evaluated), n	261	130	85	46	<0.001
Positive, n (%)	100 (38.3)	44 (33.8)	33 (38.8)	23 (50)	
Negative, n (%)	111 (42.5)	69 (53.1)	21 (24.7)	21 (45.7)	
Unknown, n (%)	50 (19.2)	17 (13.1)	31 (36.4)	2 (4.3)	
Lymph nodes resected, n					<0.001
Mean ± SD	7.3 ± 9.9	4.7 ± 3.9	6.8 ± 6.4	22 ± 20.6	
Median	3	3	1	0	
Range	0–94	0–20	0–33	0–94	
Positive lymph nodes (patients evaluated), n	100	44	33	23	<0.001
Mean ± SD	1.3 ± 3.8	0.8 ± 1.4	1.1 ± 1.5	3.04 ± 7.6	
Median	1	1	1	2	
Range	1–43	1–9	1–7	1–43	
Margin, n (%)					<0.001
R0 resection	160 (61.3)	91 (70)	33 (38.8)	36 (78.3)	
R1/2 resection or no resection	101 (38.7)	39 (30)	52 (61.2)	10 (21.7)	
Stage†, n (%)					<0.001
IA	21 (8.05)	6 (4.6)	7 (8.2)	8 (17.3)	
IB	53 (20.3)	29 (22.3)	15 (17.6)	9 (19.5)	
IIA	35 (13.4)	30 (23.1)	3 (3.5)	2 (4.3)	
IIB	66 (25.3)	30 (23.1)	22 (25.9)	14 (30.4)	
III	2 (0.8)	0	0	2 (4.3)	
IV	72 (27.6)	34 (26.2)	28 (32.9)	10 (21.7)	
Unknown	12 (4.6)	1 (0.8)	10 (11.7)	1 (2.2)	

*3 patients from MSKCC had high grade neuroendocrine tumor.
†Lymph-node involvement not assessed when M1 disease was identified.
FALP, Instituto Oncológico Fundación Arturo López Pérez; MSKCC, Memorial Sloan-Kettering Cancer Center; YCU, Yokohama City University.

11.1%) ($p < 0.03$), although there was no significant difference in biliary tract involvement (Table 3). For the entire cohort, the final disease staging is detailed in Table 4 and was as follows: stage I or II, 175 (67%); stage III or IV, 74 (28.4%); not classifiable, 12 (4.6%). There were fewer FALP patients with stages I to II tumors (n = 47, 55.3%) compared with MSKCC (n = 95, 73.1%) and YCU (n = 33, 71.7%) patients ($p < 0.001$). By contrast, FALP had a greater proportion of patients with more advanced disease (n = 28, 32.9%) ($p < 0.001$) (Table 4).

Differences among centers in several histopathologic variables became much less apparent when the analysis was limited to patients treated with curative intent resection (Table 5). The most notable difference was in regard to extent of nodal resection or evaluation, although the overall proportion of node positive patients was not different. Likewise, 36% of patients underwent bile duct resection, and the proportion was higher at YCU and MSKCC; however, bile duct involvement by tumor (determined histologically) was seen in only 14.4% of patients and was not significantly different across centers. The proportion of patients with more locally advanced (T3) tumors was slightly different (Table 5).

Table 5. Histopathologic Characteristics and Disease Stage in Patients Treated with R0 Resection

Variable	Total (n = 160)	MSKCC (n = 91)	FALP (n = 33)	YCU (n = 36)	p Value
Pathology, n (%)					0.745
Adenocarcinoma	142 (88.8)	79 (86.8)	31 (94)	32 (88.8)	
Adenosquamous	12 (7.5)	8 (8.8)	2 (6.1)	2 (5.6)	
Squamous	2 (1.25)	2 (2.2)	0	0	
Endocrine	3 (1.9)	2 (2.2)	0	1 (2.8)	
Undifferentiated	1 (0.6)	0	0	1 (2.7)	
Differentiation, n (%)	128				0.299
Well	13 (10.2)	6 (6.6)	7 (21.2)	No information	
Moderated	71 (55.5)	52 (57.1)	19 (57.6)	No information	
Poor	40 (31.3)	33 (36.3)	7 (21.2)	No information	
T stage, n (%)					0.023
T1a	9 (5.6)	0	4 (12)	5 (13.8)	
T1b	14 (8.8)	7 (7.7)	4 (12)	3 (8.3)	
T2	83 (51.9)	46 (50.5)	21 (63.6)	16 (44.4)	
T3	52 (32.5)	38 (41.8)	4 (12)	10 (27.8)	
T4	2 (1.3)	0	0	2 (5.6)	
Bile duct involvement, n (%)					0.49
Yes	23 (14.4)	15 (16.5)	5 (15.2)	3 (8.3)	
No	137 (85.6)	76 (83.5)	28 (84.8)	33 (91.7)	
Lymph nodes (patients evaluated), n	160	91	33	36	0.596
Positive, n (%)	54 (33.8)	28 (30.8)	11 (33.3)	15 (41.7)	
Negative, n (%)	100 (62.5)	63 (69.2)	17 (51.5)	20 (55.5)	
No data, n (%)	6 (3.8)	0	5 (15.2)*	1 (2.7)†	
Lymph nodes evaluated (all patients), n					<0.001
Mean ± SD	8 ± 8	5 ± 4	11.3 ± 6.2	18.6 ± 14	
Median	6	4	9	13	
Range	(0–55)	(1–20)	(0–33)	(0–55)	
Lymph nodes evaluated (node positive only), n					<0.001
Mean ± SD	1 ± 3.7	0.6 ± 1.4	0.7 ± 1.3	2 ± 7.4	
Median	1	2	2	2	
Range	1–43	1–9	1–6	1–43	
Stage, n (%)					0.180
IA	21 (13.1)	6 (6.6)	7 (21.2)	8 (22.2)	
IB	51 (31.9)	29 (31.9)	13 (39.4)	9 (25.0)	
IIA	30 (18.8)	26 (28.6)	2 (6.1)	2 (5.6)	
IIB	47 (29.4)	26 (28.6)	11 (33.3)	10 (27.8)	
III	1 (0.6)	0	0	1 (2.8)	
IV	9 (5.6)	4 (4.4)	0	5 (13.9)	
Unknown	1 (0.6)	0	0	1 (2.8)†	

*4 T1a patients and 1 T1b patient treated with cholecystectomy.
†One T2 patient treated with cholecystectomy.
FALP, Instituto Oncológico Fundación Arturo López Pérez; MSKCC, Memorial Sloan-Kettering Cancer Center; YCU, Yokohama City University.

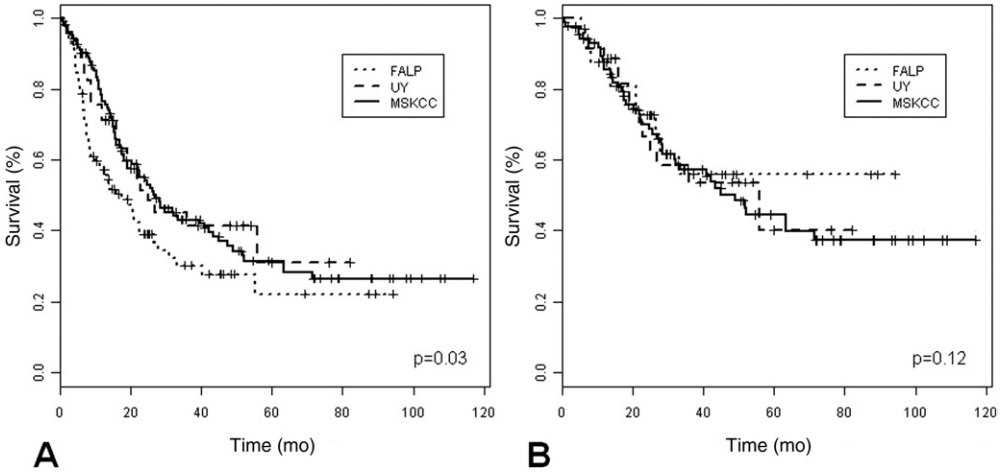

Figure 1. (A) Disease-specific survival among all patients evaluated at MSKCC, FALP and YCU. (B) Disease-specific survival among patients treated with curative intent at MSKCC, FALP and YCU. FALP, Instituto Oncológico Fundación Arturo López Pérez; MSKCC, Memorial Sloan-Kettering Cancer Center; YCU, Yokohama City University.

Survival analysis

Median DSS of all patients of the series (n = 255) was 16.97 months (range 1 to 117 months), and it was higher in patients treated at MSKCC (median 18.9 months; range 1 to 117 months) and YCU (median 19 months; range 3 to 82 months) versus FALP (median 13.2 months; range 3 to 82 months) (Fig. 1A, $p < 0.003$). By contrast, the median DSS of patients treated with curative intent (R0 resection; n=157), again excluding patients with neuroendocrine tumor, was 25.4 months (range 1 to 117 months), and it was not significantly different among the 3 groups: MSKCC (median 28.4 months; range 1 to 117 months), FALP (median 24.7 months; range 5.5 to 94.2 months), and YCU (median 23 months; range 3 to 82 months) (Fig. 1B, $p = 0.12$). The median DSS of patients who did not undergo resection (n = 91) was 9 months (range 1 to 55 months) and was slightly but not significantly different among the 3 groups: MSKCC (median 11.8 months; range 2 to 48 months), FALP (median 8.5 months; range 1 to 55 months), and YCU (median 8.3 months; range 1to 17 months, $p = 0.17$)

Because of the significant variability in disease extent at presentation, analysis of variables predictive of outcomes was limited to patients submitted to an R0 resection. Univariate analyses identified the following predictors of DSS: pre- or intraoperative diagnosis, jaundice, weight loss at presentation, number of lymph nodes sampled, and number of positive lymph nodes (Table 6). On multivariate analysis, T stage, N stage, and bile duct involvement were the only independent predictors of survival; center of origin was not a significant factor (Table 7).

DISCUSSION

GBCA is the most common biliary tract malignancy worldwide.[1] Many studies have compared various aspects of this disease between different regions of the world, demonstrating some variability in ethnic, racial, and gender distribution.[4,7,16] However, earlier publications have not extensively evaluated differences in disease presentation, treatment, and survival among institutions in different countries. This study did identify a number of differences in demographics, presentation, surgical treatment, and disease extent among the 3 centers. However, although there was a modest survival difference in the entire cohort, DSS of patients treated with curative intent was similar at all sites, and in the final analysis, only factors related to disease extent independently predicted outcomes.

This study confirmed the findings of previous reports that, in general, the rate of GBCA among women is almost twice that for men in Chilean and American populations, but not in Japan.[1,6,7] Additionally, patients treated at centers in Chile and America were significantly younger than Japanese patients, and those treated in Japan had fewer incidental tumors.

The basis of these observed differences is not clear, but molecular biologic studies support the existence of different pathways of carcinogenesis, as well as the potential for regional pathogenetic differences. For example, mutations in the *K-ras* gene have been shown to be frequent in patients with anomalous pancreaticobiliary duct junction, a cancer risk factor that appears to be relatively common in Japanese patients,[17] but are rarely identified in GBCA associated with an adenoma.[18-21] Furthermore, differences

Table 6. Univariate Analysis of Variables Associated with Survival in Patients Treated with R0 Resection

Variable	n	Median survival, mo (range)	Hazard ratio	95% CI	p Value
Incidental diagnosis					
Yes	104	26.2 (1–117)	0.26	0.15–0.42	<0.001
No	56	22.5 (2–98)	1		
Abdominal pain					
No	112	27 (1–117)	0.84	0.44–1.62	0.62
Yes	19	27 (2–98)	1		
Jaundice					
No	123	28 (1–117)	0.43	0.25–0.72	<0.001
Yes	8	20 (7–32)	1		
Weight loss					
No	128	27 (1–117)	0.59	0.36–0.98	<0.05
Yes	3	2 (27–88)	1		
Hepatic resection					
No	17	25 (12–56)	1.03	0.62–1.7	0.9
Yes	143	26 (1–117)	1		
Bile duct resection					
No	82	27 (1–98)	1.04	0.59–1.83	0.8
Yes	78	22 (1–117)	1		
Bile duct involvement					
Yes	23	18 (6–108)	1.57	0.96–2.57	0.06
No	134	27 (1–117)	1		
Tumor size (continuous variable)			0.92	0.58–1.48	0.75
Histology					
Adenocarcinoma	143	26 (1–117)	0.65	0.09–1.52	0.28
Adenosquamous	12	24 (11–94)	0.27	0.04–3.67	
Squamous	2	39 (5–74)	0.09	0.01–1.32	
Endocrine	3	14 (4–28)	1		
T stage					
T3–4	54	21 (1–117)	1.66	1.04–2.67	0.03
T1–2	106	27 (1–109)	1		
Lymph node metastases					
Positive	54	19 (3–108)	1.87	0.87–4.03	0.1
Negative	100	28 (1–117)	1		
Number of lymph nodes examined (continuous variable)			1.04	1.01–1.06	<0.001
Number of positive lymph nodes (continuous variable)			1.07	1.00–1.15	0.03
Grade					
Poor	40	21 (1–98)	2.81	0.67–11.74	0.32
Moderate	70	27 (1–117)	2.82	0.68–11.72	
Well	13	37 (6–94)	1		
Poor differentiation					
Yes	40	21 (1–98)	1.10	0.69–1.76	0.7
No	83	28 (1–117)	1		
Perivascular invasion					
Yes	40	17 (1–99)	1.47	0.81–2.69	0.19
No	57	25 (1–98)	1		
Perineural invasion					
Yes	37	22 (1–99)	1.22	0.64–2.32	0.5
No	60	22 (1–82)	1		
Stage					
3–4	10	16 (3–108)	1.51	0.91–2.53	0.1
1–2	150	26 (1–117)	1		
Treatment center					
YCU	36	23 (3–82)	1.99	0.98–4.02	0.08
MSKCC	91	28 (1–117)	0.89	0.56–1.42	
FALP	33	25 (6–94)	1.0		

FALP, Instituto Oncológico Fundación Arturo López Pérez; MSKCC, Memorial Sloan-Kettering Cancer Center; YCU, Yokohama City University.

the spectra of deregulatory mutations in the *TP53* gene have been documented in areas of high disease prevalence (Japan and Chile).[18,22] So, epidemiologic and molecular data suggest that GBCA may arise and progress through different mechanisms; however, it remains to be proven that such differences result in biologically distinct cancers, with clear and measurable dissimilarities in clinical behavior.

Previous studies have shown that gallstones are an important risk factor for GBCA, and in patients with GBCA due to gallstones, the cancer risk appears to be related to the duration of the calculus disease.[23] In Chile and high-risk populations of the US, the main risk factor for GBCA is gallstones,[5,24] and these tend to be present at a relatively young age, particularly in women. Diet and obesity also contribute to the risk of GBCA.[25] People with high fat diets appear to have a greater risk of GBCA, in contrast to those with high intake of fish.[26] In a recent study of 4,424 Japanese patients with GBCA by Kayahara and colleagues,[17] less than half (44.6%) were associated with cholelithiasis, and 50% had no obvious risk factors. The average age in the former group was 66.9 years, similar to that of Japanese patients in this study, although the gender distribution was more than 2:1 in favor of women; by contrast, in the largest group without stone disease, the male-to-female ratio was nearly 1:1. The results of this study are in line with those from previous reports showing a lower incidence of gallstone-associated GBCA in Japanese patients. This fact, combined with the higher dietary fat content and obesity rates in Western countries compared with Japan[23] could well account for the age and sex differences observed in this study, with later development of gallstones in Japanese patients. However, the Kayahara study[17] would suggest an important carcinogenetic pathway independent of biliary calculus disease, which seems to be particularly prevalent in Japanese patients.

Table 7. Multivariate Analysis of Variables Associated with Survival in Patients Treated with R0-Resection

Variable	Hazard ratio	95% CI	p Value
Treatment center			
YCU	1.26	0.50–3.15	0.54
MSKCC	0.84	0.42–1.69	
FALP	1.0		
T Stage			
3–4	1.9	1.14–3.18	0.01
1–2	1.0		
Lymph node metastases			
Positive	1.88	1.14–3.11	0.01
Negative	1.0		
Incidental diagnosis			
No	1.56	0.89–2.92	0.16
Yes	1.0		
Bile duct involvement			
Yes	2.5	1.41–4.78	0.002
No	1.0		

FALP, Instituto Oncológico Fundación Arturo López Pérez; MSKCC, Memorial Sloan-Kettering Cancer Center; YCU, Yokohama City University.

The very low proportion of incidental GBCA was another area of notable discrepancy between patients from Japan compared with those from Chile and America. Worldwide, the proportion of patients with incidental tumors (diagnosed after cholecystectomy) has increased over the past several years, likely a consequence of the increasing use and availability of laparoscopic cholecystectomy.[27,28] Although most patients in this study had incidental GBCA, the rate in the Japanese patients was 19.5%, far lower than in the other 2 centers. The reason for this discrepancy is unclear, although the finding is in line with the data reported by Kayahara and associates,[17] in which 84% of 4,424 cases were diagnosed preoperatively, a figure that is much greater than typically seen in studies from Western centers. A high proportion of patients with advanced tumors, and therefore more easily identified on imaging, could account for this observation, and although plausible in the large population-based study,[17] the data in this study showed just the opposite, with more than 70% of Japanese patients having T1 and T2 tumors. Differences in imaging techniques or interpretation and/or level of suspicion for a cancer diagnosis are all potential contributing factors in this regard.

When considering the entire study cohort, notable variations in disease extent were evident among the 3 centers, particularly the higher proportion of Chilean patients presenting with more advanced stage disease. This resulted in differences in the R0 resection rate and the type of surgical therapy rendered, as well as an overall decreased DSS compared with the other 2 groups. It is tempting to invoke disease biology as a possible explanation for this observation, but other factors would seem more plausible, such as differences in access to health care and treatment approaches to patients with advanced disease. Support for this argument is apparent when the analysis was limited to patients submitted to a complete resection. Although minor disease-related disparities persisted, they were not important enough to result in significant differences in disease stage. Most importantly, when completeness of resection was not a variable, survival was nearly identical at all 3 sites, and only T stage, nodal involvement, and bile duct involvement were independent predictors of survival.

From a technical standpoint, the results of this study do not support any particular operative approach, other than achievement of an R0 resection. The majority of hepatic

resections were segmental in nature, reflecting the general trend in the management of GBCA. Differences were noted in the number of lymph nodes evaluated among the 3 centers. Although this may be related to differences in pathologic review, there were likely also disparities in the extent of lymphadenectomy; however, given the lack of survival difference in patients submitted to a complete resection, the data would argue against any benefit of extended lymphadenectomy. A similar argument may be made for empiric bile duct resection. The proportion of patients who underwent bile duct resection varied widely across centers, although the proportion with actual bile duct involvement was similar and relatively low. Again, given the survival rates across centers after an R0 resection, removal of the bile duct empirically (ie, not needed to achieve a complete resection) would appear to offer little benefit.

Several limitations of this study must be recognized. First, any suggestion of location-specific differences in disease pathogenesis, although possible based on the demographic data, is speculative and cannot be proved definitively, given the limitations of the dataset. Second, if these differences are real, the relative contributions by genetic and environmental factors are unknown. In a recent epidemiologic study,[29] the high mortality of GBCA in first-generation South Asian immigrants to the United Kingdom was reduced in later generations, suggesting not only an important environmental influence in disease pathogenesis, but also that GBCA incidence in immigrants ultimately reflects that of the adopted country; whether disease behavior in these patients is the same as that for the native population is unclear. For this study, this observation is germane primarily for the American cohort, which was more ethnically diverse compared with patients at the other 2 centers. Finally, the subjects in this study represent a small sample of GBCA patients in each country, with the assumption that they reflect their respective national populations; however, the small sample size makes it impossible to account for differences in small subgroups.

CONCLUSIONS

In summary, in patients with GBCA, disease extent at presentation appears to be a more important and powerful predictor of survival than center of origin. Regional differences in pathogenesis are likely, particularly regarding gallstone-related disease among Japanese patients compared with those from Chile and America, but do not result in tumors with significantly different clinical behaviors. It should be emphasized that this report does not represent a comprehensive analysis of patients from each of the 3 regions. Studies with larger numbers of patients, and indeed, patients from other regions of the world, will be needed to confirm these results.

Author Contributions

Study conception and design: Butte, Matsuo, Jarnagin
Acquisition of data: Butte, Matsuo, Waugh, Endo, De La Fuente, Jarnagin
Analysis and interpretation of data: Butte, Matsuo, Gonen, D'Angelica, Waugh, Allen, Fong, DeMatteo, Blumgart, Endo, De La Fuente, Jarnagin
Drafting of manuscript: Butte, Matsuo, Gonen, Jarnagin
Critical revision: Butte, Matsuo, Gonen, D'Angelica, Waugh, Allen, Fong, DeMatteo, Blumgart, Endo, De La Fuente, Jarnagin

REFERENCES

1. Hueman M, Vollmer C, Pawlik T. Evolving treatment strategies for gallbladder cancer. Ann Surg Oncol 2009;16:2101–2115.
2. Cobourn N, Cleary S, Tan J, et al. Surgery for gallbladder cancer: A population-based analysis. J Am Coll Surg 2008;207: 371–382.
3. Tewari M, Kumar V, Mishra R, et al. Is there a role for cholecystectomy in gallbladder carcinoma discovered to be unresectable for cure at laparotomy? World J Surg 2008;32:2683–2687.
4. Randi G, Malvezzi M, Levi F, et al. Epidemiology of biliary tract cancers: An update. Ann Oncol 2009;20:146–159.
5. Andia M, Gederlini A, Ferreccio C. Gallbladder cancer: Trend and risk distribution in Chile. Rev Med Chile 2006;134:565–574.
6. Kayahara M, Nagajawa T. Recent trends of gallbladder cancer in Japan. Cancer 2007;100:572–580.
7. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: Geographical distribution and risk factors. Int J Cancer 2006;118:1591–1602.
8. Wistuba I, Gazdar A. Gallbladder cancer: lessons from a rare tumour. Nat Rev Cancer 2004;4:695–706.
9. Hsing AW, Bai Y, Andreotti G, et al. Family history of gallstones and the risk of biliary tract cancer and gallstones: a population-based study in Shanghai, China. Int J Cancer 2007;121:832–838.
10. D'Angelica M, Moore Dalal K, DeMatteo R, et al. Analysis of the extent of resection for adenocarcinoma of the gallbladder. Ann Surg Oncol 2009;16:806–816.
11. Reddy S, Marroquin C, Kuo P, et al. Extended hepatic resection for gallbladder cancer. Am J Surg 2007;194:355–361.
12. Araida T, Higuchi R, Hamano M, et al. Hepatic resection in 485 R0 pT2 and pT3 cases of advanced carcinoma of the gallbladder: results of a Japanese Society of Biliary Surgery survey. A multicenter study. J Hepatobiliary Pancreat Surg 2009;16:204–215.
13. Gallbladder. In: American Joint Committee on Cancer: AJCC Cancer Staging Manual, 6th ed. Philadelphia, PA: Lippicontt-Raven; 2002: 115–120.
14. Butte JM, Redondo F, Waugh E, et al. The role of PET-CT in patients with incidental gallbladder cancer. HPB 2009;11:585–591.
15. Shimada H, Endo I, Fujii Y, et al. Appraisal of surgical resection of gallbladder cancer with special reference to lymph node dissection. Langenbecks Arch Surg 2000;385:509–514.

16. Hariharan D, Saied A, Kocher H. Analysis of mortality rates for gallbladder cancer across the world. HPB 2008;10:327–331.

17. Kayahara M, Nagakawa T, Nakagawara H, et al. Prognostic factors for gallbladder cancer in Japan. Ann Surg 2008;248: 807–814.

18. Goldin RD, Roa JC. Gallbladder cancer: a morphological and molecular update. Histopathology 2009;55:218–229.

19. Nakayama K, Konno M, Kanzaki A, et al. Allelotype analysis of gallbladder carcinoma associated with anomalous junction of pancreaticobiliary duct. Cancer Lett 2001;166:135–141.

20. Hanada K, Tsuchida A, Kajiyama G. Cellular kinetics and gene mutations in gallbladder mucosa with an anomalous junction of pancreaticobiliary duct. J Hepatobiliary Pancreat Surg 1999;6: 223–228.

21. Yokoyama N, Watanabe H, Ajioka Y, et al. Genetic alterations in gallbladder carcinoma: a review. Nippon Geka Gakkai Zasshi 1998;99:687–695.

22. Yokoyama N, Hitomi J, Watanabe H, et al. Mutations of p53 in gallbladder carcinomas in high-incidence areas of Japan and Chile. Cancer Epidemiol Biomarkers Prev 1998;7:297–301.

23. Dutta U, Nagi B, Garg PK, et al. Patients with gallstones develop gallbladder cancer at an earlier age. Eur J Cancer Prev 2005;14:381–385.

24. Lemrow S, Perdue D, Stewart S, et al. Gallbladder cancer incidence among American Indians and Alaska Natives, US, 1999–2004. Cancer 2008;113:1266–1273.

25. Larsson SC, Wolk A. Obesity and the risk of gallbladder cancer: a meta-analysis. Br J Cancer 2007;96:1457–1461.

26. Matsuba T, Qiu D, Kurosawa M, et al. Overview of epidemiology of bile duct and gallbladder cancer focusing on the JACC Study. J Epidemiol 2005;Suppl 2:S150–156.

27. Steinert R, Nestler G, Sagynaliev E, et al. Laparoscopic cholecystectomy and gallbladder cancer. J Surg Oncol 2006;93:682–689.

28. Shih S, Schulick R, Cameron J, et al. Gallbladder cancer: the role of laparoscopy and radical resection. Ann Surg 2007;245: 893–901.

29. Mangtani P, Maringe C, Rachet B, et al. Cancer mortality in ethnic South Asian migrants in England and Wales (1993–2003): patterns in the overall population and in first and subsequent generations. Br J Cancer 2010;102:1438–1443.