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Original Article

Who benefits from R0 resection? A single-center analysis of patients with stage Ⅳ gallbladder cancer

Chen Chen [a], Lin Wang [b], Rui Zhang [a], Qi Li [a], Ya-Ling Zhao [c], Guan-Jun Zhang [d], Wen-Zhi Li [a], Zhi-Min Geng [a,*]

[a] *Department of Hepatobiliary Surgery, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China*

[b] *Department of Geriatric Surgery, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China*

[c] *Department of Epidemiology and Biostatistics, School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an, Shaanxi 710061, China*

[d] *Department of Pathology, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China*

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Abstract

Objectives: Most patients with gallbladder cancer (GBC) present with advanced-stage disease and have a poor prognosis. Radical resection remains the only therapeutic option to improve survival in patients with GBC. This study aimed to analyze the prognostic factors in patients with stage Ⅳ GBC and to identify a subgroup of patients who might benefit from R0 resection.

Methods: A total of 285 patients with stage Ⅳ GBC were retrospectively analyzed at our institution from January 2008 to December 2012. Factors potentially influencing the prognosis of GBC after surgery were analyzed by univariate and multivariate analyses.

Results: The 1-, 3-, and 5-year overall survival rates were 6.6% (15/229), 0.9% (2/229), and 0 (0/229), respectively. Ascites (relative risk [*RR*] = 1.631, 95% confidence interval [*CI*]: 1.221−2.180, $P = 0.001$), pathological grade (*RR* = 1.337, 95% *CI*: 1.050−1.702, $P = 0.018$), T stage (*RR* = 1.421, 95% *CI*: 1.099−1.837, $P = 0.000$), M stage (*RR* = 1.896, 95% *CI*: 1.409−2.552, $P = 0.000$), and surgery (*RR* = 1.542, 95% *CI*: 1.022−2.327, $P = 0.039$) were identified as independent risk factors influencing prognosis. The median survival time (MST) was significantly higher in patients undergoing R0 resection than in those undergoing R1/R2 resection (6.0 *vs*. 2.7 months; $P < 0.001$). In subgroup analyses, stage ⅣA patients benefited from R0 resection (MST for R0 *vs*. R1/R2, 11.0 *vs*. 4.0 months; $P = 0.003$), while R0 resection had a significant survival benefit than R1/R2 resection in patient with stage ⅣB GBC without distant metastasis (MST for R0 *vs*. R1/R2, 6.0 *vs*. 3.0 months; $P = 0.007$).

Conclusion: Ascites, pathological grade, T stage, M stage, and surgery were independent risk factors influencing prognosis in patients with stage IV GBC. N2 lymph node metastasis did not preclude curative resection, and radical resection should be considered in patients with stage Ⅳ GBC without distant metastasis once R0 margin was achieved.

* Corresponding author.

E-mail address: gengzhimin@mail.xjtu.edu.cn (Z.-M. Geng).

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Keywords: Gallbladder cancer; Surgery; Prognosis; Tumor-node-metastasis (TNM) stage

Introduction

Gallbladder cancer (GBC) is the most common malignant tumor of the biliary system. It is characterized by a high degree of malignancy, difficult early diagnosis, poor therapeutic efficacy and prognosis, and a generally dismal survival rate of 0%–12%.[1]

Long-term survival of patients with GBC is critically dependent on an early diagnosis; however, most patients are undiagnosed until an advanced stage of the disease and, therefore, have a poor prognosis,[2–4] with 5-year survival rates as low as 4% for stage ⅣA and 2% for stage ⅣB.[5] Radical resection remains the only therapeutic option to improve the survival in patients with GBC.[6] However, surgical resection for advanced biliary cancer remains challenging, and the 7th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system for GBC suggests that lesions in patients with N2 metastasis, T4 tumor, or distant metastasis, classified as stage Ⅳ, are largely unresectable.[5] Recently, extended radical resections, such as hepatopancreatoduodenectomy (HPD) and extended regional lymphadenectomy (ERLN), have received increasing attention for the treatment of advanced GBC and have shown curative potential with negative margins, even in patients with advanced biliary cancer.[7–10] However, whether involvement of N2 nodes precludes curative surgery for biliary tract cancer remains controversial.[11,12] Many centers treated these patients with ERLN, whereas some researchers suggested that patients with N2 disease did not benefit from lymphadenectomy.[13,14] Furthermore, its associations with high morbidity and mortality rates[15,16] reveal that HPD should be considered after careful evaluation of the risks and the expected prognosis of the patient.

In the current retrospective study, we analyzed and compared the clinical characteristics, pathological features, surgical methods, and postoperative survival in 285 patients with stage Ⅳ GBC to determine potential prognostic factors and identify a subgroup of patients who might benefit from R0 resection.

Methods

Patients

A total of 285 patients with stage Ⅳ GBC were treated at The First Affiliated Hospital of Xi'an Jiaotong University from January 2008 to December 2012. Patients' data including sex, age, and clinical manifestation were collected. Clinical end points and measurements included imaging examinations (abdominal ultrasound, computed tomography, magnetic resonance imaging), serological tumor marker assays (determination of carbohydrate antigen 125 [CA-125], carbohydrate antigen 19-9 [CA 19-9], carcinoembryonic antigen [CEA]), details of surgical methods, and other surgical data. Reanalysis of the pathological studies and patient diagnoses of GBC was performed according to the definitions published by the World Health Organization in 2010. Additionally, patients were assessed for TNM stage according to the AJCC (7th edition) TNM staging system. The study was approved by the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (No. 2018-126).

Surgical procedure

Different surgical procedures were performed according to the results of exploratory surgery and intraoperative pathological examination. In patients with advanced GBC without involvement of the liver or minimal infiltration into the liver, wedge resection of the gallbladder bed/segment ⅣB/Ⅴ resection and regional lymphadenectomy/ERLN were planned. When the massive invasion of the liver was diagnosed, major hepatectomy, such as right hemihepatectomy or right trisectionectomy, was indicated. If the tumors involved the extrahepatic bile duct or bulky regional lymph node (LN) metastasis around the bile duct, common bile duct (CBD) resection was added. Multiple peritoneal seeding and bulky LN involvement were considered contraindications for surgery. HPD was considered in patients with the following conditions: (1) lower bile duct involvement, (2) pancreatic infiltration, (3) duodenal infiltration, and (4) bulky

retropancreatic LN metastasis. Gastric resection was performed in case of macroscopic infiltration.

Palliative surgical interventions were performed when en bloc tumor removal cannot be achieved because of distant metastases, peritoneal seeding, positive para-aortal lymph nodes, or wide tumor invasion or when body conditions cannot sustain aggressive surgery. For palliative surgery, biliary tract drainage was performed once jaundice or biliary tract invasion occurred.

Follow-up

Clinical follow-up was scheduled for 1, 3, 6, and 12 months after discharge and once a year thereafter until March 2019.

Statistical analysis

Results were analyzed using Statistical Package for the Social Sciences version 13.0 software (IBM, Armonk, NY, USA). Continuous data with normal distribution were described as mean ± standard deviation, and those with non-normal distribution were described as median (Q1, Q3). Categorical data were expressed as numbers (percentages) and compared between groups using χ^2 tests. Kaplan–Meier survival curves were plotted, and log-rank statistics were calculated to assess which variables affected survival time. Survival was analyzed using the Kaplan–Meier method, and differences were measured using log-rank tests. Prognostic multivariate analysis was performed using Cox regression. $P < 0.05$ was considered statistically significant.

Results

Demographic data and clinical data

A total of 285 patients with stage Ⅳ GBC during the 5-year inclusion period included 83 men and 202 women, with a median (Q1, Q3) age of 63 (54, 69) years.

Jaundice was present in 91 patients (31.9%), and 161 patients (56.5%) had gallstones, 22 (7.7%) had diabetes mellitus, and 54 (18.9%) had hypertension. Information on preoperative tumor markers was available for some patients, among whom CA 19-9 was positive in 70.9% (124/175), followed by CA-125 in 59.1% (91/154), and CEA in 43.7% (80/183) of patients. These baseline characteristics are described in Table 1.

Table 1
Baseline characteristics of patients with stage Ⅳ gallbladder cancer (n=285).

Features	Cases, n (%)
Sex	
Male	83 (29.1)
Female	202 (70.9)
Jaundice	
Yes	91 (31.9)
No	194 (68.1)
Gallstone	
Yes	161 (56.5)
No	124 (43.5)
Diabetes	
Yes	22 (7.7)
No	263 (92.3)
Hypertension	
Yes	54 (18.9)
No	231 (81.1)

Pathological data

Information on tumor infiltration was available for 164 patients, among whom tumors were infiltrative in 76.2% (125/164) of patients. Adenocarcinoma was the main pathological type (82.8%, 236/285), and differentiation was mostly poor, with 96.8% (276/285) of grades II–III. One patient had T1, 127 had T3, and 157 had T4 stage tumors. N0, N1, and N2 were observed in 8, 125, and 152 patients, respectively, and 121 had distant metastasis. TNM staging according to tumor characteristics, presence of LN metastasis, and distant metastases showed stage ⅣA in 69 patients and ⅣB in 216 patients.

Surgical procedures

Forty-four patients underwent R0 resection, including 12 HPD, 4 right hepatectomy, and 3 subtotal gastrectomy (Fig. 1). Palliative surgical intervention was performed in the remaining 241 patients, including 58 cholecystectomy, 126 cholecystectomy and biliary tract external drainage, 6 cholecystectomy and bilioenterostomy, 23 biliary tract external drainage, 19 exploratory laparotomy, and 9 gastrointestinal bypass. The detailed clinical and pathological data for the patients undergoing R0 and R1/R2 resections are presented in Table 2, and the detailed surgical data including performed operations, operating time, amount of blood loss, intensive care unit stay, postoperative mortality, and complications are presented in Table 3. There was no significant difference in complications between R0 resection and R1/2 resection group ($P = 0.245$).

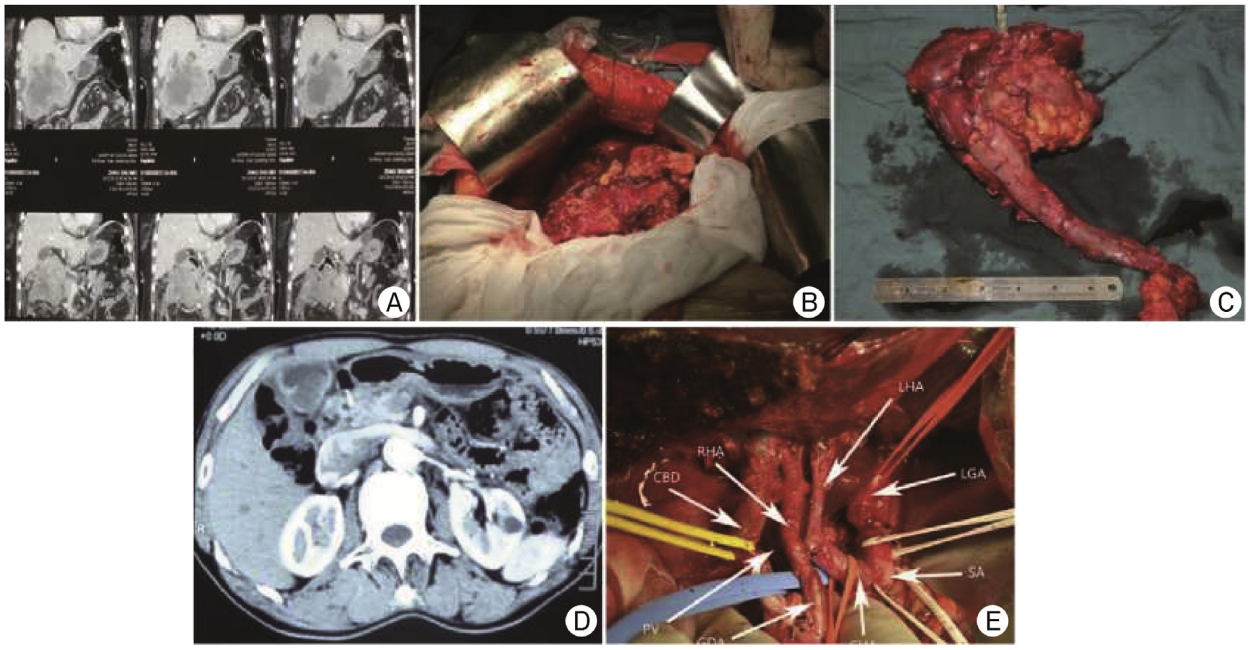

Fig. 1. R0 resection of patients with stage IV gallbladder cancer (GBC). (A-C) Hepatic pancreatoduodenectomy for T4N1M0 GBC. (A) Preoperative CT image; (B) investigation during surgery; (C) the resected tumor and adjacent organ. (D-E) Radical resection for T3N2M0 GBC. (D) Preoperative CT image; (E) the extended lymphadenectomy.

Survival in patients with stage IV GBC

The deadline for follow-up was March 2019. By that time, effective follow-up data were available for 229 (80.4%) patients; the median follow-up time was 39 months; the 1-, 3-, and 5-year overall survival rates were 6.6% (15/229), 0.9% (2/229), and 0 (0/229), respectively; and the median survival time (MST) was 3 months. Among patients with stage Ⅳ GBC who underwent resection, ascites ($P < 0.001$), pathological grade ($P = 0.020$), T stage ($P = 0.029$), M stage ($P < 0.001$), and surgery ($P < 0.001$) had significant impacts on survival, and multivariate analysis identified all these as independent risk factors affecting GBC prognosis (Table 4).

Survival in patients with stage IV GBC with R0 resection

The 1-, 3-, and 5-year overall survival rates for patients with stage Ⅳ GBC who underwent R0 resection were 20.0% (7/35), 5.7% (2/35), and 0 (0/35), respectively, and the MST was 6.0 months. These survival rates and MST were significantly higher than those in patients with stage Ⅳ GBC who underwent R1/R2 resection (4.6% [9/194], 0 [0/194], 0 [0/194], and 2.7 months, respectively) ($P < 0.001$) (Fig. 2).

The 44 patients who underwent R0 resection included 5 patients with stage M1. The remaining M0 patients included 1 T1N2M0, 26 T3N2M0, 2 T4N0M0, 7 T4N1M0, and 3 T4N2M0 (Table 5).

Comparing patients with the same TNM stage, stage ⅣA patients benefited from R0 resection (MST for R0 *vs.* R1/R2, 11.0 *vs.* 4.0 months; $P = 0.029$), and R0 resection also provided a significant survival benefit than R1/R2 resection in patients with stage ⅣB GBC without distant metastasis (MST for R0 *vs.* R1/R2, 6.0 *vs.* 3.0 months; $P = 0.007$) (Fig. 3).

Discussion

GBC is a very aggressive cancer with a dismal prognosis.[17] TNM stage has been shown to be the most important prognostic factor in patients with GBC after surgical resection.[18] Stage Ⅳ disease has commonly been considered unresectable,[5] but more aggressive surgical resection for advanced GBC has gained more support.[19,20] Kang et al[20] reported that the MST was longer in patients with stage IV GBC who underwent curative surgery than in those who underwent palliative surgery. Koh et al[21] confirmed that radical resection was appropriate for patients with even stage Ⅳ GBC, as long as the disease was localized and R0 resection was

Table 2
Clinical and pathological data of patients with stage Ⅳ gallbladder cancer (n=285).

Items	R0, n	R1/R2, n	P value
Jaundice			
No	37	157	0.013
Yes	7	84	
Ascites			
No	35	169	0.203
Yes	9	72	
Gender			
Male	10	73	0.310
Female	34	168	
Pathological differentiation			
Well	0	9	0.013
Moderately	26	92	
Poorly	18	140	
Morphology[a]			
Infiltration	22	103	0.960
Protuberance	7	32	
Age, years			
<55	13	97	0.036
55–70	26	93	
>70	5	51	
T stage			
T1	1	0	0.000
T3	30	97	
T4	13	144	
N stage			
N0	4	4	0.000
N1	9	116	
N2	31	121	
M stage			
M0	39	125	0.000
M1	5	116	
Complications			
No	35	208	0.245
Yes	9	33	
Pathological type			
Adenocarcinoma	35	201	0.533
Non-adenocarcinoma	9	40	

[a] The morphology information of 121 patients was missing.

Table 3
Surgical data of patients with stage Ⅳ gallbladder cancer (n=285).

Items	R0 resection	R1/R2 resection
Surgical procedure, n		
SRR	25	–
SRR + HPD	12	–
SRR + RH	4	–
SRR + SG	3	–
CE	–	58
CE + ED	–	126
CE + BE	–	6
ED	–	23
EL	–	19
GP	–	9
Operating time, h, median (Q1, Q3)	5.1 (3.1, 6.4)	2.7 (2.0, 3.5)
Amount of blood loss, ml, median (Q1, Q3)	600 (400, 1000)	200 (100, 300)
Postoperative mortality in 30 days, n	3	35
Complications, n		
Bile leakage	7	16
Bleeding	3	5
Abdominal infection	5	8
Hepatic insufficiency	2	12
Incision infection	3	22

SRR: standard radical resection; HPD: hepatopancreatoduodenectomy; RH: right hepatectomy; SG: subtotal gastrectomy; CE: cholecystectomy; ED: external drainage; BE: bilioenterostomy; EL: exploratory laparotomy; GP: gastrointestinal bypass; -: no data.

possible. Japanese researchers suggested that selected patients with stage Ⅳ GBC may thus achieve 5-year survival if the primary tumor is relatively localized, even if the mass is large and involves the neighboring organs.[14,17,19] However, on the contrary, other studies found that the increased morbidity and mortality associated with such aggressive resection procedures precluded their use as a standard of care.[22] Data from a high-volume center in Japan did not support any advantage of aggressive surgical resection over adjuvant chemotherapy in patients with stage Ⅳ GBC,[23] and Ercan et al[24] demonstrated that radical surgery had no benefit over palliative surgery in patients with stage Ⅳ GBC in terms of survival. In the current study, the 1-, 3-, and 5-year overall survival rates were significantly higher in patients undergoing R0 resection than in those undergoing R1/R2 resection ($P < 0.001$), with no significant difference in complications between the two groups.

According to the most recent AJCC definition, T4 disease is usually considered to be unresectable and should be treated with palliative therapies.[25] Groot Koerkamp and Fong[26] revealed that patients with T4 tumors were unlikely to benefit from surgical resection. However, currently, there is no consensus regarding unresectable factors in local extension of biliary tract cancers,[27] and several recent reports have shown improved prognoses in patients with these locally advanced cancers following surgical resection combined with arterial resection, reconstruction, or extended trisectionectomy of the liver and HPD.[16,27] T4 GBC resection has been accepted in cases where R0 surgery is achievable,[28] and Nishio et al[29] concluded that GBC involving the extrahepatic bile duct needed to be resected. Agarwal et al[30] also reported that duodenal infiltration was not an indication of unresectability in terms of HPD. In the present study, patients with stage ⅣA GBC benefited from R0 resection compared with R1/R2, thus confirming that

Table 4
Survival analysis in patients with stage Ⅳ gallbladder cancer (n=229).

Items	n	Univariate analysis					Multivariate analysis		
		Median survival time (months)	1-year survival (%)	3-year survival (%)	5-year survival (%)	P value	RR	P value	95% CI
Jaundice						0.934	–	–	–
No	161	3.0	6.8	1.2	0				
Yes	68	3.0	5.9	0	0				
Ascites						<0.001	1.631	0.001	1.221–2.180
No	156	3.3	8.3	1.3	0				
Yes	73	1.7	4.1	0	0				
Pathological differentiation						0.020	1.337	0.018	1.050–1.702
Well	7	5.0	0	0	0				
Moderately	95	4.0	7.4	1.1	0				
Poorly	127	2.0	7.1	0.8	0				
Gender						0.811	–	–	–
Male	69	3.0	4.3	0	0				
Female	160	3.0	8.1	1.3	0				
Age, years						0.059	–	–	–
<55	33	4.3	9.6	1.9	0				
55-65	113	3.0	7.4	1.1	0				
>65	83	2.5	4.8	0	0				
T						0.029	1.421	0.000	1.099–1.837
T1	1	53.2	100.0	100.0	0				
T3	97	3.3	6.2	0	0				
T4	131	2.7	6.9	0.8	0				
N						0.149	–	–	–
N0	7	7.0	14.3	0	0				
N1	98	3.0	10.2	0	0				
N2	124	2.7	4.0	1.6	0				
M						<0.001	1.896	0.000	1.409–2.552
M0	128	4.3	10.2	1.6	0				
M1	101	2.0	2.0	0	0				
Surgery						<0.001	1.542	0.039	1.022–2.327
R0	35	6.0	20.0	5.7	0				
R1/R2	194	2.7	4.1	0	0				

RR: relative risk; *CI*: confidence interval.

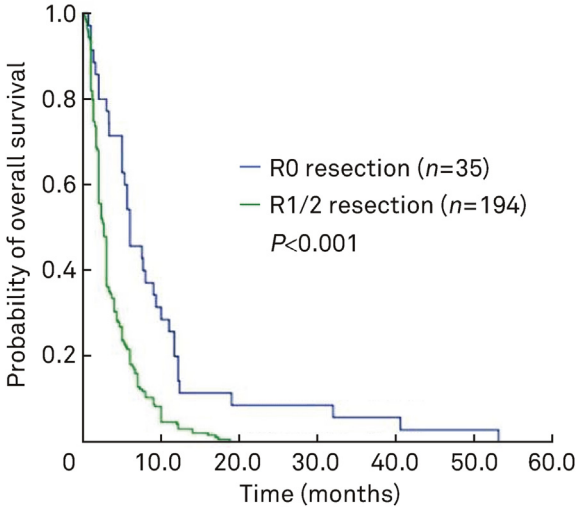

Fig. 2. Overall survival curves of patients with stage IV gallbladder cancer treated with R0 and R1/R2 resection. Survival of R0 patients was significantly higher than that of R1/R2 patients (P < 0.001).

Table 5
Tumor, node, metastasis staging of R0 patients with gallbladder cancer (n=44).

Staging	Number
T	
T1	1
T3	30
T4	13
N	
N0	2
Regional lymph node group+	42
Posterior pancreaticoduodenal lymph node+	18
Celiac artery lymph node+	21
Para-aortic lymph node+	2
M	
Solitary right abdominal wall metastasis	1
Solitary right hepatic metastasis	4

T: tumor; N: node; M: metastasis.

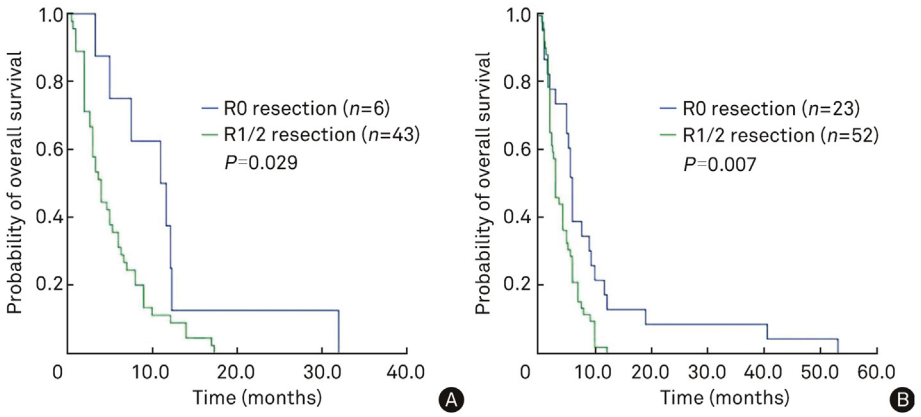

Fig. 3. Survival curves for patient in subgroups. a: T4N1M0 patients benefited from R0 resection; b: R0 resection provided a significant survival benefit than R1/R2 resection in T1-4N2M0 patients.

patients with T4 disease without distant metastasis or N2 metastasis are suitable for aggressive surgical intervention, even if the lesion involves the neighboring organs.

GBC presents with LN metastases in a high proportion of patients, including up to 80% of T4 tumors,[31–35] and LN metastasis is consistently one of the strongest predictors of survival in patients with GBC.[35–38] Birnbaum et al[28] stated that N status predicted outcome, while T status was not a prognostic indicator in locally advanced GBC. According to the 7th edition of the AJCC TNM staging system for GBC, LNs are divided into N1 (metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein) and N2 (metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes), and the presence of N2 metastasis classifies tumors as stage ⅣB.[39] In the present study, 97.2% (277/285) of patients had LN metastasis, and 53.3% (152/285) had N2 metastasis.

Patients with advanced GBC with metastases to the liver, lung, bone, peritoneum, and distant LNs (paraaortic or extra-abdominal) have generally been thought not to benefit from aggressive surgery,[40–42] and patients with N2 metastases have been considered unlikely to benefit from surgical resection.[17,41,43] Furthermore, ERLN provided no significant survival benefit for these patients,[44] and postoperative survival in patients with N2 metastasis without distant metastasis was as poor as that for patients with distant metastasis, which means that ERLN of N2 nodes has not been routinely considered.[13,14,26,45,46]

However, currently, there is no consensus regarding the indications for surgical resection in locally advanced GBC. Surgical resection improved the prognosis of patients with N2 LN involvement in some studies.[47,48] Survival was also significantly prolonged following radical resection including para-aortic LN dissection in patients with GBC with para-aortic LN metastasis compared to patients with distant metastasis or advanced, unresectable GBC.[47] The present study included 31 patients with N2 metastases who underwent R0 resection, and the procedure was associated with a significant survival benefit compared to R1/R2 resection in those patients with stage ⅣB GBC without distant metastasis, and most of the LN metastases in these patients were limited in the posterior pancreaticoduodenal LN and celiac artery LN, indicating that R0 resection could also be considered in patients with N2 metastasis, at least in these high selected patients. Muratore et al[49] also stated that positive N2 nodes did not preclude curative resection, and Birnbaum et al[28] also revealed that N2 metastases should not preclude surgery.

This study had several limitations. First, we had no information on disease-free survival time for these patients, thus limiting the statistical power of the study. Second, we did not consider the effects of postoperative chemotherapy and radiotherapy on patient prognosis. However, these adjuvant therapies have limited benefits in patients with GBC. Further studies, including larger numbers of patients and focusing on the extent of surgery in relation to LN metastasis, are needed to confirm our results.

Conclusion

In conclusion, this study provides evidence from the largest studied cohort ($n = 285$) of patients with stage Ⅳ GBC who underwent surgery. The results suggest that ascites, pathological grade, T stage, M stage,

and surgery are independent risk factors affecting prognosis in these patients. For patients with stage Ⅳ GBC without distant metastasis, R0 resection improves survival, and N2 LN metastasis does not preclude curative resection. Therefore, radical resection should be considered in patients with stage Ⅳ GBC without distant metastasis once R0 margin was achieved.

Conflicts of interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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