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Original Article

Safety of Surgical Treatment for Elderly Patients with Gallbladder Carcinoma

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Gallbladder carcinoma (GBC) is a common malignancy with a poor prognosis. With the average life expectancy increasing globally, the incidence of GBC is predicted to increase as well. We investigated the safety and feasibility of surgical treatment for elderly patients with GBC. We retrospectively compared clinical pathological data and treatment outcomes in 45 consecutive GBC patients (23 patients ≥75 years [elderly group] and 22 patients <75 years [younger group]) who underwent curative resection at the Iwakuni Center from January 2008 to December 2017. The proportion of preoperative comorbidities and anticoagulant use was significantly higher in the elderly group. The American Society of Anesthesiologists score was higher in the elderly versus the younger group, and the elderly group had significantly shorter operation times. Reduced activities of daily living was more common in the elderly versus younger group. The percentage of radical resection and overall 3-year survival (66.6% younger vs. 64.4% elderly) were similar between the groups. Controlling Nutritional Status (CONUT) score ≥3 and R0 resection were identified as prognostic factors for overall survival rate among all patients. After careful patient selection, surgery can be safely performed for elderly GBC patients, with outcomes similar to those of younger patients.

Key words: elderly patient, gallbladder carcinoma, prognostic factor, surgical treatment

The average life expectancy has been increasing in recent years in many countries. Japan has had the highest average life expectancy across the world since 2011. Gallbladder carcinoma (GBC) is the most common cancer of the biliary tract, and it has a poor prognosis [1]. The risk of GBC increases with age [2]. GBC is expected to occur at a higher rate among elderly patients in the future, and the clarification of appropriate treatment strategies for elderly patients with GBC is thus urgently needed. Surgical treatment is the only effective and commonly employed treatment for GBC, but it is associated with high morbidity. Although the quality of surgical treatment and pre-operative management continues to improve, the safety of surgical treatment for elderly patients remains unclear.

The aims of the present study were to identify the characteristics of elderly patients (≥75 years old) who underwent surgical treatment for GBC and to compare the surgical outcomes of these patients with those of younger GBC patients. We also analyzed the prognostic factors that affect the overall survival of elderly GBC patients.

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Patients and Methods

Patients. A total of 45 consecutive GBC patients (25 males [55.6%] and 20 females [44.4%]) underwent surgical treatment at the Iwakuni Clinical Center during the period from January 2008 to July 2018. The median age at operation was 74.5 years (range 38-95 years). For this study, patients ≥75 years old were classified as the elderly group (23 patients) and patients <75 years old were classified as the younger group (22 patients). The median age was 82 years (range 75-95 years) for the elderly group and 63 years (range 38-74 years) for the younger group.

We applied evidence-based clinical practice guidelines for the treatment of GBC. [3,4]. Based on preoperative imaging studies and clinical data, hepatectomy was indicated only in cases in which sufficient hepatic function would have been conserved post-surgery. According to incidental GBC, we used reported treatment strategies [5]. The pre-operative data included gender, age, body mass index, smoking history, drinking history, associated diseases (hypertension, diabetes, cardiac disease, stroke), the American Society of Anesthesiologists (ASA) Physical Status Score, and the Controlling Nutritional Status (CONUT) score [6]. The post-operative clinicopathological data included the surgical procedure, blood loss, operative time, and tumor stage per the Union for International Cancer Control (UICC) classification. Treatment results included complications and disease-free and overall survival.

This was a retrospective cohort study conducted to identify the clinical characteristics and surgical outcomes of elderly GBC patients. Patients were not required to give informed consent to the study, because the analysis used anonymous data that were obtained after patient agreed to treatment by written consent. The ethics committee at the Iwakuni Clinical Center approved the study protocol. This study was performed in accordance with the 1975 Declaration of Helsinki.

Surveillance. Each patient's follow-up duration was calculated from the day of surgery to either the day of death or the day of the last follow-up visit. The median follow-up duration was 35 months (range 3-102 months). All patients were followed-up at least every 3 months in the first year post-surgery and at intervals of 3-6 months thereafter. Abdominal ultrasonography and computed tomography were performed during the follow-up period at intervals of 3 months and 6 months, respectively.

Statistical methods. Statistical analyses were performed using the unpaired Student's *t*-test and the chi-square test with Fisher's exact test. Survival rates were calculated using the Kaplan-Meier method and were compared using the log-rank test. The duration of disease-free survival was calculated based on either death or GBC recurrence as the terminal event. We performed a multivariate analysis of prognostic factors using Cox proportional hazard modeling. A p-value <0.05 was considered significant. The statistical analyses were undertaken using JMP ver. 9 software (SAS Institute, Cary, NC, USA).

Results

The elderly and younger patients' pre-operative clinicopathological factors are summarized in Table 1. The proportion of preoperative comorbidities and anticoagulant use was significantly higher in the elderly group compared to the younger group (p-value was respectively 0.02). The ASA scores were significantly higher in the elderly group compared to the younger group ($p=0.05$). There was a greater number of patients with pancreatobiliary malfunction in the younger group than in the elderly group. The body mass index values and CONUT score did not differ significantly between the groups.

The two patient groups' tumor characteristics and intra- or post-operative data are shown in Table 2. The elderly group had significantly shorter operation times compared to the younger group. The blood loss during surgery in the elderly group was less than that in the younger group, though not significantly. There was no significant difference in the type of hepatectomy or the incidence of blood transfusion between the patient groups. The percentage of radical resection was not significantly different between the groups (68.2% for the younger group vs. 82.6% for the elderly group).

The elderly patients showed a significantly higher incidence of decline in the level of activities of daily living (ADL) after surgery compared to the younger patients ($p=0.01$). There was no significant between-group difference in the postoperative complication rate, length of postoperative hospital stay, postoperative delirium, or decrease in serum albumin levels at 3 months after surgery. Based on the patients' tumor

characteristics and the classification guidelines, there was no significant difference in tumor size, lymph node metastasis, staging, or tumor differentiation between the 2 groups.

There was no significant difference in the distribution of the cause of death between the two groups. There was one case of death unrelated to GBC in the elderly group. The patient died from panperitonitis caused by duodenal perforation after an endoscopic sphincterotomy. There were four cases of death unrelated to GBC in the younger group: primary lung cancer, pneumonia, acute myocardial infarction, and an unknown cause. The operative mortality rate was 2.2% (1 patient), and this patient (in the younger group) died

Table 1 Patient background in the elderly (≥75 years) and younger (<75 years) patients with GBC

Characteristic	Elderly (n = 23)	Younger (n = 22)	*p*-value
Male/female	12/11	14/8	0.36
Age, years (range)	82 (75–95)	63 (38–74)	< 0.01
BMI	20.3 ± 4.3	22.4 ± 3.1	0.10
Smoking history	8 (34.8%)	10 (45.5%)	0.54
Drinking history	7 (30.4%)	9 (40.9%)	0.53
Co-morbidities:	17 (73.9%)	9 (40.9%)	0.02
Diabetes mellitus	3 (13.0%)	4 (18.2%)	0.63
Hypertension	10 (43.5%)	5 (22.7%)	0.14
Cardiac disease	3 (13.0%)	3 (13.6%)	0.95
Stroke	6 (26.1%)	2 (9.1%)	0.13
Use of anticoagulant	9 (38.1%)	3 (13.6%)	0.02
Pancreaticobiliary maljunction	2 (8.7%)	8 (36.4%)	0.03
ASA score ≥3	9 (39.1%)	3 (13.6%)	0.05
CONUT score ≥3	9 (39.1%)	7 (31.8%)	0.53

ASA, American Society of Anesthesiologists; BMI, body mass index; CONUT, Controlling Nutritional Status.

Table 2 Intra- and post-operative data and tumor characteristics

Factor	Elderly (n = 23)	Younger (n = 22)	*p*-value
Intraoperative factors:			
Operative time, min (range)	299 (145–397)	358 (300–785)	0.03
Blood loss, ml	398 ± 125	640 ± 168	0.07
Blood transfusion	5 (21.7%)	4 (18.2%)	0.94
Hepatectomy	16 (69.6%)	17 (77.3%)	0.56
R0 (radical resection)	19 (82.6%)	15 (68.2%)	0.26
Postoperative factors:			
Complications: (Clavien-Dindo grade ≥II)	8 (34.8%)	7 (31.8%)	0.83
Delirium	5 (21.7%)	1 (4.6%)	0.07
Hospital stay, median (range)	13 (4–63)	11.5 (4–50)	0.71
Decline in ADL level	5 (21.7%)	0 (0%)	0.01
Alb level 3 mos. post-surgery	5 (21.7%)	2 (10.0%)	0.26
Tumor characteristics:			
Tumor size (cm)	3.75 ± 1.9	5.1 ± 2.9	0.27
Tumor depth; T1/T2/T3/T4	2/16/4/1	8/6/5/3	0.03
Lymph node metastasis	7 (30.4%)	7 (31.8%)	0.92
Stage UICC6th (I/II/IIA/IIIB/IVA/IVB)	2/12/1/7/1/0	8/6/2/3/2/1	0.07
Tumor differentiation (pap/well/mod/poor/asc/aec)	8/7/4/3/0/1	6/11/2/0/2/1	0.28

ADL, activity of daily living; aec, adenoendocrine carcinoma; Alb, albumin; asc, adenosquamous carcinoma; mod, moderately differentiated; pap, papillary adenocarcinoma; poor, poorly differentiated; UICC, Union for International Cancer Control; well, well differentiated.

of liver failure secondary to embolization of the hepatic artery for abdominal bleeding due to a pseudo- aneurysm rupture.

Overall survival rates post-surgery for the elderly group at 1, 2, and 3 years were 95.5%, 77.6%, and 64.4%, respectively, whereas those for the younger group were 81.8%, 72.2%, and 66.6%, respectively (Fig. 1). Disease-free survival rates post-surgery for the elderly group at 1, 2, and 3 years were 81.8%, 55.3% and 55.3%, and those for the younger group were 68.2%, 68.2%, and 62.3%, respectively (Fig. 2). There were no significant differences in the overall survival rates or disease-free survival rates between the 2 groups.

The prognostic factors for the overall survival rate among all patients are shown in Table 3. A CONUT score ≥3 (odds ratio [OR] = 4.69, p=0.007) and the use of radical resection (OR = 7.12, $p < 0.001$) were identified as the significant prognostic factors according to the multivariate analysis. Age was not identified as a significant prognostic factor.

Discussion

The results of our present analyses demonstrated no significant difference in the post-operative complication rates or long-term survival between the elderly and

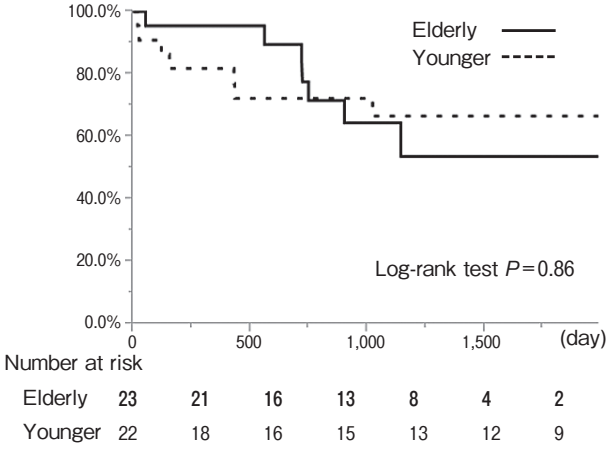

Fig. 1 Overall survival rates post-surgery for the elderly group (n = 23, *thick line*) and younger group (n = 22, *dotted line*). There was no significant difference in the overall survival rate between the 2 groups.

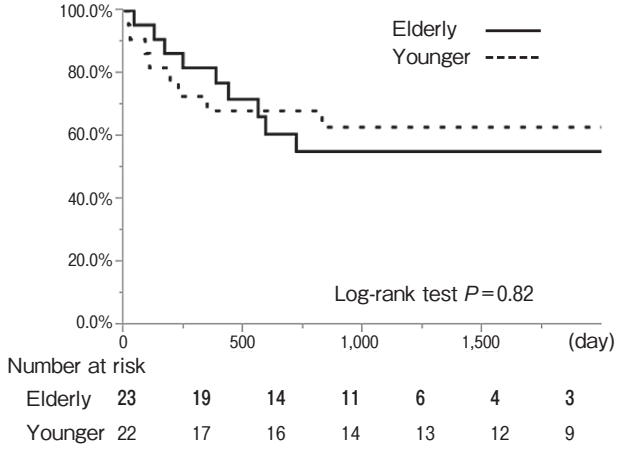

Fig. 2 Disease-free survival rates post-surgery for the elderly group (n = 23, *thick line*) and younger group (n = 22, *dotted line*). There was no significant difference in the disease-free survival rate between the 2 groups.

Table 3 Univariate and multivariate analysis of factors related to the overall survival rate for all patients

Factor	Univariate *p*-value	Multivariate *p*-value	Odds ratio (95%CI)
Gender	0.80		
Elderly age, ≥75 years	0.85		
Use of anticoagulant, yes/no	0.60		
Smoking history, yes/no	0.05		
Drinking history, yes/no	0.11		
Associated disease, yes/no	0.10		
ASA score ≥3	0.38		
CONUT score* ≥3	0.005	0.007	4.69 (1.5–15.1)
Radical resection, yes/no	<0.001	<0.001	7.12 (2.4–23.6)
Operative time ≥300 min	0.95		
Blood loss ≥500 ml	0.33		
Blood transfusion, yes/no	<0.001		
Stage ≥3, UICC 6th	<0.001		

younger patients with GBC, although the elderly patients had more associated co-morbidities. These results indicate that advanced age alone should not be a contraindication to surgical treatment for GBC.

Varying clinical outcomes have been reported for elderly patients undergoing surgical treatment for hepato-pancreato-biliary cancer [7-13]. Several research groups have proposed advanced age as a risk factor associated with increased post-operative complications and mortality [8,9,11,12], but other studies have shown no increased risk associated with advanced age [7,10,13]. Surgical treatment remains the curative therapy of choice for hepato-pancreato-biliary cancer for patients of all ages, but the use of surgical treatment for elderly patients thus remains controversial.

In the present study, the elderly patients had shorter operative times and less blood loss compared to the younger patients, though the difference was not significant. The surgery performed for the elderly patients was generally minimally invasive, *e.g.*, selective lymph node dissection. However, the surgical outcomes (*i.e.*, the morbidity, overall survival, and disease-free survival rates) were not significantly different between the elderly and younger groups. For elderly patients therefore, aggressive surgery should be avoided and minimally invasive surgery with curability should be performed.

In the present analyses, the elderly patients showed a higher incidence of decline in ADL level after surgery compared to the younger patients, although the surgeries in the elderly patients were minimally invasive. The decline in ADL level may be unavoidable, because elderly patients have a lower physiologic reserve than younger patients. Moreover, the decline is more likely to be related to the higher incidence of co-morbidities in elderly patients.

An enhanced recovery after surgery (ERAS) program was recently reported to be safe and to contribute to decreased total complication rates and hospital stays in hepatobiliary area [14,15]. The underlying principle of the ERAS program is a multimodal perioperative protocol designed to attenuate the inflammatory response and potentiate patient rehabilitation after surgery [16,17]. The adaptation of the ERAS program might be effective in elderly patients to prevent a post-surgery decline in ADL.

Our present findings demonstrated that a CONUT score ≥ 3 was an independent prognostic risk factor in patients with GBC who underwent surgery. The prognostic significance of the CONUT score in patients with colorectal cancer or hepatocellular carcinoma has been reported [18-20]. The CONUT score is a screening tool designed to easily and objectively assess patients' nutritional status [6]. The CONUT score is derived from serum concentrations of albumin, total cholesterol, and the total lymphocyte count. These three parameters are markers of protein reserves, impaired immune defenses, and caloric depletion, respectively. The CONUT score thus represents three important immunonutritional indices. Preoperative immunonutrition is reported to be beneficial in reducing overall and infectious postoperative complications [21,22]. We therefore recommend the perioperative administration of immunonutrition in patients with a high CONUT score, as doing so may improve the prognoses of these patients.

This study has limitations including its very small sample size (n = 45), single-institute analysis, patient selection bias, absence of long-term follow-up, and the inherent nature of a retrospective study. Nevertheless, our experience shows that with careful pre-operative planning that includes minimally invasive surgery with curability and postoperative care, surgery for GBC can be safe for elderly patients. Additional studies are needed to address remaining aspects including the characteristics of patients for whom surgery is contraindicated.

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