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Outcomes of surgery for gallbladder cancer: A single-center experience

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ABSTRACT

OBJECTIVE: Gallbladder cancer (GBC) is a rare clinical entity that has a poor prognosis. Radical resection with meticulous lymph node dissection is the only treatment option. The aim of the present study is to evaluate the efficacy of radical resection for GBC in the early postoperative period with the viewpoint of clinicopathological correlation.

METHODS: Patients (n=24) who underwent radical resection with lymph node dissection for GBC between 2015 and 2017 were included. Demographic data, histopathologic tumor type, preoperative tumor markers, pathologic tumor size/stage (depth of invasion), lymph node metastasis and metastasis rates, and postoperative early mortality were evaluated. The patients were grouped in two groups according to lymph node metastases: Group 1 (without lymph node metastasis) and Group 2 (with lymph node metastasis).

RESULTS: The median age of the patients in Group 1 and Group 2 was 65 (range, 42–89) years and 68 (range, 48–87) years, respectively ($p>0.05$). The female/male ratio in Group 1 and Group 2 was 4/4 and 13/3, respectively ($p>0.05$). There was a tendency for increased metastasis in Group 2 compared with Group 1 (31% vs. 0%) ($p>0.05$). Also, 88% of the tumors in Group 2 were in the advanced stage, whereas the rate was 37% in Group 1 ($p<0.05$). There was early postoperative mortality in seven patients who underwent resection. Four of the seven patients (43%) were from Group 2 and three (37%) from Group 1 ($p>0.05$).

CONCLUSION: Lymph node metastasis in GBC indicates advanced tumor stage. This causes a more complex surgical resection and therefore results in higher early postoperative mortality.

Keywords: Gallbladder cancer; radical resection; lymph node dissection; lymph node metastasis; extrahepatic biliary tree resection.

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Gallbladder cancer (GBC) has extremely poor prognosis. Its worldwide incidence is 1.1%–2%, with a slightly higher incidence in Asian countries. Its prevalence increases with increasing patient age. Women are more frequently affected, and the prevalence is five times higher in female patients. It is the 5th most prevalent gastrointestinal cancer in patients aged >65 years [1]. The five-year survival rates of untreated cases are reported to be 5%, and the median patient survival in untreated cases is reported to be approximately 8 months. GBC is associated with gallbladder stone in 1%–3% cases and anomalous pancreaticobiliary duct junction in 10%–18% cases. The common denominator is the inflammation of the gallbladder mucosa leading to atypia to dysplasia and cancer sequence [2]. Radical resection and regional lymph node dissection with clear surgical margins (R0)

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are the only treatment options in these patients. However, even in cases with R0 resection, the five-year survival rate is approximately 20% [3]. The extent of surgical resection and lymph node dissection and the resultant stage of the disease after pathologic evaluation are the main determinants of patient outcomes. Furthermore, lymph node metastasis seems to play a pivotal role in the determination of the overall survival of patients, and to achieve a reliable result, lymph node dissection should be meticulous [4]. Our liver transplantation institute is a high-volume center in the eastern part of Turkey, with particular focus on hepatobiliary surgery. The aim of the present study is to share the early postoperative results of patients with GBC who underwent radical resection at our institute and also to correlate the data of the patients with results of pathologic evaluation following resection.

MATERIALS AND METHODS

Selection of the patients and design of the study groups

Patients who underwent resection for gall bladder cancer at our institute between 2015 and 2017 were included. In addition to the preoperative demographic data such as age and sex, histopathologic tumor type, preoperative tumor markers (AFP, CEA, Ca 19-9, Ca15-3, and Ca 125), pathologic tumor size/stage (depth of invasion), lymph node metastasis and metastasis rates, and postoperative early mortality were evaluated. The patients were grouped according to the presence of lymph node metastasis. Group 1 included patients without lymph node metastasis, and Group 2 included patients with lymph node metastasis.

Pathologic staging of the tumors

The tumors were staged according to the American Joint Committee on Cancer (AJCC) 7th edition of tumor node metastasis (TNM) staging manual [5]. According to this manual, the lymph node metastasis gains importance and has a direct effect on patient survival.

Surgical resection

All the patients underwent a preoperative detailed work-up including tumor marker assessment and abdominal computerized tomography, and a surgery was planned for each patient with the suspicion of GBC. An open approach with a "hockey-stick" incision was used in each patient. We routinely perform regional lymph node dissection, but we do not perform para-aortic lymph node dissection or sampling. Generous Kocher maneuver is performed, and regional lymph nodes were dissected. The gallbladder was resected together with the segment 4 and 5 using a cavitary ultrasonic aspirator (CUSA excel, Integra). The distal surgical margin was routinely studied. If invasion to neighboring tissues was suspected, concomitant bile duct and duodenal wall resection was also performed. In cases with extrahepatic biliary tree resection, hepaticojejunostomy involving Roux-en-Y Limb was performed. Sump drainage of the sub-hepatic area was performed, and the operation was terminated.

Statistical analysis

The variables were not normally distributed, and therefore, the continuous variables are expressed as median (range). Data that require rate are expressed in percentages. The dependent and independent data are evaluated using Mann–Whitney U test. Any p-value <0.05 was considered as statistically significant. All the statistical analysis was performed using Statistics Software Program for Social Sciences version 22 (SPSS v22, IBM, USA).

RESULTS

Demographic data of the patients

A total of 24 patients were operated for gall bladder adenocarcinoma at our institute between 2015 and 2017. Only two patients among the whole study group showed neuroendocrine differentiation, and one patient had adenosquamous differentiation. There were eight patients in Group 1 and sixteen in Group 2. The data of the patients in the study groups are summarized in Table 1. Briefly, the median age of the patients in Group 1 and Group 2 was 65 (range, 42–89) years and 68 (range, 48–87) years, respectively (p=0.697). The female/male ratio in Group 1 and Group 2 was 4/4 and 13/3, respectively (p=0.238). The two groups were similar in terms of demographic characteristics.

Tumor-related characteristics of patients' tumors

There was a tendency for increased systemic metastasis rate in Group 2 compared with Group 1 (31% vs. 0%), but this did not reach a statistical significance (p=0.238). Also, 88% of the tumors in Group 2 were in the advanced

TABLE 1. Demographic data of the patients in the study group

	Group 1 (n=8)	Group 2 (n=16)	P
Age (years) [median (range)]	65 (42-89)	68 (48-87)	0.697
Female/Male	4/4	13/3	0.238
Systemic Metastasis Rate (%)	0	31	0.238
AFP (IU/mL) [median (range)]	590.36 (0.8-4712)	1126.51 (1.4-17995)	0.928
CEA (IU/mL) [median (range)]	21.91 (1.5-151)	19.30 (1.1-165)	0.653
CA125 (IU/mL) [median (range)]	43.25 (5.6-108)	84.33 (3.6-506)	0.417
CA199 (IU/mL) [median (range)]	255.30 (10.8-1320)	1558.98 (2.5-16315)	0.928
CA153 (IU/mL) [median (range)]	21.66 (7.7-39.9)	34.83 (6.6-145)	0.528

stage (T4 according to TNM staging), whereas the rate was 37% in Group 1. Therefore, the tumors in Group 2 had a statistically significant tendency to have more advanced stages than those in Group 1 (p=0.045). The tumor size/stages are summarized in Figure 1.

Postoperative early mortality of the patients

There was early postoperative mortality in seven patients who underwent resection. Four of the seven patients (43%) were from Group 2 and 3 (37%) from Group 1. Although patients with lymph node metastasis tended to have higher early postoperative mortality, this difference did not reach a statistical significance (p=0.653). When these subgroups of the patients were analyzed, it was seen that 57% (n=4) patients underwent concomitant organ resection. In addition, Roux-en-Y biliary reconstruction was performed in 71% (n=5) patients. The concomitant Roux-en-Y hepaticojejunostomy reconstruction and organ resection rates in the patients without postoperative early mortality were 29% and 35%, respectively. Although the patients with early postoperative mortality tended to have a higher rate of complex surgeries, this did not reach a statistical significance (p=0.418).

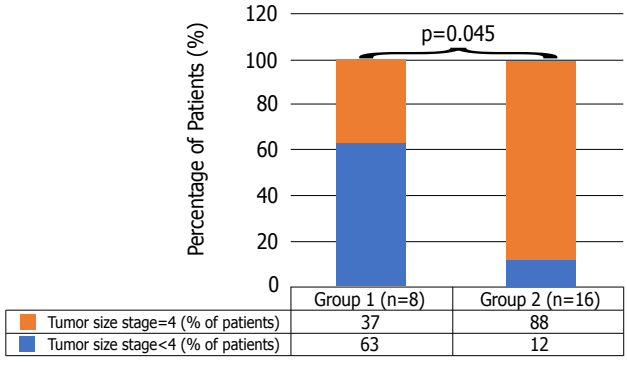

FIGURE 1. The effect of lymph node metastasis on the tumor size of the patients.

DISCUSSION

We routinely perform radical resection and regional lymphadenectomy in patients with suspected GBC in the preoperative workup. GBC is a rare clinical entity in Turkey, and our institute is one of the referral centers draining the eastern part of Turkey. Therefore, we analyzed the adequacy of extent of the resection performed at our institute by correlating our results with a clinicopathologic correlation.

In our study, one important observation was that patients with lymph node metastasis regardless of the location and number of the involved lymph nodes are a risk factor for advanced tumor size stage of patients with gallbladder tumors. This means that if the patient has lymph node metastasis, the tumor is more invasive and has a propensity to microscopically or microscopically invade the adjacent organs. Therefore, more complex surgeries were needed in these patients, leading to high rates of concomitant adjacent organ resections and hepaticojejunostomies. Therefore, this resulted in a higher frequency of early postoperative mortalities in these patient subpopulations. This is a unique finding because until now, the long-term prognostic significance of lymph node metastases has been analyzed in the current literature; however, our study is the first one to analyze the early postoperative effects of the advanced stages of the disease. The reported rates of postoperative mortality and morbidi-

ties ranged between 10% and 20% in various studies [6, 7]. However, these complications were observed following major abdominal surgery, and a stage-related correlation has not been done.

It has been previously reported by Oh et al. [8] that lymph node metastasis reduced the overall survival of patients from 67.6 months to 56.1 months. Therefore, they emphasized the role of lymph node metastasis in patients with GBC. They concluded that lymph node dissection was imperative for adequate staging and allocation of the patients to certain prognostic groups. This concept was also supported by Liu et al. [9], where they emphasized that lymph node metastasis but not the totally harvested lymph node number together with metastatic lymph node ratio was important in determining the prognoses of patients. However, they have not emphasized the early postoperative mortality or morbidity in their study [8, 9].

Vascular endothelial growth factors, vascular endothelial growth factor receptor 2 (VEGFR-2), and stromal cell-derived factor 1 (SDF1)α have been analyzed in advanced biliary tact cancers for susceptibility to targeted chemotherapy with combination of gemcitabine and sorafenib [10]. However, the diagnostic efficacy of serum tumor markers has not been evaluated. In our study, we have found a tendency of serum tumor markers AFP, CEA, Ca 19-9, Ca15-3, and Ca 125 to be elevated in patients with lymph node metastases. This difference did not reach a statistical significance. We believe that this difference will be more pronounced when the number of patients is increased.

One limitation of our study is that the patient number was low. However, this a preliminary report of the early results of an ongoing study, and as the patient number is increased, better and clear results will be obtained.

In conclusion, lymph node metastasis indicates poor prognosis in the long term and has an impact on the early postoperative period by increasing the early postoperative mortality. Furthermore, lymph node metastases regardless of the location and number of the involved lymph nodes indicate advanced tumor depth stage for GBCs.

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