Scientific Research Publishing

Surgical Science, 2025, 16(4), 235-246
https://www.scirp.org/journal/ss
ISSN Online: 2157-9415
ISSN Print: 2157-9407

Recurrence Factors of Localized Gallbladder Cancer

Salah Berkane[1,2*], Mohamed Cherifi[2,3], Faiza Taib[1], Sabeha Belhouas[1], Abdellah Boudiaf[1], Ibtissem Bezghoud[1], Salim Belkherchi[4,5]

[1]Department of Visceral and Oncological Surgery, Ibn Ziri Hospital, Algiers, Algeria
[2]Faculty of Medicine, Benyoucef Benkhedda University of Algiers, Algiers, Algeria
[3]Central Biology Laboratory, Ibn Ziri Hospital, Algiers, Algeria
[4]Surgery Department of University Hospital Center of Bejaia, Bejaia, Algeria
[5]Faculty of Medicine, Abderrahmane Mira University, Bejaia, Algeria
Email: *Salahberkane07@yahoo.fr

How to cite this paper: Berkane, S., Cherifi, M., Taib, F., Belhouas, S., Boudiaf, A., Bezghoud, I. and Belkherchi, S. (2025) Recurrence Factors of Localized Gallbladder Cancer. *Surgical Science*, **16**, 235-246.
https://doi.org/10.4236/ss.2025.164025

Received: January 13, 2025
Accepted: April 24, 2025
Published: April 27, 2025

Abstract

Introduction: The localized gallbladder cancer can be cured when it is radically resected. But even in this favorable form of disease, tumoral recurrence will occur in some cases. The aim of this retrospective study is the recognize factors that are associated with tumoral recurrence. **Material and Method:** All tumors that do not extend the serous layer of the gallbladder wall and are treated with radical surgery were included in this retrospective study. Several factors, such as clinical, biological and histological, were retrospectively analyzed. We divided patients into two groups: group A with recurrence and group B without recurrence. **Results:** One hundred-twenty-two patients were included. The group A was constituted by twenty-nine patients (23.8%) and ninety-three patients constituted the group B. Univariate analysis of the 2 groups shows that lymph node involvement, serosal involvement, the presence of vascular emboli, the presence of perineural sheathing, and capsular rupture of the lymph nodes have a negative impact on tumor recurrence. In multivariate analysis, only 4 elements favor the risk of recurrence which are lymph node involvement with a number of lymph nodes equal to or greater than 4 nodes, a high CA 19.9 rate, serosa involvement (pT3) and stage III of the ASA classification. Near all recurrences (96.6%) were located in the peritoneal cavity and their four sites are represented by peritoneal carcinomatosis, the main bile duct, hepatic metastases and lymph nodes. The 5-year survival is 3.4% in group A (patient died 85 months after her recurrence and after palliative secondary resection) and 83.7% in group B. **Conclusion:** The 4 factors predicting tumoral recurrence isolated in our study, can help to provide a new approach in the radical surgery of the localized form of gallbladder cancer to improve

its prognosis. We propose to add efficacious adjuvant therapy for patients with these predicting factors of recurrence after radical surgery.

Keywords

Localized Gallbladder Cancer, Radical Surgery, Recurrence Factor

1. Introduction

Gallbladder cancer remains a disease with a reserved prognosis once the diagnosis has been established [1]. The overall 5-year survival remains around 5 to 8% mainly due to late diagnosis with the presence of locally advanced and/or metastatic disease [2]. Indeed, 80% of patients are beyond surgical possibilities with these locally advanced and/or metastatic forms at the time of diagnosis [3]. A long survival is anecdotic for these locally advanced and /or metastatic forms of gallbladder cancer. Conversely, gallbladder cancer in its localized form (tumor not extending beyond the serosa) present in 20% of patients can be cured by well-conducted radical surgery [4]. These localized tumors are made up of early and invasive forms at stages IA, IB, IIA, IIB, IIIA and IIIB. These last tumors constitute the overwhelming majority of potential cancer cures. But even in this localized form, a significant number of patients will present a tumor recurrence after surgical resection considered as radical. This tumor recurrence has no therapeutic solutions once diagnosed and leads to the death of these patients [5]. This fact indicates that these factors of tumor recurrence at present serve as pejorative factors. Thus, highlighting these predictive factors of cancer recurrence means seeking surgical adapted associated with efficacious adjuvant therapy in this localized form in order to prevent this recurrence or control this last. We propose, through this retrospective study, an analysis of the evolution of our patients operated on for localized gallbladder cancer and to isolate the predictive factors of tumor recurrence after radical surgical resection.

2. Material and Method

We define localized gallbladder cancer as a tumor whose extension does not exceed the serosa of the organ, i.e. without involvement of neighboring organs and regardless of lymph node involvement. These localized tumors are made up by early and invasive forms at stages IA, IB, IIA, IIB, IIIA and IIIB. For the stage III, only tumor with serous layer extent are considered in this retrospective study. We have excluded all tumors that exceed the serous layer of gallbladder and/or with metastatic localisation (liver or peritoneal metastasis). These forms are rarely amenable to radical surgery and their prognosis remains very poor even when resected.

Radical surgery is defined by resection of segments IVb-V associated with lymphadenectomy. The latter concerns the lymphatic and lymp node structures

of the hepatic pedicle (level 1 or L1), the lymphatic and lymph nodes structures of the posterior surface of the duodenopancreatic block and the common hepatic artery (level 2 or L2) and the lymphatic and lymph node structures of the coeliac flank and that of the inter-aortico-caval area (level 3 or L3). For some patients, an extension of the hepatic resection is performed for a suspicion of tumor extension to a neighboring organ which proves to be healthy after histological study.

After sugery 62.5% and 35.5% of group A and group B benefited from 2 protocols of adjuvant chemotherapy:

6 cycles of protocole 1 (GEM-CIS): Day 1 Gemcitabine (1000 mg/m^2) + Cispaltine (70 mg/m^2); Day 8 Cisplatine (70 mg/m^2).

12 cycles of Protocole 2 (LFC): Day 1 Lederfoline (20 mg) + Fluorouracile (1000 mg/m^2) + Cisplatine (70 mg); Day 2 Lederfoline (20 mg) + Fluorouracile (1000 mg/m^2).

The systematic preoperative assessment carried out is as follows:

A complete clinical examination with search for systemic defects and in particular cardiac, pulmonary, renal, blood and hepatic crasis.

Biological tests: Complete Blood Count, blood urea and creatinine, blood clots (thrombin levels, Howel time and Kaolin cephalin time), protein levels, liver function (alkaline phosphatases, transaminases, gamma-glutamyl-transferase).

An abdominal ultrasound, a thoraco-abdomino-pelvic computed tomography are systematically performed with in certain cases and if necessary a magnetic resonance imaging.

The dosage of tumor markers: Carbohydrate antigen (CA19.9) with the upper threshold level according to the laboratory as a reference and the carcinoembryonic antigen (CEA) with the threshold double the upper level of the laboratory.

For cancers discovered on a cholecystectomy specimen, a histological review is systematically requested to obtain the following information: the macroscopic appearance, the histology with the tumor grade, the degree of transparietal extension (pT), the exact location of the tumor, for pT2 cancers the exact location on the serosal surface or the hepatic surface (since the 2017 classification), the presence of perineural sheathing, the presence of vascular emboli, the specific study of the cystic duct section, the possible presence of the cervical lymph node and its infiltration. A supplement to the operative report is requested from the surgeon who performed the cholecystectomy concerning the progress of the cholecystectomy with a focus on the opening of the gallbladder and the operative difficulties encountered. Resumption for additional surgery is performed as soon as the preoperative assessment is complete. All cases meeting the definition of localized cancer who underwent radical surgery and long-term follow-up (minimum of 12 months for recurrences and 5 years or more for patients still alive) were included in this study.

The following parameters were analyzed: age, sex, ASA (American society of anesthesiology), macroscopy, microscopy, tumor location and size, operating

time, surgical procedure, type of lymphadenectomy, transparietal extension, tumor marker levels, lymph node status, perineural sheathing, vascular emboli, fat infiltration, capsular rupture (lymph node), postoperative outcomes, additional treatment, recurrence, sites of recurrence and long-term outcome.

The TNM classification used is that of 2017 (Eight Edition).

Patients were divided into 2 groups:

Group A: Patients with recurrence and Group B: Patients without recurrence.

All patients were followed according to the following protocol:

Clinical control, abdominal ultrasound + tumor markers (Ca19.9 and CEA) every 3 months for 2 years.

Clinical control, abdominal ultrasound + tumor markers (Ca19.9 and CEA) every 6 months for 2 years.

Tumor recurrence is diagnosed by the clinic, morphological examinations, tumor markers and treated by chemotherapy and/or a new surgical resection.

We performed a univariate and multivariate analysis using the Student test for quantitative variables and the X2 test for qualitative variables. For multivariate analysis, logistic regression was used. Significant variables in univariate analysis were analyzed in multivariate.

The difference is considered significant if the P value is less than 0.05. The strength of association between two parameters was assessed by the odds ratio.

The statistical data were analyzed by IBM SPSS Statistics 20.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

Out of a total of 187 cases of gallbladder tumors meeting the inclusion criteria in the study, 122 cases were included after excluding 65 cases (8, postoperative deaths, 6 deaths from intercurrent causes, 38 cases without information on lymph node infiltration and cases with insufficient follow-up of less than 12 months (**Figure 1**). The patients were divided into 97 women and 25 men, with a mean age of 58.67 ± 10.84 (26 - 83 years). Sixty-one patients were classified ASA I (52.5%), 51 (41.8%) ASA II and 07 ASAII (05.7%). The 122 patients underwent radical surgery. Nine patients underwent L1 lymphadenectomy (07.4%), 09 (07.4%) L2 lymphadenectomy and 104 (85.2%) L3 lymphadenectomy. The dominant macroscopic types were polyp with 67 cases (57.2%) and parietal thickening with 33 cases (28.2%). One hundred and twenty-one patients (99.1%) had adenocarcinoma and only one had squamous cell carcinoma. Seventy-eight (69.6%) patients had grade 1 adenocarcinoma, 21 (18.8%) grade 2 and 13 (11.6%) grade 3. The CA 19.9 and CEA were elevated in 09.3% and 05.6% of patients, respectively. The mean tumor size was 31.81 ± 17.80 mm and a median of 30 mm. Fat infiltration was found in 04.5%. Eighty-three (68%) patients did not have lymph node infiltration, 24.6% had N1 type infiltration and 09 07.4% had N2 type infiltration. Vascular emboli, perineural sheathing and capsular rupture of the lymph nodes were found in 29.3%, 30.9% and 05.4% respec-

tively. Adjuvant systemic chemotherapy was associated in 62% and 35.5% of groups A and B respectively. Twenty-nine patients (23.8%) had tumor recurrence and constitue the group A and ninety-three did not have recurrence and constitue group B. All patients who had a recurrence died of their disease between 03 and 36 months, regardless of the attitude towards this recurrence. On the contrary, only 1 patient died of intercurrent diseases without recurrence at the time of his death. The rest of the patients are alive with an overall 5-year survival of 83.7% for the group B. The characteristics of the entire series are reported in Table 1. Univariate analysis of the 2 groups shows that lymph node involvement, serosal involvement, the presence of vascular emboli, the presence of perineural sheathing, capsular rupture of the lymph nodes have a negative impact on tumor recurrence, while fatty infiltration and involvement of the gallbladder opposite the gallbladder bed had no impact on the occurrence of recurrence (Table 2). In multivariate analysis, only 4 elements favor the risk of recurrence which are lymph node involvement with a number of lymph nodes equal to or greater than 4, a high CA 19.9 rate, serosa involvement (pT3) and stage III of the ASA classification (Table 3). Twenty-nine patients (96.6%) presented a recurrence in the peritoneal cavity and the 04 sites of recurrence are represented by peritoneal carcinomatosis, the main bile duct, hepatic metastases and lymph nodes. Table 4 and Table 5 show respectively the odd ratio of recurrence of the four factors and sites of the recurrence. Despite that, 62.5% and 35.5% of patients in respectively group A and group B, benefited from adjuvant chemotherapy (GEM-CIS or LFC protocols), it should be noted that the 5-year survival is 3.4% in group A and 83.7% in group B.

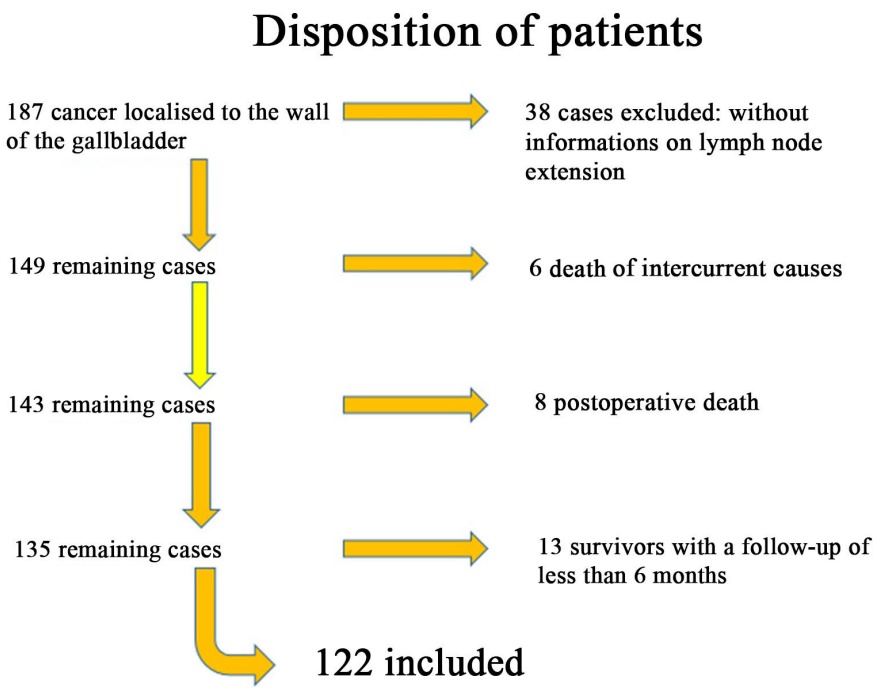

Figure 1. Flow-Chart.

Table 1. Characteristics of all patients.

Age, n = 122, M ± SD (58.67 ± 10.84) Minimum 26 years and maximum 83 years	
Sex	F = 97 (79.5%)
	M = 25 (20.5%)
ASA	I: 64 (52.5%)
	II: 51 (41.0%)
	III: 07 (5.7%)
Serous tumor (T3)	Yes = 64 (52.5 %)
	No 58 (47.5%)
Lymphadenectomy	L1: 09 (7.4%)
	L2: 09 (7.4%)
	L3: 104 (85.2%)
Number of nodes uncoded	N0 83 (68.0%)
	N1 30 (24.6%)
	N2 9 (7.4%)
Number of nodes coded	N0 + N1 < 04 g 113 (92.6%)
	N2 ≥ 4 g 09 (07.4%)
CA 19.9	Elevated: 10 (09.3%)
	Normal: 98 (90.7%)
CEA	Elevated: 06 (05.6%)
	Normal: 102 (94.4%)
Adjuvant treatment	Yes: 51 (41.9%)
	No: 71 (58.1%)
Grade	1: 78 (69.6%)
	2: 21 (18.8%)
	3: 13 (11.6%)
Diameter, M ± SD	31.81 ± 17.80 mm, with a median of 30 mm
Macroscopy	Polyp: 67 (57.2%)
	Thickened wall: 33 (28.2%)
	Nodule: 12 (10.2%)
	Inapparent: 05 (04.2%)
Infiltrated adipose tissue	Yes: 04.5%
	No: 95.5%
Capsular rupture of node	Yes: 06 (5.4%)
	No: 105 (94.59%)
Vascular emboli	Yes: 26 (29.3%)
	No: 63 (70.7%)
Perineural invasion	Yes: 30 (30.9%)
	No: 67 (69.2%)
Postoperative course	Complicated: 38 (31.1%)
	Uncomplicated: 84 (68.9%)
Recurrence	Yes: 29 (23.8%)
	No: 93 (76.2%)

Table 2. Recurrence and clinical characteristics of tumors.

Clinical and pathological features	Number of patients	Group A	Group B	% of recurrence	P-value χ^2 test
Lymph node involvement					

Continued

N0, N1	113	21	92	18.5	**0.0000**
N2	9	8	1	88.9	
Serous tumor					
Absent	58	7	51	12.1	**0.004**
Present	64	22	42	34.4	
Lymphovascular involvement					
Absent	63	10	53	15.9	**0.008**
Present	26	11	15	42.3	
Perineural invasion					
Absent	67	10	57	14.9	**0.002**
Present	30	13	17	43.3	
Capsular effraction of lymph node					
Present	105	20	85	19	**0.006**
Absent	6	4	2	66.7	
TSSCH*					
Present	112	25	88	22.1	0.130
Absent	9	4	5	44.4	
Infiltrated adipose tissue					
Present	108	25	83	23.1	0.139
Absent	6	3	3	50.0	

*: TSSCH: subserous tumor on hepatic side (pT2b).

Table 3. Multivariate analysis.

Variables in the Equation						
	B	**S.E.**	**Wald**	**df**	**Sig.**	**Exp (B)**
Step 1[a] Lymph node (1)	**3.528**	**1.154**	**9.352**	**1**	**0.002**	**34.041**
CA19.9 (1)	**−1.850**	**0.794**	**5.430**	**1**	**0.020**	**0.157**
T3 (1)	**−1.379**	**0.640**	**4.644**	**1**	**0.031**	**0.252**
ASA NEW (1)	**2.791**	**0.927**	**9.060**	**1**	**0.003**	**16.304**
Constant	**−3.466**	**1.402**	**6.111**	**1**	**0.013**	**0.031**

This table shows the power of 4 risk factors. [a]: It shows that the infiltrative node is the greatest one (see on the column "Power".

Table 4. Unadjusted risk associated with the occurrence of recurrence.

Parameter	OR	95% CI	P
Number of nodes ≥ 4	31.89	3.6 - 275	0.000
Serous tumor (Infiltrated)	3.35	1.26 - 8.9	0.012
High CA 19.9	6.23	1.6 - 24.31	0.004
ASA (III)	5.07	1.05 - 18.47	0.027

For the variables that showed a significant difference in the bivariate analysis, a logistic regression was performed to study the main factor associated with the occurrence of recurrence.

Table 5. Sites of recurrence.

Sites of recurrence	Number	Percentage
Peritoneal carcinomatosis	14	46.7
Bile duct	07	23.3

Continued

Liver metastasis	06	20
Retroperitoneal lymp node	06	20
Ovarian metastasis	01	3.4
Lung metastasis	01	3.4

Some patients presented several sites of recurrences. Twenty-nine patients (96.6%) presented a recurrence in peritoneal recurrence.

4. Discussion

Gallbladder cancer remains a pathology with a serious prognosis due to the advanced stage of its diagnosis. Indeed, 80% of patients have their disease discovered when the tumor is locally advanced with involvement of one or more neighboring organs or metastatic represented mainly by hepatic metastases and peritoneal carcinomatosis [6]. In our opinion, it is essential to distinguish between 3 forms of gallbladder cancer. The form localized to the organ which is the subject of this work. The locally advanced form which is characterized by an extension of the tumor to a neighboring organ such as the liver, the main bile duct and the digestive tract essentially which requires a more extensive surgical procedure on one side and a greater tumor extension. Finally, the metastatic form whose control at present remains marginal. Each form has its own characteristics in the context of diagnosis, surgical approaches and prognostic aspect. These are forms of gallbladder cancer that are completely different from each other and therefore must be analyzed according to their characteristics. The localized form must be, in our opinion, isolated because it complies with the following criteria: the surgery applied is less aggressive and is represented by either a cholecystectomy (pT1a and possibly pT1b or a radical surgery such as a bisegmentectomy IVb-V and a lymphadenectomy of variable importance depending on the teams [7] [8]. Our results show that the more significant the parietal involvement, the greater the risk of recurrence from the mucosa to the serosa [9]. This lymph node involvement has prompted us since the beginning of our experience to perform an extented lymphadenectomy which allows us to resect a maximum number of lymph nodes and therefore to have the most precise idea of the extent of the spread of the tumor [10] [11]. This is the only lymphadenectomy which brings back the maximum number of lymph nodes and especially the 3 levels of lymph node infiltration of cancer of the gallbladder. The multivariate analysis carried out in this series clearly shows that from 4 lymph nodes, the prognosis is negatively impacted. For example and to focus on the importance of profil of lymph nodes, some authors [12], use this extented lymphadenectomy associated with cholecystectomy alone for pT2 cancer with interesting results thereby indicating the greater frequency of lymph node involvement than that of the liver at this stage of the disease. Much work has been done on the reality, importance and impact of lymphadenectomy in gallbladder cancer by others [13] [14].

A high level of CA19.9 has been shown to have a negative impact in our series. We interpret this as an indicator of more or less advanced disease even if the mor-

phology shows a localized tumor [15]. It is logical to think that in front of a high CA 19.9 outside of cholestasis and this is the case of this localized form, the disease presents a tumor diffusion not yet detectable by current morphological examinations and intraoperative exploration. It is also possible to focus in more aggressive tumor profile [16]. The ASAIII factor (Associated defect with impact on the body) has emerged as an indicator of tumor recurrence. It is probably linked to the immune state through conditions and pathologies that interfere with the immune state [17] [18]. This factor shows all the consequences that could result from organic diseases as diabetes, high blood pressure, metabolic diseases, which through degenerative lesions will interfere negatively with the cancer. They interact through the negative impact on the immune status that with the oncological surgical act and what surrounds it such as anesthesia, transfusions or infection. It seems to us of the utmost importance to undertake work in the future in order to finely understand this aspect of the importance of the interference between tumor and certain conditions altering the organism in a patient with gallbladder cancer

In the literature, all authors agree to note that lymph node involvement is an indicator of poor prognosis compared to its absence [19] [20]. Our study shows this, but relativizes this notion by showing that N2 involvement (4 lymph nodes and more) is more pejorative than that in N1 and the absence of involvement (N0). In other words, lymph node involvement up to 1 and 3 lymph nodes does not have a very negative impact, even if lymph node involvement in N1 is negative compared to its absence N0. Only one patient classified N1 had lymph node involvement beyond the hepatic pedicle (10%) while 13 patients out of 28 classified N2 had involvement beyond the hepatic pedicle (46.2%) (Data not shown). It indicates that more the number of lymph node is great, more it could be situated far of hepatic pedicle.

For the CA 19.9 rate, few studies have shown its pejorative role [20]. The involvement of the serosa came out as pejorative in our series unlike the involvement of the other layers of the gallbladder. For Park J.S. *et al.* [21], the infiltrative form and the high grade are the predictive factors of tumor recurrence for a cancer classified at stage II (Infiltration of the subserosa without lymph node involvement). These 2 factors were not found in our present series. If the presence of vascular emboli, perineural sheathing and capsular rupture had an impact on the occurrence of recurrence in multivariate analysis, they were not in multivariate analysis, unlike the experiences of Yamaguchi [22]-[24].

In the present series, the sites of recurrence are represented by the peritoneal cavity and primarily the peritoneal serosa in the form of peritoneal carcinomatosis. Maplanka C. [25] reports in an update the same observation for the recurrence of gallbladder cancer. As this study shows, adjuvant chemotherapy did not add any effect to radical surgery.

Our study also presents certain biases that could limit its scope. First, it is retrospective with all the hazards of this type of study (lack of certain data, etc.). The number of patients included is not, in our opinion, important to come out with

more solid conclusions. Nevertheless, our series is homogeneous insofar as it is monocentric and it was carried out with the same surgical resection protocol including a constant hepatic resection and a type 3 lymphadenectomy for the overwhelming majority of patients (85.2% of patients). In addition, we find 3 of the factors that are highlighted to varying degrees in the literature, namely lymph node involvement when it concerns 4 or more lymph nodes, serosa involvement and a high rate of CA19.9. The ASA III classification as a factor in favor of the occurrence of tumor recurrence remains to be confirmed in the future on a larger scale and by our or other teams.

5. Conclusion

The localized form of gallbladder cancer must be isolated from other forms (locally advanced form and metastatic forms). It must currently be treated by radical surgery, both IV-V hepatectomy and especially extensive lymphadenectomy. The surgeon must focus before the operation on a precise morphological exploration and meticulous and maximal surgery. Our study shows that until now the two regimens of chemotherapy are not effective against gallbladder cancer. The factors predicting tumor recurrence in the postoperative period must push the multidisciplinary teams dealing with this cancer to seek complementary treatment in order to make this surgery more effective. The localized form of gallbladder cancer must be isolated. Further studies need to be conducted to confirm our results and/or find other factors in the future.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Cubertafond, P., Gainant, A. and Cucchiaro, G. (1994) Surgical Treatment of 724 Carcinomas of the Gallbladder Results of the French Surgical Association Survey. *Annals of Surgery*, **219**, 275-280. https://doi.org/10.1097/00000658-199403000-00007

[2] Dixon, E., Vollmer, C.M., Sahajpal, A., Cattral, M., Grant, D., Doig, C., *et al.* (2005) An Aggressive Surgical Approach Leads to Improved Survival in Patients with Gallbladder Cancer. *Annals of Surgery*, **241**, 385-394. https://doi.org/10.1097/01.sla.0000154118.07704.ef

[3] Higuchi, R., Ono, H., Matsuyama, R., Takemura, Y., Kobayashi, S., Otsubo, T., *et al.* (2022) Examination of the Characteristics of Long-Term Survivors among Patients with Gallbladder Cancer with Liver Metastasis Who Underwent Surgical Treatment: A Retrospective Multicenter Study (ACRoS1406). *BMC Gastroenterology*, **22**, Article No. 152. https://doi.org/10.1186/s12876-022-02234-9

[4] Ogura, Y., Mizumoto, R., Isaji, S., Kusuda, T., Matsuda, S. and Tabata, M. (1991) Radical Operations for Carcinoma of the Gallbladder: Present Status in Japan. *World Journal of Surgery*, **15**, 337-343. https://doi.org/10.1007/bf01658725

[5] Jarnagin, W.R., Ruo, L., Little, S.A., Klimstra, D., D'Angelica, M., DeMatteo, R.P., *et al.* (2003) Patterns of Initial Disease Recurrence after Resection of Gallbladder Carcinoma and Hilar Cholangiocarcinoma. *Cancer*, **98**, 1689-1700. https://doi.org/10.1002/cncr.11699

[6] Wiggers, J.K., Groot Koerkamp, B., Ovadia, Z., Busch, O.R.C., Gouma, D.J. and van Gulik, T.M. (2014) Patterns of Recurrence after Resection of Gallbladder Cancer without Routine Extrahepatic Bile Duct Resection. *HPB*, **16**, 635-640. https://doi.org/10.1111/hpb.12188

[7] Ouchi, K., Susuki, S., Saijo, K. and Matsuno, I.S. (1993) Do Recent Advances in Diagnosis and Operative Management Improve the Outcome of Gallbladder Carcinoma? *Surgery*, **113**, 324-329.

[8] Chijiiwa, K., Noshiro, H., Nakano, K., Okido, K., Sugitani, A., Yamaguchi, K. and Tanaka, M. (2000) Role of Surgery for Gallbladder Carcinoma with Special Reference to Lymph Node Metastasis and Using Western and Japanese Classification System. *World Journal of Surgery*, **24**, 1271-1276.

[9] Chijiiwa, K., Nakano, K., Ueda, J., Noshiro, H., Nagai, E., Yamaguchi, K., *et al.* (2001) Surgical Treatment of Patients with T2 Gallbladder Carcinoma Invading the Subserosal Layer. *Journal of the American College of Surgeons*, **192**, 600-607. https://doi.org/10.1016/s1072-7515(01)00814-6

[10] Tsukada, K., Hatakeyama, K., Kurosaki, I., Uchida, K., Shirai, Y., Muto, T., *et al.* (1996) Outcome of Radical Surgery for Carcinoma of the Gallbladder According to the TNM Stage. *Surgery*, **120**, 816-821. https://doi.org/10.1016/s0039-6060(96)80089-4

[11] Kondo, S., Nimura, Y., Hayakawa, N., Kamiya, J., Nagino, M. and Uesaka, K. (2000) Regional and Para-Aortic Lymphadenectomy in Radical Surgery for Advanced Gallbladder Carcinoma. *Journal of British Surgery*, **87**, 418-422. https://doi.org/10.1046/j.1365-2168.2000.01384.x

[12] Chong, J.U. and Lee, W.J. (2019) Oncologic Outcomes of Extended Lymphadenectomy without Liver Resection for T1/T2 Gallbladder Cancer. *Yonsei Medical Journal*, **60**, 1138-1145. https://doi.org/10.3349/ymj.2019.60.12.1138

[13] Xiao, Z., Shi, Z., Hu, L., Gao, Y., Zhao, J., Liu, Y., *et al.* (2019) A New Nomogram from the SEER Database for Predicting the Prognosis of Gallbladder Cancer Patients after Surgery. *Annals of Translational Medicine*, **7**, 738-738. https://doi.org/10.21037/atm.2019.11.112

[14] Lin, J., Bai, D., Zhou, B., Chen, P., Qian, J., Jin, S., *et al.* (2018) Positive Relationship between Number of Negative Lymph Nodes and Duration of Gallbladder Cancer Cause-Specific Survival after Surgery. *Cancer Management and Research*, **10**, 6961-6969. https://doi.org/10.2147/cmar.s187857

[15] Liu, F., Hu, H., Ma, W., Yang, Q., Wang, J. and Li, F. (2019) Prognostic Significance of Neutrophil–Lymphocyte Ratio and Carbohydrate Antigen 19-9 in Patients with Gallbladder Carcinoma. *Medicine*, **98**, e14550. https://doi.org/10.1097/md.0000000000014550

[16] Wang, Y. (2014) Combined Detection Tumor Markers for Diagnosis and Prognosis of Gallbladder Cancer. *World Journal of Gastroenterology*, **20**, 4085-4092. https://doi.org/10.3748/wjg.v20.i14.4085

[17] Yuan, Y., Wang, Y., Zhang, N., Mao, X., Huang, Y., Huang, J., *et al.* (2021) Influence of American Society of Anesthesiologists Score on Oncologic Outcomes in Patients with Upper Tract Urothelial Carcinoma after Radical Nephroureterectomy: A Large-Sample Study in Two Institutions. *Frontiers in Oncology*, **11**, Article 723669. https://doi.org/10.3389/fonc.2021.723669

[18] Cubillos, L., Gonzalez, S., Sepulveda, C., Rivero, S., Calvo, A., Caracci, M., *et al.* (1993) Immunological Evaluation of Patients with Invasive Carcinoma of the Gallbladder. *Journal of Cancer Research and Clinical Oncology*, **119**, 497-500. https://doi.org/10.1007/bf01215932

[19] Tharmalingam, S., Flemming, J., Richardson, H., Hurlbut, D., Cleary, S. and Nanji, S. (2022) Surgical Practice Patterns and Outcomes in T2 and T3 Gallbladder Cancer: A Population-Based Study. *Canadian Journal of Surgery*, **65**, E16-E24. https://doi.org/10.1503/cjs.019719

[20] Kim, W.S., Choi, D.W., You, D.D., Ho, C.Y., Heo, J.S. and Choi, S.H. (2010) Risk Factors Influencing Recurrence, Patterns of Recurrence, and the Efficacy of Adjuvant Therapy after Radical Resection for Gallbladder Carcinoma. *Journal of Gastrointestinal Surgery*, **14**, 679-687. https://doi.org/10.1007/s11605-009-1140-z

[21] Park, J.S., Yoon, D.S., Kim, K.S., Choi, J.S., Lee, W.J., Chi, H.S., *et al.* (2007) Actual Recurrence Patterns and Risk Factors Influencing Recurrence after Curative Resection with Stage II Gallbladder Carcinoma. *Journal of Gastrointestinal Surgery*, **11**, 631-637. https://doi.org/10.1007/s11605-007-0109-z

[22] Yamaguchi, R., Nagino, M., Oda, K., Kamiya, J., Uesaka, K. and Nimura, Y. (2002) Perineural Invasion Has a Negative Impact on Survival of Patients with Gallbladder Carcinoma. *British Journal of Surgery*, **89**, 1130-1136. https://doi.org/10.1046/j.1365-2168.2002.02184.x

[23] Ahn, Y., Park, C., Hwang, S., Jang, H., Choi, K. and Lee, S. (2016) Incidental Gallbladder Cancer after Routine Cholecystectomy: When Should We Suspect It Preoperatively and What Are Predictors of Patient Survival? *Annals of Surgical Treatment and Research*, **90**, 131-138. https://doi.org/10.4174/astr.2016.90.3.131

[24] Arakami, M., Matsumoto, T., Shibata, K., Himeno, Y., Yada, K., Hirano, S., Kawano, K. and Kitano, S. (2004) Factors Influencing Recurrence after Surgical Treatment for T2 Gallbladder Carcinoma. *Hepatogastroenterology*, **51**, 1609-1611.

[25] Mappanka, C. (2014) Gallbladder Cancer, Treatment Failure and Relapses: The Peritoneum in Gallbladder Cancer. *Journal of Gastrointestinal Cancer*, **45**, 245-255. https://doi.org/10.1007/s12029-014-9597-8