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PECULIARITIES OF CLINICAL PRESENTATION AND SURGICAL TREATMENT OF PATIENTS WITH OCCULT CARCINOMA OF GALLBLADDER

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141 patients with gallbladder cancer (GBC) were operated from 2003 to 2016. 29 (20.6 %) patients were diagnosed with occult GBC. In most (88.4–100 %) cases, GBC was accompanied by cholelithiasis; furthermore, cholelithiasis lasted much longer if patients had occult GBC ($P = 0.032$). The signs of acute or chronic calculous cholecystitis were clinically detected in patients with occult GBC. For this group of patients, tumours were more often located in the body or fundus of gallbladder ($P < 0.05$) and were less locally spread ($P < 0.04$); however, the level of differentiation ($P > 0.3$) and the presence of distant metastases ($P > 0.4$) were not statistically different from those in patients with manifest GBC. Cholecystectomy was performed in all patients with occult GBC and in 50 (44.6 %) patients with manifest GBC ($P < 0.001$). Liver resection and/or operation on the extrahepatic bile ducts was performed in 8 (27.6 %) and 50 (44.6 %) patients, respectively ($P < 0.001$). Postoperative complications were detected in 2 (6.9 %) patients with occult GBC and in 27 (24.1 %) patients with manifest GBC ($P < 0.05$). III–IV stage of tumour was identified in 5 (17.2 %) patients with occult GBC. Treatment result in this case was less satisfactory.

Key words: gallbladder cancer; surgery.

Introduction. Gallbladder cancer (GBC) is detected in 2 % of patients with malignant tumours and its frequency ranges from 1.2 per 100,000 in the U. S. to 21.5 per 100,000 in the Northern India [12]. High incidence of GBC can be found also in Pakistan, Ecuador, Korea, and Eastern European countries (Poland, Czech Republic, and Slovakia). In Ukraine, approximately 900 patients are diagnosed with GBC annually [1].

Among the risk factors of GBC are the presence of cholelithiasis (CL), polyps of gallbladder (GB), diabetes mellitus, obesity and chronic viral hepatitis B, parasites and gastrointestinal infection, chronic intoxication with alcohol, and household cancerogens [7, 15]. During the diagnostic procedure, radical operation is possible only for 10–40 % of patients [8, 10, 13]. For 5–25 % of patients, GBC is diagnosed only during the operation or after the histopathological examination of GB (the so called occult or incidental GBC) [15, 16]. In this case, treatment strategy is generally not fully determined [3, 11]; however, the development of the laparoscopic minimally invasive techniques and the usage of surgical robots are expected to provide a solution to this problem [2, 6].

The purpose of this investigation is to analyze the peculiarities of the clinical course and surgical treatment of patients with occult GBC.

Patients and methods. During 2003–2016, 141 patients with GBC were operated. Their age ranged from 43 to 84 years – (67.4 ± 6.53) years on average. The patients were divided into two groups. The first group included 29 (20.6 %) patients with occult GBC. The second group consisted of 112 (79.4 %) patients with GBC that was diagnosed before an open surgery or minimally invasive procedure.

Besides the general clinical examination of patients, biochemical tests of blood serum were made and tumour markers were determined. Furthermore, transabdominal ultrasonography (US), X-ray examination of thorax and gastrointestinal tract with barium, and computed tomography were carried out. In the presence of indications, endosonography of GB, bile ducts, and hepatoduodenal ligament, magnetic resonance cholangiopancreatography and/or diagnostic or therapeutic endoscopic retrograde cholangiography were performed. Histopathological examination of the obtained specimens was performed after the surgical removal of the tumour or its biopsy.

Data analysis and statistical tests (Student's t-test, Mann – Whitney U-test, χ^2 -test) were performed in SPSS 11.5 for Windows. The significance level is set to 0.05.

Result and discussion. The average age of patients with occult GBC was (67.1 ± 10.8) years and of patients with manifest GBC – (67.5 ± 8.2) years old. Females constituted the majority in both groups ($\chi^2 = 93.064$; $P < 0.001$): 24 (82.8 %) and 87 (77.7 %) persons, respectively ($\chi^2 = 0.355$; $P > 0.25$). Cholelithiasis was detected in all patients in the first group (it was the primary reason for operative treatment) and in 99 (88.4 %) patients in the second group ($\chi^2 = 3.708$; $P > 0.05$). This confirms the connection between CL and GBC [7, 15].

19 (65.5 %) patients in the first group and 79 (70.5 %) patients in the second group ($\chi^2 = 0.274$; $P > 0.25$) were admitted to the hospital with acute cholecystitis or biliary colic, obstructive jaundice and/or cholangitis. In particular, the majority of the patients in the first group had acute cholecystitis (58.6 %) and in the second group – obstructive jaundice (61.6 %) ($\chi^2 = 36.74$; $P < 0.001$). The process of transfer to the hospital of the patients in the first group lasted from 3 days to one month (Me = 14 days) and in the second group – from 5 days to 1.5 months (Me = 12 days) from the last exacerbation of the disease or the appearance of life-threatening symptoms ($P = 0.828$). Among 10,878 patients with calculous cholecystitis that underwent treatment in the hospital during the aforementioned period, occult GBC was ascertained in 0.27 % patients and manifested – in 1.03 %. The period starting from the detection of cholelithiasis to the hospitalization lasted from 0.5 to 480 months (Me = 36) for the first groups of patients and from 1 to 288 months (Me = 6; $P = 0.032$) for the second group.

Table presents the comparison of tumour characteristics based on the TNM staging system (2016).

Table. Comparison of tumour characteristics of patients with GBC who underwent surgery

Characteristics	Group I ($n = 29$)	Group II ($n = 112$)	χ^2	P-value
Size of tumour T1a	5 (17.2 %)	–	20.02	< 0.001
Size of tumour T1b-T2	16 (55.2 %)	9 (9 %)	35.088	< 0.001
Size of tumour T3	5 (17.2 %)	46 (41.1 %)	5.666	< 0.02
Size of tumour T4	3 (10.3 %)	57 (50.9 %)	15.493	< 0.001
Lymph node metastasis N1	5 (17.2 %)	43 (38.4 %)	4.59	< 0.04
Distant metastasis M1	3 (10.3 %)	15 (13.4 %)	0.192	> 0.4
III–IV stage	5 (17.2 %)	52 (46.4 %)	8.148	< 0.005

The tumour was located in the neck of GB in 7 (24.1 %) patients with occult GBC and in 52 (46.4 %) patients with manifest GBC ($\chi^2 = 4.703$; $P < 0.05$) and near the body or the fundus of gallbladder in 20 (69 %) and 33 (29.5 %) patients, respectively ($\chi^2 = 15.321$; $P < 0.001$). Total GB damage with invasion in other organs was diagnosed in 2 (6.9 %) and 27 (24.1 %) patients, respectively ($\chi^2 = 4.176$; $P < 0.04$).

In the first group, the clinical signs of acute cholecystitis were detected in 18 (62 %) patients and of chronic – in 11 (37.9 %) patients. According to US data, 3 (10.3 %) patients had, in addition, GB polyps. During the operation, the macroscopic inspection of the gallbladder led to the GBC suspicion in 10 (34.5 %) patients, whereas histopathological examination of the obtained specimens led to the GBC suspicion in 17 (58.6 %) more cases. In 2 (6.9 %) patients, GBC was diagnosed only after the appearance of port site direct implantation metastases of poorly differentiated adenocarcinoma in the middle epygastrium (place of extraction of GB out of the abdominal cavity without a protective bag) and of local recurrence with metastases after 3 and 5 months after laparoscopic cholecystectomy because of the acute calculous cholecystitis.

Choledocholithiasis was found in 3 (10.3 %) patients in the first group and in 5 (4.5 %) patients in the second group ($\chi^2 = 1.488$; $P > 0.25$). Obstructive jaundice was diagnosed in 2 (6.9 %) and 63 (56.3 %) patients, respectively ($\chi^2 = 22.581$; $P < 0.001$).

Obstructive jaundice in all patients in the first group was caused by choledocholithiasis. In the second group, 60 (95.24 %) patients had jaundice caused by the obstruction of extra- and intrahepatic bile ducts with advanced tumour, and 3 (4.8 %) patients had jaundice caused by the metastatic liver damage. The total level of bilirubin in blood serum in 2 patients with jaundice in the first group was 48.7 and 72.6 mcM/l, whereas in the second group – (103.60 ± 23.14) mcM/l respectively.

Concomitant somatic diseases (cardiac ischemia, arterial hypertension, obesity, diabetes mellitus, varicose veins etc) were detected during examination of 14 (48.3 %) and in 59 (52.7 %) patients in the first and the second group, respectively ($\chi^2 = 0.179$; $P = 0.2$).

All patients in the first group were operated and initially underwent cholecystectomy, which was laparoscopic in 27 (93.1 %) cases. 5 (17.2 %) patients, whose GBC diagnosis was evident from the inspection of the obtained specimens and/or its intra-operative frozen section, promptly underwent IVb + V wedge liver resection and pericholedochic hepatoduodenal lymphadenectomy, according to the existing recommendations [3, 5]; 4 out of 5 operations were laparoscopic. In the beginning of the post-operative period, 3 patients in the first group – in total 8 (27.6 %) underwent an open surgery without resection of bile duct [4]. In one case, the borders of the port of abdomen wall, through which the uncovered GB was removed, were cut off in order to prevent implantation metastasis [3]. Patients with T1a underwent only cholecystectomy with deep intensive cauterization of GB bed.

In the second group, 50 (44.6 %) patients ($\chi^2 = 28.653$; $P < 0.001$) were operated predominantly (96 %) with an open approach. Cholecystectomy or extended excision of GB in the combination with wedge liver resection and operations on the extrahepatic bile ducts (resection of the common bile duct, biliodigestive anastomoses, internal and external bile duct drainage) was performed in 46 (41.1 %) patients. Explorative laparotomy/laparoscopy with a biopsy was performed in 4 (3.6 %) patients. Therapeutic ERCP (biliary stenting) was performed in 58 (51.8 %) patients, whereas percutaneous transhepatic procedures – in 4 (3.6 %) patients.

Histopathological examination allowed to detect well-differentiated adenocarcinoma (G1) in 5 (17.2 %) patients in the first group and in 14 (12.5 %) patients in the second group, moderately differentiated adenocarcinoma (G2) – in 14 (48.3 %) and in 48 (42.9 %) patients, poorly differentiated adenocarcinoma (G3) – in 10 (34.5 %) and in 50 (44.6 %) patients, respectively ($\chi^2 = 0.275$ – 0.973 ; $P > 0.3$).

2 (6.9 %) patients in the first group and 27 (24.1 %) patients with manifest cancer developed complications in the post-operative period (less than 30 days) or after the minimally invasive procedures ($\chi^2 = 4.176$; $P < 0.05$). 2 (4 %) patients in the second group needed relaparotomy.

14 (10.7 %) patients in the second group died after operations or/and minimally invasive procedures ($\chi^2 = 4.025$; $P < 0.05$).

In the remote post-operative period, 1-year survival rate in the patients with occult GBC, irrespective of the placement on chemotherapy, was 96.6 %, 3-year rate – 51.7 %, and 5-year rate – only 13.8 %. These rates are significantly higher than the corresponding rates for manifest GBC ($P = 0.012$ – 0.001). In addition to US, the results of the computed tomography, magnetic resonance imaging, and endosonography were used for early detection of the relapse of the disease. The measurement of such recommended oncomarkers as AFP, CEA, CA 19-9, CA 72, CA-125, and CA-242 [9, 14] demonstrated high sensitivity.

In summary, occult carcinoma of the GB was confirmed in 29 (0.27 %) patients that were operated because of CL. GB tumours were coupled with CL in the majority of cases (in 100 % of patients with occult GBC and in 88.4 % of patients with manifest GBC). The period from the detection of cholelithiasis to the admittance to the hospital was significantly longer in the first group than in the second ($P = 0.032$).

Tumors were located in the body or in the fundus of GB in patients with occult GBC much more frequently ($P < 0.05$) and were characterized by less local spreading and less metastases. In particular, stages III, IVa, and IVb were diagnosed only in 5 (17.2 %) patients with GBC ($\chi^2 = 8.148$; $P < 0.005$). However, the difference in the stage of differentiation between two groups was not statistically significant ($P = 0.324-0.971$).

Patients with occult GBC had the signs of acute or chronic calculous cholecystitis which were identified clinically. In two thirds of all patients, a correct diagnosis was made only after the operation and histomorphological examination of GB or after the recurrence of tumour. Hence, it is recommended to perform the intraoperative frozen section for patients who are in the high-risk group (of age more than 70, long anamnesis of CL, or the thickening of the GB wall of more than 3 mm caused by chronic cholecystitis) in order to improve the diagnostics of GBC and to avoid additional operations [16].

Peculiarities of the clinical course of GBC had direct influence on the volume of an operation and the results of surgical treatment. Consequently, cholecystectomy could be performed in all patients with occult GBC and only in 41.1 % of patients in the second group ($\chi^2 = 8.165$; $P < 0.005$). Operations aimed at the reduction of the jaundice were initially performed only in patients with manifest GBC (40 %) ($\chi^2 = 17.678$; $P < 0.001$). Larger volume of an operation and more severe condition of patients with manifest GBC led to the higher frequency of postoperative complications and higher mortality.

In conclusion, the course of occult GBC resembles the course of acute or chronic calculous cholecystitis and, at the time when diagnosis is made, stage III–IV of malignance is detected in 17.2 % of patients. This significantly worsens the results of the treatment of patients with this pathology. Accurate examination (i.e., US, computed tomography, magnetic resonance imaging, endosonography) of patients with cholelithiasis enables early diagnostics of GBC, whereas early cholecystectomy can be used to prevent the development of this life-threatening disease.

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ОСОБЛИВОСТІ КЛІНІЧНОГО ПЕРЕБІГУ І ХІРУРГІЧНОГО ЛІКУВАННЯ ХВОРИХ НА ОКУЛЬТНИЙ РАК ЖОВЧНОГО МІХУРА

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Впродовж 2003–2016 рр. у клініці прооперовано 141 хворого на рак жовчного міхура (РЖМ). Окулярний РЖМ діагностовано у 29 (20,6 %) осіб. У більшості хворих (88,4–100 %) РЖМ поєднувався з холелітіазом, при цьому у хворих окулярним РЖМ жовчнокам’яна хвороба була тривалішою ($P = 0,032$). Клінічно в осіб з окулярним РЖМ визначали симптоми гострого або хронічного калькульозного холециститу. При окулярному РЖМ пухлина частіше локалізувалася в області дна і тіла жовчного міхура ($P < 0,05$), мала менш виражене локальне поширення ($P < 0,04$), але ступінь диференціації ($P > 0,3$) і віддалені метастази ($P > 0,4$) статистично достовірно не відрізнялися у хворих окулярним і маніфестним РЖМ. Холецистектомія виконана у всіх хворих окулярним РЖМ і тільки у 50 (44,6 %) хворих маніфестним РЖМ ($P < 0,001$), а резекцію печінки і/або операції на позапечінкових протоках – відповідно у 8 (27,6 %) і 50 (44,6 %) хворих ($P < 0,001$). Післяопераційні ускладнення виникли у 2 (6,9 %) хворих на окулярний РЖМ і у 27 (24,1 %) – на маніфестний РЖМ ($P < 0,05$). При встановленні діагнозу у 5 (17,2 %) пацієнтів з окулярним РЖМ констатовано III–IV стадію захворювання, що значно погіршувало результати лікування цих хворих.

Ключові слова: рак жовчного міхура; хірургічне лікування.

ОСОБЕННОСТИ КЛИНИЧЕСКОГО ТЕЧЕНИЯ И ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ БОЛЬНЫХ ОККУЛЬТНЫМ РАКОМ ЖЁЛЧНОГО ПУЗЫРЯ

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В течение 2003–2016 гг. в клинике прооперирован 141 больной раком жёлчного пузыря (РЖП). Окулярный РЖП диагностирован у 29 (20,6 %) лиц. У большинства больных (88,4–100 %) РЖП сочетался с холелитиазом, при этом у больных окулярным РЖП жёлчнокаменная болезнь была более длительной ($P = 0,032$). Клинически у лиц с окулярным РЖП определяли симптомы острого или хронического калькулёзного холецистита. У больных окулярным РЖП опухоль чаще локализовалась в области дна и тела жёлчного пузыря ($P < 0,05$), имела менее выраженное локальное распространение ($P < 0,04$), но степень дифференциации ($P > 0,3$) и отдалённые метастазы ($P > 0,4$) статистически достоверно не различались у больных окулярным и маніфестным РЖП. Холецистэктомия выполнена у всех больных окулярным РЖП и только у 50 (44,6 %) больных маніфестным РЖП ($P < 0,001$), а резекцию печени и/или операции на внепечёночных протоках – соответственно у 8 (27,6 %) и 50 (44,6 %) больных ($P < 0,001$). Послеоперационные осложнения возникли у 2 (6,9 %) больных с окулярным РЖП и у 27 (24,1 %) больных маніфестным РЖП ($P < 0,05$). Таким образом, при постановке диагноза у 5 (17,2 %) больных окулярным РЖП констатирована III–IV стадия заболевания, что значительно ухудшает результаты лечения этих больных.

Ключевые слова: рак жёлчного пузыря; хирургическое лечение.