

Gallbladder Cancer (GBC)-Contemporary Aspects of Diagnosis and Treatment

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1. Abstract

1.1. Background: Gallbladder cancer is an uncommon malignant disease leading to the fact that even big centers only analyze small series of patients over a long time. GBC is the most common biliary tumor and the fifth most common gastrointestinal cancer.

1.2. Material and Methods: For the period of 7 years - from 01.2010 to 01.09.2017 we have radically operated 32 patients in different GBC stages. Women are more frequently affected - 20(62%) vs. 12(38%) men. 30 of the patients had long-term cholelithiasis (symptomatic in 22 and non-symptomatic in 8 patients). 2 of the patients developed GBC from polyps. Ultrasonography is a base study conducted in all patients; CT with contrast applied by injection with liver enhancement protocol was conducted in 28(87%) patients as a main diagnostic and staging method.

1.3. Results: We have 9 patients (28%) with complications. Perioperative mortality in our population was 3.1%. 75% of the patients survived for 3 years with a 100% survival rate of I-IIA patients.

1.4. Conclusion: GBC remains a challenge in contemporary surgical and oncological practice for its variable course, late diagnosis, clinical manifestation with complications, different surgical approaches depending on the specific case, lack of randomized studies and rarity of the disease.

2. Introduction

The aim of this material is to analyze our experience in the diagnosis and treatment of Gallbladder Cancer in the context of contemporary medicine. Gallbladder cancer is an uncommon malignant disease leading to the fact that even big centers only analyze small series of patients over a long time. This makes carrying out a randomized trial with a high degree of evidence very difficult and also makes difficult answering some clinical questions about the disease.

3. Material and Method

For the period of 7 years - from 01.2010 to 01.09.2017

we have radically operated 32 patients in different GBC stages. Women are more frequently affected - 20(62%) women and 12(38%) men. 30 of the patients had long-term cholelithiasis (symptomatic in 22 and non-symptomatic in 8 patients). 2 of the patients developed GBC from polyps. Almost all patients report of epigastric or right upper quadrant pain at different times before the diagnosis was made. Ultrasonography is a base study conducted in all patients; CT with contrast applied by injection with liver enhancement protocol was conducted in 28(87%) patients as a main diagnostic and staging method. In 26(93%) patients GBC diagnosis was made based on the CT imaging. MRI

cholangiography facilitated the diagnosis in 7 patients (in 1 case the disease was falsely diagnosed as Klatskin tumor). Mechanical icterus was the main syndrome in 9(28%) patients. Therapeutic ERCP was carried out in 5 of these patients with high grade hyper bilirubinemia (serum bilirubin > 250MMOL/L) – an endoprosthesis was applied. Within 40 days of endoprosthesis placement all of these patients were radically operated. 2 of them were diagnosed with cholangitis due to prosthesis obstruction and other 3 who had no clinical or paraclinical data supporting cholangitis a pathogen was isolated from microbiological study of the endoprosthesis (**Table 1**). PTC was carried out in 2 patients with hyper bilirubinemia and distinct intra hepatic cholestasis, both patients had radical operations within the following month. Two of the patients with mechanical icterus and bilirubin values bellow 200mmol/l and no cholangitis were radically operated on after CT and MRI diagnosis of GBC. In 6(18%) patients the diagnosis was made during laparoscopic cholecystectomy (2 of the patients had US and CT findings preoperatively consistent with polyps). Two of the patients were staged as T1A, 3 as 51B and 1 WAS staged T2.

4. Staging

The most common histological type was adenocarcinoma in 28 (87.5%) of our patients - 12(37%) had papillary, 10(31%) tubular and 6(18, 7%) nodular subtype. Adenosquamous type of GBC was established in 4(12.5%) patients. Grade 2 differentiation was the most common G stage - in 14(40%) of the patients. Ten of the patients had highly differentiated GBC (G1 - 31%) and G3 (28%) was observed in 9 patients. Poorly differentiated forms of GBC are observed more frequently in advanced stages according to our materials. Operative interventions in different stages, perioperative complications and mortality (**Table 2**).

Table 1: Two of the patients were staged as T1A, 3 as 51B and 1 WAS staged T2.

Stage	o	Tis	No	Mo	G
Stage	1A-5 PAT.(15,6%)	T1	No	Mo	G1-2, G2-3
Stage	1B- 1 PAT.(3,1%)	T2	No	Mo	G1-1
Stage	IIA- 8 PAT.(25%)	T3	No	Mo	G1-3,G2-3, G3-2
Stage	IIB- 14 pat. (43,7%)	T1 T2 T3	N1 N1 N1	Mo-1P Mo-4p Mo-9p.	G1-1 G1-1, G2-2,G3-1 G1-2, G2-4,G3-3
Stage	III- 2 PAT.(6,2%)	T4	anyN	Mo	G2-1,G3-1
Stage	IV- 2 PAT.(6,2%)	anyT	anyN	M1	G3-2

Table 2: Operative interventions in different stages, perioperative complications and mortality.

Operation	Stage	Complications	Mortality/Survival
5p.-Laparoscopic cholecystectomy (LC)	IA		
1p.-LC with gallbladder bed excision	IB		
1p.- Laparoscopic central hepatectomy(IVBs, Vs)	IIA		
1p.-CONVENTIONAL cholecystectomy with gallbladder bed excision, regional lymph node dissection (RLND) 4p.-Central hepatectomy with RLND. 4p.- Central hepatectomy with choledochus resection, RLND, peritonectomy, hepaticojunostomy	IIB IIB	2p.- hepaticojunostomy leak – Clavien-II	Sudden cardiac arrest (fibrinopurulent cholangitis, long-term mechanical icterus, moderately high cardiovascular risk, EOSG -3
3p. – Central hepatectomy with hepaticocholedochal resection, peritonectomy, RLND, bihepaticojunostomy	IIB	1p.- Biliary anastomosis leak - Clavien-III 11.-SUPPURATION, Clavien-III(Endoprosthesiswith cholangitis)	.
2-P.- Central hepatectomy with Whipple procedure, peritonectomy, RLND	IIB	1p.-LOW grade pancreatic fistula.- Clavien-II	5-year survival
1p.- Central hepatectomy with Whipple procedure, right hemicolectomy, peritonectomy, RLND 1p.-RIGHT hepatic bisectionectomy +IVBs resection, Whipple procedure, RLND, segmental portal vein resection	III	1p.-OPERATIVE wound dehiscence- Clavien-III	3-year survival 2-YEAR survival. Death due to disease progression
1p.- Right hepatic bisectionectomy with IVBs, choledochus resection, peritonectomy, RLND. 1p.- Right hepatic bisectionectomy with IVBs and Whipple procedure, RLND, tangential resection of portal vein		1p.-SUPPURATION, Clavien-II(choledochusendoprosthesis with cholangitis). 1p.-TRANSITIONAL liver failure- Clavien-I. 1p.-BILOMACLAVIEN-II	6 months. 6 months. Death due to disease progression

5. Perioperative Mortality and Complication

We have 9 patients (28%) with complications. Two of the patients had to be re operated due to hepaticojejunostomotic leak with biliary peritonitis and wound dehiscence. One patient was diagnosed with severe wound suppuration and necrotizing fasciitis, which necessitated surgical debridement and VAC therapy (Clavien-Dindo-III). Two of the patients had partial hepaticojejunostomy insufficiency with bile leak detected in the drainage which formed a biliary fistula that was managed conservatively with gradual withdrawal of the drain. One wound infection managed by draining the operative wound, one patient with infected biloma that was managed by percutaneous drain placement. One patient had low grade pancreatic fistula after a Whipple procedure (a duct-to-mucosa modified Blumgart technique pancreaticojejunostomy with soft pancreas and a narrow pancreatic duct). Fistula was healed with drain management (Clavien-Dindo-II). Transitory liver failure was detected in one patient after right hepatic bisectionectomy with IV B. segmentectomy and choledochus endoprosthesis placement. The patient was successfully managed conservatively (Clavien-Dindo-I). Perioperative mortality in our population was 3.1%. One patient with PT3N1M0G2 IIBstage accompanied by purulent cholangitis and mechanical icterus and moderately increased cardiovascular risk, EOSG -3 performance status and ASA-III died. The immediate reason for the 3rd postoperative day lethality was ventricular tachycardia with a systole. 75% of the patients survived for 3 years with a 100% survival rate of I-IIA patients.

6. Discussion

6.1. Risk Factors

Undisputed risk factors related to GBC are gallstone disease, gallbladder polyposis, obesity anomalies of the pancreas to biliary junction, selective mucosal calcifications [2-5]. GBC risk in gallstones population is 1.5 to 6 times higher. (Strength of recommendation IIb, level of evidence B).

6.2. Clinics

Patients with GBC can present with three clinical models.
 1 Advanced unresectable GBC.
 2 Preoperative diagnosis of a resectable lesion to be operated after staging.
 3 Incidental finding of GBC during or after cholecystectomy

for a benign disease. Symptoms associated with GBC are not specific. The disease most frequently presents in an advanced stage when it is unresectable or borderline resectable. The most common symptoms are pain and obstructive jaundice.

6.3. Diagnostic Algorithm and Screening

Ultrasonography has 85% sensitivity and 80% specificity in advanced GBC. Doppler ultrasonography is useful not only in verification of arterial and portal flow. It also leads to better specificity in differentiating malign from benign lesions through inspecting blood flow in the areas in question [6-9]. Endoscopic retrograde cholangio pancreatography (ERCP) and percutaneous trans hepatic cholangiography (PTC) are diagnostic and potentially curative procedures that help in verifying GBC spread in the biliary tree and can also provide definitive biliary drainage. For icteric patients cholangiography is useful for localization of the obstruction, stent placement and diagnosis through brush biopsy [10]. When GBC is suspected computer axial tomography or magnetic resonance imaging (MRI) is necessary for the exact localization of the tumor, the presence of local lymphadenopathy and distant metastases. Lymph node metastases of GBC are usually bigger than 1cm, round and with heterogeneous structure. Ohtani et al. report positive predictive value of CT in defining the lymph node status (75%-100%) and despite low sensitivity of the method (17%-78%). Same authors report sensitivity of CT (50-65%) in defining involvement of the liver, common hepatic duct and adjacent organs like the pancreas, transverse colon, and a positive predictive value of 77%-100%. MRI cholangiography and MRI angiography are more informative than US and CT. Schwartz et al. demonstrate in a retrospective study in patients with GBC that a combination of conventional MRI and MRI cholangiography reaches 100% sensitivity for liver infiltration and 92% sensitivity for lymph node involvement [11-13]. Early GBC extends to the muscle layer of the gallbladder. Preoperative assessment of the depth of wall invasion is difficult even with the use of US, CT and endoscopic US. The sensitivity of US for defining GBC is about 40%. If the tumor involves the liver or distant metastases are present the diagnostic value of US increases. (Strength of recommendation IIIb, level of evidence B). Endoscopic US are very useful for

preoperative staging. This method enhances sensitivity in diagnosing GBC from 74% up to 90% compared to conventional US. This method can be useful for obtaining samples for cytologic and histological study. Multi detector CT insures 84% accuracy in defining the local status of GBC which translates to acceptable sensitivity and specificity. Trans 2

The accuracy of CT in the diagnosis of HBC can vary depending on the morphology of the neoplasm. T1 tumors only spreading in the gallbladder wall can be omitted (54% sensitivity). If the tumor spreads deep inside the wall the sensitivity of this method can raise to 89%. GBC Methastatic lymph node establishment with MRI remains low (57%). When standard MRI is combined with MRI cholangiography and 3D MRI angiography the sensitivity and specificity of the method can reach 100% and 87% respectively. MRI has lower sensitivity and specificity in detecting GBC compared to multi detector CT (Strength of recommendation IV, level of evidence C). Sensitivity of Positron Emission Tomography (PET) for identifying GBC is 86%. Some benign lesions like adenomyomatosis can show increased metabolic activity that leads to a high number of false-positive results. When conventional imaging methods established potentially resectable GBC PET scan can show the presence of distant metastases thus changing the therapeutic strategy for 20%-25% of the patients. PET scan is also useful in diagnosing relapsing tumors after primary operation [14].

6.4. Surgical Approach

GBC treatment must be defined by a multidisciplinary team. If imaging studies show data consistent with GBC open cholecystectomy is advised. It should be performed by a surgeon with experience in oncology and hepato biliary surgery. Laparoscopy is useful for ruling out peritoneal and liver dissemination in potentially resectable tumors [15].

The definitive role of laparoscopy in the treatment of GBC is still not fully defined. There is evidence of worse prognosis in patients who had laparoscopic rather than open cholecystectomy in whom there was no preoperative data of cancer. In these patients gallbladder rupture during operation and not using endoscopic bag extractor lead to higher frequency of local relapses [16]. Extensive surgery is recommended in patients with primary operation for GBC or definitive treatment for patients

who have had cholecystectomy. In these cases the surgical interventions begins with the dissection of retro duodenal lymph nodes between the aorta and inferior cava vein. If these lymph nodes are metastatic the prognosis is poor and survivability is a matter of months which makes surgery futile. If retro duodenal lymph nodes are negative the procedure is carried out hepato duodenal ligament dissection and dissection along the common hepatic artery. Radical surgery requires the removal of 4B + 5 liver segments, as well as pre renal peritonectomy. In patients who have had laparoscopic cholecystectomy excision of the trocar sites is recommended which lowers local relapse frequency [17]. Currently there is controversy about common bile duct excision. If gallbladder infundibulum or/and cystic duct are infiltrated by the neoplasm removal of ductuscholedochus is recommended. Despite this routine excision of the bile duct is under debate and is not currently recommended [18]. Extensive surgery is recommended for neoplasm of the cystic duct, N1 stage, and mechanical icterus and in big-sized tumors. Morbidity and complications after surgery are more common in these conditions. Therefore surgery under these circumstances should be evaluated and recommended by future studies [19].

6.5. Therapeutic Strategy Based on Tumor Stage

The intensity of the treatment and volume of surgery in GBC depend on TNM staging.

6.6. In-Situ Tumors or Tumors Infiltrating the Mucosa (T is T1a)

In these patients the disease is limited to gallbladder mucosa and dissemination is unlikely. This suggests that cholecystectomy alone is enough. A great percentage of these patients are diagnosed after open or laparoscopic cholecystectomy and pathological examination of the specimen. The perfect surgical specimen has to include lymph nodes surrounding the gallbladder. These patients have 5-year survival rate above 90%. There are more unusual situations with Rokitansky Aschoff sinuses invasion. In these patients tumor cells are situated deep in the gallbladder wall which requires extensive surgery [20].

6.7. Tumors Infiltrating Muscularispropria (T1b)

These patients have very good prognosis with 5-year survival rate of more than 80%, independent of the chosen

treatment. There is no consensus whether laparoscopic cholecystectomy or extensive surgery lead to better results. Diagnosis is frequently made postoperatively during the pathological exam of the specimen. Factors that can indicate reoperation and greater volume surgery are: young age, cystic duct invasion, micro invasion in perivesical lymph nodes, non-differentiated or flat tumor, lymph vessel invasion [21].

6.8. Tumors Extending Through the Submucosa (T2)

These patients have unquestionable benefit from extensive surgery. 5-year survival of patients treated with cholecystectomy alone is 25%. Extensive surgery in T2NoMo patients raises 5-year survival rates to 50%-65%. Lymph node involvement is more frequent in these patients (up to 50%) [22]. The presence of lymph node metastases or infiltration of liver segments 4B+5 after large volume surgery is associated with significantly poorer prognosis thus requiring adjuvant treatment [23].

6.9. Tumors Invading Serosis, Liver Infiltration or Adjacent Organ Infiltration (T3 And T4)

Only single cases of T3 or T4 tumors with long term survival after extensive resection are reported. Infiltration of the common bile duct, vena cava inferior and hepatic artery is common. There are no exact criteria for resectability in vessel involvement. For most authors this is an indication of non-resectable tumor and they recommend biopsy followed by chemoradiotherapy. Exploration is justified for the assessment of "down staging" after neo adjuvant therapy and supposed RO resection during the surgical intervention [24].

6.10. Therapeutic Algorithm Based on the Clinical Presentation

Patients who had GBC diagnosed accidentally after cholecystectomy should have their liver function assessed with serum biochemistry, CT scan or MRI should be performed in search of synchronous dissemination. Inflammation changes after recent cholecystectomy lead to difficulties in the interpretation of image studies. If the gallbladder is removed intact with negative resection margins and patients are staged as T1 and T1A there are no indications for another surgery or adjuvant therapy. T1 patients with risk factors (young age, micro invasion in perivesical lymph nodes, non-differentiated or flat

tumor, and lymph vessel invasion) could benefit from an extensive reoperation. Patients with T2 tumors diagnosed after cholecystectomy are recommended for reoperation with larger volume surgery. Prognosis is poor in these patients if pathology report shows metastatic lymph nodes or infiltration of the removed liver segments 4B+5.

Patients with T3 and T4 tumors diagnosed during cholecystectomy usually have no benefit from another operation. Despite all T3 a second more extensive surgery is recommended for T3 patients with microscopic gallbladder fossa invasion. Unfortunately during reoperation even a week later, these patients often have different type of progression (peritoneal carcinosis, paraaortic lymph node involvement).

6.11. Accidental Finding Of GBC During Cholecystectomy

If GBC is diagnosed during laparoscopic cholecystectomy conversion to open surgery should be made which enables the evaluation of local tumor status, peritoneal involvement, involvement of near vessels and organs. During cholecystectomy the harsh manipulation and rupture of the tumor which can lead to peritoneal dissemination should be avoided. Timely pathology examination of the specimen including the gallbladder and perivesical lymph nodes is mandatory. The Kocher maneuver is performed so that lymph nodes around the inferior vena cava and aorta can be evaluated and dissected. The surgeon should not perform extensive surgery, if peritoneal spread, common bile duct, portal vein, hepatic artery infiltration, or paraaortic or caval lymph node involvement is present and adequate conditions for large volume surgery are not present (surgical team with less experience, the center is not specialized, inadequate operating theatre equipment, high risk patients, infections, lack of informed consent).

6.12. Suspicion of GBC in Icteric Patients

Patients with mechanical icterus require additional diagnostic tests like MRI cholangiography and/or ERCP with bile duct stenting in high grade hyper bilirubinemia patients. Retrograde stenosis cannulation and stenting is often impossible. PTC with cholangiography and external biliary drainage is performed in these patients. Only a small number of these patients are candidates for surgical exploration according to the before mentioned T3-T4 treatment criteria.

6.13. Metastatic Disease

In metastatic disease biliary decompression and pain management are required. Systemic chemotherapy with Gemcitabine or according to clinical studies is applied.

6.14. Role of Minimally Invasive Surgery in the Treatment of Gallbladder Cancer

Extensive use of laparoscopy in current surgical practice accumulation of experience have overcome the initial fears of using minimally invasive approach in the treatment of GBC. Retrospective analysis by Ouchi et al from the Japanese cancer registry including 498 patients shows that patients with higher than T2 stage are operated classically and those with T2 and lower are treated with laparoscopic surgery. The results for laparoscopy show 5-year survivability of 99% for T1A, 95% for T1B, 70% for T2, 20% for T3 and 0% for T4. Open surgery results demonstrate 100% survivability for T1 tumors, 75% for T1B, 87% for T2, 17% for T3 and 0% for T4. These findings demonstrate that laparoscopic cholecystectomy for T1 and T2 tumors don't show worse results while T1 survivability is significantly longer. These findings correlate to other studies according to which laparoscopic approach does not decrease survivability in T1 and T2 stages of GBC.

7. Conclusion

GBC remains a challenge in contemporary surgical and oncological practice for its variable course, late diagnosis, clinical manifestation with complications, different surgical approaches depending on the specific case, lack of randomized studies and rarity of the disease. Laparoscopy has advantages in short-term results with better long-term results in T1A-T1B tumors. Contemporary laparoscopic techniques allow for a radical surgical treatment of T1-T2 tumors with T1B tumors requiring lymph node dissection. An excessive use of the method leads to delayed surgery and an increased percentage of early biliary complications. When a T2N0M0 and higher grade tumors are discovered in laparoscopy or laparotomy in a non-specialized center the patients should be referred to a specialized center in the next 2 WEEKS. Mechanical icterus in GBC is a sign of ductus choledochus infiltration and/or metastatic lymph node compression. In resectable patients primary surgery without endoprosthesis is recommended in patients with bilirubin values up to 250MMOL/L except

in cases where image studies show right hepatic artery infiltration necessitating right hepatic bisectionectomy + IVB segmentectomy because of the risk for postoperative liver failure. Extensive surgical interventions in advanced GBC can lead to better long-term results in carefully selected patients with good performance status (EOSG -3, ASA – II).

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