Cancer of the gallbladder – own experience

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ABSTRACT

Gallbladder cancer is a relatively rare cancer of the gastrointestinal tract, most commonly detected (approximately 95% of cases) in the most advanced clinical stage IV and burdened with high mortality rate. This is mainly due to the nonspecific symptoms in the early stages of the disease. The remaining cases of gallbladder cancer are usually detected after surgery due to gallstone disease. Gallstones, their size and pancreatic juice reflux into the gallbladder are risk factors in the development of gallbladder cancer. In this paper the authors carried out a retrospective research based on an evaluation of a group of 38 patients treated surgically due to the gallbladder cancer in the years 2005-2012 in the Second Department of General and Gastroenterological Surgery in Białystok Medical University Hospital. In this group there were 29 women and 9 men, in age between 48-86 years. Although women suffered from gallbladder cancer more often than men, their survival rate was significantly better after the surgery. The research showed some benefits of extended surgical procedures even in patients with advanced stages of the disease, while the effectiveness of surgical treatment depends mainly on the possibility of radical resection of the primary lesion and, eventually, the resection of lymph nodes and other infiltrated tissues.

Key words*:* Gallbladder cancer, survival, surgery, gallstones, cholecystectomy

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INTRODUCTION

Cancer of the gallbladder is a relatively uncommon cancer of the gastrointestinal tract and was first described by Maximillian de Stroll in 1777 [1]. Five-year survival rates in this type of cancer are in the range between 5 - 10% [2,3]. The average life expectancy of patients with cancer of the gallbladder does not exceed six months [2-4]. Adverse prognosis, mainly due to the recognition in the advanced stage of the gallbladder cancer, is caused by non-specific symptoms of the disease [5].

The etiology and pathogenesis of gallbladder cancer is still not fully recognized [6], and its incidence in the world is correlated with many unspecific factors. The incidence in Poland is approximately 6 per 100 000 persons per year, with women suffering almost 6 times more often than men. Also, this tumor occurs mostly in people over 70 years of age [7-9].

There is a direct relationship between the presence and size of gallstones in the gallbladder and the incidence of gallbladder cancer [1-6]. Gallstones are observed in 65% - 90% of patients with gallbladder cancer [10-12]. Gall stone diameter greater than 3 cm and a tendency to their familial occurrence is also a potential factor in the development of gallbladder cancer [13,14].

Other factors include: lifestyle (dietary factors, obesity, smoking), chronic biliary tract infections (*E. coli, Streptococcus sp., Klebsiella, Enterobacter, Salmonella sp., Opistohorchis viverrini, Helicobacter sp., HCV*), calcified wall of the gallbladder or a so-called porcelain gallbladder, biliary cysts, primary sclerosing cholangitis, ulcerative colitis, isolated polyps, and gallbladder Mirizzi syndrome [12-15]. Effect on the development of cancer of the gallbladder is also combined with the environment and some substances occurring in it, such as pesticides, heavy metals, radiation, vinyl chloride, oil, and the compounds used for the production of textiles and rubber [12,14,15].

In some patients, there is a tendency to reflux pancreatic juice into the interior of the gall bladder, which probably starts the cycle metaplasia - dysplasia - carcinoma [16]. The transition from dysplasia through carcinoma in situ to invasive cancer takes approximately 15 years [17-20]. Gallbladder metastases are rare in clinical practice and are found in correlation with malignant melanoma and neural cell carcinoma [21-24].

Despite the availability of a number of diagnostic tests, gallbladder cancer is diagnosed in 1-2% of patients undergoing laparotomy or laparoscopy in order to treat gallstone disease [25, 26]. Gallbladder Cancer treatment involves a surgical procedure, the scope of which is dependent on the stage of the cancer. The total resection (total resection is encoded by R0) can be performed only in about 43% of patients with recognized cancer of the gallbladder [27,28].

MATERIALS AND METHODS

The study was carried out based on a retrospective evaluation of a group of 38 patients treated surgically due to the gallbladder cancer in the years 2005-2012 in the Second Department of General and Gastroenterological Surgery in Białystok Medical University Hospital.

The group consisted of 29 women (76% of patients) and 9 men (24% of patients). The mean age was 68.37 ± 10.72 years (48 - 86 years).

In 37 patients histopathology demonstrated adenocarcinoma, and in 1 patient the diagnosis was squamous cell carcinoma. There was one case of each I and II clinical stages of gallbladder cancer among the study population of patients, while grade IV was diagnosed in 35 operated patients. Data on tumor stage of one of the patients remains unknown. The majority of patients had grade G2 (29 patients) and other stages were G3 (7 patients), G1 (1 patient). Both clinical data and information about cancer are summarized in Table 1.

Table 1. Clinical characterization of gallbladder cancer patients.

Characteristics	**N=38**
Sex	
Male	9 (24%)
Female	29 (76%)
Age	
Median	68 years
Range	48- 86
Pathology	
Adenocarcinoma	37 (97%)
Carcinoma planoepitheliale	1 (3%)
Tumor Staging	
Stage I	
T1N0M0	1 (3%)
Stage II	
T2N0M0	1 (3%)
Stage IV	35 (91%)
T1N1M1	1 (3%)
T2N1M1	4 (10%)
T3N1M1	11 (29%)
T3N2M1	2 (5%)
T4N1M1	10 (26%)
T4N2M1	7 (18%)
Unknown Stage	1 (3%)
G (grade)	
1	1 (3%)
2	29 (76%)
3	7 (18%)
Unknown grade	1 (3%)

RESULTS

Of the 38 cases presented, women were 76% (29/38 patients) of patients and men were 24% (9/38). The mean age was 68.37 ± 10.72 years (48 - 86 years). In most patients - 45% (17/38) the status of gall bladder cancer required extended procedure, performed mainly because of the infiltration of other organs such as the liver and the greater omentum. In 5% (2/38) of patients due to the spreading of malignant tumor in the peritoneal cavity cancer proved to be inoperable. In 3% (1/38) of patients during the surgery only material for histopathological examination of the omentum and peritoneum was collected. With cholecystectomy was performed with lymphadenectomy in 13% (5/38) of patients. Further 8% (3/38) patients underwent cholecystectomy with bile duct excision. Radical cholecystectomy (R0) was performed in 26% (10/38) of patients. In 21% (8/38) of patients treated surgically there were postoperative complications such as: biliary fistula - 13% (5/38 patients), bleeding from the postoperative wound - 5% (2/38) and bleeding into the peritoneal cavity - 3 % (1/38). 8% (3/38) of patients had cardio-respiratory failure after surgery, one patient in this group was transferred to the Intensive Care Unit, and two were declared dead. All patients were observed and their survival after surgery was assessed – Table 2. The assessment of risk factors for mortality was carried out using Cox proportional hazards model. The model takes all the independent variables into account. The variable with the smallest significance for the model were removed stepwise based on the criterion of likelihood ratio. Calculations were performed using the statistical package IBM SPSS Statistics 20.0.

Table 2. Survival of patients treated surgically due to gallbladder cancer.

Survival	**Unresectable**			**Resectable**		
	Organs invasion n= 17 (45%)		**Other n= 3 (8%)**	**Simple cholecystectomy + lymphadenectomy n= 5**	**Cholecystectomy + bile duct resection n= 3**	**Radical cholecystectomy (IVb/V resection) n= 10**
	Liver invasion n= 5 (13%)	Other organs invasion n= 12 (32%)				
1-3 months	3 (8%)	3 (8%)	1 (3%)		1 (3%)	3 (8%)
4-6 months		3 (8%)	1 (3%)	1 (3%)		1 (3%)
7-9 months	2 (5%)	2 (5%)	1 (3%)	3 (8%)		
10-12 months		1 (3%)			1 (3%)	3 (8%)
>1 year		2 (5%)				1 (3%)
>2 years					1 (3%)	1 (3%)
>3 years		1 (3%)				1 (3%)
>5 years				1 (3%)		

The histopathological examination showed adenocarcinoma in 97% (37/38) of patients, and squamous cell carcinoma in 3% (1/38) patients. Grading: G1 rated at 3% (1/38 patients), G2 was found in 76% (29/38) of patients, G3 in 18% (3/38), while in 3% (1/38) the grading remained unknown. Clinical staging was estimated to be IV in 91% of patients (35/38). 3% (1/38) of patients was characterized by a stage I, further 3% (1/38) – II, and 3% (1/38) remained unknown. The median survival time of patients in clinical stage IV was 12.89 ± 17.76 (0-87) months for the entire population. Among women it was 14.2 ± 19.5 (1-87) months, men 7.2 ± 4.2 (0-14) months. 2 - year survival in this group was 24%, while the 5-year survival was only 3% (1/38).

DISCUSSION

Cancer of the gallbladder in both pre-invasive and early invasive stages is commonly diagnosed after previous cholecystectomy, which is at the same time considered the standard treatment at this stage of cancer [29,30,31]. A pre-invasive

lesion in terms of gallbladder cancer means that primary tumor is set upon the inner epithelium of the gallbladder and does not exceed lamina propria of its wall. In pathologic staging this stadium is known as pTis (carcinoma in situ, or Tis). Second early stage is described in a two-way manner, as pT1a and pT1b, respectively. A tumor stage pT1a corresponds to a tumor grown into lamina propria of the gallbladder. As for pT1b stage, the tumor described as this has grown beyond lamina propria in the gallbladder wall, infiltrating its muscular layer. Cancer stage pT2 means a tumor grown beyond muscular tissue of the gallbladder and infiltrating surrounding tissues. In stage pT3 cancer surpasses the mucose tissue of the gallbladder and / or invades the liver and / or one of the surrounding organs (stomach, duodenum, large intestine, extrahepatic bile ducts). The most advanced stage of the gallbladder cancer, pT4 means a tumor that has grown into one of major blood vessels (for example portal vein or one of the hepatic arteries) or that has infiltrated two or more of the surrounding organs.

5-year survival rate in case of carcinoma in situ reaches 83-100% [1,2,4,5,11,13,18]. In stages pT1a and pT1b long-term survival rate decreases to 60% [1]. However, use of cholecystectomy combined with extended resection of the liver lobes and lymph nodes gives 60% -100% [5,11] 5-year survival.

In stage pT2 it is recommended to perform a radical resection combined with the removal of 2cm margin of liver tissue around the gallbladder, or segments IVb and V of the liver, both with local lymphadenectomy. Such a procedure is known as the extended cholecystectomy [29]. 5-year survival after classical cholecystectomy in this stage go around 20-61% [4,5,13,18], and after extended cholecystectomy – respectively 10-100% [1,4,5, 18].

In stage pT3 5-year survival rate after extended surgery resection ranges from 15-44.8% [1,4]. Using this method, along with a local lymphadenectomy and biliary reconstruction gives a 30% -50% survivals [2].

Although cancer of the gallbladder in its most advanced stage (pT4) used to be considered inoperable, some authors propose an aggressive surgical procedure in this case. It consists of an extended cholecystectomy with resection of surrounding tissues and infiltrated organs. 5-year survival in stage pT4 rates around 7-50% [4,11,18] after extended cholecystectomy, and after pancreatoduodenectomy with liver resection it reaches 57% [18].

Despite the inoperability of some cases of gallbladder cancer in the fourth clinical stage, described in the literature, the authors of this work have shown some benefits of conducting extended surgical procedures in this group of patients. Unfortunately, there is an increased risk of serious postoperative complications after such procedures.

CONCLUSIONS

Gallbladder cancer is most often detected in an advanced stage (95% of patients in clinical stage IV). Late detection of gallbladder cancer is associated with poor prognosis (3% 5-year survival). Because of this it is necessary to continue to search for new diagnostic methods for detecting gallbladder cancer in its early stage when there is a possibility for effective surgical treatment - R0 resection. Women suffer from gall bladder cancer more often (76% of patients) compared to men (24%), but their prognosis as to the length of survival is better (14.2 vs. 7.2 months). The study demonstrated the benefits of extended surgical procedures even in clinical stage IV of gallbladder cancer (87 month survival). Postoperative complications related only to patients with stage IV cancer.

Conflicts of interests

The authors declare no conflicts of interest.

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