Review Article

GALL BLADDER CANCER: A REVIEW

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ABSTRACT

INTRODUCTION: Gall bladder cancer is the most aggressive cancer and the commonest malignant tumor of the biliary tract worldwide. The incidence increases with age and women are more commonly affected. Surgical resection is the only chance for complete cure, however only 10% of patients are candidates for curative surgery at initial presentation.

OBJECTIVE: To review the current concepts and key issues in the diagnosis and management of gallbladder cancer.

METHODOLOGY: A systematic review of published literature was done using search Google Search Engine, Highwire press and Springer Link selected papers were taken and books from author's collection used for further reference.

RESULTS: The risk factors of gallbladder cancer include race (like India), cholelithiasis, polyps, pancreatico-biliary maljunction anomalies, chronic inflammation, exposures to heavy metals and chemicals and infections (e.g. liver flukes). It may present as mass lesion, localized wall thickening or polypoid growth. Adenocarcinoma is the commonest histological type. The clinical presentation is divided into 5 syndromes namely acute cholecystitis, chronic cholecystitis, biliary tract disease, non specific symptomatology and symptoms related to metastatic disease. Complete surgical treatment is the only curative treatment for gallbladder cancer but only a few cases are seen at this curative stage.

CONCLUSION: Gallbladder cancer is relatively uncommon with high mortality rate. Risk factors include advance age, female gender, cholelithiasis, porcelain gallbladder, gallbladder polyps, congenital biliary cysts, chronic infection and smoking. Most are discovered incidentally at routine cholecystectomy or present at advance stage of the disease. Surgery is the only curative therapy for gallbladder cancer and the extent is dependent on the TNM stage. However, at diagnosis, only 10% of patients are candidates for curative surgery.

KEY WORDS: Gallbladder, Cancer.

NigerJMed2017: 76-81

INTRODUCTION

Gall bladder cancer is the most aggressive cancer and commonest malignant tumor of the biliary tract worldwide with the shortest median survival from the time of diagnosis[1,2]. The incidence increases with age, commoner in whites than blacks and women are 2 to 6 times more affected than men[2]. The aggressive biologic behavior and lack of sensitive screening tests for early detection are partly responsible for the poor prognosis of this condition[3].

Surgical resection is the only chance for a complete cure; however, only 10% of patients are candidates for curative surgery at the initial presentation[2]. Factors like anatomical complications of the portobiliary hepatic system, the morbidity / mortality associated with liver resection and risks of tumor spread due to manipulation even confer a high mortality rate among those suitable for resection4. Furthermore, recurrence rates are high among those that undergo surgical resection[2].

This paper seeks to review the current concepts and key issues in the diagnosis and management of gallbladder cancer.

METHODOLOGY

A systematic review of published literature was done using search Google Search Engine, Highwire press and Springer Link selected papers were taken and books from author's collection used for further reference.

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RESULTS

RISK FACTORS

RACIAL FACTORS: There is geographical variability in the prevalence of gallbladder cancer worldwide. Some areas with high incidence include Delhi, India (21.5/100000), Lapaz, Bolivia (15.5/100000), South Karachi, Pakistan (15.8/100000), Quito, Ecuador (12.9/100000)[1]. Low incidence of 0.4-0.8/100000 in men and 0.6-1.4/100000 in women have been reported in the western world (United States of America, United Kingdom, Canada, Australia and New Zealand)[5].

Environmental exposures and regional genetic predisposition to carcinogenesis have been described as reasons for this geographical variability[6]. This variability has also been attributed to dietary factors, with diets high in calories, carbohydrates, red meats, oils and red chili pepper conferring a higher risk while intake of green leafy vegetables and fruits may be protective[7]. In keeping with this observation, obesity is a well recognized risk factor for the development of gallbladder cancer[6,8]. For each 5 point increase in body mass index, the relative risk of developing gallbladder cancer increases by 1.59 for women and 1.09 for men[6,8]

CHOLELITHIASIS: Gall stone is the most important risk factor for the development of gallbladder cancer with an 8.3 times higher risk than the general population[7,10]. The percentage of gallbladder cancer patients with a history of cholelithiasis is about 70-90%[7,10]. Larger stones portend a greater risk, with stones ?3cm being 9.2-10.1 times greater than stones ?1cm1. This increased risk is most likely attributable to greater local epithelial irritation. The exact mechanism whereby cholelithiasis predisposes to gallbladder cancer remains debatable.

Gallbladder cancer has been discovered incidentally in 0.5-1.5% of patients who undergo cholecystectomy for presumed cholelithiasis[1]. Autopsy studies have revealed a 1-2% incidence of gallbladder cancer in patients with cholelithiasis[10].

GALLBLADDER POLYPS: Nearly 5% of all adults have gallbladder polyps, but majority are pseudopolyps with no neoplastic potential: cholesterolosis (60% of gallbladder polyps), adenomyosis (25%) or inflammatory (10%)[6]. Other potential gallbladder polyps include non neoplastic (hyperplastic and inflammatory) and neoplastic polyps (adenomas, leiomyomas, fibromas and lipomas). Benign adenomas, constituting 4% of all gallbladder polyps, play an unclear role in neoplastic transformation; however, the absence of adenoma remnants in mucosa adjacent to adenocarcinoma suggests these tumors may not play a role in carcinogenesis in all cases[6].

Polyps at risk of malignant transformation are typically rapidly growing and ?10mm in size and solitary/sessile polyps in patients $\geq$50years with gallstones[6].

General concensus guidelines for removal of gallbladder polyps ? 10mm in size, patients ? 60 years, increasing growth on serial imaging and/or presence of gallstones[11]. A study suggests that polyps ? 2cm can be followed by serial ultrasound every 3-6 months[12]. Conversely, other authors point out that up to 40% of malignant gallbladder polyps may be ? 1cm in size and thus patients with a polyp of 5-10mm should not be excluded from investigation[13].

PANCREATICOBILIARY MALJUNCTION ANOMALIES (PBM): This is a congenital anomaly in which there is an abnormal union of the biliary and pancreatic ducts located outside the duodenal wall in which a sphincter is not present. It allows pancreatic fluid to reflux into the biliary system causing inflammation and genetic alterations, leading to increased cellular proliferation resulting in hyperplasia, dysplasia and then carcinoma. About 10% of patients with gallbladder cancer have this anomaly[6]. These patients also have a higher frequency of K-ras mutations[14].

Among non PBM patients, pancreaticoduodenal reflux may occur secondary to a long common channel or high confluence of pancreaticobiliary ducts. A channel length of ? 8mm is more frequent in patients with gallbladder cancer (3%)[5]. The pancreaticobiliary reflux causes severe irritation of the gallbladder mucosa.

CHRONIC INFLAMMATION: This is considered a major factor in carcinogenesis causing DNA damage, tissue proliferation and cytokine and growth factor release. It also causes deposition of calcium within the gallbladder wall, making the gallbladder to develop a bluish hue and becoming fragile-the “procellain gallbladder”. Less than 1% of gallbladder specimens demonstrate this change, but in about 25% of cases, associated with gallbladder cancer[11]. Only specimens with stapled calcification on imaging are considered potentially premalignant as transmural calcification is less likely to develop malignancy[6].

Chronic inflammatory diseases such as primary sclerosing cholangitis are reported to be associated with a higher incidence of gallbladder cancer. Therefore, it is recommended that patients with primary sclerosing cholangitis should undergo annual gallbladder surveillance screening with ultrasound for the detection of abnormal lesions[6].

EXPOSURES: Many substances including heavy metals and radon have been thought to increase gallbladder cancer. Patients with gallbladder cancer have been shown to have low levels of selenium and zinc (which are anti oxidants) and higher levels of copper, lead, cadmium, chromium and nickel (well recognized carcinogens) in serum and bile compared to patients with cholelithiasis[7,15]. Workers in oil, paper, chemical, shoe, textile and cellulose acetate fiber manufacturing have an increased risk of developing gallbladder cancer. Tobacco, methyldopa and isoniazid may increase the risk of gallbladder cancer while risk associated with intake of oral contraceptives remain controversial[7,15].

INFECTIONS: Liver flukes particularly Clonochis sinesis and Opisthorchis viverrini have been implicated in gallbladder cancer[6]. An association between Helicobacter infection of the bile and gallbladder carcinogenesis may be related to bacteria induced degradation of bile acid; however, precise mechanisms remain poorly understood[9]. Chronic bacteria cholangitis usually due to Salmonella and Helicobacter increases the risk of biliary tree malignancy. The microorganisms degrade bile constituents by hydrolyzing bile salts and forming carcinogens. Chronic typhoid carrier status is thus a significant risk factor, with 6% of carriers developing gallbladder cancer (a 12 times increased risk)[6].

PATHOLOGY

Gallbladder cancer may arise in the fundus (60%), body (30%) or neck (10%)[16]. The development of gallbladder carcinoma occurs over a span of 5-15 years, with tissue alterations including metaplasia, dysplasia, carcinoma in situ and invasive cancer[6].

Gallbladder cancer may present as a mass lesion, localized wall thickening with induration of the wall or polyposis growth[11]. Obstruction of the neck and/or cystic duct may cause distension or collapse of the gallbladder; neoplasms in the body may constrict the lateral wall resulting in an hour-glass deformity[11]. These lesions are typically greyish-white in colour; however, mucinous and signet ring lesions have a gelatinous cut surface.

Adenocarcinoma is the commonest histological type, accounting for 98% of all gallbladder tumors, two-thirds of which are moderately/poorly differentiated while the remaining common histological variants include papillary, mucinous, squamous and adenosquamous sub types[6]. Other rare types of gallbladder cancer include carcinosarcoma, small cell carcinoma, lymphoma, signet ring cell-type tumors and metastasis[17]. Tumors may contain more than one histological variant[18].

Immunohistochemistry shows that these tumors are positive for cytokeratin 7 (CK 7) with focal expression of carcinoembryonic monoclonal antibody (CEA-M), CA 19-9, MUC1, B72-3 and MUCSAC[18]. Spread of gallbladder cancer occurs via 4 routes:

A) Local invasion of the liver (segments IV and V) or other nearby structures i.e bile duct, duodenum, colon, parietal wall and/or abdominal visceras[1,10]. Invasion of the liver is the most common form of direct local spread because of the absence of serosa where the gallbladder attaches to the liver[14,19].

B) Lymphatic dissemination C) Peritoneal spread and D) Haematological spread.

A number of staging systems have been described for gallbladder cancer including Nevin's staging system, the Japanese Biliary Surgical Society staging systemand the Tumor Node Metastasis (TNM) staging system of the American Joint Committee on Cancer.

TABLE 1- TNM STAGING[20]

T groups for gallbladder cancer

TX: The primary tumor's extent cannot be assessed.
T0: There is no evidence of primary tumor.
Tis: Cancer cells are only found in the epithelium.
T1: The tumor has grown into the lamina propria or the muscle layer (muscularis).
T1a: Tumor has grown into lamina propria.
T1b: Tumor has grown into the muscularis.
T2: The tumor has grown into perimuscular fibrous tissue.
T3: The tumor has grown through the serosa and/or it has grown directly into the liver and/or a nearby structure such as stomach, duodenum, colon, pancreas or bile ducts.
T4: The tumor has grown into one of the main blood vessels leading into the liver (portal vein or hepatic artery) or it has grown into 2 or more structures outside the liver.

N groups for gallbladder cancer

NX: Regional lymph nodes cannot be assessed.
N0: The cancer has not spread to regional lymph nodes.
N1: The cancer has spread to regional lymph nodes such as those along the cystic duct, common bile duct, hepatic artery, and portal vein.
N2: Metastasis to the peri aortic, pericaval, superior mesenteric artery and/or celiac artery lymph nodes.

M groups for gallbladder cancer

M0: No metastasis
M1: Presence of metastasis

Stage grouping
Stage 0: Tis,N0,M0
Stage I: T1,N0,M0
Stage II: T2,N0,M0
Stage IIIA: T3,N0,M0
Stage IIIB: T1 to T3, N1,MO
Stage IVA: T4,N0,M0
Stage IVB: Any T, N2,M0 or any T, any N M1

CLINICAL PRESENTATION
The symptoms of gallbladder cancer are relatively non specific which in part accounts for the often delayed diagnosis.

The presentation can be divided into 5 syndromes[21].

ACUTE CHOLECYSTITIS: Cancer incidence of 6-8% has been reported in elderly patients with acute cholelithiasis especially when associated with abnormal liver enzymes[22].

CHRONIC CHOLECYSTITIS: Recurrent cholecystitis in patients over age 50with known gallstone disease should raise suspicion for gallbladder cancer[23].

BILIARY TRACT DISEASE: Symptoms of biliary obstruction such as jaundice, right upper quadrant pain, nausea, vomiting and in later stages, pruritus are often associated with unresectable disease. Mirizzi syndrome has been associated with a high incidence of gallbladder cancer[24].

NON SPECIFIC SYMPTOMATOLOGY: Anorexia, weight loss and generalized weakness are common symptoms related to gallbladder cancer. Symptoms can also result from local complications such as fistula formation, invasion of adjacent organ presenting with haemobilia, gastrointestinal bleeding and intestinal obstruction. The presence of a palpable right upper quadrant mass indicates unresectability in most cases[25].

SYMPTOMS AND SIGNS RELATED TO METASTATIC DISEASE: Include ascites, hepatomegaly and paraneoplastic syndromes such as acanthosis nigricans

INVESTIGATIONS
ULTRASOUND (US): Most often, this is the initial diagnostic study when the gallbladder is diseased. Gallbladder cancer may appear as a mass replacing or invading the gallbladder, intraluminal growth/polyp or an assymetric gallbladder wall thickening. In advanced disease, the sensitivity and specificity are 85 and 80% respectively; however, in early disease, it fails to detect any abnormality, particularly when the tumor is flat or sessile and is associated with cholelithiasis[9].

Ultrasound may also stage the disease defining the extent of biliary tree involvement and confirming the presence hepatic, arterial or portal vein invasion.

ENDOSCOPIC ULTRASOUND: It's currently the definitive imaging modality staging of gallbladder cancer, allowing the precise imaging and acquisition of fine needle aspiration (FNA) biopsy.

COMPUTERIZED TOMOGRAPHY (CT) SCAN: This is the most common evaluative imaging in gallbladder cancer and its utilization has been increasing over time[26]. It is useful in diagnosis and staging and can detect liver or porta hepatis invasion, lymphadenopathy and involvement of adjacent organs. The 4 patterns of gallbladder cancer that have been described on CT scan include a polypoid mass within the gallbladder lumen, focal wall thickening, diffuse wall thickening and a mass replacing the gallbladder[11].

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATICOGRAPHY (ERCP): It may demonstrate anomalous junction of pancreaticobiliary ducts and allows for the collection of bile samples, brush cytology and/or intralesional biopsy[10].

MAGNETIC RESONANCE IMAGING (MRI), MAGNETIC RESONANCE ANGIOGRAPHY (MRA) AND MAGNETIC RESONANCE CHOLANGIOPANCREATICOGRAPHY (MRCP): Combination of these 3 is useful in detecting vascular invasion, biliary tree involvement, liver invasion and lymph node involvement[9]. MRI has been shown to be superior to CT scan for differentiating T1a lesions from T1b or greater and as such may be useful in pre operative management planning[27].

FLUORODEOXYGLUCOSE-POSITRON EMISSION TOMOGRAPHY (FDG-PET) SCANNING: This may be useful in detecting ambiguous primary lesions and residual disease after cholecystectomy.

PERCUTANEOUS APPROACHES: Image (US or CT) guided FNA biopsy has the potential for a diagnostic accuracy of 80-90%[10]. False negative results of 11-41% may be attributed to incorrect sampling, necrosis or fibrosis.

LAPAROSCOPY: Staging laparoscopy is often helpful to assess for peritoneal spread or discontigous liver disease. Weber et alreported that unresectable disease was identified in 48% of their study patients by laparoscopy, thereby, preventing unnecessary morbidity with open laparotomy[9].

SURGICAL TREATMENT

Complete surgical resection is the only curative treatment for gallbladder cancer[2]. The extent of surgical intervention may range from simple cholecystectomy to being combined with partial hepatectomy, with or without regional lymph node dissection. The appropriate surgical intervention may be estimated using TNM staging[11].

Tis/T1a Disease: Diagnosis of this is usually made after cholecystectomy. For patients at this stage, simple cholecystectomy is adequate[28]. With this, the 5 year survival rate is reported at 100% with no possible of more aggressive surgical management but only a few cases are seen at this curative stage[2].

T1b Disease: These tumors invade the muscular wall of the gallbladder. Some authors advocate simple cholecystectomy as adequate with 5 year survival of up to 100%[1]. Others call for radical cholecystectomy because locoregional recurrence has been well reported with 5 year survival rates as low as 37.5-68%[1]. Radical cholecystectomy has been recommended for T1b lesions by the National Comprehensive Cancer Network (NCCN)[30].

T2 Disease: Radical cholecystectomy with wedge resection of the gallbladder bed (segments IV and V) and regional lymph node dissection are recommended1. En-block resection increases 5 year survival to 80-90%. The extent of hepatic resection depends on the involvement of the major hepatic arterial or portal venous structures. Involvement of right portal pedicle necessitates a right hepatectomy; however, in its absence, resection of segments IV and V is adequate[9].

T3/T4 Disease: The NCCN recommends that T3 tumors should undergo radical re operation including hepatic resection and lymph node dissection with or without common bile duct resection and reconstructive hepaticojejunostomy[11]. T4 tumors are usually not amenable to surgical resection, and palliation is indicated.

MEDICAL TREATMENT

This is used in the management of gallbladder cancer as adjuvant therapy alone or in combination with radiation following surgical resection, in locally advanced non metastatic disease alone or in combination with radiation therapy and in advanced metastatic disease.

ADJUVANT THERAPY FOLLOWING SURGICAL RESECTION: NCCN guidelines for gallbladder cancer support adjuvant fluoropyrimidine chemoradiation or fluoropyrimidine or gemcitabine chemotherapy in patients with ? T1N0 gallbladder cancer following curative surgery.

LOCALLY ADVANCED UNRESECTABLE METASTATIC GALLBLADDER CANCER: The options include fluoropyrimidinechemoradiation or gemcitabine based chemotherapy (such as gemcitabine/cisplatin combination) or fluoropyrimidine based chemotherapy. Tumor control is rarely achieved with external beam radiation alone[31]. However, it is not known if chemoradiation therapy is superior to chemotherapy alone.

METASTATIC GALLBLADDER CANCER: Systemic chemotherapy has shown significant but modest survival benefit in the management of advanced gallbladder cancer. In a randomized trial compared systemic chemotherapy of gemcitabine plus oxaloplatin or 5 fluorouracil plus leucovorin versus best supportive care alone in 81 patients with unresectable gallbladder cancer, median overall survival in best supportive care and 5 fluorouracil/leucovorin group was 4.5 and 4.6 months respectively versus 9.5 months in gemcitabine plus oxaloplatin group[32].

CONCLUSION

Gallbladder cancer is relatively uncommon with high mortality rate. Risk factors include advance age, female gender, cholelithiasis, porcelain gallbladder, gallbladder polyps, congenital biliary cysts, chronic infection and smoking. Most are discovered incidentally at routine cholecystectomy or present at advance stage of the disease. Surgery is the only curative therapy for gallbladder cancer and the extent is dependent on the TNM stage. However, at diagnosis, only 10% of patients are candidates for curative surgery.

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