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Review Article

Comprehensive review of current trends in adenocarcinoma of gall bladder in northern Indian region: An imperative clinico-histological approach

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ABSTRACT

We are aware that epidemiological studies have established significant geographical and ethnic differences and this disproportionality is quite high in Southeast Asia, but the numbers are few in the America and other parts of world. Age, female gender, congenital biliary tract abnormalities and genetic predisposition represent imperative irreversible risk factors. Environment factors too have been implicated in causing gallbladder carcinoma. Other causes of gall bladder carcinoma include bile duct cholelithiasis, chronic inflammatory conditions and parasite infestation. These occurrences are associated with high mortality rates. Countries with highest gallstone prevalence usually suffer with greatest gallbladder cancer mortality. Indistinct and unclear clinical signs frequently prolong the gallbladder cancer diagnosis and lead to its eventual development and poor prognosis. Therefore, surgery seems to be viable treatment option which is practiced all around the globe since decades. Some patients are lucky to have gallbladder cancer treated incidentally when cholecystectomy is performed for cholelithiasis. This review is an attempt to genuinely explore the current trends in adenocarcinoma of gall bladder in Northern Indian region by clinico-histological approach.

1. Introduction

Literature has well evidenced that gallbladder carcinoma (GBC) is one of the highly malignant carcinoma with relatively low survival rate. Being first identified by M deStoll in 1777, it still remains a dilemma for the clinicians and surgeons due to its unknown etiology, delayed presentation and poor prognosis.[1,2] Older age groups (>60 years) are most commonly affected, and coexisting gallstones and chronic cholecystitis are present in most cases (68% to 98%).[1,3] High occurrence amongst women indicates key role of female hormones in disease progression. An association between early menarche and increased reproductive duration was found to be significant and is reported by some pioneer workers.[3,4] A patient having chronic typhoid disease has an increased risk for gallbladder carcinoma.[5] High prevalence of this carcinoma is recorded in relation to lower socioeconomic status, low educational and lifestyle variables such as smoking, chewing tobacco and alcohol intake. Some studies have pointed out that dietary factors also play a role in gallbladder carcinoma etiology.[6–9] Usually gallbladder carcinoma is non-specific in its clinical presentation.

2. Epidemiology

Various geographical and ethnic variations have association with the incidence of Gall bladder carcinoma.[10] The areas having higher rate of gallbladder cancer/disease are south, west, northeast and central India.[11] North India's incidence is 10–22/100,000 people, which is close to that of other high-incidence countries such as Chile, Bolivia, and Columbia. Mild incidence is found in Eastern Asia which includes China, Japan, Korea and parts of Europe which includes Slovakia, Poland, Czech Republic. The neighboring Indian subcontinent

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countries such as Pakistan, Bangladesh, Nepal and Bhutan have also reported an increased incidence of GBC.[12–18] India is a region of significant occurrence for GBC. Gall bladder cancer accounts for one among the three cases of cancer reported among female population in Northern India and North-east India. The Age Standardized average (ASR) for GBC in North and North-East Indian women is reported to be 11.8/1,00,000 population and 17.1/1,00,000 population respectively.[19] This is equivalent to the reports found in high-incidence areas such as Bolivia (14/1,00,000) and Chile (9.3/1,00,000) and parts of Asia such as Thailand (7.4), South Korea, Nepal (6.7), and Bangladesh (5.1) per 1,00,000.[20] In India, the occurrence of gallbladder carcinoma in both women and men has been gradually increasing. The women's overall age-adjusted rates jumped from 6.2/1,00,000 in 2001–2004 to 10.4/1,00,000 in 2012–2014.[21] These statistics has been obtained from thirty population based cancer registries across India, presented by the Indian Council of Medical Research (ICMR).[19] The incidence is increasing in the Mumbai region because of heavy migration of people from miscellaneous regions. Higher numbers of fresh cases were reported in India, China, Japan, Korea and Bangladesh among the Asian countries. These five countries account for 88 percent of all Asian GBCs reported. India constitutes 10 per cent of GBC's global load. Maldives, Yemen, Tajikistan, Turkmenistan and Uzbekistan have a standardized occurrence rate of less than 0.1/100,000 among the Asian countries.[22] Increasing pattern of GBC incidence in India is comparable to sharply decreasing incidence in countries like North America and Western Europe.

2.1. Risk factors

The following are several risk factors that were found to be related with the pathogenesis of GB carcinoma as are discussed hereby-

2.1.1. Age/Gender

Typically, the mean age for its development is 50–55 years. Increasing age is usually related to increase GBC risk.[23] This is probably due to the existence of several risk factors which function additively.[24] Most of the patients of GBC have more than 1 potential risks that generally work in combination and thus accelerating pathogenesis of GBC.GBC incidence shows an upward trend from 30 years of age onwards. Consequently, in areas which have higher incidence, younger patients can be affected and this requires a high level of suspicion. An increasing trend in both genders is also noted in Delhi region regarding GBC. Women pose a 2 - 6 fold higher risk of being diagnosed with GBC.[25] In patients with gallstone, women face a 2.4-fold increased risk of GBC.[26] Women during their lifespan are subject to elevated levels of estrogen and progesterone that may occur during pregnancies. Indian women are young during their 1st delivery, conceive early and have more child births compared to that of western counterparts in developing nations.[27]

2.1.2. Gallstones

In the early 19^{th} century, association was found between Gallstones and GBC. The incidence of symptomatic gallstones in north India is roughly 20 times greater than in southern India. Stone composition in Northern India is mainly cholesterol/mixed relative to pigment stones in South India.[28] In association with GBC, surgical references have commonly found increased prevalence of gallstone.[29] The correlation may be concurrent, causative or may be triggered by reverse causation. In GBC environment, a diseased gallbladder is found to be hypomobile, and thus may collect sludge instead of forming stones.

2.1.3. Obesity, Body Mass Index (BMI)

As evidenced by the literature, obesity and >30 body mass index (BMI) is frequently associated with greater GBC frequency. The relative risk noted is 1.88 (95% CI: 1.66–2.13). A large multi-centric study conducted by Zatonski et al. displayed that increased BMI is related to enhanced risk of developing GBC and the optimized relative ratio (RR) was 2.1 (95% CI: 1.2–3.8) between the highest quartile and the lowest quartile for BMI.[30] Few researchers have shown enhanced incidence of GBC with increase in BMI.[31] A case control study done on a large cohort in India showed inverse relation between BMI and GBC.[32]

2.1.4. Parity

Higher parity is linked to the higher risk with GBC both globally and in India. The adjusted age relative risk (RR) ranges from 1.3 to 4.2[33–35] for parity. In GBC cases, parity was higher than in gallstone patients (5.5 ± 2 vs. 3.3 ± 2, P=0.001).[34] Greater than 4 births is related to elevated risk of a variety of gallbladder conditions as seen in a large population based case control sample (RR 1.86; 95 percent CI: 1.3–2.65) in comparison to those of healthier control group.[36] In another study conducted in Banaras city, the mean number of pregnancies were 6 compared to 4 in gallstone cases (OR 6.66; 95 per cent CI: 1.8–23.4).

2.1.5. Family history

Having a first-degree relative with GBC was related to 5-fold increased incidence of GBC (RR 4.8; 95 % CI: 2.6–8.9).[2] Hsing and colleagues found that gallstone family incidence is linked with a 5.3-fold rise in GBC frequency (95 per cent CI: 1.5–18.9).[37] A positive family history of gallbladder disease is consistent with greater risk of disease (OR 1.79; 95 per cent CI: 1.3–2.4) in a broad population-based sample in Gangetic belt. Varanasi's Kumar et al Showed that a positive history in family consisting of biliary diseases is linked with higher risk of GBC (OR 3.48; 95 per

cent CI: 1.38–8.98).[38]

2.1.6. Rural residence

Rural location of patients is linked with greater GBC occurrence. This was tested in various case-control trials from various parts of the world. Kumar et al. analyzed that 80% of cases with GBC lived in rural areas in contrast to 54% patients with gallstones (OR 3.52; 95% CI: 2.48–4.99).[36] In a Delhi based study,59% cases with gallstones were in rural areas versus 32% from urban areas. Barbhuiya et al. indicated an occurrence of 5.56/100,000 in rural population compared to 3.62/1,00,000 in urban population (RR 1.62; 95 per cent CI: 1.4–1.8).[39] Rural residency is related to low levels of literacy, poor socio-economic status and reduced accessibility to medical services in Indian subcontinent.

2.1.7. Socio-Economic Conditions

A number of researches in India have shown that GBC patients are likely to be part of a lower socioeconomic class. Dutta et al. documented through his study in north India, that 32% of patients belong to lower socio-economic group compared to 11% patients of higher socioeconomic group.[35] Socio-economic scale was described on the Kuppuswamy scale, standardized for India.75 % of patients with GBC belong to the lower-socio-economic status.[40] In another study by Dubey et al. lower socio-economic class is correlated with low literacy rate, increased population and limited availability of health related care, inadequate sanitation and reduced access to clean drinking water relative to people of the upper socio-economic class.This, however, is associated with an improved susceptibility to faeco-oral infections such as S. Typhi, H. Pylori.[41].Some studies assessed the literacy rate in GBC patients and found that lower literacy rates are linked with higher GBC Relative Risk (1.49, 95 per cent CI: 1.3–1.7).[39]

2.1.8. Smoking

Smoking is linked with an increased risk of GBC and is documented by various studies globally as well as in India. Smoking is an independent risk factor for GBC and the overall Relative Risk is 11 (95 per cent CI: 1.7–71) for cases who smoked greater than 10 cigarettes a day for at least 5 years compared to that of non-smoking population.[42] Chewing tobacco is also linked with greater risk of GBC.[43,44] in another report from East India.

2.1.9. Exposure to Chemicals

In a large population-based cohort with samples from Bihar and Uttar Pradesh states, water and soil examination was done to determine amount of cadmium, nickel, chromium, and Dichlorodiphenyltrichloroethane (DDT).[45] Areas with increased prevalence of Gall Bladder diseases had high levels of these pollutants in the water as well as soil samples.[46] This was also confirmed by Pandey et al. through their study that higher occurrence of heavy metals and toxins in Gall Bladder bile was seen among GB stasis patients in comparison to those without GB stasis.[33] In Kanpur city,leather tanneries spill heavy metal toxins into the flowing water. Such toxins continue to be excreted into the bile by the liver in the detoxified conjugated form. These toxins tend to be concentrated in the gallbladder.[47–49]

2.1.10. Structural Bilary Abnormalities

Anomalous pancreatico-biliary junction is a congenital malformation wherein the pancreatic duct joins outside the duodenal wall to the biliary duct. In Japan and other East Asian countries this has been linked with higher risk of GBC and warrants prophylactic cholecystectomy. The reflux of pancreatic enzymes into the gallbladder causes chemical inflammation of the mucosa and mutation in K-ras of the gallbladder leading to papillary adenocarcinoma. Pancreatic enzymes along with secondary bile acids cause chronic damage to the mucosal system due to hyperplasia and dysplasia. Patients with anomalous Pancreatico-biliary Ductal Union (APBDU) and GBC tend to have reduced prevalence of gallstones.[50] The incidence of anomalous pancreatico-biliary junction in India is very small. In a sample of 3,827 endoscopic retrograde cholangiopancreatography (ERCPs) from our centre, just 2.6 per cent had APBDU.[51] Japanese studies have indicated that quite a lot of GBC patients have APBDU.[52]

GB polyps occur in about 5% of adult patients. Most of them are non-neoplastic (95 per cent).Benign adenomas make up <5 percent of all Gall Bladder polyps, which vary from 0.5–2 cm in height. The appearance of larger polyps (>10 mm), solitary polyps, sessile polyps, related gallstones, increased age, steadily increasing size indicates the polyp's neoplastic character.[53] Ultrasound endoscopy is helpful in differentiating benign from malignant polyps. Hypoechoic, heterogeneous lesion with ratio of height / width (0.8), decreased vascularity indicates elevated risk of neoplasia.[54] If the polyps are indicative of neoplasia, it is safest to extract these polyps by cholecystectomy. Other polyps need close follow-up for 3–6 months to evaluate polyp size increase.[53,54]

Gallbladders having central, stippled or multiple punctate calcification, and others with related wall thickening and symptomatic porcelain gallbladder are more likely to harbor carcinoma and thus can benefit from prophylactic cholecystectomy.[55,56]

2.1.11. Genetic Factors

Over the past decade hereditary influences have been widely researched in the literature. The mutation in p-53 is the main GBC production pathway. In India, 50–70% of tumor exhibits p-53 overexpression.[57,58] GBC exon sequencing considered ERBB pathway to be the most dysregulated

pathway in this disease.CERBB2 mutation has been found in 9.4 per cent and is indicator of bad prognosis. In Northern India the study identified K-ras mutation on codon 13 as opposed to codon 12 or 61 in global findings.[59] HER2 / Neu overexpression that had therapeutic consequences for molecular targeting was observed in 14 per cent. In 10 per cent of GBC cases, micro satellite instability was observed.[60] In another North India study, heterozygosity loss was found more frequently in pre-neoplastic lesions than those without pre-neoplastic lesions.[61] More than 1,281 mutations have been found in GBC, but most of these mutations are yet to be defined.[62]

2.1.12. Histologic Type

The histologic form of Gall bladder carcinoma (GBC) with few exceptions, did not affect disease pathology.[63] In comparative analysis, well differentiated or moderately differentiated tubular adenocarcinomas are associated with prolonged survival periods than poorly differentiated carcinomas, the latter having an increased incidence of hematogenous metastases.[64] The most favorable prognosis for papillary GBC was found in some series and patients had long survival compared to all other histological types.[65–69]

2.1.13. Histologic grade

In an Eastern Cooperative Oncology Group (ECOG) review of 30 patients with advanced GBC classified into either low-grade or high-grade lesions, the 13-week survival of the GBC patient with low-grade lesion was substantially longer than the 7-week survival of the GBC patient with high-grade lesion.[70] In case of GBC, isolated single cells or clusters of lesser than five cancer cells are formed by less differentiated tumor cells at the invasive front. Similarly in colorectal carcinomas, this spectacle is termed as tumor budding, a lesion that represents prognosis, predominantly for T2 tumors (Kai et al. 2011).[71]

2.1.14. Invasion patterns

The occurrence of peri-neural invasion in GBC-patients is a negative prognostic indicator.[72–75] Patients with perineural invasion had a five year survival rate of 7 per cent in comparison to 71 per cent for patients without detectable perineural invasion.[73]

The preservation of bile ducts in resected GBC has weak prognosis.[76,77] In early GBC, an adverse prognostic factor is the intraepithelial extension into the Rokitansky-Aschoff sinus.[78]

Like in other carcinomas, vascular invasion is a negative prognostic factor for GBC. Expression of the vascular endothelial growth factor-C (VEGF-C) was expressed in 63 percent of GBC and this expression was correlated with invasion of lymph vessels and metastasis of lymph nodes, indicating that VEGF-C is involved in tumor progression by lymphangiogenesis and facilitation of invasion of lymph vessels.[79]

Invasion of the hepatic artery in patients with GBC is an important prognostic indicator, as invasion of this artery is associated with higher risk and a poor prognosis.[80]

2.2. Clinical Presentaion

It is tough to distinguish the clinical presentation of gallbladder cancer from the one of biliary colic. allbladder cancer is found either early as an incidental finding during cholecystectomy done for cases of symptomatic cholelithiasis, or in late cases when the tumor has reached the bile duct or metastasized intra-abdominally. The disorder is limited to gallbladder at diagnosis in just 20 per cent of patients. Therefore, the majority of individuals at first presentation have advanced or metastatic disease.[59,81] There is no clear clinical description of an early carcinoma gallbladder and preoperative diagnosis is difficult. Many of these patients are asymptomatic while others present with apparent clinical features of benign disease such as right upper abdominal pain interspersed with occasional nausea and vomiting.

In a 2002 study performed by Cunningham et al, 48.2 percent of carcinoma gallbladder patients had a pre-operative diagnosis of symptomatic cholelithiasis.[81] Early symptoms such as recurrent pain, loss of weight, and jaundice are also indicators of this dilemma. Elder patients having a history of biliary colic that progresses to a persistent, relentless, dull aching pain should be suspected of having gallbladder carcinoma, especially when there is weight loss or a mass in the right-upper quadrant. An especially alarming finding is the presence of jaundice. The mean survival of jaundice patients was 6 months relative to jaundice-free patients with 16 months of survival.[60,61] Typical symptoms of advanced carcinoma like anaemia, hypoalbuminemia, leukocytosis, and increased alkaline phosphatase, gamma glutamyl transpeptidase, or bilirubin are usually not very beneficial for laboratory analysis.

Tumor markers can be of importance when suspecting cancer of the gallbladder. The serum carcinoembryonic antigen >4 ng / mL is specific to 93 percent and sensitive to 50 percent. For the identification of cancer of the gallbladder in the presence of symptoms, serum level CA-19-9 > 20 U / mL, is 79.4 percent sensitive and 79.2 percent specific.[62,82] A research by Kaufman et al found that EGFR in patients with gallbladder carcinoma was overexpressed. He found that 3+EGFR patients were associated with poorly differentiated carcinoma, and 1+EGFR patients correlated with well-differentiated carcinoma.[83] The better understanding of the function of EGFR in oncogenesis has made it an appealing target for therapeutic action.

2.3. Clinical management

2.3.1. Surgical management

The most important factor in AJCC staging requirements is primary tumor invasion (T); it decides the surgical approach.[84,85] Stages I and II are curatively resectable. Stage IIIA can be potentially resectable if not involving the aortocaval lymphnodes. Stage IIIB generally refers to locally un-resectable disease as a result of vascular invasion or multiple adjacent organs being involved. Stage IV stands for non-resectability due to distant metastases.[86] Overall 5-year survival ranged between 21% to 69% for patients with gall bladder carcinoma who had microscopically margin-negative curative resection and 0% for patients who do not undergo microscopically margin-negative resection.[87] For gallbladder carcinoma, the method of liver resection ranges from atypical resection of segments IVb and V to right hepatectomy.

2.3.2. Adjuvant chemotherapy

Two groups of chemotherapeutic agents -gemcitabine and platinum compounds can be used. The influence of mono-therapy is minimal.[88] In one trial, 26 patients received single-agent gemcitabine with metastatic or un-resectable cancer of the gallbladder, and no prior chemotherapy. A cumulative response rate of 36 percent (95 percent confidence interval [CI], 17.1 percent –57.9 percent) and 30 weeks median survival were observed of the 25 evaluable patients.[89] The survival values reported in these limited Phase II trials are observational in nature and not statistically significant due to the single-arm aspect of these trials.44 patients were assessed for gemcitabine and cisplatin. There were four absolute responses and 16 partial responses among 42 evaluable patients, for a response rate of 48 percent (95 percent CI, 32 percent -71 percent). The median survival duration was seven months (95 per cent CI, 6–8.5 months) with acceptable toxicity.[90] A second experience with the two drug regimen has shown 36.6 percent overall response rate with moderate hematological toxicity.[91] A new norm for this disease has been set by recent research showing greater survival with gemcitabine and cisplatin combination than with gemcitabine alone.

2.3.3. Molecular targeted therapy in gall bladder carcinoma

Distinctive molecular aspects in gallbladder cancer include Kras, INK4a and p53 mutations, as well as human epidermal growth factor receptor (HER)-2 / Neu amplification.[92] Apart from a relatively higher rate of BRAF hotspot mutations (33 percent) mutually exclusive of Kras mutation, rare mutations in PI3K are identified.[93] Activating epidermal growth factor receptor (EGFR) mutations have also been identified in a group of biliary tract cancer cases (13.6 per cent – 15 per cent), including 1 case of gallbladder carcinoma[94] as having EGFR amplifications. Amplification of the EGFR gene as well as case reports on the efficacy of cetuximab in combination with either gemcitabine or gemcitabine and oxaliplatin were also reported.[95] Malka and coworkers showed their experience with a Phase II randomized trial comparing gemcitabine plus oxaliplatin alone with the same chemotherapy regimen in conjunction with cetuximab and found a higher 4-month progression-free survival rate with cetuximab (44% vs. 61%, respectively).[96] Presence of the vascular endothelial growth factor (VEGF), a main mediator of tumor angiogenesis, was detected in biliary tract cancer, with enhanced expression of VEGF associated with advanced disease and poor prognosis.[97] In a multicenter Phase II trial, bevacizumab, a humanized monoclonal antibody against VEGF, was tested in combination with gemcitabine and oxaliplatin in patients with biliary tract cancer, including a significant number of patients with gallbladder cancer.[98] Of the 35 patients enrolled, 40% had a partial response, the overall median survival time was 12.7 months (95 % CI, 7.3–18.1 months), and the mean progression-free survival time was 7.0 months (95 % CI, 5.3–10.3 months). In a Phase II trial involving 31 patients, Sorafenib, which targets VEGF receptors (VEGFR-2, VEGFR-3) and platelet-derived growth factor receptors and less active B-RAF and C-RAFkinases, was tested as a single agent.[99] Significant toxicities affected around two-third of patients, and two patients (6%) had an unconfirmed partial reaction, whereas nine patients (29%) had a stable condition.

3. Conclusion

Within the limitations of the study, authors have concluded some very imperative outcomes. Increased age, female sex, cholelithiasis, porcelain gallbladder, polyps of the gallbladder, congenital biliary cyst, chronic infection and smoking are risk factorsfor GBC.Sadly, numerous gallbladder cancers are eventually identified at regular cholecystectomy or are diagnosed as end stage disease. Consequently, radiological imaging is bounded to the use of USG, CT scans and endoscopic / FNAC procedures for diagnosis and staging purposes. The bulk of gallbladder tumors are due to adenocarcinoma. Surgery is the only therapeutic cure for carcinoma in the gallbladder. Less than ~20% of patients are subjects for curative surgery at diagnosis. The scope of surgery depends on the disease TNM level, ranging from simple cholecystectomy in T-1a tumor to partial hepatectomy and regional dissection of the lymph nodes in some T-2 tumors. Our study results should be considered as suggestive for presuming prognosis for similar clinical circumstances. Nevertheless, authors expect some other large scale studies to be conducted that can further establish real-time and authentic norms in these perspectives.

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5. Conflict of Interest

The authors declare they have no conflict of interest.

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