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CARCINOMA GALLBLADDER: A REVIEW ARTICLE

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ABSTRACT

Gallbladder cancer (GBC) is the third most common cancer of the gastrointestinal tract malignancies worldwide. Due to bad prognosis associated with the aggressive nature of the tumor, deficiency of sensitive screening evaluating tools for timely detection give rise to late diagnosis at advanced stage. The only curative treatment for gallbladder malignancy is surgical resection. This article supplements to the body of former literature in GBC to augment understanding of this rare but surely a curable disease. Carcinoma gallbladder having Stage I and II is unquestionably resectable with therapeutic goal. But, because of high percentage of recurrence, adjuvant therapy comes in combined form of chemotherapy plus radiotherapy. Chemotherapy regimens using gemcitabine have revealed a better effectiveness over 5 fluorouracil (5-FU) regimens. In order to improve the local disease control and to decrease the distant recurrences it is better if combination of radiotherapy and chemotherapy is given in the patients where it is achievable. Various molecular variations can be used as a marker for the gallbladder cancer, and Several molecular changes are detected in gallbladder cancer, but yet it is difficult to find out the ones which are the predominate one or directs the neoplastic process and to differentiate them from the other non-dominated genes. Immunotherapy is a form of therapy that promotes the immune system of an individual to identify and destroy the cancer cells that cannot be tackle by the surgery or have widely metastasized. Currently chemotherapy is the mainstay treatment for patients with advanced GBC. Similar to the immunotherapy, target therapy is used to treat the carcinoma gallbladder that is beyond the scope of surgery and have widely spread, they precisely target certain mutations that makes the tumour cell different from the normal healthy cells.

INTRODUCTION

Gallbladder cancer (GBC) is the third most common cancer of the gastrointestinal tract malignancies worldwide (1,3). Initially, at the time of diagnosis, GBC patients are mostly represented with short term mean survival (3,2). Due to bad prognosis associated with the aggressive nature of the tumor, deficiency of sensitive screening evaluating tools for timely detection give rise to late diagnosis at advanced stage (1-3). The only curative treatment for gallbladder malignancy is surgical resection. At the time when patients were presented, barely 10% of them are the potential candidate for surgical resection (1-9). This article supplements to the body of former literature in GBC to augment understanding of this rare but surely a curable disease (11, 12). In this review article, we assess the obvious features of the epidemiology and risk factors, pathogenesis, clinical features, radiological evaluation, and prognosis of carcinoma gallbladder with special emphasis on its surgical management.

Incidence And Epidemiology

Carcinoma gallbladder outweigh in female population with uneven ubiquity in worldwide. In USA, the reported frequency is less than 2 out of 100,000 persons, whereas in Asia particularly in India, it manifests a clear geographical difference (1, 3). Almost $1/10^{th}$ GBC worldwide burden is contributed by India (2,3). In the Northern part of India (Delhi), the incidence is nearly 22/100,000 females and female: male incidence ratio is around 3(3-5). The incidence is somehow equivalent to that of other regions of world with high incidence like Bolivia, Chile, Thailand, Korea and Columbia (1-3). In India, the incidence is reported to be markedly higher in the northern than in the southern region (4.5 per 100,000 for males and 10.1 per 100, 000 for females in North India compared to 1.2 per 100,000 for males and 0.9 per 100,000 for females in South India).

Risk Factors

The risk factors associated with GBC are mainly divided into four categories as follows:

- Demographic
- Pathology associated with gallbladder carcinoma
- Exposure
- Infections

Demographic Factors

A significant geological inequality is seen in the incidence of GBC across the globe (3, 5). Geographical areas reporting a high incidence of GBC comprise Chile (27/100,000), New Delhi, India (21/100,000), La Paz, Bolivia (15/100,000) and Pakistan (14/100,000), whereas the western part of world like USA, Canada, UK has much lower incidence rates (4, 5).

Pathology Associated With Gallbladder

- Cholelithiasis
- Chronic inflammation
- Primary sclerosing cholangitis
- Gallbladder Polyps
- Pancreaticobiliary Maljunction Anomalies

Exposures

Numerous materials have been postulated to augment the risk of GBC. This includes heavy metals and radon (4, 5). Researches have revealed that GBC patients have much lesser levels of Selenium and Zinc. Furthermore, elevated levels of copper, lead, cadmium, chromium, and nickel in patients with cholelithiasis has also been reported (2-4).

Infection

A connection among Helicobacter infection of bile and GBC has been studied. Though, the exact mechanisms remain inadequately understood (4,5). Liver flukes' infection particularly with *Clonorchis sinensis* and *Opisthorchis viverrini,* has mostly been reported in GBC (5). Also, chronic typhoid carrier condition has also been reported as the major risk factor (4-6).

Genetic And Molecular Alteration In GBC

Genetic mutations

The exact genetic alterations concerned with the progression of gallbladder cancer are not very well elaborated. However, adiversity of genetic variations, possibly involved in GBC might incorporate oncogene activation associated with the inhibition of tumor suppressor gene, microsatellite instability, along with gene promoter methylation (3-6).

Microsatellite Instability (MSI)

Contribution of microsatellite instability (MSI) in the tumor-genesis in GBC is not very well understood (5, 7). However, it is well advocated that MSI is very likely usual in patients developing GBC that result in atypical anatomy and is not allied with Lynch syndrome (6, 7).

Chromosomal Abnormality

Loss of heterozygosity (LOH) is a usual cancer genetic change. Chromosomal aberration such as heterozygous loss of one or two alleles (deletion), or duplication of chromosome either maternal or paternal and concomitant loss of the further allele produce LOH (7-9). Cytogenetic locations such in repeated loss of heterozygosity *i.e.,* 3p, 8p, 9p, and 22q loci have also been recognized in GBC from diverse populations; in addition to this it is also describe in a number of other tumors like Retinoblastoma, melanoma, Squamous cell carcinoma of larynx (7, 8). ADAM-17 expression is amplified in tumors with high histological grade and pT stage associated with decreased overall survival. Genetic factors have been deliberated broadly over past decades but the present prevailing evidence about hereditary and molecular variations in GBC is still very much incomplete (5-7).

KRAS

KRAS plays as an early important inducer in several signal transduction mechanisms and their associated pathways (7-9). Codons that are usually linked with KRAS gene mutations in GBC are 12, 13 and 61. Among the above mention, mutation in codons no. 13 is most common associated with GBCs of northern Indian belt (7, 8).

TP53

TP53 is one of the most active tumor suppressor gene with a diverse anti-cancerous function. It plays a major role in the preservation of genome integrity, apoptosis, genomic stability, and inhibition of angiogenesis, etc. (60-62). Defect in *TP53* function lead to neoplastic changes. However, missense mutations constitute the majority of TP53 mutations related with GBC (7-9).

C-ERB-B2

The oncogene *c-erb-B2* is an analogue for the epidermal growth receptor, that possess a tyrosine kinase type of activity (7, 8). Nearly 10% -46% of patients having GBC have found to be positive for c-erb-B2 (7-9).

Pathology

Multi-step Pathogenesis Of Gallbladder Carcinogenesis

Gallbladder adenomas and dysplasia are two separate pathologic identity of the epithelial mucosa. The below two orders in the progression of GBC have been anticipated and built on laboratory evidence:

1. Dysplasia – Carcinoma
2. Adenoma – Carcinoma

Based on the prior evidence, a carcinoma sequence from metaplasia, dysplasia and ultimately carcinoma *in situ* that appears to be the more frequent course over an adenoma carcinoma sequence (7-9)

Multi-step Pathogenesis Of Gallbladder Cancer From Normal Gallbladder

GBC progresses over a series of events before translating into invasive malignancy. Any introduction to carcinogens may convert normal gallbladder epithelium to a state called metaplasia which later forms dysplasia to carcinoma *in situ* (CIS), and lastly going on to an invasive state in approximately 15 years (8, 9).

Two different self-regulating biological pathways based on morphological, genetic, and molecular signal leading to GBC are theorized (7-11). One is Dysplasia carcinoma order rising from metaplastic epithelium and other one is adenoma-carcinoma sequence.

WHO Classifies Carcinoma Gallbladder Into Various Morphological Sub-types.

Cytological subtype:

- Adenocarcinoma NOS
- Papillary adenocarcinoma
- Mucinous adenocarcinoma
- Signet ring cell carcinoma
- Adeno-squamous carcinoma
- Squamous cell carcinoma
- Neuroendocrine tumor
- Small cell carcinoma
- Mixed adeno-neuroendocrine carcinoma
- Undifferentiated Carcinoma NOS
- Spindle Cell undifferentiated carcinoma
- Giant Cell undifferentiated carcinoma

Methods Of Invasion

Gallbladder tumors invades through direct, lymphatic, vascular, neural, intraperitoneal, as well as intraductal. The first level of invasion involved in the carcinoma gallbladder is the one that are along the biliary ductal system. Following which drainage happens to at the superior, anterior, and posteriorpancreaticoduodenal lymph nodes. The lymph nodes posterior to the portal vein (retro portal) and lymph node surrounding the common hepatic artery—the subsequent level (level two) of lymph nodes (11-14).

Metastasis may include lymph nodes posterior to the head of pancreas (retro pancreatic) and posterior to the portal vein (retro portal) (12, 13). Next draining lymph nodes are coeliac, superior mesenteric, and para-aortic lymph nodes— the 3rd level of nodes. Lymph nodes that are present at the hilum of liver are involved in retrograde direction. However, the global rate of nodal metastasis in gallbladder carcinoma varies between 55%–65% and is firmly linked with the invasion depth (13, 15).

Clinical Presentation

Several symptoms of gallbladder carcinoma have been categorized into five clinical syndromes. The patients belonging to the 1st category have symptoms of acute cholecystitis—around 1% of patients who have been operated for acute cholecystitis have gallbladder carcinoma (15, 17). 2nd category are the Patients with chronic cholecystitis. The 3rd group of patients are represented with symptoms such as jaundice, weight loss, general weakness, and pain in the right upper quadrant. Patients who fall under this category have widespread disease. Patients under the 4th category have various symptoms including anorexia, weight loss, fatigue (17, 19). These patients usually have widespread disease. The last syndrome comprises benign appearances outside the biliary tract, the minor cluster of patients with this syndrome present with gastrointestinal hemorrhage and upper gastrointestinal obstruction.

Jaundice in carcinoma gallbladder is one of the common indicators of poor prognosis. It was related with unresectable disease in nearly 40% of patients. Sign of advance disease in patients include palpable gallbladder mass, hard nodular liver, and malignant ascites from carcinomatosis.

Staging

Presently, as with most other tumors, the American Joint Committee on Cancer (AJCC) practices the TNM staging classification.

With the most recent version of the TNM staging system, nodal status appears to the most indicative of global prognosis (15-17). Based on the American Joint Committee on Cancer guidelines, on tumor invasion and the level of spread is used for staging the carcinoma gallbladder.

T	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades the lamina propria or muscular layer
T1a	Tumor invades the lamina propria
T1b	Tumor invades the muscular layer
T2	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum) Or tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T2a	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa(visceral peritoneum)
T2b	Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T3	Tumor perforates the serosa(visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

N	N Criteria (At least ≥ 6 LNs)
NX	Regional LN cannot be assessed
N0	No regional LN metastasis
N1	Metastases to 1^3 regional LNs
N2	Metastases to ≥ 4 regional LNs

M	M Criteria
M0	No distant metastasis
M1	Distant metastasis present

T	N	M	Stage
Tis	N0	M0	0
T1	N0	M0	I
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T3	N0	M0	IIIA
T1-3	N1	M0	IIIB
T4	N0-1	M0	IVA
Any T	N2	M0	IVB
Any T	Any N	M1	IVB

As the tumor progression occur from T2 to T3 and T4, the five-year survival rate changes from 70% to 0% (18, 19). The tumor stage evolves from T2 to T4 the chances of metastasis to the distant organs increases drastically from 16% to 79% and the chances of lymph node involvement also increase from 30% to 70%.

Investigations

Various laboratory findings are related with it, but none is very precise for the gallbladder carcinoma.

Ultrasonography

Ultrasonography is generally the first study to be requested for as it is readily accessible as well as non-invasive. Advance tumors may be known as an echogenic mass in place of the gallbladder, which is not linked with acoustic shadowing along with loss of interface among liver and gallbladder (17-20).

Endoscopic Ultrasound

Endoscopic ultrasound is beneficial in perceiving the depth of gallbladder carcinoma invasion. Overall detection rate of GBC tumors was approximately 90% (20-22). Nearly all patients with pedunculated lesion were appropriately diagnosed with endoscopic ultrasound. While only 85% of tumors with broad base and 70% with flat elevated lesions were detected correctly.

Computed Tomographic (CT) Scanning

Computed tomography scan (CT) has the capability to spot local hepatic invasions, nodal spread, including the occurrence of liver and peritoneal metastasis. Thin slice Spiral CT scan has more than 90% precision for deciding resectability of gallbladder tumors (22-24). Computed Tomography (CT) has been shown to detect carcinoma gallbladder appropriately in 65% of cases.

Magnetic Resonance Cholangio Pancreatography (MRCP):

Magnetic resonance imaging or MRI might be beneficial in recognizing invasion in the bile duct along with vascular involvement (22-24). Though, the sensitivity for identification of metastatic lymph node was only 56%. The primary tumor along with associated tumor spread outside the gallbladder, was observed to be hyperintense on T2 and hypointense on T1-weighted imaginings when related to liver parenchyma.

Fine Needle Aspiration Cytology (FNAC)

USG guided FNAC is very a precise technique to identify and plan a surgery earlier because of its high diagnostic ability. In general, sensitivity and specificity of FNAC in perceiving the gallbladder carcinoma is reported to be 91% and 95% respectively (22,25). However, malignancy when associated with Xanthogranulomatous cholecystitis, the sensitivity of FNAC drops from 90% to 80%.

GBC Tumor Markers

Till now, no compatible tumor marker has been established which can be used in the accurate diagnosis of carcinoma gallbladder. However, two markers namely carbohydrate antigen 19-9 and carcino embryonic antigen (CEA) have been most frequently raised in advanced progressive stages but with a little low specificity (25, 26).

Surgical Treatment

Cancer Of The Gallbladder: Surgical Treatment

The surgical management of GBC is a not a unimodal task and involves a collaborative teamwork. The purpose of surgical resection is to mostly attain Ro resection; hence the level of the resection mainly necessitates to attain that may differ with the disease advancement (26). Unfortunately, incomplete resection, R1 or R2 in GBC has no good rate of survival chances (25, 26). The radical or extended cholecystectomy includes the wedge resection of hepatic segment IVb & V to a minimum 3 cm depth from sideways gallbladder bed along with the removal of regional lymph node (26). Carcinoma gallbladder having Stage I and II is unquestionably resectable with therapeutic goal. But stage III generally specifies non-resectable disease from vascular or next to organ involvement. However, distant metastases had made the Stage IV tumors to be unresectable.

Incidentally Detected Gallbladder Cancer

Cholecystectomy which is performed for the benign gallbladder disease, but diagnosed as gallbladder carcinoma (GBC) intraoperative or postoperative period is defined as Incidentally discovered gallbladder cancer (IDGC). Most frequent surgery done for benign gallbladder disease is laparoscopic cholecystectomy. Most of the GBC patients also have gallstone (26). Out of total cholecystectomy performed for benign disease, nearly 0.2-2.9% is found to have IGBC. It constitutes 27% -41% of all GBC. Patients with IGBC having Tis and T1a stage, with negative cystic duct margin can be treated by simple cholecystectomy alone. IDGC with TNM staging Tis and T1a, with negative cystic duct margin preferably manage by simple cholecystectomy. While those with stage T1b and more must be restage and managed by radical re- resection (R0) (26, 27). Patient who under re-resection has similar survival rates as of patients underwent primary radical surgery.

It should be kept in mind that all the cholecystectomy performed for benign gallbladder disease, gallbladder specimen should be opened and if any doubt is present than specimen must be sent for immediate frozen section. Every gallbladder specimen must be sent for histopathology.

Incidental GBC Discovered During Cholecystectomy

Most of the time it is difficult to diagnose the early gallbladder cancer due to vague symptoms and absence of specific sign. GBC should be suspected if on ultrasound there is mass lesion, polyp (>1cm), asymmetric wall thickening (focal/diffuse) or porcelain gallbladder with wall calcification. One must have high index of suspicion for GBC specially in northern part India. If any doubtful lesion is present instant frozen section should be sent (27). If CGB is confirmed and surgeon is experienced enough to do radical cholecystectomy should be done. But if surgeon is not experienced patient should be referred to the higher centre for completion radical cholecystectomy.

Incidental GBC After Cholecystectomy

Patients who are diagnosed with GBC after cholecystectomy, their specimen or block should be reviewed for depth of

invasion. It is important to grade the tumor, involvement of vascular, lymphatics and to look for cystic duct margin. Simple cholecystectomy is sufficient if the T stage is Tis and T1a with negative cystic duct margin since the probability of lymph node involvement is less than 2.5%. Re- exploration and bile duct resection is recommended if cystic duct margin is found to be positive. Radical resection should be done with T1b (muscle invasion) since lymph node metastasis chances are 16%. T2 tumor on histopathology should be treated with radical cholecystectomy with segment IVB and V of liver with lymphadenectomy(26, 27). Palliative chemotherapy should be done in patients with T3 and T4 disease or having metastasis.

Extent Of Hepatic Resection:

The main principal behind the surgical resection for gallbladder tumors is to attain Ro resection. The incomplete resection, R1 or R2 have a certain life expectancy comparable to that of patients completely not undergoing surgery (28).

Massive hepatic invasion may necessitate substantial hepatectomy in the configuration of the extended right hepatectomy. The selection for such extensive hepatic resection in large tumor entails vigilant judgement and is only suggested when R0 resection is attained.

Extended hepatic resection is similarly beneficial as long as negative resection margins for patients having inflammation close to the cystic plate after cholecystectomy (28,29).

Lymph Node Dissection

The Lymph node expansion in carcinoma patients is of significant concern. Among the regional group of gallbladder lymph nodes, the cystic as well as peri choledochal group of lymph nodes have been looked upon as the 1st echelon nodes of the gallbladder, while the postero-superior pancreatico-duodenal nodes, retro portal nodes and the right celiac nodes have been viewed as second echelon gallbladder lymph nodes (28-30).

Removal of 1stand 2nd echelon nodes together is defined as an extended portal lymph node dissection (29,32).

Bile Duct Resection

The resection of extrahepatic portion of bile duct has not involved any benefit in terms of survival in patients with carcinoma gallbladder (30-32). Its excision is conducted if the margin of cystic duct stump is found to be involved with tumor or lesion present at the gallbladder neck, thus infiltrating directly into the common bile duct. Frozen section of cystic duct stump margin must be carried out during the intraoperative period and resection of bile duct may be essential if positive margin is achieved (32,33).

Adjacent Organ Involvement

When carcinoma gallbladder involves the portal vein and hepatic artery, their resection is not possible. However, surgery is indicated when large bowel, duodenum or liver are involved. There are numerous studies that report that extended resections such as right extended hepatectomy or combined hepatic & pancreatic resections as pancreaticoduodenectomy have better long-term survival chances (32,33).

Surgical Management Of GBC

During several instance, while performing laparoscopic cholecystectomy, when the diagnosis of carcinoma gallbladder is made intraoperatively, it is important to follow oncological principles during the initial operation, a two-step method is essential. Also, incidental opening of gallbladder or bile leak occurs during the intraoperative period, it has a worse prognosis (32-34).

The Intra-operative staging should be completed as it recognizes occult disseminated disease. The frozen section should be sent if there is any uncertainty of metastatic disease or lymph node involvement. When GBC diagnosed incidentally, the level of surgery is based on the depth of invasion or T-Stage of tumor (32, 34). The repetition of surgical operation for incidental diagnosed GBC has two essential objectives: Firstly, to achieve Ro resection of hepatic parenchyma and secondly, the removal of loco-regional lymph nodes. (34).

Patients having carcinoma *in situ* or tumor invading the mucosa such as Tis and T1a, simple cholecystectomy is the only therapeutic procedure (33, 34). But, if the muscle layer (pT1b) is involved in the tumor, likelihood of metastasis to the lymph-node is around 20%, while that of perineural involvement is up to 50%. pT1b tumor treated with simple cholecystectomy has manifested only with one-year survival rate of 40% to 50% (32-35).

Thus, patients with hepatic and peritoneal tumors have difference in 5-year survival rate (40% vs. 65%). Based on better survival of the patients with peritoneal tumor, the 8th edition AJCC staging system has divided the T2 into distinct category as T2a (Stage IIA) and T2b (Stage IIB). Although, in T3 tumor, the incidence of lymph node metastasis and residual disease are a respective of 45% and 35% (34-36).

T4 tumors in maximum cases are not resectable, surgery offer no such additional benefits in term of survival of patients (35 - 37).

Palliative Treatment

The importance of palliative treatment in the patients having non-resectable GBC is to provide better quality of life to the patients. Jaundice associated with pruritus, pain in right subcostal or intestinal obstruction are some of the features associated with patients with advanced stage often presents. The best palliative method is one that offers the diminution of symptoms with a least morbidity (36,37). Palliative treatment for jaundice can accomplished whichever way minimal invasive (endoscopically) percutaneous transhepatic biliary drainage and conventional surgical approach, though the endoscopic palliation for jaundice has lower rate of complications reported (36). In advance peritoneal disease where intestinal obstruction occur bypass procedure should be undertaken with care since chances of morbidity is high.

Adjuvant Treatment

Insights into the practice's statistics of adjuvant treatment for GBC are inconsistent, thus harmony concerning the best adjuvant therapy has not been yet attained. But, because of high percentage of recurrence, adjuvant therapy comes in combined form of chemotherapy plus radiotherapy (36, 37). Chemotherapy regimens using gemcitabine have revealed a better effectiveness over 5 fluorouracil (5-FU) regimens. Authors such as Sharma et al (37) advocated the combination of gemcitabine with 5FU and revealed enhanced median OS in GBC. In Japanese trial (Phase III) it is described that survival is better by adjuvant mitomycin along with 5-FU (20.3%) as compared to surgical resection alone (11.6%) (37). Combine effect of gemcitabine with oxaliplatin or cisplatin has shown beneficial effect in some of the trials (37-39).

Role Of Post Operative Chemo Radio Therapy

Radiotherapy in the form of adjuvant therapy is best advised in carcinoma gallbladder disease T2 or node positive in order to take care of micro metastasis and to improve the overall survival. In order to improve the local disease control and to decrease the distant recurrences it is better if combination of radiotherapy and chemotherapy is given in the patients where it is achievable.

Recent radiation techniques intensity modulated radiotherapy (IMRT), image guided radiotherapy have made

possible to deliver suitable dose to the target organ while at the same time it keeps the adjacent organ within bearable limits. With the help of radiological imaging and improve radiation techniques it is possible to deliver the increased radiation dose (40). Various ongoing multicentric trials may assist us in developing the understanding regarding the role of radiotherapy in adjuvant therapy of carcinoma gallbladder.

Role Of Neoadjuvant

Radical surgical resection is an established treatment for gallbladder cancer. With the aim to achieve the better survival in patients with locally advanced T3/T4 tumours and lymph node involvement, adjuvant chemotherapy and chemoradiotherapy following surgical resection is a suggested treatment approach (37,38). Advanced stage carcinoma gallbladder patients have shown better long-term survival on adjuvant therapies according to the results of many multi-institutional analysis. While the neoadjuvant chemotherapy (NACT) or chemoradiotherapy (NACRT) has been fruitful for many malignancies, it has better effect in down grade and stage of the tumour biology, better resectability rate and improve overall survival but its potential capacity in advanced stage carcinoma gallbladder is not clear yet due to the lack of evidence (39). Most of the studies conducted to evaluate the role of neoadjuvant therapy have used Gemcitabine and Cisplatin as a chemotherapeutic agent. All the important trials have shown a significant improvement in median overall survival but only for the patients who go through curative resection following neoadjuvant therapy. The potential candidates who will be benefited from the neoadjuvant therapy are the one having advanced gallbladder cancer and would go on to have subsequent R0 resection. However according to some oncologist, use of neoadjuvant chemotherapy can delay the surgical resection and support the upfront surgery for those patients with resectable, locally advanced GBC (39, 40). Among all the prognostic factors in the carcinoma gallbladder R0 surgical resection is the most important one to predict the outcome. Some of the studies have compared the outcome in term of R0 resection among the neoadjuvant versus adjuvant approach and the results were similar in both the approaches in terms of accomplishing a R0 resection. Among the advanced carcinoma gallbladder, the routine use of neoadjuvant therapy is not proven yet. The only candidates who will be benefited from neoadjuvant therapy in carcinoma gallbladder are the one who will subsequently achieve an R0 resection. The possible role of neoadjuvant therapy in advanced carcinoma gallbladder should be investigated in future.

Molecular and Immuno oncology in carcinoma gallbladder

Various molecular variations can be used as a marker for the gallbladder cancer, and Several molecular changes are detected in gallbladder cancer, but yet it is difficult to find out the ones which are the predominate one or directs the neoplastic process and to differentiate them from the other non dominated genes. NGS is now the technique of choice for genomic profile of multiple cancer markers. The most commonly mutated genes in CAGB are: TP53 (41%), CDKN2A (28%), KRAS (19%), TERT (8%), CTNNB1 (8%) and PI3K (7%). Most common signal pathway mutated is ERBB in CAGB. Massive variety of downstream pathways such as RAS-RAF-MEK-ERK1/2 or PI3k-AKT-MTOR has an excess stimulus on cell proliferations after dimerization of HER2/NEU receptor. One of the best way to evaluate the functional state of the PTEN protein is IHC expression. PTEN is a tumour suppressor gene that deactivates PI3K, and its absence leads to activation of PI3K. The uncontrolled production of PIP3 is one of the most important effectors of the PI3K/AKT pathway with mTOR stimulating protein synthesis that regulate apoptosis. The immunohistochemical expression of the PTEN protein is considered a good way to evaluate the functional state of the gene. NGS is now considered as an innovative tool for the genetic profiling of various cancers (41).

Newer Therapies

In the recent time a lot of focus has been given toward the immunotherapy and targeted therapy.

Immunotherapy

Immunotherapy is a form of therapy that promotes the immune system of an individual to identify and destroy the cancer cells that cannot be tackle by the surgery or have widely metastasized. Currently chemotherapy is the mainstay treatment for patients with advanced GBC; but this therapy is very toxic and offers patients partial survival benefit. Besides, pembrolizumab was accepted for advanced GBC patients with deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) (42). Patients with Carcinoma gallbladder has various mutations. Commonly occurring mutations that are targeted by FDA are ATM, ERBB2, PIK3CA and amplifications in ERBB2. FDA has approved pembrolizumab (immune checkpoint inhibitor) for the solid tumours with MSI-high or TMB-high, including GBC (42,43).

Targeted Therapies

Similar to the immunotherapy, target therapy is used to treat the carcinoma gallbladder that is beyond the scope of surgery and have widely spread, they precisely target certain mutations that makes the tumour cell different from the normal healthy cells (45).

Some examples of targeted therapies are:

- Ivosidenib, which targets a specific mutation in the IDH1 gene.
- Pemigatinib, which targets certain mutations in the FGFR2 gene, inhibit the proliferation of cancer cells and occasionally kill them.

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