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Original Research Article

Prevalence of Gallbladder Carcinoma According to TNM Classification

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Abstract

Introduction: Gall Bladder Carcinoma is an aggressive malignant condition that is found mainly among the elderly population. In average, the affected population is about 65 to 70 years old which is found to comprise of 2/3rd of the biliary tract carcinoma. Due to high incidence, it is needed to be properly staged and managed. TNM classification and AJCC's staging system can be used in this regard which is the most accepted one.

Aims and Objectives: The study intended to find out the number of patients in each staging and how the staging varies with other parameters of the patients like age, BMI and etiologies.

Materials and Methods: The study is retrospective design which has included patients staged according to TNM classification and their prevalence was analyzed with several parameters. Therefore, the prevalence of each staging was determined. Again, this prevalence was analyzed with several other population characteristics.

Results: The study found that the mean value of the patients in this study was 58.25 ± 9.08 years old. There were 57 females while 43 males in this study. The study found that 38% of the patients had Stage IB while 32% of the patients were in Stage 0.

Conclusion: The study found out that the most prevalent TNM stage in this sample is Stage IB. Also, lower BMI is more prevalent in severe TNM stages. It has been found that cholelithiasis is more prevalent with Stage IIB and Stage III.

Keywords: TNM, Gall bladder Carcinoma, Carcinoma, Gall bladder.

Introduction

Gall Bladder Carcinoma is an aggressive malignant condition that is found mainly among the elderly population. In average, the affected population is about 65 to 70 years old which is found to comprise of 2/3rd of the biliary tract carcinoma. This shows that gall bladder carcinoma is the most common biliary tract malignancy and 5th most common cancer in gastrointestinal origin [1]. More than 80%

of the gall bladder carcinomas are adenocarcinoma, whether it is well differentiated or moderately differentiated. The remaining percentages of Gall bladder carcinomas are adenosquamous type, squamous type or undifferentiated type. Minor percentage also pertains to neuroendocrine type, sarcoma or lymphoma [2].

In case of gall bladder carcinoma, the malignant growth occurs in fundus region of gall bladder (about 60%), body of the gall bladder (about 30%) and about 10% in the neck of the gall bladder. The pathological process of gall bladder malignancy occurs in a range of 5 to 15 years. This accounts for pathological changes like dysplasia, metaplasia, carcinoma in-situ and invasion of the tumour tissue. Histologically, gall bladder tumour comprises of several layers like mucosa, lamina propria, smooth muscle layer, perivascular tissue (connective tissue type) and serosal layer. This was studied by the direct invasion of the gall bladder tumour. Another point to be noted is that the gall bladder lacks the submucosal layer [3].

Serosa is not present in the region where gall bladder is connected to the liver which basically makes very easier for the gall bladder tumour to invade liver. Hence, direct penetration of the gall bladder tumour into liver is the most common type in this carcinoma. The direct spread of gall bladder cancer is the most common type found. There are other routes through which the carcinoma can spread. They are lymphatic spread, peritoneal spread, spreading through hematogenous route. In majority of direct spread to liver, hepatic section 4th and 5th are affected. Apart from this, bile duct, colon, duodenum, abdominal viscera are also affected by the direct spread. Metastasis to liver is the mostly resulted from direct spread and also due to the invasion into portal tract. Lymphatic spread can also affect portal tract [4].

During the surgery of the tumour, the staging is done based on several factors like invasion depth, lymph nodes invasion and involvement, spread of the tumour to the adjacent anatomical structures, whether metastasis occurred or not. This staging is in accordance with TNM staging protocol defined by American Joint Committee On Cancer (AJCC) [5]. The grouping of TNM staging is well known and its evidence is well accepted throughtout the world. Stage 0 defines the cancer tissue has spread in-situ (Tis, N0, M0). Stage 1 implies a tumour which is present inside the gall bladder and did not spread till that time (T1, N0, M0). Stage IIA implies the extension of connective tissue (perimuscular) but has not significantly spread elsewhere (T2, N0, M0). In stage IIIA, a tumour spread outside the gall bladder but nearby arteries and veins still have not affected [6]. Even no lymph node get affected in this stage or any other anatomical structure (T3, N0, M0). In stage IIIB, nearby lymph node has affected but arteries and veins still not affected by the tumour invasion or other structures are spared (T1 or T2 or T3; N1; M0). Stage IVA is characterized by the spread of tumour to nearby arteries and veins or lymph nodes. In this stage, the spread occurs upto other parts of the body (T4, N0 or N1, M0). Stage IVB implies any tumour which has spread to the other parts of the body (any T, any N, M1) or tumour which has affected the distant lymph node. This stage also includes the tumour that has not metastasized (any T grading, N2, M0). In this stage, there can be metastasis or no metastasis with distant lymph node affected [7].

The current accepted staging system (TNM staging) was devised by AJCC (7^{th} edition) which shows the prognostic characteristics of the tumour and can be utilized for planning the effective

management for an individual patient. Several factors are considered while staging which ultimately give clue to the clinicians about the status of the tumour in each patient which helps the clinician to execute the management. From the staging itself, the clinician can understand nodes involvement, depth of the tumour invasion, regions where the tumour has invaded, spread to the distant organs, etc. TNM staging is upgraded and revised continuously to maintain its efficiency and applicability. The earliest stages like Stage I and II without nodal involvement can be well managed by the surgical procedure. T1 occurs with nodal involvement and T1B are associated with nodal involvement in 10% to 20% of the patients. In T2, nodal involvement is also common in about 30% of the patients while T3 and T4 have nodal involvement in about 80% of the cases [5].

The advanced stages like T3 and T4 are defined as locally advanced condition which is not possible to simply resect. T3 staged tumour perforates serosal layer and also involve the end organs, most commonly the liver tissue while T4 involve the vascular structures and other end and distant organs. N1 staging implies the lymph node involvement which is restricted to the porta hepatis and in N2 staging, distant nodes also get involved. Any tumour with N1 classification, is staged at IIIB and N2 is staged at IVB. If distant nodes are affected, then, mostly they are aortocaval, periaortic, retropancreatic, superior mesenteric and celiac nodes situated around celiac artery. Stage III locally progress and regional nodal involvement are now a days resectable. Stage IV is considered to be unresectable T4 or IVA staging, if distant metastasis is present. Hematogenous spread occurs to liver, peritoneum, pleura and lungs as well [5,6].

Aims and Objectives

The study aimed to find out the TNM staging prevalence and their variation with other parameters in the sample like the age of the patients, Body Mass Index (BMI) and prevalence of major etiology with respect to the TNM staging.

Materials and Methods

The study was conducted between November 2019 and December 2021 which has considered 100 patients. The included patients are those who visited our outpatient department and were diagnosed with gall bladder carcinoma. The patients, who did not continue diagnostic procedure in our hospital, were not considered for our study.

The included patients were staged according to TNM classification (American Joint Committee on Cancer) and their prevalence was analyzed with several parameters. Therefore, the prevalence of each staging was determined. Again, this prevalence was analyzed with several other population characteristics.

TNM classification (AJCC) was done by following the protocol as given. T denotes status of the Primary Tumor, N denotes the status of regional lymph nodes and M denotes presence of absence of metastasis. The explanation of finding and denotion of sub-classification for TNM are given in Table 1.

Table 1: TNM explanation according to its classification

Classification	Explanation
T_x	Primary Tumor / cannot be determined accurately
T_0	No evidence of primary tumor presence
T_{is}	Carcinoma in-situ
T_1	tumor invades lamina propria layer or muscular layer. Further, Lamina propria invasion is T1a and muscular layer invasion is T1b
T_2	tumor invades perimuscular connective, not extending beyond serosa
T_3	serosal perforation caused by tumor or invasion of tumor directly to adjacent organ or can be both the conditions
T_4	tumor extension occurs into the liver which is more than 2 cm or into few adjancent organs
N_x	Regional lymph nodes cannot be assessed
N_0	absence of metastasis to regional lymph node
N_1	metastasis present in cystic duct, hilar lymph nodes or pericholedochal nodes
N_2	metastasis in peripancreatic, periduodenal, celiac, periportal or superior mesenteric lymph node
M_x	Metastasis cannot be assessed
M_0	Absence of distant metastasis
M_1	Metastasis is present with evidences

Table 2 represents the staging of Gall Bladder cancer after assessing the TNM classification.

Table 2: Staging of Gall Bladder Cancer according to TNM classification

Stage	T	N	M
Stage 0	T_{is}	N_0	M_0
Stage IA	T1	N_0	M_0
Stage IB	T2	N_0	M_0
Stage IIA	T3	N_0	M_0
Stage IIB	T1 or T2 or T3	N_1	M_0
Stage III	T4	Any N	M_0
Stage IV	Any T	Any N	M_1

Results

The study found that the mean value of the patients in this study was 58.25 ± 9.08 years old. There were 57 females while 43 males in this study. The study has found that older ages more than 60 years old is more vulnerable to severe TNM stage of gall bladder carcinoma.

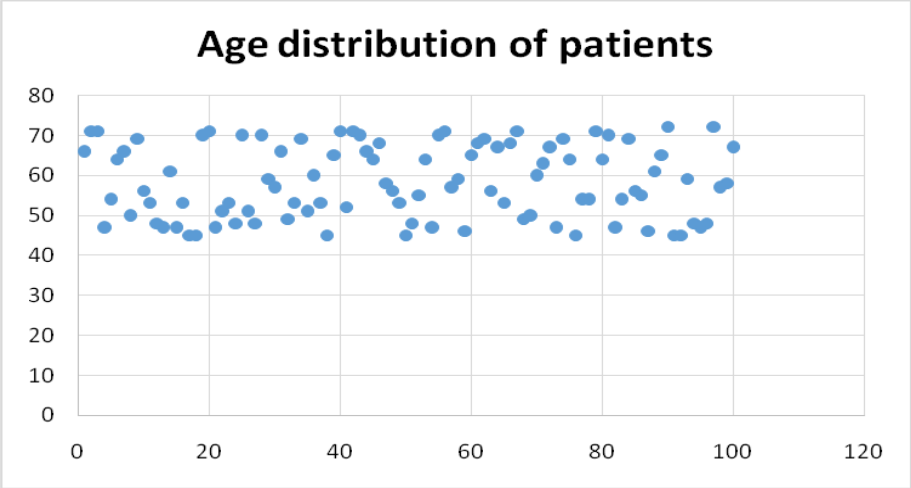

Figure 1: The age distribution of patients in

It was found that there are more females than males in the study. Figure 2 shows the percentage of males and females.

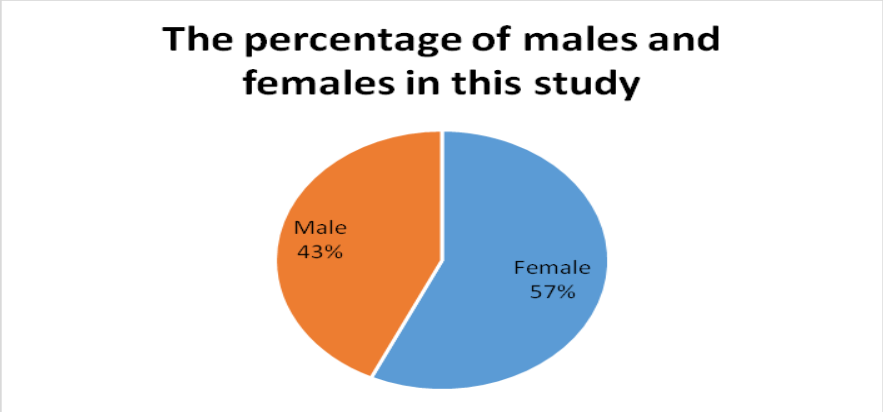

Figure 2: The percentages of males and females in this study

The study found that 38% of the patients had Stage IB while 32% of the patients were in Stage 0. The study also found that there were 26% of the patients who were classified as Stage IA. Although very less, the study showed 3% of patients had Stage IIB and only 1% of patient was in Stage III.

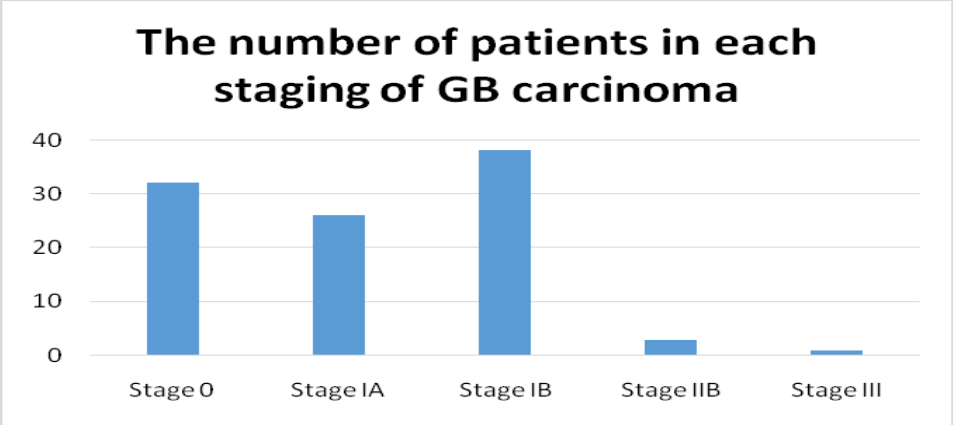

Figure 3: The number of patients found to be present in each group

The study notably found that Body Mass Index (BMI) decreases with increasing TNM stages in terms of severity. The patients with TNM stage III and stage IIB were found to have BMI < 18 which is lower than the normal. The patients with Stage 0 and Stage IA had normal BMI and some even with tendency towards overweight. Figure 4 shows the detailed variation in a graph form with respect to the TNM stagings.

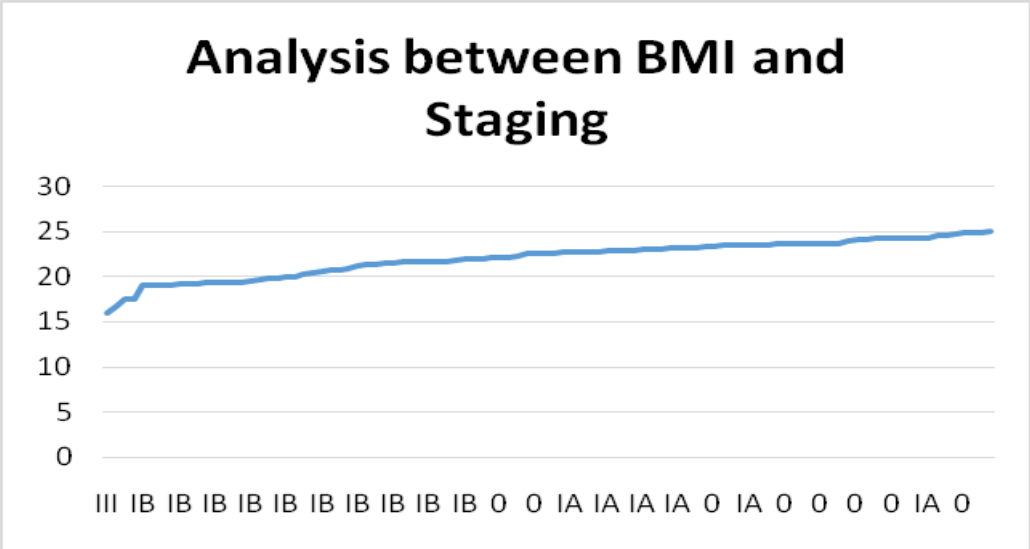

Figure 4: The variation of BMI with that of TNM staging

The study further reveals that the major etiologies of the patients were hormonal exposure, family history, cholelithiasis and there were 32 patients whose etilogies were not determined. The study revealed that severe TNM stages are more prevalent with cholelithiasis as the etiology while hormonal exposure has played bigger role in patients with Stage I. The study further reveals that no such major etiology was determined in patients with Stage 0. Table 3 gives the details of number of patient in each stage along with their major etiology.

Table 3: Staging of Gall Bladder Cancer according to TNM classification

Major Etiologies	Number of Patients	Stages Found	Number of Patients
Cholelithiasis	4	IIB	3
		III	1
Family History	20	IA	8
		IB	12
Hormonal Exposure	44	IA	18
		IB	26
Not determined	32	0	32

Discussion

Gall bladder carcinoma is one of the well known and most often malignant condition encountered with a incidence rate of about 95% of all the biliary tract tumour conditions.

There is a essential need to diagnose the carcinoma and staging as early as possible which is likely to give better prognosis if management procedure can be started early. The pathological mechanism follows through metaplasia-dysplasia-carcinomagrouping. Thorough pathological staging and radiological results are required for planning efficient management procedure for an individual patient [3,4].

Epidemiological examinations have recognized striking geographic and ethnic variations - exorbitantly high events in American Indians, raised in Southeast Asia, yet very low somewhere else in the America and the world. Age, female sex,

inherent biliary tract abnormalities, and a hereditary inclination address significant risk factors that are changeless. Natural triggers assume a critical part in malignant growth creating in the gallbladder, best exemplified by cholelithiasis and chronic inflammation from biliary tract and parasitic contaminations[8].

Death rates intently follow frequency; those nations with the most elevated commonness of gallstones experience mortality from gallbladder malignant growth. Obscure side effects regularly postpone the finding of gallbladder malignant growth, adding to its general progression and unfortunate result. surgery addresses the main potential for a fix. A few people are lucky to be unexpectedly found to have gallbladder cancer at the hour of cholecystectomy being performed for cholelithiasis. Such an early finding is basic as a late show indicates progressed staging, nodal involvement, and conceivable repeat following endeavoured resection[9].

Continuous modification and revision in TNM classification has led American Joint Committee on Cancer (AJCC) 6th edition to bring some new changes in the staging of gall bladder staging proceess. One of the remarkable change that was brought by AJCC in 7th edition is TNM classification of T2N0M0 was re-staged as stage IB from stage II. Another remarkable was T3N1M0 was restaged as IIB from III while T4NxM0 was restaged to stage III from stage IVA. In 6th edition of AJCC's TNM classification, stage III and stage IV was not a separate staging [9,10]. It was found that 5-year survival for stage IIA, IIB, III and IV according to AJCC 6th edition, were 7%, 9%, 3% and 2% respectively. The National Cancer Database or NCDB was used for developing and improving the 6th edition and helped to form the newly introduced stages [10]. The latest changes in AJCC says that the tumour of growth more than 2cm invasion into the hepatic tissue were restaged from T4 to T3. A tumour of T4 stage (as per current specification) is characterized by as an invasion of tumour cells into the portal veins, hepatic artery or several extra hepatic organs. Again, the can with T2N0M0 TNM classification, were re-located to stage IB from stage II. In another instance, T3N0M0 and T1-3N1M0 classification were both re-staged as II from their previous stage III. Lastly, tumour with TNM classification T4NxM0 was moved from stage IV to stage III [8-10].

Till date, TNM classification is universally accepted staging system and prognostic determinant which is used in clinical setup with complete acceptability due to its simple design, basic pre-requisite knowledge from the patient, information regarding its spread, inputs can be obtained from the radiological exams and clinical checkups [9,11].

However, its simplicity is its main limitation. This TNM system has the inability to adapt to the advances occurring in biology and incorporate the new prognostic variables. Many disadvantages such as lack of predictive power, lack of balance and differentiation between groups, failure to account for other tumour and host factors[12].

TNM classification was distributed the 8th version of Union for International Cancer Control or UICC where some notable changes were brought in T2 sub-class. Although the clinical acceptance is not sufficient for gall bladder cancer in 8thedition. The current edition was made to stage the patients more efficiently in prognostic point of view. Another study showed that over 300 patients were treated as per the TNM classification due to which their prognosis was much better [12,13].

The standards set by UICC used by other studies showed survival time between each stage which came to be less 0.05 as

significance level. The introduction of new changes in the TNM staging imply newer interpretation of T2A and T2B which is quite different from the previous staging system. This difference is statistically significant [14]. It has been found that the survival rate of stage IIA patients are far more than the patients with stage IIB which other studies have shown that this is statistically significant. Many studies have shown the significance between the stages and justified them with statistical analysis [15].

The newlly introduced "N" class implies the involvement of lymph node. Multivariate studies proved that TNM latest version is clinically efficient and useful to management. The guidelines of management procedures are clinically correlating and efficient in increasing the survival rate and to have better prognosis. The staging also highlighted the location of the tumour presence and whether they should surgically resected or not in a given situation [16].

Conclusion

This current study is a centre-specific study. However, this study has came up with some notable conclusions. The study found out that the most prevalent TNM stage in this sample is Stage IB followed by Stage 0. The study also concluded that there is possible linkage with BMI and TNM stage in a way that lower BMI is more prevalent in more severe TNM stages. It has been found that cholelithiasis is more prevalent with Stage IIB and Stage III while family history and hormonal exposure are more prevalent with IA and IB. In Stage 0, there is no such major etiology found. The study effectively brought different prevalence and notable findings with respect to the TNM staging. The authors suggest that there should be more studies on larger sample size to get clearer picture of prevalence. This would help in epidemiology and diagnosis of gall bladder carcinoma which would eventually bring effective managements.

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