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Original Article

EGFR Expression in Gallbladder Carcinoma in North Indian Population

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Abstract

Objective: Gallbladder carcinoma is the most frequentbiliary tract carcinoma with over all very poor prognosis. Epidermal growth factor receptor (EGFR) is known to be involved in carcinogenesis and overexpressed in various malignancies including head and neck, breast, lung and colon carcinomas. This study was done to explore the expression of EGFR in gallbladder carcinomacases in the north Indian population so that it may be used as a therapeutic target in these patients.

Materials and Methods: 59 cases of gallbladder carcinoma diagnosed by histopathological examination were included in study. Expression of EGFR was seen by immunohistochemistry method on histopathology slides.

Results: Out of 59 gallbladder carcinoma cases 46 (78%) were female and 13 (22%) were male with female to male ratio of 3.54:1. Mean age was 51.71±11.32 years. On histopathological examination 51 (86.4%) cases were conventional adenocarcinoma, 2 (3.4%) adenosquamous carcinoma, 2 (3.4%) mucinous adenocarcinoma, 2 (3.4%) papillary adenocarcinoma, 1 (1.7%) signet ring cell carcinoma and 1 (1.7%) squamous cell carcinoma histological subtypes. EGFR expression was present in 31 (52.5%) of gallbladder carcinoma cases and strong EGFR expression was significantly associated with poor differentiation of tumour.

Conclusion: In our study EGFR was positive in the majority of gallbladder carcinoma cases. There was inverse correlation between differentiation of tumor and EGFR expression. Strong EGFR expression was significantly higher in poorly differentiated tumors compared to well differentiated tumors suggesting its role in prognosis. This also suggest that EGFR might have a role in tumor progression and aggressiveness. Therefore, EGFR have potential to be used as therapeutic target in significant number of patients. More larger sample studies are required to confirm our findings. EGFR may be further studied as therapeutic target in clinical trials in the Indian population to improve morbidity and mortality of gallbladder carcinoma patients.

Key words: EGFR Expression, Gallbladder Carcinoma, Immunohistochemistry, Targeted Therapy

Introduction

Biliary tree cancer arises from the gallbladder, extrahepatic or intrahepatic biliary ducts. Gallbladder is the most frequent site of biliary tree cancer.[1, 2] Women are 3 to 5 times more frequently involved than men.[2] Gallbladder cancer has particularly higher incidence in Northern India, Pakistan, Bangladesh, Nepal, South America and East Asia.[3, 4] Risk factors for Gallbladder cancer include gallstones, obesity, female gender, female hormones, multiparity and infectious agents.[2] Overall prognosis of gallbladder carcinoma is poor with overall 5–year survival rate less than 5%.[4, 5]

Conventional adenocarcinoma is the most common histological subtype that can be well differentiated, moderately differentiated or poorly differentiated. Poor differentiation correlates with the poor prognosis. In early–stage disease surgery can be curative treatment. But most of patients are diagnosed with advanced–stage disease and have very poor prognosis.

Gemcitabine with cisplatin is the first line systemic chemotherapy regimen for advanced biliary track

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cancers.[6] Multiple molecular therapeutic targets are now being evaluated with some promising results to improve survival in patients including human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), programmed death receptor–1 (PD–1), TP53, KIT, CDKN2A/B, phosphatidylinositol 3–kinase (PI3K), RAS, BRAF.[7]

EGFR also known as ErbB1 or HER1 was first found to be associated with development of cancer in chicken. It activates many intracellular downstream signal pathways including ERK/MAPK, PI3K, JAK–STAT that mediate cancer cell proliferation, angiogenesis, adhesion and metastasis.[7, 8] Increased expression of EGFR is seen in colon cancer, head and neck cancer, non–small cell lung carcinoma and breast cancers.[9] Constitutional activation and overexpression of EGFR may be due to mutation in gene itself or upregulation via some other molecule like pleckstrin–2 (PLEK2) and PI3K that promote cancer invasion and metastasis.[8, 10] Overexpression of EGFR is also found to be associated with poor prognosis in gallbladder cancer patients.[11, 12]

Because of varied risk factors and pathogenesis of gallbladder cancer in different geographic region population, expression of EGFR is studied by authors to find out its role as therapeutic target.[9, 13, 14] Only few studies have been done to see overexpression of EGFR in Indian population.

Therefore, we conducted this study to see expression of EGFR in gallbladder cancer in North Indian population and find its role as possible therapeutic target in patients.

Materials and methods:

This was an observational study conducted in the Department of Pathology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. A total of 59 cases of gallbladder carcinoma diagnosed by histopathological examination were included in study. Study was approved by the Institute ethical committee. Patient data was collected from the hospital records.

Gallbladder specimens were fixed in 10% formalin and tissues were processed as per standard procedure. 4µm sections were prepared and stained with hematoxylin and eosin stain for histopathological examination. By histopathological examination diagnosis of gallbladder carcinoma was confirmed. Tumor with 95% or more gland formation, 40 to 95% gland formation and less than 40% gland formation were graded as well differentiated, moderately differentiated and poorly differentiated adenocarcinoma respectively as per WHO criteria. There was no case of undifferentiated carcinoma (gland formation less than 5%).

Sections containing tumor areas were selected for performing immunohistochemistry. EGFR (clone EP38Y) immunohistochemistry kit of BioGenex were used. Sections of 3µ were placed on 1% poly–l–lysin coated slides and fixed at 60ºC for 1 hour. Dewaxing was done with xylene for 20 minutes and gradual rehydration was done by graded concentration of alcohol. Staining was done as per kit protocol. Antigen retrieval was performed in citrate buffer (pH 6.0) in 2 cycles at 95ºC for 10 minutes and 97 ºC for 10 minutes. Tissue peroxidase activity was blocked with 3% hydrogen peroxide in methanol for 20 minutes. Counterstaining of nucleus was done with Harris's hematoxylin for 10 to 20 seconds. Mounting was done with DPX and sections were viewed in upright light microscope. Head and neck squamous cell carcinoma were used as positive control in each immunohistochemistry run.

Cases in which there was staining in less than 10% of cancerous cells were scored as 0. A faint/ barely perceptible membrane staining in more than or equal to 10% of cancerous cells in which only part of the membrane stained was scored as 1+. A weak to moderate complete membrane staining in more than 10% of the cancerous cells was scored as 2+. A strong complete membrane staining in more than 10% of the cancerous cells was scored as 3+. Each staining was interpreted as negative (0 and 1+) and positive (2+ and 3+) for protein overexpression. TNM staging of tumor was done as per AJCC 8th edition criteria.

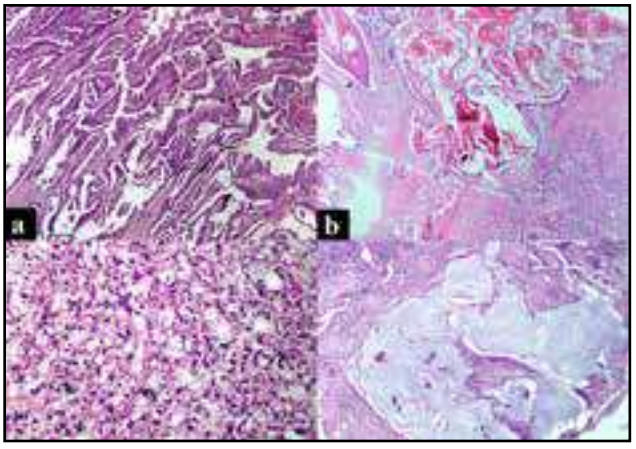

Figure1. Histological subtypes (a)Papillary adenocarcinoma, (b)Adenosquamous carcinoma, (c) Signet ring cell carcinoma, (d) Mucinous adenocarcinoma

Figure2. (a) Well differentiated adenocarcinoma, (b) Moderately differentiated adenocarcinoma, (c) poorly differentiated adenocarcinoma

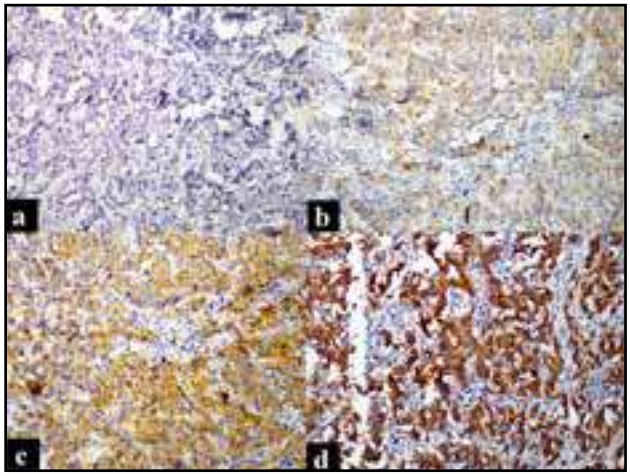

Figure 3. Immunohistochemistry for EGFR (a) No staining, (b) 1+ staining, (c) 2+staining, (d) 3+ staining

Results

Total 59 cases of gallbladder carcinoma were included in the study out of which 46 (78%) were females and 13 (22%) were male patients with female to male ratio of 3.54:1. Patients age was ranging from 34 years to 72 years with mean age of 51.71±11.32 years. 32 patients were 50 years or less of age and 27 patients were above the age of 50 years. Body mass index (BMI) was ranging from 15.14 to 27.34 kg/m^2 with mean of 21.82±3.18 kg/m^2 . Only 9 (15.2%) patients had BMI of 25 or more while rest of 50 (84.8%) patients had BMI less than 25. Most common presenting symptom in our study was pain in right upper quadrant in 52 (88.1%) patients followed by dyspepsia and vomiting in 16 (27.1%) patients each, belching and jaundice present in 10 (16.9%) patients each, lump in right upper quadrant present in 6 (10.2%) patients and additional symptoms like fever, weight loss and loss of appetite found in 49 (83.1 %) patients. (Table 1) 36 patients (61.01%) had gall stones while 23 patients (38.98%) didn't have gall stones. Out of 46 females 31 (64.4%) females were postmenopausal and 17 (35.4%) females were premenopausal. Among 59 gallbladder carcinoma cases 51 (86.4%) were conventional adenocarcinoma, 2 (3.4%) adenosquamous carcinoma, 2 (3.4%) mucinous

Presenting Symptoms	Number of Carcinoma Gallbladder patients (n=59)
Pain	52(88.1%)
Dyspepsia	16 (27.1%)
Vomiting	16(27.1%)
Belching	10(16.9%)
Jaundice	10(16.9%)
Lump	6(10.2%)
Malena	1(1.7%)
Others (Fever, weight loss, appetite loss)	49(83.1%)

Table 1. Frequency of presenting symptom in gallbladder carcinoma patients

Histological subtype	Carcinoma Gallbladder (n=59)
Conventional Adenocarcinoma	51(86.4%)
Adenosquamous carcinoma	2(3.4%)
Mucinous adenocarcinoma	2(3.4%)
Papillary adenocarcinoma	2(3.4%)
Signet ring cell carcinoma	1(1.7%)
Squamous cell carcinoma	1(1.7%)

Table 2. Frequency of histological subtypes in our study

Stage	Number of patients (n=59)
I	1(1.7%)
II	2(3.4%)
IIIA	2(3.4%)
IIIB	45(76.3%)
IVA	6(10.2%)
IVB	3(5.1%)

Table 3. Frequency of TNM stage at presentation

Tumor Differentiation	EGFR Expression		P value
	Positive (2+, 3+expression)	Negative (0,1+ expression)	
Well Differentiated	1(1.7%)	5 (21.7%)	0.38
Moderately Differentiated	2(3.4%)	5 (21.7%)	
Poorly Differentiated	2(3.4%)	13 (56.5%)	
Total	**45(76.3%)**	**23 (100%)**	

Table 4. Correlation between EGFR expression and differentiation of tumour

Tumor Differentiation	EGFR Expression				Total
	Negative		Positive		
	No staining	Weak (1+)	Moderate (2+)	Strong (3+)	
Well Differentiated	4 (20%)	1 (33.33%)	7 (58.3%)	4 (25%)	16 (31.4%)
Moderately Differentiated	4 (20%)	1 (33.33%)	2 (16.7%)	2 (12.5%)	9 (17.6%)
Poorly Differentiated	12 (60%)	1 (33.33%)	3 (25%)	10 (62.5%)	26 (51%)
Total	**20 (100%)**	**3 (100%)**	**12 (100%)**	**16 (100%)**	**51 (100%)**

Table 5. EGFR expression in conventional adenocarcinoma

Tumor Differentiation	EGFR Expression		P value
	Moderate (2+)	Strong (3+)	
Well Differentiated	7 (70%)	4 (28.6%)	0.045
Poorly Differentiated	3 (30%)	10 (71%)	
Total	**10 (100%)**	**14 (100%)**	

Table 6. Correlation between tumor differentiation and EGFR expression among EGFR positive cases

		EGFR Expression		Total	P Value
		Positive (2+, 3+)			
Age	50 years or less	16 (50%)	16 (50%)	32 (100%)	0.67
	More than 50 years	15 (55.6%)	12 (44.4%)	27 (100%)	
Gender	Female	26 (56.5%)	20 (43.5%)	46 (100%)	0.25
	Male	5 (38.5%)	8 (61.5%)	13 (100%)	
Body Mass Index (BMI) (kg/m^2)	Less than 25	24 (48%)	26 (52%)	50 (100%)	0.10
	25 or more	7 (77.8%)	2 (22.2%)	9 (100%)	
Menopausal Status	Premeno pausal	8 (53.3%)	7 (46.7%)	15 (100%)	0.76
	Postmeno pausal	18 (58.1%)	13 (41.9%)	31 (100%)	
Gall Stones	Present	19 (52.8%)	17 (47.2%)	36 (100%)	0.96
	Absent	12 (52.2%)	11 (47.8%)	23 (100%)	
Lymph Nodes Status	Positive	27 (50%)	27 (50%)	54 (100%)	0.19
	Negative	4 (80%)	1 (20%)	5 (100%)	
Stage	Early stage (T1, T2)	2 (66.7%)	1 (33.3%)	3 (100%)	0.61
	Advanced Stage (T3, T4)	29 (51.8%)	27 (48.2%)	56 (100%)	

Table 7. Correlation between EGFR expression and various patient parameters

Studies	Region	Year	EGFR expression in gallbladder carcinoma	Number of cases
Lee et al. [17]	Australia	1995	100%	13
Zhou et al. [18]	China	2003	70.7%	41
Kaufmann et al. [9]	North America	2008	93.57%	16
Shafizadeh et al. [19]	North America	2010	83%	6
Pais–Costa et al. [11]	Brazil	2014	51.2%	39
Hadi et al. [20]	India	2016	77.78%	18
Kumar et al. [13]	India	2016	88%	50
Neyaz et al. [14]	India	2018	61.2%	214
Das et al. [15]	India	2021	93.33%	30
Present study	**India**	**2021**	**52.5%**	**59**

Table 8. Frequency of EGFR expression in gallbladder carcinoma reported in other studies

adenocarcinoma, 2 (3.4%) papillary adenocarcinoma, 1 (1.7%) signet ring cell carcinoma and 1 (1.7%) squamous cell carcinoma histological subtypes. (Table 2, Figure 1) Out of these 51 conventional adenocarcinoma cases 16 (31.4%) were well differentiated; 9 (17.6%) were moderately differentiated and 26 (51%) were poorly differentiated adenocarcinoma. (Figure 2) As per AJCC 8th edition TNM staging criteria 76.3% patients were stage IIIB at diagnosis. (Table 3) Regional lymph node metastasis was present in 54 (91.5%) cases. Distant metastasis was present in 3 (5.09%) cases. In our 59 cases positive EGFR expression was present in 31 (52.5%) cases, out of which 28 (90.3%) were conventional adenocarcinoma, 1 (3.2%) was adenosquamous carcinoma and 1 (3.2%) was papillary adenocarcinoma. Mucinous adenocarcinoma, signet ring cell carcinoma and squamous cell carcinoma were negative for EGFR expression. In 28 EGFR positive (2+, 3+ expression) conventional adenocarcinoma cases, 11 (39.3%) were well differentiated, 4 (14.3%) were moderately differentiated and 13 (46.4%) were poorly differentiated adenocarcinoma. (Table 4, Figure 3) But there was no statistically significant association between positivity of EGFR and grade of tumor. Majority of strong EGFR positive (3+) conventional adenocarcinoma were poorly differentiated (62.5%), while majority of moderate positive (2+) adenocarcinoma were well differentiated (58.3%). (Table 5) Weak staining (1+) was seen in one each case of well, moderate and poorly differentiated adenocarcinoma. In 20 cases tumor cells did not pick up any staining for EGFR. Among conventional adenocarcinoma positive EGFR cases (moderate and strong positive) strong EGFR positivity was significantly higher in poorly differentiated adenocarcinoma as compared to well differentiated adenocarcinoma (p value= 0.045). (Table 6) We did not find any significant association between EGFR positivity and age, gender, body mass index, gall stones, lymph node status, stage and menopausal status. (Table 7)

Discussion

Gallbladder carcinoma is a type of biliary tract cancer arise from the gallbladder mucosa epithelia. It is the most frequent malignancy of the biliary tract and 6th most common malignancy arising from gastrointestinal tract.[16] Overall prognosis of gallbladder carcinoma is poor and patient usually present in advanced stage disease.[4–6] Surgery is the only curative treatment option but only in early stages. Therefore, apart from standard chemotherapeutic agents, new molecules for targeted therapy are being explored to reduce the morbidity and mortality in patients with advanced disease.[7]

One of the candidate for targeted therapy is EGFR that acts as receptor for downstream signal transduction of

cancer pathways and is found to be overexpressed in some head and neck, breast, colon and non–small cell lung cancers.[7–9] Therefore, in this study we explored the expression of EGFR in gallbladder cancer and its association with various clinical and pathological parameters.

Total 59 cases of gallbladder carcinoma diagnosed by histopathological examination were included in the study. In our study mean age of patients was 51.71 ± 11.32 years which was lower than reported in western countries where peak incidence is in 6th and 7th decade of life. Similar mean age of 49.5 years, 52.33 years and 57.66 years were also reported by other Indian studies.[13–15] This difference in age distribution may be due to lower life expectancy of females in India compared to western countries.

In our study females were 3.5 times more than males suggesting higher incidence of gallbladder carcinoma in females than males and possibly some role of female hormones in pathogenesis. Obesity is a known risk factor for gallbladder carcinoma. In our study none of the patients were obese (BMI >30 kg/m2). Only 9 (15.2%) patients had BMI between 25 kg/m2 and 30 kg/m2, while rest of 50 patients had BMI less than 25 kg/m2.

Most of the patients at diagnosis were at advanced stage of disease and stage IIIB being most common (76.3%). This may be due to fact that gallbladder is small intra–abdominal organ and symptoms appear late in course of disease. Therefore, majority of patients require additional treatment modality apart from surgery to improve prognosis.

In our study EGFR was positive in 31 (52.5%) out of 59 gallbladder carcinoma cases. EGFR positivity is reported in gallbladder carcinoma between 51% to 100% in various studies.[9, 11, 13–15, 17–20] (Table 8). As EGFR positivity is seen in majority of carcinoma gallbladder cases, the role of drugs that target EGFR can be explored to improve patient morbidity and mortality. Cetuximab and panitumumab are humanized monoclonal antibodies against extracellular domain of EGFR that prevent its activation. Gefitinib, erlotinib and afatinib are tyrosine kinase inhibitors that blocks downstream pathways.[7] There are clinical therapeutic trials to check effectiveness of these drugs in biliary tract cancer patients with inconsistent results.[21–24]

In our study strong EGFR positivity was significantly higher in poorly differentiated tumor compared to well differentiated tumors also suggesting EGFR to be poor prognostic factor.[11] There are other studies which also reports inverse correlation between EGFR positivity and tumor differentiation.[9, 13] This may also imply some role of EGFR in loss of differentiation in EGFR positive tumors. Role of EGFR in loss of cohesion, epithelial mesenchymal transition (EMT) and cancer progression is known that may leads to poor differentiation of a tumor.[25, 26] Our findings also indicate the same.

In our study we did not find any significant association between EGFR positivity and age, gender, body mass index, menopausal statues, gall stones, lymph node status and stage of tumor.

Based on significant expression of EGFR found in other studies and this study we can suggest for therapeutic trial of anti EGFR therapy in gallbladder carcinoma patients in Indian population to be carried out to find its role in improving patient outcome.

Our study is limited by the fact that it is performed in small number of cases from single center. More studies with large number of samples are required to confirm our findings. We only included the gallbladder carcinoma cases in which cholecystectomy was performed, therefore our study misses the cases which were unresectable and probably are of higher grade. Molecular testing was not available to confirm the finding of immunohistochemistry.

Conclusion

As gallbladder carcinoma is tumor with very poor prognosis and present in late stages, there is search for new modalities of treatment like targeted therapy to improve patient survival. Our study shows EGFR to be potential candidate for targeted therapy. In our study EGFR was positive in majority of gallbladder carcinoma cases. There was inverse correlation between differentiation of tumor and EGFR expression. Strong EGFR expression was significantly higher in poorly differentiated tumors compared to well differentiated tumors suggesting its role in prognosis. This also suggest that EGFR might have role in tumor progression and aggressiveness. Therefore, EGFR have potential to be used as therapeutic target in significant number of patients. More larger sample studies are required to confirm our findings. EGFR may be further studied as therapeutic target in clinical trials in Indian population to improve morbidity and mortality of gallbladder carcinoma patients.

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Funding and Conflict of Interest

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There is no conflict of interest.

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