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RESEARCH ARTICLE

ROLE OF MUC1, MUC2, MUC4 AND CYCLIN D1 IN THE EVALUATION AND PROGNOSTICATION OF BILIARY TRACT MALIGNANCY AND ANALYSIS

Gupta Lav and Ratnagar Akhilesh

1. Department Of Surgery, BMC sagar, India.

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Abstract

Introduction: Biliary tract malignancies (BTM) represent a significant global health challenge, ranking as the third leading cause of cancer-associated mortality. Despite their clinical impact, prognosis remains poor, necessitating the discovery of robust molecular markers to guide risk stratification and precision oncology.

Objectives:1.to study the distribution of molecular markers among cases and control for predictive value,sensitivity and specificity.2.to study the role of molecular markers in outcome of BTM.

Material and methods: Retrospective observational study done in radiologically suspected 70 patients in department of surgery between 2013 to 2015.Specimen sent for IHC & HPE and the result of molecular markers are compared among cases and control..Conclusion and

Result: In our study,Muc-1 expression is more specific whereas cyclin D1 expression is more sensitive indicator in differentiating between benign and malignant biliary tract carcinomas, Expression of Muc1 and Muc 4 significantly($p<0.05$) correlates with high grade of malignancy whereas Muc2 and Cyclin D1 is associated with low grade malignancy but statistically insignificant.($p>0.05$) .Among these molecular markers expression of Muc-2 significantly affect outcome and its expression is associated with better outcome in patients with Biliary tract malignancy

Introduction:-

Biliary tract cancers (BTC) represent a clinically and pathologically heterogeneous spectrum of malignancies, encompassing gallbladder cancer, intrahepatic and extrahepatic cholangiocarcinoma, and occasionally, ampullary carcinoma. Although relatively rare—accounting for less than 1% of all human malignancies—these tumors pose a formidable therapeutic challenge. Their frequent presentation at advanced, non-resectable stages results in a poor prognosis and limited intervention options. Consequently, contemporary research has pivoted toward the identification of robust molecular biomarkers. Integrating such markers into diagnostic protocols and therapeutic frameworks is essential for improving early detection and clinical outcomes in high-risk populations. This review delineates the molecular landscape of biliary neoplasms, focusing on the diagnostic and prognostic significance of key markers, including Mucin 1 (MUC1), Mucin 2 (MUC2), Mucin 4 (MUC4), and Cyclin D1.

Corresponding Author:- Gupta Lav
Address:-Department Of Surgery, BMC sagar, India.

Aims and Objectives:-

1.To study the distribution of molecular markers among cases and control for predictive value,sensitivity and specificity.

2.To study the role of molecular markers in outcome of BTM{prognosis of BTM}

Materials and Method:-

A Retrospective observational study was conducted in Department Of Surgery, NORTHERN RAIlways Central Hospital, New Delhi, from August 2013 to May 2015.In our study we have taken 70 patients who fulfilled the inclusion and exclusion criteria, in all these patients, thorough history was taken and detailed clinical examination was performed, alone with relevant investigations, After preliminary investigation, pre anesthetic checkup, patients were taken up for surgery (whose investigation suggestive of malignancy and are operable) and specimen sent for histopathology and for molecular markers study. Patients whose biopsy are positive for malignancy were taken under case group and those whom investigation were suggestive of malignancies but histopathology negative for malignancy are categorized under control group. Follow up: All cases were followed up at regular interval of 3 months for first year and 6 monthly there after. At each visit a thorough clinical examination was done to look for features suggestive of metastasis and relevant radiological investigation(USG Abdomen, CECT whole Abdomen) done accordingly whereas controls were followed at 6 monthly interval for first year then annually thereafter.

Patient Selection-

Inclusion criteria:

1.Patients whose radiological investigations are suspicious of biliary tract malignancies.

Exclusion criteria:

2.Patient with multiple malignancies.

3.Patients in whom biopsy is not feasible. Observations

Table- 1: Distribution of Age Groups (years)

AGE (YEARS)	NO. OF PATIENTS	PERCENTAGE %
30 – 40	2	2.86%
40 – 50	18	25.71%
50 – 60	36	51.43%
60 – 70	14	20.00%
TOTAL	70	100%

Table-2: Sex variation

SEX	N	%
Male	24	34.29%
Female	46	65.71%
TOTAL	70	100%

Out of 70 patients, maximum no. of patients are female with 65.71 % having an approximate ratioof male:female of 1:2.

Table -3: Histological Vs radiological Diagnosis

Histopathology	N	%
Positive	30	42.86%
Negative	40	57.14%
TOTAL	70	100%

Since all patients were suspicious of malignancy on radiological background but true positive (biopsy proven malignant) were only 42.86%.

Table 4: Grade of Malignancy Among Histologially Positive Patients:

HPE GRADE	N	%
High	18	60.00%
Low	12	40.00%
TOTAL	30	100%

Table 5: Distribution of molecular markers among cases and controls with their sensitivity, specificity and predictive values:

Histopathology →	Positive		Negative		p-value	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
	n	%	n	%						
Mucin 1	16	53.33%	10	25.00%	0.043	53.33%	75.00%	61.54 %	68.18 %	65.71%
Mucin 2	6	20.00%	4	10.00%	0.201	20.00%	90.00%	60.00 %	60.00 %	60.00%
Mucin 4	16	53.33%	12	30.00%	0.082	53.33%	70.00%	57.14 %	66.67 %	62.86%
Cyclin D1	22	73.33%	12	30.00%	0.006	73.33%	70.00%	64.71 %	77.78 %	71.43%

Table-6:Distribution of molecular markers in relation to grade of malignancy:

HPE Grade →	High		Low		p-value
	n	%	n	%	
Mucin 1	12	66.67%	6	50.00%	0.259
Mucin 2	2	11.11%	4	33.33%	0.146

Mucin 4	6	100.00%	12	33.33%	0.005
Cyclin D1	12	66.67%	12	100.00%	0.057

Table-7: Outcome of patients Vs molecular markers:

Outcome →	Expired		Alive		p-value
	n	%	n	%	
Mucin 1	6	37.50%	20	37.04%	0.491
Mucin 2	4	11.11%	6	25.00%	0.162
Mucin 4	6	40.74%	22	37.54%	0.435
Cyclin D1	8	50.00%	26	48.15%	0.463

Discussion:-

This review aims to introduce the main features of the some important molecular markers of biliary tract tumors. My study include 70 patients who were suspicious of biliary tract malignancy, there is uneven age and gender distribution with maximum number of patients (36 of 70) between 50-60 years age group and female (n=46,65.71%) to male (n=24,34.29%) ratio of 2:1. Among these 70 patient biopsy was positive for malignancy in 30 (42.86%), these were designated as cases and those found negative were designated as controls 40/70(57.14%). Among cases all 30/30(100%) were adenocarcinoma and as per tumour differentiation categorize as high grade18/30(60%) and low grade12/30(40%) (Well differentiated). In our study when distribution of molecular markers was observed as per benign (controls) and malignant carcinoma (cases) it was found to have significant difference (P-value <0.05) for Muc-1 and Cyclin D1. Among these markers Muc-1 expression are more specific whereas cyclin D1 expression is more sensitive indicator in differentiating between benign and malignant carcinomas. Expression of Muc-2, Muc-4 was also higher in malignant cases than benign conditions mimicking carcinoma on radiological background but was statistically insignificant(P-value>0.05). In present study when distribution of molecular markers among cases (BTC) was observed it was found to be statistically significant (P-value <0.05) for Muc-1, Cyclin D1 thereby signifying their role in pathogenisis of BTC.

Expression of molecular markers among biliary tract malignancy (cases) in present study and their comparison with different studies:

Markers	My study(cases)	Hyeon Kook Lee et al[2]	ShugoTamada et al[5]
Muc-1	53.33% p-value 0.043	81.0%	87.00%
Muc-2	20.00% p-value 0.201	18.0%	Not included in their study.
Muc-4	53.33%p-value 0.082	55.6%	51.00%

Marker	My study	Hong-Bing Ma et al[6]	Ai-Min Hui et al[7]
CyclinD1	73.33%p-value 0.006	68.3%p-value< 0.05	41%

Expression of molecular markers as per grade of malignancy among different studies and present study:

Markers	My Study (Histopathological Grade)			Others Study (Histopathological Grade)			
	High grade	Low grade	p-value	Hyeon Kook Lee et al[2]	High grade	Low grade	p-value
Muc-1	66.67%	50%	0.259		84%	76%,	0.517
Muc-2	11.11%	33.33%	0.146		34%,	20%,	0.222
Muc-4	33.33%	100%	0.005		63%	44%	0.134
Cyclin D1	66.67%	100%	0.057	Ai-Min Hui et al[7]	44%	50%	>0.05

In our study when expression of molecular markers was observed as per grade of malignancy,expression of Muc-4 significantly (p-value <0.05) correlates with high grade of malignancy.Expression of Muc1 is also more frequent in high grade malignancy, whereas expression of Muc-2, Cyclin D1 is usually associated with low grade malignancy but is statistically insignificant.

❖**Comparison of Prognostic significance of molecular marker among different studies and my study:**

M	My study			Others Study			
	Survival	Prognostic significance	p-value		Affect on survival	Prognostic significance	p-value
Muc-1	Decrease	Poor prognosis	0.434	Hyeon Kook Lee et al[2]	Decrease	Poor	>0.05
Muc-2	Better	Good Prognosis	0.042		Better	Good	>0.05
Muc-4	Decrease	Poor	0.		Decrease	Poor	0.048
Cycli	Decrease	Poor prognosis	0.844	Ai-Min Hui et	Decrease	Poor prognosis	<0.05

n D 1				al[7]			

Also in present study Muc-2 expression is significantly associated with better survival then those without Muc-2 expression (P-value <0.042) and other molecular markers (Muc-1, Muc-4,Cyclin D1) is associated with poor survival rates but these are not statistically significant (P-value >0.05). These finding indicates that expression of these markers are associated with poor prognosis though statistically insignificant, Hyeon Kook Lee et al (2012)[2] concluded that patients with MUC4 expression had significantly worse survival than those without MUC4 expression (P = 0.048), in a study on cyclin D1significance in BTC[155] Ai-Min Hui et al concluded that cyclin D1 over expression was significantly related to decreased overall survival (P < 0.05) in patients with GBC[7].

Conclusion:-

Cholangiocarcinoma is commonly considered a rare cancer. However, if we consider the hepato-biliary system a single entity, cancers of the gallbladder, intra-hepatic and extra-hepatic biliary tree altogether represent approximately 30% of the total with incidence rates close to that of hepatocellular carcinoma, which is the third most common cause of cancer-related death worldwide.The treatment is still quite unsuccessful and bile duct malignancies have overall poor prognosis. When untreated, bile duct malignancies lead to death usually within a few months [3][4].Biomarkers for screening programs and for follow-up of categories at risk are under investigation, however, currently none of the proposed markers has reached clinical application. For all these considerations, cancers of the biliary tree system should merit much more scientific attention also because a progressive increasein incidence and mortality for these cancers has been reported worldwideMuc-1 expression are more specific whereas cyclin D1 expression is more sensitive indicator in differentiating between benign and malignant biliary tract carcinomas in our study. The expression of Muc-4 significantly correlates with grade of malignancy and is more frequent in high grade malignancy in our study.Among these molecular markers expression of Muc-2 significantly affect outcome and its expression is associated with better outcome in patients with Biliary tract malignancy in our study. Given the smaller number of patients with BTC as compared with other common solid tumors, coordination of trials among institutions and cooperative groups, both nationally and internationally, and optimizing trial design, will be the key to future progress.

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