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Comparison of Serum Biomarkers Cifra 21-1 and ca 19-9 in Biliary Tract Cancers

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ABSTRACT

Background: Biliary malignancy is common in Asia and has high fatality. CA 19-9 has been used in diagnosis of biliary malignancy but can be raised in benign obstructive jaundice as well. CYFRA 21-1 can have an important role in patients with biliary tract cancer. The objective of this study is to compare accuracy of biomarkers CYFRA 21-1 with CA 19-9 for diagnosis of biliary tract cancers and to correlate level of biomarkers with the stage of disease.

Methods: Patients with histopathological diagnosis of biliary tract cancers managed at Tribhuvan University Teaching Hospital, Kathmandu, Nepal were enrolled in the study. Measurement of serum CK 19 fragments was performed and compared with CA 19-9. Demographic characteristics, physiological variables and laboratory values were analyzed.

Results: Of the 61 patients included the mean age was 53.41±12.5 years. Amongst the biliary malignancies, carcinoma of the gallbladder was commonest. Most patients (64%) were in the middle age group (40 to 60 years) and presented in advanced stage (Stage III and IV). CYFRA 21-1 had sensitivity of 80.3% and CA 19-9 of 68.9 % for the detection of Biliary Tract Cancers. Comparing the means of CYFRA 21-1 and CA 19-9 for stage of the disease, progressive rise of CYFRA 21-1 with the rise in stage of the disease was observed ($p< 0.03$).

Conclusions: CYFRA is a more reliable test than CA 19-9 in all stages of biliary malignancy and can assist in distinguishing early and advanced malignancy. In carcinoma of gallbladder, highest CYFRA 21-1 values were observed.

Keywords: Biliary tract cancers; CA 19-9; cholangiocarcinoma; CYFRA 21-1

INTRODUCTION

The detection of biliary tract cancers in the early stage is difficult as the clinical and laboratory findings are nonspecific and minimal. Obtaining tissue diagnosis for biliary tract cancers may not be feasible due to their difficult location, smaller size and desmoplastic characteristics.[1] Though aggressive surgery aimed at curative resection offers the best survival, most of the patients present with advanced disease.[2-4]

Circulating CK fragmments (CYFRA 21-1) has been used as a biomarker.[5,6] It was first reported in intrahepatic cholangiocarcinoma in 1998.[7] A study done in Japan in 2008 has shown CYFRA 21-1 to have sensitivity of 75% and specificity of 92% and low CYFRA 21-1 (<2.7 ng/ml) has been shown to be a strong predictor of disease free survival after surgery.[8] Elevated CA 19-9 has been found to have widely variable sensitivity of 50 - 90 % and specificity of 54 - 98%.[9-14] CYFRA 21-1 is a serum marker and can be assessed by ELISA hence the sample can be obtained easily and it is economical.

In a developing country like Nepal with limited resources CIFRA 21-1 can have an important role to detect Cholangiocarcinoma. The objective of this study is to compare CYFRA 21-1 and CA 19-9 in patients with biliary tract cancers and to correlate the level of biomarkers with the stage of the disease.

METHODS

This is a prospective observational study conducted at the Surgical Gastroenterology Units of Department of Surgery and Biochemistry Department of Tribhuvan University Teaching Hospital, Kathmandu, Nepal, over a period of 2 years (13 April, 2012 to 14 April, 2014). Ethical approval was obtained from the Institutional Review Board of Institute of Medicine. Informed consent was taken from all the patients before enrolling them into the study. Sample size calculated was 61, with a difference of 10% and a dropout rate of 10% ($\alpha< 0.05$). All patients diagnosed with biliary tract cancers were included in the study. Patients not giving consent to the study, tissue diagnosis inconclusive, those with renal failure, lung cancer and COPD were excluded from the

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study.

Following written informed consent, Patients diagnosed with biliary tract cancers were included in the study. Blood samples were taken from all the patients (10ml each) and stored at - 8^0 C for testing for CYFRA 21-1 and CA 19-9. Routine biochemical and Hematological tests were sent. Radiological examination was done by Ultrasonography, MRCP and MDCT. Diagnosis was confirmed by fine needle aspiration cytology (FNAC) or histopathology whenever applicable.

Measurement of serum or plasma CK 19 fragments will be performed using the CYFRA 21-1 EIA KIT provided by the Fujirebio Diagnostics AB, 201 Great Valley Parkway, Malvern, PA, US.

Staging criteria for biliary tract cancers will be based on the clinical staging system of the American Joint Committee on Cancer (AJCC) TNM classification 2010.[15]

CA 19-9, MRCP or MDCT and the other tests are routine tests done in all patients with suspected biliary tract cancers. CYFRA 21-1 was measured using the commercially available enzyme-linked immunosorbent assay (Fujirebio Diagnostics AB, Göthenburg, Sweden) which was provided free of cost by the manufacturers. Each Kit has 90 wells with about 80 tests available in each kit.

RESULTS

Of the 61 patients with biliary malignancy, there were 34 females (56%). The commonest presenting symptoms were Jaundice (80%), pruritus (67%), weight loss (59%), pain abdomen (57%). About 12% of patients presented with an abdominal lump. Use of tobacco was observed in 48% of them whereas 6% were regular consumer of alcohol. Most of the patients had icterus observed during clinical examination (94%), five patients had peripheral lymphadenopathy and 15% had ascites. Carcinoma of the gall bladder was the commonest malignancy followed by hilar cholangiocarcinoma (Figure 1). Most of the patients were in the middle age group (40 to 60 years). Except for a male patient with Intrahepatic cholangiocarcinoma and ampullary carcinoma, biliary malignancies were more common in females (Figure 2).

Most of the malignancies were in advanced stage (Stage III and IV) (Figure 3). Using the standard cut-off value for CA 19-9 of 37 U/ml, the upper limit of normal used in our institute and ≥ 3.0 ng/ml for CYFRA 21-1 (as proposed by Michael H Chapman), cross tabulation between these variables shows CYFRA 21-1 to have sensitivity of 80.3% and CA 19-9 of 68.9 %.

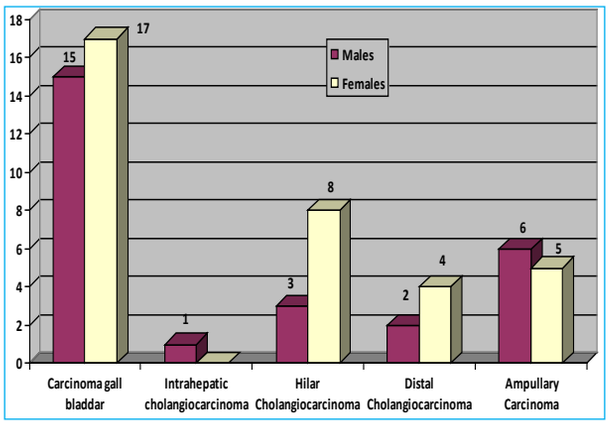

Figure 1. Distribution of various cases of biliary malignancy.

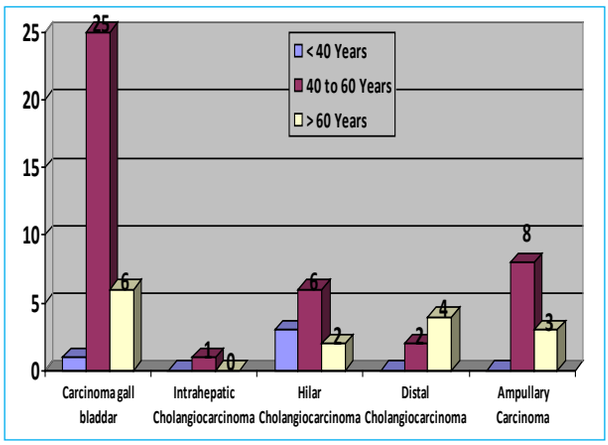

Figure 2. Age distribution of patients with biliary malignancy.

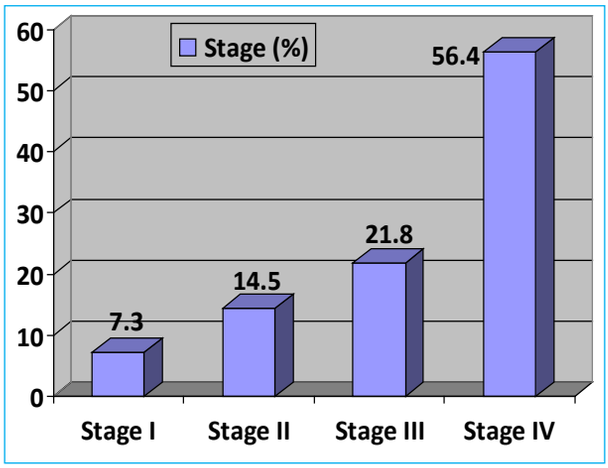

Figure 3. Stage of patients with biliary malignancy.

While comparing the median values of CYFRA 21-1 and CA 19-9 across the cancer stages according to AJCC 7th Edition, there was rise of both of them across Stage III

and IV. (Table 1) Box plot analysis of patients with Stage I, II disease revealed significantly lower median values of CA 19-9 (median: 28.5 ng/ml, standard deviation 379.5 ng/ml, range 0.45 – 1000) than for stage III, IV (median: 217 ng/ml, standard deviation 420 ng/ml, range 0.83-1000). Similarly for CYFRA 21-1 the median for Stage I, II disease was 2.87 ng/ml (standard deviation 5.16 ng/ml, range 20.0 to 1.95) whereas for Stage III and IV, the median was 6.1 ng/ml (standard deviation 31.69, range 104.1 – 1.6). The variance for CA 19-9 was 177114.9 ng/ml which was much higher than that for CYFRA (870.2) hence CYFRA could be a more reliable test than CA 19-9 in all stages of biliary malignancy (Figure 4).

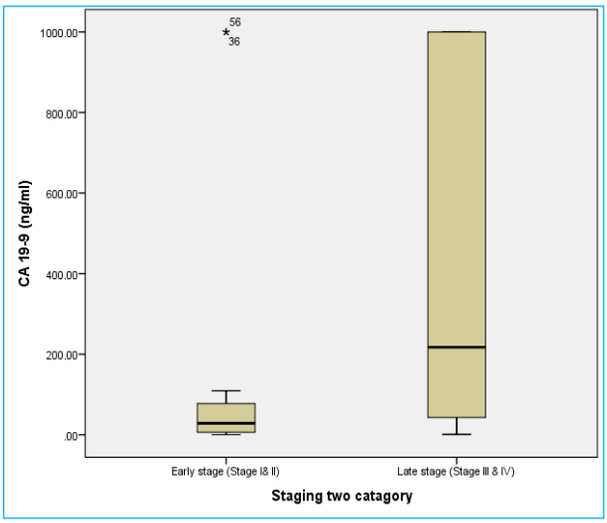

Figure 4. Box plot analysis of CA 19-9 for Stage I, II and III, IV.

Table 1. Comparison of means of CYFRA 21-1 and CA 19-9 for Stage I to IV.

	CYFRA 21-1	CA 19-9
Stage I	4.22 (8.1-2.2)	529.1 (1000.0 - 6.75)
Stage II	5.69 (20.0-1.9)	20.4 (45.4 - 0.45)
Stage III	11.5 (71.1-2.4)	554.2 (1000.0-26.0)
Stage IV	30.6(104.1-1.6)	375.4 (1000.0 -0.8)

Using independent't-test', the association between pruritus and raised CYFRA 21-1 and CA 19-9 was observed to be statistically significant ($p<0.05$). The association of jaundice at presentation was found to be significant by CA 19-9 ($p<0.05$). However, there was no association found with duration of symptoms, abdominal lump at presentation and weight loss. Chi square test did not show significant relationship among the genders and CYFRA 21-1 and CA 19-9.

There was so statistically significant difference among these two tests with regards to serum bilirubin, alkaline phosphatase levels, SGPT. However, there was statistically significant association of CYFRA 21-1 with SGOT ($p<0.05$).

DISCUSSION

Though Biliary tract cancers are uncommon in the western population, they are relatively quite common in the East Asian countries like Japan, Thailand, Northern India. Of them Gallbladder cancer is the commonest malignancy with dismal 5 years survival (5-10%).[16] Bile duct tumors arising from the bifurcation of the hepatic ducts (Klatskin tumors), comprise 60%-70% of bile duct tumors; 20%-30% are in the distal common bile duct while 5%-10% of CCAs arise within the intrahepatic ducts of the liver parenchyma.[17]

In our study, 56% of the patients with biliary malignancy were females and carcinoma gall bladder was the commonest of the biliary malignancy (52%) followed by hilar cholangiocarcinoma (18%) and ampullary cancer (18%). In our subcontinent, Gall bladder cancer is commonest of the biliary tract cancers[18,19]

Biliary tract cancers usually present in an advances stage. Since these cancers are usually detected late in the course of the disease, treatment options are often limited and of minimal utility. Hence, there is a need for markers of neoplasia that can be incorporated into diagnostic tests for use in individuals with these lethal malignancies.

The marker commonly in use for biliary malignancy is CA 19-9. Though its role in the assessment of disease progression and response to therapy in pancreatic malignancy is well established, its role in biliary malignancy is controversial.[20] With a cut-off value of 100U/ml, CA 19-9 has been seen to have sensitivity of 53% - 68% and specificity of 92% - 87%.[12,21]

Moreover, expression of CA 19-9 depends on the Lewis phenotype and hence for the 7% of population who are Lewis- negative, it is uninformative. CA 19-9 may remain high in benign biliary diseases such as Mirizzi syndrome, autoimmune pancreatitis, benign biliary stenosis secondary to PSC and pancreatic exocrine dysfunction.[22-24] Hence, for malignant causes of obstructive jaundice, it is recommended to rely on CA 19-9 levels that remain unchanged or measure more than 90U/ml after biliary decompression which is not usually possible in routine practice though in this study, CA 19-9 decreased in 50% of patients after decompression and was elevated in only 42%.[25] However with CYFRA 21-1, it is considered

that serum bilirubin levels of up to 850 µmol/L do not interfere with the CYFRA 21-1 assay.[9]

The increase of CA19-9 is also useful to predict respectability. A marked elevation of serum CA 19-9 is associated with advanced and unresectable biliary cancers. Elevated levels of CA 19.9 are correlated with advanced disease and poor prognosis and high preoperative values correlate with poor survival.

The association between CYFRA 21-1 serum concentrations and the tumor stage has also been observed in cholangiocarcinoma. Serum CYFRA 21-1 high values are correlated to tumor progression and poor post-operative outcomes in these patients.[8] In this study, across the cancer stages III and IV there was rise of the median values of both CYFRA 21-1 and CA 19-9. For CYFRA 21-1 the median for Stage I, II disease was 2.87 ng/ml whereas for Stage III and IV, the median was 6.1 ng/ml. Hence, both these tumor markers could be a marker of the severity of the disease when their values are markedly raised. As the variance for CA 19-9 was much more than that for CYFRA 21-1, CYFRA 21-1 could be a more reliable marker.

CYFRA 21-1 was initially reported in 1998 in four cases of intrahepatic cholangiocarcinoma, it has been found to have sensitivity and specificity of 75% and 92% respectively. In patients who underwent attempted curative resection, CYFRA 21-1 (< 2.7 ng/mL) was found to be a strong predictor of disease-free survival (76% vs 25% in those with elevated levels). Hence CYFRA 21-1 can have a definite role for predicting the prognosis of patients with biliary malignancy.

The main limitation of CYFRA 21-1 and CA 19-9 as tumor markers is that both have significant false negative rates. Another limitation of our study is that the majority of our patients had advanced disease (78% for stage III-IV) and the utility of circulating CYFRA 21-1 for the diagnosis or screening for early disease requires further investigation.

CONCLUSIONS

CYFRA is a more reliable test than CA 19-9 in all stages of biliary malignancy and can assist in distinguishing early and advanced malignancy.

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