HEPATIC MALIGNANCY - A CHALLENGE FOR EARLY DIAGNOSIS
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Abstract
Liver cancer is the third most common cause of death from cancer. This is despite the fact that damaged liver has an amazing ability to regenerate itself and the body needs only about 10% of the liver to live. Liver cancer starts within a single cell and it starts dividing in a disorganized and uncontrolled manner. They fail to perform the normal functions. Eventually a lump or tumor is formed which may be benign or malignant. Malignant mass is inclined to spread and is called metastasis. Liver is very common place for it, since it offers a soft, spongy blood-rich tissue. The diagnosis of hepatic malignancy in early stages is extremely judicious as it can expedite treatment in the budding stage. It is a multimodal approach of a surgeon, a radiotherapist, an interventional radiologist and a biochemist. Various biochemical parameters have decisive role in making diagnosis in the early stages. Obstruction of bile duct increases 5’NT values even in preclinical phase. But dependence on a single enzyme may lead to erroneous diagnosis so its sensitivity and specificity was compared with alkaline phosphatase, AST, ALT and serum bilirubin in a variety of malignancies. The results were extremely satisfactory. 5’NT has an edge over the other biochemical parameters when comparison was made. But single handed approach was not enough. So when it was juxtaposed with ALP, aminotransferases and bilirubin levels, it provides immaculate results in making diagnosis at an early stage.

Key words:--Hepatocellular carcinoma, Biopsy, metastasis, MRI, clotting time, transplantation.

Introduction
The liver is an organ in the abdomen which is necessarily to live. It is the main site of purine base degradation and synthesis of nucleoproteins in liver is much greater than other tissues; this may be interpreted as an index of high rate of regeneration of parenchymal cells. The liver has as a major blood supply the hepatic artery; hepatic vein collects blood from intestine. There is also a system of draining "lymph glands" around the liver which help to purify the blood. These lymph glands ultimately drain back into the bloodstream via the "left thoracic duct"; they are important as they may serve as conduits for spread of cancer. Among its functions are purification of the blood, removing poisonous ammonia from proteins, detoxifying alcohol and drugs, controlling the body's sugar and cholesterol balance, making bile to digest fats, forming clotting factors for the blood and generating new blood cells. This myriad of functions makes clear why the liver is essential to life. The most common types of benign liver tumors are hemangiomas and adenomas The most common malignant liver cancers are hepatocellular carcinoma (80% of cases) also known as a hepatoma. Cholangiocarcinoma (15% of cases) arise from bile ducts in the liver as they proceed down toward the gallbladder. Bowel, lung, breast, bladder, prostate and esophagus cancers have particular propensities for liver spread. These comprise secondary carcinoma.

Primary liver cancer
Primary liver cancer can arise from the liver cells themselves (hepatocellular carcinoma) or from the system of tubes that drains the bile from the liver (cholangiocarcinoma, gall bladder cancer). Patients had suffered from chronic hepatitis, cirrhosis or those who have been exposed to poisons from plants ( aflatoxins).

Surgical removal is the best option but these tumours are often too large and too extensive for surgery.
Liver transplant may also be an option.
Percutaneous ethanol injection (PEI) or heating them with electrodes (RFA – radiofrequency ablation) can be done by using needles passed through the skin or by using keyhole surgery.
A technique called TACE (transarterialchemoembolisation) can be used for more advanced tumours. 

**Chemotherapy** is occasionally used for inoperable tumours.

SIRT – Selective internal radiation therapy has an important place in treatment. Unfortunately, survival rates for primary liver cancer are very low.

There are various factors which act as predisposing factors called risk factors. These hasten the primary carcinoma:

1. **Chronic Hepatitis** can lead to hepatocellular carcinoma (HCC).
   - A) **Hepatitis B** – Leads to 75% of liver cancer patients.
   - B) **Carcinogens** (chemicals inducing cancer) such as aflatoxin.

2. **Cirrhosis of the liver** – Causes of cirrhosis include:
   - a) **Alcoholism**
   - b) **Hemochromatosis**
   - c) **Alpha1-antitrypsin deficiency**

3. **Miscellaneous irritants** The common thread to liver cancer risk factors is **chronic irritation**, which causes the cancer cells to divide more quickly.

**Secondary liver cancer**

When a cancer metastasizes from its original site to another area of the body, it is termed metastatic cancer. Secondary (metastatic) cancer reaches the liver by spreading through the blood system from a primary tumour at a separate site. Secondary liver cancer is more difficult to treat than primary due to spread. Metastatic liver cancer is the most common cause of fatal liver disease. The treatment of metastatic cancer depends on where the cancer started. About 5 percent of the time, metastases are discovered but the primary tumor cannot be identified. The treatment of these metastases is dictated by their location rather than their origin. Intestine, breast, lung and lymphoma cancer are very common.

Important parameters to diagnose liver cancer include:

**ALT**
Small amounts of ALT (alanine aminotransferase) are normally found in blood. When the liver is damaged, ALT is released into the bloodstream.

**AST**
AST (aspartate aminotransferase) Like ALT, AST is found mainly in the liver but also in other parts of the body. AST and ALT are usually measured together and are good indicators of liver disease or damage.

**ALP** (alkaline phosphatase) Like ALT and AST, ALP leaks into the bloodstream when liver cells are damaged.

**GGT**
GGT refers to gamma-glutamyl transferase. High levels of GGT are found in the liver, bile ducts, and the kidney.

**5’N’Tase**
Higher levels of the enzyme 5’N’Tase (5’nucleotidase), also known as 5’NT, in blood indicate a problem with bile secretion

**Albumin**
Albumin is the major blood protein made by the liver. It can cause fluid retention in the ankles (edema), lungs, or abdomen (ascites).

**Bilirubin**
When the liver is diseased, bilirubin is increased leading to jaundice.
PT test
The PT (prothrombin time) test. The PT test is used as a marker of advanced liver disease. It indicates blood-clotting problems where it is increased.

Complete blood count (CBC)
The complete blood count includes the following tests:
White blood cell (WBC) count, Red blood cell (RBC) count, Hematocrit (HCT, Anemia, Platelet count, AFP (alpha-fetoprotein), Iron, Creatinine
4. There is a "tumor marker" to help diagnosis liver cancer. This is alpha fetoprotein (AFP) In HCC patients, especially younger ones, the "alpha-fetoprotein" (AFP) blood test is elevated in over 50% but it may represent some other malignancy besides liver cancer.
5. Radiologic Tests, include standard Chest X-ray
6. Ultrasound (US) remains useful for looking at the shape of the liver, identifying a tumor, and tracking the progress of therapy. A CT scan is very accurate for detecting tumors larger than 1 cm.
7. CEA (carcinoembryonic antigen) test, in someone with a history of bowel cancer.
8. MRI scan which uses no radiation shows the organs in the abdomen very clearly and is excellent for showing local spread and imaging nearby lymph glands.
9. Other more exotic tests, such as bone scans, liver-spleen scans, or CT scans of the brain are only gotten if their are symptoms is these particular areas.
10. The only way to absolutely diagnose any cancer is by getting a biopsy of the tumor.
11. Fine-needle biopsy is safe and effective; it is a very common procedure in hospital. It also tells spread of cancer.
12. Gamma PET scan: a tool used in determining a prognosis for metastatic liver cancer.
13. Extreme Drug Resistance test: EDR is a highly accurate test for solid tumors to determine the probability of the tumor's resistance to specific chemotherapy.
14. Percutaneous cryoablation is a very recent addition to the liver cancer treatment armamentarium.

Treatment
The management of hepatic malignancy is one of the most controversial areas in medicine. There can be following approaches.
2. Conducting the operation by keyhole surgery is preferred over conventional surgery.
3. Patients with limited cancer may benefit from chemotherapy infused directly into the liver.
4. Selective internal radiation therapy (SIRT) is an experimental technique.
5. Hormone treatment is an additional option for patients with cancers of the breast or prostate that has spread to the liver.
6. Metastatic Liver Cancer Treatment through Cryotherapy

Material and Method:
Present study included a total of sixty cases. Twenty cases comprised of normal healthy individuals without any evidence of cancer of any part of body. They were mostly attendants and relatives of patients admitted to Rajindra Hospital, Patiala or coming along with the patients coming to OPD of the Hospital. They were examined thoroughly and any hepatobiliary disease, pregnancy and other factors related to rise in serum levels of 5’NT, ALP, AST, ALT, and Bilirubin were ruled out. For the tests, forty patients suffering from clinically diagnosed cancer
of any part of the body admitted to Rajindra Hospital, Patiala or attending the OPD of the hospital were taken. A detailed history was taken and examined thoroughly. All this was recorded on special proforma. Each case was investigated as under:

Collection of blood: ---

About 10 cc. of blood was collected by venepuncture using disposable syringe and needle was taken. It was allowed to clot at room temperature and then centrifuged at room temperature at 3000 rpm for ten minutes to separate the serum. The serum was separated in dry test tube to carry out the following special tests as: ---

1. Serum bilirubin by Malloy and Evelyn.
2. Serum 5’Nucleotidase—Method of Campbell (1962)
3. Serum alkaline phosphatase—kind & King 1954 using aminoantipyrine.

Later all the tests were carried out in a fully automated device. Purpose was to rule out any error and touch with traditional methods.

OBSERVATIONS: ---

In the present study twenty healthy attendants of the patients were examined for special tests as 5’NT, ALP, AST, ALT, Bilirubin. This comprised the control group and comprised by attendants of patients without any evidence of cancer of any part of the body including liver. This was done to equilibrate socioeconomic status and age.

Study cases were forty patients of clinically diagnosed cancer. These were either attending OPD or admitted cases in wards of Rajindra Hospital, Patiala. A detailed clinical examination was carried out as per plan already outlined under materials and methods. Diagnosis of these patients was made on the bases of clinical findings.

1. Routine investigations as Hb, TLC\DLC, and complete urine examination.
2. FBS, blood urea, flocculation tests (as per varley’s 1975) were carried out.
3. Bleeding and clotting time were recorded.
4. Complete examination of fresh urine was done in each case was carried out by standard methods.
5. All the special investigations were carried out as per plan already mentioned.

**Analysis of various biochemical parameters in control group (Table-- 1)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Range</th>
<th>Mean± S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>5’ Nucleotidase (IU/L)</td>
<td>2—8</td>
<td>5.00±1.69</td>
</tr>
<tr>
<td>Alkaline phosphatases (KAU/100 cc.)</td>
<td>3—10</td>
<td>6.42±2.19</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td>4—12</td>
<td>7.55±2.42</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>5—12</td>
<td>9.15±2.42</td>
</tr>
<tr>
<td>Serum bilirubin (mg %)</td>
<td>0.4—0.8</td>
<td>0.57±0.166</td>
</tr>
</tbody>
</table>

Table 1 depicts average values of serum 5’NT, ALP, AST, ALT and Bilirubin level in control group. Out of the control group 10% belonged to upper middle class while rest of the patients belonged to lower uneducated class of laborers who were by and large alcohol and drug addicts. Diet factor also failed to make any impact thou’ stray cases showed excessive fatty meals. 75 %
cases were non-vegetarian. Out of 40 cases of test 28 cases reported with clinical jaundice and they showed raised values of bilirubin variably. Anaemia was found in 75 % cases (>8G%). Abnormal urine with bile salts, bile pigments and urobilinogen was found in 70% cases.

**Age break up of hepatic malignancy and control Group (Table 2)**

<table>
<thead>
<tr>
<th>Age of patient in years</th>
<th>Groups according to age variations</th>
<th>Hepatic Malignancy group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percentage</td>
<td>Number</td>
</tr>
<tr>
<td>20—35 yrs.</td>
<td>07</td>
<td>17 %</td>
<td>04</td>
</tr>
<tr>
<td>36—50 yrs.</td>
<td>13</td>
<td>32 %</td>
<td>05</td>
</tr>
<tr>
<td>51—65 yrs.</td>
<td>12</td>
<td>31 %</td>
<td>06</td>
</tr>
<tr>
<td>&gt;65 yrs.</td>
<td>08</td>
<td>20 %</td>
<td>05</td>
</tr>
</tbody>
</table>

Table 2 shows that majority of age group fall in above 50 years. Although there was equal chances of age group of 36 to 50 and more than 65 years of age. What we conclude here is that the middle and upper age group was involved in majority. This finding strengthen the fact that as the age increases the chances of effect of predisposing factors like jaundice in the past, alcohol, drugs increases. This is to equilibrate with control group.

**Sex distribution of hepatic malignancy and control cases (Table 3)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic malignancy</td>
<td>40</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>14</td>
<td>06</td>
</tr>
</tbody>
</table>

Table 3 depicts the sex wise morbidity. Out of total 40 patients of hepatic malignancy 60 % belonged were found out to be males while females were affected to the extent of 40 %. This is understandable as all the predisposing were prominent in males.

**Statistical relation of various biochemical parameters in the study group (Table—4)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>5'NT</th>
<th>ALP</th>
<th>AST</th>
<th>ALT</th>
<th>Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (20)</td>
<td>20</td>
<td>5.0±1.69 (2—8)</td>
<td>6.42±2.19 (3—10)</td>
<td>7.55±2.42 (4—12)</td>
<td>9.15±2.42 (5—12)</td>
<td>0.57±0.166 (0.4—0.8)</td>
</tr>
<tr>
<td>Age group--1</td>
<td>07</td>
<td>17.32±5.87 (5—13)</td>
<td>12.23±6.98 (9—17)</td>
<td>15.32±6.34 (15—21)</td>
<td>15.65±4.09 (13—21)</td>
<td>2.87±0.9 (1.98—2.98)</td>
</tr>
<tr>
<td>20—35 yrs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group--2</td>
<td>13</td>
<td>24.43±6.87 (9—23)</td>
<td>26.43±5.78 (18—29)</td>
<td>31.65±5.64 (31—39)</td>
<td>19.87±4.98 (19—25)</td>
<td>4.87±2.76 (4—8)</td>
</tr>
<tr>
<td>36—50 yrs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group--3</td>
<td>12</td>
<td>29±4.90 (14—22)</td>
<td>29±4.21 (16—34)</td>
<td>33.67±4.08 (34—49)</td>
<td>21.05±3.98 (22—28)</td>
<td>9.87±5.23 (9—17)</td>
</tr>
<tr>
<td>51—65 yrs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group--4</td>
<td>08</td>
<td>33±2.9 (20—26)</td>
<td>37±3.98 (26—40)</td>
<td>37.65±5.09 (39—52)</td>
<td>29.98±4.96 (29—36)</td>
<td>8.92±2.98 (9—15)</td>
</tr>
<tr>
<td>65 yrs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The table 4 allowed us to compare various biochemical parameters in hepatic malignancy and control group. It was found that in group 1 and group 2, the values of 5’NT was Significant. But in group 3 and group 4 there was marked rise in the levels of 5’NT. So age factor comes into picture which may be due to exposure to various predisposing factors with age. Along with this the average values of ALP was markedly raised. In this rise again there were glimpses of 5’NT values following ALP values. The increase in aminotransferase viz. AST/ALT level was again having significant say in all cases of liver malignancy. Average values of ALP showed very significant rise in all the cases of hepatic malignancy. All the values followed 5’NT particularly in cases of clinical jaundice. Levels of aminotransferases showed same pattern and were found this to be increased in cases where damage to the liver was significant, jaundice was clinically exhibited. Their average rise in serum bilirubin level was significant. This was particularly significantly high in patients having worse clinical condition where all the other parameters were significant i.e. 5’NT, ALT, AST, ALP.

Serum 5’NT levels when compared with serum levels of ALP, AST, ALT and bilirubin had significant increase in level. But this was more so in age group 3 and 4.

Discussion
1. 5’NT has an important place in differential diagnosis of liver malignancy of all age groups. In majority of cases the rise in level followed the jaundice and biliary obstruction. A number of cases has been seen where ALP of hepatic region was raised in cases of normal level of 5’NT. It has been seen that ALP is released in blood with increased denovo synthesis of ALP. On the other hand 5’NT levels are raised in cases of severe damage of liver. Both enzymes are found in bile canaliculi and in lipid membranes together. The details of release of these enzymes were not available but it is possible that this might be possible by splitting and solubilization by bile salts. Since these two enzymes reflect similar but not identical. So one can easily predict that serum concentration may not be parallel in any single patient. So they should not be used interchangeably e.g. ALP was found to be increased in pregnancy and bone disease in which 5’NT levels were normal. This shows that 5’NT level was more significant when compared with ALP.
2. Elevation of aminotransferases was increased more in cases of damaged liver cells. This followed the rise in ALT|AST in case of ligation of bile duct. Their rise reflects leakage from damaged cells. But their level was not following the level of 5’NT. They were raised in clinically positive cases of jaundice.
3. As far as bilirubin level is concerned, it shows obstruction in bile canaliculi. To some extent it also follows aminotransferases where extensive liver damage is seen. But when compared with 5’NT, rise in levels of 5’NT was more significant
4. It is evident from the present study that estimation of serum 5’NT levels in cases of hepatic malignancy are welcome addition if juxtaposed with other clinical findings. Data showed that 5’NT is superior to ALP as far as bile duct obstruction is concerned. In all these cases it was superior in specificity and sensitivity as compared to ALP. While AST|ALT provided information about hepatic cell damage, 5’NT signifies bile duct obstruction or cholestasis. But used as a solitary index it doesn’t measure up to expectations.

Conclusion
Thus it’s concluded that enzyme 5’ NT level in hepatic malignancy cases contributes as an encouraging boost for diagnosis if juxtaposed with other clinical and laboratory data. The study
delineates 5’NT to be superior to ALP due to its sensitivity and specificity. But if used as a solitary index, it doesn’t measure up to expectations.

REFERENCES
control

- No. of cases
- ALP
- AST
- ALT
- Bilirubin
- 5'NT