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RESEARCH ARTICLE

Screening for Occult and Overt Hepatitis B Virus Infection in Patients of Cancer before Receiving Chemotherapy: Looking Beyond HBsAg Testing

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Abstract

Background: Hepatitis B virus (HBV) infection is increased in cancer patients and those receiving chemotherapy are at risk of HBV reactivation with high mortality. Screening for occult and overt HBV infection is not widely practiced in cancer patients.

Objectives: To assess the prevalence of occult and overt HBV infection in cancer patients at initial diagnosis prior to receiving chemotherapy(CT).

Methods: At initial diagnosis of cancer, patients were examined for any evidence of liver disease followed by screening for serum markers of HBV infection (HBsAg, total anti HB core, anti HBs antibody and HBV DNA).

Results: Isolated anti HBsAg positivity and previous resolved HBV infection was seen in 98(14.2%) and 88/690 (12.7%) patients respectively. HBV infection was seen in 68/690(9.8%) patients which included overt and occult HBV infection in 55/690 (8%) and 13/690 (1.9%) respectively. Overt and occult HBV infection in hematological cancers was more as compared to solid cancers [16/140(11.4%) vs 39/550 (7%), p=0.09] and 5/140(3.6) vs 8/550(1.4) p=<0.15] respectively. There was no significant difference in HBsAg positivity based on sex [31/393(7.8%) men vs 24/297(8%) women, p=0.9)], age [7/74(9.4 %) < 20yrs, 39/490 (7.9 %), 21-60 yrs, 9/126 (7.1%) > 60yrs), p=0.84], previous blood transfusions (BT) [13/170 (7.6%) BT vs 42/520 (8.0%), no BT, p=0.9)], history of jaundice [7/88 (8%) vs 35/602 (5.8%, p=0.8)] or ALT values, [42/545(7.7%) vs 13/145(7%), p=0.8)].

Conclusion: HBV infection is increased in cancer patients. Patients should be screened for both occult and overt HBV infection by testing serum HBsAg, HBV DNA and anti HB core antibody.

INTRODUCTION

Hepatitis B virus (HBV) infection is a major public health problem worldwide. About 2 billion people are infected with HBV during their life time and 350 million have chronic HBV infection. The prevalence of chronic HBV infection (HBsAg positivity) ranges between 8-25% in high endemic areas like Southeast Asia (except Japan) and Africa to less than 0.5% in western countries (Lavanchy; 2004; Lok et al;1987). In India prevalence rate of HBV infection is 1-5% and in a Kashmiri population (India) it is 0.56-1.1% (Lodha et al; 2001; Makroo et al; 1989; Sodhi et al 2013). Prevalence of occult HBV infection among healthy blood donors is common in the developing countries with high endemicity for HBV infection (Huang Chen et al; 2008; Kim et al 2007; Hui et al; 2005).Occult HBV

infection is the major cause of transfusion-transmitted HBV infection in countries like Taiwan and India (Arora et al;2003).

The prevalence of HBV infection in patients of cancer is increased with prevalence of 10% in Asian Chinese to 1% in USA (Lau et al; 1999; Takai et al; 2005).Most cancer patients are at risk for HBV reactivation due to immunosuppression or they acquire HBV infection due to exposure to potentially contaminated blood products and infected needles. Despite conventional screening for HBsAg in blood banks, occult HBV transmission can occur (Yeo et al; 2006).Prevalence of occult HBV infection is higher in immune compromised patients such as intravenous drug abusers, patients on maintenance haemodialysis, (Lin et al; 2007; Gerald et al; 2004) organ transplant recipients, patients with human immunodeficiency virus (HIV) infection (Samuel et al; 2006; De Feo et al; 2005; Mphahlele et al;2006) and various cancers (Huang et al;2014;Massimo et al;2012).

Missing of overt or occult HBV infection in cancer patients who is planned for CT can be detrimental as some may develop HBV reactivation leading to severe hepatitis or acute liver failure with high mortality and majority of them become chronic carriers of HBV. It may also interrupt and delay CT because of hepatitis with reduced chances of survival (Yeo et-al; 2000). High rates of HBV reactivation is seen in HBV-positive patients undergoing hematopoietic stem-cell transplantation and treatment for lymphoma. The risk of HBV reactivation is less clear in solid tumors (STs) compared to patients with hematologic cancers.

A policy of universal screening with HBsAg and anti HB core antibody before CT in cancer patients has been recommended in various countries but this practice has not been adopted widely among medical Oncologists including India (Fiona et-al;2011). HBV infection testing rates before CT in Canada and the United States are only 14% and 16.7%, while as in Asian countries like China it is reported in less than 20% of cancer patients (Lee et-al;2010;Hwang et-al;2011). India with its huge population of 1.25 billion is an intermediate zone for HBV infection (Lodha et-al; 2001; Makroo et-al; 1989; Sodhi et-al 2013). In our knowledge, only few studies are carried out regarding the prevalence of occult or overt HBV infection in patients of cancer before they received CT and are mostly related to hematological cancers especially in children (Arora et-al;2003 Marwaha et-al; 2001). Some studies have reported increased prevalence and reactivation in solid tumors, especially in breast cancer patients (Alexopoulos et-al; 1999; Yeo et-al; 2003). In this study we aimed to estimate the prevalence of overt as well as occult HBV infection in both solid and hematological cancers (Prior to CT), irrespective of age, by using serum HBV-DNA as a screening tool besides HBsAg, antiHBcore antibody,antiHBs antibody testing.

Material and Methods

Regional cancer center (RCC) is the only center at Sher-i-Kashmir Institute of Medical Sciences (SKIMS) in Jammu and Kashmir State of India, where all patients of cancer are registered, evaluated and managed. CT is given to patients as per standard protocol according to the type of cancer. The study was approved by the institutional ethics committee. A written informed consent was taken from the patients before conducting the study.This was a prospective study which included patients of cancer who attended RCC from March 2011 to March 2013.A detailed history and physical examination was conducted at first contact to look for the presences of liver disease.Patients were screened for the markers of HBV infection at the time of initial diagnosis. Those having evidence of CLD and underlying hepatocellular carcinoma were excluded from the study group.

Definitions:

Occult HBV infection: Patients who were HBsAg negative, anti HB core positive and low level HBV DNA in the serum (<200 IU/mL) .**Overt HBV infection**: Patients who were HBsAg positive. **Resolved HBV infection**: Patients who were HBsAg negative, IgG anti HB core positive and serum HBV DNA negative. **HBV Reactivation:** Sudden rise in serum aspartate and alanine aminotransferase (AST, ALT) levels more than 5 times the upper limit of normal or more than three times the base line levels associated with 10 fold rise in HBV DNA levels.**Acute HBV infection:** Hepatic injury that resolves within 6 months after exposure to HBV with elevated ALT, AST, HBsAg positive/ IgM anti-HBcore positive. **Chronic active HBV infection:** Patients who are HBsAg positive > 6 months, elevated ALT and AST. **Chronic inactive HBV infection:** Patients who are HBsAg positive >6months with normal ALT and AST levels, HBeAg negative, HBV DNA negative or low positive $<10^5$ copies/ml in serum. **Seroprotection.** Anti HBs titers more than 10 mIU/ml.

Screening for markers of HBV infection: HBsAg testing was done by ELISA (Micro screen, HBsAg ELISA kit, Span Diagnostics). Total anti-HBc antibodies and IgM anti-HBc antibody was tested by enzyme immunoassay [EIA-Anti-HBc-MScreen,DSI S.R.I. Serono (VA), Italy].Anti-HBs antibodies were detected by (DS-EIA-Anti-HBsAg kit, DSI S.RI). Hepatitis B viral DNA quantification was done by real time PCR assay on COBAS Ampliprep/Cobas TaqMan on the patient's plasma. The lower limit of detection of this assay is 20.0 IU/mL.

Statistical analysis Data was analyzed by descriptive statistics like means, median, range, standard deviations and percentage. Chi square test was used for studying the association between various variables. Student independent t-test was used to see the difference in two means. P-value <0.05 was considered statistically significant. SPSS (version) 16.0 was used to carry out the statistical analysis of data.

Results

Over a period of two years 716 patients of proven cancer to be planned for CT were screened for markers of HBV infection. Of 716 patients, 690 consented to participate. This included Men, 393(57%) and women 297(43%), age, median (range), 52 (1 – 85 yrs).One hundred and forty (20%) had hematological cancers and 550(80%) had solid cancers. Colorectal cancers and lymphoma were the most common cancers among solid and hematological cancers. [127(18.4%) and 71(10.3%)] respectively. The other base line characteristics of these patients are shown in [Table 1].

Prevalence of HBV markers in cancer patients before CT.

Among 690 patients of cancer, 436 (63.2%) had all HBV markers negative; 98(14.2%) had isolated anti HBs antibodies; 88/690 (12.7%) had previous resolved HBV infection. The remaining 68(9.8%) had HBV infection. Among 68 patients of HBV infection, 55 (8%) had overt (HBsAg positive) and 13 (1.9%) occult HBV infection [Table 2]. Prevalence of HBsAg positivity in hematological and solid cancers was 16/140 (11.4%) and 39/550 (7%) respectively (p=0.09) [figure 1] and was highest in NHL (9/71, 12.7%). There was no significant difference in HBsAg positivity based on sex [31/393(7.8%) men vs 24/297(8%) women, p=0.9)], age [7/74(9.4 %) < 20yrs, 39/490 (7.9 %), 21-60 yrs, 9/126 (7.1%) > 60yrs), p=0.84], previous blood transfusions (BT) [13/170 (7.6%) BT vs 42/520 (8.0%), no BT, p=0.9)], history of jaundice [7/88 (8%) vs 35/602 (5.8%, p=0.8)] or ALT values [42/545(7.7%) vs 13/145(7%), p=0.8)].

Occult HBV infection was found in 13/690(1.9%) patients and was more in hematological cancers compared to solid cancers [5(3.6%) vs 8(1.4%) p=<0.15] (figure 2). Prevalence was highest in NHL both in overt and occult HBV infection [9/71(12.7%) and 7/71 (9.8%)] respectively. Among 55 patients who were HBsAg positive, 10 had asymptomatic transaminitis (anicteric), three had acute hepatitis, while as others were asymptomatic with normal liver enzymes. Occult HBV infection was asymptomatic with normal liver enzymes. Low level HBV DNA was seen in all patients with IgG anti HB core positivity in 9 (69.2%), IgM anti HB core was seen in 4 patients.

Table 1: Base line characteristics of Cancer patients (n= 690)

Age (years), median; range	52 (1 – 85)
<18 (n %)	74 (10.7).
18-60 (n %)	490 (71).
>60 (n %)	126 (18.2).
Sex, n%	
Men	393 (57).
Women	297 (43).
Cancer type (n %)	
Hematological	140 (20).
Solid	550 (80).
Blood Transfusion (n %)	170 (24.6).
Jaundice (n %)	88 (12.7)
Baseline ALT	
Median; range (IU/ml)	64(14-734)
Normal (<45 IU/ml) n %	545 (79).
Mild (<3 times ULN*), n%	110 (16).
>3 times ULN	35 (5).
History of HBV Vaccination (n %)	117 (17)
Children	95 (81.1)
Adults	22 (18.8)

ULN: upper limit of normal, ALT:alanine aminotransferase

Table 2: Markers for HBV infection in patients of cancer before CT (n=690)

Negative for all HBV markers (n %)	436(63.2)
HBV infection (n %)	68/690(9.8)
Overt HBV (n %)	55(8)
Hematological cancers	16 (11.4)
Solid cancers	39 (7)
Occult HBV (n %)	13(1.9)
Resolved HBV infection (n %)	88(12.7)
Isolated anti HBs positive (<10 mIU/ml)	98(14.2)

CT-Chemotherapy, HBV-Hepatitis B virus

Table 3: Prevalence of HBV infection as per type of cancer prior to CT (n %)

		Type of Infection	
Cancer type	Total	Overt HBV	Occult HBV
Hematological cancers	140	16(11.4)	5(3.6)
Solid cancers	550	39(7)	8(1.4)

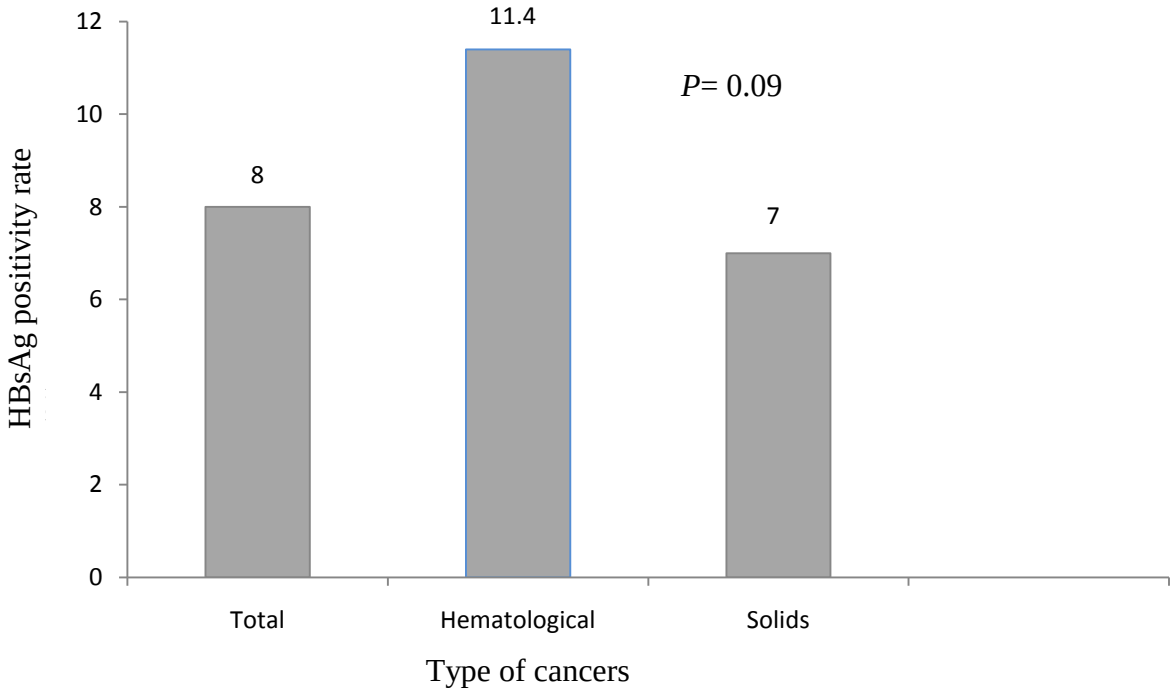

Figure 1: Prevalence of HBsAg positivity in patients of cancer before chemotherapy.

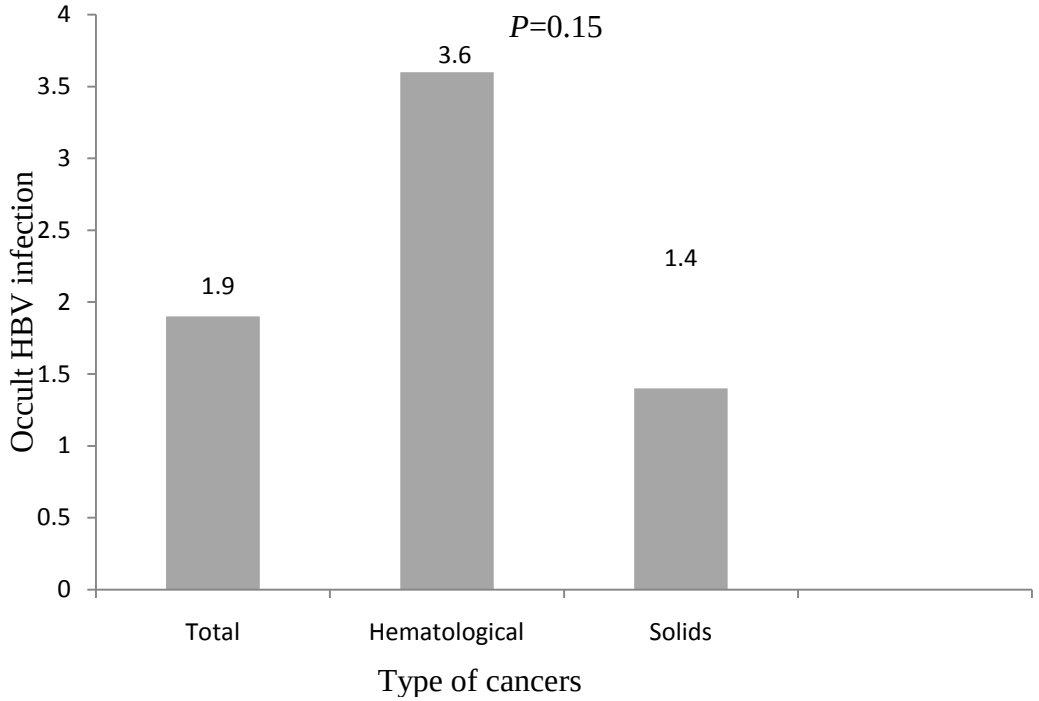

Figure 2: Prevalence of occult HBV infection in patients of cancers before chemotherapy

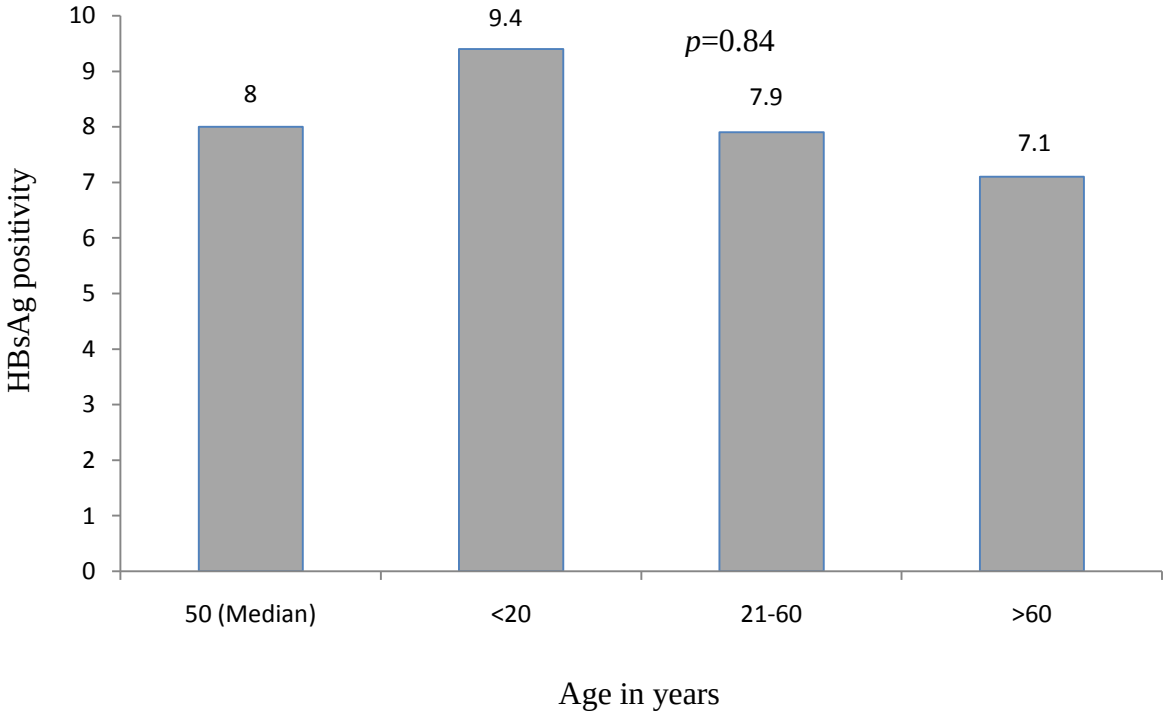

Figure: 3- Age wise prevalence of HBsAg positivity in patients of cancer

Discussion:

This study from North India screened large number of cancer patients by using four HBV serum markers i.e. HBsAg, antiHBcore antibody, antiHBs antibody and HBV DNA. The overall prevalence of HBV infection was seen in 68(9.8%) patients which included overt and occult HBV infection in 8% and 1.9% respectively. Previous resolved HBV infection was seen in 88(12.7%) patients.

Anti HBs antibody positivity as a sole HBV marker was seen in 98(14.2%) patients; majority of them were children, which possibly reflects effect of previous HBV vaccination. Seventeen percent of cancer patients gave history of vaccination against HBV at the time of diagnosis of cancer and majority of them were children (81.1%)[Table 1].Vaccination rates against HBV in general population is low in many countries including India due to financial constraints and lack of knowledge about HBV and its vaccine [Sharma et al; 2004]. Besides this there is no effective implementation of using HBV vaccine in Universal Immunization Programme (UIP).

This study revealed HBsAg positivity rate of 8% in cancer patients which is increased compared to HBsAg positivity in general Indian population. The prevalence was significantly more in hematological cancers compared to solid cancers with highest prevalence rate in NHL.There was no significant difference in HBsAg positivity rate based on sex, age, history of previous BT, history of jaundice or ALT values.The prevalence of HBsAg positivity rate in general population in India is about 1-5% (Lodha et al; 2001; Makroo et al; 1989 Choudhury et al; 2001) and in Kashmir (India) the prevalence of HBsAg positivity in healthy blood donors is in the range of 1.1% to 0.56% (Makroo et-al; 1989; Sodhi et al; 2013). In India Marwaha et al; 2001 reported 1% HBsAg positivity in childhood cancers prior to CT. HBsAg positivity rate in children with cancers has ranged from 9% to 60% in different studies.Alexopoulos et al; 1999 reported 44% patients of cancer having at least one marker of HBV infection prior to receiving CT while as HBsAg positivity rate was 5.3%, with highest prevalence in NHL group (12.4%).Takai et al; 2005 reported prevalence of HBV and HCV in 7.3% and 10.1% respectively in NHL which was higher compared to leukemia (1.7% and 2.9%, p=0.005) and in general Japanese population (1.2 and 2.6%) .Ying Wang et al; 2013 reported HBV prevalence of 13.4% in cancer patients before they received CT. Utkan et al;2006 and Kose et al; 2011 reported increased seropositivity of HBs Ag of 4.8% and 4.2% respectively in solid cancers which indicates that patients should be screened for HBV markers in both solid and hematological cancers.

In this study occult HBV infection was present in 1.9% of cancer patients and was higher in hematological cancers (3.6%) compared to solid cancers (1.4%), p=0.09. Data on occult HBV infection in general Indian population is very scanty Occult HBV infection is increased in immune compromised patients such as intravenous drug abusers, patients on maintenance hemodialysis, organ transplant recipients and patients of HIV (Lin et al; 2007; Gerald et al;2004; Samuel et al;2006; De Feo et al; 2005; Mphahlele et al; 2006).The reasons for increased prevalence of overt or occult HBV infection could be multifactorial which includes immunosuppression due to underlying cancer with falling antiHBs titers and subsequent reactivation of covalently closed circular DNA in liver tissue especially in patients who are anti HBcore positive; as was seen in the present study which revealed antHBcore positivity of (12.7%).This sero reversion in previously resolved HBV infection can be prevented at this stage by higher, accelerated and multiple doses of HBV vaccine along with HBV immunoglobulin's before and during the aggressive phase of chemotherapy (Ghosh et al; 2010, Pullukcu et al;2008).Newer vaccines with new adjuvants have shown promising results in raising the anti HBs antibody titers in immune compromised conditions (Kundi et al; 2007, Bode et-al; 2011). In India the reported incidence of anti HB core positivity among healthy blood donors ranges from 17%-29% suggesting chronic endemicity (Kant 1996).Occult HBV infection can be transmitted via blood transfusion in cancer patients unless transfused blood is tested for antiHBcore antibody and HBV DNA (Sodhi et al;2013).Occult HBV infection is the major cause of transfusion-transmitted HBV infection in countries like Taiwan and India (Arora-et al;2003;Wands et al; 1975; Regan et al;2000).The reason for increased prevalence of HBV infection in hematological cancers could be increased baseline disturbance of immune function compared to solid cancers.

This study reveals that not only HBsAg testing should be done in patients of cancer before receiving CT but also they should be tested for occult or resolved HBV infection by estimating their HBV DNA levels, although it may not be cost effective at this stage but the benefit of estimating HBV DNA seems to outweigh the cost effectiveness. Patients of occult HBV may develop HBsAg sero reversion with subsequent HBV reactivation following CT especially in cases of severe immunosuppression like patients of hemopoietic stem cell transplant or those receiving rituximab based CT.HBV reactivation following CT leads to increased morbidity and mortality. Acute hepatitis in these patients causes delay in CT schedule with increased chances of relapse. Some patients may develop liver failure and death. Majority of such patients remain in chronic carrier state and may develop chronic liver disease with its antecedent complications (Lalazar et al; 2007; Onozawa et al; 2005, Hui et al; 2006)

A policy of universal screening with HBsAg and hepatitis B core antibody (HBcAb) before CT has been recommended in various countries but this practice has not been adopted widely among medical oncologists including India were the antiHBcore positivity rate is high (19-25%) (Fiona et al; 2011).The observations in the present study

again emphasizes the importance of screening for HBV markers especially HBV-DNA to pick up occult HBV infection besides other markers like HBsAg, anti HBs, anti HBcore antibodies.

Keeping in view the high incidence of HBV reactivation following CT and its associated morbidity a**n**d mortality; those who have negative markers for HBV infection or low antiHBsAg titers need prophylaxis against HBV infection by immunization and those who are HBV positive need antiviral drugs to prevent HBV reactivation. Further studies are needed to see the cost effectiveness of HBV-DNA estimation as screening method for HBV infection in immune compromised patients like patients of cancer who are to be planned for aggressive CT.

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