Journal of Advanced Medical and Dental Sciences Research

@Society of Scientific Research and Studies

Journal home page:www.jamdsr.com doi:10.21276/jamdsr Index Copernicus value [ICV] =82.06

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Original Research

Role of trans-arterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma

Vishal Singh

Associate Professor, Department of Radiology, Icare Institute of Medical Sciences and Research and Dr. Bidhan Chandra Roy Hospital, Haldia, West Bengal, India

ABSTRACT:

Background: Portal vein thrombosis is seen as a relative reason to avoid transarterial chemoembolization (TACE) in hepatocellular cancer. The aim of our study was to assess the effectiveness of TACE treatment in patients with hepatocellular cancer and portal vein (PV) thrombosis. **Material and methods:**Patients diagnosed with hepatocellular carcinoma (HCC) who came to our hospital between 2001 and 2007 had clinical, biochemical, and radiological examinations. TACE was carried out in individuals who met the inclusion criteria. Further evaluation was conducted using a series of CT scans of the liver at 1, 3, and 6 months. Estimates were made for tumour response and survival rate. Analyses were conducted to determine the factors influencing survival, both individually and collectively. **Results:**Among the 70 patients involved in the study, 39 were male (55.7%) and the remaining 31 were female (44.3%). Patients were evaluated for tumour response using imaging at regular intervals and the data was compared with the initial laboratory and imaging features obtained before to therapy. Single-variable analysis was employed to evaluate the effect of the treatments on patient survival. An investigation of survival was conducted using Kaplan-Meier calculations. **Conclusion:**TACE provides a viable palliative treatment option for HCC. Tumour size in the beginning is a factor that can predict survival on its own.

Keywords: Hepatocellular carcinoma, survival rate, transarterialchemoembolisation

Received: 18 December, 2017 Accepted: 23 January, 2018

Corresponding author: Vishal Singh, Associate Professor, Department of Radiology, Icare Institute of Medical Sciences and Research and Dr. Bidhan Chandra Roy Hospital, Haldia, West Bengal, India

This article may be cited as: Singh V. Role of trans-arterial chemoembolization (Tace) in patients with unresectable hepatocellular carcinoma. J Adv Med Dent Scie Res 2018;6(2):193-198.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequent main cancer of the liver. It is closely linked to cirrhosis, caused by both alcohol and viral factors. HCC makes up about 5% of all malignancies, in part because of the high incidence of hepatitis B infection in certain areas. HCC is the fifth most prevalent cancer globally and ranks third in terms of cancer-related mortality, following lung and stomach cancer. The occurrence of HCC is increasing, mostly due to a rise in hepatitis C infection. The demographics are greatly impacted by the regions where chronic hepatitis B infection is prevalent, which make up more than 80% of cases globally. Asia has the highest occurrence. In Western countries, the rate is lower and alcohol is responsible for a larger percentage of cases.[1-4]

Risk factors include:

- hepatitis B (HBV) infection: 10% 5-year cumulative risk
- hepatitis C (HCV) infection: 30% 5-year cumulative risk
- alcoholism: 8% 5-year cumulative risk
- biliary cirrhosis: 5% 5-year cumulative risk
- food toxins, e.g. aflatoxins
- congenital biliary atresia
- inborn errors of metabolism
  - haemochromatosis: ~20% 5-year cumulative risk
  - alpha-1 antitrypsin deficiency
  - type 1 glycogen storage disease
  - Wilson disease
  - tyrosinaemia type I
- obesity and diabetes mellitus
- chronic cholestatic syndromes

HCC is usually detected in individuals in their late middle age or older adults (with an average age of 65 years) and is more prevalent in males (accounting for 75% of cases). The tumour can also happen in children; nevertheless, it is the second most common

liver tumour in children after hepatoblastoma. Regrettably, the identification of HCC is sometimes delayed until the illness has progressed and patients are experiencing symptoms and some level of liver dysfunction. At this advanced point, there is almost no medication that would effectively enhance survival.[5,6]Furthermore, the level of illness linked to treatment is excessively high. TACE is the initial treatment typically utilised for locoregional HCC, as well as for downstagingtumours that exceed criteria. Prior to considering HR and RFA, TACE can potentially be seen as a neoadjuvant treatment option to decrease tumour size or target micrometastasis. The reason for utilising TACE is the ability of HCC to form new blood vessels and its effect on the blood supply to the tumour in the liver. In the early stages of its growth, the tumour receives its blood supply from the portal system. As the tumour grows larger, the blood supply changes to become more like an artery, so even a well-differentiated HCC primarily relies on the blood supply from the hepatic artery. This tumour characteristic forms the pathological foundation for the radiographic findings employed in the diagnosis of HCC. Blocking the hepatic artery branch causes specific oxygen deprivation in the tumour, which finally leads to the death of the tumour cells. This is achieved via a substantial decrease in the flow of blood through the arteries using a catheter-based infusion of particles guided by images.[7,8] Possible agents such as polyvinyl alcohol beads, alcohol, starch microspheres, metallic coils, autologous blood clots, and gelfoam have all been utilised for embolisation. Before arterial embolisation, a chemotherapy drug is delivered. Several drugs have been traditionally used for chemotherapy, including doxorubicin, cisplatin, mitomycin, and epirubicin. Furthermore, doxorubicin-releasing beads have recently emerged as a substitute for conventional TACE. Drug-coated beads are seen as a better option in terms of both how well the treatment works and how much of the tumour is destroyed, as compared to standard TACE. Some contraindications for TACE include advanced cirrhosis (Child–Pugh B), large tumour that has spread to both lobes, significantly reduced portal flow (portal vein blockage or hepatofugal blood flow), and a creatinine clearance of less than 30 mL/min. Llovet et al discovered that the chances of survival for TACE were 82% and 63% at 1 and 2 years, respectively, for unresectable HCC. The outcome of TACE is a separate factor that can predict survival. Further research has indicated that patients who underwent TACE treatment experienced a survival rate increase of 20%–60% after 2 years. The occurrence of complications with embolisation is relatively low, at less than 5%. These complications commonly include abdominal pain, nausea, ileus, and fever, which are in line with postembolization syndrome. In the past, portal vein tumour thrombosis has been seen as a reason to not do TACE therapy. This blockage of blood flow to the liver through the hepatic artery can cause severe liver tissue death when combined with a blockage in the portal vein due to a tumour clot, which already reduces blood flow to the affected part of the liver. Multiple studies, both prospective and retrospective, have indicated that TACE can enhance the overall survival of patients with hepatocellular carcinoma (HCC) who have portal vein tumour thrombosis and Child-Pugh class A cirrhosis. In addition, the combination of TACE and sorafenib may have a synergistic effect.[9,10]

MATERIAL & METHODS

PATIENT SELECTION

This research A total of 70 patients were sent to the Radiology Department of Radiology at medical College in Haldia, India between April 2016 and June 2017. The patients showed signs of possible hepatocellular cancer. All patients underwent a medical interview and initial diagnosis, and each patient had blood tests done, including a complete blood count, liver function tests, and tests for viral indicators of hepatitis B and C infection. Serum alpha-fetoprotein (AFP) was measured using a particle enzyme immunoassay (Axsym System; Abbott Laboratories, Abbot Park, Illinois, USA; normal value <20 ng/ml). TACE was provided to BCLC-B/C HCC patients who met the following criteria: patients with Child's A or B cirrhosis, normal main portal vein, less than 50% involvement of liver by HCC, and patients who were willing to undergo therapy and follow-up. Additionally, the study also included patients classified as BCLC A who were not eligible for ablative therapy or surgery.

The criteria for exclusion involved non-liver diseases; blood clotting disorders; blockage of the bile duct; other health conditions such as heart disease, heart failure, kidney disease, etc.; and a past occurrence of encephalopathy or upper gastrointestinal bleeding within the past 6 months.

STATISTICAL ANALYSIS

Several lung function metrics were taken into account as the main outcome variables. The main factor that was being studied was whether or not there was exposure to air pollution and how long the air pollution lasted. Analysed the data by using frequency and percentage for categorical variables, and mean and standard deviation for quantitative variables. The average values of the pulmonary function parameters were compared among different research groups. Analysis of variance (ANOVA) was employed to evaluate the statistical significance of the relationship. A P value of 0.05 was regarded as statistically significant. Statistical analysis was conducted using IBM SPSS version 21.

RESULTS

Among the 70 patients involved in the study, 39 were male (55.7%) and the remaining 31 were female (44.3%). The average age of the group was 57 years,

with ages ranging from 16 to 74 years. 73 (81.6%) individuals underwent DWI. The results are displayed in Figure 1. The patients were categorised into seven categories based on age: 10-19, 20–29, 30–39, 40–49, 50–59, 60–69, and 70-79 years. These groups are referred to as group I - VII. The researchers examined the demographic features of the patients, including their gender, age, and comorbidity data.

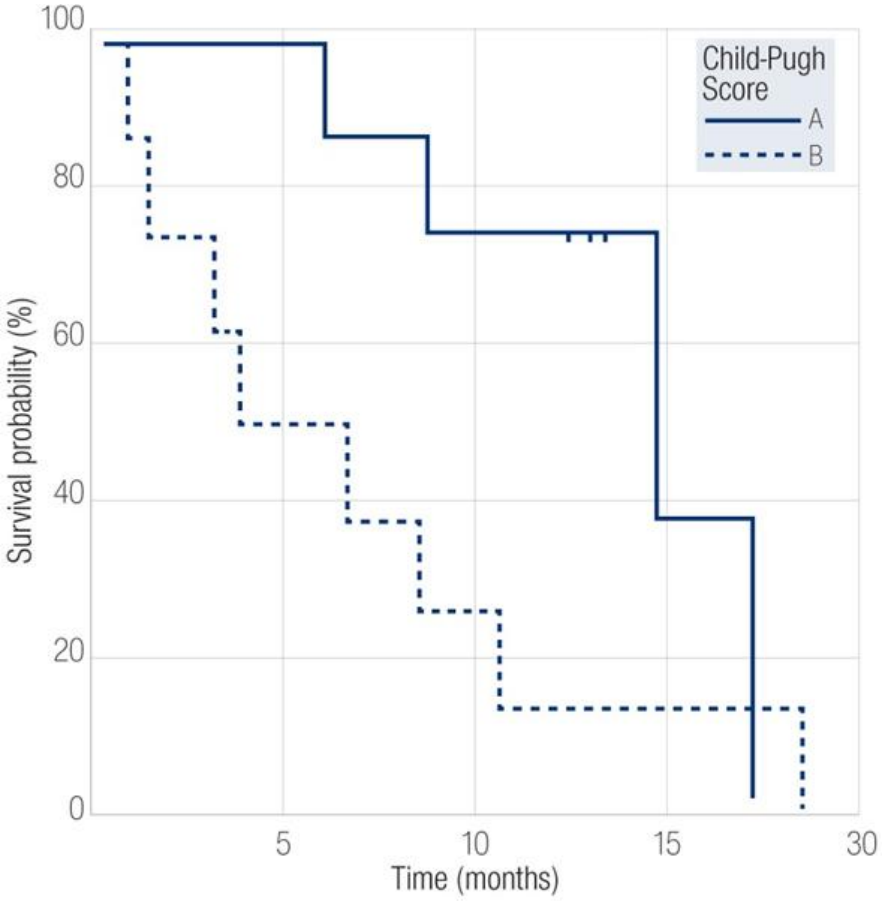
Following the demographic analysis, we did not find any notable variation in the age distribution, gender distribution, expression of HBsAg, levels of ALT, AST, TBil, ALB, PT, and AFP, Child-Pugh class, maximum HCC size, number of HCC foci, Barcelona Clinic Liver Cancer (BCLC) stage, presence of extrahepatic metastasis, vascular invasion, and APF/AVF between the two groups (Table 1).

The TACE procedure was well tolerated by all of our patients. No issues were found during the treatment and the complications after the procedure were not severe. The most frequent complication, occurring in 13.6% (10 out of 73), was postembolization syndrome. This condition is characterised by abdominal pain, fever, nausea, and vomiting. Abnormal kidney function in 10 out of 73 patients (13.6%) and liver failure in 3 out of 73 participants (4.1%) were also seen.

Table 1 displays the comparison of background factors and the outcomes of univariate analysis using the Cox proportional hazard model. The presence of related characteristics of portal hypertension (fluid accumulation in the abdomen, enlargement of the spleen, etc.) did not have a notable impact on survival. The factors of Child's stage, AFP greater than 1000ng/ml, size of the mass, and BCLC stage revealed significant potential for relationship with mortality (P less than .05) on univariate analysis [Table 1]. The variables were included in a stepwise multivariate Cox regression model, and the size of the mass at the beginning of the treatment was identified as the most important independent predictor of survival.

Table 1: displays the comparison of background factors

Measured Properties	Frequency	Percentage
Presenting Symptoms		
Asymptomatic	11	15
Pain	32	44
Weight Loss	25	34.2
Anorexia	23	31.5
Abdominal Distension	14	19.1
Abdominal Mass	7	9.5
Fever	7	9.5
Child’s Class		
A	54	74
B	19	26
Etiological Factors		
HBV	52	71.2
HCV	11	15.0
AST (IU/L)		
<40	11	15
>40	62	84
ALT (IU/L)		
<40	23	31.5
>40	50	68.5
AFP ng/ml		
<20	29	40
21-300	18	25
300 -1000	12	16.5
>1000	14	20
BCLC Stage		
A	20	27.4
B	38	52.05
C	15	20.5
Size of HCC		
<5cm	28	38.3
5-10cm	28	38.3
>10cm	17	23.29



DISCUSSION

TACE is the most commonly utilised therapeutic choice for people with HCC who are not acceptable candidates for curative treatment. The developing world has a unique epidemiological diversity in terms of the causes and the stage of HCC at diagnosis. Over 80% of HCC cases are found in Asia and Africa.[11]

In this investigation, HBV infection was found to be the most prevalent underlying cause of HCC. This aligns with the findings of research conducted at other institutions in India. On the other hand, in nations such as Japan, Spain, and others, HCV-related HCC is mostly found. Most of our patients showed symptoms when they first came to us (66 out of 73 patients, or 90.41%). Additionally, they had quite large tumours at the beginning, which suggests that they had progressed disease. Taking care of these patients was quite difficult. The biggest documented occurrence of TACE from Japan, with a research group of 8510 patients, included individuals with smaller tumours (24% with tumours smaller than 2 cm and 75% with tumours smaller than 5 cm). There is a limited amount of research on the use of TACE for liver tumours that are relatively substantial in size (with an average diameter of around 7 cm).[12]

Doxorubicin, mitomycin, and cisplatin are often utilised anticancer medications either individually or in combination during TACE. There is no universally accepted technique for determining the chemotherapeutic drug, dosage, dilution, pace of injection, and appropriate re-treatment approach. Likewise, there is no universally accepted option for the embolising agent to be utilised or the amount required. In this investigation, we utilised a mixture of cisplatin (100 mg), doxorubicin (50 mg), and lipiodol (10–20 ml), followed by particle embolisationutilising gelatin sponge. The surgery was carried out by inserting a cannula into the feeding artery in a very precise manner (getting as close to the tumour as feasible using small catheters), in order to reduce the chance of unintended embolisation. This technique of highly specific cannulation has been recognised as a positive prognostic factor for the disease-free survival of patients after TACE.[13]

The procedure was well tolerated by our patients. The frequently experienced mild issues after the treatment were temporary and got well within approximately 5-7 days. In addition, when we repeated the TACE session in the same individuals, we noticed that the intensity of the side effects was significantly lower. Approximately 13.7% of our patients experienced abnormal kidney function, which may have been caused by the administration of the chemotherapy medication doxorubicin.[14]

TACE is considered a safe technique with a low death rate. Additionally, the mortality rate has decreased over the past two decades, with reported rates of 10% in 1991, 1.1% in 1999, and 0.5% in 2006. In the greatest documented occurrence of TACE, the different reasons for death were as follows: liver

failure (40.1%), death from malignancy (18.2%), and rupture of HCC. Two patients died within one month of undergoing the treatment, one due to liver failure and the other due to kidney failure. This resulted in a procedure-related mortality rate of 2.7%. We did not come across any instances of HCC rupture or infections after TACE, as mentioned by other publications.[15,16]

There appears to be no agreement on the practice of subjecting patients to multiple sessions of TACE. Certain centres conduct repeated TACE procedures at regular intervals, typically every 2-3 months. We conducted further TACE sessions depending on the results of a follow-up CT scan performed four weeks after the therapy. This policy was comparable to the one implemented in the nationwide multicenter Japanese trial conducted by Takayasu et al. The effectiveness of TACE is higher when the operation is repeated based on follow-up imaging results rather than at predetermined planned intervals.[17-20]

Following undergoing TACE, a considerable number of cases (ranging from 17% to 61.9%) obtain a noticeable reduction in tumour size. However, achieving a total disappearance of the tumour (ranging from 0% to 4.8%) is uncommon, as some tumour cells may still survive following TACE treatment.

We achieved a full response in 31.2% of patients, but 15 out of 64 patients (23.4%) saw local disease progression, either through recurrence or the development of new lesions. The effectiveness of TACE for relieving symptoms of unresectable HCC has been shown in multiple randomised controlled trials. The rate of survival and the response in the local area in our study were promising. The combined survival rate at 1, 2, and 3 years was 66%, 47%, and 36.4%, respectively. Table 3 displays the survival rates of various studies, indicating a noticeable improvement in the rates throughout the past twenty years. The improved outcomes of HCC following TACE in recent studies may have several reasons. Firstly, the implementation of screening programmes for HCC has led to the detection of small tumours. Secondly, there have been advancements in imaging techniques for diagnosis, such as multiphase CT scan and contrast-enhanced MRI, which have high sensitivity and specificity. Thirdly, there has been a strict application of well-defined staging criteria for the disease. Fourthly, clear-cut inclusion criteria have been used, resulting in study populations that are more similar. Lastly, there have been refinements in the technique of the TACE procedure, such as the use of tiny microcatheters that allow for better placement of the catheter tip in the lumen, resulting in improved coverage of the tumour with chemotherapeutic drugs.[21,22]

The overall survival rate in our study is comparable to or even better than that in several previous studies conducted in other countries. Because of variations in the criteria used for selection, it is likely that our study population had a greater tumour size and a more advanced stage of disease. Developed nations have screening programmes for HCC, which allow for "early detection and early treatment." As a result, these countries often handle individuals with early-stage HCC.[23]

An examination of the factors influencing survival found that the Child-Pugh score, serum AFP levels above 1000 ng/ml, BCLC stage, and tumour size were significant variables that impacted survival after TACE. All the characteristics stated above are interconnected and indicate the complex nature of the disease. As the size of the tumour increases, the BCLC stage also increases and the function of the underlying liver (Child's status) worsens. Nevertheless, the existence of vascular invasion and accompanying portal hypertension did not have a noteworthy impact on the overall survival. In the multivariate study, tumour size was found to be the most significant independent predictor of survival. This discovery is comparable to the findings made in other investigations.[24]

Given that the size of the mass is a significant factor in determining survival, this finding has serious consequences in a country like ours where most patients are diagnosed with large tumours. In India, there is a lack of screening programmes for HCC. In order to improve treatment results, it is crucial to start screening patients at high risk of cirrhosis in order to detect HCC at an early stage. In addition, as HBV infection is the main reason for HCC, it would be very beneficial to implement preventive measures for HBV infection, such as hepatitis B vaccination programmes.[25]

In conclusion, TACE is a secure and effective palliative technique. In India, most patients have advanced disease when they first seek medical attention. Although our study population had large-sized tumours, TACE had positive local results and the survival rates were similar to those reported by other authors. The initial size of the tumour was the most significant factor in predicting the survival of our patients with HCC.[26,27]

REFERENCE

1. Kumar V, Abbas AK, Fausto N et-al. Robbins and Cotran pathologic basis of disease. W B Saunders Co. (2005)
2. Dähnert W. Radiology review manual. Lippincott Williams & Wilkins. (2003).
3. Smith MT, Blatt ER, Jedlicka P et-al. Best cases from the AFIP: fibrolamellar hepatocellular carcinoma. Radiographics. 28 (2): 609-13.
4. Antila KM, Mäkisalo H, Arola J et-al. Best cases from the AFIP: biliary papillomatosis. Radiographics. 28 (7): 2059-63.
5. Willatt JM, Hussain HK, AdusumilliS et-al. MR Imaging of hepatocellular carcinoma in the cirrhotic liver: challenges and controversies. Radiology. 2008;247 (2): 311-30.
6. Kim KW, Kim MJ, Lee SS et-al. Sparing of fatty infiltration around focal hepatic lesions in patients with hepatic steatosis: sonographic appearance with CT and

MRI correlation. AJR Am J Roentgenol. 2008;190 (4): 1018-27.
7. Choi BI, Lee KH, Han JK et-al. Hepatic arterioportal shunts: dynamic CT and MR features. Korean J Radiol. 3 (1): 1-15.
8. Lau WY. Hepatocellular Carcinoma. World Scientific Pub Co Inc. (2008)
9. Grendell JH, Friedman SL, McQuaid KR. Current diagnosis & treatment in gastroenterology. McGraw-Hill Medical. (2003)
10. Stubbs RS, Wickremesekera SK. Selective internal radiation therapy (SIRT): a new modality for treating patients with colorectal liver metastases. HPB (Oxford). 2004;6 (3): 133-9.
11. Caturelli E, Siena DA, Fusilli S, Villani MR, Schiavone G, Nardella M, et al. Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with cirrhosis: Evaluation of damage to nontumorous liver tissue-long-term prospective study. Radiology. 2000;215:123–8.
12. Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology. 2006;131:461–9.
13. Ji SK, Cho YK, Ahn YS, Kim MY, Park YO, Kim JK, et al. Multivariate analysis of the predictors of survival for patients with hepatocellular carcinoma undergoing transarterial chemoembolization: Focusing on superselective chemoembolization. Korean J Radiol. 2008;9:534–40.
14. Savastano S, Miotto D, Casarrubea G, Teso S, Chiesura-Corona M, Feltrin GP. Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with Child's grade A or B cirrhosis: A multivariate analysis of prognostic factors. J ClinGastroenterol. 1999;28:334–40.
15. Miyayama S, Yamashiro M, Okuda M, Yoshie Y, Sugimori N, Igarashi S, et al. Chemoembolisation for the treatment of large Hepatocellular carcinoma. J VascIntervRadiol. 2010;21:1226–34.
16. Pisani P, Parkin DM, Ferlay J. Estimates of the world wide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden. Int J Cancer. 1993;55:891–3.
17. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
18. Paul SB, Chalamalasetty SB, Vishnubhatla S, Madan K, Gamanagatti SR, Batra Y, et al. Clinical Profile, Etiology and Therapeutic Outcome in 324 Hepatocellular Carcinoma Patients at a Tertiary Care Center in India. Oncology. 2009;77:162–71.
19. Acharya SK, Madan K, Dattagupta S, Panda SK. Viral hepatitis in India. Natl Med J India. 2006;19:203–17.
20. Kumar R, Saraswat MK, Sharma BC, Sakhuja P, Sarin SK. Characteristics of hepatocellular carcinoma in India: A retrospective analysis of 191 cases. Q J Med. 2008;101:479–85.
21. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of esophagus for bleeding esophageal varices. Br J Surg. 1973;60:646–8.
22. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. EASL Panel of Experts on HCC. EASL panel of experts on HCC: Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona EASL conference. European Association for the study of liver. J Hepatol. 2001;35:421–30.
23. Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, et al. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol. 2006;44:723–31.
24. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003;362:1907–17.
25. Sarin SK, Thakur V, Guptan RC, Saigal S, Malhotra V, Thyagarajan SP, et al. Profile of hepatocellular carcinoma in India: An insight into the possible etiologic associations. J GastroenterolHepatol. 2001;16:666–73.
26. Murugavel KG, Mohan KV, Pramod NP, Rajasambandam P, Mathews S, Jyanthi V, et al. Correlation of hepatitis B and C viral markers with aflatoxin and AFP in Hepatocellular carcinoma cases from Tamil Nadu. Abstract. Indian J Gastroenterol. 1999;18:S37.
27. Kapoor S, Gupta SK, Sehgal RK, Dhiman RK, Chawla Y, Jyotsana Hepatocellular carcinoma at PGI Chandigarh. Indian J Gastroenterol. 1999;18:S36–24.