Management of Large Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world. There is increasing incidence of HCC in India. More than 70% of HCC are not suitable for curative treatment. Majority of the HCCs are large when diagnosed all over the world. There is no standard treatment for large HCCs. Different palliative treatments like arterial embolization/chemoembolization, intraarterial lipiodol chemotherapy, hormonal compounds like tamoxifene, octreotide systemic chemotherapy, immunotherapy with interferon, internal radiation with $^{131}$I or $^{99}$Yttrium. Arterial chemoembolization is the treatment of choice with proved efficacy in selected group of patients. The newer modalities and strategies need to be tried in controlled randomized trials.

Hepatocellular carcinoma (HCC) is fifth most common cancer in world.1 Approximately 5,64,000 cases/year are detected all over the world.2 Though HCC was rare in western world and common in asian pacific region, there is worldwide increasing incidence of HCC.1 In India also there is increasing incidence of HCC.3 In spite of being important cause of morbidity only 25 to 30% of the HCC patients may receive radical curative treatment.4 More than 90% HCCs occur in the cirrhotic livers.5 Almost 30 to 60% patients have multicentric HCC.6 More than 70% patients develop recurrence after curative resection in 2 years time.7 As majority of HCCs occur in cirrhotic liver, management of HCC depends upon not only size of tumors but also on condition of underlying liver. Cirrhosis is precancerous condition and development of HCC at multiple sites increases the chance of recurrence after curative treatment. Ideally liver transplantation is appropriate treatment of HCC.

Various staging systems have been described for HCC.8 These staging systems are based on the size of tumor, Child Pugh score, alpha-fetoprotein levels, portal invasion and metastasis. HCC more than 5 cms in size is considered as large HCC. In cirrhotic liver large HCCs are not suitable for curative treatment. More than 70% tumors belong to this category. Solitary tumor less than $\leq$ 5 cms in diameter or three tumors less than 3 cms in diameter is considered as early HCC suitable for transplantation. Tumor recurrence strongly correlates with size of tumor, nodules and presence of vascular invasion. Hepatic resection is second best to liver transplantation as curative treatment for HCCs. Patients suitable for resection are patients with HCC less than 5 cms in non-cirrhotic liver, or well compensated Child A cirrhosis without vascular invasion and extrahepatic spread. Patients with small HCC who are not fit for surgery or transplantation can be treated with local ablative therapy e.g. ethanol or acetic acid injection, cryoablation, radiofrequency ablation, microwave coagulation and injection of hot saline. These local ablative therapies can have equal efficacy as surgical resection in properly selected groups of patients.9,10

MANAGEMENT OF LARGE HCC

Majority of the HCCs are large when diagnosed all over the world. When profile of HCC was compared in developed countries and developing countries; hepatitis B was common cause and tumors were much larger at the time of identification in developing countries. Hepatitis C was common cause in developed countries and tumors were comparatively detected at early stage.11 In spite of these differences more than 70% of HCC detected all over the world are large or advanced HCC not suitable for curative treatment. Natural history of untreated patients with large HCC suggest 1 year, 3 years and 5 years survival 30 to 40%, 5 to 15% and 0% respectively.10 There is no standard established treatment for large HCC. Different palliative treatments include arterial embolization/chemoembolization, intraarterial lipiodol chemotherapy, hormonal compounds like tamoxifene, octreotide, systemic chemotherapy, immunotherapy with interferon, and internal radiation with $^{131}$I or $^{99}$Yttrium.12,13,14

Arterial Embolization

This is widely utilized treatment modality for large HCC. Embolization of artery supplying tumor is done with gelfoam cubes/coils/Ivalan particles. Gelfoam cube is commonly used agent. Intraarterial chemotherapeutic agent injection prior to embolization is done. Chemoembolization can be done with 5 Fu, Doxorubicin, cisplatinum, mitomycin C. Systemic review
of randomized trials for unresectable HCC has shown that chemoembolization improves survival in selected group of patients.\textsuperscript{12-14} Chemoembolization with cisplatinum or doxorubicin but not embolization alone improved response rate. Complete response is seen in 5% while partial response in 25 to 50% patients. Chemoembolization is recommended for a subset of patients with unresectable HCC having well preserved liver function and asymptomatic multinodular tumor without vascular invasion and extrahepatic spread.\textsuperscript{12} In small number of patients arterial chemoembolization has been used to down grade the tumors and effectively reducing the size of tumor and making them amenable to curative resection or liver transplantation or local ablative therapy like ethanol injection.\textsuperscript{15-18} Combination of arterial chemoembolization and thymosin alpha injections in treatment of HCC have shown improving result in preliminary study.\textsuperscript{16} Arterial lipoidalization with chemotherapy has been tried in 10 randomized controlled trials without significant benefit.\textsuperscript{12}\textsuperscript{12} At present arterial chemoembolization is only modality of proven benefits in treatment of Large HCC. Adverse effects of chemoembolization are (1) due to chemotherapeutic agent and (2) complications of embolization which are pain, fever, hepatic decompensation, rarely infarction of other organs. Serious complications are encountered in 3 to 5% patients.\textsuperscript{12-14}

\textbf{Tamoxifene}

The antiestrogen agent tamoxifene showed initially promising results in unresectable HCC. But majority of patients included in these trials had contraindication for locoregional therapies or more advanced tumoural disease including tumor related symptoms, impaired performance status, vascular invasion and extrahepatic spread. Metaanalysis of seven randomized controlled trials including 898 patients failed to demonstrate anti-tumoral effect and survival benefit with tamoxifene therapy.\textsuperscript{12-14}

Systemic chemotherapy by intravenous route has limited role in treatment of large HCC. The sole single agent with efficacy of 10 to 15% is doxorubicin. More aggressive combination chemotherapy regimes show no improvement in response but reduce survival due to side effects.\textsuperscript{12}

Interferon therapy and octreotide therapy showed promising results in initial studies but subsequent studies failed to show benefits of treatments.\textsuperscript{12-14} Adaptive immnotherapy and antiangiogenic gene therapy are experimental modalities in the management of HCC.

Internal irradiation using $^{131}$I or $^{90}$Yttrium has been tried in clinical trials. Clear benefit of these strategies is not established.\textsuperscript{15}

In our centre 92 HCC patients were evaluated. More than 80% were diagnosed HCC due to symptoms. 20% patients were detected on screening of cirrhotic patients. More than 70% tumors were unresectable at the time of diagnosis. In these patients with large HCC 70% patients were not eligible for any treatment, 25% patients with large HCC were suitable and treated with chemoembolization.

In conclusion, majority of the patients with HCC present in advanced stage chemoembolization is treatment of choice in selected group of patients. Newer treatment modalities/strategies need to be tried in controlled randomized trials.

\textbf{References}


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**Announcement**

**AWARDS SESSIONS**

1. Dr. DP Basu Young Award in Cardiology.
2. E. Merck Award
3. Dr. JN Berry Memorial Award and
4. Dr. MJ Shah Memorial Award in Tropical Medicine

There will be four award sessions at the 2005 Annual Conference of API at Mumbai. The rules and regulations of these awards are as under.

1. Papers that are accepted for presentation in the Award Session at the Annual Conference will be divided subject wise into four groups.

   GROUP I  CARDIOLOGY  DP BASU YOUNG AWARD
   GROUP II  CHEST DISEASES  E. MARCK AWARD
   GROUP III  OTHER SPECIALITIES  JN BERRY MEMORIAL AWARD
   GROUP IV  TROPICAL MEDICINE  MJ SHAH MEMORIAL AWARD

   The Award of Dr. JN Berry Memorial Award and E. Merck Award are given in alternate years in Group II and III papers. At the 2004 Annual Conference at Mumbai, Dr. JN Berry Memorial Award will be for "Other Specialties" and E. Merck Award for "Chest Diseases", Dr. DP Basu Young Award will be for "Cardiology" and Dr. MJ Shah Memorial Award for "Tropical Medicine".

2. The competitor must be the first author of the paper submitted for presentation at the API sessions of the Annual Conference. A testimonial must be submitted from the Head of the institution that the major work has been done by the competitor. Papers which are previously presented or published will not be considered. The competitor should also give a written pledge stating that the work has not been presented or published before. He should be a member of API.

3. Dr. JN Berry Memorial and DP Basu Young Awards are worth Rs. 1000/- each. E. Merck Award Rs. 2,000/- and Dr. MJ Shah Memorial Award is worth Rs. 2500/-

4. The upper age list of the competitor is 40 years.

5. The decision will be taken by a panel of judges appointed by the Governing Body of API.

6. The candidate must apply for the award and full manuscript of the paper will have to be submitted. The paper will be presented in separate award session.

7. Eight copies of full manuscript will have to be submitted Dr. SB Gupta, President Elect, Chairman - Scientific Committee, APICON 2005, 18, Greyclands, Rly. Officer's Flats, New Marine Lines, Mumbai 400 020 of API by 31st July, 2004. One copy of the paper should be sent to Dr. Sandhya Kamath, Hon. General Secretary of API at Mumbai.

8. The decision of the panel of judges will be final and binding to all concerned.

**PRESTIGIOUS AWARDS OF API**

2. Distinguished Member (2004)

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