Aims and objectives

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy.[1, 2] In a developing country like India, most patients present with advanced unresectable disease. These patients cannot be offered curative treatment options like surgical resection, liver transplant, and percutaneous ablative therapies.[2, 3] Therefore, palliative management forms the mainstay of therapy for most patients with the relatively advanced disease. [4, 5, 6] Transarterial chemoembolization (TACE) has evolved as an effective and widely used palliative treatment for unresectable HCC. A number of studies have been published on the efficacy of TACE comparing its outcome with supportive therapy. [7, 8, 9, 10] However, most of this experience is from the developed countries. There is not much-published information regarding its technique, efficacy, and survival outcome in developing countries like India. [11, 12, 13]

HCC is frequently the long-term sequel of chronic viral infection, mainly hepatitis B (HBV) and hepatitis C (HCV) infection. While hepatitis C (HCV) infection is the overwhelming cause of HCC in the West; hepatitis B (HBV) is the most prevalent cause in India. [14, 15] It is responsible for 35%-60% of chronic liver disease and 60%-80% of HCC in India. [16] Also, due to lack of screening programs and delayed care-seeking of the patients, HCC is often diagnosed only at an advanced stage. This precludes the use of the curative options, making TACE the most commonly employed treatment modality for patients with unresectable HCC.[17, 18, 19, 20]

There is a paucity of information on the outcome of HCC patients treated with TACE in India. This study is designed to bridge this gap in knowledge.
Methods and materials

*Study Design & Population:* In this retrospective study, all patients undergoing Transarterial Chemoembolization (TACE) with Lipiodol for treatment of unresectable hepatocellular carcinoma at our tertiary care oncology hospital between January 2013 and December 2016, were included. Approval of the Institutional Ethics Committee was obtained prior to the study.

The objectives of the study were to analyze the tumor response post TACE using mRECIST criteria and to evaluate overall survival outcomes in these patients. The secondary objective was to correlate intra-tumoral lipiodol accumulation with tumor response.

*TACE Procedure:* For diagnosis of HCC, the modified European Association for Study of Liver (EASL) criteria was followed. This requires either (a) fine needle aspiration cytology (FNAC) or (b) any two of the following: AFP more than 300 ng/ml, arterialization of the mass on contrast-enhanced CT, or MRI. Staging of HCC was done based on the Barcelona Clinic Liver Cancer (BCLC) staging protocol. The patients who underwent TACE during the study period had to satisfy the following inclusion criteria: patients with BCLC stage B/C HCC, patients with associated Child's A or B cirrhosis, normal main portal vein and patients willing for therapy and follow-up. Some patients of BCLC A, who were unsuitable for ablative therapy or surgery, were also included. The exclusion criteria included extrahepatic disease spread, main portal vein thrombosis, and hepatic arterio-portal shunting.

TACE was performed through the transfemoral route. Celiac axis arteriogram was obtained, to begin with. Selective cannulation of the hepatic artery supplying the tumor was performed using a 4F Yashiro catheter (Terumo Interventional Systems, New Jersey) and a 0.032-inch angled-tip Terumo guidewire (Terumo Interventional Systems, New Jersey). The catheter was placed as close as possible to the tumor. A 2.7 F microcatheter (Progreat microcatheter system, Terumo Interventional Systems, New Jersey) was used to access small and tortuous feeders.

The chemotherapeutic drug emulsion consisted of doxorubicin 50 mg (Doxilyd 50, Celon Laboratories, India), 6-8 ml of iohexiton non-ionic contrast media diluted in saline and 10ml of iodized oil (Lipiodol, Guerbet LLC, USA). The emulsion was prepared by repeated agitation of the mixture using two 20cc glass syringes connected by a three-way stop-cock connector.

The chemotherapeutic drug emulsion was then delivered through this cannulated feeding hepatic artery. The amount of emulsion to be injected was decided during the procedure. When the lesion showed complete coverage with lipiodol or if there was reflux of emulsion into normal branches, further injection of the emulsion was stopped. Each arterial branch
supplying the tumor was selectively catheterized and the drug emulsion was injected. The amount of emulsion injected varied from case to case. This was followed by embolization with gelatine sponge pledgets. Gelfoam embolization was avoided when microcatheter was used or no flow in the hepatic arterial branch was noted.

Follow-up after TACE included a detailed clinical examination, serum AFP estimation, and triphasic CT at a 1-month interval to assess response. If the follow-up CT showed the following findings: (1) residual or recurrent disease, or development of fresh lesions, (2) patients having raised serum AFP level and (3) insufficient intra-tumoral lipiodol deposition, a repeat TACE was undertaken after a gap of 12 weeks following the previous session of TACE, only if the Child's status was A/B. If the follow-up imaging showed disease progression then, depending upon the BCLC stage of the disease, the other available treatment options like oral sorafenib were considered. If all clinical and biochemical parameters were normal at 6 months following treatment, then triphasic CT was done at yearly intervals.

Data collection: Clinical, laboratory and radiological data of all these patients were collected. Post-TACE follow-up data, including details of clinical examination; serum AFP estimation and multiphase CT at 1 month to assess response was tabulated. The main outcome variable of interest was the local tumor response to TACE as estimated on the basis of multiphase CT. The tumor response was classified based on mRECIST Criteria for solid tumors. The overall survival of the patient was assessed from the date of patient's first procedure until death, loss to follow up or status at the time of data collection. All patients were followed up for a minimum period of 6 months. Patients with underlying cirrhosis were classified into Child's A, B or C based on the Child-Pugh classification.

Radiological workup comprised mainly of triphasic CT scan of the liver or contrast-enhanced multiphasic MRI for establishing the diagnosis.

Data Analysis:

The main outcome variable of interest was the local tumor response to TACE as estimated on the basis of triphasic CT. The tumor response was classified as disease-free status (complete response), residual disease, recurrence, or development of fresh lesions. These entities were defined as follows: (a) complete response (CR) - when the tumor was fully covered with lipiodol and had no enhancing viable tissue; (b) partial response (PR) - when the tumor was partially covered with lipiodol and enhancing viable tissue was seen; (c) Stable disease (SD) - when the enhancement was seen at the previously treated tumor site with no significant difference in lesion size (d) progressive disease (PD) - when new lesions were detected at different sites in the liver and not at the site where the previously treated tumors were located.
Statistical analysis: All analyses were performed with SPSS (ver 18.1) program. Continuous data were expressed as mean (SD) or median (range) and categorical data as proportions. Overall Survival was estimated using Kaplan-Meier analysis and the difference between child-pugh categories was tested using the log-rank test. Comparison of means was done with Wilcoxon signed rank test. Correlations between variables would be done with Pearson's tests.
Fig. 1: Contrast enhanced axial CT of the liver shows hepatocellular carcinoma in segment 8 (A) which shows avid FDG uptake on PET (B). DSA after selective catheterization of segment 8 hepatic artery branch shows tumor blush (C). Post chemoembolization image shows good lipiodol fixation within the tumor (D). Plain axial CT scan on 1 month follow up shows homogeneous uniform intra-tumoral lipiodol deposition (E) with no FDG uptake on PET (F).
Fig. 2: Four types of lipiodol deposition on plain axial CT scan: A: Type 1 - diffuse homogeneous opacification of the tumor focus; B: Type 2 - mostly homogeneous opacification; C: Type 3 - weak heterogeneous opacification; D: Type 4 - very weak or no opacification of the tumor focus

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Results

The study population consisted of 78 patients (71 males, 7 females) subjected to a total of 126 sessions of TACE (one session in 48 patients, two sessions in 15 patients, three sessions in 12 patients and four sessions in 3 patients).

The patients were grouped according to Child's classification as: A - 61 patients (78.2%) and B - 17 (21.8%) patients.
BCLC A patients were 8 (10.2%), BCLC B patients were 59 (75.6%), and BCLC C patients were 11 (14.1%).

The mean tumor size was 7.5 cm and the smallest and largest tumors measured 1 cm and 17 cm in largest dimensions respectively. A single HCC was present in 37 (47.4%) patients and multiple HCC in 40 (51.3%) patients.

All patients were followed up for at least 6 months after the TACE procedure until the end of June 2017. Patients were followed up for a mean period of 14.8 ± 9.2 months (range: 3-36 months; median: 12 months). A total of 37 (47%) patients died, while the remaining 41 patients were alive at the end of the study. The overall survival from the date of diagnosis at the end of the follow-up period was 21.6 ± 1.6 months. The survival time from the date of treatment was 20.6 ± 1.8 months.

The presence of extrahepatic disease had no significant effect on overall survival outcome. The variables of Child's stage, size of the mass, prior treatment and BCLC stage showed significant promise of association with mortality (P<.05) on univariate analysis. The size of the mass at the start of the treatment, number of lesions, BCLC stage and lipiodol deposition at the end of treatment emerged as the most significant independent predictors of survival.

The tumor response was assessed by mRECIST criteria for hepatocellular carcinoma. 33 (42.3%), 24 (30.7%) and 21 (26.9%) patients had partial response (PR), stable disease (SD) and progressive disease (PD) respectively. The overall survival of PR, SD, and PD groups was 24.7 ± 2.4, 23.3 ± 3.0 and 15.8 ± 2.5 months respectively.

Lipiodol deposition was also semi-quantitatively assessed by opacification on unenhanced CT. Four types of lipiodol deposition were defined as follows: type 1, diffuse homogeneous opacification of the tumor focus; type 2, mostly homogeneous opacification; type 3, weak heterogeneous opacification; type 4, very weak or no opacification of the tumor focus. 15 (19.2%), 33 (42.3%), 21 (26.9%) and 9 (11.5%) patients show types I, II, III and IV lipiodol deposition. The overall survival among types I, II, III and IV lipiodol deposition groups was 31.1 ± 1.5, 21.8 ± 2.5, 13.7 ± 1.6 and 13.1 ± 1.5 months respectively.
Multivariate analysis showed that local tumor response, intra-tumoral lipiodol deposition is a significant predictor of survival (p<0.05).
Fig. 3: Kaplan Meir curve for survival in patients after TACE with lipiodol with respect to tumor size

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Fig. 4: Kaplan Meir curve for survival in patients after TACE with lipiodol with respect to BCLC staging

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Fig. 5: Kaplan Meir curve for survival in patients after TACE with lipiodol with respect to intra-tumoral lipiodol accumulation

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Fig. 6: Kaplan Meir curve for survival in patients after TACE with lipiodol with respect to mRECIST tumour response

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (in months)</th>
<th>95% confidence limit</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>from time of diagnosis</td>
<td>21.65 ± 1.6</td>
<td>18.4 – 24.8</td>
<td></td>
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<tr>
<td>from time of treatment</td>
<td>20.65 ± 1.87</td>
<td>16.9 – 24.3</td>
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<td>Tumor Size:</td>
<td></td>
<td></td>
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<tr>
<td>= 3 cm</td>
<td>26.9 ± 2.7</td>
<td>21.6 – 32.23</td>
<td>0.027</td>
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<tr>
<td>&gt;3 cm</td>
<td>18.78 ± 1.95</td>
<td>14.9 – 22.61</td>
<td></td>
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<tr>
<td>Number of lesions</td>
<td></td>
<td></td>
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<tr>
<td>Single</td>
<td>23.3 ± 2.5</td>
<td>18.4 – 28.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Multiple</td>
<td>16.5 ± 2.0</td>
<td>12.5 – 20.6</td>
<td></td>
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<tr>
<td>Lipiodol accumulation</td>
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<td></td>
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<tr>
<td>Type 1</td>
<td>31.1 ± 1.5</td>
<td>28.0 – 34.1</td>
<td></td>
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<tr>
<td>Type 2</td>
<td>21.8 ± 2.5</td>
<td>16.9 – 26.8</td>
<td>0.001</td>
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<tr>
<td>Type 3</td>
<td>13.7 ± 3.7</td>
<td>10.0 – 16.2</td>
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<tr>
<td>Type 4</td>
<td>13.1 ± 1.5</td>
<td>6.4 – 21.1</td>
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<tr>
<td>mRECIST</td>
<td></td>
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<tr>
<td>PD</td>
<td>15.8 ± 2.5</td>
<td>10.9 – 20.7</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>24.7 ± 2.4</td>
<td>19.9 – 29.5</td>
<td>0.02</td>
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<tr>
<td>SD</td>
<td>23.3 ± 3.0</td>
<td>17.4 – 29.2</td>
<td></td>
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</table>

**Table 1:** Table describing the survival outcomes against various variables

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Conclusion

TACE is a safe and efficacious palliative procedure. In India, the majority of patients have advanced disease at presentation. Despite the presence of large-sized tumors in our study population, TACE showed favorable local outcome and the survival rates were comparable with those reported by other authors. Initial tumor size and intra-tumoral lipiodol deposition were the most important independent predictor of survival in our patients of HCC.
References


