Size of Hepatocellular Carcinoma as a Predictor of Radiologic Response to Transarterial Chemoembolization

MOHAMMAD A. AL-SHATOURI, M.D.*; AHMAD T. AHMAD, M.D.*; TALAL A. AMER, M.D.**; TAREK H. KHALIL, M.D.* and MOHAMMAD R. HABBA, M.D.*
The Department of Radiodiagnosis, Faculty of Medicine, Suez Canal* and Mansoura** Universities

Abstract

Background: Hepatocellular carcinoma (HCC) is common in Egypt and is expected to rise. Transarterial chemoembolization (TACE) is the most common treatment modality as a standard of care for intermediate stage HCC. Lesion size is a decisive factor in management of HCC. Large size is hypothesized to be a prognostic factor against complete radiologic response.

Objective: To assess the value of lesion size in predicting radiologic response to TACE.

Material and Methods: Forty seven HCCs were assessed for its distribution of lipiodol after TACE. Multiphase computed tomography (CT) was done 1 month after TACE to assess Radiologic response. HCC was classified according to the size <5cm, 5-10cm and >10cm in diameter.

Results: Lesions size ranged from 6mm to 15cm with a median of 7.3cm. Twenty five lesions (53.2%) were <5cm in diameter. Nine lesions (19.2%) were >10cm in diameter. Using modified RECIST, complete response was noted in 13 lesions (27.7%), partial response in 25 lesions (53.2%) and stable disease in 9 lesions (19.1%) one month after TACE. Lipiodol covered >75% of the lesion in 30 lesions (63%) and <75% in 13 lesions (27.7%) and 0% in 4 lesions (8.5%). Eight out of 9 lesions >10cm in diameter (88%) and 17 out of 25 lesions <5cm in diameter (68%) showed Lipiodol defects one month after TACE. A diameter >10cm was significantly correlated with incomplete Radiologic response (p-value 0.0002). A diameter of <5cm was not significantly correlated with Radiologic response. Lesion size >10cm was predictive of complete response showing a positive predictive value (PPV), prevalence weighted likelihood ratio (pwLR+), post test probability and odds ratio of 88.7% (95% CI 50.7-99.4%), 7.85 (95% CI 1.24-51.5), 95.4% (compared with pretest probability of 72.3%) and 20.7: 1 (compared with pretest odds ratio of 0.18: 1 respectively).

Conclusion: HCC >10cm in diameter are very likely to show lipiodol defects after TACE. Lesions <5cm are not in advantage towards complete response.


Introduction

HCC is an important malignancy in Egypt occurring in 1.2 every 1000 person per year [1]. About 5.9% of cirrhotics in Egypt have HCC [2]. Its incidence is expected to rise reaching its peak in 2020 [3]. TACE is the most common treatment modality, being the standard of care for intermediate stage HCC [4]. Size of HCC is an important prognostic factor. It predicts the survival and recurrence after treatment. It is used as an important selection criterion for surgery, transplantation, local ablative therapies as well as TACE. However the suggested upper limit for a lesion to be eligible to TACE is limited in literature. The University of California Los Angeles algorithm for treatment of HCC limits TACE in Child B to patients within Milan Criteria i.e. one lesion <5cm or up to three lesions each <3cm [5].

Aim of the work:

This study was designed to assess the predictive value of lesion size in predicting radiologic response to TACE.

Patients and Methods

The study was performed at the Radiology Department, Suez Canal University Hospital, Ismailia, Egypt and Gastrointestinal Surgery Center, Mansoura University, Egypt from 8/2008 to 7/2011 after approval of the research ethics committee. Forty seven HCCs were included. Inclusion criteria include: Age ≥ 18 years, proved HCC according the published guidelines [6]. Incurable HCC stage B
according to Barcelona clinic liver Cancer (BCLC criteria), or stage 0/A not suitable for Surgery or local ablative Therapy. Exclusion criteria include renal failure, previous HCC treatment or bacterial infection, gastrointestinal bleeding, encephalopathy, refractory ascites, serum total bilirubin >3mg/L serum albumen <2.5mg/L, White blood cell count less than 3000/cm³, Hemoglobin less than 8gm/dl, any major vascular invasion, hepatofugal flow, significant extra-hepatic spread, Child-Pugh C, Okuda stage 3 as well as contraindication to angiography [7]. Patients with unsatisfactory multiphase CT images were also excluded [8]. Lesions were classified as <5cm, 5-10cm and >10cm in diameter. The TACE procedures and revising the multiphase CT were done by a radiologist with more than 10 years experience in this technique using angiographic unit Philips Integris 3000 and Philips Diagnostic 96 machines. TACE was done as described in literature using trans-femoral approach. The lipiodol/Adriblastina emulsion was done at a ratio of 10ml: 50mg dissolved in 5ml saline [9]. The dose is calculated according to tumor size, vascularity and liver function. Injection was done as selective as possible using 4F Cobra catheter with the aid of 2.7F Progreat microcatheter (Terumo). Gelfoam embolization was done using slurry of Gelfoam particles mixed with contrast till acquiring grade 3 using subjective angiographic chemoembolization endpoint scale if technically feasible [10]. Multiphase CT was done 1 month after the procedure to assess radiologic response according to modified RECIST [11]. Area within the tumor that shows less than 50HU in the non-contrast scan is considered lipiodol negative area [12]. Data collected was managed by statistical package SPSS (statistical package for social sciences) SPSS for windows base system user guide 10.1 Chicago, SPSS INC., 2001.

Results

Forty seven lesions were included in the study. Forty two of the patients (89.4%) are males. Their ages range from 40-67 years (mean 53.5 years). Eight patients (17%) are over 65 years old. Thirty eight patients (80.8%) had HCV infection, seven patients (14.8%) had HBV infection and two patients (4.4%) had combined infections.

Staging was assessed in the sample population. Thirty four patients (72.3%) were stage B according to BCLC staging system, six patients (12.8%) stage C, five patients (10.6%) stage A, and two patients (4.3%) very early stage HCC. Thirty two patients were Child-Puch class A (68.1 %), and fifteen patients were Child-Pich class B (31.9%). No patients in the study belong to Child-Puch class C.

Multifocality (>3 lesions) was presented in 15 patients (31.9%). Lesions size ranged from 6mm to 15cm, with a median of 7.3cm. Twenty five lesions (53.2%) were <5cm in diameter. Nine lesions (19.2%) were >10cm in diameter. The growth pattern was presented as follows: 27 lesions (57.4%) were nodular and encapsulated, 6 lesions were infiltrative (12.8%), and 7 lesions (14.9%) showed >50% pedunculation.

Level of embolization was lobar in 31 of the procedures (66%), segmental in 15 procedures (31.9%) and extraparenchymatous in one case in which the hepatic artery was occluded and the tumor was supplied by the suprarenal as well as inferior phrenic arteries. Microcatheter was used in 9 lesions (19.2%) to inject superselectively due to poor liver function and inability to reach the segmental arterial supply using the conventional 4F catheter.

The radiologic response to TACE was assessed using Modified RECIST criteria when comparing the CT before and 1 month after TACE. It is known to be superior to 3D and 2D assessment which are not practical and result in significant intraobserver and interobserver errors. Complete response was noted in 13 lesions (27.7%), partial response in 25 lesions (53.2%), and stable disease in 9 lesions (19.1%). None of the patients showed disease progression 1 month after TACE. Lipiodol covered >75% of the lesion in 30 lesions (63.8%) and <75% in 13 lesions (27.7%). No Lipiodol deposition was found in and 0% in 4 lesions (8.5%) (Fig. 1).

Eight out of the 9 lesions >10cm in diameter (88%) showed Lipiodol defects after TACE. Seventeen out of the 25 lesions <5cm in diameter (68%) showed Lipiodol defects after TACE (Figs. 2, 3). A diameter >10 cm was significantly correlated with incomplete radiologic response (p-value 0.0002). A diameter of <5cm was not significantly correlated with radiologic response. Lesion size >10cm was predictive of incomplete response showing a positive predictive value (PPV), prevalence weighted likelihood ratio (pwlR+), post test probability and odds ratio of 88.7% (95% Confidence interval (CI) 50.7-99.4%), 7.85 (95% CI 1.24-51.5), 95.4% (compared with pretest probability of 72.3%) and 20.7: 1 (compared with pretest odds ratio of 2.6: 1) respectively (Table 1).

Lesion size <5cm did not predict complete Radiologic response as the PPV, pwlR+, post test probability and odds ratio were 32.2% (95% CI 15.7-53.6), 0.47% (95% CI 0.25-0.89), 15.4% (compared with a pretest probability of 27.6%) and 0.18: 1 (compared with pretest odds ratio of 0.38), respectively (Table 1).
Fig. (1): Evaluation of tumor response to TACE using mRECIST.

Fig. (2): Pre TACE multiphase CT showing large HCC at Lt. lobe. (A) Noncontrast phase, (B) Early arterial phase and (C) Venous phases.

Fig. (3): Post TACE plain CT showing Lipiodol uptake 60%.

Table (1): Value of lesion size in predicting radiologic response after TACE.

<table>
<thead>
<tr>
<th></th>
<th>Size &gt;10cm</th>
<th>Size &lt;5cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity %</td>
<td>24 (11.4-41.6)</td>
<td>62 (32.3-85)</td>
</tr>
<tr>
<td>Specificity %</td>
<td>92 (62.1-99.6)</td>
<td>50 (32.8-67.3)</td>
</tr>
<tr>
<td>PPV % (95% CI)</td>
<td>88.7 (50.7-99.4)</td>
<td>32.2 (15.7-53.6)</td>
</tr>
<tr>
<td>NPV % (95% CI)</td>
<td>31.6 (18.0-48.8)</td>
<td>77.5 (54.2-91.3)</td>
</tr>
<tr>
<td>LR+ (95% CI)</td>
<td>3.06 (0.42-22.1)</td>
<td>1.23 (0.71-2.12)</td>
</tr>
<tr>
<td>pw LR+ (95% CI)</td>
<td>7.85 (1.24-51.5)</td>
<td>0.47 (0.25-0.89)</td>
</tr>
<tr>
<td>LR- (95% CI)</td>
<td>0.83 (0.68-1.0)</td>
<td>0.77 (0.37-1.62)</td>
</tr>
<tr>
<td>pwLR- (95% CI)</td>
<td>2.16 (1.56-3.0)</td>
<td>0.29 (0.13-0.65)</td>
</tr>
<tr>
<td>Pretest probability (odds)</td>
<td>72.3 (2.6)</td>
<td>27.7 (0.38)</td>
</tr>
<tr>
<td>Posttest probability of a positive test (odds)</td>
<td>95.4 (20.7)</td>
<td>15.4 (0.18)</td>
</tr>
<tr>
<td>Posttest probability of a negative test (odds)</td>
<td>68 (2.2)</td>
<td>23 (0.33)</td>
</tr>
</tbody>
</table>

For a size >10cm, values are for probability of incomplete response. For a size <5cm, values are for probability of complete response.

Discussion

Complete Lipiodol uptake correlates with higher tumor necrosis, lower recurrence rate, better survival and better transplantation outcome [13-15]. Several factors have been suggested as predictors of TACE outcome. One important factor is lesion size. It predicts the survival and recurrence after treatment. It is used as an important selection criterion for Surgery, transplantation, local ablative therapies as well as TACE. However the suggested upper limit for a lesion to be eligible to TACE is limited in literature. The University of California Los Angeles algorithm for treatment of HCC limits TACE in Child B to patients within Milan Criteria i.e. one lesion \( \leq 5cm \) or up to three lesions each \( \leq 3cm \) [8]. The Barcelona Clinic Liver cancer
Giant HCC >10cm were more likely to show lipiodol defects (PPV 88.7%, post test probability 95.4%, and odds 20.7: 1). In literature, the role of lesion size as predictor of Radiologic response to TACE is controversial. It is stated that lesions <3cm are more likely to show complete response after the first session [18]. Indeed, the rate of complete necrosis according to the HCC size class was: 69%, 69%, 52%, 68%, 50% and 13% for lesions of <2.0, 2.1-3.0, 3.1-4.0, 4.1-5.0, 5.1-6.0, and >6.0cm, respectively [9]. Others claimed that lesion size and number does not predict response to TACE with the only predictive variable is hypovascularity [14, 19-20]. Also tumors >10cm are known to be correlated with poor response and loss of liver function after TACE. Tumors <8cm and occupying <5% of liver volume are favorable for TACE [21].

HCC <5cm in this series shows a lower rate of complete response compared with the larger lesions (post test probability and odds of complete response 15.4% and 0.18: 1 compared with 27.7% and 0.38: 1 generally in the series). This finding could be due to confounders or limited sample size.

This study has important clinical implications. TACE should be avoided in patients with aggressive tumors having borderline liver functions (Late Child B) and poor performance status if lesion size is >1 0cm due to the high probability of incomplete response that requires further sessions and is considered by the patients as incomplete treatment.

Time factors and resources restrictions have been the main limitations of this study. As a direct consequence of our Methodology, the study encountered a number of other limitations like lack of confounders’ control, and the small sample size. Also, stratifying patients into complete/incomplete Radiologic response as an outcome measure is not optimal because even >50% lipiodol deposition is associated with improved survival [22].

**Conclusion:**

We conclude that lesion size >10cm significantly increases the probability of incomplete Radiologic response to TACE. This is clinically relevant in cases of aggressive tumors with borderline liver functions and performance status; the decision makers shall err to avoiding the TACE due to the need for repeated session to achieve satisfactory response.

**References**


