# Current Modalities for Treatment of Intermediate and Advanced Hepatocellular Carcinoma Considering Different Staging Approaches

Ashraf M. Enite, Ehab Adel [1] and M. El-Wahsh[2]

[1]Department of Diagnostic and Interventional Radiology, Al Azhar University
[2]Hepatobiliary & Liver Transplant Unit, Al Zahraa University Hospital, Abasia
Cairo, Egypt
ashraf.enite@yahoo.com

**Abstract: Aim:** The aim of this study is to assess the outcome of intermediate and advanced hepatocellular carcinoma treatment approached through three different staging systems which are Okuda, Child-Turcotte-Pugh (CTP), and Barcelona Clinic Liver Cancer (BCLC). At the same time to predict patient prognosis and survival in each staging system. **Material and methods:** We retrospectively identified HCC patients from the database of the Hepato-biliary and liver transplantation Unit/General Surgery and Radiology departments, Al Zahraa University hospital, between April 2011 and July 2012. The patients included after confirmed pathology by radiologic criteria of tri-phasic CT and/or AFP level $\geq$ 400 ng/ml. The data collected to stage all patients by CTP, Okuda and BCLC systems. It is included demographics, risk factors for developing HCC, performance status, cirrhosis clinical manifestations. Laboratory data, including coagulation profile, different cirrhosis parameters and AFP, were captured as well as bilirubin references. Tumor characteristics that were reported were number of lesions, diameter of largest lesion, and extent of disease, MVI and metastatic disease status. **Results:** We identified 56 patients with radiology and laboratory confirmed HCC. Their age ranged from 40 to 76 years and mean age is 56.6$\pm$ 6.73 years. There are 41(73%) males and 15(27%) females. All patents presented with cirrhosis, which is induced by hepatitis C virus in 49 patients, hepatitis B virus in 6 patients. One of these hepatitis B patents is addict and alcoholic. The patients divided into 3 groups. The first group included 35 patients who were treated with TACE/TAC. The second group included 17 who were treated with sequential TACE/RFA. The third group included 4 patients who were treated by symptomatic and oral chemotherapy. MVI was present in 10 (28%) patients of TACE group and the 4 (100%) patients of the oral chemotherapy group. The patients were followed for 1 year and the mean duration of follow-up in the study was 8.0 months. 19 (29.4%) patients in this study died during follow-up. The complications are Liver dysfunction in 15(26.7 %); Hepato-renal syndrome in 4 (7.1%) ; Pleural effusion in 3 (5.3%) ; inguinal hematomas; 1 (1.8%).

[Ashraf M. Enite, Ehab Adel and M El-Wahsh. **Current Modalities for Treatment of Intermediate and Advanced Hepatocellular Carcinoma Considering Different Staging Approaches.** *J Am Sci* 2012;8(10): 204-212]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 31

**Key words**: Hepatocellular carcinoma staging; Treatment; Radiofrequency ablation; Trans-Arterial Chemo-Embolization.

**Abbreviations:**

**BCLC:** Barcelona Clinic Liver Cancer; **BCLC-B: BCLC** Intermediate stage of HCC; **BCLC-C: BCLC** advanced stage of HCC; **CTP:** Child-Turcotte-Pugh.; CI: Confidence Interval; **HCC:** Hepato-Cellular Carcinoma.; **INR**: International Normalized Ratio Values.; **MVI**: Macro-Vascular Invasion; **RCTs**: Randomized Controlled Trials; **RFA**: Radio-Frequency Ablation. **TACE:** Trans-Arterial Chemo-Embolization.; **TACE-RFA**: sequential TACE followed by RFA.

## 1. Introduction

HCC is the sixth leading cause of cancer mortality. It is usually develops in patients with liver cirrhosis. (Pinter *et al.*, 2012). It is responsible for over 16,000 deaths annually in the United States alone. (Mendiratta-Lala *et al*., 2010).

The prognosis and treatment options for HCC patients depend on the tumor stage and the extent of liver dysfunction. A staging system is needed to help predict survival outcome and deciding optimal choice for the treatment of advanced HCC,(Abou-Alfa, 2009) and more appropriate therapeutic approach in the more advanced cases.(Huitzil-Melendez *et al.*, 2010).

Identification of relevant prognostic factors for both liver cancer and its function has led to the development of staging systems that include both. Reported staging systems for HCC include TNM sixth edition, Okuda, BCLC, Cancer of the Liver Italian Program (CLIP), Chinese University Prognostic Index (CUPI), Japan Integrated Staging Score (JIS score), and the Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire Prognostic classification (GETCH). The utility of most of these

staging systems in predicting survival in patients with advanced HCC. The characteristics of patients with advanced disease might significantly differ from a population of patients balanced between early and advanced disease, for which the available staging systems were originally developed. (Huitzil-Melendez *et al*., 2010).

BCLC staging system has been constructed on the basis of the results obtained in the setting of several cohort studies and RCTs. (Ponsi *et al.,* 2005). It is endorsed by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases (Bruix & Sherman, 2005 and Forner *et al.,* 2010). It is an algorithm for the management of HCC that links different stages of HCC with appropriate therapeutic strategies. Accordingly, potentially curative treatments (eg, liver transplantation, resection, or RFA) are available but are reserved for patients with early stage HCC (Pinter *et al.,* 2012).

RFA is an interventional procedure that is increasingly used in the treatment of liver tumors and has a good therapeutic profile. RFA has proved to be a safe technique for control and treatment of localized HCC; however, certain complications can arise from this procedure (Mendiratta-Lala *et al*., 2010).

TACE is the recommended treatment for patients with asymptomatic, large, or multifocal HCC without MVI or extra-hepatic metastasis (i.e, intermediate BCLC-B) (Forner *et al.,* 2010). TACE induces an objective tumor response in 36-50% of patients, resulting in delayed tumor progression and prolonged survival (Forner *et al.,* 2010, Raoul *et al.,* 2011 and Pinter *et al.,* 2012).

## 2. Material and methods

### Patients

We retrospectively identified HCC patients who were evaluated clinically and laboratory in the Hepato-biliary and liver transplantation Unit. They were included if they had confirmed pathology or had fulfilled radiologic criteria of tri-phasic CT. Radiologic criteria are focal lesion greater than 3 cm with arterial enhancement and/or AFP level $\geq$400 ng/ml. These patients were not eligible for curative therapies or had progressive disease after surgical or percutaneous treatment. Patients were excluded: (a) If complete main PV thrombosis, Child-Pugh stage C disease, marked thrombocytopenia, massive ascites, and acute renal or liver failure were considered to be contraindications for TACE; (b) If there was no follow-up information, patients with a diagnosis or history of other concurrent malignancies; (c) Patients who had previous liver transplantation, resection and hepatic metastasis.

### Data Collection

The data of HCC patients obtained from the database of the Hepato-biliary and Liver Transplantation Unit/General Surgery and Radiology departments, Al Azhar university hospitals at Faculty of Medicine. It is collected to stage patients. These included demographics, risk factors for developing HCC, clinical data including performance status, parameters of liver cirrhosis manifestations (e.g. ascites and encephalopathy). Laboratory data, including coagulation profile, different cirrhosis parameters and AFP, were captured as well as bilirubin references.

Tumor characteristics that were reported were number of lesions, diameter of largest lesion, extent of disease, vascular invasion, PV thrombosis, organ invasion, nodes status, and metastatic disease status; these were retrospectively recorded from the radiology report, with the exception of tumor extent, that was prospectively determined by review of the available baseline CT and/or US of the liver by Radiologist and Hepato-biliary surgeon.

### Staging

The collected clinical, radiological and laboratory data were used to restage all patients by CTP, Okuda and BCLC systems.

### Treatment protocol

All patients were allocated to undergo RFA and/or TACE between April 2011 and July 2012). Informed consent was obtained from all patients before any interventional procedures

### RF ablation procedure:

Patients positioned supine. A local anesthetic 10cc of 1% Lidocaine was injected from the skin insertion site down to the peritoneum. The skin was incised with a small (no. 11) lancet, and a needle was advanced to the chosen area. Conscious analgesic sedation with intravenous Fentanyl citrate and Droperidol was applied before the procedure. RFA was performed under real-time US guidance (AU5 and Mylab 50 X vision esaote Italy) in most of patients and in some patients under CT guidance. A (RITA), 15-gauge insulated RFA needle with 9 expandable electrode tines that had a diameter of 5 cm at expansion used in the study. RFA needle was first inserted into the tumor and start RFA procedure.

No more than three applications of RFA were given in a treatment session. For tumors $\leq$3.0 cm, a single ablation was performed. For tumors > 5.0 cm in greatest dimension, multiple Overlapping RFA were performed. The first ablation was started at the location farthest away from the skin puncture site. After ablation was completed, the needle was withdrawn to the second predetermined location. This process was repeated until the entire lesion was adequately covered.

During RF ablation, a hyperechoic area was observed around the electrode tip at ultrasonic

monitoring. The aim of the treatment was to have this hyperechoic area cover an area larger than 1cm around the HCC. At the end of the procedure, the generator was reactivated to ablate the needle tract to prevent bleeding (Liang *et al.,* 2008). After the procedure, the patients were closely monitored. For tumors > 5.0 cm in greatest dimension, multiple Overlapping RFA were performed. The first ablation was started at the location farthest away from the skin puncture site. After ablation was completed, the needle was withdrawn to the second predetermined location. This process was repeated until the entire lesion was adequately covered.

During RF ablation, a hyperechoic area was observed around the electrode tip at ultrasonic monitoring. The aim of the treatment was to have this hyperechoic area cover an area larger than 1 cm around the HCC. At the end of the procedure, the generator was reactivated to ablate the needle tract to prevent bleeding (Liang *et al.,* 2008). After the procedure, the patients were closely monitored.

**TACE Procedure**

All TACE procedures were performed by combined Interventional Radiologists and Hepato-Biliary Surgeons .TACE was performed by using a selective Cobra (C2) 5-F catheter and hydrophilic 0.035" guide wire. It is originating in the femoral artery. Visceral DSA assesses the arterial blood supply to the liver and confirm the patency of PV. Most of patients underwent distal super-selective catheterization of the hepatic arteries by using a coaxial technique and a 2.8-F Renegade micro-catheter Kit, Boston Scientific USA to achieve stasis in the tumor-feeding artery. Regardless of tumor number and size intra-arterial injection of an emulsion of doxorubicin hydrochloride (adjusted for serum bilirubin concentration, with 75, 50, and 25 mg/m2 of doxorubicin administered for bilirubin levels of ≤1.5, 1.5–3.0, and >3.0 mg/ dl, respectively). (Llovet *et al.*, 2002 and Pinter *et al.*, 2012). It is mixed with 5-10 ml of Lipiodol (Lipiodol Ultra-Fluide; André Guerbet Laboratories, Aulnay- Sous-Bois, France).

Embolization was performed until stasis was achieved in the second- or third-order branches of the right or left hepatic artery. If the territory of the chemolipiodolized artery did not show stagnant flow, pure iodized oil was then injected. TACE performed with absorbable gelatin sponge particles (Gelfoam; Hanzhou Alc, Hanzhou, China , 1–2 mm in diameter) or Contour (Embolization particles 250-355µ in diameter, Boston scientific).

**Assessments**

The clinical, laboratory, and radiologic records were reviewed. Side effects of RFA and TACE were reported. The side effects that occurred within 4 weeks after the interventional procedures were recorded. Post TACE syndrome (i.e. abdominal pain, fever without any infection focus, nausea, vomiting) was expected and, therefore, was not documented. Tumor response was evaluated with Triphasic CT. Furthermore, we compared the outcome and overall survival of patients groups and according to intermediate and advanced BCLC subgroups

**Follow up**

Triphase spiral CT was performed 4 weeks after sequential TACE or RFA and every 3 months thereafter. At each of these follow-up visits, serum liver and AFP tests performed. Chest radiography was performed every 6 months.

When a non-enhancing area with a diameter greater than that of the accumulated Lipiodol and/or RFA coagulative necrosis at post-treatment CT was detected, the treatment was considered finished.

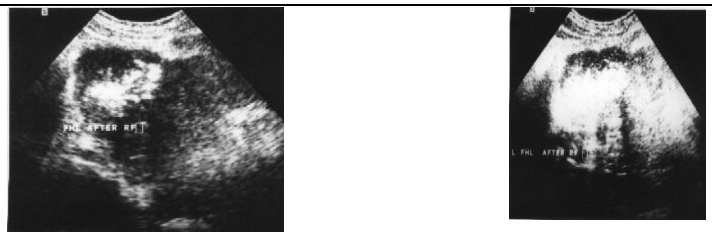
Local tumor progression was defined as the appearance of tumor enhancement around the ablated/embolized area after treatment. Distant recurrence was defined as the appearance of new HCC in the untreated liver or extra-hepatic regions. The choice of treatment for local tumor progression or distant recurrence was determined by tumor characteristics, patient preference, and results of the discussion by Hepato-biliary and radiology team.

For patients with local tumor progression or distant recurrence RFA, TACE, systemic chemotherapy, or conservative treatment was recommended, depending on the tumor, liver function, and general condition of the patient.

All examinations were performed with the MDCT unit by using a sequential acquisition of 5-mm thick sections at 120 kV and 250 mA. All images were interpreted by experienced radiologists. Major complications were defined as those that, if left untreated, threatened the patient's life, led to substantial morbidity and disability, or lengthened the hospital stay. All other complications were considered to be minor. Pain was defined according to World Health Organization criteria (Peng et al., 2012). The medical observation, determination of complications, and grading of pain were done by referring hepatobiliary-surgones. All complications were observed clinically when patients were admitted and were reported by telephone after patients were discharged.

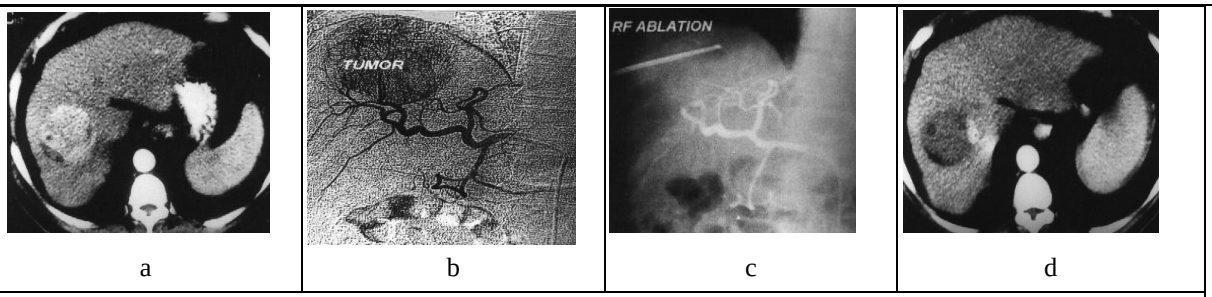
The primary end point was overall survival, the secondary end point was recurrence-free survival, and the tertiary end point was side effects of treatment. Survival time was defined as the interval between the time HCC staging and the time of death or the last follow-up.

Patients lost to follow-up were censored at the date of the last observation.



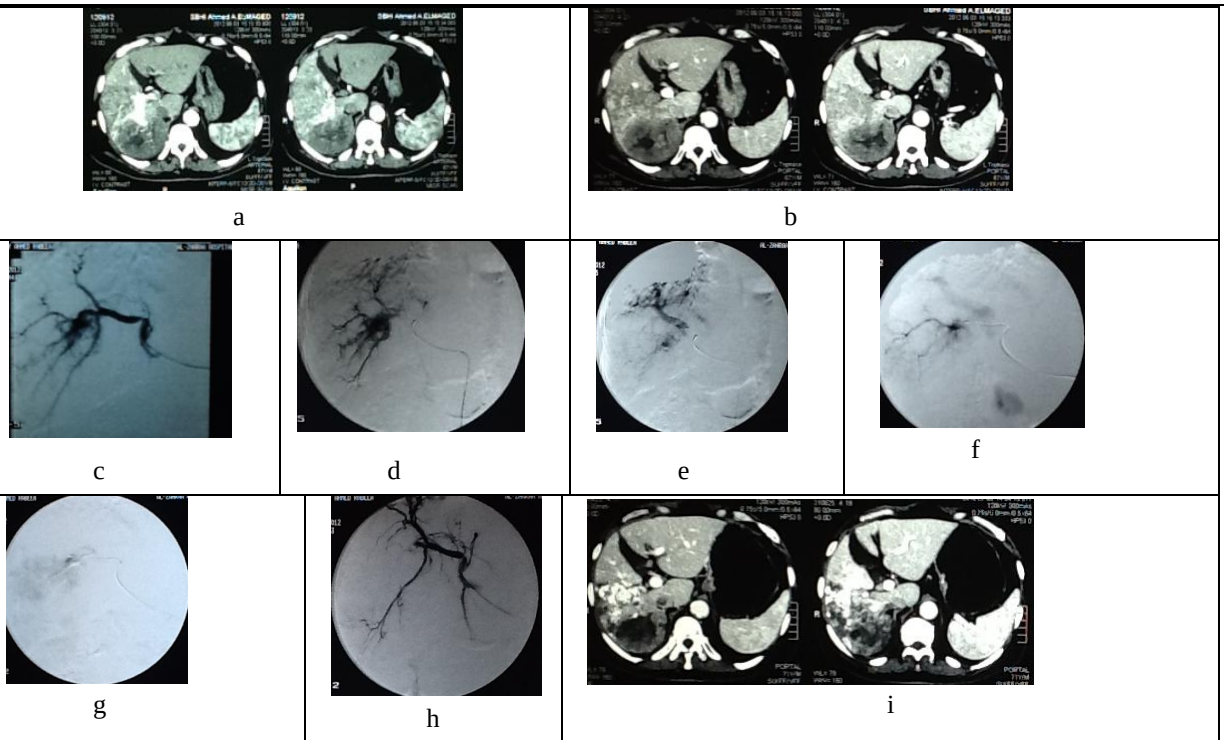
a b

Fig 1: US guided RFA shows progressive area of increased echogenicity at expected anatomical location of HCC (a & b).




a b c d

Fig 2: a) right hepatic lobe segment 8 enhanced focal lesion at arterial phase; B) intense tumor blush at DSA arterial phase; c) RFA needle at proper position; d) Post TACE-RFA follow up CT presents focal coagulative necrosis of HCC.



a b c d e f g h i

Fig 3: **(a&b)** Right hepatic lobe infiltrative lesion at arterial & portovenous phases. It present heterogeneous enhancement & arterio-portal fistula. **(c, d & e)** DSA demonstrates arterio-portal fistula and tumor blush. **(g & h)** DSA with micro-catheter arterio-portal fistula embolization, & infusion of Lipiodol/ doxorubicin mixture. **(i)** Follow up CT demonstrates heterogeneous Lipiodol concentration at the right hepatic lobe focal lesion.

## 3. Results

### Study Population

Detailed baseline patient characteristics are shown in Table (1). In our study we identified 56 patients with radio-logically and laboratory confirmed HCC. Their age ranged from 40 to 76 years and mean age is 56.6± 6.73. As regard the gender, there are 41(73%) males and 15(27%) females. All the 56 patents presented with cirrhosis. The cirrhosis is induced by hepatitis C virus in 49 patients, hepatitis B virus in 6 patients. One of these hepatitis B patents is addict and alcoholic. They divided into 3 groups.

The first group included 35 patients who were treated with TACE/TAC. None of our patients were underwent TACE with drug-eluting beads, due to economic factors and lack of its availability. There are 25(71.4 %) males and 10(28.6%) are females. 25(71.4 %) patients were intermediate BCLC-B and 10(28.6%) patients were advanced BCLC-C HCC. 20 (57 %) patents were child Pugh class A/ Okuda stage I and 15 (43%) patients were Child Pugh class B/Okuda stage II.

Collectively, 47 TACE procedures were carried out. 23 (65.7%) patients treated with conventional TACE and 12 (34.3%) with chemo-lopoidol injection/TAC. The mean number of TACE procedures per patient was 1.5 .

The second group included 17 who were treated with sequential TACE/RFA. There are 12(70%) males and 5 (30%) are females. All patients were intermediate BCLC-B. 14 (82%) patients were child Pugh class A/ Okuda stage I, and 3 (18%) patients were Child Pugh class B/Okuda stage II. Collectively, 23 RFA procedures were carried out. 1.4 is the mean value of RFA procedures per patient.

The third group included 4 patients who were treated by symptomatic and oral chemotherapy. There are 4 (100 %) males. They were advanced BCLC stage C HCC/Child Pugh class B/Okuda stage II.

MVI was present in 10 (28%) patients of TACE group and the 4 (100%) patients of the oral chemotherapy group. None of the 17 sequential TACE/RFA patients group are presenting MVI or extra hepatic metastases.

The patients were followed for 1 year and the mean duration of follow-up in the study was 8.0 months. 19 (29.4%) patients in this study died during follow-up.

Side effects noticed in the study are Liver dysfunction in 15(26.7 %); Hepato-renal syndrome in 4 (7.1%) ; Pleural effusion in 3 (5.3%) ; inguinal hematomas; 1 (1.8%) : Non of our patients developed Liver abscess.

Table (1): Demonstrates the patients' characteristics.

| | TACE /TAC | Sequential TACE/RFA | Oral chemo and symptomatic therapy |
|---|---|---|---|
| Age ;mean 56.6±6.73 | 57.6± 7.64 | 55.1 6 ± 9.5 | 57.5± 6 10.0 |
| Sex<br>Male 41(73%)<br>Female 15(27%) | <br>25<br>10 | <br>12<br>5 | <br>4<br>0 |
| Cirrhosis etiology<br>HCV 49<br>HBV 6<br>Association | <br>30<br>4<br>1 of HBV patents is addict and alcoholic | <br>15<br>2<br>0 | <br>4<br>0<br>0 |
| Child-Pugh A/ Okuda I<br>Child-Pugh A/ Okuda I | 20<br>15 | 14<br>3 | 0<br>4 |
| BCLC<br>B:intermediate<br>C : advanced | <br>23<br>12 | <br>17<br>0 | <br>2<br>2 |
| MVI | 10 | 0 | 4 |
| Albumin<br><3<br>>3<br>Bilirubin<br><2<br>>2 | <br>22<br>13<br><br>23<br>12 | <br>17<br>0<br><br>17<br>0 | <br>3<br>1<br><br>3<br>1 |
| AFP<br>>400 ng/ml<br><400 ng/ml | <br>26<br>9 | <br>10<br>7 | <br>4<br>0 |
| Survival<br>6 months<br>1 year | <br>27<br>24 | <br>16<br>13 | <br>0<br>0 |

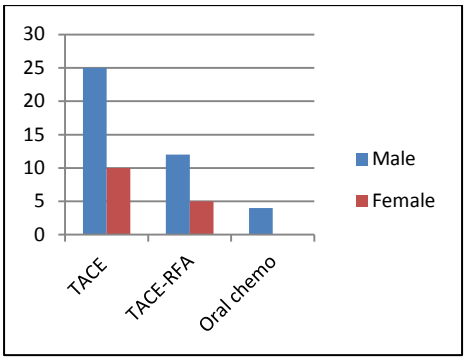



Fig. (4): Demonstrates the patient's gender distribution among the various groups

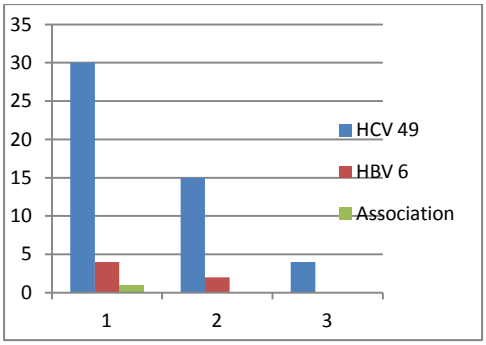



Fig. (5): shows incidence of hepatitis as a risk factor.

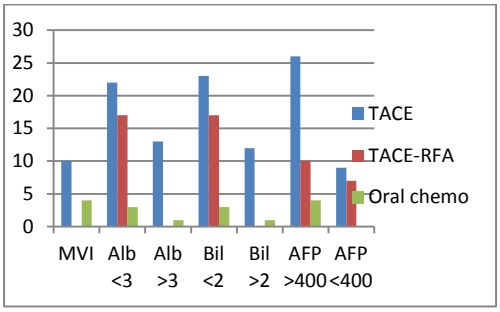



Fig. (6): demonstrates MVI and laboratory values

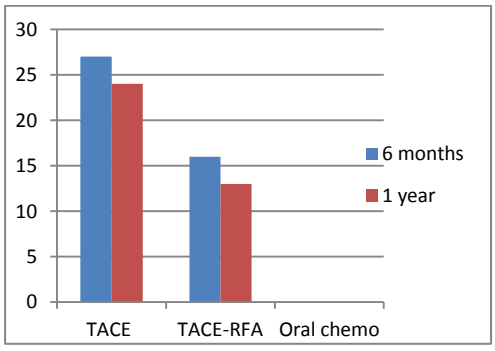



Fig. (7): demonstrates the patients' survival.

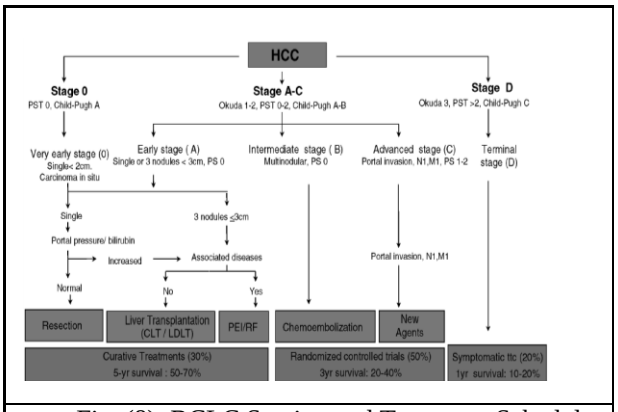



Fig. (8): BCLC Staging and Treatment Schedule

## 4. Discussion

The prognosis and treatment options for HCC patients depend on the tumor stage and the extent of liver dysfunction. (Abou-Alfa, 2009). Identification of relevant prognostic factors for both the liver cancer and function has led to the development of staging systems that include both. (Huitzil-Melendez *et al.*, 2010).

Ponsi *et al.*, 2005 reported that Child-Pugh score described the liver function. However, in the last decade the Okuda classification which includes parameters of the liver functional status – albumin, ascites, bilirubin – and the tumor stage, less than or greater than 50% of liver area involved. Okuda classification properly stratified patients when most of them were diagnosed at an advanced/symptomatic stage. Nowadays, this classification is not adequate to stratify patients prior to radical or palliative therapies, even when dividing Okuda stage I patients into two subgroups according to tumor size. When compared with modern staging systems, it has been shown to have lower predictive capacity

BCLC staging system has been endorsed by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases (Bruix & Sherman 2005 and Forner *et al.*, 2010). BCLC staging system uses variables related to tumor stage, liver functional status, physical status, and cancer-related symptoms, and links the four stages described into algorithm for appropriate therapeutic strategies (Figure 8). (Ponsi *et al.*, 2005 and Pinter *et al.*, 2012).

In brief, patients at very early BCLC-0 HCC are optimal candidates for resection. Patients at early BCLC-A HCC are candidates for radical therapies (resection, liver transplantation or percutaneous treatments). (Pinter *et al.*, 2012).

Unfortunately, > 50% of all HCC patients diagnosed at an intermediate BCLC-B or advanced BCLC-C. >20% of all patients with advanced BCLC-

C at diagnosis (Hucke *et al.,* 2011). Only palliative treatment is available, resulting in a limited prognosis with a median survival of 11–20 months. (Mendiratta-Lala *et al.,* 2010).

Intermediate BCLC-B HCC is characterized by large or multi-nodular tumor with performance status (0). It is not associated with MVI or extra-hepatic extension. These patients may benefit from TACE and/or RFA. (Pinter *et al.,* 2012).

Advanced BCLC-C HCC is characterized by a large or multifocal tumor with a performance status of 1–2 and/ or the presence of MVI or extra-hepatic metastasis. These patients may receive new agents in the setting of RCTs . (Ponsi *et al.,* 2005). End-stage BCLC-D HCC will receive symptomatic treatment. Pinter *et al.,* 2012).

It has been suggested that this classification is best suited for treatment guidance, and particularly to select early stage patients who could benefit from curative therapies. In that sense, it has recently been validated as the best staging system in a cohort of patients with early HCC. (Ponsi *et al.,* 2005).

TACE is the recommended treatment for intermediate BCLC-B HCC patients with asymptomatic, large, or multifocal HCC without MVI or extra-hepatic metastasis. (Forner *et al.,* 2010). TACE induces an objective tumor response in 36-50% of patients, resulting in delayed tumor progression and prolonged survival (Forner *et al.,* 2010, Raoul *et al.,* 2011 and Pinter *et al.,* 2012).

Occlusion of the tumor-feeding artery with TACE causes a variable degree of hypoxia, which may lead to tumor necrosis (Pinter *et al.,* 2012). TACE induced complete or partial radiologic response in 20 patients (57%) of patients at the 6-month radiologic evaluation. In 1 year follow up, however, TACE is also subject to tumor progression and considered palliative. TACE reasonable and effective for advanced BCLC-C HCC, even in the presence of MVI or extra hepatic metastases.

Furthermore, Selection of candidates for TACE is a key point. The benefits of the procedure should not be offset by treatment-induced liver failure. in the original BCLC classification, TACE was the preferred treatment option for patients with intermediate BCLC-B and advanced BCLC-C HCC devoid of extra-hepatic spread and portal invasion (Forner *et al.,* 2010). By contrast, patients with liver de-compensation or hepatic failure should be excluded since the ischemic insult can lead to severe adverse events. The best chemotherapeutic agent or combination of agents, as well as the best treatment schedule, should be determined by further new RCTs.

TACE targets the primary tumor in the liver but not extra-hepatic spread. However, more than two-thirds of patients with advanced HCC die owing to intra-hepatic tumor progression or liver failure rather than progression of extra-hepatic metastasis (Uka *et al.,* 2007 and Yoo *et al.,* 2011). Thus, one can assume that delaying intra-hepatic tumor progression with TACE has some potential to incur a survival benefit even in the presence of extra-hepatic disease. Several studies (Yoo *et al.,* 2011 and Luo *et al.,* 2011) have found some beneficial effects of TACE in patients with MVI or extra-hepatic metastasis. In patients with Child-Pugh class A disease and MVI or extra-hepatic metastasis, the median survival was 10 months with TACE.

Importantly, main PV involvement is a known predisposing factor for acute hepatic de-compensation after TACE (Pinter *et al.,* 2012). Consequently, only patients with segmental portal vein invasion should be considered candidates for TACE (Raoul *et al.,* 2011), although Chung *et al.,* 2011, and Luo *et al.,* 2011 reported no major complications or procedure-related deaths after TACE in patients with main portal vein invasion. Most interestingly, even early survival was similar between patients with BCLC stage C disease who underwent TACE

Our results imply that TACE could be a possible treatment option, reasonable outcomes in patients with MVI or extra-hepatic metastasis (advanced HCC, BCLC stage C).

BCLC-C is known to include a quite heterogeneous group of patients (Huitzil-Melendez FD), and it is possible that the clinical decision to forgo TACE in patients within the same BCLC stage could well be based on clinical judgment related to patients with clinical characteristics relevant for the outcome but not depicted with BCLC staging.

For all these patients, TACE might be a reasonable therapeutic option if proved to be equally effective. The Furthermore, TACE-related side effects improved substantially with the implementation of TACE with drug-eluting beads (Lammer *et al.,* 2010), which will further improve compliance with repeat interventions.

In conclusion, TACE achieved a promising outcome in select patients with advanced HCC (BCLC stage C). Therefore, TACE might be a valuable option for select patients who have no access to curative treatment options, . The selection seems to be limited to patients with Child-Pugh class A disease with advanced BCLC-C HCC and class A Child-Pugh disease seem To be warranted.

Peng *et al.,* 2012 stated that the main cause of treatment failure is the high incidence of HCC recurrence. Reports demonstrated cumulative 5-year recurrence rates after curative treatment for HCC of 77%–100% (Poon *et al.,* 2001). Recurrence is due to micro-metastases in the liver remnant, which are undetected before or at surgery, or multi-centric

carcinogenesis in the underlying cirrhotic liver (Peng *et al.*, 2012).

Mendiratta-Lala *et al.*, 2010 reported that RFA is one of several local treatment strategies that can be used for the destruction of HCC. Successful ablation requires meticulous technique, knowledge of potential complications and treatment failures. RFA is less invasive than surgery and carries a low risk of major complications. Successful prevention of complications and treatment failures begins at initial consultation and continues with pre-ablation evaluation of specific patient factors such as coagulation profiles, use of medications, and risk factors for infection. Other predisposing factors include background liver cirrhosis, prior hepatectomy, and portal hypertension. For large or multiple ablations, separate ablation sessions can help reduce the prevalence of post-ablation syndrome and multiple overlapping treatment zones may be used to reduce the risk of treatment failure. It is critical to reevaluate tumors during ablation to determine the best approach and to compensate for changes in size and relative location due to patient positioning. With use of these strategies, hepatic RF ablation can be performed with greater safety, better patient tolerance, and a reduced risk of complications and treatment failures.

Combined TACE and RFA has been reported to be a more effective treatment alone for medium-sized HCC and multiple-tumor HCC (Veltri *et al.*, 2006 and Peng *et al.*, 2010). The 1 year clinical results of sequential TACE-RFA as compared with TACE ablation alone for appear better

The results of our study showed that performing TACE before RF ablation is beneficial in that it achieves better tumor response than TACE alone in selected candidates with HCC smaller than 5 cm. Our study indicated that the overall survival of patients treated with TACE-RFA was higher than that of patients treated with TACE alone. The outcome of survival for the sequential TACE-RFA group was also better than that for the TACE group.

Peng *et al.*, 2012 explained that TACE before RFA is beneficial as follows:

First, occlusion of hepatic arterial flow before RFA reduces the cooling effect of hepatic blood flow. Furthermore, Lipiodol and occlusion particles reduce the portal flow around the tumor by filling the peripheral portal vein around the tumor via multiple arterio-portal communications. Thus, the necrotic area induced by RFA may be increased. An enlarged ablation zone may be one of the most important prognostic factors of HCC after RFA. An enlarged ablation zone might improve the chance of clearance of micro-metastasis and reduce the chance of recurrence.

Second, the effect of anticancer agents on cancer cells during treatment was enhanced by the hyperthermia.

Finally, performing TACE before RFA can control the micro-lesions that may exist. It is generally believed that these micro-lesions may contribute to recurrence after treatment.

In our study, the major and minor complications are Liver dysfunction in 15(26.7 %) ; Hepato-renal syndrome in 4 (7.1%) ; Pleural effusion in 3 (5.3%); inguinal hematomas; 1 (1.8%).

Although, to our knowledge, the rate of major complications after sequential TACE-RFA has not been evaluated in any multicenter study, some reports have shown TACE-RFA safe for the initial treatment of HCC (Veltri *et al.*, 2006 and Peng *et al.*, 2010). Our results were similar to those of these studies. Therefore, we considered TACE-RFA a safe treatment for intermediate BCLC-B HCC.

The efficacy of sequential TACE-RFA treatment is better than that of TACE alone for patients with HCC recurrence 1 year or less after initial treatment, patients with tumors measuring 3.1–5.0 cm, and patients in whom tumor recurred after initial treatment with RFA .

Our study has some limitations. First is its retrospective nature. Second the number of patients in this study is relatively small. Third, this is a single-University hospitals experience and results may not be generalizable. Fourth, is the variable equipments (US, CT and angiographic units) in the study may have added some uncertainty to the results. However, we think that the effect may not be significant because the CT, US and angiographic machines had the same technical parameters.

**Conclusion**

**Child-Pugh** score described the liver function not the tumor stage. **Okuda** classification includes parameters of the liver functional status and the tumor stage. However it is properly stratified patients prior to radical or palliative therapies and when compared with modern staging systems, it has been shown to have lower predictive capacity. **BCLC** staging system uses variables related to tumor stage, liver functional status, physical status, and cancer-related symptoms, and links the four stages described into algorithm for appropriate therapeutic strategies.

**RFA** is of promising out come in patients with intermediate BCLC-B HCC. While, TACE achieved a promising outcome in select patients with intermediate BCLC-B and advanced BCLC-C HCC.

Conventional TACE must be adjusted for serum bilirubin concentration, with 75, 50, and 25 mg/m2 of doxorubicin administered for bilirubin levels of, 1.5, 1.5–3.0, and .3.0 mg/ dl, respectively.

Efficacy of TACE-RFA treatment is better than that of TACE alone for intermediate BCLC-B HCC and should be recommended.

**Corresponding authors**
**Ashraf M. Enite**
Department of Diagnostic and Interventional Radiology, Al Azhar University.
ashraf.enite@yahoo.com

**References**

1. Abou-Alfa GK: Selection of patients with HCC for sorafenib. J Natl Compr Canc Netw., 2009; 7:397-403.
2. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005;42(5):1208–1236.
3. Chung GE, Lee JH, Kim HY, *et al.* TACE can be safely performed in patients with HCC invading the main portal vein and may improve the overall survival. Radiology 2011;258(2):627–634.
4. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis., 2010;30(1):61–74.
5. Hucke F, Sieghart W, Schöniger-Hekele M, *et al* . Clinical characteristics of patients with HCC in Austria: is there a need for a structured screening program? Wien Klin Wochenschr 2011;123(17-18):542–551.
6. Huitzil-Melendez FD, Capanu M, O'Reilly EM, *et al.* Advanced Hepatocellular Carcinoma: Which Staging Systems Best Predict Prognosis? J Clin Oncol 2010; 28:2889-2895.
7. Lammer J, Malagari K, Vogl T, *et al.* Prospective randomized study of doxorubicin eluting-bead embolization in the treatment of HCC: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33(1):41–52.
8. Liang HH , Chen MS , Peng ZW , *et al.*. Percutaneous RFA versus repeat hepatectomy for recurrent HCC: a retrospective study . Ann Surg Oncol., 2008 ; 15 ( 12 ): 3484 – 3493 .
9. Llovet JM, Real MI, Montaña X, *et al.* Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359(9319):1734–1739.
10. Luo J, Guo RP, Lai EC, *et al.* TACE for unresectable HCC with portal vein /*tumor thrombosis: a prospective comparative study. Ann Surg Oncol 2011;18(2):413–420.
11. Mendiratta-Lala M, Brook O, Midkiff B, *et al.* Quality Initiatives Strategies for Anticipating and Reducing Complications and Treatment Failures in Hepatic RFA. RadioGraphics 2010; 30:1107–1122.
12. Peng ZW , Chen MS , Liang HH , *et al.* A case-control study comparing percutaneous RFA or combined with TACE for HCC . Eur J Surg Oncol., 2010 ; 36 ( 3 ): 257 – 263 .
13. Pinter M, Hucke F, Graziadei I, *et al.* Advanced-Stage Hepatocellular Carcinoma: Transarterial Chemoembolization versus Sorafenib. Radiology, 2012; 263 (2): 590-599.
14. Poon RT , Fan ST , Lo CM , *et al.* Improving survival results after resection of HCC: a prospective study of 377 patients over 10 years . Ann Surg., 2001 ; 234 ( 1 ): 63 – 70 .
15. Ponsi F, Varela M1 & Llovet J . Staging systems in HCC. HPB, 2005; 7: 35–41
16. Raoul JL, Sangro B, Forner A, *et al.* Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev., 2011;37(3):212–220.
17. Veltri A , Moretto P , Doriguzzi A , Pagano E , Carrara G , Gandini G . RFA after TACE as a combined therapy for unresectable non-early HCC . Eur Radiol., 2006 ; 16 ( 3 ): 661 – 669 .
18. Uka K, Aikata H, Takaki S, *et al.* Clinical features and prognosis of patients with extrahepatic metastases from HCC. World J Gastroenterol., 2007;13(3):414–420.
19. Yang W , Chen MH , Yin SS , *et al.* RFA of recurrent HCC after hepatectomy: therapeutic efficacy on early- and late-phase recurrence . AJR Am J Roentgenol 2006 ; 186 ( 5 ): 275 – 283 .
20. Yoo DJ, Kim KM, Jin YJ, *et al.* Clinical outcome of 251 patients with extrahepatic metastasis at initial diagnosis of HCC: does TACE improve survival in these patients? J Gastroenterol Hepatol 2011;26(1):145–154.

.

9/5/2012