A simple scoring system to predict early prognosis of patients undergoing loco-regional therapy for hepatocellular carcinoma

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Abstract: Introduction: Hepatocellular carcinoma (HCC) is the sixth most common cancer and is the third leading cause of cancer-related deaths worldwide and its incidence is increasing. **Aim of work**: was to identify potential prognostic factors affecting survival in patients with unresectable HCC treated with local ablation. and proposing a new scoring system to predict early prognosis of those patients. **Patients and methods:** 150 consecutive patients with HCC who underwent RFA and/or TACE at National Liver Institute, Menoufiya University during 1 year were included in the study. Data of demographic, clinical, laboratory parameters and Triphasic spiral CT scan were collected. All patients were re-evaluated one month after intervention by laboratory testing and CT or MRI for detection of complications and detection of the effect of intervention Then all patients were followed up for 6 months for detection of mortality rate and prognostic factors related to survival. **Results:** 79.3% were males with mean age of 57.8 ± 9 year. Total bilirubin and serum creatinine significantly elevated one month after intervention ($p< 0.001$). Serum albumin and AFP significantly decreased ($p< 0.001$). Most of our patients were Child A and B. One month after intervention 49 (32.6%) remain Child (A) and 28 of them had no added points to their baseline child score, 76 (50.7%) patients had Child (B), Child (C) patients increased to 25 (16.7%). During 6 months follow up, upper GIT bleeding (due to bleeding esophageal varicies) occurred in 3 patients. Also, 3 patients developed infections and 12 patients developed hepatic decompensation. Development of complications was seen with (4.95 cm, tumor size with sensitivity of 78.9% and ($p < 0.01$), AFP level of 184 ng/ml with sensitivity of 73.7% and ($p < 0.05$), serum albumin level < 2.35 g/dl with sensitivity of 73.7%, Child score > 6.5 with sensitivity of 94.7%, MELD score > 14.5 with a sensitivity of 78.9%. 14 patients died within 6 months of intervention (the mortality rate was 9.3%). The cause of death in most cases was progression of disease and/ or development of hepatic failure. The number of nodules significantly correlated with mortality ($p < 0.01$). Tumor size above 5.9 cm, AFP >330.5, serum albumin <2.55 g/dl associated with increased mortality rate. Moreover, increased mortality was associated with Child score >8.5 and MELD score >13.5. Finally, we proposed a simple scoring system that could be used to predict outcome and stratify patients with unresectable HCC undergoing loco-regional therapy. Three factors; albumin < 2.9 g/dl, AFP > 330 and size of dominant tumor > 5.3 cm were used in this score. A scoring system was derived by allocating one point for each factor that was elevated above the defined cut-off for AFP and tumor size or below the cut-off for the albumin; score 1=0 points, 2=1 point and score 3=>1 point. The survival rate after six month from intervention for those with a score 1, 2 and 3 was 100%, 92.4% and 86.4% respectively. **Conclusion**: the new scoring system can be used easily to predict outcome in patients with HCC who are eligible to locoablative therapy. This scoring system needs to be validated on more patients.

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1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and is the third leading cause of cancer-related deaths worldwide (1). Its reported incidence is increasing because of a better ability to diagnose the disease and because of the long-term consequences of HCV and HBV infection. The incidence of HCC is higher in China, south Asia and South Africa than in Western populations due to high prevalence of HBV which is the single most important cause of HCC worldwide.

In Egypt, the incidence of HCC has been increasing with a doubling in the incidence rate in the past 10 years. Hepatitis C and B virus infections are major risk factors. Egypt has the highest prevalence rate of HCV worldwide (2).

Hepatocellular carcinoma (HCC) typically occurs in patients who have cirrhotic livers and in patients who have HBV infection even in the absence

of cirrhosis. Aflatoxins have attracted a great importance nowadays. Aflatoxin B1 may play an important role in the occurrence of HCC in the north Nile delta area (in Egypt) and especially in males, farmers, with chronic HCV infection or liver cirrhosis. Aflatoxin B1 in high concentration was found to be associated with high incidence of chronic HCV, and presence of multifocal lesions (3). Other factors (2) such as cigarette smoking, occupational exposure to chemicals as pesticides may have additional roles in the etiology or progression of the disease.

Symptomatic HCC has a very poor prognosis (4), with a median survival of 1 to 8 months and a 5-year survival rate of only 3%).

Regional ablative therapies (Transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection (PEI) and percutaneous radio frequency ablation (RFA) are performed frequently in patients with HCC who are not candidates for either resection or orthotopic liver transplantation (OLT) (5).

Radiofrequency ablation (RFA) is safe, technically simple, well tolerated in patients with unresectable HCC, with a low morbidity rate ranging from 0- 28% and a perioperative mortality rate of 0-2% (6). A randomized controlled trial suggested that percutaneous RFA was as effective as hepatic resection in terms of overall and disease-free survivals in the treatment of solitary resectable HCC $\leq$ 5 cm (7). Local recurrence at a RFA treatment site is common (8), varying from 2- 36% in reported studies.

Radiofrequency ablation is an approach to induce necrosis of inoperable primary or metastasis tumors in the liver (9). Randomized controlled trials have shown that RFA is superior to ethanol injection in the treatment of small HCC. RFA results in a higher rate of complete necrosis and requires fewer treatment sessions than percutaneous ethanol injection (PEI). Long-term survival rates are also better with RFA (10). Short-term outcomes are excellent, with overall survival rates of 100% and 98% at 1 and 2 years, respectively, but long-term outcomes are consistent with the noncurative nature of radiofrequency ablation, with 5-year recurrence rates as high as 70%.

TACE is a targeted therapy that combines intra-arterial therapy and arterial embolization. Hepatic arterial embolization induces not only ischemic necrosis of tumor but also failure of transmembrane pumps in tumor cells (11), resulting in greater absorption of chemotherapeutic agent and because this is not safe for patients with poor liver function, TACE is not recommended in those patients.

Several studies have reported that a combination of TACE and RFA was more effective and yielded a better survival rate compared with TACE alone (6). However it is not known whom patient will benefit from this therapy and who will develop complications and may die.

The aim of this study was to identify prognostic factors which influence survival in patients with unresectable HCC treated with local ablation therapy. Also, we proposed a new scoring system to predict early prognosis of patients undergoing loco-regional therapy for HCC.

2. Patients and methods

150 consecutive patients with HCC who underwent RFA and/or TACE at National Liver Institute, Menoufiya University during a period of 1 years (August 2010 to August 20011) were enrolled in this study after obtaining their consent.

Patients were excluded if they had undergone resection or received systemic chemotherapy. HCC patients with distant metastasis and patients with portal vein thrombosis were also excluded from this study.

Data collection

Demographic (age, gender), clinical (aetiology, complications, ascites, history of hepatic encephalopathy, history of haematemsis), laboratory parameters (bilirubin, albumin, creatinine, international normalized ratio [INR], alphafetoprotein [AFP], complete blood count) were collected from patient case records.

All patients were examined using triphasic spiral CT scan with contrast media to detect the number of lesions, distribution, size, presence of PVT

Hepatocellular carcinoma with more than five discrete nodules was referred to as diffuse tumour. Mean tumour size was calculated by the sum of the longest diameter of all measurable tumours.

Complete blood picture was done using Sysmix instrument KX-21, Sysmex Inc., Japan. Liver and renal function tests were done using Cobas Integra 400, Hoffman La Roche Company, and Switzerland. Prothrombin time concentration was assessed using Thromborel S, Behring Inc., Germany.

Follow-up

All patients were re-evaluated one month after intervention by laboratory testing and CT or MRI for detection of complications and detection of the effect of intervention by assessing tumour burden and presence of PVT. Further treatments were based on clinical evaluation, laboratory values and imaging response. Patients with progressive disease

underwent repeat treatments with the same modality. Patients with stable disease were followed with cross-sectional imaging every 3 months.

Then all patients were followed up for 6 months for detection of mortality rate and prognostic factors related to survival.

Statistical analysis

Data was statistically analyzed using SPSS (statistical package for social science) program version 13 for windows and for all the analysis a p value < 0.05 was considered statistically significant. Data are shown as mean, range or value and 95% confidence interval (95% CI) and frequency and percent.

Sensitivity: true positive cases divided by all positive cases. Specificity: True negative cases divided by all negative cases. Accuracy: all true positive plus true negative cases divided by all cases (either true positive or true negative or false positive or false negative).

Roc curve (Receiver operating characteristic curve): was done to detect cut level of any tested variable where at this level there is a the best sensitivity and specificity cut off values of the variables for the presence of the disease moreover, they were used to identify the cut off the prevalence adjusted negative and positive values for the presence of the disease. The validity of the model was measured by means of the concordance © statistic (equivalent to the area under the Roc curve). A model with a c value above 0.7 is considered useful while a c value between 0.8 and 0.9 indicated excellent diagnostic accuracy.

Paired t test was done to detect mean and standard deviation of normally distributed pre and post values of the same variable of the same group of patients and p-value < 0.05 was considered significant. Wilcoxon test was done to detect mean and standard deviation of not normally distributed pre and post values of the same variable of the same group of patients and p-value < 0.05 was considered significant.

3. Results

Fifty patients underwent RFA, 50 patients underwent TACE and 50 patients underwent combined TACE & RFA were included in the study.

One hundred and nineteen patients (79.3%) were males and 31 (20.7%) were females with a mean age of 57.8 ± 9 year. Demographic, clinical, laboratory, tumour staging and imaging characteristics are summarized in Table 1.

Laboratory findings at baseline and one month after intervention (Table 2)

Total bilirubin was significantly elevated one month after intervention (p< 0.001). Serum albumin was significantly reduced (p< 0.001). Serum AFP was significantly reduced (p< 0.01). In addition, serum creatinine was elevated one month after treatment.

Except few (7 patients of Child C) most of our patients were Child A and B. 58 patients (38.7%) had a baseline Child Pugh score (A), 85 patients (56.7%) had a score (B) One month after intervention 49 (32.6%) remain Child (A) and 28 of them had no added points to their baseline child score, 76 (50.7%) patients had Child (B), Child (C) patients increased to 25 (16.7%).

Upper GIT bleeding occurred in 3 patients who were treated by TACE or combination therapy. As regarding infection, one patient treated by RFA suffered from subdiaphragmatic abscess and two treated by combination therapy one of them suffered from liver abscess and the other suffered from acute cholecystits. As regarding hepatic decompensation, 3 patients (treated by RFA) and 9 patients (treated by TACE or combination therapy) developed hepatic encephalopathy and or ascites (Table 3).

At cut off level of 4.95 cm, tumor size showed sensitivity of 78.9% and it was highly significantly correlated with development of complication (p < 0.01). AFP at cut off level of 184 ng/ml gave a sensitivity of 73.7% and it was significantly correlated with development of complication (p < 0.05) as shown in table 6. In addition, serum albumin cut off level less than 2.35 g/dl predict complications with a sensitivity of 73.7%. Child score more than 6.5 can predict complications with a sensitivity of 94.7%. MELD score more than 14.5 as cut off level can predict complications with a sensitivity of 78.9% (Table 4).

Mortality rate of studied patients

There was no procedural related mortality (death within 30 days of intervention) and the mortality rate within 6 month of intervention was 9.3% (14 patients); 7 patients treated by TACE, 3 patients treated by RFA and 4 patients treated by combined therapy. The cause of death in most cases was progression of disease and/ or development of hepatic failure. We studied the relationship between the available variables and mortality. There was no significant correlation between mortality and gender or treatment modality. The number of nodules was highly significantly correlated with mortality (p < 0.01) (Table5). Tumor size above 5.9 cm, AFP >330.5, serum albumin <2.55 g/dl were associated with increased mortality rate. Moreover, increased

mortality was associated with Child score >8.5 and MELD score >13.5 (Table 6).

A simple scoring system that can be used to predict outcome and stratify patients with unresectable HCC undergoing loco-regional therapy was proposed table (7). Three factors; albumin < 2.9 g/dl, AFP > 330 and size of dominant tumor > 5.3 cm were used in our score. A scoring system was derived by allocating one point for each factor that was elevated above the defined cut-off for AFP and tumor size or below the cut-off for the albumin; score 1=0 points, 2=1 point and score 3=>1 point. The survival rate after six month from intervention for those with a score 1, 2 and 3 was 100%, 92.4% and 86.4% respectively.

Table 1. Characteristics of included patients

Variable	Value	%
Age, years (Range) (Mean ± SD)	35-98 57.8 ± 9.02	
Male, n	119	79.3
Number of tumor nodule, n One Two Three More than three	 100 29 6 15	 66.7 19.3 4 10
Size of largest nodule, M ± SD	5.1 ± 2.1	

Table 2. Changes in Child score and laboratory findings at baseline and one month after intervention

Variable	Before intervention (M ± SD)	After intervention (M ± SD)	p-value
Bilirubin (mg/dl)	1.58 ± 0.92	2.18 ± 1.17	< 0.001**
Albumin (g/dl)	3.30 ± 0.47	3.09 ± 0.49	< 0.001**
INR	1.38 ± 0.28	1.41 ± 0.25	0.103
AFP (ng/ml)	602.69 ± 81.21	458.01 ± 230.41	< 0.01**
Creatinine (mg/dl)	0.8 ± 0.24	1.0 ± 0.29	< 0.001**
Hb (g/dl)	11.9 ± 1.53	11.3 ± 1.40	< 0.001**
TLC (x103/dl)	5.2 ± 1.90	5.4 ± 4.00	0.55
PLT (x103/dl)	107.5 ± 50.43	91.9 ± 40.99	< 0.001**
Child score	6.73 ±1.43	7.67 ±2.06	< 0.05*

** Highly significant * significant

Table 3. Major complications occurred within one month in studied patients

Complication	Value (n)	Percent %
Infection	3	2
Upper GIT Bleeding	3	2
Hepatic decompansation	12	8
Total number of complications	18	12

Table 4. Cut off level of variables used to predict complications

	Sensitivity	Specificity	AUC	Accuracy	P- value	SE	CI
Size of largest tumor Cut Level 4.95 cm	78.9 %	66.7 %	0.79	82.4 %	< 0.01**	0.07	0.65 – 0.93
AFP Cut level 184 ng/ml	73.7 %	58.1 %	0.68	68.9 %	< 0.05*	0.07	0.56 – 0.79
Albumin Cut Level 2.35 g/dl	73.7 %	3.4 %	0.15	11.8 %	< 0.01**	0.07	0.06– 0.23
Child score Cut level 6.5	94.7 %	19.1 %	0.48	46.8 %	> 0.05	0.07	0.35– 0.60
MELD score Cut Level 14.5	78.9 %	76.2 %	0.85	83.7 %	< 0.01**	0.05	0.74– 0.95

* Significant * * highly significant

Table 5. Univariate analysis of baseline predictors of survival

Variable	Number	Number of died cases	P –value
Sex Male Female	 119 31	 11 2	0.6
Number of tumor nodule One Two Three Multiple	 100 29 6 15	 7 0 2 4	0.01
Treatment modality RFA TACE Combined	 50 50 50	 3 7 4	0.8

Table 6. Cut off level of variables used to predict mortality

	Sensitivity	Specificity	AUC	Accuracy	P- value	SE	CI
Size of largest tumor Cut Level 5.9 cm	71.4 %	75.7 %	0.79	79.3 %	< 0.01**	0.04	0.69 – 0.89
AFP Cut level 330.5 ng/ml	71.4 %	69.1 %	0.75	75.6 %	< 0.01**	0.04	0.66– 0.84
Albumin Cut Level 2.55 g/dl	71.4 %	51 %	0.1	10.5 %	< 0.01**	0.03	0.04 – 0.17
Child score Cut level 8.5	71.4 %	89.6 %	0.87	87.2 %	< 0.01**	0.04	0.8– 0.94
MELD score Cut Level 13.5	100.0 %	63.7 %	0.91	90.8 %	< 0.01**	0.03	0.85– 0.97

Table 7. New score

New score		Frequency (n)	Percent %
No points score 1	Survived	12	100.0
One point Score 2	Died Survived	6 73	7.6 92.4
Two points or more Score 3	Died Survived	8 51	13.6 86.4

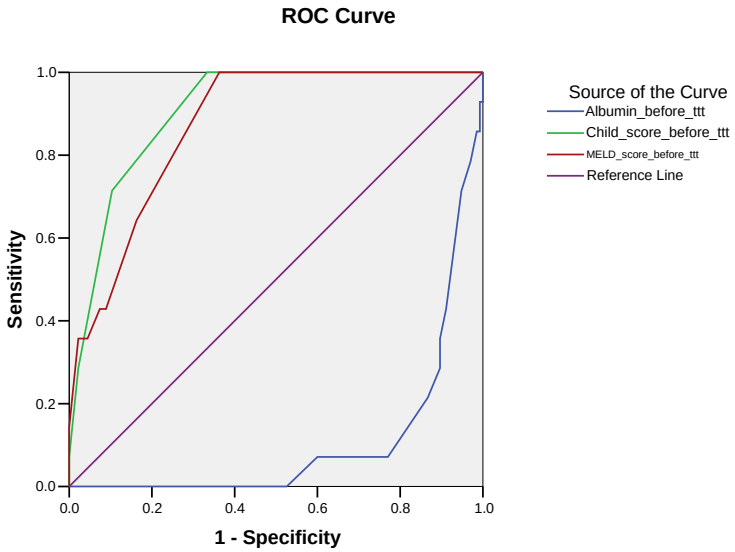

Figure (1): sensitivity and specificity of pre-treatment serum albumin, MELD and Child scores in prediction of mortality.

4. Discussion

Hepatocellular carcinoma (HCC) is the sixth most common cancer and is the third leading cause of cancer-related mortality worldwide (1). Its incidence is increasing owing to the long-term consequences of HCV and HBV infection beside increased ability to diagnose the disease early. This increasing tendency will continue over the next 20 years (12).

Treatment of HCC is multidisciplinary involving hepatologists, oncologists, surgeons and interventional radiologists. TACE has been the most frequently used treatment for large multifocal hepatic tumors. It has been widely accepted as mainly palliative approach to treat HCC in patients who are not candidates for curative therapy (13,14). RFA is well tolerated in patients with unresectable HCC (6), with a low morbidity rate ranging from 0% to 28% and a perioperative mortality rate of 0-2%.

We first evaluated the impact of TACE and RFA on baseline laboratory findings for all the studied patients one month after intervention.

We found that there was significant decrease of haemoglobin and platelet count ($p< 0.001$) one month after intervention. The fall in platelet count after TACE had been recognized by Munk et al. and Herber et al. (15,16). In most instances, these changes are not clinically evident and are only detected by laboratory evaluation. The mechanism may involve DIC in combination with a subclinical tumor necrosis syndrome as low grade DIC with platelet and fibrinogen consumption could be observed in a large number of patients post-chemoembolisation (15).

There was a strongly significant impact on biochemical liver function tests except INR in this study. Child-Pugh score also significantly increased from 6.73 ±1.43 to 7.67±2.06 ($P< 0.05$). This comes in harmony with a study done by Sacco et al. (17) who studied 117 cirrhotic patients with HCC. They reported significant increase in Child-Pugh score and serum bilirubin one month after TACE.

The level of AFP has been reported to be correlated with tumor burden (18) and it may be useful in measuring the true degree of response when imaging fails to distinguish residual tumor activity and necrotic tumor remnants (19). In our study, both TACE and RFA significantly reduced tumor burden detected by significant reduction of the mean serum AFP one month after the procedure but the size of tumor did not significantly changed. TACE can induce extensive tumor necrosis in most patients and this has been substantiated by a decrease in tumor marker concentration after procedure (20,21). In contrary Jaeger et al (22) found that a decrease in the tumor size is observed in (16% to 61%) of patients treated with TACE.

During follow up of our patients within one month after intervention we found that there was no TACE or RFA related mortality between studied patients. TACE and RFA were well tolerated by all included patients despite its impact on their liver function. Marelli and colleagues (19) evaluated loco-regional therapies for HCC and reported that deaths within 30 days of TACE due to procedural complications ranged from 0-9.5% (median 2.4%) in 37 trials involving 2858 patients. The reported most frequent cause of death was acute liver failure and the risk factors for hepatic failure were Child B and C disease and PVT (19).

A study on 117 Child A and B patients was done by Fuke et al. (23) who found that survival rates after RFA were 98.2% and 64.7% at 1 and 5 years, respectively and Child B patients had a significantly worse survival than Child A.

We also found that the rate of complications within one month after intervention was 12%. The main complication in all groups was hepatic decompensation (development of ascits and or hepatic encephalopathy) which was reported in 8% of the studied patients. Haematemsis occured in only three cases treated by TACE or combination therapy and infection was noticed in 3 cases (sub diaphragmatic abscess, liver abscess and acute cholecystits). Complicated cases were admitted to hospital until improved. This comes in harmony with Morante et al (24) who found that in HCC patients treated by TACE, most patients suffered from a postembolization syndrome with transitory abdominal pain, ileus, and fever. The major complication rate is lower than 10% with ischemic cholecystitis, hepatic abscess, and biliary strictures (24,25).

Probably the largest series to date demonstrating the complications of RFA is a series published by Livraghi and colleagues (26), in which they surveyed 41 Italian centres that perform percutaneous RFA as part of a collaborative group to evaluate associated complications rate. Complete response was achieved in only 70% of all tumors. The mortality rate was 0.3% with a complication rate of 2.2%.

In this study, it was found that some variables can be used as predictive for occurrence of complications after treatment of HCC by RFA, TACE or both. These factors include: Size of largest tumor more than 4.95cm, AFP > 184 ng/dl, serum albumin <2.35 g/dl, Child score > 6.5 and MELD score > 14.5.

In agreement with our study a study done by Jeon et al., (27) found that major complications occurred in 76 (12%) of the 632 TACE sessions within 14 days. Univariate analysis revealed that Child-Pugh class, total serum bilirubin level, number of lesions and total size of tumor are the main predictive factors for occurrence of complications. Also, Masafumi et al., (28) found that serum albumin and bilirubin can be used as prognostic factors in patients with HCC treated by TACE. Serum albumin is one of the most important factors in evaluating hepatic synthetic function (18) and it was therefore included in the Okuda staging system and Child Pugh classification. It was reported that Liver function deterioration after TACE is more common in patients with less liver reserve (29).

Follow up of our patients for 6 months showed that 14 patients (9.3%) died. The cause of death in most cases was progression of disease which resulted in hepatic decompansation and liver cell failure.

In our study we found that age and gender of patients were not significant in prediction of mortality and this comes in harmony with a study involved 82 patients who received initial RFA (30). Other factors as number of focal lesions, serum albumin level above 2.55 g/dl, Child score >8.5, MELD score > 13.5, AFP> 330.5 ng/ml and size of largest tumor > 5.9 cm were associated with increased mortality rate. This comes in harmony with a recent meta-analysis which showed an improvement of overall survival in patients with well-preserved liver function treated with TACE (31). Also: Kao et al, found that both multinodularity and Child classification are associated with worse overall survival and recurrence for patients with HCC after RFA therapy (32). Fuke et al. (23) found that Although RFA enables good local control for initial HCC, distant recurrence and increased rate of mortality is observed at high rates in low albumin and high AST patients.

A recent study conducted by Sawhney et al., (33) on 60 patients underwent TACE as treatment for HCC. They found that an initial AFP level of greater than 200 ng/ml and a MELD score of greater than 10 were associated with a greater risk of mortality. Tyson et al (34) also found that an AFP level at the time of diagnosis with HCC is an independent predictor of mortality in patients treated by TACE.

In a recent study, combined TACE and RFA were performed in 84 tumors with a successful rate of 100% and a complete ablation rate of 94%. The major complication rate was 6.7%. Univariate analyses indicated that tumor size > 7 cm, multi-nodularity and pretreatment AFP > 200 ng/ml were unfavourable prognostic factors for the long-term survival (35). On the other hand, Memon and colleagues (36) found that baseline tumor size was not a significant factor affecting survival in HCC patients treated by TACE. Also Lin et al. (30) found that hepatitis marker (P=0.083) and Child-Pugh were not related to prognosis and survival rates were significantly related to the pre-treatment tumor size (P=0.008) in patients treated by RFA.

Finally, we have derived a simple scoring system that can be used to predict outcome and stratify patients with unresectable HCC undergoing loco-regional therapy. This scoring system include three factors with defined cutoff; albumin < 2.95 g/dl, AFP >330.5 and size of dominant tumor >5.35cm. A scoring system was derived by allocating one point for each factor that was elevated above the defined

cut-off for AFP and tumor size or below the cut-off for the albumin; score 1=0 points, 2=1 point and score 3=>2 points. The survival rate after six months from intervention for those with a score 1, 2 and 3 was 100%, 92.4% and 86.4% respectively.

None published preliminary data done in Royal Free Hospital, (United Kingdom) by Latha Kadalayil, Laura Marelli, jonalhen Dick, Neil Davies and Tim Meyer. The aim of their study was to define key prognostic factors in patients undergoing TACE for unresecteble HCC and develop a simple scoring system to predict outcome. They found that the median survival of the whole group was 1.3 year and three factors; albumin< 3.5g/dl, AFP > 400 ng/ml and size of largest tumor > 7cm were each independently associated with 2-3 times increase in risk of death and they developed a scoring system by allocating 1 point for each factor and they found that the median survival for those with a score of 1, 2 and 3 was 25.6, 13.3 and 6.5 months respectively.

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