Outcome of Different Modalities of Management of Hepatocellular Carcinoma: Surgical Resection and Interventional Radiology [TACE]

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Abstract:

Background: Hepatocellular carcinoma is an aggressive malignancy and has multiple treatment options, usually multimodality therapy is used. The choice of treatment depends on many factors including the staging of the tumor, patient characteristics, and liver functions. This study aimed to provide a descriptive analysis of patients diagnosed with HCC in NCI and to evaluate the outcome of treatment by surgical resection and interventional radiology.

Materials and Methods: The study included 84 patients of both sexes diagnosed with HCC in NCI and was retrospectively reviewed for patients' characteristics, mode of presentation, investigations done, staging, and treatment received. Treatment outcome was compared between the two groups regarding local control and survival.

Results: Mean age was found to be 56.1 and 58.3 in the surgical resection and interventional radiology groups, respectively. HCV was positive in 88% of the patients. 41 patients (48.8%) were child class A, 35 patients (41.7%) were child class B and 8 patients 9.5%) were class C. The Median follow-up time was 15.21 months. The recurrence rate was (42.2%) in the SR group compared to (58.9%) in patients in the IR group. The 1-, 3- and 5-year overall survival for the SR group was 79%, 54%, and 28% respectively while it was 55%, 11%, and 5% for the IR group respectively.

Conclusions: Surgical treatment remains the only curative therapy for HCC, with lower recurrence rates and longer survival. However, other modalities can be used in conjunction with surgery or as a bridge to liver transplantation. Further studies are required in NCI to develop the optimum therapy or combination of therapies for HCC.

Keywords: HCC, TACE, Surgical resection, Interventional radiology

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Introduction:

Liver cancer is the fifth most common cancer in men and the seventh in women. Most of the disease burden (85%) is borne in developing countries, with the highest incidence rates reported in regions where infection with hepatitis B virus (HBV) is endemic[1].

Hepatocellular carcinoma risk development in patients with cirrhosis ranges between 5% and 30%, depending on the cause with the highest risk among those infected with HCV[1]. Laboratory studies should include a complete blood count, electrolytes, liver function tests, coagulation studies (e.g., INR, PTT), and alpha-fetoprotein determination.

Accurate diagnosis and surgical planning require adequate imaging studies.

Ultrasound is commonly used for screening while triple-phase CT scanning is highly accurate in diagnosing and characterizing hepatocellular

carcinomas but, like ultrasound, may miss smaller lesions.

MRI provides an excellent method to characterize hepatocellular carcinoma with reduced scanning time and without the need for radiation, especially in small lesions[2]**.** While helpful in determining a prognosis in patients undergoing resection, the TNM (tumor, node, metastasis) staging system is not as useful in planning treatment, as it fails to include measures of the severity of the liver disease.

Likewise, the Child-Pugh score predicts perioperative survival following resection, but it does not incorporate tumor size, number, and location, which have important implications for respectability and treatment. The Barcelona Clinic Liver Cancer (BCLC) is one of the most widely used staging systems as it helps choose among the potential treatment options and correlates best with patient outcomes among the major staging systems[3]**.**

In the past decade, improvements in nonsurgical treatment platforms allowed the incorporation of more eligibility criteria for a liver transplant.

Comorbid conditions influence treatment eligibility, liver-related variables such as Child-Pugh score and tumor-related variables such as size, number, the pattern of spread within the liver, and vascular involvement are the main challenges that determine the treatment modality[4]**.**

The Milan eligibility criteria for liver transplant is based on the size and number of tumors, and criteria have been established to optimize cancer-specific outcomes[5]**.**

Liver resection remains the gold standard for patients with resectable HCC. Preservation of the liver parenchyma is critical in diseased liver and treatment requires a balance between the effect of any surgical intervention and a vulnerable high-risk remnant. Most published resection series focus on patients with single tumors and well-preserved (Child-Pugh score class A) functions. The recurrence rate after resection is approximately 50% at 2 years and 75% at 5 years in most series [6,7]**.**

Most patients are not candidates for resection or transplantation at the time of diagnosis because of either the extent or distribution of the tumor, underlying liver function, or medical comorbidities. Catheter-based techniques take advantage of the liver's dual blood supply to deliver intra-arterial therapy directly to the tumor bed. Several different treatments have been administered by catheter via the artery to treat patients with HCC, including bland embolization, trans-arterial chemoembolization (TACE), chemoembolization with drug-eluting beads (DEBs), and radio-embolization. The treatment of patients with HCC is particularly challenging because of the array of patient-specific (medical comorbidities), tumor-specific and liver-specific (parenchymal reserve) variables that impact our ability to treat patients safely and effectively. Risk stratification schemes such as the CLIP score or the BCLC staging system attempt to assess risk and better select patients[4]**.**

Patients and Methods:

This study aims to present the NCI experience the treatment of HCC on top of liver cirrhosis and to evaluate the management either by surgical resection or interventional radiology; TACE and radiofrequency ablation (RFA).the long term outcome of both treatment modalities is also reported. This study included 84 patients (70 males and 14 females) of HCC from both sexes who attended the national cancer institute.

Patients were divided into 2 groups, one who underwent surgical resection and the other who underwent interventional radiology (TACE or RFA) as a modality of treatment.

From 2005 to 2015, patients who underwent surgical resection for HCC in NCI were identified (148). Only 45 patients were identified, and their files were collected.

Patients who underwent TACE or RFA as a primary treatment for HCC in NCI were identified and 39 patients were randomly selected.

Adults diagnosed with HCC on top of liver cirrhosis underwent surgical resection or interventional radiology (TACE or RFA) to treat the lesions were included in the study.

Patients with metastatic HCC or very advanced lesions only need palliation were excluded.

Patients' files for both groups were reviewed and comprehensive baseline information was reviewed and recorded.

For both groups, the following information was collected. Hospital number, age, gender, hepatitis virus status, serum biochemistry (Albumin, bilirubin, alkaline phosphatase, serum ALT and AST, INR), Child classification, clinical presentation, comorbidities, history of FNAC or true cut biopsy, Alfa fetoprotein, type of radiological diagnosis, tumor characteristics, last follow up date and last follow up status. For the surgical resection group, the type of operation, date, intra or postoperative complications, and pathology results were reviewed and recorded.

For the interventional radiology group, the type of interventional radiology used (TACE or RFA), and the date of starting the treatment were reviewed and recorded.

A descriptive analysis was performed for all the patients, then for the surgical resection group and the interventional radiology group.

The outcome of both groups was assessed regarding the local control (local recurrence) and survival.

Results:

The study included 84 patients treated in NCI, Cairo university. 45 patients underwent surgical resection and 39 patients underwent interventional radiology (TACE or RFA).

Overall, 49 patients (58.3%) were less than 60 years while 35 patients (41.7%) were more than 60 years of age. In the surgical resection (SR) group, 27 patients (60%) were less than 60 years while 18 patients (40%) were more than 60 years of age, with a mean age of 56.13. In the interventional radiology group (IR), 22

patients (56.4%) were less than 60 years while 17 patients (43.6%) were more than 60 years of age, with a mean age of 58.3.

In this study, males (69) formed 82.1% while females (15) formed 17.9% of all the patients with a ratio of 4.6:1 respectively. In the SR group, 34 patients (75.6%) were males while 11 patients (24.4%) were females. In the IR group, 35 patients (89.7%) were males while 4 patients (10.3.%) were females.

An accidental discovery of HCC during routine follow-up of high-risk patients was the main presentation representing 55.9% (47 patients) while other symptoms including pain, jaundice, or hematemesis were 44.1%.

In the SR group, Abdominal pain was the main presenting complaint in 22 patients (48.9%). HCC was accidentally discovered in 21 patients (46.7%). Only 1 patient (2.2%) presented with pain and jaundice and another one (2.2%) presented with hematemesis. In the IR group, HCC was accidentally discovered in 26 patients (66.7%) while 12 patients (30.8%) presented with abdominal pain, and only 1 patient (2.6%) presented with pain and jaundice. More than half of the patients (25) (55.6%) had no comorbidities in the SR group while 2 patients (4.4%) were missed. 18 patients (40%) had comorbidities as follows, 7 (15.6%) had diabetes while 4 (8.9%) had hypertension, combined diabetes and hypertension were found in 2 (4.4%) patients and ischemic heart disease in 4 (8.9%) patients and only 1 patient (2.2%) had bilharziasis. In the IR group, 23 patients (59%) had no comorbidities while 16 (41%) had comorbidities as follows, 8 (20.5%) had diabetes, 3 (7.7%) had hypertension and 5 (12.8%) had both diabetes and hypertension. Overall, diabetes was found in 22 patients (26.1%) and hypertension in 14 patients (16.6%).

All the patients in the IR group were positive for hepatitis C virus (HCV) whereas, in the SR group, 35 patients (77.8%) were positive for HCV, 1 (2.2%) positive for hepatitis B virus, 5 (11.1%) negatives for hepatitis virus infection and 4 were missing. Overall, 74 patients (88%) were positive for HCV and 1 patient for HBV.

In this study, 41 patients (48.8%) were child class A, 35 patients (41.7%) were child class B and 8 patients (9.5%) were class C.

In the SR group, 32 patients (71.1%) were child class A and 13 patients (28.9%) were child class B. In the IR group, child classes A, B, and C were 9 (23.1%), 22 (56.4%), and 8 (20.5%) respectively.

Alfa fetoprotein ranged from 2 to 54000 in the SR group with a mean value of 2727.31 while it ranged from 4 to 35000 in the IR group with a mean value of 2211.49.

Triphasic CT was used for diagnosis in 39 patients (86.7%) in the SR group while MRI was only used in 6 patients (13.3%). In the IR group, 37 patients (94.8%) were diagnosed using Triphasic CT and 1 (2.6%) using MRI and 1 was missed.

Fine needle aspiration cytology (FNAC) was done in 1 patient (2.2%) in the SR group and 1 patient (2.6%) in the IR group with overall 2 patients (2.4%) in the study.

True cut biopsy was done in 7 patients (15.6%) in the SR group and 2 patients (5.1%) in the IR group. 9 patients (10.7%) underwent true cut biopsy for diagnosis in this study.

In the SR group, the tumor was located in the right lobe of the liver in 29 patients (64.4%) and the left lobe in 16 patients (35.6%). In the IR group, it was located in the right lobe in 19 patients (48.7%), in the left lobe in 4 patients (10.3%), and was bilobar in 16 patients (41%).

The tumor was less than 5 cm in 34 patients (41%) and more than 5 cm in 49 patients (59%) with a mean size of 5.74 cm ranging from 2 to 16 cm. In the SR group it was <5 cm in 15 patients (34.1%) and >5 cm in 29 patients (65.9%). In the IR group, <5 cm in 19 patients (48.7%) and >5 cm in 20 patients (51.3%).

In the surgical resection group, postoperative pathology showed negative resection margins in 38 patients (84.4%), a close margin in 2 patients (4.4%), and positive margins in 5 patients (11.1%). Tumor grades 1, 2, and 3 were 5 (11.1%), 22 (48.9%), and 12 (26.7%) patients respectively.

Non-anatomical resection was the most common technique, it was done in 25 patients (55.6%). Right hepatectomy was done in 11 patients (24.4%), left hepatectomy in 5 patients (11.1%), left lateral hepatectomy in 2 patients (4.4%), and extended right hepatectomy in 2 patients (4.4%). Complications were recorded in 10 patients (22.2%). Massive bleeding in 8 patients (17.7%), colon injury in 1 patient (2.2%), and splenic injury in 1 patient (2.2%). Postoperative liver abscess occurred in 2 patients (4.4%) and mortality occurred in 4 patients (8.9%) with overall postoperative complications in 13.3%. TACE was done in 33 patients (84.6%) and RFA was done in 14 patients (35.9%).

In local control in the SR group, 20 patients (44.4%) were found free at the last follow-up visit compared to 6 patients (15.4%) in the IR group. Recurrence occurred in 19 patients (42.2%) in the SR group compared to 23 (58.9%) patients in the IR group. Residual tumor was found in 9 patients (23.1%) in the IR group and 1 patient (2.6%) developed liver failure. Two patients (4.4%) developed metastasis in the SR group.

The recurrence rate in patients with tumor size <5 cm was 58.8% while in those with tumor >5 cm, it was 71.4%. The Median follow-up time was 15.21 months (range from 2-122). The 1-, 3- and 5-year overall survival for the SR group was 79%, 54%, and 28% respectively while it was 55%, 11%, and 5% for the IR group respectively. survival functions are drawn in figure (1) and (2).

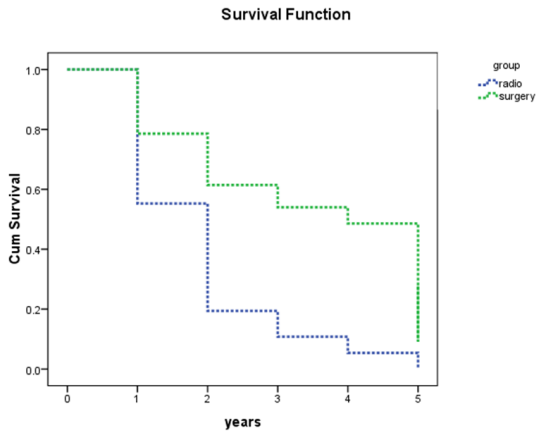

Figure (1): cumulative survival for group1 and 2 in years

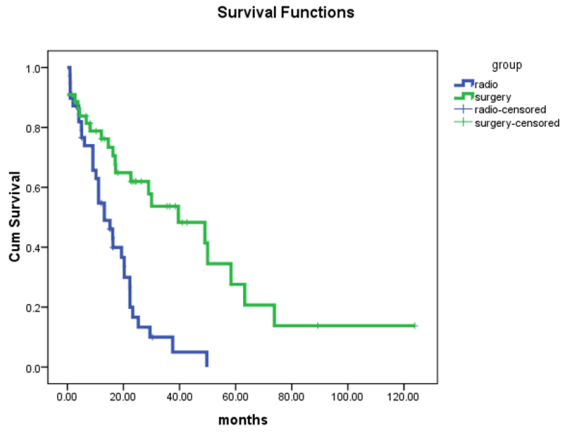

Figure (2): cumulative survival for group1 and 2 in months

Discussion:

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is the fifth most common cancer in men, worldwide, and seventh among women, with over half a million new cases diagnosed annually worldwide. It is the second leading cause of cancer-related mortality in the world[8].

HCC presentations are compounded by the status of liver parenchyma. The choice of the best first line of treatment is challenging and should be undertaken by a multidisciplinary team (MDT) that includes hepatologists, medical and surgical oncologists, transplant surgeons, diagnostic and interventional radiologists, radiation oncologists, and pathologists[9] or sequential multi-modal therapies can improve patient outcomes.

In our study, we aimed to provide a view of the NCI experience in the management of HCC by surgical resection or interventional radiology techniques (TACE or RFA). The studied patients were predominantly males (82.1%) while females were (17.9%) with a ratio of 4.6:1, as males have a higher incidence of HCC than females. The male: female ratio is approximately 3:1 or 4:1 in the Asia-Pacific region and in sub-Saharan Africa, as well as in medium-risk countries, compared with 2:1 in regions with a low incidence of the tumor[10].

Regarding age, 58.3% of them were <60 years old while 41.7% were ≥60 years old. The mean age was 57.15 in concordance with what Waghray, et al. stated; that the average age of diagnosis is 65 years with a shift in the last decade toward diagnosis at an earlier age. This trend is especially seen in developing countries and has implications for treatment[11].

HCC classically arises and grows silently, making its discovery challenging before the development of later-stage disease. Cirrhotic patients frequently present with nonspecific signs and symptoms of hepatic decompensation such as jaundice, hepatic encephalopathy, anasarca, or variceal bleeding. Routine surveillance of high-risk patients has discovered asymptomatic HCC is more common[12]. This is evident in our study where accidental discovery in high-risk patients was the main presentation representing 55.9% of the cases while other symptoms including pain, jaundice, or variceal bleeding represented 44.1%.

Co-morbidities such as diabetes mellitus were found in 26.1% of the studied patients which is considered a high prevalence. This is close to the results of Hassan, Manal M., et al., which stated that the prevalence of diabetes mellitus was 33.3% in patients with HCC and 10.4% in the control group, yielding an adjusted odds ratio (AOR) of 4.2[13].

Chen et al. concluded that diabetes is associated with increased HCC risk in people with chronic liver disease, HCV infection, or cirrhosis[14].A meta-analysis showed HCC risk is 66% higher in diabetics[15] and a cohort study showed HCC risk may increase with the duration of diabetes[16].

Development of HCC in a healthy liver is rare; the majority of patients who develop HCC have a background of chronic hepatitis/cirrhosis, so HCC frequently recurs after primary treatment due to the underlying liver disease[17]. In our study, 93.7% (75 cases) developed HCC on top of liver cirrhosis which was due to HCV in the majority of cases (98.6%).

Liver cirrhosis has been previously reported in many studies as the most predominant pathological lesion behind the development and progression of HCC[18]. In a similar study for prognostic factors of HCC in Italy, liver cirrhosis accounted for 96% of HCC cases[19], which is similar to our results. The strong association between cirrhosis and HCC was supported by the evidence of its intermediating role in the pathogenesis of HCC due to chronic viral hepatitis[20](Darwish et al., 2001).

For hepatitis seroprevalence among HCC cases, a worldwide systematic review documented a predominance of anti-HCV in Japan, Pakistan, Mongolia, and Egypt, while; HBsAg predominated among HCCs from most Asian, African, and Latin American countries[21]. Many prospective studies have shown a significant increase in the incidence of HCC

among HCV-infected cohorts, compared to HCV-negative cohorts[22]. A case-control study was done to assess epidemiologic risk factors in rural Egypt in 2010, confirming the independent effect of the hepatitis virus in the etiology of HCC[23]. AFP level of 400 ng/mL is included in two HCC staging systems, the Cancer of the Liver Italian Program (CLIP) and the Taipei Integrated Scoring (TIS) system, to predict long-term outcomes of unselected HCC patients[24], it is reported that 70% of patients had an AFP level lower than the diagnosis criteria (400 ng/mL) proposed by the European Association for the Study of the Liver in the same year (2001)[25], similarly in our study, 35.7% were ≥400 ng/ml and 57.1% were lower than 400 ng/ml.

AFP ranged from 2 to 54000 ng/ml which was mentioned by Koteish, et al, that HCC can produce a range of AFP values from normal to>100000 ng/ml[26].

Amanullah, et al suggested that serum AFP has a significant correlation with the size of the tumor, and AFP level may serve as a useful marker for the detection of HCC and to differentiate between early and advanced stages, based on which proper treatment strategy can be planned[27].

Concerning the tumor size, treatment options for HCC and prognosis are dependent on many factors but especially on tumor size and staging. The overriding importance of tumor size comes across in all of the staging systems of HCC, screening of high-risk cirrhotic patients has gained wide acceptance and there is clear evidence that such strategies can detect cancers of a smaller size [28]. A study conducted on 403 patients with HCC found the size of the tumor in addition to serum albumin, bilirubin, and the number of tumor nodules to be independent predictors of survival[29]. Another study conducted in 140 previously untreated cases of HCC found that tumor size was a significant prognostic factor of survival upon multivariate analysis[30], also, Chen et al. confirmed that tumor size is an independent prognostic factor in resected small HCC, and the prognostic significance of tumor size may vary according to different cut-off points[31].

In our study we divided the patients according to tumor size, in 41% tumor was ≤5 cm, and in 59% >5 cm, In the SR group, it was <5 cm in 34.1% and >5 cm in 65.9%. In the IR group, <5 cm in 48.7% and >5 cm in 51.3%.

There was a clear effect of tumor size on the local control and rate of recurrence whereas, in the SR group, 27.3% of patients who developed recurrence had tumor size <5 cm and 72.7% had a tumor size >5 cm. In the IR group, 42.4% of patients who developed recurrence had a size of <5 cm and 57.6% had a size >5 cm.

Although the management guidelines for HCC recommend monotherapies as a treatment option, combined or sequential treatment modalities are effective in improving the outcome of patients with HCC. In practice, a multi-modal approach combining various treatments is used, and a multidisciplinary team should be involved in the management of every case[32, 33].

In our study, 45 patients underwent surgical resection as curative treatment and 39 patients underwent interventional radiology (TACE or RFA). In the surgical resection (SR) group, 4.4% received radiofrequency ablation (RFA) preoperatively and 20% received transarterial chemoembolization (TACE) postoperatively.

The two main aims of hepatic resection, especially in the cirrhotic liver are to leave functional liver parenchyma to prevent postoperative liver failure and to remove all the malignant tissue with a clear surgical margin. This explains why most centers perform limited resections for small HCCs, especially in patients with poor liver function[34]. This is clear in our results because most of our patients have a poor liver function, so non-anatomical resection was done in 55.6% while Right hepatectomy was done in 24.4%, left hepatectomy in 11.1%, left lateral hepatectomy in 4.4% and extended right hepatectomy in 4.4%.

The main risk of limited resections is tumor recurrence in the adjacent or distal liver segments through tumor portal venous territory. Several studies demonstrated that anatomical resections of small solitary HCC achieve significantly better overall and disease-free survival than limited resections, without increasing the postoperative risk. Therefore, when possible, anatomical resection should be the treatment of choice and considered as the reference surgical treatment when comparing it to other treatments[34].

With advances in surgical skills and perioperative care, the mortality rate after major hepatectomy has decreased from 58% to <10% [35] and the operative mortality in cirrhotic patients ranged from 3% to 8% [34], which is similar to our study which showed a mortality rate of 8.9% in SR group. However, current standards describe a mortality rate of between 2 and 3% and a blood transfusion rate of under 10%[35].

Assessment of the severity of liver fibrosis or cirrhosis before hepatic resection is crucial.

In NCI the Child-Pugh classification is routinely used. Our study showed that In the SR group, 71.1% of the cases were Child class A, 28.9% were Child class B and no cases were Child class C. A similar retrospective study for liver resection of HCC on top of cirrhosis showed that 82.6% of patients were Child A, 16.5% were Child B, and 0.9% were Child C[36].

Recurrence rates after treatment of HCC are still high and this is mainly due to the presence of the chronic underlying liver disease which is a preneoplastic state. Therefore, because liver transplantation (LT) removes the tumor and the preneoplastic underlying chronic liver disease, LT appears to be the treatment of choice for small HCCs. However, LT indications for HCC are restrictive and the limited availability of grafts and the cost of the LT represent the main potential limiting factors for its development[37]. The results of Ercolani, et al. showed that tumor recurrence after surgical resection appeared in 41.5% of patients and was the leading cause of death in 56%[36]. This is close to our results where recurrence appeared in 42.2% of patients after surgical resection. Higher recurrence rates were reported by

Portolani, et al. who stated that Cancer recurrence, generally in the hepatic remnant, occurs in 70% to 100% of cases after resection surgery for HCC[38].

Transcatheter arterial chemoembolization (TACE) is the current standard of care for intermediate-stage Barcelona Clinic Liver Cancer (BCLC) staging system patients. An important limitation of all TACE regimens is the high rate of tumor recurrence. In RCTs, a sustained response lasting >3 to 6 months was observed in only 28 to 35% of patients who received conventional TACE, and in nonresponders, no survival benefit was identified compared with best supportive care. Even in those patients in whom an initial response was achieved, the 3-year cumulative rate of intrahepatic recurrence reaches 65%[39]. Our results showed a rate of recurrence of 58.9% and a residual tumor was found in 23.1%.

Overall survival of HCC patients varied greatly between different studies, some papers recorded considerably low survivals at 3.5 months[1] and 1.9 months in Malaysia [40], while; some other papers reported rates as high as 25.7 and 26.8 months in Italy and Taiwan respectively[41, 42]. this discrepancy in survival rates can be explained by many factors such as the biological behavior of the tumor, the underlying state of chronic liver disease and cirrhosis, the sum of predisposing risk factors and the available therapeutic options, in addition; the application of screening and surveillance to early detect HCC can provide higher survival rates[43, 44].

In our study, as expected the overall survival rates for the surgical resection group were better than those of the IR group. For the SR group, it reached 79% at 1 year, 61% at 2 years, and 54% at 3 years, while for the IR group it was 55%, 19%, and 11% respectively. The lower survival rates in the IR group are probably because those patients were diagnosed at a later stage of the disease and had poor liver function. These results can be compared to a study by Ercolani, et al. for hepatic resection of HCC on top of liver cirrhosis, which showed 1-, 3-, and 5-year overall survival rates of 83%, 62.8%, and 42.5%, respectively[36]. However, some studies showed that interventional radiology techniques are a valid option for the treatment of HCC in patients who are not suitable for surgical resection. In a study by Terzi, et al., where TACE was done in patients with single HCC; 1-, 3- and 5-year survival rates were 85%, 50%, and 26%, respectively[45].

The retrospective study design and the existence of patient selection bias for surgical resection or TACE pose limitations to our study. In addition, the frequency of TACE administration or RFA for individual patients varies in our study, which was influenced by tumor progression and severity of cirrhosis during the follow-up period. Therefore, large cohort studies are required to further evaluate the optimum treatment strategy for different stages of HCC patients.

Conclusion:

Surgical treatment remains the only curative therapy for HCC, with lower recurrence rates and longer survival. However, other modalities can be used in conjunction with surgery or as a bridge to liver transplantation. Further studies are required in NCI to develop the optimum therapy or combination of therapies for HCC.

Abbreviations:

HCC: hepatocellular carcinoma, TACE: transarterial chemoembolization, SR: surgical resection, IR: interventional radiology

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