ARTICLE

Comparison of Microwave Ablation and Transcatheter Ablation and Transcatheter Arterial Chemoembolization in the Treatment of Early Hepatocellular Carcinoma

Lawrence A Shirley, Jon Henry, Lavina Malhotra, Mark Bloomston, Carl R. Schmidt

Department of Surgery, Wexner Medical Center, Ohio State University, Columbus, OH

Corresponding author: Dr. Carl Schmidt Email: carl.schmidt@osumc.edu
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Abstract

Background: Patients with cirrhosis and early stage hepatocellular carcinoma (HCC) may not be candidates for surgical resection due to liver dysfunction. Two common alternative therapies to treat HCC are transcatheter arterial chemoembolization (TACE) and microwave ablation (MWA). We compared outcomes between HCC patients within Milan criteria after initial treatment with these two therapies. **Methods:** The records of 58 patients diagnosed with HCC within Milan criteria and treated initially with either TACE or MWA were reviewed. Pre-treatment factors, perioperative outcomes and survival were compared between groups. **Results:** There were 36 patients treated with MWA and 22 with TACE. Pre-treatment AFP levels were higher in the TACE group. Treatment with MWA was associated with progression-free survival (PFS) of 17.1 months versus 8.9 months after TACE (p=0.56). Disease-specific survival (DSS) was higher in the MWA group (median not reached) than the TACE group (32.0 months, p=0.047). Nine (15.5%) patients in this cohort went on to receive liver transplantation. **Conclusions:** Treatment with either MWA or TACE for patients with cirrhosis and unresectable HCC within Milan criteria is generally safe and initially effective, but recurrence and eventual death due to HCC or cirrhosis is common. These therapies should be a bridge to transplantation for all appropriate candidates.

Key words: Hepatocellular carcinoma (HCC), Transcatheter arterial chemoembolization (TACE), Microwave ablation (MWA), Hepatic cirrhosis, Milan criteria,

Introduction

Hepatocellular carcinoma (HCC) is a worldwide epidemic, ranking 3rd in cancer-related deaths, and the 5th-most common cancer in men and 8th-most common in women overall.(1-4) Additionally, the incidence is increasing, especially in the United States. (5) The most common risk factors for HCC are cirrhosis and chronic hepatitis infection. The fact

that HCC develops in the background of liver parenchymal disease creates a unique challenge for surgical treatment in that simply resecting the liver segments involved is often prohibitive due to pre-existing liver dysfunction.

Patients with early stage HCC within Milan criteria are likely to benefit from orthotopic liver transplant (OLT). Local and regional treatment options are now used commonly for patients with unresectable HCC or as bridge therapy prior to OLT. Transcatheter arterial chemoembolization (TACE) is arguably the most commonly used regional therapy and is generally associated with favorable tumor response and improved survival versus untreated controls. (6,7) Additionally, studies have shown a role for TACE in downstaging patients with tumors outside of Milan criteria. (8) Commonly used thermal local ablation methods such as radiofrequency ablation (RFA) and microwave ablation (MWA) are generally associated with favorable oucomes especially for small tumors (< 3 cm) (9-14). Also, when these methods are used as a bridge for OLT they are associated with lower rates of dropout from the transplant waiting lists (9-14).

For patients with early stage HCC within Milan criteria, the decision to use either local therapy such as MWA or regional therapy such as TACE usually depends on number of tumors or size and location of tumors. Whether these therapies are equivalent in similar patients is unknown. We compared our initial experience with use of TACE or MWA as the initial treatment in patients with early HCC in order to determine the outcomes associated with each therapy.

Patients and Methods

This retrospective cohort study included patients treated at a single tertiary cancer hospital with a tissue or radiographic diagnosis of HCC in the background of cirrhosis and who were initially treated with either TACE or MWA. All patients' radiologic pattern of HCC was within Milan criteria. We reviewed outcomes based on our surveillance patterns: a contrast-enhanced CT or MRI is performed one month post-procedure to determine if repeat or other intervention needed followed by imaging and labs every 3 months for one year followed by every 6 months. Once the data was pooled, the TACE and MWA groups were compared across three broad categories: pre-treatment factors, peri-procedural outcomes and survival. Patient factors compared prior to treatment included age, gender, race, alpha fetoprotein (AFP) level, Child-Pugh score, Model for End-Stage Liver Disease (MELD) score, serum albumin level, platelet count, intent to transplant, and number and size of tumors present on axial imaging. Peri-procedural outcomes included short-term complications, length of stay after the procedure, readmission within 30 days, and 30-day mortality.

Survival analysis included percentage of patients successfully bridged to transplant, progression-free survival (PFS), disease-specific survival (DSS), and overall survival (OS). PFS was measured from date of initial treatment with MWA or TACE to progression of HCC as determined by radiologic evidence, DSS initial treatment to death from HCC or last follow-up date if alive, and OS from initial treatment until death from any cause or last follow-up. These three outcomes were estimated using Kaplan-Meier survival curves, and the log rank test was used to assess for differences between groups. Statistical analysis was conducted using SPSS v.18 software (SPSS, Inc, Chicago, IL), and $p<0.05$ was considered statistically significant. Institutional Review Board approval was obtained for this study.

Results

In total, 58 patients met inclusion criteria, 36 patients in the MWA group and 22 patients in the TACE group. All patients were treated between January 1, 2007 and December 31, 2011. Median follow-up was 11.4 months for the MWA group and 17.7 months for the TACE group. The groups were comparable in terms of general demographics (Table 1), including age, gender, and race. Additionally, they had similar measurements of liver function, including Child-Pugh score, MELD score, platelet count, and serum albumin level. In terms of tumor burden, both groups were comparable in terms of number of tumors seen radiographically and maximum tumor size. No patient in either cohort had major vascular invasion. Notably, the AFP level in the TACE patients was significantly higher than in the MWA patients. The groups were similar also in the percentage of patients that were being treated with the intent to later undergo liver transplantation. Reasons for not initially being considered for transplant ranged from other unrelated comorbidities (4 patients), social issues/patient preference (4 patients), presence of a second malignancy (3 patients), active substance abuse (2 patients), advanced age (2 patients), questionable lung metastases (1 patient), and presence of portal vein thrombosis (1 patient).

During the peri-procedural period, there was a trend to lower complications in the MWA group (Table 2). Length of stay was lower in the MWA group as compared to the TACE group. The percentage of patients who were readmitted to the hospital within 30 days was similar between groups.

Table 1. Comparison of pre-treatment factors between the MWA and TACE groups, including general demographic data, measurements of liver function, and HCC characteristics. All numbers reflect the median in each group.

	MWA	TACE	P value
AFP (ng/mL)	75.9	918.6	0.0004
Age (years)	61.9	57.9	0.889
Albumin (g/dL)	3.3	2.9	0.807
Child-Pugh score	7.2	7.5	0.234
Gender (% Male)	88.9	77.3	0.278
Intent to Transplant (%)	72.2	68.1	0.484
Largest tumor size (cm)	2.4	2.85	0.136
MELD score	11.2	11.3	0.905
Patients with >1 tumor (%)	19.4	31.8	0.225
Pre-procedure platelet count (K/ul)	89.9	99.0	0.932
Race (% White)	86.1	77.3	0.481

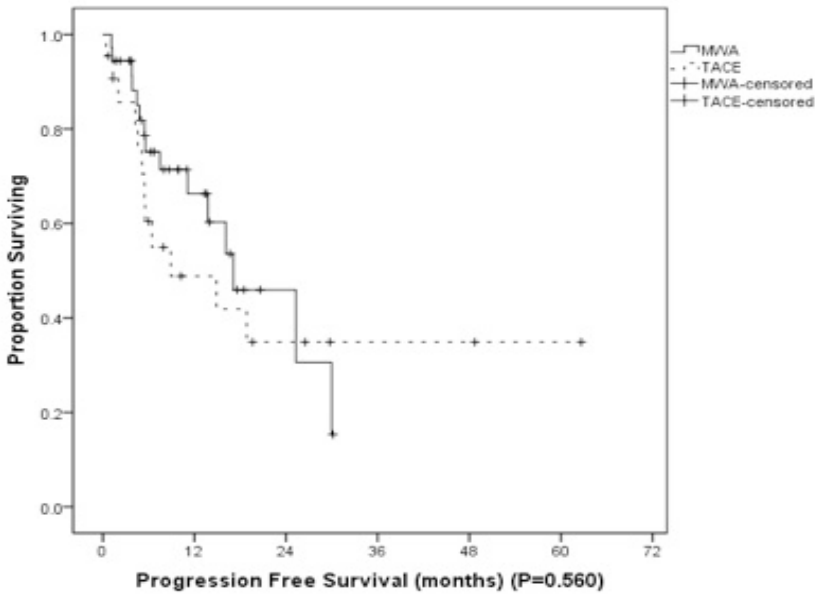

Figure 1. Kaplan-Meier curve comparing progression free survival (PFS) in those treated with MWA (solid line) versus those treated with TACE (dashed line). Median PFS was 17.1 months in the MWA group and 8.9 months in the TACE group (p=0.560).

Table 2. Comparison of periprocedural factors between MWA and TACE groups.

	MWA	TACE	P value
Complications (%)	5.6	22.7	0.065
Length of stay (days)	2.1 (range 1-7)	3.0 (range 1-12)	0.004
30-day Mortality (%)	0	13.6	0.05
Readmissions within 30 days (%)	16.7	27.3	0.261

Table 3. Causes of death between the two groups.

	MWA	TACE
Death from any cause	11	12
Death due to HCC	4	9
Death due to ESLD	5	3
Other cause of death	1	0
Unknown cause of death	1	0

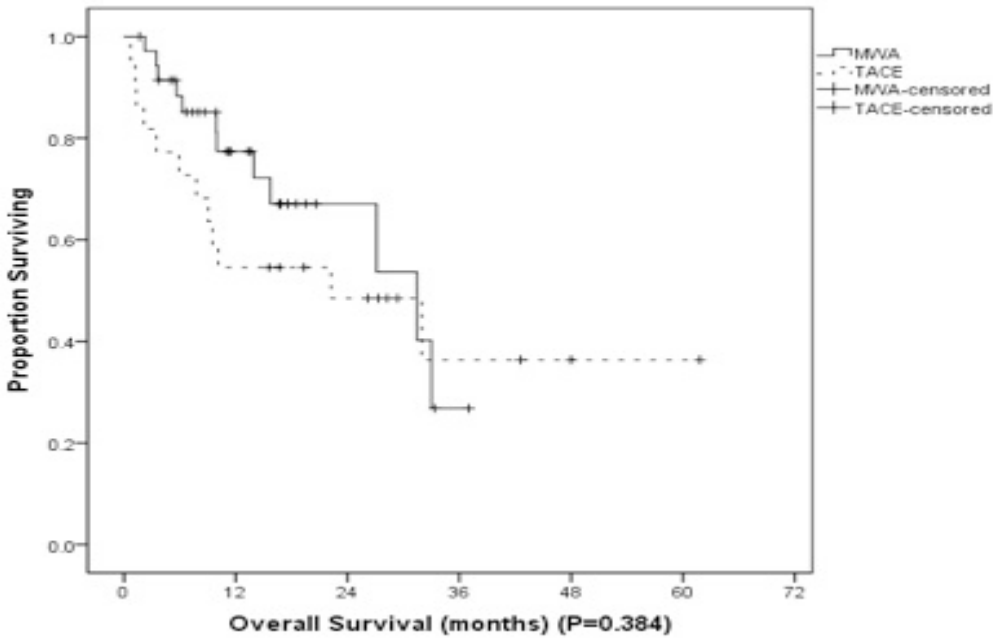

Figure 2. Kaplan-Meier curve comparing overall survival (OS) in those treated with MWA (solid line) versus those treated with TACE (dashed line). Median OS was 31.4 months in the MWA group and 22.2 months in the TACE group (p=0.384).

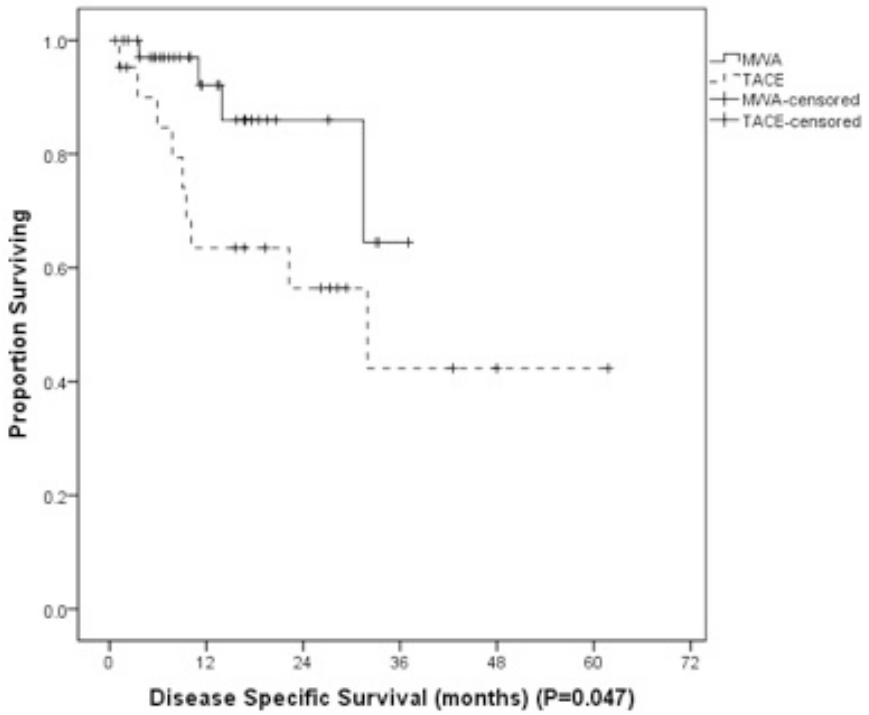

Figure 3. Kaplan-Meier curve comparing disease specific surviva1 (DSS) in those treated with MWA (solid line) versus those treated with TACE (dashed line). Median DSS was not reached in the MWA group but was 32.0 months in the TACE group (p=0.047).

Finally, 30-day mortality was higher in the TACE group, with 3 deaths as compared to no deaths in the MWA group. There were 9 patients (16%) from both groups who received OLT after bridging therapy (11.1% in MWA group vs. 22.7% in TACE group, p = 0.278). In the MWA group, the local recurrence rate was 14% at one year. Sixteen of 22 patients (72.7%) in the TACE group required further therapy after treatment, ranging from additional TACE (27.2%) to OLT (22.7%). Among those treated with MWA, 38.8% had recurrence, with treatments including TACE (5 patients), repeat ablation (2 patients), chemotherapy (2 patients), and radiation therapy (1 patient). Median follow-up was 11.4 months in the MWA group and 17.7 months in the TACE group. Median progression free survival was 17.1 months in the MWA group vs. 8.9 months in the TACE group (p=0.560) (Figure 1). Median overall survival was 31.4 months in the MWA group vs. 22.2 months in the TACE group (p=0.384) (Figure 2). Disease-specific survival was not reached in the MWA group and was 32.0 months in the TACE group (p=0.047). A total of 23 patients (39.7%) died during the period of follow-up, and most patients died as a result of HCC progression or worsening liver function due to cirrhosis (Table 3).

Discussion

The majority of patients with HCC have concomitant cirrhosis; this makes treatment decisions complex even for patients with early HCC. For patients with early HCC but severe liver dysfunction or portal hypertension, surgical resection is often not feasible. OLT for such patients is associated with superior outcomes, but bridging therapy is often needed due to average wait times for OLT of 6-12 months at most centers in the U.S.(15,16) Due to these issues preventing typical curative modalities, locoregional therapies such as MWA and TACE have become essential in treating these patients. We have shown that treatment with either MWA or TACE for patients with early stage HCC is generally safe, and MWA is associated with shorter length of stay and lower 30-day mortality when compared to TACE. Nonetheless, when looking at long-term outcomes both groups show comparable trends in progression and survival. While bridge to OLT was the intent in over 60% of patients this goal was achieved in less than 20%. This is of concern since PFS after either therapy was less than

two years emphasizing the limitations of both strategies as definitive therapy even with early HCC. Our data support the notion that patients with early stage HCC have limited options due to the well-known issue of severe organ shortage in the United States. Both locoregional therapies compared here can control disease burden, but for a finite period of time.

Several studies have looked at the role of ablative therapies in the treatment of early stage HCC. They have shown initial local control rates ranging from 91-100%, but with local recurrence rates from 2-34% (17-21). Long-term outcome for such patients include overall survival of 82-90% at one year and 59-81% at 3 years. (17-21) Additionally, for patients treated with this modality, studies have demonstrated lower than expected drop-out rates for patients awaiting OLT.(9-14) There is currently controversy over the use of ablation as definitive therapy, especially for tumors <3cm, but substantial evidence is still lacking. For TACE, several RCTs have shown tumor response rates ranging from 16-60% (22-24) and improved survival in nonsurgical patients treated with this regional therapy in comparison to untreated controls.(6,7) However, survival benefit is only definitively demonstrated in highly selected patients, such as those in our cohort(6, 25). As a bridging therapy, several studies have shown low dropout rates achieved in patients treated with TACE, ranging from 0–15% at 6 months and 0–25% at 12 months. (26,27) Our study reflects the good initial response rate of patients treated with either ablative therapies or TACE, but also recapitulates the lack of convincing evidence that either type of therapy could be used as definitive therapy due to high recurrence rates.

Some authors have proposed combining both local and regional therapies for treatment of early and later stage HCC. A recent RCT was performed to evaluate the efficacy of combined TACE and RFA in the treatment of HCC.(28) The study showed that combination therapy had significantly lower tumor progression rates when compared to using RFA alone, 6% versus 39% (p=0.012). Studies have also looked at the role of regional therapies in combination with surgical resection. In the adjuvant setting (29-31) the use of TACE showed similar recurrence rates, but improved DSS and OS in those treated with TACE postoperatively. Another RCT compared patients treated with preoperative TACE and surgical resection versus those treated with resection alone.(32) They found no improvement in recurrence rates, DSS, or OS with the addition of TACE. Thus, the optimal combination of treatments for this disease has yet to be determined.

There are several limitations to this study. First, although Table 1 suggests the groups are comparable, it is most likely selection bias favors use of MWA in patients with smaller and lower number of tumors. Second, the sample size in both groups was relatively small as this is a single-institution study and MWA has been adopted within the past few years. Third, the overall follow-up time was relatively short, and therefore our findings about periprocedural outcomes may be more relevant at this point than survival outcomes. In the future, studies that can include larger cohorts and longer follow-up may help to better elucidate out our current findings.

As others have show previously, our study confirms that initial treatment with either MWA or TACE for patients with unresectable HCC within Milan criteria is generally safe but that recurrence or progression of disease are common as is eventual death from either HCC or complications of cirrhosis. Ideally these therapies are a bridge to transplant for all appropriate patients, however many patients do not ultimately reach this goal for a variety of reasons. In our early HCC population, initial therapy with MWA or TACE is generally not curative. For this reason, we maintain close radiologic imaging surveillance after initial treatment. Further, these results emphasize the need for novel therapies and clinical trials specific to this population.

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References

1. Venook AP, Papandreou C, Furuse J, de Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. Oncologist. 2010;15(Suppl 4):5–13.
2. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol. 2009;27(9):1485–91.
3. International Agency for research on cancer. ABOUT CANCER Mondial. Lyon, France: WHO; 2002.
4. Parkin DM, Muir CS. Cancer Incidence in Five Continents. Comparability and quality of data. IARC Sci Publ. 1992;(120):45–173.
5. Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med. 1999;(340):745–750.
6. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or

chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. Lancet 2002;(359):1734-1739.
7. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;(35):1164–1171.
8. Chapman WC, Majella Doyle MB, Stuart JE, Vachharajani N, Crippin JS, Anderson CD, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. Ann Surg 2008;(248):617-25.
9. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma Ann Surg 2006;(243):321-8.
10. Mazzaferro V, Battiston C, Perrone S, Pulvirenti A, Regalia E, Romito R, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. Ann Surg 2004;(240):900–9.
11. Murakami T, Ishimaru H, Sakamoto I, Uetani M, Matsuoka Y, Daikoku M, et al. Percutaneous radiofrequency ablation and transcatheter arterial chemoembolization for hypervascular hepatocellular carcinoma: rate and risk factors for local recurrence. Cardiovasc Intervent Radiol 2007;(30):696–704.
12. Shibata T, Isoda H, Hirokawa Y, Arizono S, Shimada K, Togashi K. Small hepatocellular carcinoma: is radiofrequency ablation combined with transcatheter arterial chemoembolization more effective than radiofrequency ablation alone for treatment? Radiology 2009;(252):905–13.
13. Mahnken AH, Bruners P, Gunther RW. Local ablative therapies in HCC: percutaneous ethanol injection and radiofrequency ablation. Dig Dis 2009;(27):148–56.
14. Bouza C, Lopez-Cuadrado T, Alcazar R, Saz-Parkinson Z, Amate JM. Meta -analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. BMC Gastroenterol 2009;(9):31.
15. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;(334):693–9.
16. Roayaie K, Feng S. Allocation policy for hepatocellular carcinoma in the MELD era: room for improvement? Liver Transpl. 2006;(13):S36–43.
17. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 2003;(228):235 – 40.
18. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma > or =4 cm. Gastroenterology 2004;(127):1714-23.
19. Shiina S, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology 2005;(129):122-30.
20. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC . Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. Gut 2005; (54):1151-6 .
21. Brunello F, Veltri A, Carucci P, Pagano E, Ciccone G, Moretto P, et al. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: A randomized controlled trial. Scand J Gastroenterol 2008;(43):727-35.
22. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003;(37):429-42.
23. Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma.Gastroenterology 2004;(127):S179-88.
24. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;(362):1907-17.
25. Giannini EG, Bodini G, Corbo M, Savarino V, Risso D, DI Nolfo MA, et al. Impact of evidence-based medicine on treatment of patients with unresectable hepatocellular carcinoma. Aliment Pharmacol Ther 2010;(31):493-501.
26. Maddala YK, Stadheim L, Andrews JC, Burgart LJ, Rosen CB, Kremers WK, et al. Drop-out rates of patients with hepatocellular cancer listed for liver transplantation: outcome with chemoembolization. Liver Transpl 2004;(10):449-55.
27. Graziadei IW, Sandmueller H, Waldenberger P, Koenigsrainer A, Nachbaur K, Jaschke W, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor

progression while on the waiting list and leads to excellent outcome. Liver Transpl 2003;(l9):557-63.
28. Morimoto M, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer 2010;(116):5452-60.
29. Xi T, Lai EC, Min AR, Shi LH, Wu D, Xue F et al. Adjuvant transarterial chemoembolization after curative resection of hepatocellular carcinoma: a non-randomized comparative study. Hepatogastroenterology 2012;(59):1198-203.
30. Zhong C, Guo RP, Li JQ, Shi M, Wei W, Chen MS, Zhang YQ. A randomized controlled trial of hepatectomy with adjuvant transcatheter arterial chemoembolization versus hepatectomy alone for Stage III A hepatocellular carcinoma. J Cancer Res Clin Oncol 2009;(135):1437-45.
31. Peng BG, He Q, Li JP, Zhou F. Adjuvant transcatheter arterial chemoembolization improves efficacy of hepatectomy for patients with hepatocellular carcinoma and portal vein tumor thrombus. Am J Surg 2009;(198):313-8.
32. Zhou WP, Lai EC, Li AJ, Fu SY, Zhou JP, Pan ZY, et al. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. Ann Surg 2009;(249):195-202.