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ASSESSMENT OF PERCUTANEOUS RADIOFREQUENCY ABLATION WITH NEEDLES CHOSEN SUITABLY TO TUMOR SIZES FOR HEPATOCELLULAR CARCINOMA PATIENTS

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SUMMARY OF PHD THESIS

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ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AFP	Alpha Fetoprotein
APASL	Asian Pacific Association for the Study of Liver
BCLC	Barcelona
CR	Complete response
CT	Computed Tomography
EASL	European Association for the Study of the Liver
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
MRI	Magnetic Resonance Imaging
PD	Progressive disease
PEI	Percutaneous ethanol injection
PR	Partial response
RFA	Radiofrequency ablation
RUQ	Right upper quadrant
SD	Stable disease
TACE	Transarterial chemoembolization

THESIS INTRODUCTION

1. Background

Primary liver malignancy in which hepatocellular carcinoma (HCC) has proportion of 85 - 90% is a common disease. In Vietnam, this cancer ranks the second incidence rate and the first mortality rate among malignancies. In recent years, radiofrequency ablation (RFA) has been considered a vital therapy in many centres worldwide with advantages of good efficacy, low complication rate, reasonable cost and applicablity to other centres. However, the efficacy depends on many factors in which the kind of needles is important. In Vietnam, this therapy was first applied in 2002, however, until now, most of hospitals are using unipolar needles for tumors with different sizes. Extent to our knowledge, there was no study in Vietnam conducted to evaluate efficacy and technical aspects of RFA using needles chosen suitably to tumor sizes including both Soloist and LeVeen™ needles. For this reason, the study "**Assessment of percutaneous radiofrequency ablation with needles chosen suitably to tumor sizes for hepatocellular carcinoma patients**" was conducted with two aims:

1. *To evaluate efficacy of percutaneous radiofrequency ablation treatment with needles chosen suitably to tumor sizes for hepatocellular carcinoma patients.*
2. *To identify advantages, disadvantages and safety of percutaneous radiofrequency ablation treatment with needles chosen suitably to tumor sizes for hepatocellular carcinoma patients.*

2. The topicality of thesis

The thesis was conducted in the context Vietnam has high incidence and mortality rate of HCC. Most of medical centres are using unipolar needle for any size of tumors leading to poor response for tumors > 3 cm, more number of ablation sessions and high rate of adverse events. Choosing needles suitable to tumor sizes could overcome drawbacks of traditional unipolar needles. Therefore it is necessary to evaluate thoroughly efficacy, advantages, disadvantages and safety of this technique.

3. Scientific contributions of thesis

- This is the first study conducted in Vietnam to assess the efficacy of RFA with needles chosen suitably to tumor sizes for HCC patients.

- The study demonstrates that this therapy has good results with response rate after 1 month being 96.1%, the cumulative overall survival rate at 1 year, 2 year and 3 year is 94.6, 72.3 and 26.9%, respectively. The mean overall survival (OS) time is 48.5 months (CI 95%: 44.7 - 52.4 months). The mean progression free survival (PFS) time is 30.9 months (CI 95%: 28.7 - 33.0 months).

- The study demonstrates that this therapy is realatively safe with the complication rate being 1.7%, side effects being 20.5% and 16 patients (12.3%) having tumors in difficult locations were performed artificial ascites or pleural effusion combinedly.

4. Thesis structure

The thesis has 146 pages with (excluding appendices and references) Background (2 pages), Literature Review (41 pages), Subjects and methods of study (20 pages), Results (42 pages), Discussion (38 pages), Conclusion (2 pages) and Recommendations (1 page). There are 57 tables, 9 figures and 18 images. The reference includes 186 documents in which 21 are Vietnamese and 165 are English.

CHAPTER 1: LITERATURE REVIEW

1.1. Epidemiology of hepatocellular carcinoma

HCC ranks the fifth of common malignancies worldwide. Southeast Asia including Vietnam is a region with high age-adjusted prevalence (>20/10^5) in which Vietnam ranks the second.

1.2. Risk factors

The main risk factors of HCC are HBV, HCV, alcohol and non alcoholic fatty liver disease. The less common causes include aflatoxin, hemochromatosis, alpha 1- antitrypsin deficiency autoimmune hepatitis and Wilson disease. In different geographic areas with different races, the etiologies of HCC also vary.

1.3. Diagnosis

There are many methods to diagnose HCC including imaging, biomarkers and histology. In 2012, Ministry of Health in Vietnam released a protocol to diagnose and treat HCC in which Barcelona (BCLC) classification was recommended to use.

1.4. Treatment

1.4.1. Surgery

Surgery is now a first-line option for HCC in early stage with stable liver functions, especially for patients without liver cirrhosis. However, the number of patients detected in this stage was small.

1.4.2. Liver transplantation

Milan criteria is used worldwide. In Vietnam, due to high cost and lack of donor organs, most of patients having indications could not approach this therapy.

1.4.3. Local therapies

Percutaneous ethanol injection (PEI) was applied commonly in Vietnam. The follow-up study in 10 years by Mai Hong Bang showed the survival rate after 1 year, 3 years and 5 years were 81%, 60% and 37%, respectively. For tumors with multiple walls inside, percutaneous acid acetic injection is an option. Microwave ablation is a therapy using microwave with frequency ≥ 900 MHz having similar indications compared to RFA. Laser ablation and cryoablation are still in research.

1.4.4. Transarterial chemoembolization (TACE)

This therapy was indicated in patients with intermediate stage (BCLC B), multiple tumors, stable liver functions and health status (Child Pugh A-B, PS 0) to destroy the tumor, control the extention of disease and protect normal liver tissue.

1.4.5. Radiotherapy

Transfering radioactive particles to tumors via hepatic artery is a local therapy to destroy tumors and control toxicity to normal liver tissue. The common agent is ^{90}Y. However, the dosage and official indications were not recommended.

1.4.6. Sorafenib

Since launching, Sorafenib has become an effective systemic therapy for late stage patietns. According to EASL, sorafenib is indicated for patietns with good liver funciton (Child Pugh A) and late stage (BCLC C) or tumors extent local indications.

1.5. Radiofrequency ablation

1.5.1. Mechanism

RFA uses high frequency of 200 kHz - 20 MHz. A circuit was set up among machine, needles, patient and pad guards. Because of huge difference of impedance between needle tip and body tissue, when the alternating electric current passes, it causes ionic agitation and friction heat.

1.5.2. Indications and contraindications

According to EASL, AASLD and APASL, RFA is indicated for HCC patients with BCLC A, which means a single tumor ≤ 5 cm or ≤ 3 tumors with each tumor size ≤ 3cm and Child Pugh A or B. Contraindications include extrahepatic metastasis, life expectancy less than 6 months, mental changes, infection or main bile duct invasion. Relative contraindications include tumor >5cm, severe liver cirrhosis, more than 4 tumors, severe comorbid diseases and severe coagulation disorders.

1.5.3. Complications

Complications post RFA could be classified on time: in the procedure, early complication (within 6 - 24 hours post RFA), late complications (within 30 days) or later complications.

1.5.4. Imaging after RFA

After RFA, the necrosis zone must be larger than tumor zone from 0.5 - 1cm so according to EASL, the response should be evaluated on enhanced tissue (viable tumor) and non enhanced tissue (necrosis zone) - mRECIST criteria.

1.6. Researches on radiofrequency ablation

In Vietnam, RFA was applied more popularly in many medical centres with positive results. In recent years, more new advancements were used to improve efficacy. The study of Le Thi My on 52 patients with Cooltip needles demonstrated the necrosis rate being 91.9%. In Gastroenterology department of Bach Mai hospital, RF3000 was used since 2011 with Soloist and LeVeen^{TM} needles chosen suitably to tumor sizes. This system allows to ablate tumors 4 - 5cm because the heat can spread along the array tines and each tine can play a role as a unipolar needle to create larger necrosis zone.

CHAPTER 2: SUBJECTS AND METHODOLOGY

2.1. Subjects

2.1.1. Inclusion criteria

* Patients with ***HCC diagnosis*** based on Diagnosis Protocol released by Vietnam Ministry of Health 2012: Pathology evidence *or* typical images on enhanced CT-Scan/MRI + AFP > 400 ng/ml *or* typical images on enhanced CT-Scan/MRI + elevated AFP (< 400ng/ml) + HBV/HCV carriers.

* ***RFA indications*** based on APASL 2010 recommendations: BCLC A (1 single tumor ≤ 5 cm *or* ≤ 3 tumors with each tumor size ≤ 3 cm; Child Pugh A, B; PS 0). For patients BCLC A with past history of other therapies without response, RFA could be indicated.

2.1.2. Exclusion criteria

Child-Pugh C; severe coaglulation disorders (PLT < 50 G/l; PT < 50%); Metastasis (Portal vein, hepatic vein thrombosis, lympho node and other organs); Patients with pregnancy or pacemakers or

severe comorbid diseases (kidney failure, heart failure). Relative contraindication was tumor in difficult location to observe, choose needle tract or at high risk of complications.

2.1.3. Sample size

The study assumed to compare response rate bewtween group with unipolar needles and group with LeVeen needles chosen suitably to tumor sizes. The formula to compare two proportion was used:

$$n = Z^2_{(\alpha,\beta)} \frac{p_1q_1 + p_2q_2}{(P_1 - P_2)^2}$$

In which $\alpha = 0.05$ and $1 - \beta = 80$, $P_1 = 0.3$ (the successful response proportion in the study using unipolar needle by Dao Van Long), $P_2 = 0.6$ (the successful response proportion in the study using LeVeen needle by Cabassa). Applying the formula, the sample size needed for each group $n_1=n_2=40$ and the total number of patients is 80 patients. This study followed up patients along time so if assuming 10% of patients were lost of follow-up, the minimum sample size is 88 patients.

2.1.4. Study location and duration

- Study location: Gastroenterolgoy department - Bach Mai hospital

- Study duration: October 2011 - June 2016

2.2. Study methods

2.2.1. Study design

Clinical interventional study with one group, no control.

2.2.2. Study facilities

- Boston Scientific RF 3000 ablation machine, Pad Guard ™.

- RFA neesles:

+ Soloist needle: for tumor size 1 - 1.5 cm.

+ LeVeen ™ needles: 2.0 needle for tumor size 1.5 - 2 cm; 3.0 needle for tumor size 2.1 - 3cm; 4.0 needle for tumor size 3.1 - 4cm; 5.0 needle for tumor size 4 .1- 5cm

- Veress needle for artificial ascites/pleural effusion

- Ultrasound machines: Samsung Acuvix A30, Hitachi Aloka Arietta V60 with Convex probes having 2.5 - 7.5 kHz frequency.

- Monitor machine. Sterile instrument and emergency box.

2.2.3. Research steps

2.2.3.1. Patient selection and evaluation before treatment

- Patient selection: according to inclusion criteria

- Evaluation before treatment: clinica examination, lab tests (biochemistry, hematology, hepatitis virus screening), chest X-ray, esophagealgastroendoscopy, Imagings (Abdominal ultrasound, enhanced CT-Scan/MRI). Fine needle aspiration or biopsy to confirm diagnosis. Evaluate Child Pugh Score, Okuda and BCLC classification.

2.2.3.2. RFA technique

**** Patient preparation:***

Explain to patients the technique and patients sign in procedure agreement document.

**** Technique:***

Based on technique protocol released by Ministry of Health and it is important to choose needle suitably to tumor size. In difficult locations, artificial ascites/pleural effusion with Veress needle 14G was performed.

2.2.3.3. Monitor side effects and complications

- Complications in procedure relating to anesthesia.
- Early complications within 6 - 24 hours and side effects (pain, fever).
- Late complications within 30 days.
- Later complications.

2.2.3.4. Follow up and evaluation efficacy of therapy

Follow-up time: after RFA 1 month then 3 months/time periodically in the first year then 6 months/time.

**** Technical results:*** The mean ablation sessions, the necrosis rate, side effects and complications.

**** Clinical results:*** classify into different categories.

- Good response: less pain, weight gain
- No change
- Bad response: weight loss, more pain, jaundice, ascites

**** Lab test result: monitor the change of***

- AFP: Decrease, No change, Increase after treatment
- AST, ALT, Bil, Albumin, PT

**** Imaging of tumor on CT-Scan/MRI***

mRECIST criteria were used: Complete response, Parital response, Stable disease and Progressive disease.

**** Follow up OS and PFS time***

**** Follow up other events***

Include: Local recurrence, new lesion appearance, portal vein thrombosis, metastasis (lympho node, lung, bone or other organs).

2.2.4. Data collection

Data were collected according to one form of medical records.

2.2.5. Data process

The data were processed with SPSS 20.0 software. The algorithm used were Chi square, paired T, Cox regression analysis, survival analysis with Kaplan- Meier graph.

CHAPTER 3: STUDY RESULTS

The study was conducted from October/2011 to June/2016 on 130 patients.

3.1. Patient characteristics

- Mean age was 57.5 ± 10,2. Male:female ratio was 4.7:1.

- Clinical symptoms: 40,8% without symptoms. In patients with symptoms, fatigue (30%) and RUQ pain (22.3) were common.

- Risk factors: 96 patients (73.5%) had HBV, 11 patients (8.5%) had HCV and 59 patients (45.4%) drank alcohol regularly.

- 59 patients (45.4%) had comorbid diseases.

- 30 patients (23.1%) had past history of other therapies: 28 patients with TACE, 1 patient with PEI, 1 patient with surgery.

- Most patients were liver cirrhosis Child Pugh A (87.7%), 3 patients had no liver cirrhosis (2.3%) and 13 patients were Child Pugh B (10%).

- 66 patients (50.8%) had AFP level < 20 ng/ml. The numer of patients with AFP ≥ 200ng/ml was 38 (29.2%).

3.1.1. The tumor characteristics

- 87 patients had 1 tumor (66.9%), 35 patients had 2 tumors (26.9%) and 8 patients had 3 tumors (6.2%). 130 patients had 181

tumors under ultrasound in which 53 tumors with size < 2cm (29.3%), 83 tumors with size 2 - 3cm (45.9%) and 45 tumors with size > 3 cm (24.8%).

- 97 patients (75%) had pathology results, 33 patients (25%) were diagnosed by typical CT-Scan/MRI + AFP ≥ 400 ng/ml.

- Classification: Okuda I - 89.2%, Okuda II -10.8%; Barcelona A - 87.7%, Barcelona 0 -12.3%.

3.2. Technical results

- The number of ablation - 410 times. The mean number of ablation times for each tumor was 2.0 ± 1.1. The tumors with size >3cm had more mean number of ablation times than tumors with size ≤ 3cm and the difference was statistically significant ($p<0.05$).

- There was difference of mean number ablation times among needles: Soloist 1.8 ± 1.0 times, LeVeen 2.3 ± 1.3 times ($p<0.05$).

3.3. Response after rfa

3.3.1. Clinical symptom change

- The percentage of patients with clinical improvement after 1 month, 3 month, 6 month, 1 year, 2 years, 3 years was 53%, 51.5%, 45%, 46.3%, 33% and 19.4%, respectively. The rate of improvement in the group with initial symptoms was 40/59 (67.8%).

- After RFA, most of the patients maintained or gained weight. The proportion of patients gaining weight after 1 month, 3 month, 6 month, 1 year, 2 years, 3 years was 46.2%, 47.7%, 45.7%, 45.5%, 34% and 19.4%, respectively.

- The median value of AFP after treatment 1 month, 3 month, 6 month and 1 year decreased compared to before treatment and the difference was statistically significant (Wilcoxon test, $p <0.05$). In the subgroup with initial AFP level ≥ 200ng/ml (n = 38), the percentage of patients decreasing AFP after 1 month was 86.8%.

3.3.2. The tumor response after treatment

3.3.2.1. The tumor size change

- The tumor size after 1 month under ultrasound and CT-scan/MRI was larger than initial size and the difference was statistically significantly ($p<0.05$).

- There was statistically significant difference between tumor size before and after RFA 1 month for Soloist and LeVeen 3.0 needles ($p<0,05$). For other needles, there was no difference recorded.

3.3.2.2. Complete necrosis rate

After 1 month, 142 tumors achieved complete necrosis (79,3%) in which the tumors ≤ 2cm had highest necrosis rate (95,5%). There was no difference among various needles.

3.3.2.3. mRECIST response

- The mean follow up time in the study: 30.0 ± 11.1 months.

Table. mRECIST response over time

mRECIST over time	***1 month*** (N=130)		***3 months*** (N=130)		***6 months*** (N=129)	
	n	*%*	n	*%*	n	*%*
CR	93	*71,5*	105	*80,8*	101	*78,3*
PR	32	*24,6*	20	*15,4*	16	*12,4*
SD	3	*2,3*	2	*1,5*	2	*1,6*
PD	2	*1,6*	3	*2,3*	10	*7,7*
mRECIST over time	***1 year*** (N=123)		***2 years*** (N=94)		***3 years*** (N=36)	
	N	*%*	n	*%*	n	*%*
CR	106	*86,2*	71	*75,5*	30	*83,3*
PR	6	*4,9*	4	*4,3*	2	*5,6*
SD	2	*1,6*	1	*1,1*		
PD	9	*7,3*	18	*19,1*	4	*11,1*

- There was no difference of response after 1 month, 3 months, 6 months, 1 year, 2 years and 3 years among groups with different age, gender, number of tumors, tumor sizes, AFP level, Child Pugh score, BCLC classification. There was difference in mRECIST response at 2 year between groups with and without past history of other therapies (p=0.05).

- Cox regression analysis demonstrated tumor size, response after 1 month and past history of other therapies had correlation with response over time.

3.2.4. Survival time

- The overall survival time of patients in study was 48.5 months (CI 95%: 44.7 - 52.4 months). 31 patients died during follow up time (23.8%), including 10 patients due to gastrointestinal bleeding (32.3%), 9 patients due to liver failure (29.0%), 7 patients due to metastasis (22.6%), 2 patients due to liver tumor rupture (6.5%) and 3 cases of unknown cause. Cumulative overall survival rate at 1 year, 2 years, 3 years is 94.6%, 72.3% and 26.9%, respectively.

- The mortality risks increased in patients with Child Pugh B, tumor > 3cm or multiple tumors. Cox regression analysis showed that past history of other therapies and response after 1 month correlated with mortality.

- The mean PFS time of patients in study was 30.9 months (CI 95%: 28.7 - 33.0 months).

3.2.5. Events during follow up time

- 49 patients (37.6%) had progression after the average duration of 15.2 ± 8.9 months including 41 patients (31.5%) having local recurrence, 35 (26.9%) patients having new lesions, 6 patients having portal vein thrombosis, 1 patient having liver metastasis spread and 5 patients having distant metastasis. Cox regression analysis recorded male gender, mean times of ablation and mRECIST response after 1 year correlated to the progression and past history of other therapies correlated to local recurrence.

3.2.6. Combined therapies after RFA

34 patients were treated by other therapies after RFA including: 21 patients with TACE, 7 patients with PEI for tiny lesions or lesions in difficult locations; 4 patients with surgery; 1 patient with liver transplantation and 2 patients with chemotherapy when having metastases.

3.3. Advantages, disadvantages and safety

3.3.1. Side effects and complications

- In 410 RFA times, after procedures, 4.1% cases had fever mainly mild, 16.1 cases had RUQ pain mainly mild and 1 patient had mild headache. All patients responded to internal therapies. Univariate and multivariate analysis showed no correlation between tumor size, type of needles, ablation time and intensity to side effects.

- Complications: 4 patients had bradycardia during procedures, 7 patients had complications after procedures including 2 cases of right pleural effusion, 1 case with hemothorax, 2 cases with hematoma under Glisson, 1 case with liver abscess and 1 case with tract seeding.

3.3.2. Lab test change after treatment

Lab tests after treatment did not change statistically significant.

3.3.3. RFA with artificial ascites/pleural effusion

3.3.3.1. Patient characteristics

16 patients with tumors locating adjacent to other organs were performed artificial ascites/pleural effusion before RFA. The most common location was in VI segment adjacent to kidney or gastrointestinal tract, then in VII or VIII segments adjacent to diaphragm or pleura. The mean tumor size was 3.0cm with the smallest lesion being 1.8 cm in VI segment adjacent to kidney and the largest being 4.5cm in VII segment adjacent to pleura.

3.3.3.2. Technique characteristics

16 patients were performred aritifical ascites/pleural effusion in which 13 patients were performed aritficial ascites with the mean volume of 1904 ± 474 ml, 3 patients were performed artificial pleural effusion with the mean volume of 900 ± 173 ml. 13 cases used 3.0 needles and 3 cases used 4.0 needles.

3.3.3.3. Response in artificial ascites/pleural effusion group

The complete response rate is 87.5%, partial response rate is 6.3% and 1 patient had stable disease.

3.3.2.4. Side effects and complications

- Side effects: 1 case had pain (6.3%).

- Complications: 2 patients had right pleural effusion after artificial ascites, 1 patient had liver abscess requiring surgery when infection status and liver function stabilized.

3.3.2.5. Events during follow up time

- 3 patients died, 1 patient had local recurrence and 1 patient had liver abscess after artificial pleural effusion. In surgery, that patient was discovered to have right branch of portal vein thrombosis.

- Cox regression analysis demonstrated Child Pugh score, AFP and response after 1 month correlated to mortality.

CHAPTER 4: DISCUSSION

4.1. Patient characteristics

Our research recorded mean age, gender distribution ratio as well as etiologies of HCC similar to other studies conducted in Vietnam. There were 27 patients with esophageal varices (20.8%) of whom 8 patients were hospitalized with gastrointestinal bleeding. It indicates that comprehensive management of complications in chronic liver disease and liver cirrhosis patients should be more focused. Most patients had chronic liver disease with stable stages (Child Pugh A - 87.7%).

30 patients (23.1%) were treated with other methods before RFA in which 28 patients recieved TACE. Although TACE demonstrates the ability to slow disease progression and improve survival for patients, it is difficult to achieve the target lesion necrosis. In this study, patients having past history of TACE failure were indicated RFA or angiogenesis tumors with size of 4-5cm could be treated combinedly TACE and RFA .

**** Tumor characteristics***

130 patients had 181 tumors observed under ultrasound in which 87 patients had 1 tumors (66.9%), 35 patients had 2 tumors (26.9%) and 8 patients had 3 tumors (6.2%). This result is similar to foreign

studies and the number of patients with multiple lesions is higher than domestic studies. For this group of patients, surgery indication is very difficult especially when tumors are located in different lobes. Therefore, RFA is an effective option. The proportion of tumor with size > 3 cm was 24.8%, more than other studies with unipolar or Cooltip needles in Vietnam. It could be explained that for LeVeen needles 4.0 and 5.0, the prongs can spread out and cover the whole volume of tumor with size> 3 cm.

**** Disease stage***

There are 87.7% of patients in BCLC A and 12.3% of patients in BCLC 0. According to EASL, 5-year survival rate of patients BCLC 0 was 70%.

4.2. Technical results

Our study also recorded similar results to foreign studies that when the tumor size increases, the mean number of ablation increases. When comparing to other studies using unipolar needles in Vietnam, the number of ablation times in our study was lower. It could be explained that when using unipolar needle for tumors > 3cm, more sessions must be performed. The mean number of ablation time in Soloist group was lower than LeVeen group and the difference was statistically significant ($p<0.05$).

4.3. Response after rfa

4.3.1. Clinical symptom change

After RFA, the percentage of patients with clinical improvement and weight gain is 53.1% and 46.2%, respectively. This helps patients to relieve mental pressure and improve quality of life.

4.3.2. AFP level change

AFP level reduced at 1 month,3 months, 6 months, 1 year after treatment and this difference was statistically significant (Wilcoxon test, p <0.05). In subgroup with initial AFP level ≥ 200ng/ml (n = 38), the percentage of patients having AFP decrease after RFA 1 month was 86.8%. AFP decrease in this subgroup is a good prognostic factor in follow up time.

4.3.3. The tumor response after treatment

4.3.3.1. The tumor size change

The mean tumor size after treatment 1 month under ultrasound and CT-scan/MRI was larger than initial tumor size and the difference was statistically significant (p<0.05). It was explained because the aim of technique is to achieve necrosis zone larger than tumor at least 0.5cm.

4.3.3.2. Complete necrosis rate

After 1 month, 142 tumors achieved complete necrosis (79.3%) in which the tumors ≤ 2cm had highest necrosis rate (95.5%). The necrosis rate decreased as the tumor size increased and the difference was statistically significant (p<0.05). This result is similar to foreign studies and higher than the study using unipolar needle conducted by Dao Van Long.

4.3.3.3. mRECIST response

Currently, EASL recommends using mRECIST criteria to assess post-treatment response for local therapies. After 1 month, 96.1% of patients had treatment response in which complete response was

71.5%. In studies with large sample sizes using LeVeen needles, most authors evaluated treatment response after RFA 1 month by complete necrosis rate. Therefore, further studies are needed to conduct to evaluate validity of mRECIST criteria in Vietnam and to provide general guidance in clinical practice. Cox regression analysis recorded tumor size, mRECIST after 1 month and past history of other therapies correlated to treatment response over time. This result is similar to many foreign studies.

4.3.4. Survival time

In the study, 31 patients (23.8%) died during follow up time with mean survival time of non survivors being 33.6 months (CI95%: 31.7 - 35 ,6 months). Cumulative overall survival rate at 1 year, 2 years, 3 years was 94.6%, 72.3% and 26.9%, respectively. The mean PFS time was 30.9 months. Our cumulative OS rate at 1 and 2 year is similar to other publications in the world but OS rate at 3 year is lower because the number of patients having follow-up time more than 3 year is low (33 patients). However, the survival rate in our study is higher than other studies using unipolar needles in Vietnam.

4.3.5. Events during follow up time

During follow-up time, 49 patients (37.6%) had progression after 15.2 ± 8.9 months. Cox regression analysis recorded male gender, multiple ablation times and response at 1 year correlated to disease progression and past history of other therapies correlated with local recurrence. Our study had similar results with other researchers around the world in the rate of new lesion appearance but the local recurrence rate was higher. Comparing to domestic studies using unipolar needles, our study had lower new lesion appearance rate.

4.3.6. Combined therapies

34 patients required other therapies during follow-up time after RFA, whch has become the new trend mentioned in HCC treatment in recent years - multidisciplinary treatment..

4.4. Advantages, disadvantages and safety

4.4.1. Side effects and complications

The rate of side effects was similar to foreign studies and lower than domestic studies using unipolar needles. It can be explained that for tumors >2cm, it was necessary to ablate many sessions when using unipolar needles. The complication rate was 1.7% which was similar to other reports in the world with complication rate ranging from 2.2 to 10.6%. There was one case having tract seeding after 20 months despite complete necrotic zone and this patient was performed fine needle aspiration for pathology evidence. Currently, to resolve this situation, tract ablation was performed for all patients.

4.4.2. Lab test changes

There was no difference between lab tests before and after treatment. The results of our study has contributed to prove that RFA is an effective, less invasive and safe therapy.

4.4.3. RFA with artificial ascites/pleural effusion

4.4.3.1. Patient characteristics

16 patients (12.3%) were performed artificial ascites/pleural effusion before RFA in which 13 patients were performed artificial ascites and 3 patients were performed artificial pleural effusion.

4.4.3.2. Technical characteristics

The volume of fluid for artificial pleural effusion in our study was similar to other foreign studies. For artificial ascites, there is no recommended volume. In our study, the minimum volume was 1000ml, maximum volume was 2500ml and no pain or discomfort was recorded. 13 patients used LeVeen 3.0 and 3 patients used LeVeen 4.0 needles. Comparing to subgroups using these kinds of needles, there was no difference in ablation intensity and duration. That means artificial ascites/pleural effusion ensured ablation intensity and duration.

4.4.3.3. Response in artificial ascites/pleural effusion group

After RFA, the complete response rate in this group is 87.5%, and only 1 patient did not respond. Our result is similar to other publications worldwide with necrosis rate ranging 88 - 100%. However during follow-up time, 3 patients (18.8%) died in which 2 patients were performed artificial ascites and 1 patient was performed artificial pleural effusion. Cox regression analysis showed that Child Pugh score, AFP before treatment and treatment response correlated to mortality. It was similar to other publications in the world. 1 patient (6.3%) had local recurrence after 21 months. 1 patient had hepatic abscess after 4 weeks and surgery results recorded besides the abscess, right branch of portal vein had thrombosis.

4.4.4. Advantages and disadvantages of technique

4.4.4.1. Advantages

- Effective therapy for tumors $\leq$ 3cm.

- Choosing needles suitably to tumor size helps to reduce ablation sessions and duration.

- Higher necrosis rate comparing to unipolar needle.

- Less side effects, shorter length of stay, normal lifestyle after discharge, reduced symptoms and weight gain brings good impact on patients to improve quality of life.

- Low complication rate proved the safety of technique.

- New advancement in technique including artificial ascites/ pleural effusion for tumors adjacent to other organs improved efficacy, ensured safety; needle ablation is required to prevent tract seeding.

4.4.4.2. Disadvantages

- High local recurrence and progression rate

- Many patients required mulitple ablation times.

- The cost is relatively high to apply more popularly.

CONCLUSION

1. RFA with needles chosen suitably to tumor sizes is an effective therapy in clinical, lab test and imaging response aspects.

- After 1 month, the percentage of patients having clinical improvement in the group with initial symptoms was 67.8% and the percentage of weight gain was 46.2% of patients.

- AFP level after treatment 1 month, 3 month, 6 month, 1 year was statistically lower than before treatment ($p < 0.05$).

- After RFA 1 month, necrosis rate was 79.3%.

- At 1 month, 3 month, 6 month, 1 year, 2 years and 3 years after RFA, the rate of treatment response according mRECIST was 96.1%,

96.2%, 90.7%, 91, 1%, 79.8% and 88.9%, respectively. Tumor size, response after 1 month and past history of other therapies correlated to treatment response over time.

- 31 patients (23.8%) died during follow up time with mean survival time being 33.6 months (CI95%: 31.7 - 35.6 months). Cumulative survival rate at 1 year, 2 years, 3 years were 94.6%, 72.3% and 26.9%, respectively. Past history of other therpies and response after 1 month correlated to mortality.

- The mean PFS time was 30.9 months (CI95%: 28.7 - 33.0 months).

- 49 patients (37.6%) had disease progresion including local recurrence (31.5%), new lesion appearance (26.9%), portal vein thrombosis (4.6%) and metastasis (4.6%). Male gender, multiple ablation times and no response at 1 year after treatment were factors correlating to disease progression.

2. RFA with needles chosen suitably to tumor size is a relatively safe therapy with low complication rate, unchanged liver function and good results for tumors in difficult locations with artificial ascites/pleural effusion technique.

- Side effects after RFA: right upper quadrant pain (16.1%), fever (4.1%). Complication rate was 0.97% in procedure and after procedure was 1.7%.

- There was no change in lab tests before and after treatment.

- 16 patients were performed artificial ascites/pleural effusion: 93.8% responded to treatment in which 87.5% had complete response. During follow-up time, 3 patients died, 1 patient had local recurrence and 1 patient had hepatic abscess.

RECOMMENDATIONS

Through this study we would recommend:

1. To use the needle suitalbly to tumor size helps to reduce number of ablation times and side effects after treatment so it should be applied widely.
2. To develop aritifical ascites/pleural effusion techniques for tumors in a difficult location adjacent to other organs.
3. To use mRECIST criteria to evaluate treatment response after RFA
4. With the complication rate being1.7%, this is a relatively safe technique. To avoid tract seeding, ablation along needle tract is required.

PUBLICATIONS

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