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光學追蹤系統於超音波導引肝癌射頻消融治療效果之研究

Therapeutic Outcome with Optical Tracking System in Ultrasound-Guided Radiofrequency Ablation for Hepatocellular Carcinoma

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摘要

介紹：

超音波導引射頻消融是一種很值得期待的肝癌治療微創手術。這項手術仰賴即時影像來做探針的導引和監測消融的過程。傳統超音波導引射頻消融依靠徒手操作超音波探頭和探針位置，這可能導致附近重要結構的損傷和不完全消融。為了克服這些挑戰，不同的影像導引導航系統已被研發出來。本研究藉由一個 66 位病人的臨床試驗，探索一種新的光學追蹤系統用於超音波導引肝癌射頻消融的治療益處。

目的：

使用光學追蹤系統於超音波導引肝癌射頻消融和傳統徒手超音波導引肝癌射頻消融，手術過程和治療效果之比較。

方法：

在這個小病例數前瞻性研究中，我們將患有早期單顆肝癌病人隨機分派至光學追蹤超音波導引射頻消融組及傳統徒手超音波導引射頻消融組。試驗主要終點為腫瘤定位時間及下針準確度（包括針尖偏移及技術成功率）。 試驗次要終點為比較兩組的安全性和併發症發生率。

結果：

試驗總計納入 66 為肝癌病人。其中 36 位分派至光學追蹤組，30 位分派至傳統徒手（控制）組。光學追蹤組相對於控制組有比較短的腫瘤定位時間（5.55±1.04 min vs 6.22±0.87 min，p 0.007）。光學追蹤組相對於控制組電極比較能放置入腫瘤中心（OR 4.89，95% CI 1.37 to 17.50，p 0.015）。光學追蹤組相對於控制組有比較高的技術成功率 （97.2% vs 80%，p 0.04 on Fisher’s exact test）。光學追蹤組有減低併發症發生率的趨勢（5.6% vs 20%，p 0.08）。光學追蹤組的腫瘤局部復發率較低（2.8% vs 20%，p 0.04 on Fisher’s exact test）。疾病無惡化存活期中位數為 12 個月。其中光學追蹤組的疾病無惡化存活期中位數為 13 個月，控制組的疾病無惡化存活期中位數為 11

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個月。光學追蹤組的 1 年疾病無惡化存活率為 66.7%，控制組的 1 年疾病無惡化存活率為 43.3%。兩組的疾病無惡化存活率無差別（HR 0.55，CI 0.25 to 1.23，p 0.144）。

討論：

之前並無有關光學追蹤系統於超音波導引肝癌射頻消融治療定位時間的文獻。在我們的研究中，光學追蹤組定位時間平均減少 0.67 分鐘。雖然減少的時間並不多，但我們相信光學追蹤系統可能可以幫助肝癌射頻消融的學員或初學者克服學習曲線。將來需要更多的研究來調查光學追蹤系統的使用和學習曲線的關係。

電極偏移與技術成功率（OR 27.33，95% CI 3.43-217.99，p 0.02）和完全消融率（OR 5.37，95% CI 1.29-22.29，p 0.021）高度相關，但與併發症發生率、局部復發率和惡化無關（p>0.05）。

本研究中，技術成功率與較高的完全消融率（OR 43.5，95% CI 3.64-519.25，p 0.003）和較低的併發症發生率（OR 0.12，95% CI 0.21-0.71，p 0.019）高度相關，但與局部復發率和惡化無關（p>0.05）。

光學追蹤組的局部復發率較低。光學追蹤組和控制組有相似的無惡化存活期。然而局部復發和惡化受許多因素影響，並不能單純用是否使用導航系統來解釋。

結論：

超音波導引射頻消融治療的早期單顆肝癌病人，使用光學追蹤導航系統相較於傳統徒手操作，有較短的手術時間、較準確的探針導引、較低的局部復發率和減少併發症發生率的趨勢。

關鍵詞：肝癌、射頻消融、超音波導引、導航系統、光學追蹤系統

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Abstract

Introduction:

Ultrasound-guided radiofrequency ablation (RFA) is a promising minimally invasive procedure for treating hepatocellular carcinoma (HCC). This procedure relies on real-time imaging to precisely guide the needle and monitor the ablation process. Conventional ultrasound guidance relies on manual manipulation of the probe and needle positioning, which may lead to injury of adjacent critical structures and suboptimal ablation. To overcome these challenges, various image-guided navigation systems have been developed. This study explores the therapeutic benefits of a novel optical tracking system used in ultrasound-guided radiofrequency ablation for hepatocellular carcinoma from a clinical trial with 66 participants.

Objectives:

To compare the operative procedure and therapeutic outcome of optical tracking ultrasound-guided radiofrequency ablation for hepatocellular carcinoma with those of conventional manual ultrasound-guided RFA.

Methods:

In this small sample-sized prospective trial, we randomly assigned previously untreated early solitary HCC patients to receive optical tracking ultrasound-guided RFA or conventional manual ultrasound-guided RFA. The primary end points were time for tumor targeting and localization and rate of accurate needle placement (electrode deviation and technique success rate). Secondary end points were to compare the security and complication rate between the two groups.

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Results:

Totally 66 HCC patients were included, of which 36 patients were assigned to optical tracking group, and 30 patients were assigned to conventional (control) group. The optical tracking group exhibited decreased procedure time for tumor targeting and localization compared to the control group (5.55±1.04 min vs 6.22±0.87 min, p 0.007). Optical tracking group also demonstrated more centrally localization of electrode than the control group (OR 4.89, 95% CI 1.37 to 17.50, p 0.015). Technique success rate was higher in optical tracking group (97.2%) than in control group (80%) (p 0.04 on Fisher's exact test). Optical tracking group had the trend of lower complication rate than control group (5.6% in optical tracking group vs 20% in control group, p 0.08). Local recurrence rate was lower in optical tracking group (2.8%) than in control group (20%) (p 0.04 on Fisher's exact test). The median follow-up period for progression-free survival was 12 months. The median progression-free survival was 13 months in optical tracking group and 11 months in control group. The 1-year progression-free survival rates were 66.7% in optical tracking group and 43.3% in control group. Progression-free survival had no difference between the two groups (HR 0.55, CI 0.25 to 1.23, p 0.144).

Discussion:

There was no former literature about targeting time of optical tracking ultrasound-guided RFA for HCC. In our study, mean decrease of targeting time was 0.67 min in optic tracking group. Although the decreased time was not long, we believed that the optical tracking system may help trainee or beginner of RFA for HCC to overcome the learning curve. Further studies may be needed to survey the relationship between use of optical tracking system and learning curve.

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Electrode deviation was highly correlated with technique success (OR 27.33, 95% CI 3.43-217.99, p 0.02) and complete ablation (OR 5.37, 95% CI 1.29-22.29, p 0.021), but it was not related to complication, local recurrence, and progression (p>0.05).

Technique success was highly correlated with higher complete ablation rate (OR 43.5, 95% CI 3.64-519.25, p 0.003) and lower complication rate (OR 0.12, 95% CI 0.21-0.71, p 0.019), but it was not related to local recurrence and progression (p>0.05) in our study.

Lower recurrence rate was noted in optical tracking group. Progression-free survival was similar between optical tracking and control group. However, local recurrence and progression are affected by multiple factors, which could not be simply explained by use of navigation system.

Conclusions:

When performing ultrasound-guided RFA for early solitary HCC, optical tracking system has the advantages of shorter operation time, more accurate needle guidance, lower local recurrence rate and trend of lower complication rate, as compared with conventional manual method.

Keyword: hepatocellular carcinoma, radiofrequency ablation, ultrasound-guided, navigation system, optical tracking system

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Introduction

Ultrasound-guided tumor ablation has emerged as a promising minimally invasive procedure that has gained significant popularity in the field of interventional oncology for treating various types of tumors.[1] This procedure relies on real-time imaging to precisely guide and monitor the ablation process.[2] By utilizing real-time ultrasound imaging to guide the delivery of thermal energy to destroy cancerous cells, this technique offers an effective means to destroy tumors while minimizing the need for surgery. While ultrasound-guided tumor ablation has shown promising results, there are challenges in achieving optimal outcomes and ensuring precise targeting, the success and precision of ultrasound-guided tumor ablation can be influenced by the technique of precise ultrasound guidance, and it need long learning curve for physicians.[3,4]

Despite the wide adoption of ultrasound-guided tumor ablation, current ultrasound-guided techniques have limitations that impact their precision and efficacy in tumor ablation procedures.[5] Traditional ultrasound guidance relies on manual manipulation of the probe and needle positioning, introducing the potential for human error and suboptimal targeting accuracy. Achieving precise needle placement within deep-seated lesions or in the presence of adjacent critical structures such as blood vessels is particularly challenging. These limitations can impact the overall success and outcome of the procedure.

To overcome these challenges, various image-guided systems have been developed, aiming to improve the therapeutic outcome and operative procedure of ultrasound-guided tumor ablation. This study explores the advancements and benefits of a novel

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image-guided NAVIRFA® optical tracking navigation system and how this system can improve the therapeutic outcome and operative procedure of ultrasound-guided radiofrequency ablation for hepatocellular carcinoma from a clinical trial with 66 participants.

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Methods

NAVIRFA®

One of the challenges faced in needle-based interventions is finding the optimal needle entry point and path to the target[6]; knowing whether the needle has hit the target or if it will unintentionally puncture a blood vessel in its path can save significant operation time and patient trauma.[7,8]

Previous predicates for needle-tip guidance have been submitted for various imaging modalities, including ultrasound. How NAVIRFA® system differs from them is that it combines a flexible optical tracking system with a portable, economical, and user-friendly design. While the system can be used for most needle-based interventions using ultrasound for imaging.

The system utilizes an optical camera and supporting software to integrate the trajectory information of needle instruments towards improving interventional procedures. The camera is fixed onto an ultrasonic transducer. The camera observes and detects the motion of a needle through an optical tracking marker attached on it. The needle position is calculated and mapped onto a real-time ultrasonic image via software. The trajectory information of the needle during surgical procedures is integrated onto real-time ultrasonic diagnostic images via software. The control of ultrasonic scanning parameters for the specific ultrasonic system is also retained from the official original source code.

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The system is intended to provide physicians with the trajectory information of needle instruments when used in conjunction with medical ultrasound. Electrode used with the NAVIRFA® system is Medtronic Cool-tip™ RF Ablation Single Electrode Kits for in this study.

Clinical Trial for Therapeutic Outcome Comparison

To evaluate the impact of optical tracking system on therapeutic outcomes, a robust clinical trial was conducted involving 36 patients who underwent ultrasound-guided tumor ablation using NAVIRFA® system and compared with a control group of 30 patients who received conventional ultrasound-guided tumor ablation. The patients were matched based on tumor type, size, and location.

From February 1, 2022 to January 30, 2023, 66 patients with hepatocellular carcinoma (HCC) less than 3.7cm in largest diameter and 20 years of age or older underwent tumor ablation in National Taiwan University hospital. All of them had solitary nodule. Medtronic Cool-tip™ RF Ablation Single Electrode Kits were used for ablation. Those who had bleeding tendency, abnormal renal function, or allergy to contrast medium were excluded.

Patients were randomly assigned into optical tracking group and conventional manual (control) group after they had signed inform consent. Surgeries of both groups were performed by the same surgeon. Within one month before surgery, patient had to check CBC, differential count, CRP, AST, ALT, bilirubin, BUN and creatinine. During the operation, the time of the first ultrasound scan to the star of ablation was measured.

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Contrast CT was performed to evaluate technique success within 12 hours after RFA. CBC, differential count, CRP, AST, ALT, bilirubin, BUN and creatinine were rechecked on postoperative day 1 and 30. Contrast CT was performed to evaluate effect of ablation on postoperative day 30 (POD 21 to POD35). The follow-up period after ablation ranged from 6 to 16 months.

Primary end points

To compare the procedure time for tumor targeting and localization and rate of accurate needle placement (electrode deviation and technique success rate) of optical tracking group with control group.

Secondary end points

To compare the security and complication rate between the two groups.

Tumor size

Tumor size was measured preoperatively by sonography, CT or MRI.

Time for tumor targeting and localization

Time for tumor targeting and localization was defined as the time of the first ultrasound scan to the star of ablation.

Electrode deviation

Electrode deviation ranked 1, 2 and 3, which presented the electrode located more than 3mm away from the center of tumor, the electrode located between 0mm to 3mm away from the center of tumor and the electrode located in the center of tumor respectively.

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Technique success

The treatment was considered technically successful if the RFA zone entirely covered the index tumor on contrast-enhanced CT performed within 12 hours of the procedure.

Complete ablation

To evaluate the tumor response to RFA therapy, contrast-enhanced CT was performed 1 month post-ablation and the complete ablation of the tumor was considered to be achieved if the scans revealed: (1) the ablation zone was beyond the tumor borders, (2) the margin of the ablation zone was clear and smooth, and (3) no contrast enhancement was detected within or around the tumor.

Complications

Any major or minor complications were recorded postoperatively.

Local recurrence

A local recurrence was defined as a tumor recurrence at the RFA site after complete ablation.

Progression-free survival

Progression-free survival was defined as the time from random assignment in a clinical trial to disease progression or death from any cause.

Overall survival

The overall survival was defined as the time from the date of HCC diagnosed to death

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owing to HCC or other causes.

Statistical Analysis

We used *t-test* to compare the time for tumor targeting and localization. *Fisher's exact test* was used to evaluate the association of electrode deviation, technique success, complete ablation, complications, local recurrence and progression between optical tracking and control groups. *Logistic regression model* was used to determine the odds ratios of electrode deviation, technique success, complete ablation, complications, local recurrence and progression between the two groups. The risk factors of progression-free survival and overall survival were analyzed with *Cox proportional hazards model*.

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Results

The Characteristics of Patients

Totally 66 HCC patients were included, of which 36 patients underwent optical tracking ultrasound-guided RFA, and 30 patients underwent conventional ultrasound-guided RFA. There were no differences in tumor size, age, Child-Pugh classification, albumin-bilirubin (ALBI) grade, bilirubin, albumin, ALT, platelet, creatinine, CRP, rates of HBV and HCV carrier, and AFP level between the two groups ($p>0.05$), except AST (p 0.044) (Table 1).

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Table 1 Characteristics of patients

	Optical tracking group (n=36)	Control group (n=30)	P value
Tumor size (cm), mean±SD (range)	2.09±0.80 (0.5-3.7)	2.1±0.95 (0.5-3.2)	0.959
Age (years), mean±SD	55.1±8.1	55.1±8.0	0.985
Child-Pugh classification, n (%)			
Class A	35 (97.2%)	28 (93.3%)	0.587
Class B	1 (2.8%)	2 (6.7%)	0.587
Albumin-bilirubin (ALBI) grade, n (%)			
Grade 1	35 (97.2%)	29 (96.7%)	1.00
Grade 2	1 (2.8%)	1 (3.3%)	1.00
Bilirubin (mg/dL), mean±SD	0.94±0.30	0.88±0.31	0.425
Albumin (g/dL), mean±SD	3.9±0.5	3.7±0.5	0.111
AST (U/L), mean±SD	31±7	37±16	0.044
ALT (U/L), mean±SD	84±21	84±23	0.957
Platelet ($x10^3/\mu L$), mean±SD	177±41	172±33	0.582
Creatinine (mg/dL), mean±SD	0.86±0.24	0.79±0.23	0.238
CRP (mg/dL), mean±SD	0.05±0.02	0.05±0.02	0.714
HBV carrier, n (%)	23 (63.9%)	20 (66.7%)	1.00
HCV carrier, n (%)	6 (16.7%)	5 (16.7%)	1.00
AFP (ng/mL), mean±SD	272±231	280±222	0.889

Tumor Size

Tumor size of the optical tracking group ranged from 0.5 to 3.7cm (2.09±0.80cm). Tumor size of the control group ranges from 0.5 to 3.2cm (2.1±0.95cm) (Table 1).

Time for Tumor Targeting and Localization

The optical tracking group exhibited decreased time for tumor targeting and localization compared to the control group (5.55±1.04 min vs 6.22±0.87 min, p 0.007)

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(Table 2).

Table 2 Comparison of intraoperative and postoperative variables between the two groups

Variables	Optical tracking group (n=36)	Control group (n=30)	t-test/ Fisher's exact test	Logistic regression		
			P value	Odds ratio	95% CI	P value
Time for tumor targeting and localization (min), Mean±SD	5.55±1.04	6.22±0.87	0.007			
Electrode deviation			0.019	4.89	1.37-17.50	0.015
0mm, n (%)	32 (88.9%)	19 (63.3%)				
0mm to 3mm, n (%)	4 (11.1%)	8 (26.7%)				
> 3mm, n (%)	0 (0%)	3 (10%)				
Technique success, n (%)	35 (97.2%)	24 (80%)	0.04	8.75	0.99 - 77.39	0.051
Complete ablation, n (%)	35 (97.2%)	27 (90%)	0.32	3.89	0.38-39.50	0.251
Complications, n (%)	2 (5.6%)	6 (20%)	0.08	0.24	0.44-1.27	0.092
Pain, n (%)	1 (2.8%)	3 (10%)	0.32	0.26	0.25-2.61	0.251
Ileus, n (%)	1 (2.8%)	0 (0%)	1.00	2.18×10^{7}	0-.	0.997
Pleural effusion, n (%)	0 (0%)	2 (6.7%)	0.20	3.64×10^{-8}	0-.	0.996
Abscess, n (%)	0 (0%)	1 (3.3%)	0.46	1.40×10^{-8}	0-.	0.998
Local recurrence, n (%)	1 (2.8%)	6 (20%)	0.04	0.11	0.13-1.01	0.051
Progression	11 (30.6%)	13 (40.3%)	0.31	0.58	0.21-1.58	0.284

Electrode Deviation

As comparing the subgroup of centrally-located electrode position with the two

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subgroups of deviated electrode position, the optical tracking group exhibited more centrally localization of electrode than the control group (OR 4.89, CI 1.37 to 17.50, p 0.015) (Table 2).

Technique Success

Technique success occurred in 35 of 36 (97.2%) in optical tracking group as compared with 24 of 30 (80%) in the control group. Fisher's exact test showed higher technique success rate in optical tracking group than in control group (p 0.04). However, logistic regression showed borderline p value (OR 8.75, CI 0.99 to 77.39, p 0.051) (Table 2).

Complete Ablation

Complete ablation occurred in 35 of 36 (97.2%) as compared with 27 of 30 (90%) in the control group. There was no difference between the two groups (p 0.32 on Fisher's exact test; OR 3.89, CI 0.38 to 39.50, p 0.251 on logistic regression) (Table 2).

Complications

In optical tracking group, one case of pain (2.8%) and one case of ileus (2.8%) were noted. In control group, three cases of pain (10%), two cases of pleural effusion (6.7%) and one case of abscess (3.3%) were noted. The complication rate was 5.6% in optical tracking group as compared with 20% in control group. Optical tracking group had the trend of lower complication rate than control group (p 0.08 on Fisher's exact test). (Table 2).

Local Recurrence

After follow-up period of 6 to 16 months after ablation, local recurrence occurred in 1

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of 36 (2.8%) in optical tracking group as compared with 6 of 30 (20%) in the control group. Fisher's exact test revealed lower local recurrence rate in optical tracking group than in control group (p 0.04 on Fisher's exact test). However, logistic regression revealed no difference between the two groups (OR 0.11, CI 0.13 to 1.01, p 0.051) (Table 2).

Progression

Progression occurred in 11 of 36 (30.6%) in optical tracking group as compared with 13 of 30 (40.3%) in control group. There was no difference between the two groups (p 0.31 on Fisher's exact test; OR 0.58, CI 0.21 to 1.58, p 0.284 on logistic regression).

Progression-free Survival

The median follow-up period for progression-free survival was 12 months. The median progression-free survival was 13 months in optical tracking group and 11 months in control group. Progression occurred in 24 patients (36.4%). The 1-year progression-free survival rates were 66.7% in optical tracking group and 43.3% in control group. Progression-free survival was similar between the two groups (HR 0.55, CI 0.25 to 1.23, p 0.144) (Figure 1). Higher Child-Pugh score or albumin-bilirubin (ALBI) grade had shorter progression-free survival (HR 62.55, CI 9.87 to 396.56, p 0.000 and HR 31.52, CI 5.14 to 193.12, p 0.000 respectively) (Table 3) (Figure 2 and Figure 3).

Overall Survival

In this early analysis, all patients in both groups survived. Overall survival was the same between the two groups (100% in optical tracking group vs 100% in control group).

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Table 3 Cox regression for PFS (univariate)

	Hazard ratio for progression	95% CI	P value
Optical tracking system	0.55	0.25-1.23	0.144
Tumor size	1.25	0.77-2.05	0.363
Time for tumor targeting and localization	1.10	0.74-1.63	0.646
Electrode deviation	1.25	0.52-3.04	0.616
Technique success	2.45	0.33-18.19	0.380
Complete ablation	$4.33x10^{15}$	0-.	1.000
Complication	1.90	0.65-5.58	0.241
Local recurrence	27.11	9.18-80.06	0.000
Age	0.99	0.94-1.04	0.651
Child-Pugh classification	62.55	9.87-396.56	0.000
Albumin-bilirubin (ALBI) grade	31.52	5.14-193.12	0.000
Bilirubin	2.20	0.46-10.57	0.325
Albumin	0.75	0.34-1.67	0.478
AST	1.00	0.97-1.04	0.861
ALT	1.00	0.98-1.02	0.846
Platelet	0.99	0.98-1.00	0.184
Creatinine	0.86	0.16-4.71	0.866
CRP	$3.97x10^{8}$	$0.00-3.63x10^{19}$	0.124
HBV carrier	1.92	0.76-4.84	0.168
HCV carrier	0.53	0.16-1.77	0.300
AFP	1.00	0.998-1.001	0.959

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Figure 1 Kaplan-Meier curve for progression-free survival (optical tracking system)

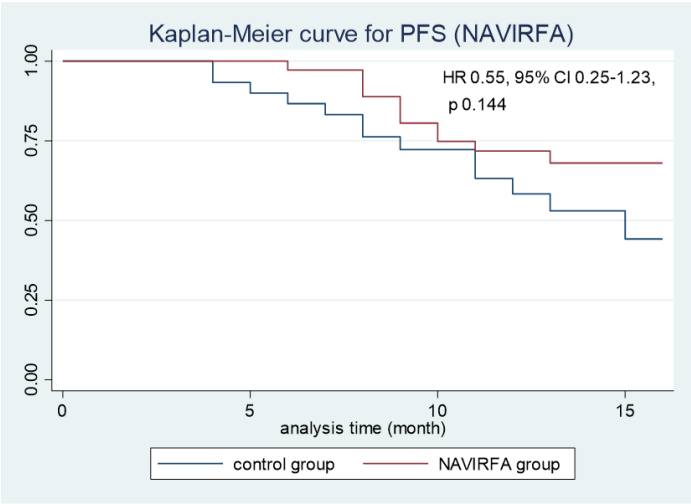


Figure 2 Kaplan-Meier curve for progression-free survival (Child-Pugh score)

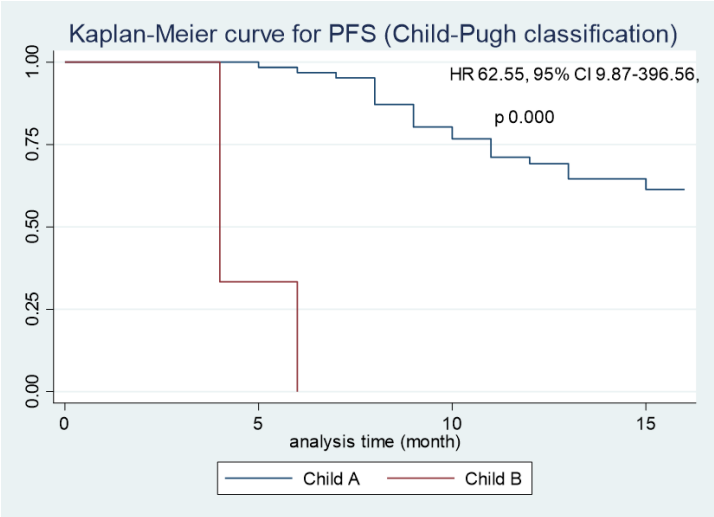
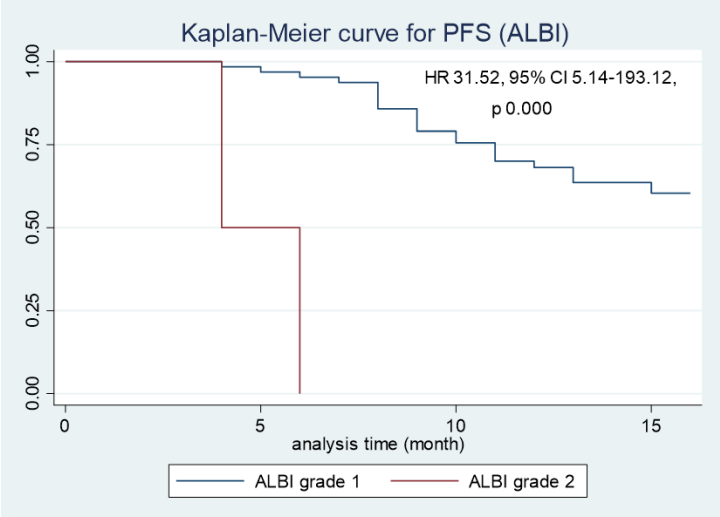


Figure 3 Kaplan-Meier curve for progression-free survival (ALBI grade)



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Discussion

Different Ablation Methods for Hepatocellular Carcinoma

In the past decades, tumor ablation has emerged as a promising minimally invasive procedure. Various tumor could be treated with ablation, which included tumors in liver, thyroid, prostate, kidney, and uterus. Ablation has been recommended as first-line or alternative therapy in early stage hepatocellular carcinoma, T1a stage renal cell carcinoma and thyroid nodules[1].

Ablation in hepatocellular carcinoma can be performed percutaneously, laparoscopically or via traditional open operation. Different ablative techniques have been applied for hepatocellular carcinoma, including radiofrequency ablation, microwave ablation, high intensity focused ultrasound, cryoablation, percutaneous ethanol injection, laser ablation and irreversible electroporation[9]. In our thesis, we focused on the percutaneous radiofrequency ablation in hepatocellular carcinoma.

Radiofrequency ablation (RFA)

Radiofrequency ablation is the most widely used ablation method. It can be guided by ultrasound, CT or MRI. Radiofrequency ablation uses oscillating electrical currents to create heat surrounding an electrode and tissue. Tumor cells will be damaged when the temperature reaches to 60°C. Radiofrequency ablation can be used in hepatocellular carcinoma of BCLC 0, BCLC A and BCLC B. It is not easy to ablate tumors located at subcapsular areas or tumors adjacent to gallbladder or diaphragm. Also, the heat sink effect which means the heat will lose in perivascular area due to the cooling effect of blood flow, leads to limited use of radiofrequency ablation in perivascular tumor.

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There are various modalities and devices for radiofrequency ablation, which include bipolar electrode, no-touch ablation, monopolar electrode, single electrode with internal cooling, adjustable electrode, multiple electrodes and expandable electrode[9].

Microwave ablation (MWA)

Microwave ablation uses high-frequency electromagnetic waves to induce vibration of water molecule. The vibration of the molecules causes rise of temperature and coagulative necrosis. The indications of microwave ablation are like radiofrequency ablation. It can be used in hepatocellular carcinoma of BCLC 0, BCLC A and BCLC B. Recent studies reveal the treatment effects are successful in hepatocellular carcinoma size of 5cm in diameter, larger than radiofrequency ablation. Microwave ablation has less heat sink effect than radiofrequency ablation because the therapeutic temperature exceeds 100°C. So, microwave ablation can be performed in tumors located at perivascular areas. The procedure time is shorter than radiofrequency ablation. However, the treatment effect varies between different devices.

High intensity focused ultrasound (HIFU)

High intensity focused ultrasound uses ultrasound waves of frequency of 0.5–2 MHz, which were partly converted to thermal energy as propagating through tissue. Temperature of tissue will reach to above 55 °C. However, it needs clinical trials in treatment of hepatocellular carcinoma to determine the optimal treatment parameters and to explore the risks and benefits.

Cryoablation (CRYO)

Cryoablation uses cryoprobes to deliver liquefied argon to reduce the temperatures to -

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160 to -180°C, which results in the formation of ice crystals within the tumor. Then cryoprobe delivers helium to warm the tissue to 25°C. This rapid changes in temperature and osmotic pressure cause cell death in tumor. Cryoablation also freezes blood vessels, which leads to an effect like transarterial embolization. The frozen tumor forms “ice ball” during cryoablation, which makes it easy to monitor the process of ablation. However, cryoablation has high complication rates of cold shock, decreased platelet count or bleeding, and needs further studies for its effects and safety in treatment of hepatocellular carcinoma.

Percutaneous ethanol injection (PEI)

Percutaneous ethanol injection induces cellular dehydration, protein denaturation and coagulative necrosis by direct injection of pure alcohol into tumors. It is suitable for hepatocellular carcinoma less 2cm in diameter and patients not suitable for surgical resection due to poor liver function. Clinically, radiofrequency ablation and microwave ablation are preferred because percutaneous ethanol injection has the drawbacks of higher recurrence rate and heterogeneously intratumoral distribution.

Laser ablation

Laser ablation introduces low-power laser energy inside tumor through one or more optic fibers, resulting in coagulative necrosis. Temperature within the tumor reaches to 140 °C. The ideal patients for laser ablation are those with well-differentiated non-infiltrating hepatocellular carcinoma and normal bilirubin levels. Laser ablation can be used in difficult locations for radiofrequency ablation due to its concentrated delivery of energy. The laser ablation reduces the risk of puncture injury because the laser beam is propagated through optic fibers encapsulated in a 21-gauge needle.

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Irreversible electroporation (IRE)

Irreversible electroporation uses two- to six-needle electrodes working in pairs to destroy tumors by intense bursts of electricity. The altered transmembrane potentials induce irreversible nano-sized microperforations of cell membrane, which cause cell death. Unlike radiofrequency ablation, microwave ablation or cryoablation, high-voltage electrical pulses have no damage to adjacent normal tissues and have no heat sink effect. Irreversible electroporation can be used in tumors located at perivascular or peribiliary areas. However, it is limited by risk of arrhythmia, need of general anesthesia and insertions of multiple electrodes.

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Result of Different Ablation Methods

Yanzhao Zhou et al. reviewed 23 retrospective and randomized controlled studies of radiofrequency ablation, microwave ablation, cryoablation, irreversible electroporation and percutaneous ethanol injection in 2021[9]. If proper patients chosen, these different ablative techniques provide their own characteristic treatment effects for hepatocellular carcinoma (Table 4).

For patients who met Milan criteria, complete ablation rates of radiofrequency ablation ranged from 90.0% to 100%. In our study, complete ablation rates were 97.2% in optical tracking group and 90% in control group (p 0.32 on Fisher's exact test).

For patients who met Milan criteria, major complication rates of radiofrequency ablation ranged from 0% to 11.1%. In our study, there was no major complication in optical tracking group. One (3.3%) patient with abscess was reported in control group.

For patients who met Milan criteria, local recurrence rates of radiofrequency ablation at 3 years ranged from 5.2% to 24.4%. In our study, after follow-up of 6 to 16 months after radiofrequency ablation, the local recurrence rates were 2.8% in optical tracking group and 20% in control group (p 0.04 on Fisher's exact test).

For patients who met Milan criteria, 3-year overall survival rates of radiofrequency ablation ranged from 60% to 84.1%. In our short-term period study up to 16 months, no patients died at optical tracking group and control group. The long-term overall survival needs further follow-up.

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Table 4 Retrospective and Randomized Controlled Studies of Radiofrequency Ablation, Microwave Ablation, Cryoablation, Irreversible Electroporation and Ethanol Injection (adapted from Yanzhao Zhou, Yi Yang, Bingyan Zhou, Zhengzheng Wang, Ruili Zhu, Xun Chen, Jingzhong Ouyang, Qingjun Li, Jinxue Zhou. Challenges Facing Percutaneous Ablation in the Treatment of Hepatocellular Carcinoma: Extension of Ablation Criteria. J Hepatocell Carcinoma. 2021; 8: 625–644.[9])

Article	**Type**	**Number of Patients**	**Complete Response (After One or More Sessions)**	**Local Recurrence**	**Overall Survival**	**Morbidity/Mortality**
Kim et al 2013	RFA	1305 patients, HCC within Milan criteria	98.5%	21.4% at 3 yr, 27% at 5 yr and 36.9% at 10 yr	77.9% at 3 yr, 59.7% at 5 yr and 32.3% at 10 yr	Major AE 2%, 0.01% death
Shiina et al 2012	RFA	1170 patients, whatever size and numbers	99.4%	3.2% at 3 yr, 5 yr and 10 yr	80% at 3 yr, 60% at 5 yr and 27.3% at 10 yr	Major AE 1.5%, 0.03% death
Rossi et al 2011	RFA	706 patients 1–2 HCC <35 mm	98.5%	12.1% at 3 yr and 13.2% at 5 yr	67% at 3 yr, 40.1% at 5 yr	Major AE 1%, 0% death
Lencioni et al 2005	RFA	206 patients, HCC within Milan criteria	90.0%	10% at 3 yr and at 5 yr	67% at 3 yr, 41% at 5 yr	Major AE 2%, 0% death
Lee et al 2014	RFA	162 patients, HCC within Milan criteria	96.7%	14.5% at 3 yr and 5 yr	84.1% at 3 yr, 67.9% at 5 yr	Major AE 3.1%, 0% death
Nkontchou et al 2009	RFA	235 patients, HCC	94.7%	11.5% at 5 yr	60% at 3 yr, 40% at	Major AE 0.9%, 0.4% death

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		within Milan criteria			5 yr, 76% at 5 yr	
Ohmoto et al 2009	MWA vs RFA	49 MWA vs 34 RFA, HCC within Milan criteria	NA	9% at 3 yr, 19% at 4 yr vs 9% at 3 yr, 19% at 4 yr (P=0.031)	49% at 3 yr, 39% at 4 yr vs 70% at 3 yr, 70% at 4 yr (p= 0.018)	Major AE 8%, 0% death vs Major AE 0%, 0% death
Zhang et al 2013	MWA vs RFA	77 MWA vs 78 RFA, HCC within Milan criteria	100% MWA vs 100% RFA	10.5% at 5 yr vs 11.8% at 5 yr (NA)	51.7% at 3 yr, 38.5% at 5 yr vs 64.1% at 3 yr, 41.3% at 5 yr (P = 0.780)	Major AE 2.6% 0% death vs Major AE 2.7% 0% death
Ding et al 2013	MWA vs RFA	113 MWA vs 85 RFA, HCC within Milan criteria	98.5% MWA vs 99% RFA	10.9% at 3 yr vs 5.2% at 3 yr (p=0.127)	77.6% at 3 yr, 6% at 4 yr vs 82.7% at 3 yr, 77.8% at 4 yr (p = 0.729)	Major AE 2.7% 0% death vs Major AE 2.4% 0% death
Abdelaziz et al 2014	MWA vs RFA	66 MWA HCC vs 45 RFA HCC within Milan criteria	96.1% MWA vs 94.2% RFA	3.9% at 2 yr vs 13.5% at 2 yr (p=0.04)	67.6 at 2 yr vs 47.4% at 2 yr (p=0.49)	Major AE 3.2%, 0% death vs Major AE 11.1%, 0% death
Ma et al 2016	MWA	433 MWA HCC whatever the size and number	94.9%	12.9% at 3 yr	58.7% at 3 yr	Major AE 5.3%, 0% death
Vietti Violi et al 2018	MWA vs RFA	71 MWA vs 73 RFA, HCC in HCC ≤4cm	95% MWA vs 96% RFA	6% at 2 yr vs 12% at 2 yr (p=0.27)	86% at 2 yr vs 84% at 2 yr (p=0.87)	Major AE 2%, 0 death vs Major AE 3%, 0 death

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Chong et al 2020	MWA vs RFA	47 MWA vs 46 RFA, HCC within Milan criteria	95.7% MWA vs 97.8% RFA	NA	67.1% at 3 yr, 42.8% at 5 yr vs 72.7% at 3 yr, 56.7% at 5 yr (p=0.899)	Major AE 2.1%, 0 death vs Major AE 2.2%, 0 death
Yu et al 2017	MWA vs RFA	203 MWA vs.200 RFA, HCC within Milan criteria	99.6% MWA vs 98.8% RFA	4.3% at 3 yr, 11.4% at 5 yr vs 5.8% at 3 yr, 19.7% at 5 yr (p=0.11)	81.9% at 3 yr, 67.3% at 5 yr vs 81.4% at 3 yr, 72.7% at 5 yr (p = 0.91)	Major AE 3.4%, 0 death vs Major AE 2.5%, 0 death
Kamal et al 2019	MWA vs RFA	28 MWA vs 28 RFA, HCC within Milan criteria	NA	9.1% at 1 yr vs 9.1% at 1 yr (p=1.00)	82.1% at 1 yr vs 78.6% at 1 yr (p=1.00)	Major AE 3.6%, 0 death vs Major AE 0%, 0 death
Wang et al 2015	Cryo vs RFA	180 RFA vs 180 Cryo 1 to 2 HCC <5 cm	98.3% Cryo vs 95.6% RFA	7% at 3 yr vs 11% at 3 yr (p = 0.043)	67% at 3 yr, 40% at 5 yr vs 66% at 3 yr, 38% at 5 yr (p = 0.747)	Same rate of major AE (4%)
Rong et al 2015	Cryo	866 Cryo, HCC within Milan criteria	96.1%	22.1% at 3 yr, and 24.2% at 5 yr	80.6% at 3 yr and 60.3% at 5 yr	Major AE, 2.4% 0% death
Sutter et al 2017	IRE	58 IRE, HCC whatever the size	92%	21% at 1 yr	96% at 1 yr	Major AE 5%, 1.8% death
Kalra et al 2019	IRE	21 IRE HCC in ≤4cm	100%	24% at 1 yr	NA	Major AE %, 0% death

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Shiina et al 2005	PEI vs RFA	114 PEI vs 118 RFA in HCC <3 cm	100% PEI vs 100% RFA	11% at 4 yr vs.1.7% at 4 yr (p = 0.003)	57% at 4 yr vs 74% at 4 yr (p = 0.01)	Major AE 2.6%, 0% death vs Major AE 5.1%, 0% death
Lin et al 2004	PEI vs RFA	62 PEI vs 62 RFA in HCC <3 cm	88% PEI vs 96% RFA	34.5% at 3 yr vs 14% at 3 yr (p = 0.01)	51% at 3 yr vs 74% at 3 yr (p = 0.01)	Same rate of major AE (5.7%), 0% death
Brunello et al 2008	PEI vs RFA	69 PEI vs 70 RFA in HCC <3 cm	65.6% PEI vs 95.7% RFA	64% at 1 yr vs 34% at 1 yr (p = 0.0005)	59% at 3 yr vs 63% RFA at 3 yr (p = 0.476)	Major AE 2.9%, 1.4% death vs Major AE 2.9%, 0% death
Lencioni et al 2003	PEI vs RFA	50 PEI vs 52 RFA in HCC <5 cm	82% PEI vs 91% RFA	38% at 2 yr vs 4% at 2 yr (p = 0.002)	88% at 2 yr vs 98% at 2 yr (p = 0.138)	Same rate of major AE (0%), 0% death

Abbreviations: RFA, radiofrequency ablation; VS, versus; MWA, microwave ablation; Cryo, cryoablation; IRE, Irreversible electroporation; PEI, percutaneous ethanol injection; AE, adverse event; HCC, hepatocellular carcinoma.

According to the 2022 update of the BCLC strategy for prognosis prediction and treatment recommendation, radiofrequency ablation is suitable for very early stage (BCLC 0) and early stage (BCLC A) of hepatocellular carcinoma[10].

BCLC 0 is defined as a solitary HCC ≤2 cm without vascular invasion or extrahepatic spread in a patient with preserved liver function and no cancer related symptoms (EOCG performance status 0). Liver transplantation, resection or ablation can be considered in BCLC 0 patients. Ablation has similar survival outcomes to resection. However, if patients have severe liver dysfunction/decompensation or pathology patterns of microscopic vascular invasion and satellite lesions, liver transplantation

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should be considered due to high recurrence rates of other treatment (Figure 4).

BCLC A is defined as solitary HCC irrespective of size or as a multifocal HCC up to 3 nodules (none of them >3 cm), with preserved liver function and without macrovascular invasion, extrahepatic spread, or cancer-related symptoms (EOCG performance status 0). The treatment strategies for BCLC A patients can be further classified into solitary and multifocal within Milan criteria (up to 3 HCC nodules, each ≤ 3 cm).

Solitary hepatocellular carcinoma

Firstly, patients should be evaluated if they have clinically significant portal hypertension (CSPH) which is defined by hepatic venous pressure gradient (HVPG) > 10mmHg. CSPH patients have higher postoperative complication rate and lower long-term survival when they receive resection. Liver transplantation offers a better long-term survival for them. However, resection and ablation could still be considered if minor degree of CSPH. If patients have no CSPH, they are considered to receive resection. If the pathology of resection reveals microvascular invasion and satellite lesions, the risk of recurrence increases postoperatively. Liver transplantation may be considered in the future. For hepatocellular carcinoma ≤ 3cm without CSPH, ablation offers competitive outcomes as resection (Figure 4). However, more recent studies reveal radiofrequency ablation or microwave ablation can be used in larger hepatocellular carcinoma successfully[11].

Multifocal hepatocellular carcinoma within Milan criteria (≤ 3 nodules, each ≤ 3 cm)

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Due to high risk of hepatocellular carcinoma recurrence for resection or ablation, liver transplantation is the first choice for this group of patients. However, if patients are contraindicated to liver transplantation, ablation can be considered (Figure 4).

BCLC B is defined as multifocal hepatocellular carcinoma exceeding BCLC A criteria, with preserved liver function, no cancer related symptoms (PS 0) and no vascular invasion or extrahepatic spread. According to this 2022 BCLC recommendation, patients with BCLC B can be further divided into three subgroups. Group 1 patients meet the extended liver transplant criteria, liver transplantation is the first choice. However, some studies reveal that ablation or TACE can reduce AFP level from >1000 to <500 ng/ml before liver transplantation, which can improve post-transplant outcomes. Group 2 patients have well-defined nodules but do not meet the extended liver transplant criteria. TACE is the first choice of treatment. Ablation plays no role in this subgroup of patients according to current studies. Group 3 patients have diffuse, infiltrative, extensive bilobar liver involvement, systemic therapy is recommended (Figure 4).

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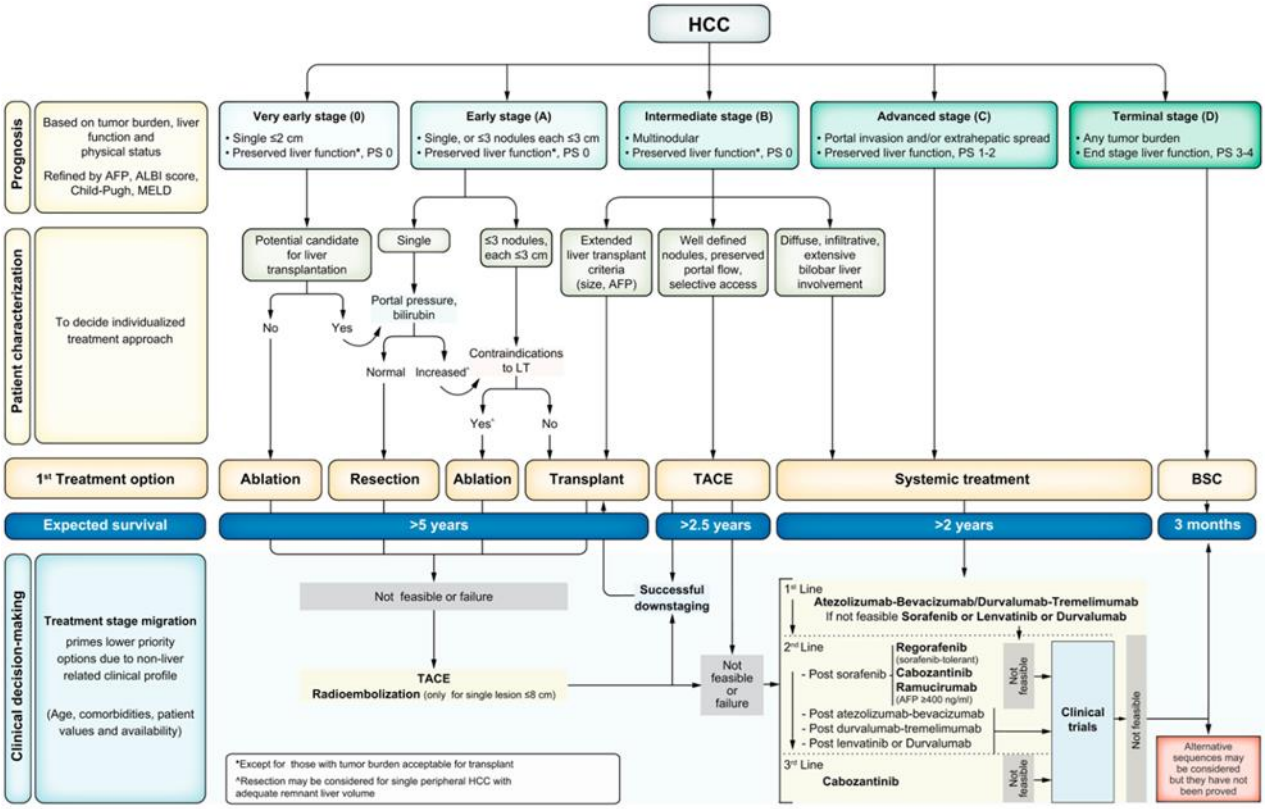
Figure 4 BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update (adapted from Maria Reig, Alejandro Forner, Jordi Rimola, Joana Ferrer-Fàbrega, Marta Burrel, Ángeles Garcia-Criado, Robin K. Kelley, Peter R. Galle, Vincenzo Mazzaferro, Riad Salem, Bruno Sangro, Amit G. Singal, Arndt Vogel, Josep Fuster, Carmen Ayuso, Jordi Bruix. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. Journal of Hepatology Volume 76, Issue 3, March 2022, Pages 681-693.)



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Different Image Guidance Devices

When performing percutaneous ablation, we need image guidance device to assure the precise trajectory of electrodes, adequate ablation zone and prevention of injury of important structures. There are different guidance devices, like ultrasound, CT, MRI and fusion images. We will introduce them in the following paragraphs. In our thesis, we use ultrasound as guidance device.

Ultrasound

Ultrasound guidance has the advantages of easy to operate, easy to move, low cost, no radiation, real-time and easy to show blood vessels and bile ducts. However, it has limitations of interference from bone and gas from gastrointestinal tract or process of ablation, blind areas in diaphragm, gastrointestinal tract and ribs, relatively low resolution in isoechoic lesions, small hepatocellular carcinoma and cirrhotic nodules, and partially displayed outline of electrodes.

CT

CT guidance has the advantages of almost no blind area and fully displayed outline of electrodes. However, it has limitations of relative low resolution of soft tissue and isodense lesions on noncontrast CT, radiation, no real-time guidance, and coverage of target tumors by large applicator artifacts.

MRI

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MRI guidance has the advantages of high resolution of soft tissue, clear display of small tumors and blood vessels, no radiation, easy to evaluate the ablation zone, and capability of being performed in any orientation. Its limitations include fewer devices designed for MRI-guided ablation, relatively complicated operation, no real-time guidance, long operation time, large artifacts of applicators, and useless in patients with pacemakers and metal implants.

Fusion Images

Recently, real-time-fusion of sonography plus CT or MR images using an electromagnetic tracking system has been introduced for radiofrequency ablation of hepatocellular carcinoma. Su Joa Ahn et al. reported that tumor visibility and technical feasibility were significantly improved with fusion images compared with conventional B-mode ultrasound ($p<0.001$)[12].

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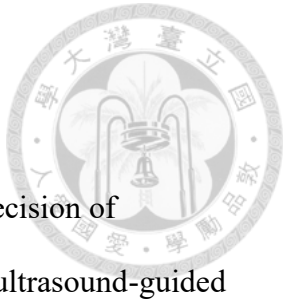

Navigation System

Traditional image-guided ablation techniques have limitations of precision of trajectory and efficacy in tumor ablation. For example, conventional ultrasound-guided ablation relies on manual manipulation of the probe and needle positioning, introducing the potential of suboptimal targeting accuracy. Needle placements within deep-seated lesions or adjacent critical structures are also challenging issues. These limitations may influence the overall success rate and outcome of the procedure. To overcome these challenges, various navigation systems have been developed.

Navigation system provides surgeons with the real-time 2D or 3D relationships between tumor, surgical instruments, and images. At pre-operative stage, navigation system is helpful to acquire medical image, process computer-assisted simulation, and make a surgical plan. At intra-operative stage, navigation system helps to localize tumor, track the surgical instruments, register, and update surgical plan. At post-operative stage, navigation system can perform computer-assisted calculation, integration, and analysis of intraoperative data[5].

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***Tracking System*[5]**

Tracking system is the core technology of navigation system. Existing mono-modular tracking systems include mechanical tracking systems (MTS), optical tracking systems (OTS), electromagnetic tracking systems (ETS), permanent magnet-based tracking systems (PTS), and fiber Bragg grating (FBG)-based tracking systems (FBGTS).

Mechanical tracking systems (MTS)

Mechanical tracking systems include frame-based and frameless stereotaxy. Frame-based stereotaxy was the earliest surgical tracking system. It has been used in brain biopsy and neurosurgery. However, its use is limited due to cumbersome and easy to affect the field of vision and movement surgeon. Frameless stereotaxy system, also termed mechanical digitizer, uses the digital control technology. This system can follow surgical instruments and extrinsic markers through forward kinematics and is widely applied in orthopedic, neuro-, craniofacial, and maxillofacial surgeries. It also has the drawback of cumbersome, difficulty in sterilizing, and tracking only one instrument at a time.

Optical tracking systems (OTS)

Optical tracking system is the gold standard of tracking system, which is further divided into infrared (IR) and video-metric tracking systems.

Infrared tracking systems involve active or passive tracking. Active tracking uses infrared LED attached to instrument as the active marker which can be detected by two or three CCD. Passive tracking uses reflective spheres on the instrument, which can be passively illuminated by infrared sources. The reflective infrared light is then

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recognized by CCD. The LED active tags are powered by external wires, whereas the passive marker has the advantage of being wireless. Flashpoint 5000 (Boulder Innovation Group Inc., USA), Optotrak 3020 (Northern Digital Inc., Canada) and Polaris System (Northern Digital Inc., Canada) have been on the market and widely used in various surgeries.

Video-metric tracking system utilizes visible light and computer vision technology to detect and track passive markers on the instrument. MicronTracker (Claron Technology Inc., Canada) and NAVIRFA (NaviFUS Corp., Taiwan) are available commercial products.

Optical tracking system is widely used system. However, it is sensitive to the ambient light in environments. Occlusion of marker or line of sight (LOS) also introduce errors in calculating the central coordinates.

Electromagnetic tracking systems (ETS)

Electromagnetic tracking systems can localize electromagnetic sensors inside a magnetic field with known geometry. The pose of the sensor coils relative to the generating coils can be calculated by approximation algorithms. Electromagnetic tracking system is superior to optical tracking system for tracking in a small volume near the sensors. Commercial electromagnetic tracking devices are now available, such as trakSTAR, driveBAY, pciBIRD (Ascension Technology Inc., USA), Aurora (Northern Digital Inc., Canada), and Fastrak (Polhemus Inc., USA).

However, short sensing range, need of wires, susceptibility to metallic distortions and electromagnetic interference, measurement jitter due to patient movement and magnetic field distortion are the limitations of electromagnetic tracking system.

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Permanent magnet-based tracking systems (PTS)

Permanent magnet tracking system uses permanent magnets as magnetic sources and localization targets. We can track the instrument equipped with the wireless magnets in a real-time manner. The famous applications are the tracking of endoscopic capsule in the gastrointestinal tract and the tracking of flexible robotic arm. However, short tracking range is its limitation.

Fiber Bragg grating (FBG)-based tracking systems (FBGTS)

FBG-based tracking system employs multiple FBG sensors to predict the tip pose of a flexible instrument. It has the advantages of small size, fast response, high sensitivity, good repeatability, excellent stability, and electromagnetic immunity. However, it has disadvantages of shape sensors limited to the local coordinate system, shape reconstruction affected by the temperature drift of FBG sensors, poor perception of torsion, and error at the distal pose.

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NAVIRFA® System

NAVIRFA® navigation system is composed of camera, optical marker, and software. It uses video-metric tracking system to track the electrode position during ablation of tumor. When using NAVIRFA® system, firstly, the optical marker is attached to the needle instrument. Secondly, camera is fixed onto the ultrasound probe. The camera will detect the position of optical marker attached to the needle. Thirdly, the algorithm will map the needle position to the real-time ultrasound image. After calibration, surgeons will get simultaneous 2D and 3D views of needle, needle tip, intersection area of needle and ultrasound probe plane, and future path to perform ablation.

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Procedure Time

In our study, optical tracking group had shorter targeting time (5.55±1.04 min vs 6.22±0.87 min, p 0.007). No former literature was mentioned about targeting time of radiofrequency ablation of hepatocellular carcinoma guided by optical tracking system or 3D-ultrasound. Antoine Hakime et al. compared the needle placement time of electromagnetic tracking for ultrasound-guided percutaneous liver biopsy with that of freehand, which reported that needle placement time was significantly lower for electromagnetic tracking (45.8 ± 48.1 sec vs 143.2 ± 122.1 sec, $p < 0.01$)[13]. Although the mean decrease of targeting time of 0.67 min was significant statistically in our study, did it significant clinically? Ronnie T. Poon et alt. reported that a low complication rate and a high complete ablation rate could be achieved after the first 50 cases of radiofrequency ablation for hepatic tumor[3]. It demonstrated a significant learning curve. However, there was no literature mentioned about learning curve of radiofrequency ablation of hepatocellular carcinoma guided by navigation system. Although the decreased targeting time was not much in our study, we believed that the optical tracking system may help beginner or trainee of radiofrequency ablation to overcome the learning curve, especially for tumor in difficult locations. Further studies may be designed to compare the learning curve and complications of trainee using optical tracking system with those using conventional method.

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Electrode Deviation

In our study, electrode was located more centrally in optical tracking group (OR 4.89, 95% CI 1.37 to 17.50, p 0.015). When using optical tracking navigation system, 88.9% electrodes locate in center of tumor, 11.1% electrodes locate ≤ 3mm away from center of tumor, and 0% electrodes locate >3mm away from center of tumor. When using conventional manual ultrasound-guided method, 63.3% electrodes locate in center of tumor, 26.7% electrodes locate ≤ 3mm away from center of tumor, and 10% electrodes locate >3mm away from center of tumor. Although we did not compare the relationships between difficult locations of tumor, tumor size, and electrode deviation in our study, optical tracking system did help surgeons to locate electrodes more centrally in the tumor.

In vertebral phantom experiment, positional accuracy of manual ultrasound-guided procedure, manual 3D ultrasound-guided procedure, and ultrasound-guided procedure using optical tracking system were 0.7 ± 0.4 mm, 0.8 ± 0.6 mm, and <0.5 mm respectively[14,15]. However, we treated electrode deviation as an ordinal rather than a continuous variable in our study. Some information might be lost during this process. Besides, the center of tumor was defined by ultrasound, which was operator dependent. This also may introduce some bias. In further studies, another image guidance device, like CT or MRI, and another group of radiologists, may be needed to define center of tumor more precisely.

How Precise Targeting (Electrode Deviation) Influences Therapeutic Outcomes

In our study, electrode deviation was highly correlated with technique success (OR

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27.33, 95% CI 3.43-217.99, p 0.02) and complete ablation (OR 5.37, 95% CI 1.29-22.29, p 0.021). However, it was not related to complication, local recurrence, and progression (p>0.05).

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Technique Success

In our study, optical tracking group had higher technique success rate (97.2% vs 80%, p 0.04 on Fisher's exact test). Technique success was highly correlated with higher complete ablation rate (OR 43.5, 95% CI 3.64-519.25, p 0.003) and lower complication rate (OR 0.12, 95% CI 0.21-0.71, p 0.019). However, technique success was not related to local recurrence and progression (p>0.05).

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Complete Ablation

In our study, two groups had similar complete ablation rates (97.2% vs 90%, p 0.32 on Fisher's exact test). Complete ablation was not related to complication, local recurrence, and progression (p>0.05).

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Complications

In our clinical trial, optical tracking group demonstrated a trend of decreased rate of complications (5.6% incidence) compared to the conventional technique (20% incidence) (p 0.08 on Fisher's exact test; OR 0.24, CI 0.38 to 39.50, p 0.251 on logistic regression). There was no major complication in optical tracking group, but there was one (3.3%) major complication (abscess) in control group (Table 5). Complications were correlated with local recurrence (OR 8.1, 95% CI 14.0-46.8, p 0.019), but not to progression (p>0.05).

Table 5 Complications of NAVIRFA Group and Control Group

	Optical tracking N=36	Control N=30
Complications, n (%)	2 (5.6%)	6 (20%)
Pain, n (%)	1 (2.8%)	3 (10%)
Ileus, n (%)	1 (2.8%)	0 (0%)
Pleural effusion, n (%)	0 (0%)	2 (6.7%)
Abscess, n (%)	0 (0%)	1 (3.3%)

The system's real-time imaging allows physicians to identify and minimize potential procedure-related complications, such as adjacent structures at risk of thermal injury. The system's advanced imaging capabilities allow for real-time monitoring of the ablation process, providing immediate feedback to the physician and enabling adjustments as needed and reduce damage to surrounding healthy tissue, then minimizing complications.

Precise needle guidance of optical tracking system reduces such risks by accurately

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guiding the needle to the target site, minimizing the chances of unintended injury. The real-time imaging of system allows physicians to identify and avoid potential complications, such as adjacent structures at risk of thermal injury. Additionally, the accurate visualization of the ablation zone helps ensure complete tumor coverage while minimizing damage to healthy tissues, further enhancing the safety profile of the procedure.

Accurate needle guidance is expected to reduce the damage to critical structures, such as blood vessels or organs. Complications of radiofrequency ablation can be caused by thermal damage, direct needle injury, infection, and co-morbidities of patients[16]. They are associated with tumor type, tumor number, tumor localization, underlying liver disease, previous liver surgery, surgeon's experience, and type of approach[17]. Some literatures reported tumor size was related to complication rate, however, some literatures reported it was not related.

Livraghi T et al. reported the complications of 3,554 hepatocellular carcinoma lesions treated by percutaneous radiofrequency ablation[8]. Six deaths (0.3%) were reported, which included 2 multiorgan failure following intestinal perforation, 1 septic shock following Staphylococcus aureus-caused peritonitis, 1 massive hemorrhage following tumor rupture, 1 liver failure following stenosis of right bile duct, and 1 sudden death of unknown cause 3 days after the procedure. There were 5 major complications (2.2%), which included peritoneal hemorrhage, neoplastic seeding, intrahepatic abscesses, and intestinal perforation. Increased sessions of radiofrequency ablation were related to a higher rate of major complications. The number of complications was not significantly different when tumor size or electrode type were compared. In their study, the minor

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complication rate was less than 5%.

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Local Recurrence

The optical tracking system enables precise needle guidance and accurate tumor targeting. This heightened accuracy ensures comprehensive tumor coverage, reducing tumor recurrence rate (2.8% vs 20%, p 0.04 on Fisher's exact test). However, local recurrence and progression are affected by multiple factors, which could not be simply explained by use of navigation system[18,19,20].

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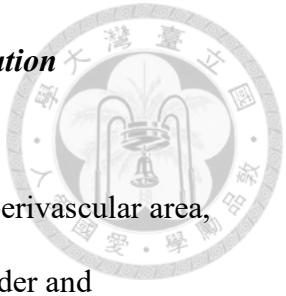

How Tumor Location Influences Outcomes of Radiofrequency Ablation

When using radiofrequency ablation for hepatocellular carcinoma, perivascular area, peribiliary area, tumors adjacent to diaphragm, liver surface, gallbladder and gastrointestinal tract were difficult locations. Wei Yang et al. compared the results of radiofrequency ablation of hepatocellular carcinoma between difficult locations group and control group[21]. They defined difficult locations as tumors located less than 5mm from major vessel, major bile duct or peripheral important structures or tumors on liver surface. Early tumor necrosis rates were similar between the two groups (difficult locations group vs control group 97.6% vs 94.3%, p 0.080). Complication rates were higher in difficult locations group (difficult locations group vs control group 4.9% vs 0.8%, p 0.041). Local progression rates were higher in difficult locations group (12.7% vs 7.1%, p 0.046). 1-, 3-, 5-, and 7-year overall survival rates were similar between the two groups (84.3%, 54.4%, 41.2%, and 29.9% vs 92.5%, 60.3%, 43.2%, and 32.8%, respectively, p 0.371). This study concluded that tumor location was not a significant risk factor for survival. In our study, we did not record the difficult locations. Further studies could be performed to determine if the optical tracking navigation system influence the outcome of hepatocellular carcinoma located at difficult locations.

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Progression-free Survival and Overall Survival

The follow-up period after ablation was 6 to 16 months. The median follow-up period for progression-free survival was 12 months. The progression-free survival was similar between the two groups (HR 0.55, CI 0.25 to 1.23, p 0.144). All patients in both groups survived. Although further follow-up is needed for long-term outcomes, local recurrence, progression-free survival, and overall survival are not expected to be influenced merely by navigation system. Local recurrence and survival are affected by multiple factors. Gisèle N'Kontchou et al. reported that multinodular forms (HR 2.34, 95% CI 1.52 to 3.6, p 0.0001) and AFP levels (HR 1.015, 95% CI 1.014 to 1.016, p 0.015) associated with higher recurrence rate[18]. Tumor size was associated with local recurrence but not with overall and tumor-free survival. Shuichiro Shiina et al. reported that serum des-γ-carboxy-prothrombin (DCP) level was related to 5- and 10-year local tumor progression rates[19]. Anti-HCV, Child-Pugh class, platelet count, tumor size, tumor number, serum AFP level, and serum DCP level were related to 5- and 10-year distant recurrence rates. Age, anti-HCV, Child-Pugh class, tumor size, tumor number, serum DCP level, and serum AFP-L3 were related to 5- and 10-year overall survival rates. Weimin Zhang et al. reported that tumor size (HR 1.27, 95% CI 1.15 to 1.40, p 0.0001), HBV-DNA (HR 7.70, 95% CI 3.57 to 16.63, p 0.0001), AFP levels before treatment (HR 2.172, 95% CI 1.256 to 3.756, p 0.006), and AFP response (HR 4.722, 95% CI 1.053 to 21.184, p 0.0427) were independently associated with the risk of recurrence of hepatocellular carcinoma after radiofrequency ablation[20]. Tumor size (HR 1.36, 95% CI 1.12 to 1.65, p 0.002), albumin levels (HR 0.76, 95% CI 0.65 to 0.91, p 0.002), prothrombin time (HR 2.18, 95% CI 1.54 to 3.10, p 0.0001), and AFP levels (HR 1.13, 95% CI 1.00 to 1.26, p 0.049) were independently associated with mortality

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after radiofrequency ablation.

In our study, higher Child-Pugh score and higher albumin-bilirubin (ALBI) grade had shorter progression-free survival (HR 62.55, CI 9.87 to 396.56, p 0.000 and HR 31.52, CI 5.14 to 193.12, p 0.000 respectively) (Table 3). Haiyi Long et al. reported that patients with ALBI grade 2 had poorer overall survival (p 0.033) and recurrence-free survival (p 0.002), and higher intrahepatic distant recurrence rate (p 0.001) than those with ALBI grade 1[22]. For Child-Pugh class A group, patients divided by ALBI grade 1 versus grade 2 showed significant differences in both OS and RFS (p 0.039 and 0.002).

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Information Loss in Navigation Systems

Information loss is a key problem of error in navigation systems, which can be caused by movement of patients, obstructions between the target and the tracker, interferences between the instruments or between the instrument and the tissue, or errors in data transmission or acquisition[5]. There exist some methods to alleviate information loss, like information fusion over multi-sensor, robot-assisted tracking, artificial intelligence, and deep learning approaches[5]. Further investigations are needed to compare the information loss of optical tracking system with other navigation systems.

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Study Limitation and Further Work to Do

Our study is of small sample size and short follow-up time. Further subgroup analyses according to age, liver cirrhosis, tumor locations, tumor number, ablation time and different electrodes are needed for investigating complete ablation, complications, and prognosis in use of optical tracking system. Further studies are needed to compare optical tracking system with other navigation systems.

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Conclusion

The emergence of image-guided systems, such as optical tracking, has revolutionized ultrasound-guided tumor ablation by providing real-time imaging, accurate needle guidance, and enhanced procedural control.

This study explores the advanced image-guided system represent significant advancements in ultrasound-guided tumor ablation procedures and therapeutic outcomes, highlighting its benefits and implications for patients and medical professionals. The robust clinical trial with 66 patients comparing NAVIRFA®-navigated ultrasound-guided radiofrequency ablation for hepatocellular carcinoma with a control group highlights the significant benefits of optical tracking system in improving accuracy, precision and real-time monitoring with feedback and compatible safety profile with current technique.

By addressing the limitations of current ultrasound-guided devices, the advanced imaging and tracking capabilities of optical tracking system enhance targeting, localization, real-time monitoring. The use of optical tracking system resulted in higher rates of accurate needle placement, successful delivery of the desired thermal dose, and a trend of lower incidence of complications. The integration of optical tracking system into clinical practice can lead to more effective and efficient treatments, ultimately benefiting patients in their battle against cancer, and paving the way for more effective and efficient treatments in the field of interventional oncology.

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