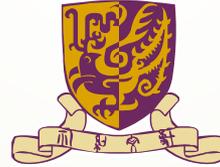




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What is the ideal therapy for HCC – Ablation?

Debate



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Local Ablative Therapy

A. Injection of Cytotoxic agents

- 1) Chemicals
 - a. Ethanol
 - b. Acetic acid
- 2) Radioactive isotopes
- 3) Hyperthermic agents
 - a. Saline
 - b. Water
 - c. Cytotoxic drugs
- 4) Chemotherapeutic agents

B. Application of an energy source

- 1) Thermal ablation
 - a. Radiofrequency
 - b. Microwave
 - c. Interstitial laser photo coagulation
 - d. High intensity focused ultrasound
- 2) Cryoablation
- 3) Conformal radiotherapy



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Advantages of Local Ablative Therapy

- Minimal invasive approach
- Little damage to surrounding liver parenchyma
- Little systemic side effects
- Safe
- Can be carried out under local anaesthesia or iv sedation

2 Systematic reviews showed radiofrequency ablation (RFA) to be better than other forms of local ablative therapy

- Overall survival
- Local recurrence rate
- Complete tumour necrosis rate
- Number of treatment required

Galandi D, et al. 2004

Sutherland LM, et al. 2006

- With the possible exception of microwave ablation (MWA)



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Local Ablative Therapy (RFA or MWA)

- ▶ Percutaneously
 - ▶ USG or CT guidance
- ▶ Laparoscopically
- ▶ Open Surgery → starting to lose advantages of minimal invasiveness, but is still less invasive than open liver resection



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Percutaneous Radiofrequency Ablation (RFA)

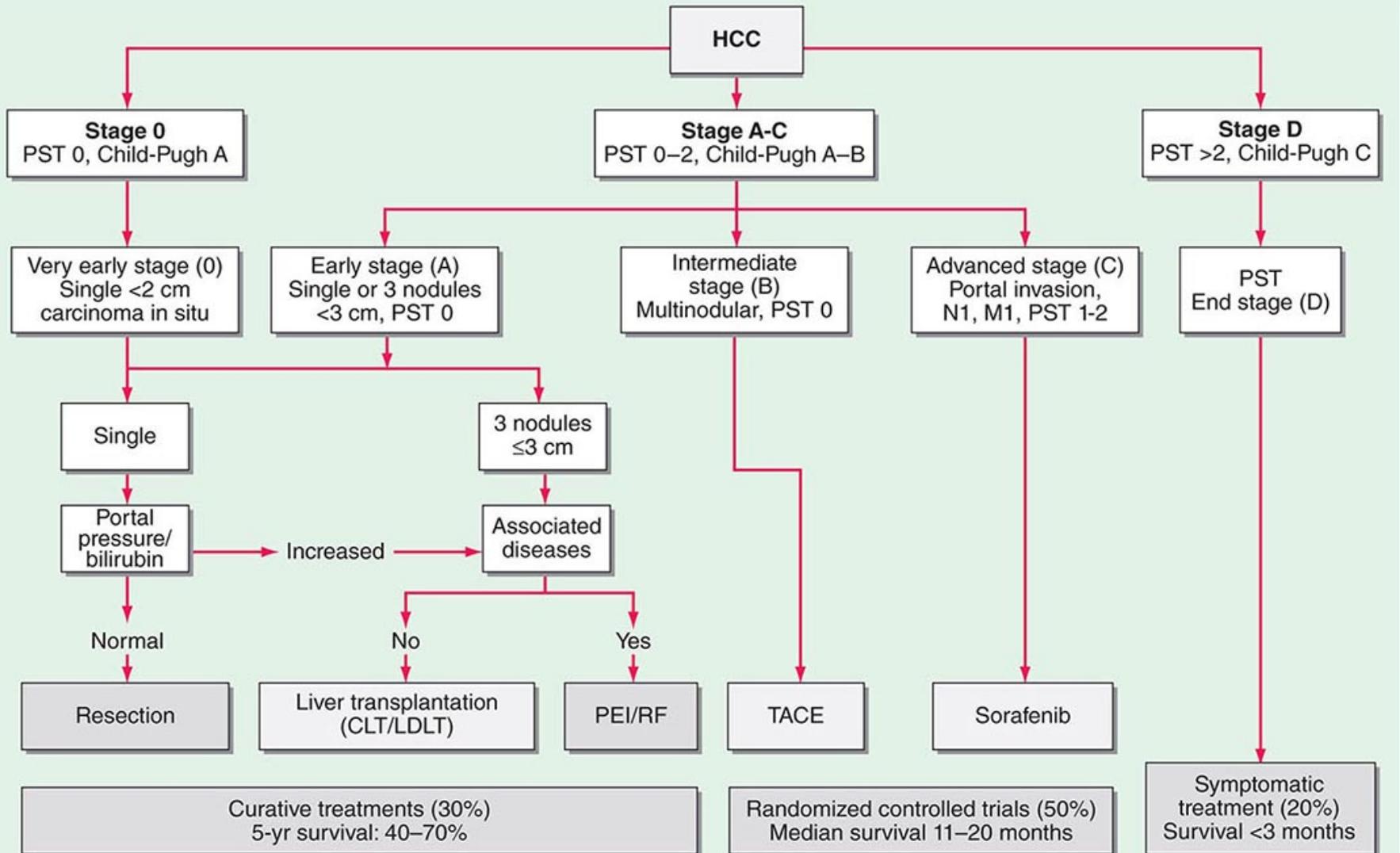
- ▶ First described by Rossi in 1993
- ▶ Radiofrequency energy leads to cell death and coagulation necrosis
- ▶ Good initial results achieved in non-randomized studies
 - ▶ Complete necrosis rate 90 to 100%
 - ▶ Local recurrence rate 3.6% at a median F.U. of 19m
 - ▶ Overall survival rate 51 - 64% at 5-year
 - ▶ Extremely low post procedural morbidity and mortality rates

Rossi et al 1993
Solbiati et al 1997
Nagata et al 1997
Lencioni R, 2005
Tateishi R, 2005
Choi JY, 2007

The excellent results obtained by RFA in treating HCC have led to:

- Some clinicians to use RFA as the first-line treatment instead of surgery
- Change in the recommendation of the BCLC in treating early HCC

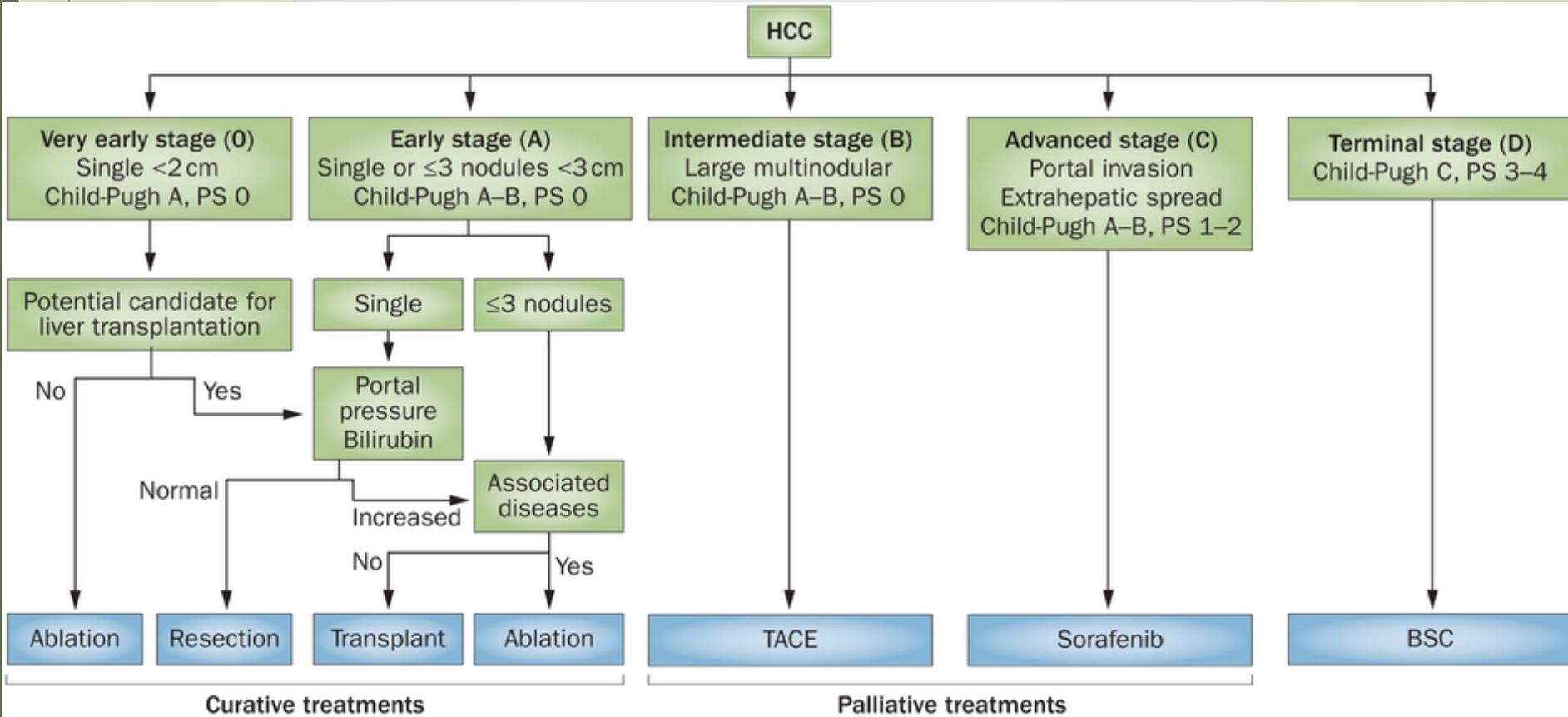
Old BCLC





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Recent BCLC





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Indications for RFA (Usually used)

- ▶ Child A to B
- ▶ Small tumour ? < 2 cm ? < 3 cm ? < 5 cm
- ▶ Small in number (< 3)
 - ▶ Otherwise needs repeated sessions
- ▶ Not candidates for liver transplantation
 - ▶ No portal hypertension
 - ▶ Child A/B
- ▶ Especially suitable for patients who are not surgical candidates because of
 - ▶ Poor general condition
 - ▶ Poor LFT
 - ▶ Recurrence after liver resection



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What is the evidence in supporting RFA in the treatment of single HCC < 2 cm (Why the change in the BCLC recommendation?)

- A multicenter prospective study reported 97% sustained complete response after RFA

Scorsetti M, 2016



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The main competitor in curative treatment of HCC with a solitary, small (< 5 cm) HCC with good liver function (Child A or B) with good general condition is

➔ Partial hepatectomy

Partial hepatectomy

- ▶ Perioperative mortality rate low
 - ▶ Non-cirrhotic liver resection approaching 0%
 - ▶ Cirrhotic liver resection < 5%
- ▶ Unfortunately only 10 – 30% of patients have resectable HCC at time of diagnosis
 - ▶ Poor general condition
 - ▶ Poor liver function
 - ▶ Unresectable or metastatic HCC



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In the East, > 80% of HCC are associated with cirrhotic livers.

Special risks of cirrhotic liver resection are:

- 1) Liver less tolerant to ischaemic-refusion injury to the liver
- 2) Opening up of collateral veins around the liver due to portal hypertension
- 3) Compromised coagulopathy due to poor liver function and low platelet
- 4) Less tolerant to infection
- 5) Less ability of liver to regenerate
- 6) More prone to postoperative liver failure
- 7) Increased risk of bleeding due to portal hypertension
- 8) Poor nutritional state of patient
- 9) Difficulty in differentiating between tumour nodules and regenerative nodules



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Furthermore, partial hepatectomy, like RFA, is a local treatment for HCC, but it has

- Higher treatment risks
- Lower feasibility rate
- Higher procedural invasiveness
- More postoperative suffering to patients
- Slower recovery from treatment

In reviewing the results of treatment between RFA and partial hepatectomy

The most important outcome measurement is

➤ Overall survival



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There are other less important secondary outcome measurements

- Recurrence free survival
- Post-treatment morbidity/mortality
- Collateral damage to adjacent tissues
- Feasibility (e.g. multiple tumour, compromised liver function)
- Chance for re-treatment for recurrent HCC
- Number of re-treatment that can be carried out for tumour recurrence

which will be discussed in detail in the latter part of this talk.

On reviewing the medical literature on:-

- ▶ Overall survival after RFA versus partial hepatectomy
- ▶ Using only Level 1 evidence in Evidence Based Medicine (RCT and meta-analysis)
- ▶ Limiting to patients who are suitable for both RFA and partial hepatectomy
 - ▶ small HCC <5 cm as HCC >5 cm is not suitable for RFA
 - ▶ and the approaches for RFA can be
 - ▶ percutaneous (majority of patients)
 - ▶ laparoscopic
 - ▶ or open approach



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- ▶ 4 RCTs showed overall survival to be similar between RFA and liver resection

Chen MS, et al. 2006

Cho YK, et al. 2010

Huang GT, et al. 2005

Lu MD, et al. 2006

- ▶ All these 4 studies have been criticized to have major methodological biases



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- A fifth RCT and a meta-analysis showed partial hepatectomy to be superior to RFA in overall survival

Huang J, et al. 2010

Wang Y, et al. 2014

How should we look at all these controversies in overall survival in Level 1 Evidence-based medicine?

The main criticism of all these studies is the failure to exclude patients with HCC which are less effective to RFA treatment

- ▶ HCC at difficult sites
- ▶ 'heat sinks'
- ▶ Size of lesion

A large meta-analysis has clearly demonstrated that RFA effectiveness rapidly decreases for HCC > 3 cm and in lesions near to a large vessel producing 'heat sink effect'



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Problems and solutions for less effective RFA lesions

- ▶ 'heat sink'
- ▶ Patient selection
- ▶ Lesions in difficult location
 - ▶ Laparoscopic approach
 - ▶ Open approach

The main limitation of effectiveness of RFA on overall survival in treating HCC is size of the lesion

A study on the biological behavior of HCC showed as HCC reached to 3 cm, it started to exhibit a tendency towards more aggressive behavior with increasing

- ▶ Capsular invasion
- ▶ Histological grades
- ▶ Satellite nodules
- ▶ Tumour nodules

which affected overall survival after liver resection

RFA

Technical solutions to treat larger lesions

- ▶ Complex electrode geometry
- ▶ Multiple puncture and treatment sessions
- ▶ For larger HCC 3 – 5 cm, RCTs have shown
 - ▶ RFA + ethanol injection produced better OS and DFS than RFA

Zhang YJ, et al. 2007

- ▶ RFA+TACE better than RFA

Cheng BQ, et al. 2008



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Evidence Based Medicine suggests for overall survival

HCC < 2 cm	RFA = Liver resection
2 – 3 cm	RFA possibly = Liver resection
3 – 5 cm	RFA should be used together with ethanol injection or TACE to achieve OS as in liver resection
> 5 cm	RFA results is worse in OS than liver resection and the latter should be the first line treatment

Other less important secondary outcome measurements

(2) Post-treatment recurrence-free survival

Unless treating HCC < 2 cm, or possible < 3 cm, studies showed recurrence free survival to be worse with RFA than liver resection. However as these patients can be treated with further sessions of RFA, the overall survival is not affected as discussed previously if patients are carefully selected and additional treatment are given.



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There is evidence to show in the first treatment

- ▶ Whether RFA can result in complete tumour necrosis is an important factor in determining long-term survival of patients with HCC (overall and disease-free survival)

Sala H, et al. Hepatology 2004

Methods to ensure complete tumour necrosis in RFA

During treatment

- ▶ Use of SonoVue
- ▶ RFA until HCC shows no contrast enhancement after SonoVue injection

Post-treatment

- ▶ Routine IV contrast CT 4 weeks after RFA
- ▶ Treat any residual HCC with RFA re-treatment

Chen MS, et al. 2006
Livraghi T, et al. 2007



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The concept of adequate RFA treatment

RFA + SonoVue

Routine IV contrast CT at 4 weeks

Re-treatment with RFA for inadequately treated patients

5-year local recurrence rate around 8%

*Chen MS, 2006.
Chang YJ, et al. 2007*

The concept is like histological examination of surgical resection margin to look for R0 liver resection.



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(3) Post-treatment mortality/morbidity

	RFA	Liver Resection
Mortality	0.2 – 0.5%	2% non-cirrhotic 5% cirrhotic 10x as high as RFA
Morbidity	2 – 4%	30 – 50% 15x as high as RFA

Livraghi T, et al. 2003
Akahane M, et al. 2005
Rhim et al, 2005
Livraghi T, et al. 2005

(4) Collateral damage to adjacent tissues

	RFA	Liver Resection
Approach	Minimal invasive	Large invasive
Liver mobilization	No need	Yes
Damage to liver parenchyma	Little	Severe
Liver blood in flow occlusion	No need	Usually required
Post-op. Pain	Little	A lot
Recovery	Fast	Slow



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(5) Feasibility

	RFA	Liver Resection
Multiple tumours	Less limitations	Unless tumours localized, otherwise not resectable
Liver function	Can be used in patients with slightly compromised liver function	Usually cannot be used in patients with compromised liver function

(5) Chance of Re-treatment

RFA	Liver Resection
High	Low
Most patients can be re-treated	Japanese National Study: only 1.6% <i>Ariel et al. 2011</i>

(6) Number of treatment for recurrent HCC

RFA	Liver Resection
Can be many times (not unusual to have 6 – 7x)	At the most 2 to 3 times



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Summary

	RFA	Liver Resection
Overall Survival	Similar in properly selected patients	
Disease-free Survival	Can be similar if proper treatment is given to selected patients	
Treatment mortality/morbidity	Low	10 x to 15x higher
Treatment invasiveness	Low	High
Collateral damage	Low	High
Feasibility (multiple tumors, poor LFT)	+++	+
Chance of re-treatment	High	Low
No. of treatment for recurrence	Many times	At most 2 – 3x



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Thus, evidence based medicine shows:

- In selected patients with small HCC, RFA can replace liver resection to be the first line curative treatment



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- Microwave ablation is an emerging technology which has the potential to achieve larger and more regular necrotic area in comparison with RFA

Reports on MWA in treatment of HCC ≤ 4 cm in size have the theoretical advantages over RFA

- Faster delivery
- A wider zone of active heating
- Higher intra-tumoral temperature
- Less susceptibility to 'heat sink' when performed near to large vessels

Scorsetti M, et al. 2016

In a study on 182 patients with a single HCC (3 to 5 cm)

MWA achieved

- Complete ablation rate of 93%
- 1-year & 3-year OS 89%, 60%
- 1-year & 3-year RFA 51%, 27%

The recurrence risk was associated with tumour size and patient age.

Sun AX, et al. 2015

In another study on 234 patients with 339 HCC nodules treated with MWA

- ▶ The 1-, 3-, 5-year OS:-
92.7%, 72.9% and 56.7%, respectively
- ▶ Local recurrence rate was 7%

Dong B, et al. 2003



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In a non-randomized comparative study comparing MWA (98 nodules in 49 patients) with RFA (72 HCC nodules in 53 patients), MWA achieved similar complete ablation rates as RFA

➤ 94.9% vs 93.1%

Slightly better but insignificant local recurrence rate

➤ 11.8% vs 20.9%

Lu MD, et al. 2006

Results of current studies on RFA/MWA for HCC

Authors, year	Mean Lesion Size cm (range)	Local Control (%)		Overall survival (%)	
		1-year	3-year	1-year	3-year
RFA					
Tateishi et al. 2004	2.6 (0.8 – 9.7)	-	-	94.7%	67.4%
Tim et al. 2013	2.2 (0.5 – 4.9)	-	-	95.5%	77.9%
Lencioni et al. 2005	2.8 (1.5 – 5.0)	96%	90%	97%	67%
Livraghi et al. 2000	5.4 (3.1 – 9.5)	-	-	-	-
N'Kontchou et al. 2009	2.92 (1.1 – 5.0)	-	-	-	60%
MWA					
Dong et al. 2000	4.1 (1.2 - 8.0)	-	-	92.7%	72.8%
Sun et al. 2014	3.72 (3.02 – 5.0)	77%	75%	89%	60%



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To the best of my knowledge,
there is no RCT comparing
MWA with RFA.



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Conclusion (1)

- Radiofrequency ablation (RFA) is an effective and safe treatment
- In selected patients, it produces similar overall survival compared to patients treated with liver resection but with better secondary outcome measurements



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Conclusion (2)

- The results of RFA can be improved by adding TACE or ethanol injection.
- MWA is a new promising treatment for patients with small HCC.