IV SESSIONE: FEGATO - HCC

Trattamenti combinati: quando e come

Dott. Andrea Contegiacomo

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Istituto di Radiologia, Fondazione Policlinico “A. Gemelli”
“Università Cattolica del Sacro Cuore” – Roma
Trattamenti combinati???
APASL 2010

Various clinical studies, involving combination of transcatheter arterial chemoembolization followed by RFA [306] or hepatic arterial balloon occlusion during RFA [307], have been attempted to increase the ablated volume of RFA by reducing the cooling effect of the blood supply. Although the extension of necrotic area was achieved, it still remains unsettled whether these trials actually improve the prognosis or not.

EASL-EORTC 2012

considered as competitive alternatives to resection is uncertain (evidence 1IA; recommendation 1C)

AASLD 2011

A recent trial comparing the combination of chemoembolization and radiofrequency suggested that this approach offered an improvement in survival as compared to chemoembolization or ablation alone. However, this article was retracted by the publishing journal.
NCCN 2016

**Recommendation**

TACE before RFA extends the range of necrosis (Grade A).

A favorable prognosis can be expected if local control is achieved. However, there is inadequate evidence demonstrating that pretreatment with TACE will improve RFA outcomes (Grade C1).

**TREATMENT**

- Refer to liver transplant center
- Consider bridge therapy as indicated

**SURVEILLANCE**

- Imaging every 3 to 6 mo for 2 y, then every 6 to 12 mo
- AFP, every 3 to 6 mo for 2 y, then every 6 to 12 mo
- See relevant pathway (C3 through C5) if disease recurs

KLCSG - NCC 2014

**CQ34 Does a combination of TACE and percutaneous ablation therapy improve prognosis?**

**Recommendation**

TACE before RFA extends the range of necrosis (Grade A).

A favorable prognosis can be expected if local control is achieved. However, there is inadequate evidence demonstrating that pretreatment with TACE will improve RFA outcomes (Grade C1).

- Caution should be exercised when ablating lesions near major vessels, major bile ducts, diaphragm, and other intra-abdominal organs.
- Ablation alone may be curative in treating tumors ≤3 cm. In well-selected patients with small properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, or with combination of an arterially directed therapy and ablation as long as tumor location is accessible for ablation.
- Unresectable/inoperable lesions >5 cm should be considered for treatment using arterially directed or systemic therapy.

ESMO - ESDO 2012

Risk in percutaneous than in laparoscopic series.

Neo-adjuvant or adjuvant therapies are not recommended to improve outcome of patients treated with resection or local ablation [II, B]. This recommendation is supported by a study of the Cochrane group that recently identified 12 RCTs with 343 patients, but concluded that there was no clear evidence for the efficacy of any of the adjuvant and neo-adjuvant protocols reviewed (including immunotherapy, retinoids, chemoembolization) [23]. The results of the STORM (Sorafenib as Adjuvant Treatment in the Prevention of Recurrence) trial also failed to show a survival benefit with adjuvant systemic therapy [24].
The dark side of the guideline

HCC

Stage 0
PST 0, Child-Pugh A

Very early stage (0)
Single <2 cm, Carcinoma in situ

Stage A-C
PST 0-2, Child-Pugh A-B

Early stage (A)
Single or 3 nodules ≤3 cm, PS 0

Intermediate stage (B)
Multinodular, PS 0

Advanced stage (C)
Portal invasion, N1, M1, PS 1-2

Stage D
PST >2, Child-Pugh C*

Terminal stage (D)

Associated diseases

Portal pressure/bilirubin

Increased

Normal

No

Yes

Resection
Liver transplantation (CLT/LDLT)
RF/PEI
TACE
Sorafenib
Best supportive care

Curative treatment (30-40%)
Median OS >60 mo; 5-yr survival: 40-70%

Target: 20%
OS: 20 mo (45-14)

Target: 40%
OS: 11 mo (6-14)

Target: 10%
OS: <3 mo

Interventional Radiologist under 40 Meeting
Interventional Oncology
Singolo nodulo

Predicting Individual Survival After Hepatectomy for Hepatocellular Carcinoma: a Novel Nomogram from the BHCC East & West Study Group

Singolo nodulo

- **3 cm < HCC < 5 cm**  
  Risposta completa 50-70%

- **HCC > 5 cm**  
  Risposta completa 30%

- Elevati tassi di recidiva anche dopo risposta completa post-RFA

Sede

- 10-25% delle lesioni difficilmente trattabili con RFA a causa della sede:
  - Lesioni sottocapsulari
  - Lesioni adiacenti al diaframma
  - Lesioni disposte lungo la superficie libera epatica

Scarsa accessibilità/visualizzazione

Rischio di complicanze (emorragiche)
Quale trattamento?

➢ No RFA (Rischio complicanze/scarsa visualizzazione ed accessibilità alla lesione)

TACE ?

Comparison of Long-Term Survival of Patients with Solitary Large Hepatocellular Carcinoma of BCLC Stage A after Liver Resection or Transarterial Chemoembolization: A Propensity Score Analysis

Comparison of Radiofrequency Ablation and Transarterial Chemoembolization for Hepatocellular Carcinoma Within the Milan Criteria: A Propensity Score Analysis

Chia-Yang Hsu,1,4 Yi-Hsiang Huang,2 Yi-You Chiu,1,4 Chien-Wei Su,2,4 Han-Chieh Lin,1,4 Rheaun-Chuan Lee,1,4 Jen-Huey Chiang,1,4 Teh-Yu Kuo,2,4 Fa-Yauh Lee,1,4 and Shou-Deng Lee1,4

LIVER TRANSPLANTATION 17:556-566, 2011
Quale trattamento?

TACE

RFA

Safety Margin
Quale trattamento?

- **TACE** è una tecnica in via di sviluppo (DEB-TACE/cTACE)
- Migliore tollerabilità del paziente
- Aumento della sopravvivenza nei pz avanzati
- >70% pz con necrosi tumorale massiva post-TACE
  
  < 20% pz ottiene una risposta completa

Intermediate HCC

- Popolazione di pazienti estremamente eterogenea
- Tumor load
- Funzionalità epatica residua
- Età/ comorbidità

Heterogeneity of Patients with Intermediate (BCLC B) Hepatocellular Carcinoma: Proposal for a Subclassification to Facilitate Treatment Decisions
Espandere le indicazioni della RFA!

- **Early stage**
  Singolo HCC > 3cm
  No RFA (sede, complicanze)

- **Intermediate stage**
  Multinodulare (7)
  Multinodulare (< 5 noduli)
  Child-Pugh A

Intervventional Radiologist under 40 Meeting
Interventional Oncology
Quali limiti (e soluzioni?)

**RF**
- **Meccanismo di azione**
  - Necrosi coagulativa “locale”
  - Numero lesioni limitato
- **Dimensioni delle lesioni**

**TACE**
- **Numero di lesioni**
  - Ischemia/tossicità “globale”
  - Numero lesioni ∞
- **Dimensioni delle lesioni**

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*Heat-Sink Effect*
Quali limiti (e soluzioni?)

- DANNO TERMICO
- ISCHEMIA
- CITOTOSSICITA'

RFA

TACE
Quale combinazione?

TAC ➢ Occlusione del vaso afferente
➢ Riduzione dell’Heat-sink effect
➢ Estensione dell’area di trattamento della RFA
➢ Aumento del “safety margin” con coagulazione di noduli satelliti
➢ Trattamento di lesioni a distanza

→ RF A

Interventional Radiologist under 40 Meeting Interventional Oncology
Quale combinazione?

RFA ➢ TAC

- Concentrazione del farmaco nel tessuto vitale residuo (porzione centrale necrotica)
- Minore resistenza cellulare al danno cito-tossico del farmaco (esposizione a temperature sub-letali)
- Miglior rilascio di farmaco (iperemia)
- Trattamento sanguinamenti

Quale combinazione?

RFA → TAC

Enfasi sul “DANNO CITOTOSSICO”

TAC → RF

Enfasi sul “DANNO TERMICO”

NO

Sequential or combined treatment? That is the question.

Iezzi R¹, Pompili M, Gasbarrini A, Bonomo L.
Combination of radiofrequency ablation with transarterial chemoembolization for hepatocellular carcinoma: an up-to-date meta-analysis

Zhenyin Liu & Fei Gao & Guang Yang & Sristi Singh & Mingjian Lu & Tao Zhang & Zhihui Zhong & Fujun Zhang & Rijie Tang

Meta-analysis of radiofrequency ablation in combination with transarterial chemoembolization for hepatocellular carcinoma

Jia-Yan Ni, Shan-Shan Liu, Lin-Feng Xu, Hong-Liang Sun, Yao-Ting Chen

Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: a meta-analysis of randomized-controlled trials

Zaiming Lu, Feng Wen, Qiyong Guo, Hongyuan Liang, Xiaonan Mao and Hongzan Sun

Efficacy and safety of radiofrequency ablation and transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma: A meta-analysis

Yulan Wang, Tianxing Deng, Li Zeng and Weiqing Chen

Department of Gastroenterology, Second Affiliated Hospital of Chongqing Medical University; and Urology, Second Affiliated Hospital, Third Military Medical University, Chongqing, China

Meta-analysis of transcatheter arterial chemoembolization plus radiofrequency ablation versus transcatheter arterial chemoembolization alone for hepatocellular carcinoma

De-jun Yang , Kun-lun Luo, Hong Liu, Bing Cai, Guo-qing Tao, Xiao-fang Su, Xiao-juan Hou, Fei Ye, Xiang-yong Li, Zhi-qiang Tian

1Department of Gastrointestinal Surgery, The Changzheng Hospital, Second Military Medical University, Shanghai, 200003, China
2Department of General Surgery, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi 214023, China
3Department of Gastroenterology and Oncology, The 101st Hospital of Chinese PLA, Wuxi 214044, China
4Tumor Immunology and Gene Therapy Center, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai 200433, China
5These authors contributed equally to this work

Efficacy and Safety of Radiofrequency Ablation Combined with Transcatheter Arterial Chemoembolization for Hepatocellular Carcinomas Compared with Radiofrequency Ablation Alone: A Time-to-Event Meta-Analysis

Xin Wang, PhD, Yanan Hu, PhD, Mudan Ren, MD, Xinlan Lu, PhD, Gulifang Lu, PhD, Shuxiang He, PhD

All authors: Department of Gastroenterology, First Affiliated Hospital of Xi'an Jiaotong University, Xian, Shaanxi Province 710061, China

Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: A systematic review and meta-analysis

Qi-Wen Chen, Hai-Feng Ying, Song Gao, Ye-Hua Shen, Zhi-Qiang Meng, Hao Chen, Zhen Chen, Wen-Jing Teng

Meta-analysis of transcatheter arterial chemoembolization plus radiofrequency ablation versus transcatheter arterial chemoembolization alone for hepatocellular carcinoma


<table>
<thead>
<tr>
<th>AUTORE</th>
<th>ANNO</th>
<th>STUDI</th>
<th>RCT</th>
<th>TACE + RFA vs.</th>
<th>Overall Survival</th>
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<th>Tumor Size</th>
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<tr>
<th>AUTORE</th>
<th>TACE + RFA vs.</th>
<th>Child group</th>
<th>Tumor Progression</th>
<th>Tumor response</th>
<th>Complications</th>
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<tbody>
<tr>
<td>Lu Z.</td>
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<td>Child-Pugh A</td>
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<td>CR + PR</td>
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</table>

**Legenda:**
- ++ Trattamento combinato
- Monoterapia = trattamento combinato
- Non valutato
- ++ Monoterapia

**Note:**
- **OS:** Overall Survival
- **RFS:** Recurrence Free Survival
- **TS:** Tumor Size
- **CP:** Complete response
- **PR:** Partial Response
- **RCT:** Randomized Control Trial
- **RFA:** RadioFrequency Ablation
- **TACE:** Trans-Arterial ChemoEmbolization
HCC non resecabile

21 studi, 6 RCT
3073 pz inclusi
RFA + TACE vs monoterapia (RFA/TACE)
HCC non resecabile

Efficacy and safety of radiofrequency ablation and transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma: A meta-analysis

Yulan Wang, Tianxing Deng, Li Zeng and Weiqing Chen

Department of Gastroenterology, Second Affiliated Hospital of Chongqing Medical University; and Urology, Second Affiliated Hospital, Third Military Medical University, Chongqing, China

5yrs - OS

Interventional Radiologist under 40 Meeting
Interventional Oncology
Efficacy and safety of radiofrequency ablation and transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma: A meta-analysis

Yulan Wang,1 Tianxing Deng,2 Li Zeng1 and Weiqing Chen1
Department of 1Gastroenterology, Second Affiliated Hospital of Chongqing Medical University; and 2Urology, Second Affiliated Hospital, Third Military Medical University, Chongqing, China

<table>
<thead>
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<th>Study or Subgroup</th>
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<th>Odds Ratio</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
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<td>Shibata et al.24</td>
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<td>46</td>
<td>32</td>
<td>43</td>
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<tr>
<td>Morimoto et al.25</td>
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<tr>
<td>Peng et al.26</td>
<td>55</td>
<td>69</td>
<td>46</td>
<td>70</td>
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<tr>
<td>Kim et al.17</td>
<td>57</td>
<td>83</td>
<td>150</td>
<td>231</td>
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<td>Peng et al.27</td>
<td>75</td>
<td>94</td>
<td>63</td>
<td>95</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>329</td>
<td>473</td>
<td>100%</td>
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<tr>
<td><strong>Total events</strong></td>
<td>245</td>
<td>305</td>
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</tbody>
</table>

Heterogeneity: Chi² = 5.70, df = 5 (P = 0.33); I² = 14%

Yang et al.33   27 | 31 | 27 | 37 | 9.7% | 2.50 [0.70, 8.96] | 2009
Shibata et al.24 46 | 46 | 43 | 43 | Not estimable | 2009
Morimoto et al.25 19 | 19 | 16 | 18 | 1.3% | 5.91 [0.26, 132.00] | 2010
Peng et al.34 112 | 120 | 107 | 120 | 21.8% | 1.70 [0.68, 4.27] | 2010
Kim et al.17 77 | 83 | 215 | 231 | 25.1% | 0.96 [0.36, 2.53] | 2012
Peng et al.26 65 | 69 | 57 | 70 | 10.0% | 3.71 [1.14, 12.01] | 2012
Peng et al.27 87 | 94 | 81 | 95 | 18.3% | 2.15 [0.83, 5.59] | 2013
| **Total (95% CI)** | 504 | 642 | 100.0% |       |
| **Total events**   | 465 | 565 |         |       |

Heterogeneity: Chi² = 4.26, df = 7 (P = 0.75); I² = 0%
Test for overall effect: Z = 3.09 (P = 0.002)
## Complications

### Efficacy and safety of radiofrequency ablation and transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma: A meta-analysis

*Yulan Wang,*¹ *Tianxing Deng,*² *Li Zeng¹* and *Weiqing Chen¹*

*Department of Gastroenterology, Second Affiliated Hospital of Chongqing Medical University; and Urology, Second Affiliated Hospital, Third Military Medical University, Chongqing, China*

### Complications

#### Study or Subgroup

<table>
<thead>
<tr>
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<th>RFA</th>
<th>Odds Ratio M-H, Fixed, 95% CI Year</th>
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<tr>
<td>Shen et al.²²</td>
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#### Total (95% CI)

- Total events: 465
- 642 events, 100.0%
- 1.94 [1.28, 2.96]

**Heterogeneity:** Chi² = 4.26, df = 7 (P = 0.75); I² = 0%

### A

<table>
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<td>Iezzi et al.²⁰</td>
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<td>Yin et al.²⁹</td>
<td>49</td>
<td>55</td>
<td>3.97 [1.59, 9.87] 2014</td>
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</table>

#### Total (95% CI)

- Total events: 143
- 246 events, 100.0%
- 4.13 [2.29, 7.45]
HCC non resecabile

Analisi univariata e multivariata fattori predittivi di insuccesso

Overall Survival

<table>
<thead>
<tr>
<th>Dimensioni &gt; 7 cm</th>
<th>Numero di lesioni</th>
<th>Tipo di trattamento</th>
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Recurrence free survival

<table>
<thead>
<tr>
<th>Dimensioni &gt; 5 cm</th>
<th>Numero di lesioni</th>
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</table>

Che fare > 5 cm?
Microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma: A systematic review and meta-analysis

Antonio Facciorusso, Marianna Di Maso & Nicola Muscatiello

CONCLUSIONS: Our results indicate a similar efficacy between the two percutaneous techniques with an apparent superiority of MWA in larger neoplasms.

Coagulation Areas Produced by Cool-Tip Radiofrequency Ablation and Microwave Ablation Using a Device to Decrease Back-Heating Effects: A Prospective Pilot Study

Francesca Di Vece · Paola Tombesi · Francesca Ermili · Cinzia Maraldi · Sergio Sartori

CONCLUSION: The MWA system can achieve significantly larger ablation areas than the internally cooled RFA system. Broader randomized trials are strongly warranted to investigate whether such superiority can translate into better long-term outcome of the ablation procedure.

META ANALYSIS AND SYSTEMATIC REVIEW

Percutaneous thermal ablation for primary hepatocellular carcinoma: A systematic review and meta-analysis

Mohamed A Chinnaratha,*† Ming-yu Anthony Chuang,‡ Robert JL Fraser,*† Richard J Woodman* and Alan J Wigg,*†

Conclusion: Overall, both RFA and MWA are equally effective and safe, but MWA may be more effective compared to RFA in preventing LTP when treating larger tumors. Well-designed, larger, multicentre RCTs are required to confirm these findings.
MWA + TACE

MWA Combined with TACE as a combined therapy for unresectable large-sized hepatocellular carcinoma

CUN LIU,1,2,3, PING LIANG, FANGYI LIU1, YANG WANG1, XIN LI1, ZHIYU HAN1, & CHANGCHUN LIU3

1From the department of Interventional Ultrasound, Chinese PLA General Hospital, 28 Fuxing Road, Beijing, 100853, P.R. China, 2From the department of ultrasound, Jinan Central Hospital, Shandong University, 105 Jiefang Xi Road, Jinan, Shandong, 250013, P.R. China, and 3School of Control Science and Engineering, Shandong University, 73 Jingshi Road, Jinan, 250061, Shandong Province, P.R. China

- Prospettico controllato
- TACE vs TACE + MWA
- 34 pazienti consecutivi (18/16)
- Nodulo > 5 cm non resecabile

> Overall Survival
> Tumor response (Completa e Parziale)
= Complications

HEPATOLOGY
Large primary hepatocellular carcinoma: Transarterial chemoembolization monotherapy versus combined transarterial chemoembolization-percutaneous microwave coagulation therapy
Lin-Feng Xu, Hong-Liang Sun, Yao-Ting Chen, Jia-Yan Ni, Dong Chen, Jiang-Hong Luo, Jing-Xing Zhou, Ren-Mei Hu and Qi-Yun Tan
Department of Interventional Radiology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, Guangdong Province, China

- Retrospettivo
- TACE vs TACE + MWA
- 136 pazienti consecutivi (88/56)
- Nodulo > 5 cm non resecabile

Survival

> Overall Survival
> Time to progression
< Complications

TACE + MWA vs TACE + RFA

Transarterial Chemoembolization Combined with Either Radiofrequency or Microwave Ablation in Management of Hepatocellular Carcinoma


Caratteristiche dello studio

- Retrospettivo, monocentrico
- Child - Pugh A/B
- Singolo nodulo ≤ 5cm o ≤ 3 noduli ≤ 3cm

67 Pazienti

22 TACE + RFA
45 TACE + MWA
<table>
<thead>
<tr>
<th></th>
<th>Complete response</th>
<th>TACE+Microwave</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>18/22 (81.8%)</td>
<td>4/22 (18.2%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>2/22 (18.2%)</td>
<td>2/45 (4.4%)</td>
</tr>
<tr>
<td>Abdominal LNs</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Abdominal LNs</td>
<td>1 (4.5%)</td>
<td>0 (1.5%)</td>
</tr>
<tr>
<td>Ascites</td>
<td>4 (8.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ascites</td>
<td>0 (0%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Ascites</td>
<td>1 (4.5%)</td>
<td>0 (1.5%)</td>
</tr>
<tr>
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<td>1 (4.5%)</td>
<td>0 (1.5%)</td>
</tr>
<tr>
<td>Ascites</td>
<td>4 (8.9%)</td>
<td>0 (0%)</td>
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<tr>
<td></td>
<td>Total patients</td>
<td>TACE+Microwave</td>
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<td>--------------------</td>
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<tr>
<td>Overall survival</td>
<td></td>
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<tr>
<td>1 year</td>
<td>80.10%</td>
<td>83.30%</td>
</tr>
<tr>
<td>2 years</td>
<td>55%</td>
<td></td>
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<tr>
<td>3 years</td>
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<td></td>
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<tr>
<td>Overall survival in relation to tumor size</td>
<td></td>
<td></td>
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<tr>
<td>focal lesion &gt; 3cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>81.20%</td>
<td>81.20%</td>
</tr>
<tr>
<td>2 years</td>
<td>42%</td>
<td></td>
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<tr>
<td>3 years</td>
<td>14%</td>
<td></td>
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</table>

Finally, we conclude that TACE-MWA led to better response rates than TACE-RFA with tumors 3-5 cm. No difference between both lines of treatment for small tumors (less than 3 cm). Better response rates did not efficiently correlated with better survival rates.
Radiofrequency vs Microwave Ablation After Neoadjuvant Transarterial Bland and Drug-Eluting Microsphere Chembolization for the Treatment of Hepatocellular Carcinoma☆,☆☆

Lindsay M. Thornton, MD, Roniel Cabrera, MD, MS, Melissa Kapp, ARNP, Michael Lazarowicz, MD, Jeffrey D. Vogel, MD, Beau B. Toskich, MD
Neoadjuvant Sphere Chemoembolization for...

Melissa Kapp, ARNP, and Michael Hosskisch, MD

<table>
<thead>
<tr>
<th></th>
<th>RFA</th>
<th>MWA</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/15 (7%)</td>
<td>8/20 (40%)</td>
<td>0.048</td>
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</tr>
<tr>
<td>3/15 (20%)</td>
<td>2/20 (10%)</td>
<td>0.377</td>
<td></td>
</tr>
<tr>
<td>Type of embolization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE</td>
<td>3/15 (20%)</td>
<td>9/20 (45%)</td>
<td>0.50</td>
</tr>
<tr>
<td>TAE</td>
<td>12/15 (80%)</td>
<td>11/20 (55%)</td>
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<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Complete response</td>
<td>12/15 (80%)</td>
<td>19/20 (95%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Median postop MELD</td>
<td>7</td>
<td>9.25</td>
<td>0.25</td>
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<tr>
<td>Median follow-up</td>
<td>18</td>
<td>14</td>
<td>0.071</td>
</tr>
<tr>
<td>Transplanted</td>
<td>2</td>
<td>5</td>
<td>0.681</td>
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</tbody>
</table>
Comparison of Combination Therapies in the Management of Hepatocellular Carcinoma: Transarterial Chemoembolization with Radiofrequency Ablation versus Microwave Ablation

Michael Ginsburg, MD, Sean P. Zivin, MD, Kristen Wroblewski, MS, Taral Doshi, MD, Raj J. Vasnani, MD, and Thuong G. Van Ha, MD

Caratteristiche dello studio

- Retrospettivo, monocentrico
- Child - Pugh A/B
- BCLC A/B/C
- Dimensioni 1,6 cm – 12,5 cm

89 Pazienti

38 TACE + RFA

51 TACE + MWA
Comparison of Combination Therapies in the Management of Hepatocellular Carcinoma: Transarterial Chemoembolization with Radiofrequency Ablation versus Microwave Ablation

Michael Ginsburg, MD, Sean P. Zivin, MD, Kristen Wroblewski, MS, Taral Doshi, MD, Raj J. Vasnani, MD, and Thuong G. Van Ha, MD
Used in isolation, there are hypothesized benefits to MW ablation, having demonstrated higher average intratumoral temperatures, larger ablation zones, and less susceptibility to the heat sink effect (17) compared with RF ablation. However, in this study, such theoretical technical advantages were not demonstrated in practice. It is possible that combination therapy lessens the advantage that MW ablation has over RF ablation on the heat sink effect because transcatheter arterial chemoembolization would mitigate such an advantage at least theoretically. Additionally, combination therapy with the two different ablative modalities had no significant differences in safety, with low complication rates for both groups.
Transcatheter Arterial Chemoembolization Plus Radiofrequency Ablation Therapy for Early Stage Hepatocellular Carcinoma

Comparison With Surgical Resection

Takeshi Kagawa, MD1, Jun Koizumi, MD2, Sei-ichiro Kojima, MD2, Nanuhiko Nagata, MD2, Makoto Numata, MD2, Norihiko Watanabe, MD2, Tetsu Watanabe, MD2, Tetsuya Mine, MD2, and the Tokai RFA Study Group

Radiofrequency Ablation Combined with Transcatheter Arterial Chemoembolization for the Treatment of Single Hepatocellular Carcinoma of 2 to 5 cm in Diameter: Comparison with Surgical Resection

Jin Woong Kim, MD1, Sang Soo Shin, MD1, Jae Kyu Kim, MD1, Sung Kyu Choi, MD1, Suk Hee Heo, MD1, Hye Soon Lim, MD1, Young Hye Hur, MD1, Chai Kyeon Che, MD1, Yong Yean Jeong, MD1, Hyeung Kwon Kang, MD1

Departments of Radiology and Surgery, Chonnam National University Hwasun Hospital, Yeosu, 547-701, Korea; Departments of Radiology, "The Goyang Graduate School of Biomedical Science, Goyang National University Medical School, Goyang, 543-751, Korea.

Early-Stage Hepatocellular Carcinoma: Radiofrequency Ablation Combined with Chemoembolization versus Hepatectomy

Koichiro Tamaike, MD
Rieko Tamaike, MD
Naoto Takahashi, MD
Hajime Yama, MD
Mitsunori Hori, MD
Horuiyuki Nakao, MD
Shinji Matsuda, MD
Kenji Sato, MD
Takeo Endo, MD
Kenji Sato, MD

Purpose: To retrospectively evaluate the long-term results of radiofrequency (RF) ablation combined with chemoembolization (CE) therapy as compared with hepatectomy for the treatment of early hepatocellular carcinoma (HCC).

Methods and Materials: This study was approved by the institutional review board, and informed consent was obtained. Patients with early-stage HCC were included if they underwent either combination therapy or hepatectomy and met the following inclusion criteria: no previous treatment for HCC, liver or liver tumors with a maximum diameter of 2 cm or less.
### Clinical outcome of small hepatocellular carcinoma after different treatments: A meta-analysis

**World Journal of Gastroenterology**

Wei Dong, Ting Zhang, Zhen-Guang Wang, Hui Liu

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95%CI)</th>
<th>% weight</th>
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<tbody>
<tr>
<td>Huang (2005)</td>
<td>0.55 (0.26, 1.15)</td>
<td>5.89</td>
</tr>
<tr>
<td>Cho (2007)</td>
<td>0.75 (0.49, 1.15)</td>
<td>14.97</td>
</tr>
<tr>
<td>Abu-Hilal (2008)</td>
<td>1.05 (0.48, 2.31)</td>
<td>3.74</td>
</tr>
<tr>
<td>Ueno (2009)</td>
<td>0.79 (0.55, 1.14)</td>
<td>19.86</td>
</tr>
<tr>
<td>Kagawa (2010)</td>
<td>0.84 (0.48, 1.49)</td>
<td>8.11</td>
</tr>
<tr>
<td>Huang (2010)</td>
<td>0.72 (0.48, 1.10)</td>
<td>16.32</td>
</tr>
<tr>
<td>Nishikawa (2011)</td>
<td>0.85 (0.55, 1.32)</td>
<td>13.33</td>
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<tr>
<td>Guo (2013)</td>
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<tr>
<td>Lai (2013)</td>
<td>1.18 (0.63, 2.19)</td>
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<tr>
<td>Overall ($I^2 = 0.0%, P = 0.910$)</td>
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<td>5.59</td>
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</tr>
<tr>
<td>Guo (2013)</td>
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</tr>
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**Interventional Radiologist under 40 Meeting**

*Interventional Oncology*

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COMBINATO vs HR

**THE CANCER JOURNAL**

Transcatheter Arterial Chemoembolization Plus Radiofrequency Ablation Therapy for Early Stage Hepatocellular Carcinoma

Comparison With Surgical Resection

Kagawa T, Cancer. 2010 Aug 1;116(15):3638-44.


Radiofrequency Ablation Combined with Transcatheter Arterial Chemoembolization for the Treatment of Single Hepatocellular Carcinoma of 2 to 5 cm in Diameter: Comparison with Surgical Resection

Korean Journal of Radiology

Interventional Radiologist under 40 Meeting

Interventional Oncology

Kagawa T, Cancer. 2010 Aug 1;116(15):3638-44.

Combination vs HR

Radiofrequency ablation combined with transarterial chemoembolization versus heptectomy for patients with hepatocellular carcinoma within Milan criteria: a retrospective case-control study

A. K. Bholee1,2 · K. Peng1,3 · Z. Zhou1,2 · J. Chen1,2 · L. Xu1,2 · Y. Zhang1,2 · M. Chen1,2

no significant difference was identified in either OS or DFS for patients with single tumor smaller than 3.0 cm, 3.0–5.0 cm, and multiple tumors. Multivariate analysis

Conclusion TACE + RFA is safe and as effective as heptectomy for patients with HCC within Milan criteria.
Criteri di inclusione

- 18 ≤ età ≤ 80, 200 pz
- No trattamenti pregressi per HCC
- Criteri di Milano
- Child - Pugh A/B
- Candidabile CH/RFA+TACE

Criteri di esclusione

- Metastasi
- Infiltrazione portale
- Controindicazioni a CH, RFA, TACE

There was no 30- or 90-day mortality after treatment in either group. The incidence of complications in the partial hepatectomy group was 23.0 per cent versus 11.0 per cent in the TACE + RFA group (P = 0.024). Complications
EARLY STAGE (NO RFA)

Early Stage Hepatocellular Carcinomas Not Feasible for Ultrasound-Guided Radiofrequency Ablation: Comparison of Transarterial Chemoembolization Alone and Combined Therapy with Transarterial Chemoembolization and Radiofrequency Ablation

Dongho Hyun¹ · Sung Ki Cho¹ · Sung Wook Shin¹ · Kwang Bo Park¹ · Hong Suk Park¹ · Sung Wook Choo¹ · Young Soo Do¹ · In-wook Choo¹ · Min Woo Lee¹ · Hyunchul Rhim¹ · Hyo Keun Lim¹
EARLY STAGE (NO RFA)

Lesioni complesse

Lesione sottodiaframmatica di 4,5 cm
EARLY STAGE (NO RFA)

Lesioni complesse

Lesione sottodiaframmatica di 4,5 cm
Radiofrequency ablation versus hepatic resection for the treatment of hepatocellular carcinomas 2 cm or smaller: a retrospective comparative study.

Peng ZW¹, Lin XJ, Zhang YJ, Liang HH, Guo RP, Shi M, Chen MS.

CONCLUSION: The efficacy and safety of percutaneous RF ablation were better than those of surgical resection in patients with HCC measuring 2 cm or smaller, especially those with central HCC.

## Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>1(S)</th>
<th>3</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACE - RFA</td>
<td>100</td>
<td>90</td>
<td>78</td>
</tr>
<tr>
<td>CHIRURGIA</td>
<td>96</td>
<td>96</td>
<td>83</td>
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## Disease free survival

<table>
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<th>5</th>
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</thead>
<tbody>
<tr>
<td>TACE - RFA</td>
<td>91</td>
<td>47</td>
<td>40</td>
</tr>
<tr>
<td>CHIRURGIA</td>
<td>89</td>
<td>68</td>
<td>28</td>
</tr>
</tbody>
</table>

No significatività!
Caratteristiche studio

- Retrospettivo
- 134 pz (TACE + RFA)
- BCLC grado C, PVTT (tipo I, II e III)
- Child - Pugh A/B

Risultati

<table>
<thead>
<tr>
<th></th>
<th>TACE + MWA</th>
</tr>
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<tbody>
<tr>
<td>1yr OS</td>
<td>63%</td>
</tr>
<tr>
<td>3yr OS</td>
<td>40%</td>
</tr>
<tr>
<td>5yr OS</td>
<td>23%</td>
</tr>
<tr>
<td>Median survival</td>
<td>29,5 mesi</td>
</tr>
</tbody>
</table>

Microwave ablation of hepatocellular carcinoma with portal vein tumor thrombosis after transarterial chemoembolization: a prospective study

Jiang Long¹ · Jia-sheng Zheng¹ · Bin Sun¹ · Ningning Lu¹

Caratteristiche studio

- Prospettico controllato
- 60 pz (TACE + MWA) vs 54 pz (TACE)
- BCLC grado C, PVTT (tipo I,II e III)
- Child - Pugh A/B

Risultati

<table>
<thead>
<tr>
<th></th>
<th>TACE + MWA</th>
<th>TACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1yr OS</td>
<td>48%</td>
<td>33%</td>
</tr>
<tr>
<td>3yr OS</td>
<td>23%</td>
<td>20%</td>
</tr>
<tr>
<td>Median survival</td>
<td>13,5</td>
<td>9,5</td>
</tr>
<tr>
<td>(mesi)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I trattamenti combinati sono un’arma importante nel trattamento dell’HCC, ma sono esclusi (o quasi) dalle linee guida delle più importanti società scientifiche e dal BCLC il quale non è attualmente sufficiente a garantire un corretto “incasellamento terapeutico”

Numerose Metanalisi recenti hanno confermato che i trattamenti combinati migliorano OS e RFS del Paziente con HCC di dimensioni tra 3 cm e 5 cm, rispetto alle monoterapie RFA e TACE, a parità di rischi procedurali

Nel paziente con tumore < 3cm il trattamento combinato TACE + RFA ha evidenziato risultati equiparabili a quelli della chirurgia in termini di OS e RFS mostrando inoltre maggiore sicurezza procedurale
CONCLUSIONI

- Nell’HCC > 5 cm entrambe TACE + RFA e TACE + MWA migliorano l’Overall Survival rispetto ai trattamenti singoli, significative differenze tra le due metodiche.

- Ruolo importante nel paziente complesso.

- Non ci sono indicazioni al trattamento combinato nel paziente very early.

- L’applicazione dei trattamenti combinati nel paziente advanced è oggi solo una prospettiva.
CONCLUSIO
NI

Come possiamo migliorare?

- Integrare alcuni dati importanti (es: Child-Pugh, Performance Status), nel tentativo di delineare nuove categorie del BCLC

- Aumentare il numero di lavori di confronto tra trattamenti combinati, con la chirurgia e con altri trattamenti

Necessità di studi randomizzati e/o multicentrici per dare maggiore “peso scientifico” alle evidenze già presenti ed identificare nuove “vie percorribili”
The dark side of the guidelines

GRAZIE!
Aumentare il tasso di pazienti candidabili a trattamenti curativi

Ridurre le indicazioni per i trattamenti palliativi

Espandere le indicazioni della RFA!
Radiofrequency ablation combined with percutaneous ethanol injection for hepatocellular carcinoma: a systematic review and meta-analysis

Zheng Li, Kai Zhang, Shu-Mei Lin, Deng-Hai Mi, Nong Cao, Zhi-Zhen Wen & Zhong-Xin Li

### Study and year | Region | Design | P/T | Treatment arms (n) | Aetiology: HBV/HCV (n) | No. of tumours (1>2) (%) | Main HCC mean size (cm) | Mean treatment sessions per tumour | Mean follow-up (months)
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Lor advisory el al. (1999) [20] | Italy | RCT | 66 (112) | RFA (42) | PEI (18) | 5/39 | 79/21 | 2.3 | 1.2 | 10
Lencioni et al. (2003) [21] | Italy | RCT | 102 (142) | RFA (52) | PEI (50) | 6/22 | 77/23 | 2.5 | 4.8 | 10
Lin et al. (2004) [22] | Taiwan, China | RCT | 157 (186) | RFA (52) | PEI (50) | 79/20 | 62/38 | 2.8 | 5.4 | 22.4
Lin et al. (2005) [23] | Taiwan, China | RCT | 124 (154) | RFA (62) | PEI (62) | 42/10 | 79/21 | 2.3 | 1.3 | 28
Brunello et al. (2004) [25] | Italy | RCT | 139 (177) | RFA (70) | PEI (69) | 64/44 | 77/23 | 2.1 | NR | 23.1
Gorgio et al. (2011) [26] | Italy | RCT | 271 (271) | RFA (128) | PEI (143) | 61/87 | 100/0 | 2.0 | 5.2 | 22
Azab et al. (2011) [27] | Egypt | RCT | 90 (98) | RFA (30) | PEI (30) | NR | NR | NR | 1.5 | 18
Shankar et al. (2004) [28] | America | CCT | 55 (58) | RFA (10) | PEI (10) | NR | NR | NR | 7.7 | 18
Kurokohchi et al. (2003) [29] | Japan | CCT | 75 (NR) | RFA (15) | PEI (15) | NR | NR | NR | 1.1 | 18
Zhang et al. (2007) [30] | China | RCT | 133 (210) | RFA (61) | PEI (61) | 65/0 | 67/13 | NR | 3.0 | NR
Wong et al. (2008) [31] | Taiwan, China | CCT | 142 (208) | RFA (154) | PEI (154) | 64/16 | NR | NR | NR | 9.8
Chae et al. (2013) [32] | Korea | CCS | 20 (20) | RFA (12) | PEI (12) | NR | NR | NR | 2.8 | NR

**RFA + PEI > RFA (PEI)**
1, 1.5, 2, 3 Qo
Local recurrence

**Febbre**

R: randomised controlled trial; CCT: controlled clinical trial; CCS: case control study; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; HCC: hepatocellular carcinoma; P: patient; T: tumour; HBV: hepatitis B virus; HCV: hepatitis C virus; NR: not reported in the text.

*Numbers of tumours instead of the number of patients because this trial divided groups by the tumour characteristics.*