The dark side of the guidelines

2nd Interventional Radiologist under 40 Meeting

Interventional Oncology

8-10 Maggio 2017

Bologna

Società Medica Chirurgica - Palazzo dell'Archiginnasio

FEGATO OLTRE HCC

Trattamenti combinati: quando e come

Sistema Socio Sanitario
Regione Lombardia
ASST Rhodense

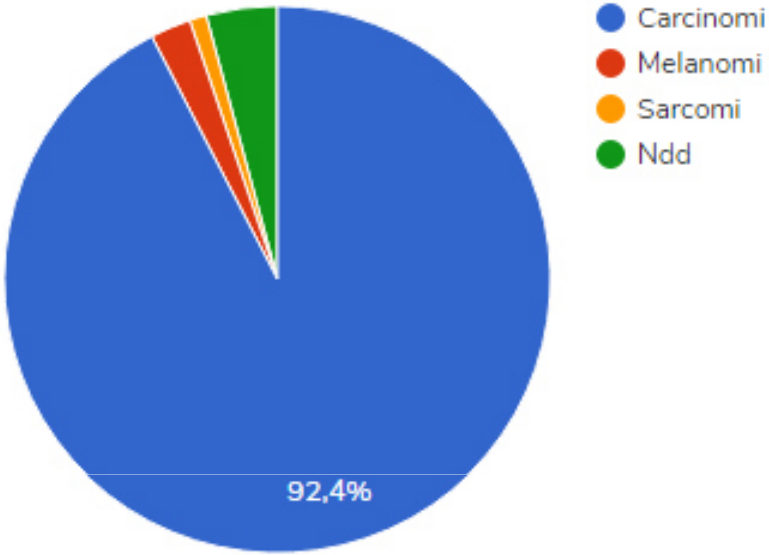
Ianniello A

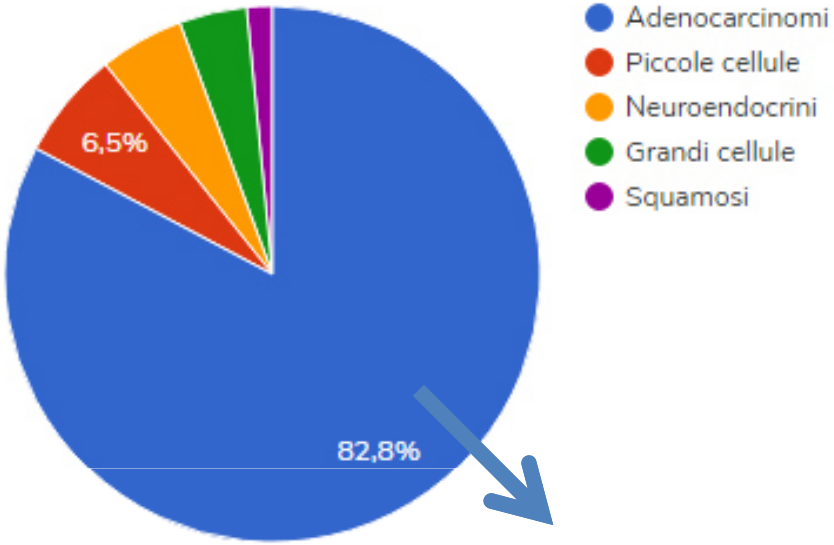
UO di Radiologia

Diagnostica ed Interventistica

Sistema Socio Sanitario
Regione Lombardia
ASST Rhodense

I tumori secondari al fegato rappresentano il 95% di tutti i tumori epatici maligni





46.1% COLON-RETTO

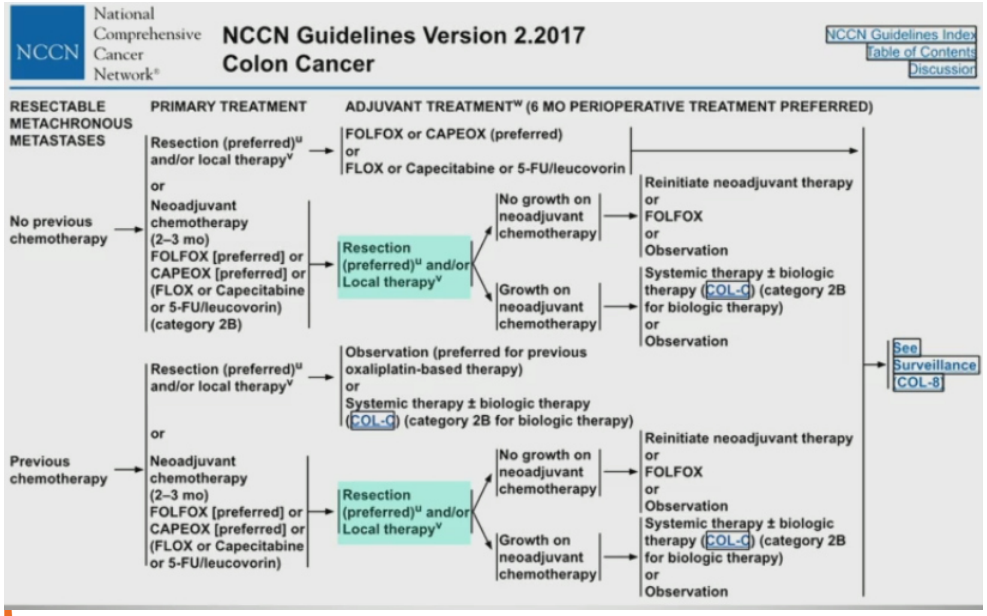
Il 32-73% dei Pazienti affetti da carcinoma del colon-retto svilupperà metastasi epatiche

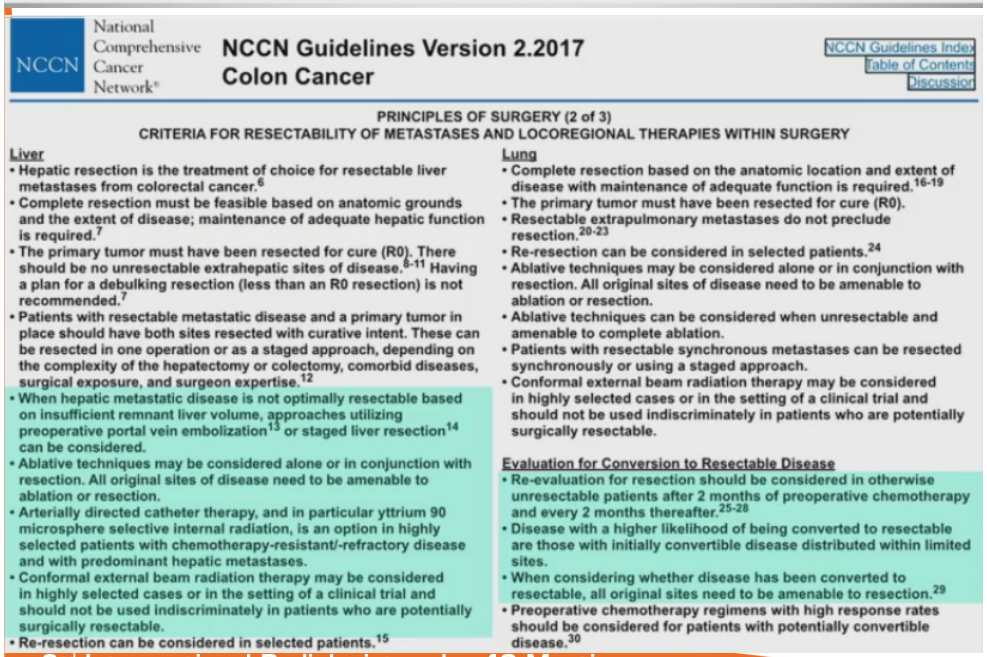
La resezione chirurgica (trattamento di scelta) è applicabile solo nel 25%

Ananthakrishnan Aet al. Epidemiology of primary and secondary liver cancers. Semin Intervent Radiol. 2006;23(1):47-63
Ridder J, et al Incidence and origin of histologically confirmed liver metastases: an explorative case-study of 23,154 patients. Oncotarget 2016;7.
Hugen N, et al. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. Ann Oncol. 2014;25:651–657

Metastasi epatiche da carcinoma colon-rettale

The dark side of the guidelines



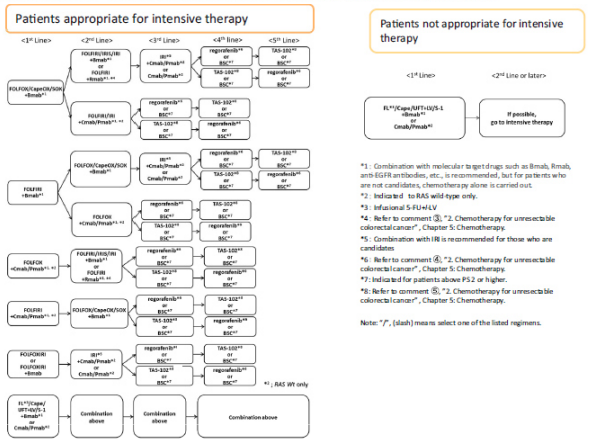


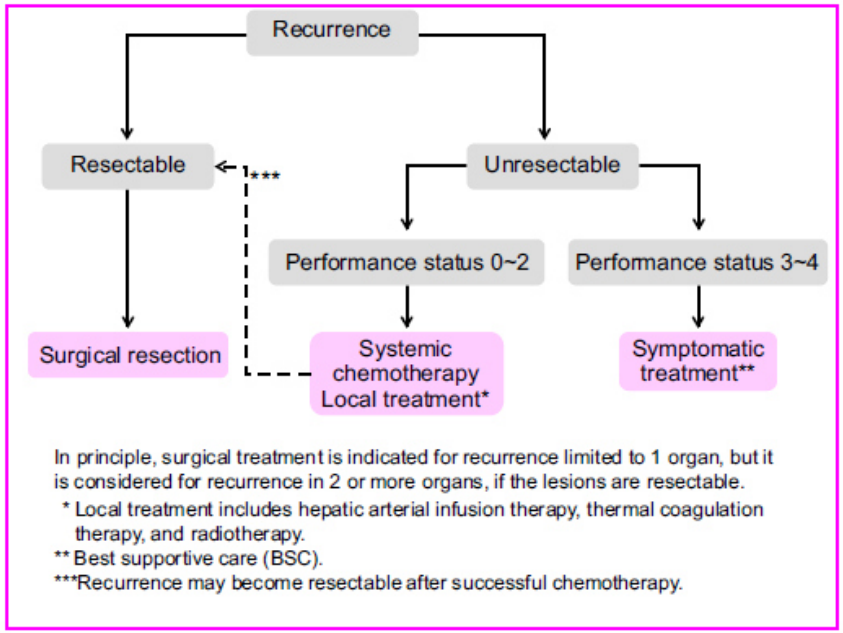
Int J Clin Oncol
DOI 10.1007/s10147-017-1101-6

CrossMark

ORIGINAL ARTICLE

Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer





Metastasi epatiche da carcinoma colon-rettale

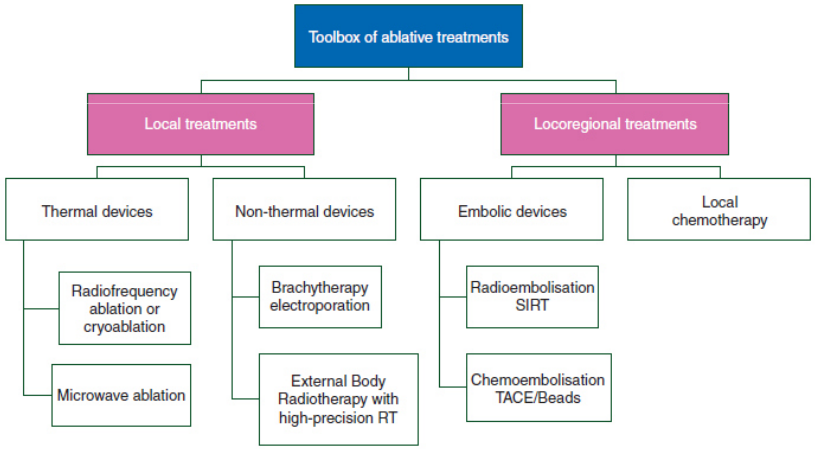
The dark side of the guidelines

special articles

Annals of Oncology

Annals of Oncology 27: 1386–1422, 2016
doi:10.1093/annonc/mdw235
Published online 5 July 2016

ESMO consensus guidelines for the management of patients with metastatic colorectal cancer



Aiom
Associazione Italiana di Oncologia Medica

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
B	In pazienti con malattia epatica limitata non suscettibili di chirurgia e che presentino le condizioni atte a garantire un completo trattamento delle lesioni, puo'essere considerata una conbinazione di terapia sistemica e radiofrequenza. (3)	Positiva debole
D*	In pazienti con malattia epatica limitata non suscettibili di chirurgia e che presentino le condizioni atte a garantire un completo trattamento delle lesioni, possono essere consideratele tecniche ablative (radiofrequenze, microonde, crioablazione) e la radioterapia esterna con metodiche conformazionali.	Positiva debole
D*	La radioembolizzazione intraepatica in combinazione alla chemioterapia sistemica può consentire un miglior controllo della malattia epatica	Positiva debole
D*	La chemioterapia intrarteriosa e la chemioembolizzazione (anche con DEBIRI) può rappresentare un opzione solo per i pazienti non candidabili ai trattamenti medici sistemici oggi convenzionalmente impiegati in I, II e III linea.	Negativa debole

*Opinione del panel

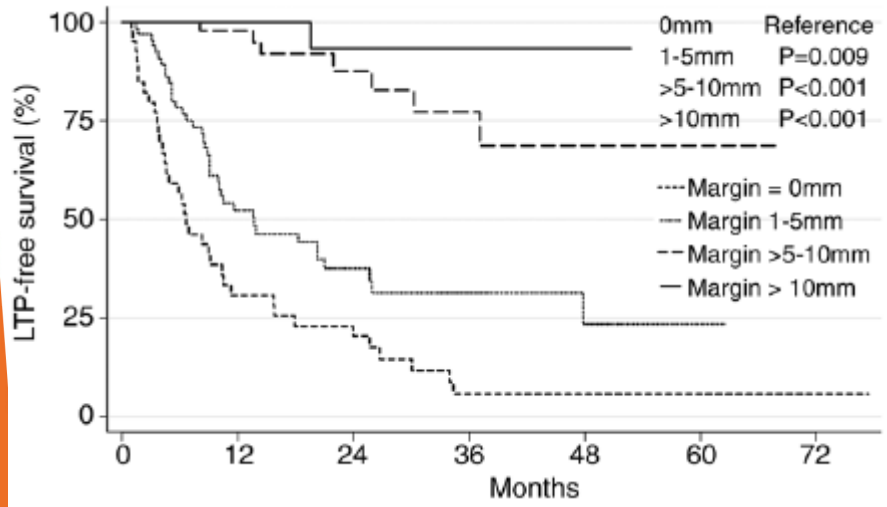
Metastasi epatiche da carcinoma colon-rettale

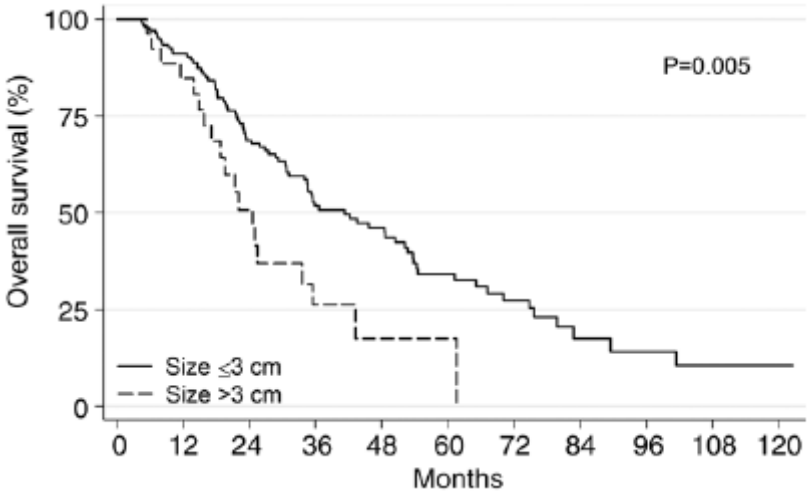
Limiti RFA:

- Diametro della lesione
- Heat-sink effect (dispersione del calore se lesione prossima vasi sanguigni con Ø > 3mm)
- Aumento impedenza per formazione di vapore acqueo, carbonizzazione

Percutaneous Radiofrequency Ablation of Colorectal Cancer Liver Metastases: Factors Affecting Outcomes—A 10-year Experience at a Single Center[1]

Margini	Recidiva Locale
0	90%
< 5 mm	60%
5-10 mm	15%
> 10 mm	5%





Metastasi epatiche da carcinoma colon-rettale

Limiti RFA:

Eur Radiol (2015) 25:3438–3454
DOI 10.1007/s00330-015-3779-z

INTERVENTIONAL

Thermal ablation of colorectal liver metastases: a position paper by an international panel of ablation experts, the interventional oncology sans frontières meeting 2013

Table 4 Summary of recommendations. Tumour and technical considerations

Parameter	Preferred
Tumour size	<3 cm
Tumour number	1–3 optimal, <5 preferable
Tumour location next to major bile ducts	Avoid
Tumours located in contact with blood vessels	Suitable for ablation with careful follow-up and repeat treatment if necessary
Tumours located within 1 cm of vulnerable structures, e.g. colon	Require displacement from the ablation zone using adjunctive measures, e.g. percutaneous hydro- or gas-dissection
Extra-hepatic disease (EHD)	Suitable for liver ablation as long as all sites of EHD disease are radically treated
Local recurrence should be minimised by:	1. Achieving >1 cm ablation margins in 3D 2. Maximising operator experience 3. GA should be available as required 4. Optimal definition of the tumour 5. Optimal intra-procedural assessment of the ablation zone

Cardiovasc Intervent Radiol (2010) 33:11–17
DOI 10.1007/s00270-009-9736-y

CIRSE GUIDELINES

Quality Improvement Guidelines for Radiofrequency Ablation of Liver Tumours

Laura Crocetti · Thierry de Baere · Riccardo Lencioni

The target tumour should not exceed 3 cm at its longest axis to achieve best rates of complete ablation using most of the currently available devices.

Thermal ablation of lesions adjacent to hepatic vessels is possible because flowing blood usually protects the vascular wall from thermal injury. In this case, however, the risk of incomplete treatment of the neoplastic tissue close to the vessel may increase due to heat loss by convection.

Metastasi epatiche da carcinoma colon-rettale

MWA:

Percutaneous Tumor Ablation Tools: Microwave, Radiofrequency, or Cryoablation—What Should You Use and Why?[1]

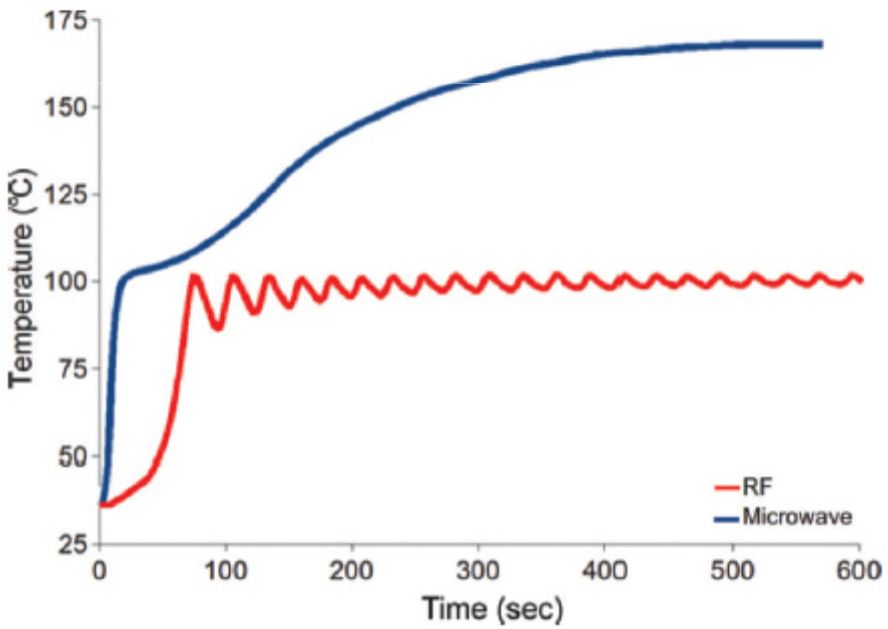
J. Louis Hinshaw, MD
Meghan G. Lubner, MD
Timothy J. Ziemlewicz, MD
Fred T. Lee, Jr, MD
Christopher L. Brace, PhD

Abbreviations: HCC = hepatocellular carcinoma, RCC = renal cell carcinoma, RF = radiofrequency

RadioGraphics 2014; 35:1344–1362

Published online 10.1148/rg.345140054

Content Codes: CT IR OI



the applicator (23). As a result, microwave energy can produce faster, hotter, and larger ablation zones in multiple tissue types compared with RF current (Fig 1). The clinical result is that, on average, fewer applicators are needed, and ablative margins are easier to obtain.

Metastasi epatiche da carcinoma colon-rettale

MWA:

Microwave Ablation for Hepatic Malignancies

A Multiinstitutional Analysis

Ryan T. Groeschl, MD, Charles H. C. Pilgrim, MBBS (Hons), PhD,* Erin M. Hanna, MD,† Kerri A. Simo, MD,† Ryan Z. Swan, MD,† David Sindram, MD, PhD,† John B. Martinie, MD,† David A. Iannitti, MD,† Mark Bloomston, MD,‡ Carl Schmidt, MD,‡ Hooman Khabiri, MD,§ Lawrence A. Shirley, MD,‡ Robert C. G. Martin, MD, PhD,¶ Susan Tsai, MD, MHS,* Kiran K. Turaga, MD, MPH,* Kathleen K. Christians, MD,* William S. Rilling, MD,‖ and T. Clark Gamblin, MD, MS**

Annals of Surgery • Volume 259, Number 6, June 2014

TABLE 3. Factors Associated With Recurrence-Free Survival

	Univariate Analysis		Multivariable Analysis	
Factor	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Age	1.00 (0.99–1.01)	0.843	—	—
Male	1.06 (0.82–1.36)	0.647	—	—
Synchronous	0.68 (0.50–0.92)	0.011	0.77 (0.54–1.09)	0.142
Approach	—	0.002	—	0.927
Open (referent)	1.00		1.00	
Laparoscopic	1.26 (0.96–1.65)	0.090	1.04 (0.66–1.62)	0.879
Percutaneous	2.12 (1.42–3.18)	<0.001	0.95 (0.54–1.57)	0.761
Number of tumors ablated	0.98 (0.94–1.02)	0.309	1.04 (0.93–1.17)	0.489
No. probe applications	0.97 (0.92–1.01)	0.144	—	—
Cumulative ablation time	1.00 (0.99–1.00)	0.129	—	—
Neoadjuvant chemotherapy	1.31 (1.02–1.67)	0.032	1.45 (0.96–2.19)	0.079
Adjuvant chemotherapy	1.16 (0.90–1.50)	0.247	—	—
Concomitant hepatectomy	1.01 (0.73–1.40)	0.797	—	—
Extrahepatic disease	0.90 (0.58–1.39)	0.629	—	—
Histology	—	0.250	—	0.866
HCC (referent)	1.00		1.00	
CLM	1.01 (0.74–1.38)	0.942	0.90 (0.35–2.31)	0.828
NLM	0.70 (0.45–1.07)	0.103	0.74 (0.27–2.03)	0.553
Other	1.00 (0.67–1.49)	0.993	0.78 (0.28–2.22)	0.647
Tumor size, ≥3 cm	1.53 (1.05–2.24)	0.026	1.60 (1.02–2.50)	0.039

Lesioni con con Ø > 3cm: maggior propensione alla recidiva locale

Microwave ablation of liver metastases from colorectal cancer: an Italian multicenter study (Presentato a CIRSE 2014)

G. Poggi, L. Solbiati, M. F. Meloni, M. Bezzi, B. Montagna, D. Gasparini, L. Carata, F. Antonella, C. Gazzera, R. F. Grasso, C. Mezzolla, A. Noto, S. Sartori, F. Stacul

Size		N° lesions	CR, n (%)	PR, n (%)
≤ 2 cm	a	91	89 (97,5%)	2 (2,5%)
> 2 ≤ 3 cm	b	107	99 (92.5%)	8 (7,5 %)
>3 ≤ 4 cm	c	67	60 (89.5%)	7 (10.5%)
> 4 ≤ 5 cm	d	27	16 (61%)	11 (39%)
> 5 cm	e	19	9 (47%)	10 (53%)

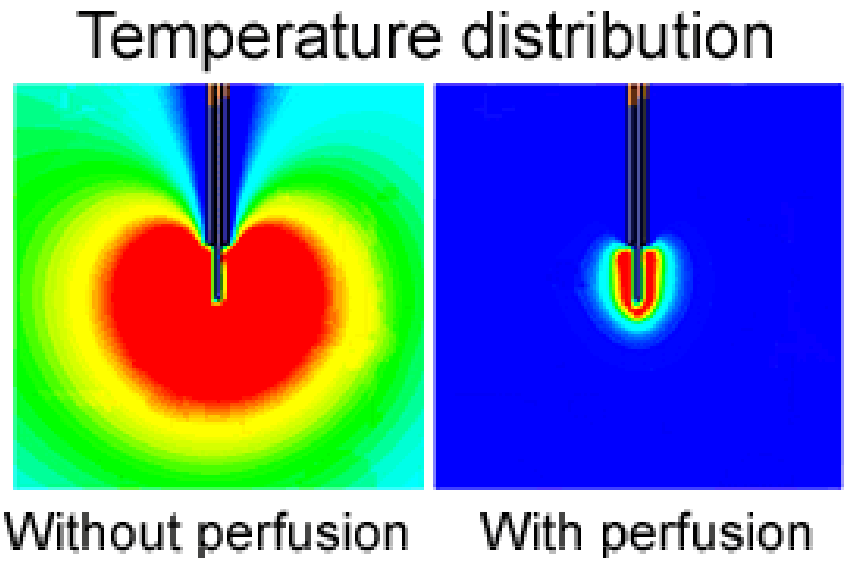
Come aumentare l'area di necrosi coagulativa?

Bioheat transfer equation:

$$\rho c(\partial T/\partial t) = \nabla \cdot k_i \nabla T + Q_2$$

P: densità tissutale (Kg/m^3)
c: calore specifico (J/kg·K)
K: conduttività termica (W/m·K)
Q_2: heat sink

Necrosi coagulativa:
- direttamente proporzionale alla densità della corrente
- inversamente proporzionale al flusso sanguigno



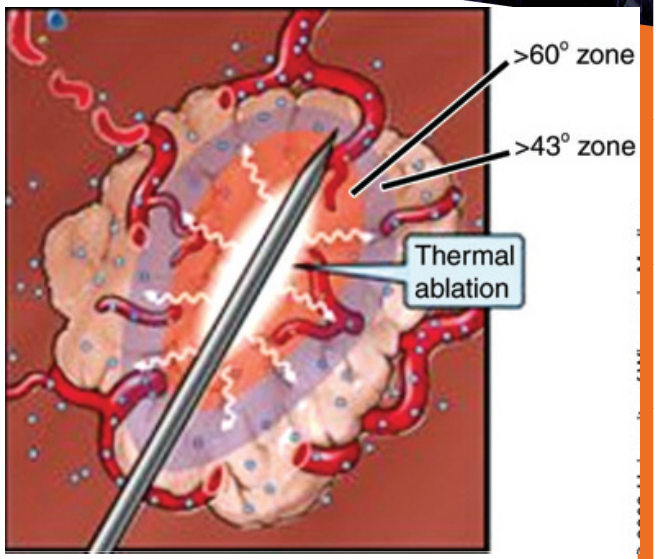
Trattamenti combinati

	Meccanismo di Azione	Raggio di Azione
RFA/MWA	Necrosi Coagulativa	Locale
TACE/TAE	Ischemia-anossia Chemio-tossicità	Regionale

Goldberg SN. Radiofrequency tumor ablation: principles and techniques. Eur J Ultrasound. 2001 Jun;13(2):129-47.
Rhim H, et al. Essential techniques for successful radio-frequency thermal ablation of malignant hepatic tumors. Radiographics. 2001;21:S17-35.

Trattamenti combinati:

1. TACE/TAE prima di RFA/MWA (90% di casi)



- Riduzione del cooling effect per occlusione vasi sanguigni afferenti la lesione con incremento area di necrosi[1]

- Margini di sicurezza più ampi con ablazione dei noduli satelliti[1]

- Minor espressione di VEGF nel tessuto peri-tumorale[2]

- Modificazioni edematose (ritenzione idrica) nel tumore e nella zona circostante indotte dall'ischemia e dall' infiammazione post-TACE amplia l'area di ablazione (le microonde agiscono principalmente sulle componenti acquose - molecole H_2O) [3]

- *Agente chemioterapico reso inefficace dal calore prodotto*[1]

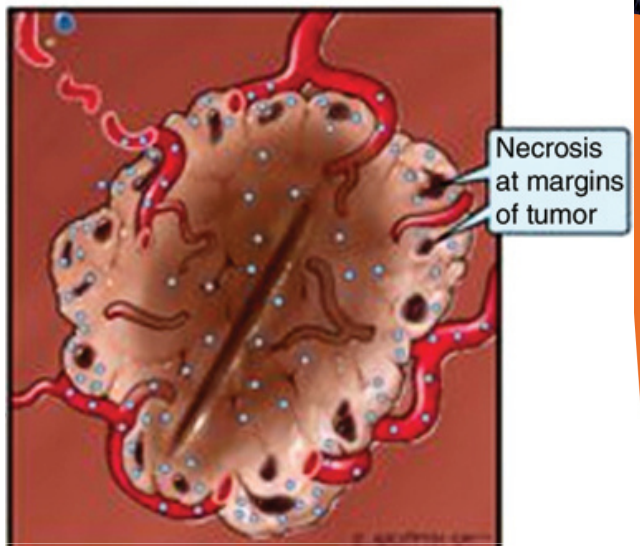
[1] Iezzi R, et al. Combined locoregional treatment of patients with hepatocellular carcinoma: State of the art. World J Gastroenterol. 2016. 14;22(6):1935-42.

[2] Vogl TJ, et al. Study on the effect of chemoembolization combined with microwave ablation for the treatment of hepatocellular carcinoma in rats. Diagn Interv Radiol. 2017;23(2):150-155.

[3] Seki T, et al. Combination therapy with transcatheter arterial chemoembolization and percutaneous microwave coagulation therapy for hepatocellular carcinoma. Cancer. 2000 15;89(6):1245-51.

Trattamenti combinati:

2. RFA/MWA prima di TACE/TAE



- Agente chemioterapico viene concentrato in un minor volume residuo tumorale (area centrale necrotica per ablazione) [1]

- L'ablazione riduce la resistenza cellulare nella zona di "sublethal heating" potenziando l'effetto dell'agente chemioterapico[1]

- L'iperemia prodotta dall'ablazione facilita la diffusione dell'agente chemioterapico[1]

- Effetto della TACE/TAE su nodulazioni satelliti, non ablate[1]

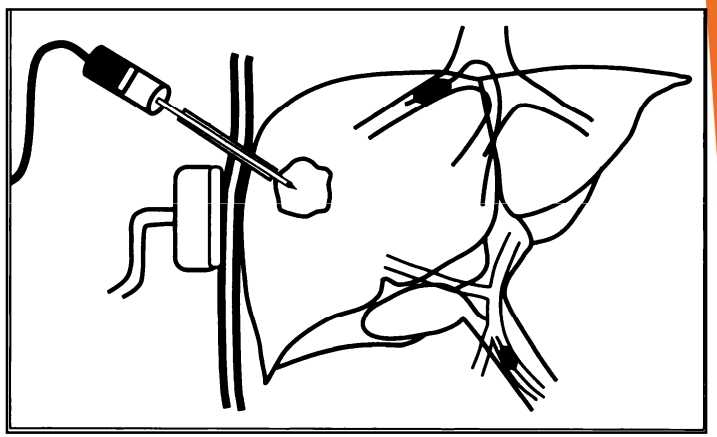
[1] Iezzi R, et al. Combined locoregional treatment of patients with hepatocellular carcinoma: State of the art. World J Gastroenterol. 2016. 14;22(6):1935-42.
Ahmed M, et al. Principles of and advances in percutaneous ablation. Radiology. 2011;258(2).

Trattamenti combinati:

3. OCCLUSIONE TEMPORANEA ARTERIA EPATICA DURANTE RFA quindi TACE

- Combina i vantaggi delle due diverse tecniche[1]

4. RFA/MWA DURANTE OCCLUSIONE TEMPORANEA VENOSA/ARTERIOSA



- Riduzione del cooling effect per occlusione vasi sanguigni afferenti la lesione con incremento area di necrosi[2]

- L'occlusione venosa acuta, producendo stasi ed iperidratazione tissutale, ridurrebbe impedenza aumentando area di necrosi[2,3]

[1] Iezzi R, et al. Single-step multimodal locoregional treatment for unresectable hepatocellular carcinoma: balloon-occluded percutaneous radiofrequency thermal ablation (BO-RFA) plus transcatheter arterial chemoembolization (TACE). Radiol Med 2013 ;118(4):555-69

[2]de Baere TPercutaneous radiofrequency ablation of hepatic tumors during temporary venousocclusion. AJR Am J Roentgenol. 2002;178(1):53-9.

[3]Murakami T. Percutaneous microwave hepatic tumor coagulation with segmental hepatic blood flow occlusion in seven patients. AJR Am J Roentgenol. 1999 Mar;172(3):637-40.

Trattamenti combinati:

A. TRATTAMENTO "SINGLE STEP"

- Maggior effetto sinergico di RFA/MWA e TACE/TAE
- Tempi di ospedalizzazione ridotti, minor disconfort per il Paziente, costi ridotti
- Ottimale gestione di eventuali sanguinamenti

B. TRATTAMENTO SEQUENZIALE (1-30 gg)

- Minor rischio di insufficienza epatica
- Completamento di un singolo trattamento inefficace

[1] Iezzi R, et al. Combined locoregional treatment of patients with hepatocellular carcinoma: State of the art. World J Gastroenterol. 2016. 14;22(6):1935-42.

[2] Takuma Y, et al.Comparison of combined transcatheter arterial chemoembolization and radiofrequency ablation with surgical resection by using propensity score matching in patients with hepatocellular carcinoma within Milan criteria. Radiology 2013;269(3):927–937.

Revisione Letteratura [1, 2, 3]:

Studio	N° Pz N° les	Ø medio Range (mm)	Tecnica	TACE/TAE/ TARE	Complete Response	Hepatic progression free survival	Sopravvivenza
Bloomston Am Surg 2002	37 22 HCC 15 mCRC		9 TACE 6 RFA + TACE	Cisplatino 100 mg Doxorubicina 50mg Mitomicina 10 mg Lipiodol Microsfere (250 µm)	1/9 (11%): TACE 4/6 (67%): RF + TACE		66%: 1 anno 100% : 1 anno
Bonomo CVIR 2012	30 36	33 16-59	TAE + RFA	Microsfere (100 µm)	97.2%	71%: 1 anno 50%: 2 anni	79%: 1 anno 60%: 2 anni
Fong Am Surg 2012	32 ??	44 17-79	14 TACE/TARE + Ablazione* (6 sett) 18 ablazione* + TACE/TARE	Cisplatino 50 mg Adrimicina 50mg Mitomicina 10 mg Lipiodol	??	??	75%: 2 anni 10.1%:5 anni
Wu OncoThargTher 2015	30 43	44 14-100	MWA + TACE	Oxaliplatino 50-100 mg Epirubicina 10-50 mg Lipiodol (Microsfere)	81.4%		46.7%: 1 anno 25.4%: 2 anni
Yamakodo CVIR 2017	25 38	2.2 10-42	TACE + RFA	Microfere degradabili + Mitomicina 2-6 mg	100%	76%: 1 anno 63.3%: 2 anni 33.7%: 3 anni	100%: 1 anno 88%: 2 anni 81.7%: 3 anni 71.5%: 4 anni

* ABLAZIONE: RFA, MWA, CRYOA

Revisione Letteratura [4]:

The dark side of the guidelines

Studio	N° Pz/Les	Ø medio Range (mm)	Vicinanza vasi sanguigni Ø > 5 mm	Tecnica Occlusione	Complete Response	Hepatic progression free survival	Sopravvivenza
Murakami AJR 1999	7 MTS	22.5 15-35	/	Arteria Vena	100%	/	/
deBaere AJR 2002	2 HCC 8 mCRC	35 14-49	5 (Ø vasi > 5 mm)	8 vene epatiche 2 porta	100%	50%	50%: 12-18 mesi anno
Sudheendra CVIR 2006	2 HCC 6 mCRC	44 24-65	5	Vene epatiche	62%%		62%: Medio 1 anni (3-38 mesi)

Hepatic Malignancies: Percutaneous Radiofrequency Ablation during Percutaneous Portal or Hepatic Vein Occlusion[1] *Radiology:* Volume 248: Number 3—September 2008

Gruppo I: 18 lesioni con Ø > 35 mm distanti da vasi sanguigni

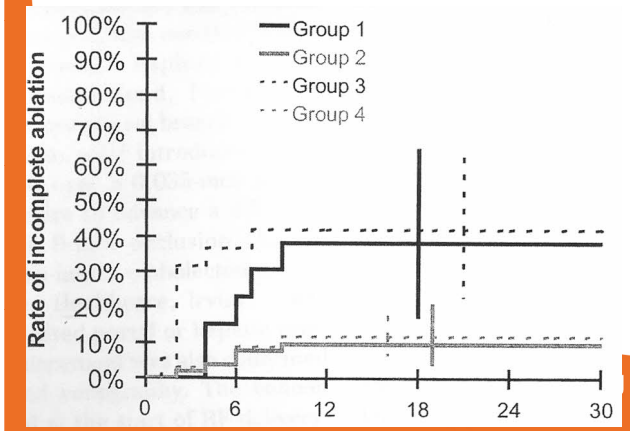
Gruppo II: 58 lesioni con Ø ≤ 35 mm adiacenti a vasi sanguigni

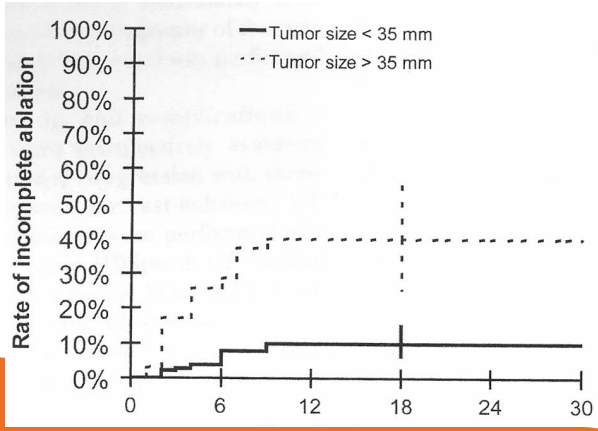
Gruppo III: 20 lesioni con Ø > 35 mm adiacenti a vasi sanguigni

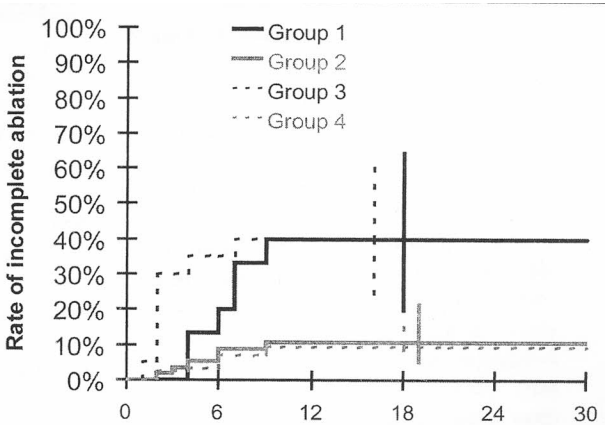
Gruppo IV: 137 lesioni Ø ≤ 35 mm distanti da vasi sanguigni

Gruppo I, II, III (80 Mts+ 19 HCC) → Occlusione vena porta/vene epatiche + RFA

Gruppo IV (119 Mts + 18 HCC) → RFA







Revisione Letteratura [4]:

The dark side of the guidelines

Studio	N° Pz/Les	Ø medio Range (mm)	Vicinanza vasi sanguigni Ø > 5 mm	Tecnica Occlusione	Complete Response	Hepatic progression free survival	Sopravvivenza
Murakami AJR 1999	7 MTS	22.5 15-35	/	Arteria Vena	100%	/	/
deBaere AJR 2002	2 HCC 8 mCRC	35 14-49	5 (Ø vasi > 5 mm)	8 vene epatiche 2 porta	100%	50%	50%: 12-18 mesi anno
Sudheendra CVIR 2006	2 HCC 6 mCRC	44 24-65	5	Vene epatiche	62%%		62%: Medio 1 anni (3-38 mesi)

Hepatic Malignancies: Percutaneous Radiofrequency Ablation during Percutaneous Portal or Hepatic Vein Occlusion[1] *Radiology:* Volume 248: Number 3—September 2008

Gruppo I: 18 lesioni con Ø > 35 mm distanti da vasi sanguigni

Gruppo II: 58 lesioni con Ø ≤ 35 mm adiacenti a vasi sanguigni

Gruppo III: 20 lesioni con Ø > 35 mm adiacenti a vasi sanguigni

Gruppo IV: 137 lesioni Ø ≤ 35 mm distanti da vasi sanguigni

CONCLUSIONI:

Lesioni Ø < 35 mm adiacenti a vasi sanguigni con Ø > 4 mm
Occlusione vena porta/vene epatiche + RFA: minor tasso di progressione locale

Lesioni Ø > 35 mm
Occlusione vena porta/vene epatiche + RFA: non migliora outcome

J Vasc Interv Radiol 2008; 19:1740–1748

Optimal Strategies for Combining Transcatheter Arterial Chemoembolization and Radiofrequency Ablation in Rabbit VX2 Hepatic Tumors

Elian M. Mostafa, MD, Suvranu Ganguli, MD, Salomao Faintuch, MD, Pawel Mertyna, MD, PhD, and S. Nahum Goldberg, MD

Diameters and Volumes of Infarcted Zones

Treatment Group	Long Axis (cm)	Short Axis (cm)	Total Treated Area (cm^2)	Infarction Volume (cm^3)
Chemoembolization, then RF	4.9 ± 0.5	3.7 ± 0.4	33.4 ± 9.4	11.4 ± 2.3
RF, then chemoembolization	4.2 ± 0.6	3.4 ± 0.5	25.0 ± 9.6	11.9 ± 6.4
Bland embolization, then RF	3.8 ± 1.0	3.7 ± 0.5	27.8 ± 14.5	17.4 ± 11.0
RF alone	—	—	—	—
Chemoembolization alone	3.0 ± 0.4	2.8 ± 0.4	12.1 ± 4.6	12.1 ± 4.6

1. **Maggior distruzione tumorale se TACE + RFA**
2. **Importanza agente chemioterapico anche dopo RFA**

Cardiovasc Intervent Radiol (2013) 36:773–782
DOI 10.1007/s00270-012-0497-7

LABORATORY INVESTIGATION

Superselective Particle Embolization Enhances Efficacy of Radiofrequency Ablation: Effects of Particle Size and Sequence of Action

Toshihiro Tanaka · Peter Isfort · Till Braunschweig · Saskia Westphal · Anna Woitok · Tobias Penzkofer · Philipp Bruners · Kimihiko Kichikawa · Thomas Schmitz-Rode · Andreas H. Mahnken

Table 2 Comparison of short-axis diameter, and volume and marginal rim of ablation zone on day 28

Group	Ablation short-axis diameter (cm)	Ablation volume (cm^3)	Marginal rim (cm)
40 µm TAE + RFA	1.70 ± 0.26	3.23 ± 0.89	0.13 ± 0.05
RFA + 40 µm TAE	1.59 ± 0.73	2.71 ± 1.40	0.23 ± 005
250 µm TAE + RFA	1.53 ± 0.17	2.68 ± 1.48	0.18 ± 0.05
RFA + 250 µm TAE	1.49 ± 0.88	2.37 ± 1.18	0.15 ± 0.06
RFA	1.56 ± 0.40	2.82 ± 0.46	0.16 ± 0.06

FEGATO OLTRE HCC

Trattamenti combinati:quando e come

1. Non esistono chiare linee guida inerenti il ricorso a trattamenti combinati

2. Quando?

   Se lesioni > 4 cm in diametro (risultati promettenti con MWA[1])

3. Come?

   TACE con micro-sfere + RFA

[1]Microwave ablation of liver **metastases** to overcome the limitations of radiofrequency ablation.Ierardi AM, et al. Radiol Med. 2013 Sep;118(6):949-61.