TERAPIA MULTIMODALE
del
Carcinoma Epatocellulare su Cirrosi

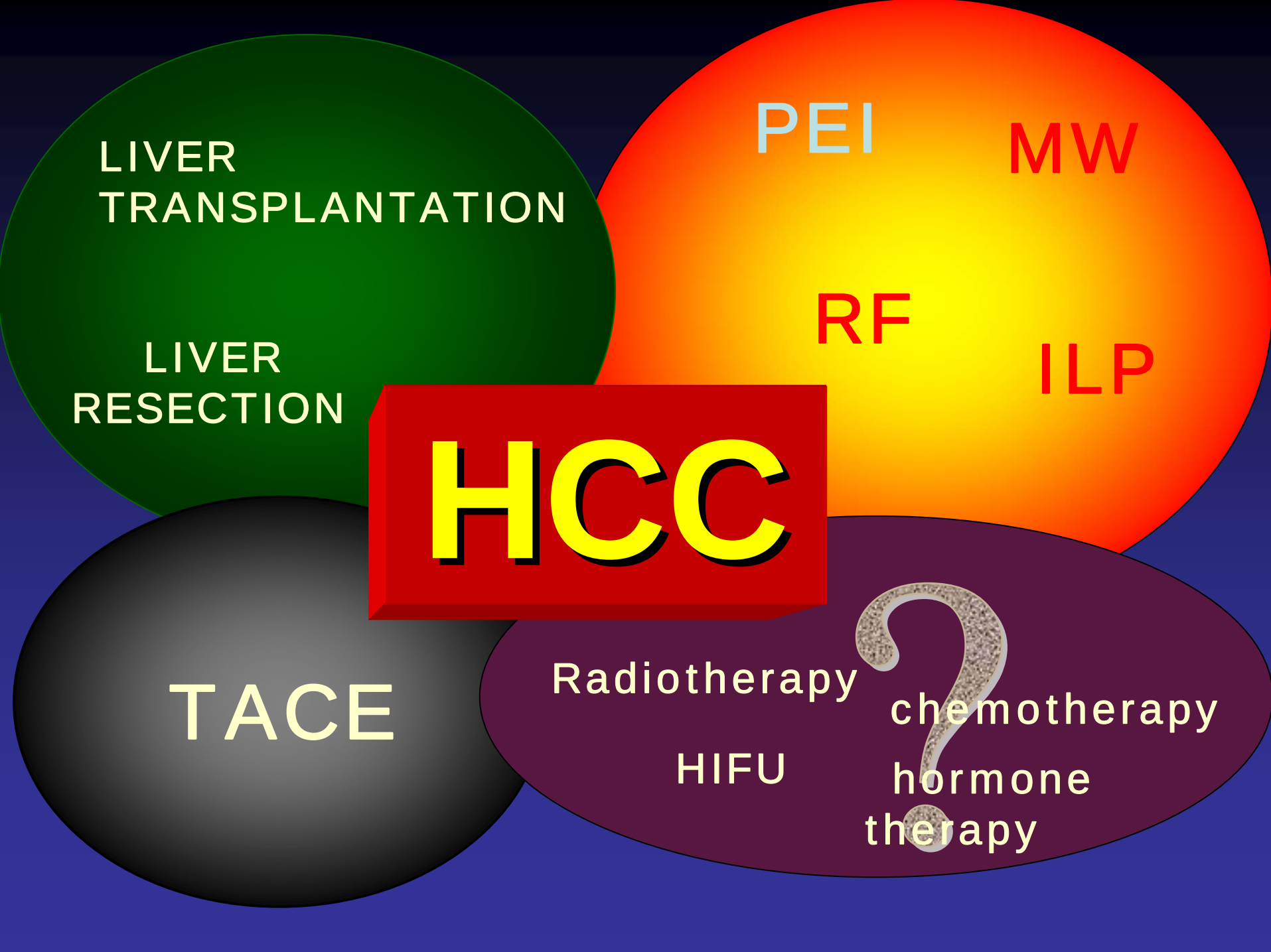
A.Giorgio

DIRETTORE IX DIVISIONE di MALATTIE INFETTIVE

ad INDIRIZZO ECOINTERVENTISTICO

AZIENDA OSPEDALIERA D.COTUGNO

NAPOLI


LIVER TRANSPLANTATION
LIVER RESECTION
PEI
MW
RF
ILP
HCC
TACE
Radiotherapy
chemotherapy
HIFU
hormone therapy
?

Sopravvivenza del paziente con cirrosi e HCC non trattato

Anni	1	3	5
• Tang			
Cancer 1989	66%	10%	0%
• Ebara			
Gastroenterology 1986	90%	12%	-
• Livraghi			
J Hepatol 1995	86%	26%	11%
• Llovet			
Hepatology 1999	80%	65%	50%

LIVER TRANSPLANTATION

LIVER RESECTION

-FEASIBILITY

-SINGLE NODULE

-UP TO 3 NODULES WITH MAXIMUM DIAMETER = 3 CM

-YOUNG PATIENTS

-CHILD A CLASS

SCREENING E TERAPIA CHIRURGICA

- Screening : US , AFP, es.lab. ogni 6 mesi
- Follow-up medio 33 mesi :
  38 (11,7%)nuovi HCC
  (31 mononodulari)
- Solo 22 (58%) resecabili o trapiantabili
- A 12 mesi 13 casi di recidiva
- A 12 mesi solo 9/38 (23%) erano liberi da malattia

Livraghi et. al. J Hepatol 1995

HCC

- MULTIFOCALITY
- INTRAHEPATIC RECURRENCES
- PORTAL VESSELS INFILTRATION
- CIRRHOSIS
- COAGULATIVE DISORDERS

MINIMALLY INVASIVE EFFECTIVE AND REPEATABLE THERAPY

ELSEVIER

Journal of Hepatology

Journal of Hepatology 35 (2001) 421–430

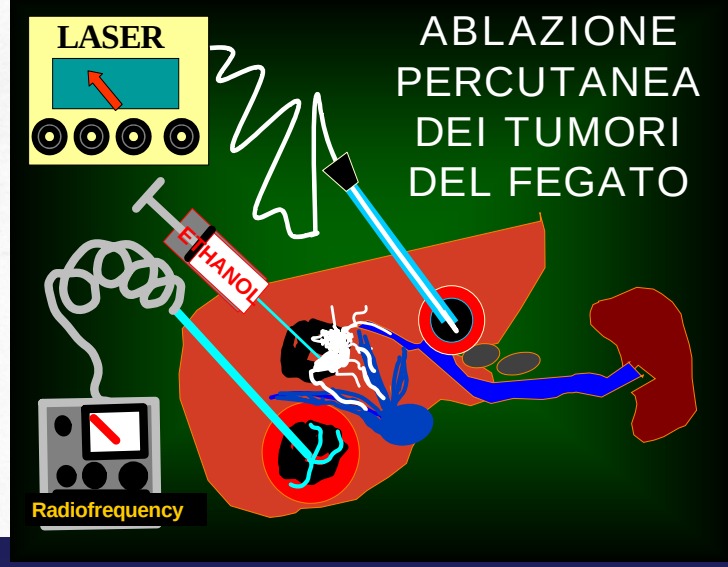
www.elsevier.com/locate/jhep

Special article

Clinical Management of Hepatocellular Carcinoma. Conclusions of the Barcelona-2000 EASL Conference

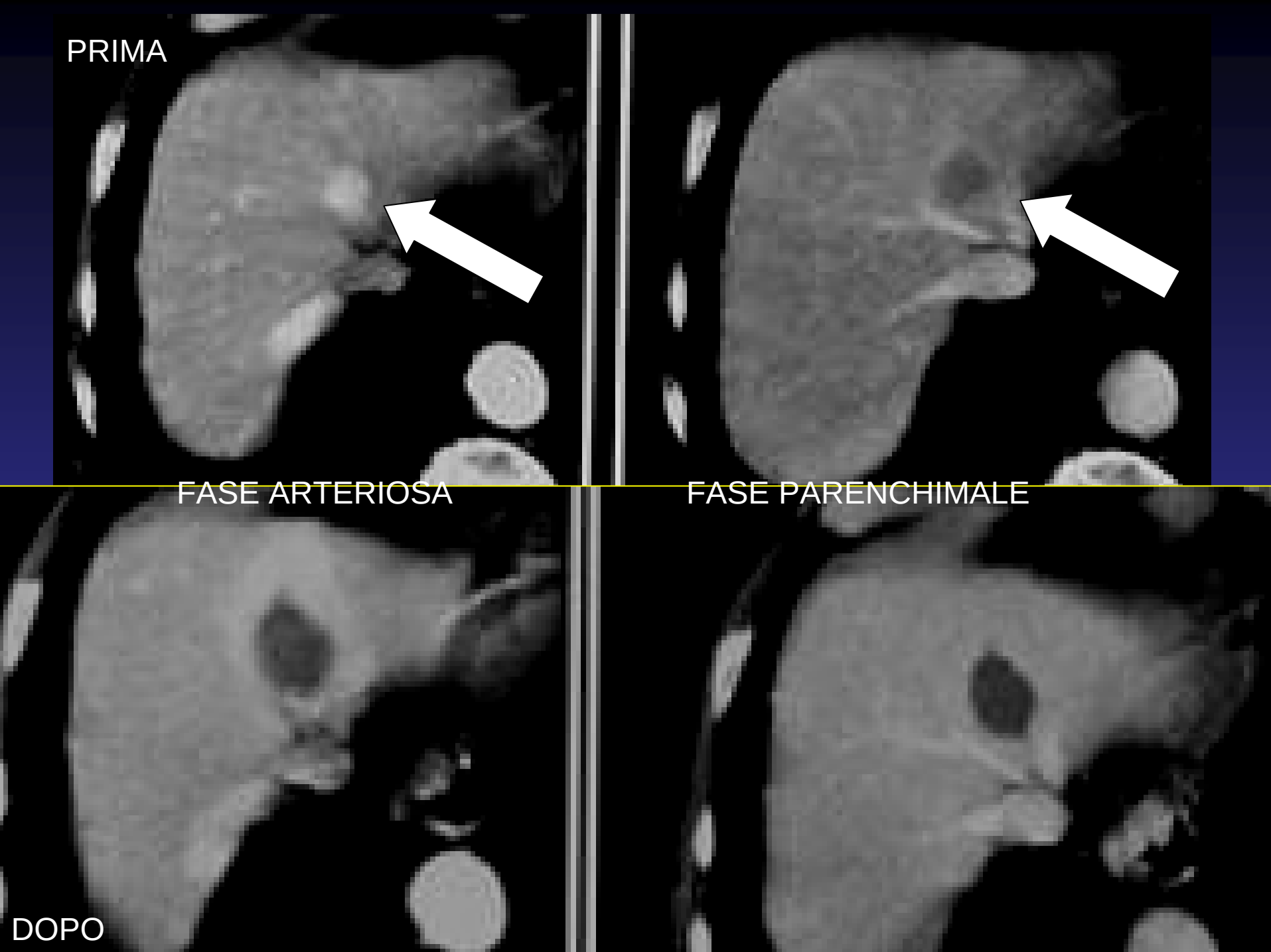
Jordi Bruix*, Morris Sherman, Josep M. Llovet, Michel Beaugrand, Riccardo Lencioni, Andrew K. Burroughs, Erik Christensen, Luigi Pagliaro, Massimo Colombo, Juan Rodés, for the EASL Panel of Experts on HCC

Organizing Committee of the Conference: Henri Bismuth, Luigi Bolondi, Jordi Bruix and Daniel Shouval



Surgical resection, liver transplantation and percutanous techniques achieve a relatively high rate of CR in properly selected candidates and thus should be classified as curative/effective treatments. At present, ethanol injection should be considered the standard percutanous technique. Thus, more expensive and invasive options such as radio-frequency, micro-wawe, cryotherapy or laser should be compared with PEI through RCTs assessing not only initial tumor response, but also long-term survival and costs.

Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL Conference. J Hepatol 2001.


PRIMA
FASE ARTERIOSA
FASE PARENCHIMALE
DOPO

PEI of HCC on CIRRHOSIS

CONVENTIONAL PEI

(SMALL TUMORS <3-5CM)

- Multiple sessions
- Out patients

ONE SHOT PEI

(LARGE AND MULTIPLETUMORS)

- Single session
- Under general anesthesia

Percutaneous ethanol injection of HCC on cirrhosis

Ethanol induces:

- Coagulative necrosis for direct contact with malignant cells
- Ischemic necrosis for thrombosis of the small vessels of the tumor
- HCC is a soft tissue in a fibrotic liver
- Fine needle, low cost, repeteable

MATERIALS AND METHODS

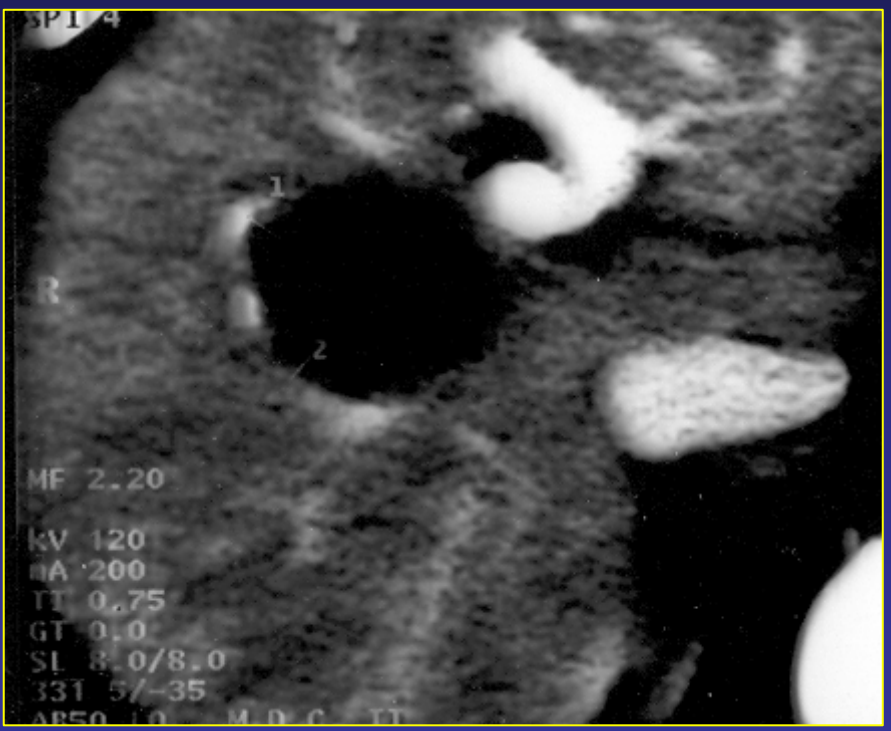
CONVENTIONAL PEI

- Up to three nodules < 3 cm ; Fine needle: 22-21 G
- Ethanol per session: 2-14 ml ; Once - twice weekly on Out patients
- Platelet count: > 50.000 ; PT: > 50%
- No sedation

Percutaneous Ethanol Injection Under Sonographic Guidance of Hepatocellular Carcinoma in Compensated and Decompensated Cirrhotic Patients

Antonio Giorgio, MD, Luciano Tarantino, MD, Giampiero Francica, MD, Vincenzo Scala, MD,

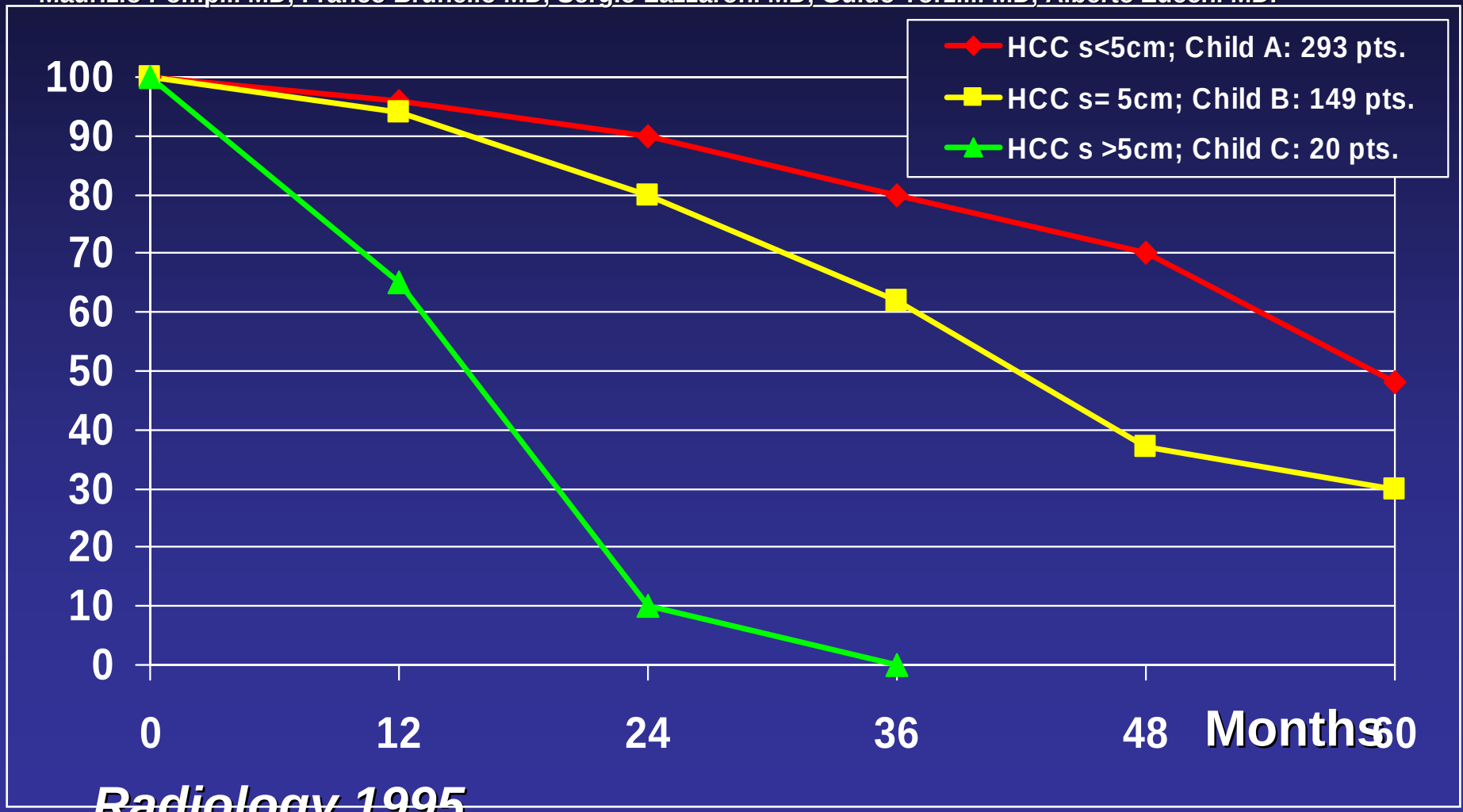
© 1992 by the American Institute of Ultrasound in Medicine • J Ultrasound Med 11:587–595, 1992



SURVIVAL RATES	1	2	3 YEARS
OVERALL	96%	86%	86%
CHILD A	100%	100%	100%
CHILD B	100%	100%	100%
CHILD C	81%	27%	0%
< 3 cm	100%	92%	92%
> 3 cm	90%	86%	-

Hepatocellular Carcinoma and Cirrhosis in 746 Patients: Long-term Results of Percutaneous Ethanol Injection

Tito Livraghi MD, Antonio Giorgio MD, Giuseppe Marin MD, Andrea Solmi MD, Ilario de Sio MD, Luigi Bolondi MD, Maurizio Pompili MD, Franco Brunello MD, Sergio Lazzaroni MD, Guido Torzilli MD, Alberto Zucchi MD.



Radiology 1995.

Complications

Death **1/1066 patients (0.09%)**

Hemoperitoneum

Complications (no of cases): 34/1066 patients (3.2%)

Hemoperitoneum (5)
Hemobilia (2)
Subcapsular hematoma (1)
Parietal hematoma (1)
Intestinal perforation (1)
Acute cholangitis (1)
Early absces (2)
Thrombosis of the caval vein (1)
Thrombosis of the portal vein (3)
Pneumothorax (2)
Right pleural effusions (5)
Hepatic infarct (3)
Tumoral seeding (7)

Di Stasi et al. Scand J Gastroenterol, 1997.

Percutaneous Ethanol Injection under US guidance for Hepatocellular Carcinoma in Cirrhosis:

can indication be extended ?

The 4-year survival rate of patients with nodules > 3 cm was 79%. Multifocality did not affect survival.

Giorgio A. , Tarantino L., de Stefano G. et al. Radiology, November 1992; 185: 237.

Percutaneous Ethanol Injection

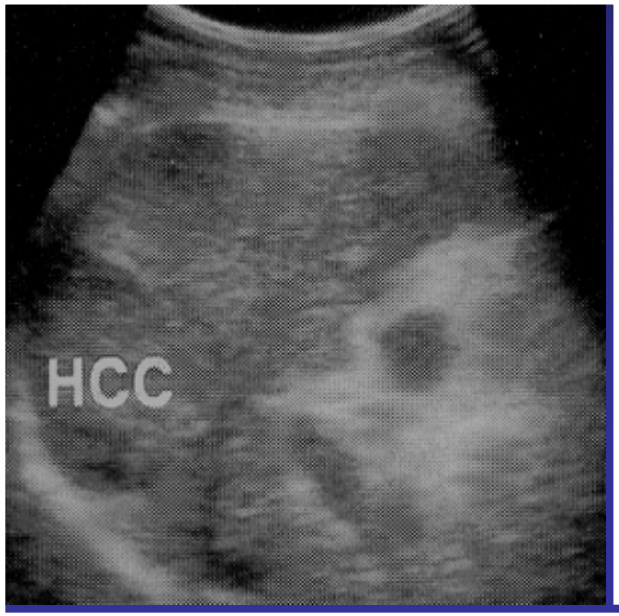
Cardiovasc Intervent Radiol (1996) 19:27–31

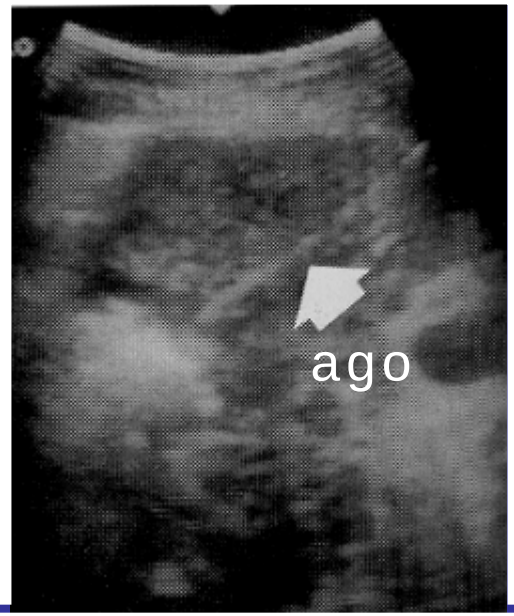
CardioVascular and Interventional Radiology

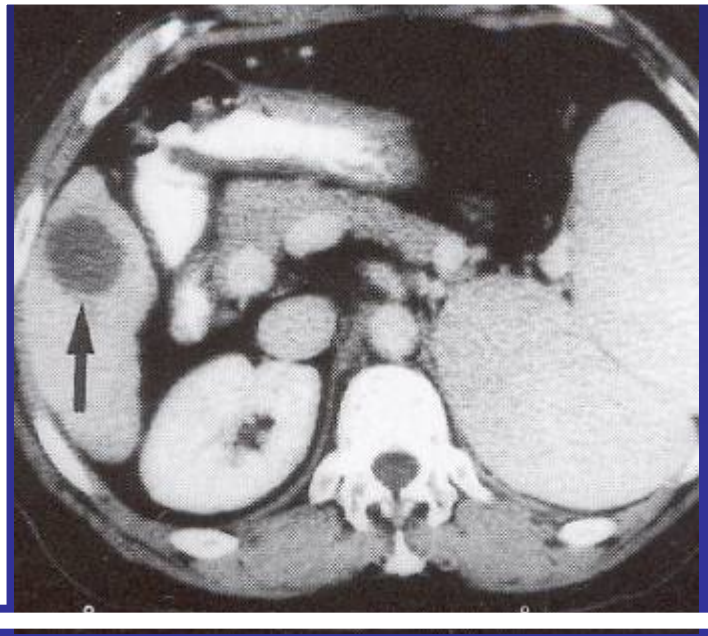
One-Shot Percutaneous Ethanol Injection of Liver Tumors Under General Anesthesia: Preliminary Data on Efficacy and Complications

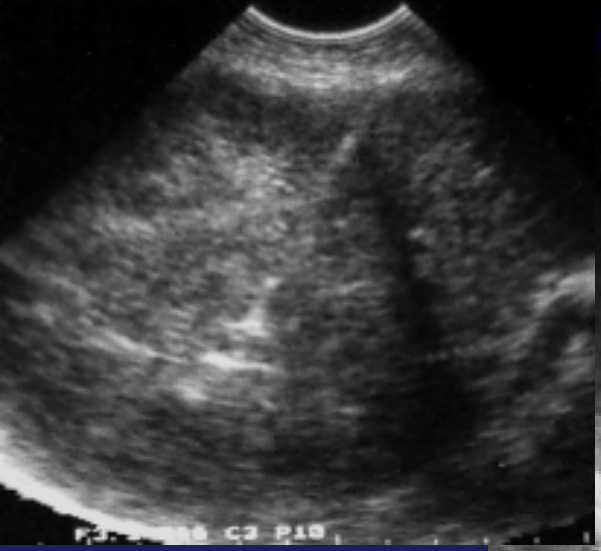
Antonio Giorgio,[1] Luciano Tarantino,[1] Giampiero Francica,[1] Nicola Mariniello,[1] Antonio Nuzzo,[1] Luca del Viscovo,[2] Antonio Rotondo[2]

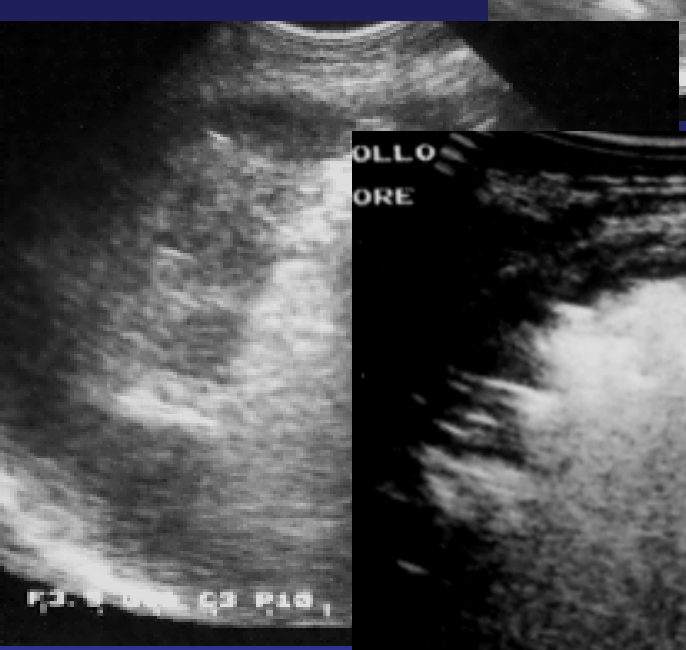
[1]Department of Infectious Diseases, Ospedale D. Cotugno, via Quagliariello, 1, Naples, Italy
[2]Department of Radiology, II Policlinico Università Federico II, Via Pansini, 5 Naples, Italy



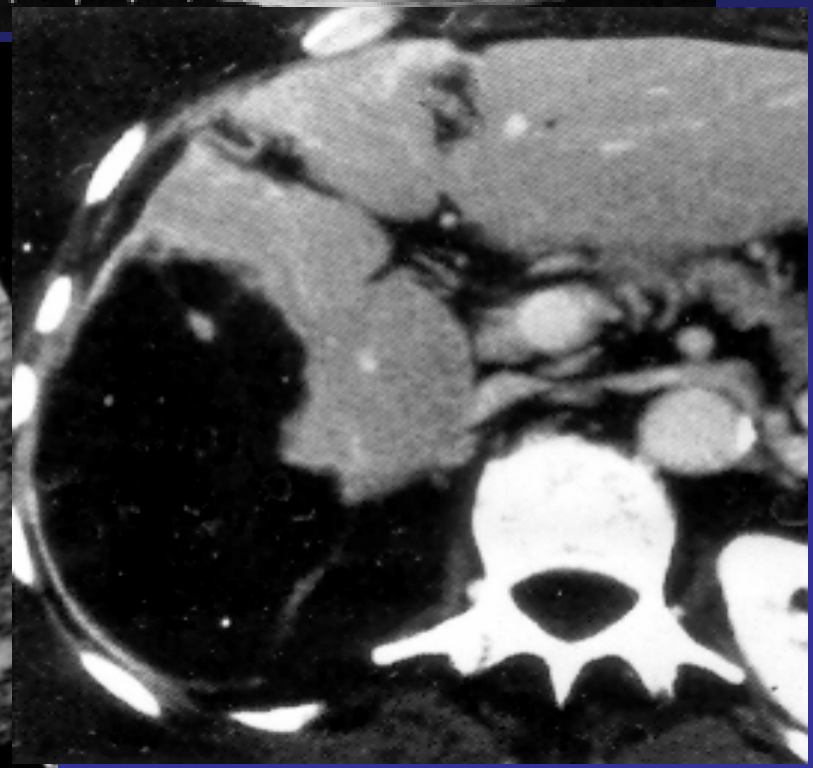


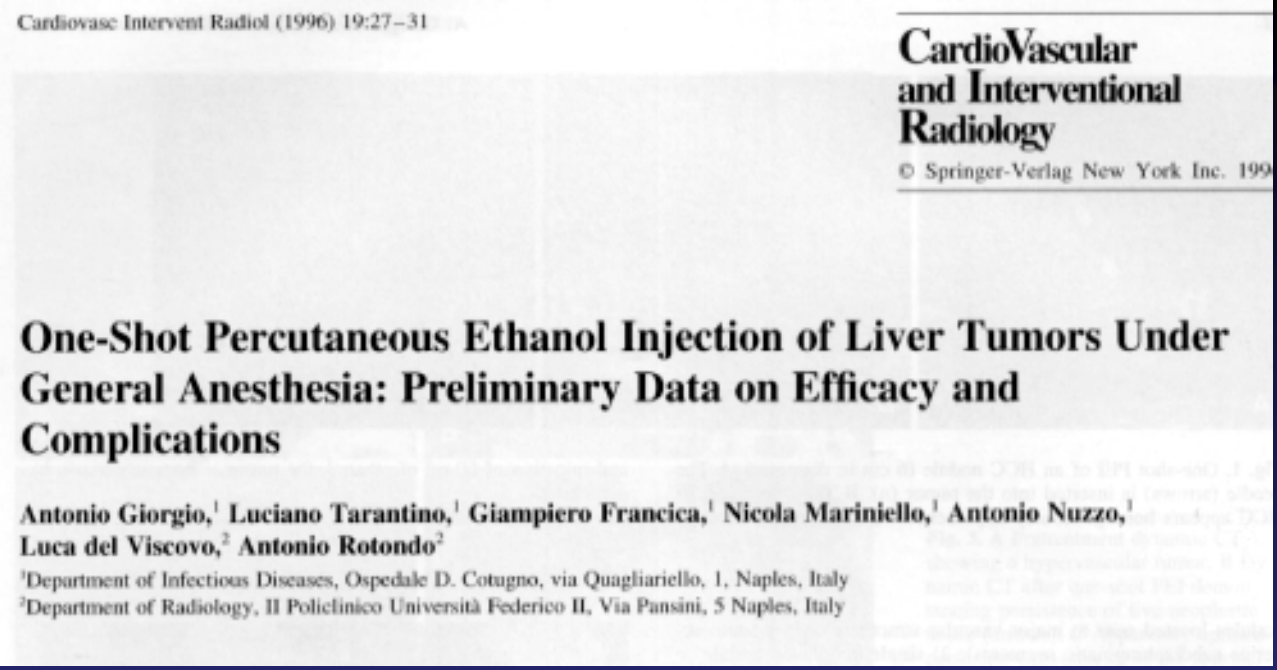







OLLO
ORE
F3.5 G58 C4 P10





Cardiovasc Intervent Radiol (1996) 19:27–31

CardioVascular and Interventional Radiology

One-Shot Percutaneous Ethanol Injection of Liver Tumors Under General Anesthesia: Preliminary Data on Efficacy and Complications

Antonio Giorgio,[1] Luciano Tarantino,[1] Giampiero Francica,[1] Nicola Mariniello,[1] Antonio Nuzzo,[1] Luca del Viscovo,[2] Antonio Rotondo[2]

[1]Department of Infectious Diseases, Ospedale D. Cotugno, via Quagliariello, 1, Naples, Italy
[2]Department of Radiology, II Policlinico Università Federico II, Via Pansini, 5 Naples, Italy

- EFFECTIVE IN INDUCING LARGE TUMOR NECROSIS
- SHORTENING THE TIME OF THE THERAPY
- HIGHER MORBIDITY COMPARED TO CONVENTIONAL PEI
- DEATH AS POSSIBLE COMPLICATION
- NOT MORE THAN 60 ml ETHANOL

ELSEVIER

European Journal of Ultrasound 12 (2000) 145–154

EUROPEAN JOURNAL OF ULTRASOUND

www.elsevier.com/locate/ejultrasou

Clinical Science: Original Paper

Ultrasound-guided percutaneous ethanol injection under general anesthesia for the treatment of hepatocellular carcinoma on cirrhosis: long-term results in 268 patients

Antonio Giorgio [a,*], Luciano Tarantino [a], Giorgio de Stefano [a], Anna Perrotta [a], Vincenza Aloisio [a], Luca del Viscovo [b], Alfredo Alaia [c], Gennaro Lettieri [a]

506/515 nodules

Evaluated by

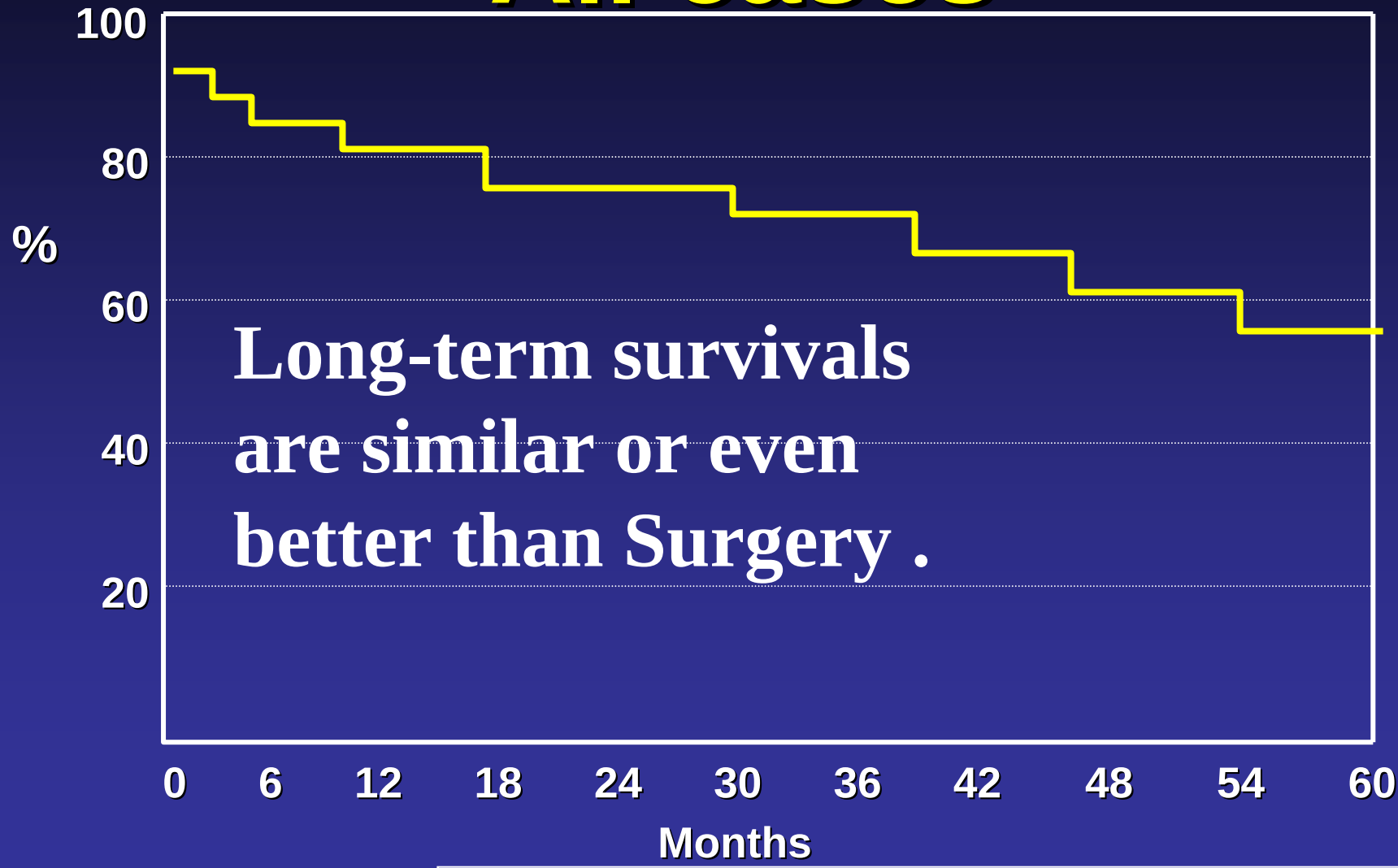
Enhanced CT

COMPLETE NECROSIS

- **overall (357/506): 70%**
- **< 6 cm: 92%**
- **> 8 cm: 60%**

134/149 incompletely treated nodules were successfully retreated with conventional PEI or ONE-SHOT PEI

Survival curve
All cases



Giorgio A, Tarantino L, de Stefano G. et al. EJUS, 2000.

Survival rate of our series according to Child Pugh Class and the sise or Tumor

Child Pugh'Class	1 year		2 year		3 year		4 year		5 year	
	SR	CI	SR	CI	SR	CI	SR	CI	SR	CI
A	98	(100-94)	88	(99-77)	79	(96-62)	70	(94-46)	70	(96-44)
B	94	(98-90)	85	(92-78)	76	(87-65)	67	(87-47)	54	(87-21)
C	60	(95-25)	24	(84-0)	-	-	-	-	-	-
Single nodule <5 cm	90	(97-83)	84	(95-75)	82	(98-66)	82	(100-51)	-	-
Single nodule >5 cm	97	(100-91)	71	(92-90)	59	(92-26)	59	(99-19)	59	(100-10)
Multiple nodules	97	(100-94)	89	(96-82)	75	(87-63)	60	(79-41)	60	(83-37)
Overal	93	(97-89)	83	(90-76)	74	(84-64)	65	(81-49)	59	(81-37)

*SR = Survival rate; CI, 95% = Confidence Interval (percentage)-

Giorgio A, Tarantino L, de Stefano G. et al. EJUS, 2000.

Complications

Five patients died

within 7hrs-10 days after the procedure

- Hemoperitoneum (1)
- Hemorrhage from rupture of aesophageal varices (3)
- Acute liver failure (1)

MAJOR COMPLICATIONS

- Hemoperitoneum (2; no need for blood transfusion)
- Acute tubular necrosis (2; only medical therapy)
- Decompensation of liver cirrhosis (8)

Giorgio A, Tarantino L, de Stefano G. et al. EJUS, 2000.

SELECTION CRITERIA

- REFUSAL OF SURGERY
- SINGLE NODULE > 3 cm
- MULTIPLE NODULES

  (al least one > 3 cm; up to 6 nodules)
- INTOLERANCE TO CONVENTIONAL PEI
- INCOMPLETE NECROSIS OF PREVIOUS CONVENTIONAL PEI

  (expecially superficial nodules)

SELECTION CRITERIA

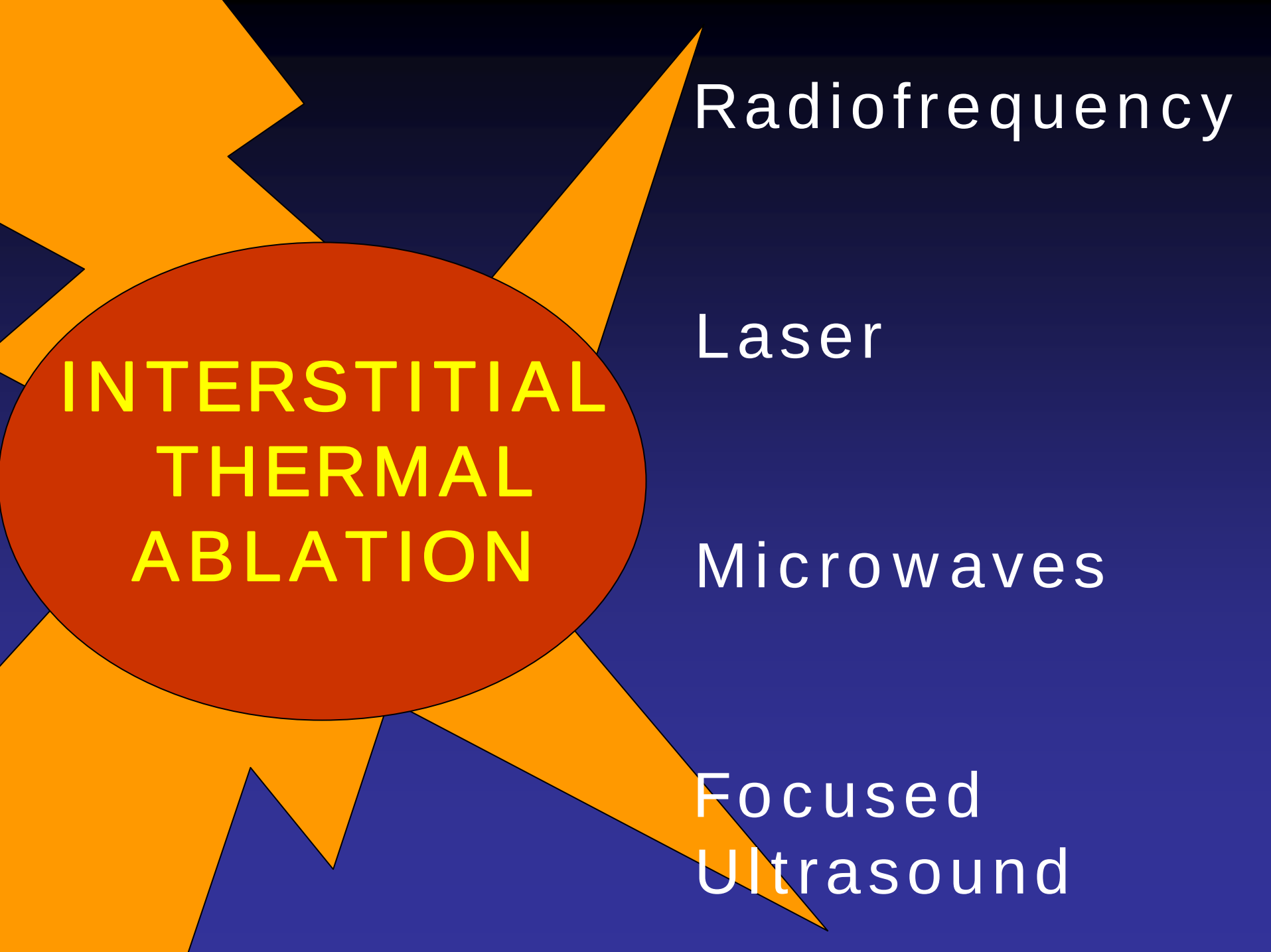
- ASCITES
- PARTIAL NEOPLASTIC THROMBOSIS OF PORTAL VESSELS (Intrahepatic or one of portal branches)

NOT ABSOLUTE CONTROINDICATION

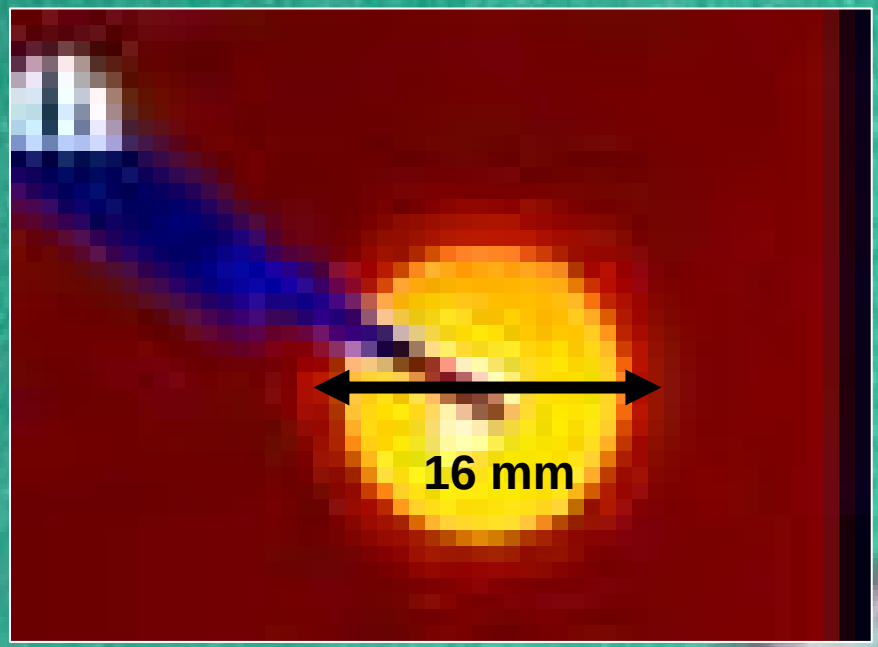
“Single Session “ Percutaneous Ethanol Injection: Conditions Considered at Risk

- Marked portal hypertension
- Marked pulmonary hypertension
- Major heart disease
- Esophageal varices at risk of bleeding
- Hyperfibrinolysis
- Chronic DIC*
- Chronic renal insufficiency
- Obstructive jaundice
- Superficial tumors with severe coagulation disorders

Livraghi, Cancer 1996


INTERSTITIAL
THERMAL
ABLATION
Radiofrequency
Laser
Microwaves
Focused
Ultrasound

Una fibra ottica del calibro di 300 micron passa agevolmente attraverso un ago di Chiba sottile (21-22 G= 0.8 - 0.7mm)



300 -600 microm.

Fibra ottica

ago

ELSEVIER

European Journal of Ultrasound 11 (2000) 181–188

EUROPEAN JOURNAL OF ULTRASOUND

www.elsevier.com/locate/ejultrasou

Clinical Science: Original Paper

Interstitial laser photocoagulation under ultrasound guidance of liver tumors: results in 104 treated patients

Antonio Giorgio [a,*], Luciano Tarantino [a], Giorgio de Stefano [a], Nunzia Farella [a], Orlando Catalano [b], Bianca Cusati [b], Luca Del Viscovo [c], Alfredo Alaia [d], Eugenio Caturelli [e]

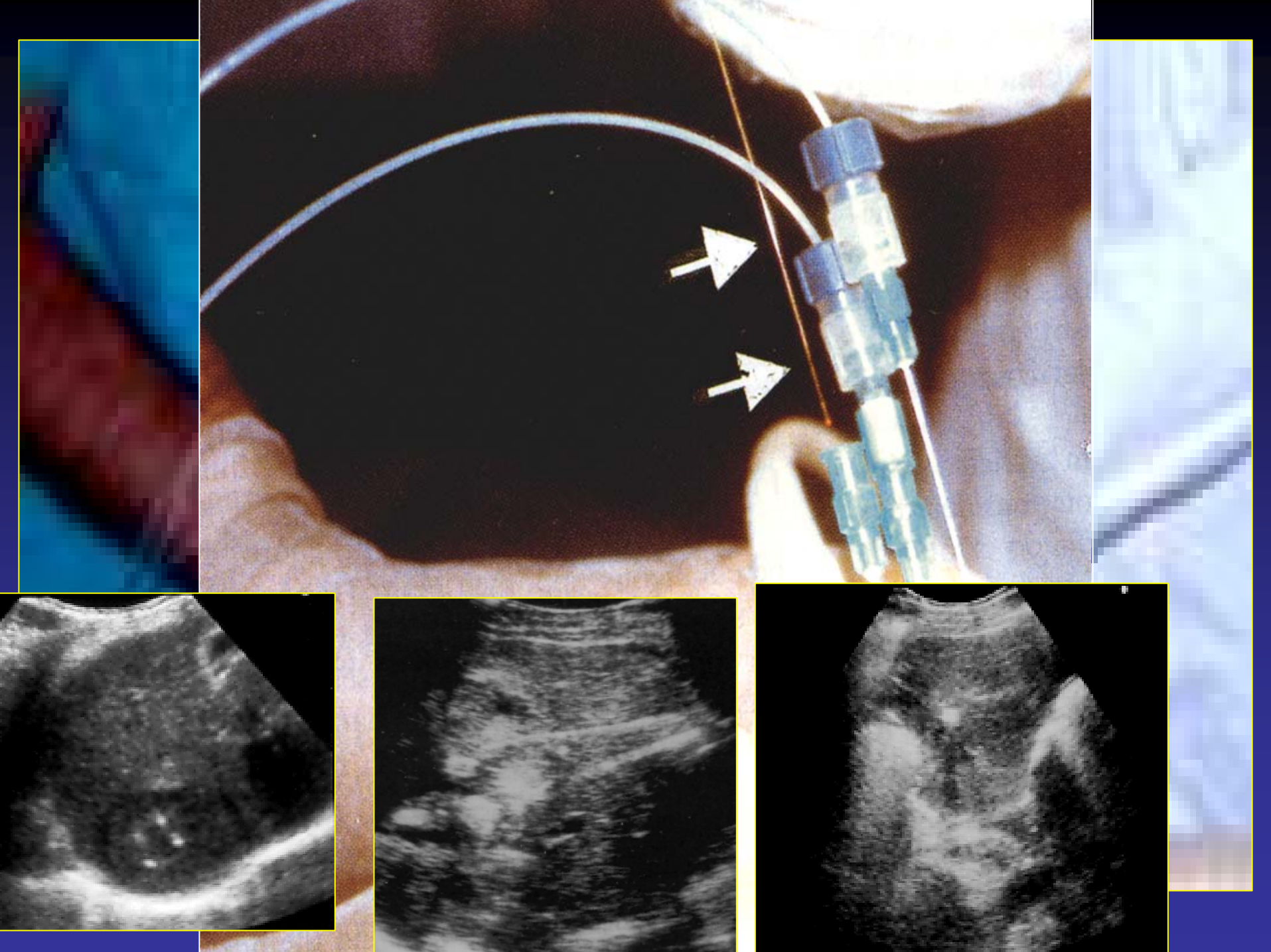
[a] *Interventional Ultrasound Service-D, Cotugno Hospital Naples, Viale colli Aminei 491, 80131 Naples, Italy*
[b] *Department of Radiology, S. Maria delle Grazie Hospital, Pozzuoli, Italy*
[c] *Department of Radiology, II University of Naples, Naples, Italy*
[d] *Department of Anesthesiology, D. Cotugno Hospital, Naples, Italy*
[e] *Department of Gastroenterology, Casa Sollievo della Sofferenza, S. Giovanni Rotondo, Italy*

Received 5 January 2000; received in revised form 10 March 2000; accepted 20 March 2000

Interstitial
Laser
Photo
coagulation

77 patients with 85 HCC nodules

diam. range:10 to 66 mm (mean 32)



Post-treatment CT

-Complete necrosis: 70/85 HCC (82%) in 65 pts

-Incomplete necrosis: 12 HCC nodules in 9 pts

Follow-up : 2 to 12 months (mean 4.5).
All patients are alive.

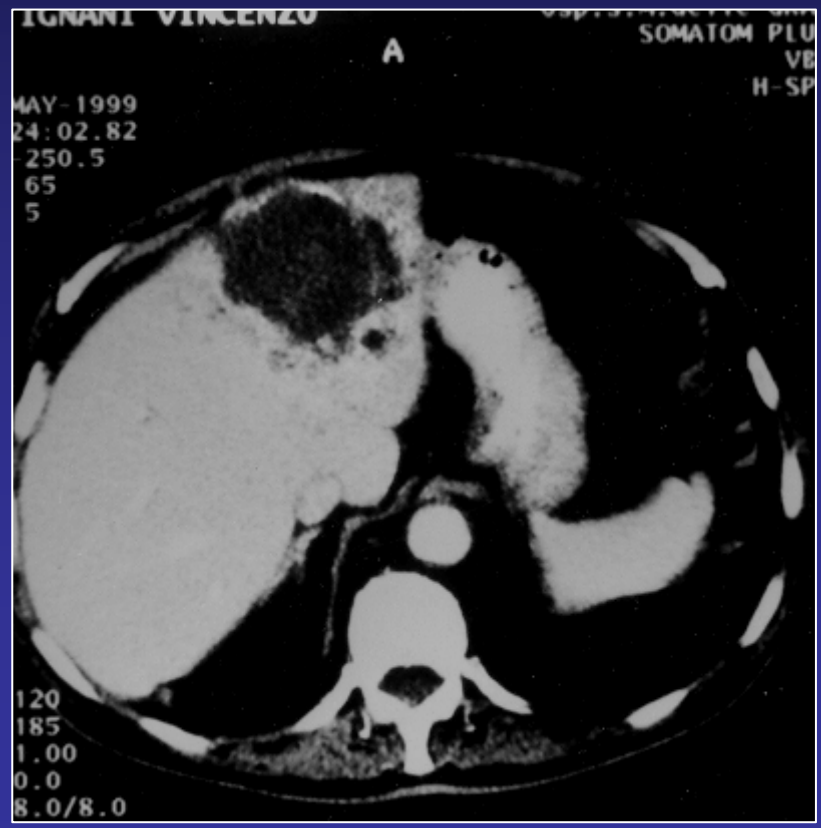
local recurrence : 1 patient

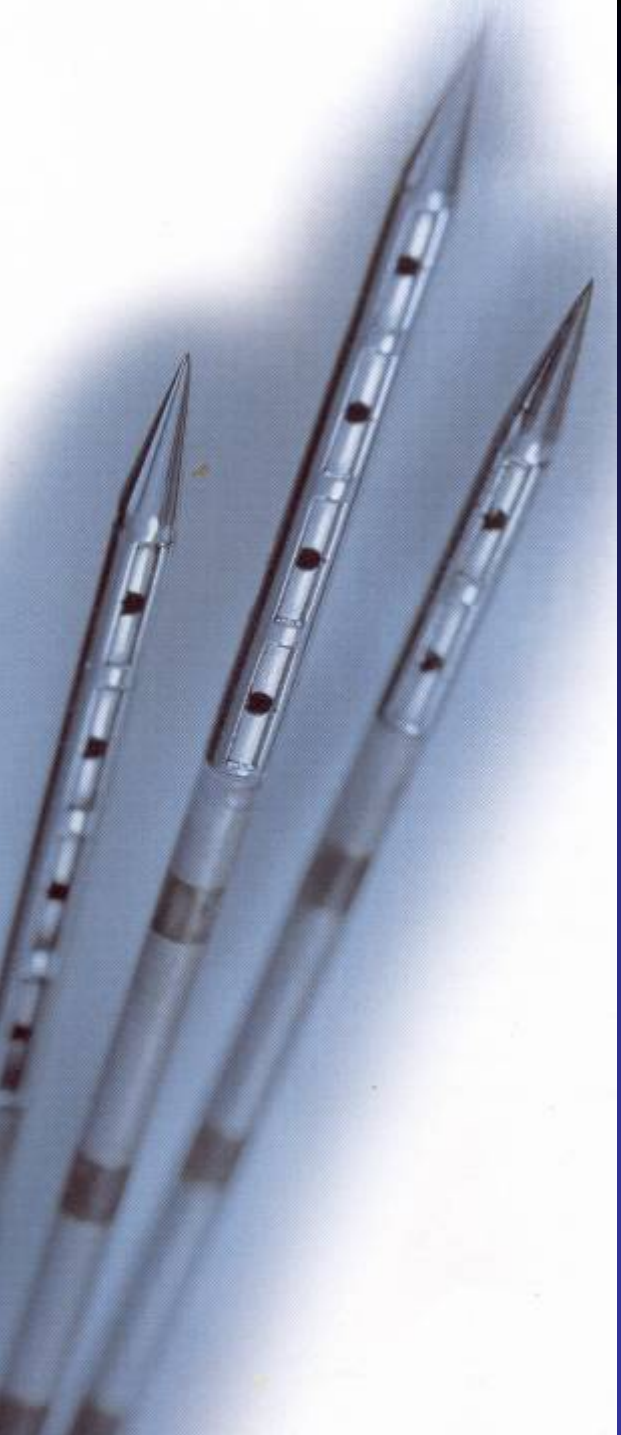
(successfully retreated by one-shot PEI)

COMPLICATIONS

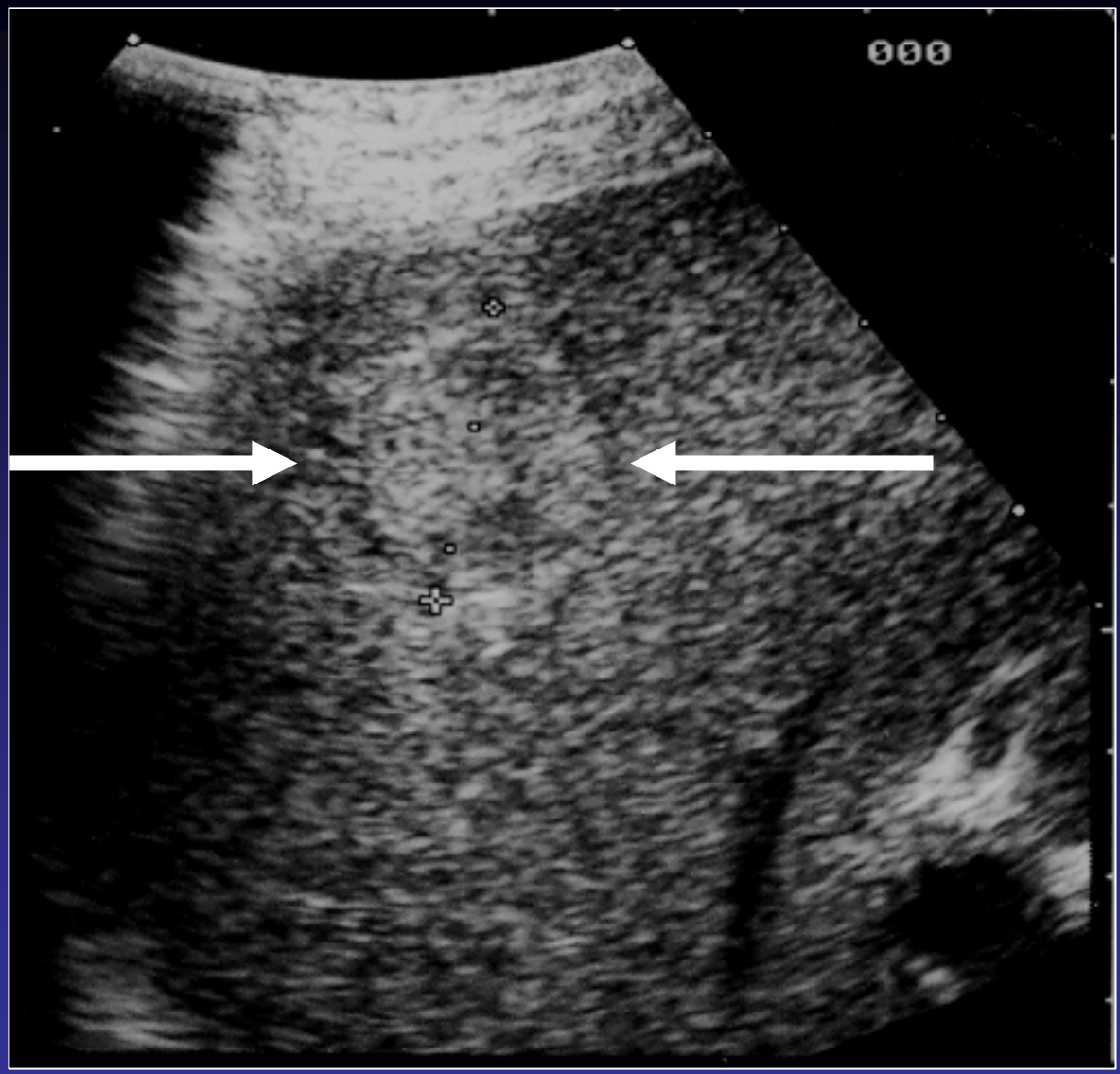
Ascites, severe jaundice: 3 cases
(One of these patients died for liver failure 2 months after ILP)

-Paralytic ileum 7 days after ILP1 case
(spontaneously resolved)

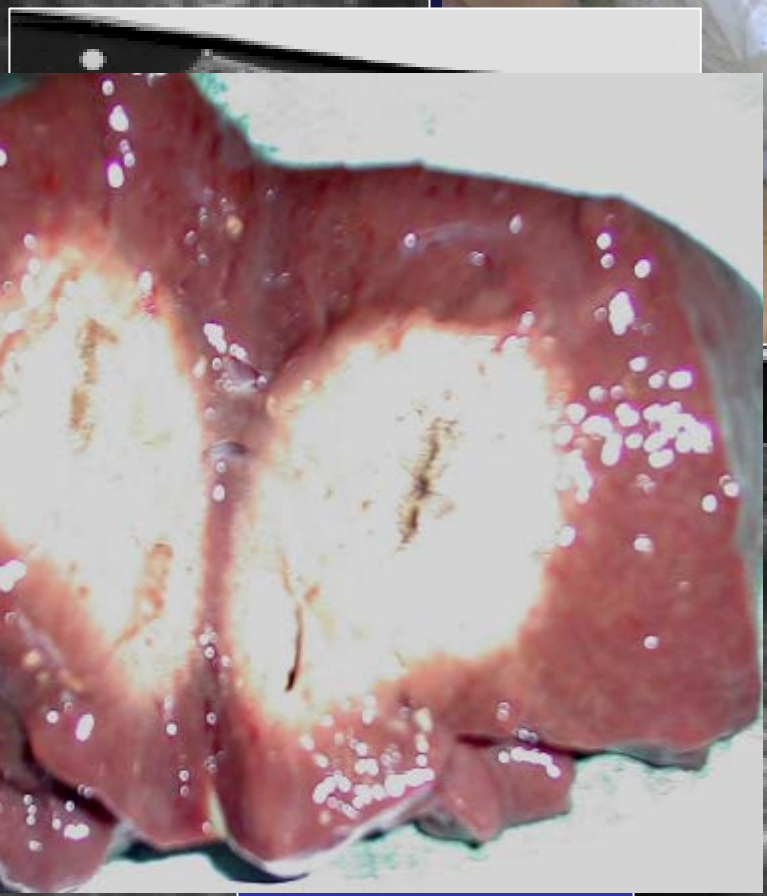


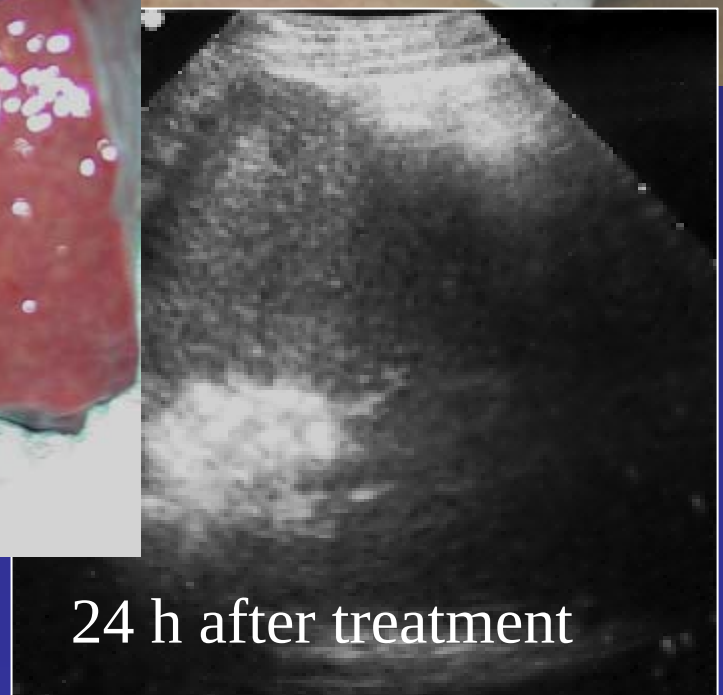



BERCHTOLD
ELEKTROTOM® 106 HITT
POWER
40
TIMER
500
TEMP --°C LIMIT 85°C
FLOW 90ml/h



HCC VI SEGMENTO. ⌀ = 26 mm





24 h after treatment

PATIENTS

84 cirrhotic patients

67 Child-Pugh A class
14 Child-Pugh B class.
(55 males; age range : 48 – 74 years)

95 nodules of HCC (7 patients with 2 and 2 with 3 nodules)

Diam. nodules : 1.5 and 8.5 cm (mean : 3.7 cm)

42 HCC nodules =/< 3 cm
45 ranged 3.1 and 5 cm
8 diameter > 5 cm

n. of nodules	Size	n. of sessions	electrode insertions per session	complete necrosis	partial necrosis	recurrences during the follow-up**
42	≤3 cm	1	1	40 (95%)	2 (5%)	1
30	3.1-4.0 cm	1	1	25 (83%)	5 (17%)	3
15	4.1-5.0 cm	1	2-3 *	7 (47%)	8(53%)	3
8	5.1-8.5 cm	2	3	1 (12%)	7 (88%)	6
Total, 95	range 1.5-8.5 cm			Total, 73 (77%)	Total, 22 (23%)	Total, 13 (14%)

Antonio Giorgio MD, Luciano Tarantino MD, Giorgio de Stefano MD et al. PERCUTANEOUS ULTRASOUND GUIDED SALINE ENHANCED HIGH-FREQUENCY-INDUCED-THERMOTHERAPY (HiTT) OF HEPATOCELLULAR CARCINOMA . AJR August 2003

COMPLICATIONS

- **No major complication occurred**
- **Fever** (1-3 days) after treatment **52/84 (62%)**
- **Pain** (12-24 hours) after treatment **66/84 (78%)**

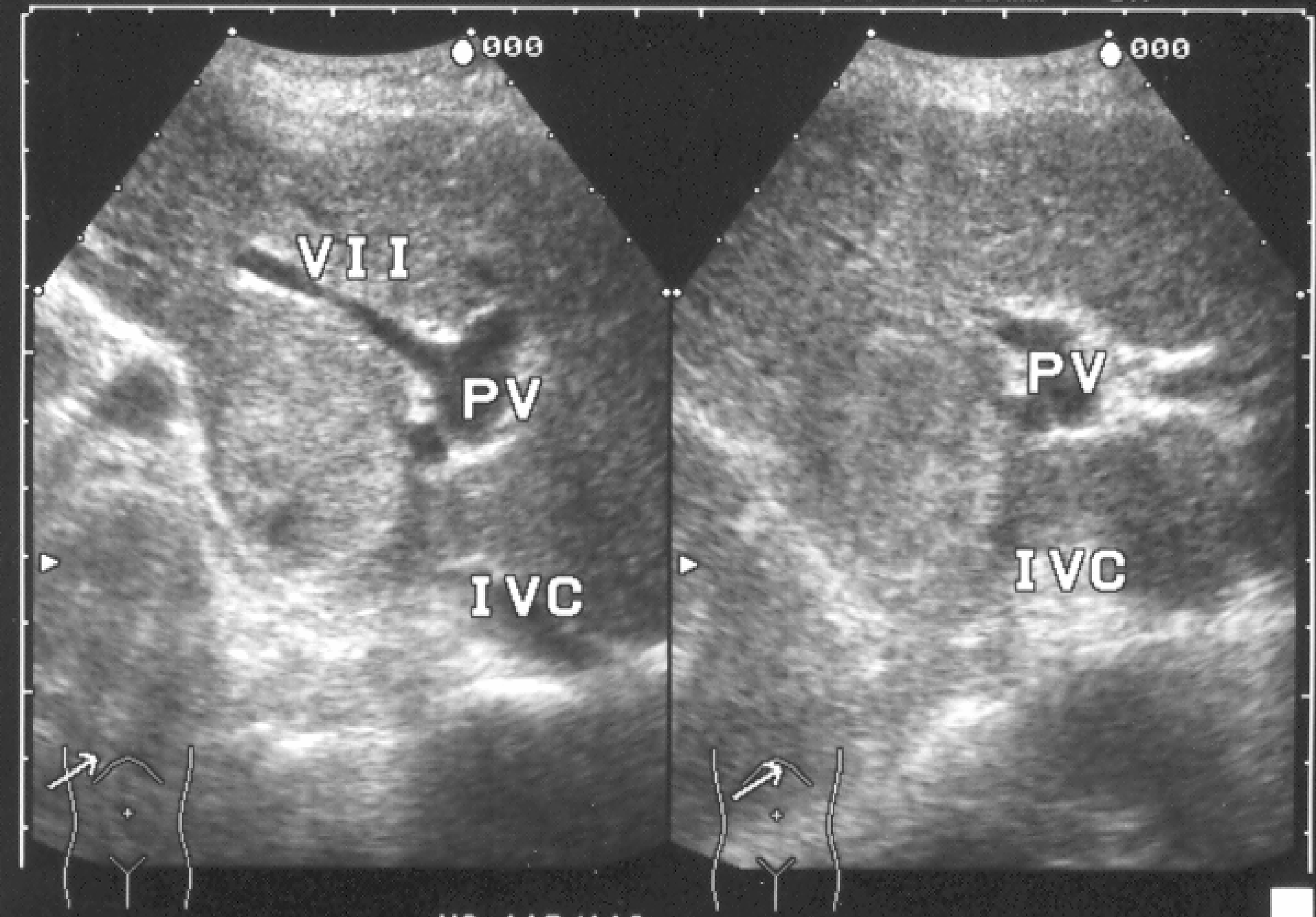
  Pain-killer necessary only in 30/84 (36%) patients .
- **No cutaneous or abdominal wall seeding have been observed clinically and/or by US during the follow-up.**

Le procedure di TERMOABLAZIONE PERCUTANEA (RF, ILP) :

- **sono meglio tollerate rispetto alla PEI**
- **Danno volumi di necrosi limitati (< 4 cm) rispetto alle estese necrosi ottenibili con la PEI**
- **Sono limitate dall'effetto "cooling" dei vasi peritumorali**
- **Meno efficaci per lesioni inervascolari**


NO.82/82
SERV.ECOINTERVENTISTICA-OSP.COTUGNO NA


000
NO.118/118
SERV.ECOINTERVENTISTICA-OSP.COTUGNO NA



NO.113/118

ID:

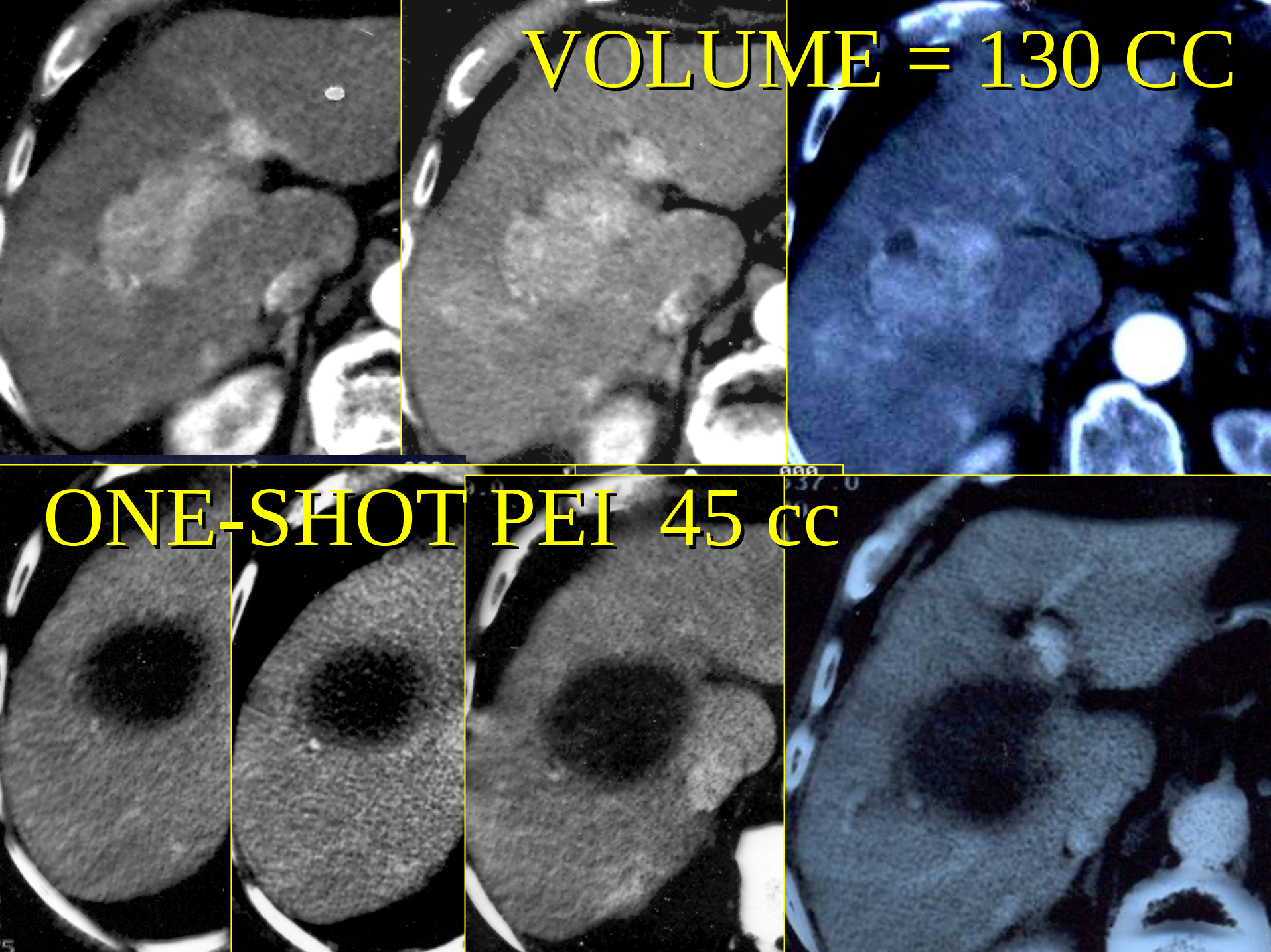
SERV.ECOINTERVENTISTICA-OSP.COTUGNO NA

'02/01/31 F5

F5


23/24
40Hz
12:30:09
3.5
PWR:100%
R10 G75 C3 A1
:ABDOM


4
5
665/668


VOLUME = 130 CC
ONE-SHOT PEI 45 cc

Confronto con altre metodiche terapeutiche

PEI e RF

Nessuna differenza statisticamente significativa

Complicanze	**> per RF**
Numero di sedute	**< per RF**

Small hepatocellular carcinoma: treatment with radiofrequency ablation versus ethanol injection. **Livraghi T, et al. Radiology 1999; 210 (3): 655-661.**

BIAS importante:
Selezione numerosità della casistica

Lencioni R et al. Small HCC in cirrhosis : randomised comparison of RF versus PEI. Radiology, july 2003

- **102 patients**
- **1 – 2 years survival rates : n.s.**
- **1 – 2 years event free survival rates :**

  RF better than PEI

Conclusions : RF is superior to PEI with respect to local recurrence free survival rates

SERVIZIO di ECOGRAFIA ed ECOINTRVENTISTICA
Azienda Ospedaliera "D. COTUGNO" Napoli

ADVERSE EVENTS DURING RADIOFREQUENCY TREATMENT OF 582 HEPATIC TUMOR

T de Baère et al.

AJR Sept 2003

ADVERSE EVENTS DURING RADIOFREQUENCY TREATMENT OF 582 HEPATIC TUMOR

- 5- years period
- 312 pts
- 350 RF sessions: 124 intraoperative / 226 percutaneous
- 115 HCCs
- 467 Mts

T de Baère et al.

AJR Sept 2003

ADVERSE EVENTS DURING RADIOFREQUENCY TREATMENT OF 582 HEPATIC TUMOR

Majors complications: 14%

5 deaths:

3/123 intraoperative; 2/216 percutaneous

---

portal vein thrombosis 2/5 Cirrhotic Livers p<0.00001 vs non Cirrhotic Livers during Pringle maneuver

Liver abscess: 7pts

P<0.00001 bilioenteric anastomosys

T de Baère et al.
AJR Sept 2003

ADVERSE EVENTS DURING RADIOFREQUENCY TREATMENT OF 582 HEPATIC TUMOR

Pleural effusion: 5

Pneumothorax: 3

Subcapsular hematoma: 1

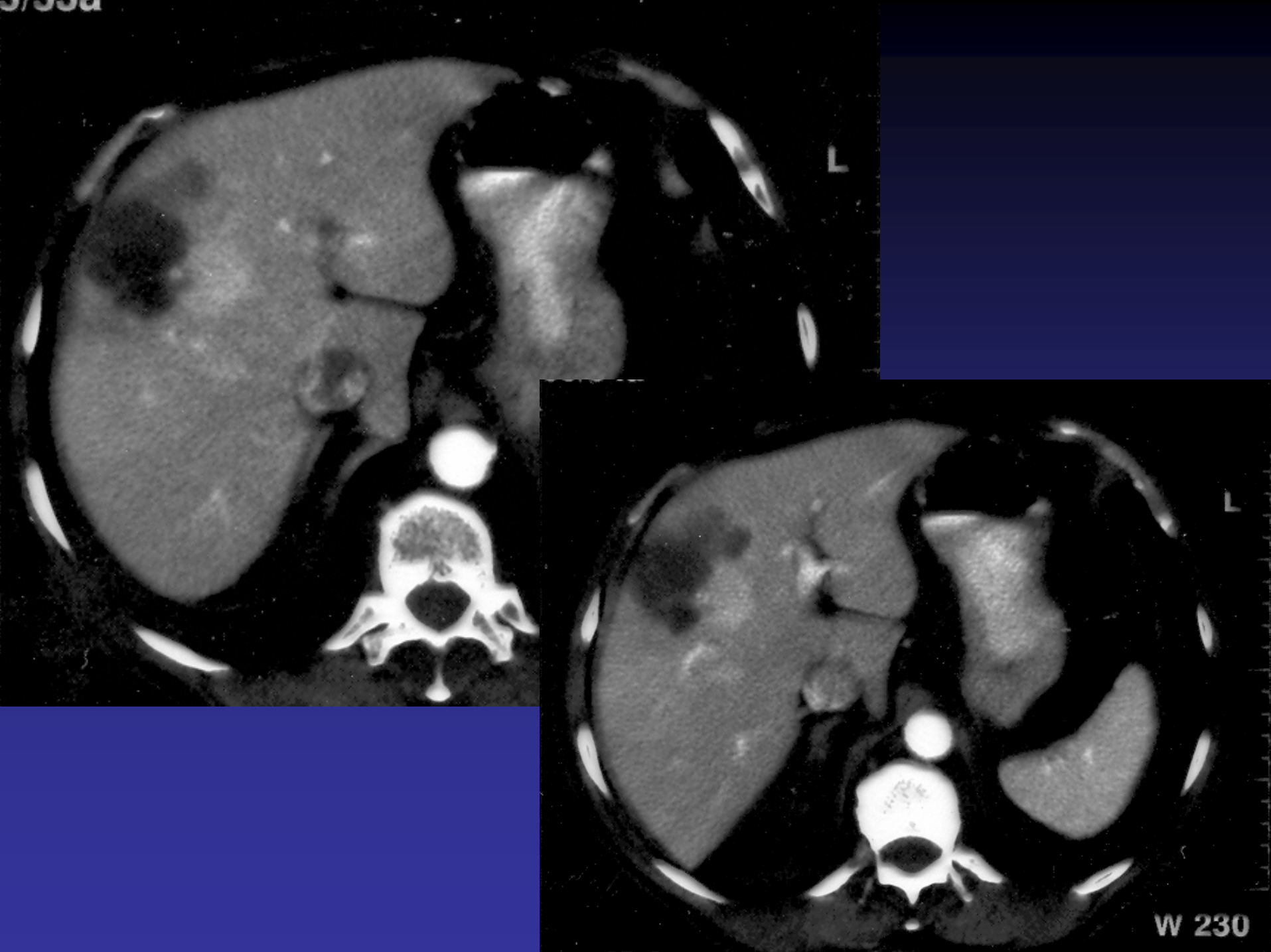
Skin burn: 5

Hemoperitoneum: 1

T de Baère et al.
AJR Sept 2003

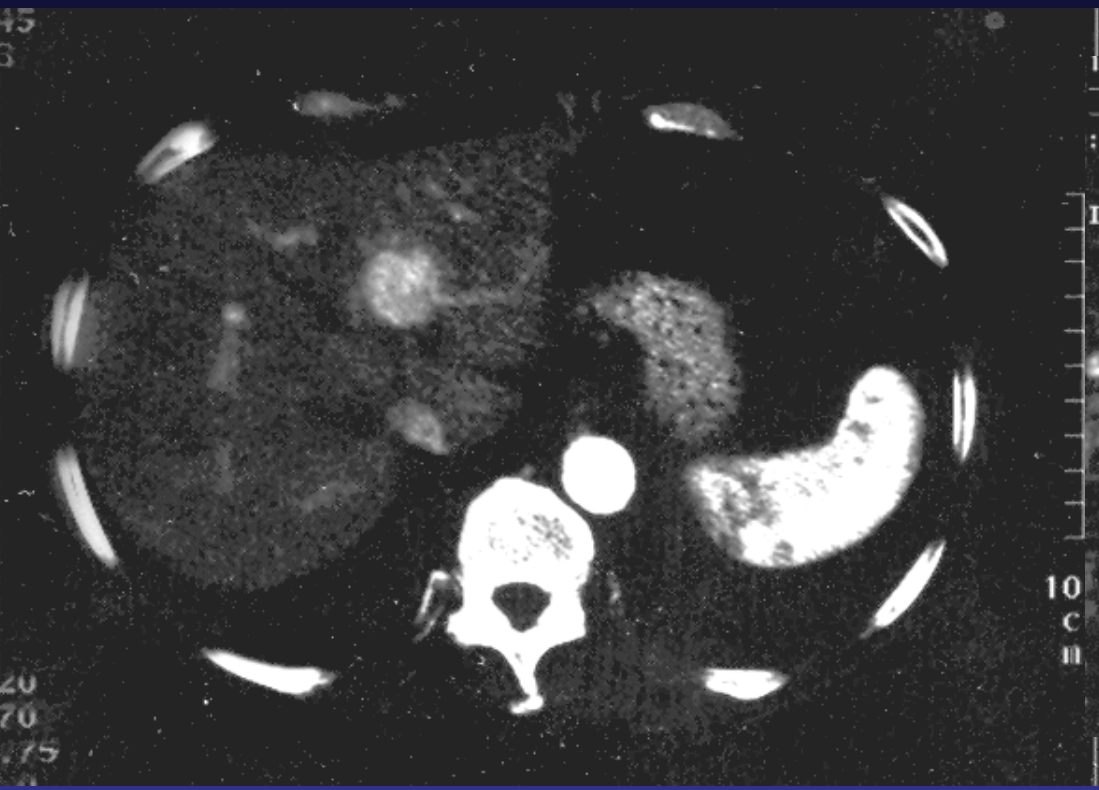
RF vs PEI: Indicazioni elettive per RF

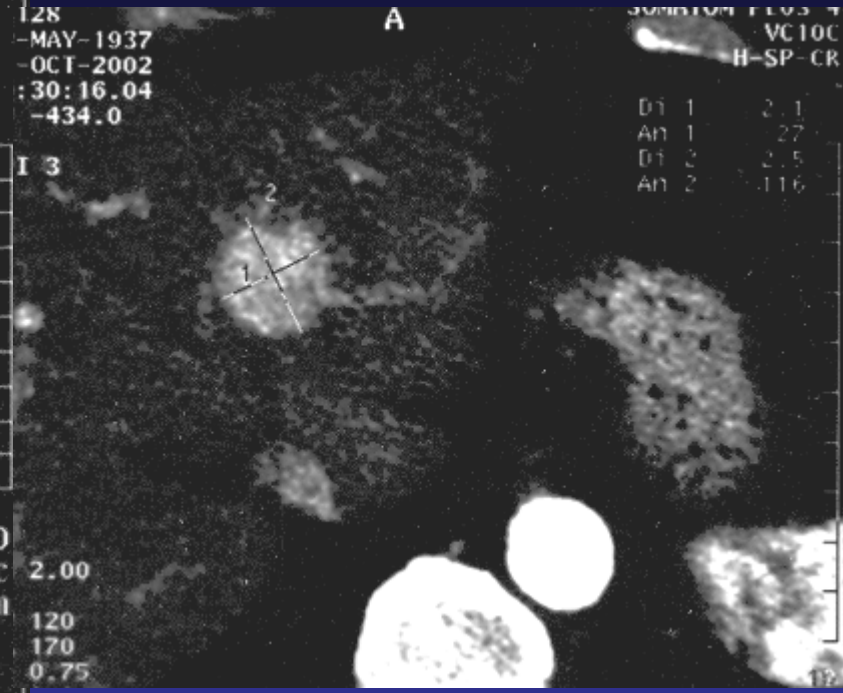
- Ipertensione portale
- Noduli avascolari alla TC e nuovi mdc ecografici
- Noduli a “mosaico”


L
L
W 230

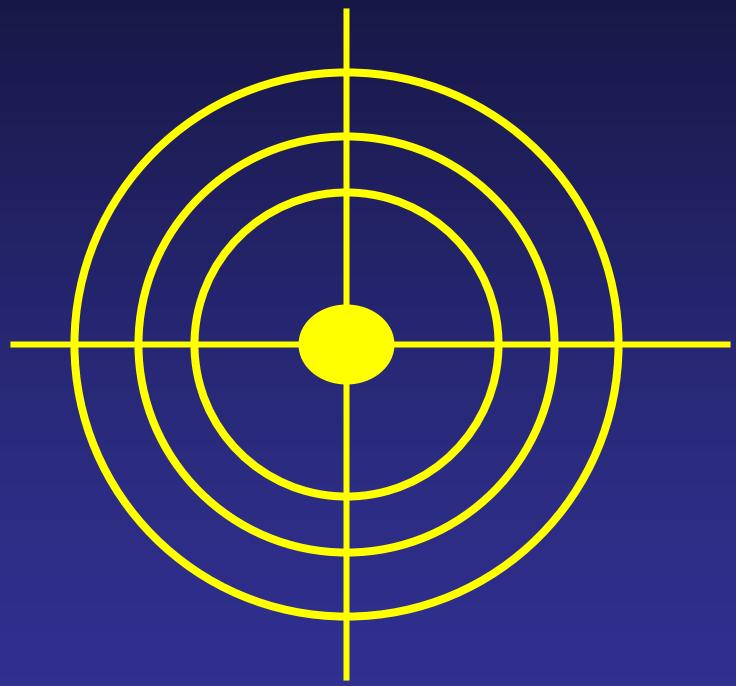

COTUGNO - NAPOLI
270/271
24Hz
R14 G65 C5 A1


408/409
29Hz
R17 G65 C5 A1




A
-MAY-1937
-OCT-2002
:30:16.04
-434.0
I 3
2.00
120
170
0.75

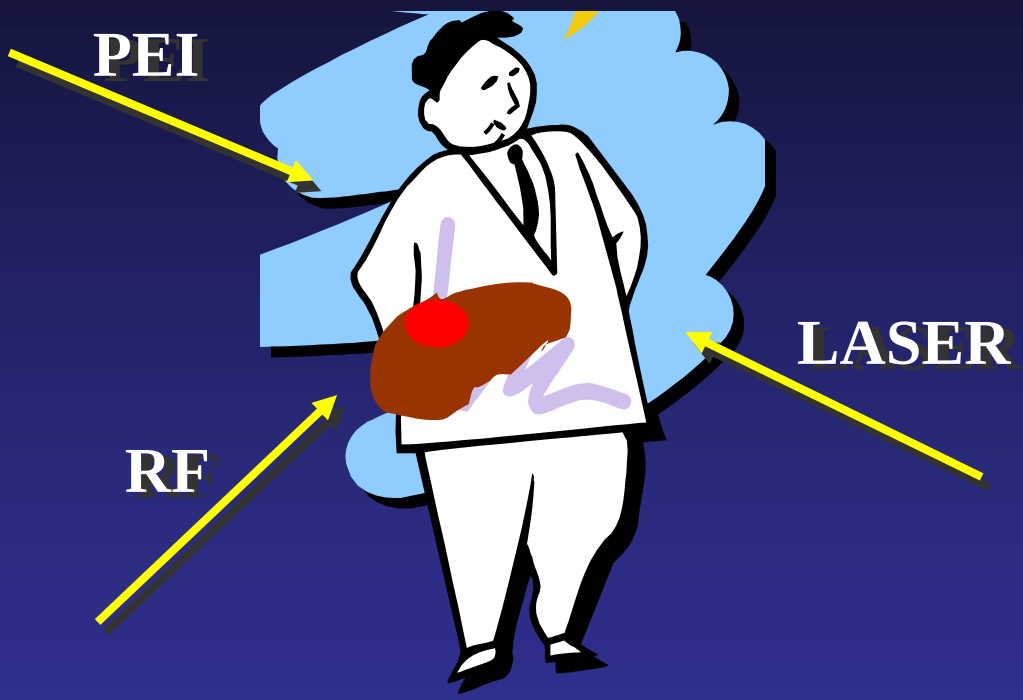
PEI: Unexpensive



RF: Higly expensive

ILP: moderately expensive

Al centro di tutte le metodiche non c'è la "tecnica" ma il PAZIENTE e ogni singola tecnica deve adeguarsi al paziente



- Numero dei noduli
- Sede del nodulo e tipo macroscopico
- Bilirubina – TP – Ipertensione portale

Più metodiche possono essere utilizzate nello stesso paziente ma sempre tenedo conto del singolo caso specifico!!!

Quale tecnica di ablazione ? (la nostra esperienza)

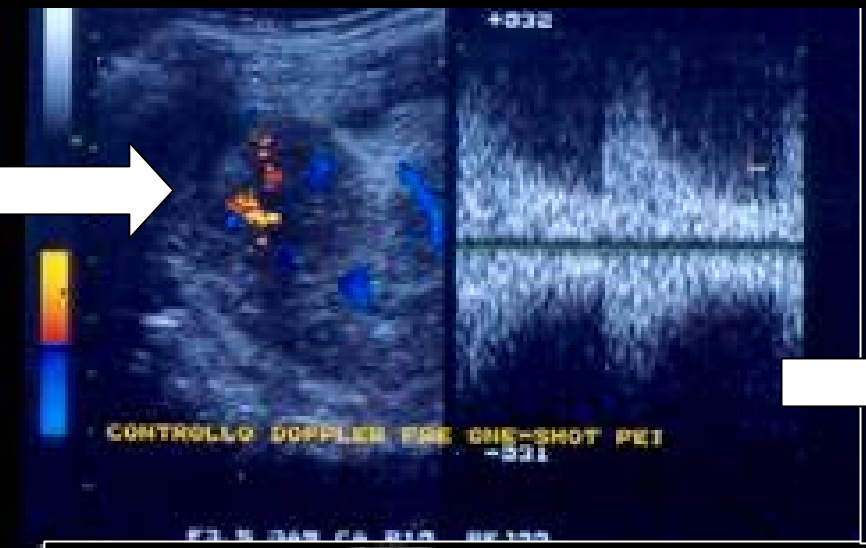
- paz. classe Child-Pugh A o B - nodulo/i < 2 cm : **ILP o RF**
- paz. classe Child-Pugh A o B con nodulo/i >2 cm<5 cm: **RF**
- paz. classe Child-Pugh A o B con nodulo/i >5 cm< 6 cm:

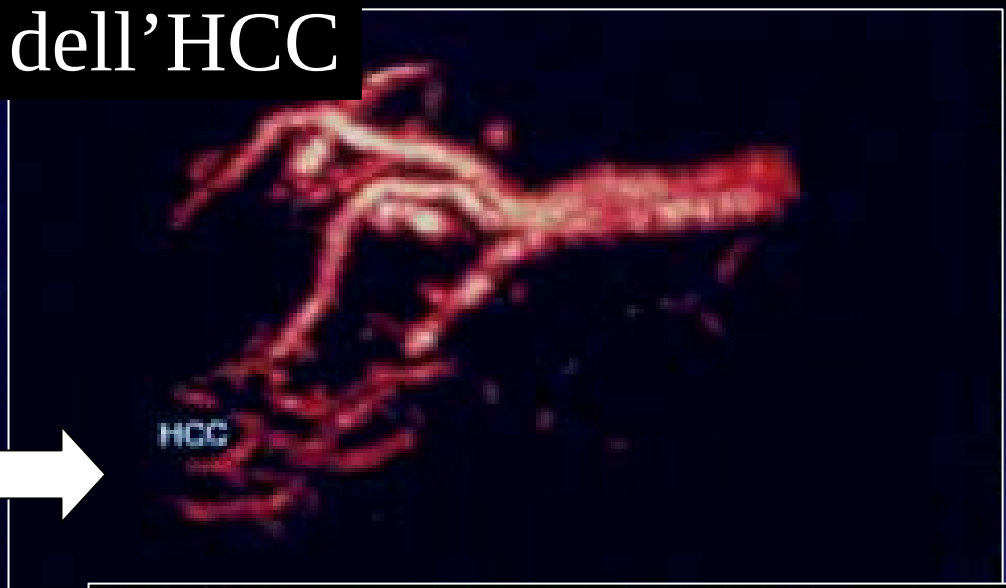
  multiple sessioni di RF o PEI in sessione singola
- paz. classe Child-Pugh A o B con grosso HCC (> 6 cm) :
- **singola o mult. sessioni di PEI in anestesia generale**
- paz. con disordini emocoagulativi severi (plt < 50.000/mmcc; I.N.R. > 1.7) :

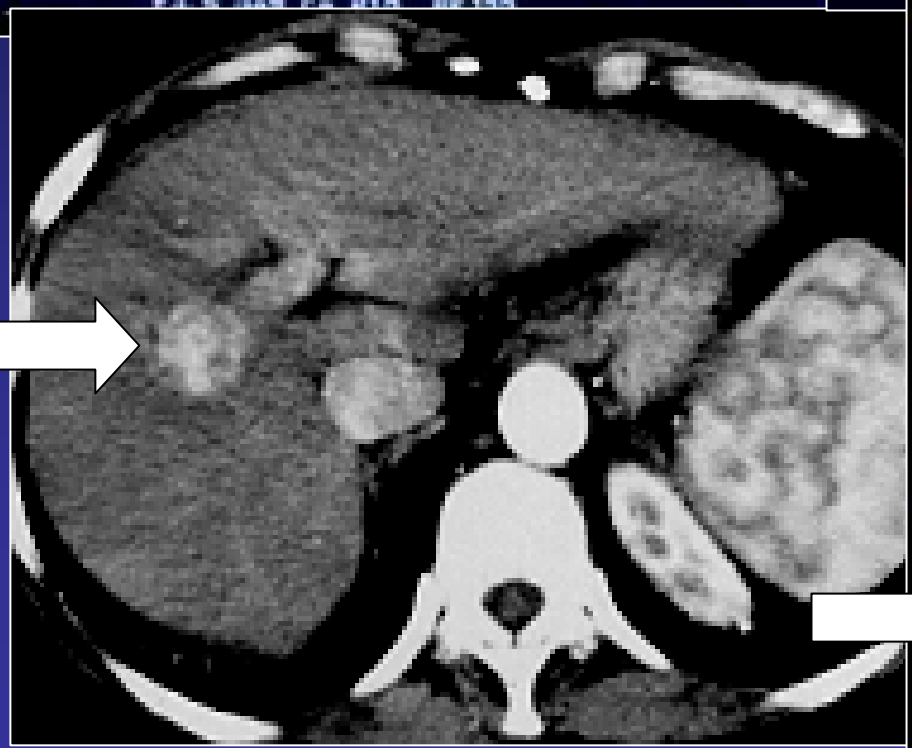
  ILP o PEI (con aghi del calibro di 21-22 G)
- paz. Child B-C con piccolo HCC (< 3 cm) : **ILP**
- paz. Child C con medio, grosso HCC (> 3 cm) : **nessun trattamento**
- Persistenza di aree vitali residue dopo ablazione di large HCC :

  PEI (RF o ILP in casi particolari)
- Piccoli noduli di recidiva a distanza dalla prima ablazione **: ILP , PEI**
- Paz. Child A o B con mult. aree tumorali ipervascolari e/o infiltranti :**TACE**

Ipervascolarità arteriosa dell'HCC







CHEMOEMBOLIZZAZIONE ARTERIOSA TRANSCATETERE (TACE)

- **Efficace sulle neoplasie con importante apporto arterioso**
- **Mai necrosi completa. La periferia del tumore è irrorata anche dai vasi portali**
- **Se non superselettiva ha effetto lesivo sulla funzionalità epatica .**
- **sempre una parziale irrorazione portale del tumore**

- **In studi randomizzati dubbia efficacia sulla sopravvivenza dei pazienti trattati .**
- **Pesanti effetti collaterali in alcuni casi**
- **Effetto puramente palliativo**
- **Migliori risultati con TACE segmentaria**

CHEMOEMBOLIZZAZIONE ARTERIOSA TRANSCATETERE (TACE)

Come terapia neoadiuvante :

..la TACE preoperativa deve essere evitata nel caso degli HCC resecabili in quanto non migliora la sopravvivenza né riduce il rischio di nuove lesioni e può peggiorare le condizioni generali del paziente ..

Adachi et al. Cancer, 1993 ; Wu C et al. Br J Surg, 1995

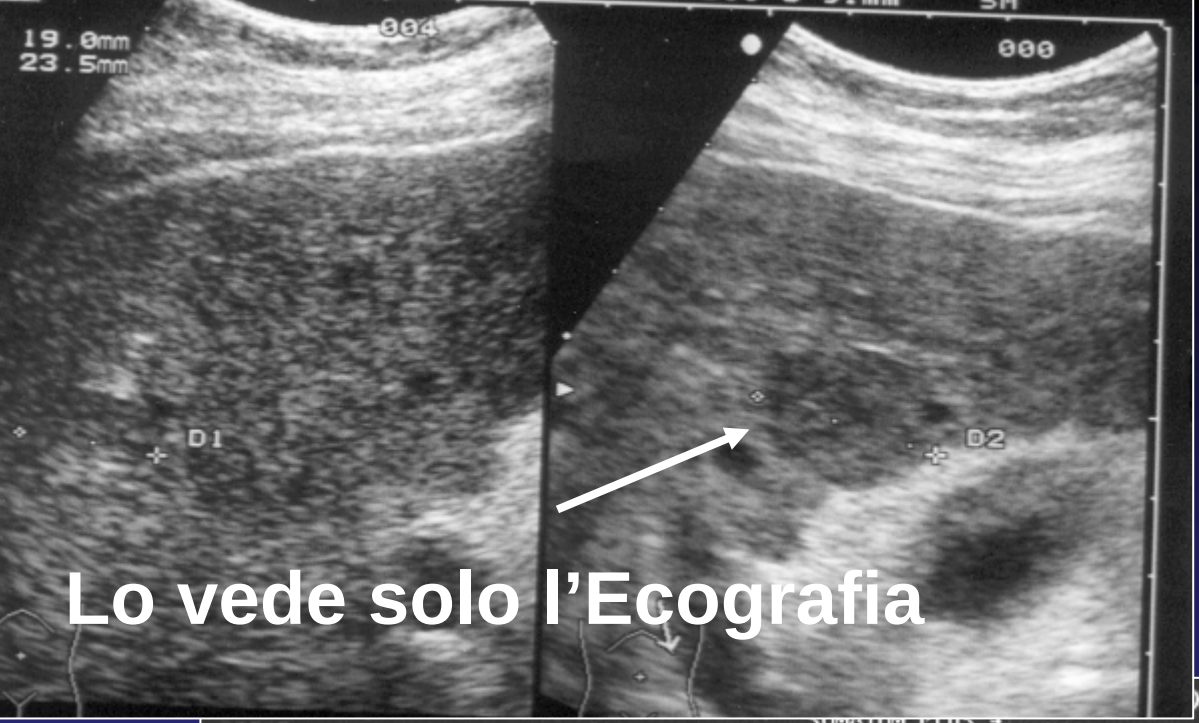
Può tuttavia rendere possibile, mediante citoriduzione, l'indicazione alla resezione di una neoplasia prima giudicata non operabile *Tang Z World J Surg, 1995*

In combinazione con la PEI (o altre tecniche di ablazione) :

La combinazione TACE + PEI non offre vantaggi rispetto alla sola PEI

Shiina S AJR, 1993 ; Tanaka K Radiology, 1992

TRATTAMENTO DI LESIONI IPERVASCOLARI NON EVIDENZIABILI CON L'ECOGRAFIA



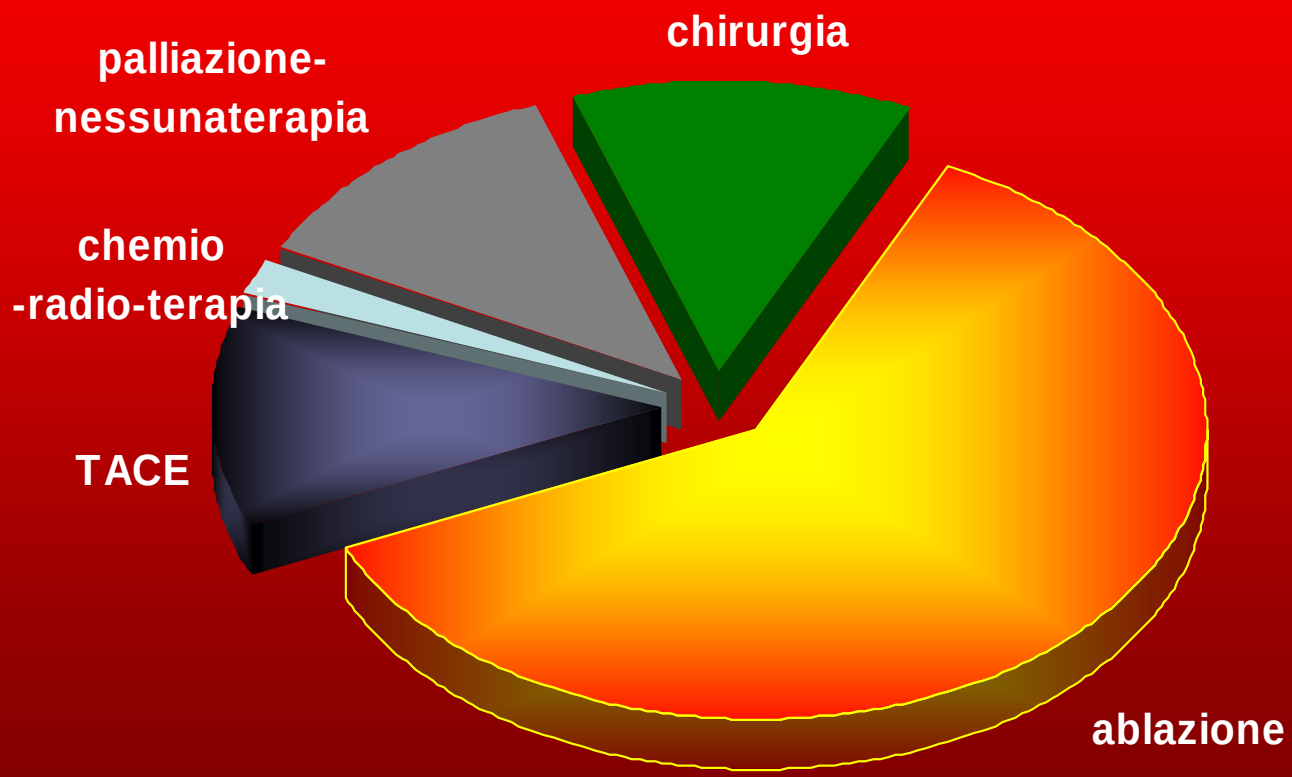
Lo vede solo l'Ecografia

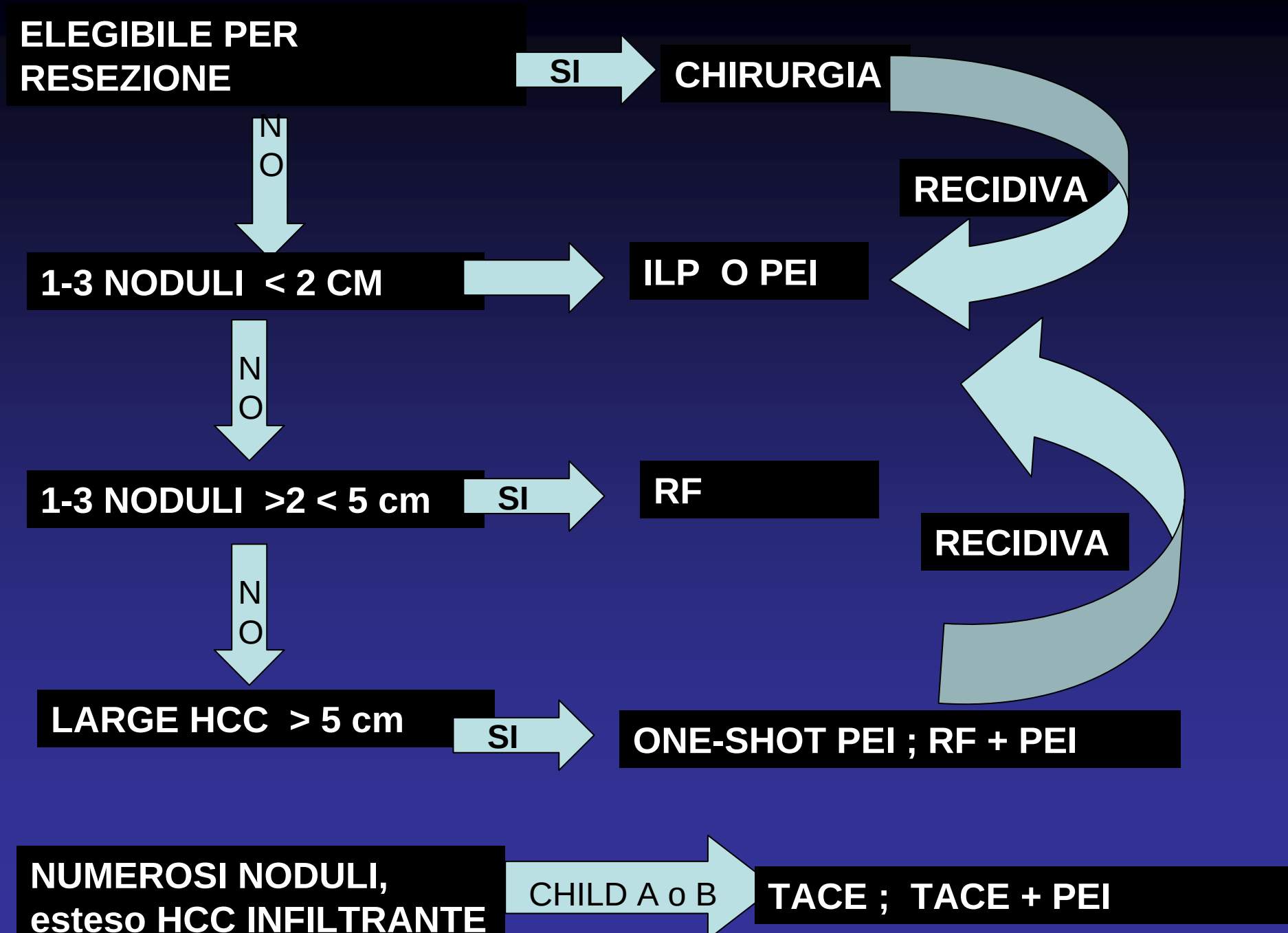
Li vede solo la TC

SOPRAVVIVENZA

ANNI	3	5
OLT	72 %	65%
RESEZIONE	71%	51%
PEI	74%	47%
RF	76%	33%
MW	56%	56%
TACE segm.	72%	44%

Non esistono trials randomizzati e le casistiche non sono comparabili .


chirurgia
palliazione-
nessunaterapia
chemio
-radio-terapia
TACE
ablazione


ELEGIBILE PER RESEZIONE
SI
CHIRURGIA
NO
RECIDIVA
1-3 NODULI < 2 CM
ILP O PEI
NO
1-3 NODULI >2 < 5 cm
SI
RF
RECIDIVA
NO
LARGE HCC > 5 cm
SI
ONE-SHOT PEI ; RF + PEI
NUMEROSI NODULI, esteso HCC INFILTRANTE
CHILD A o B
TACE ; TACE + PEI

Ultrasonics International 2003

30 June – 3 July 2003
Granada Conference and Exhibition Centre, Spain

1-3 July 2003
Conference – Ultrasonics International 2003

High intensity focused ultrasound surgery – should surgeons be worried about their futures?

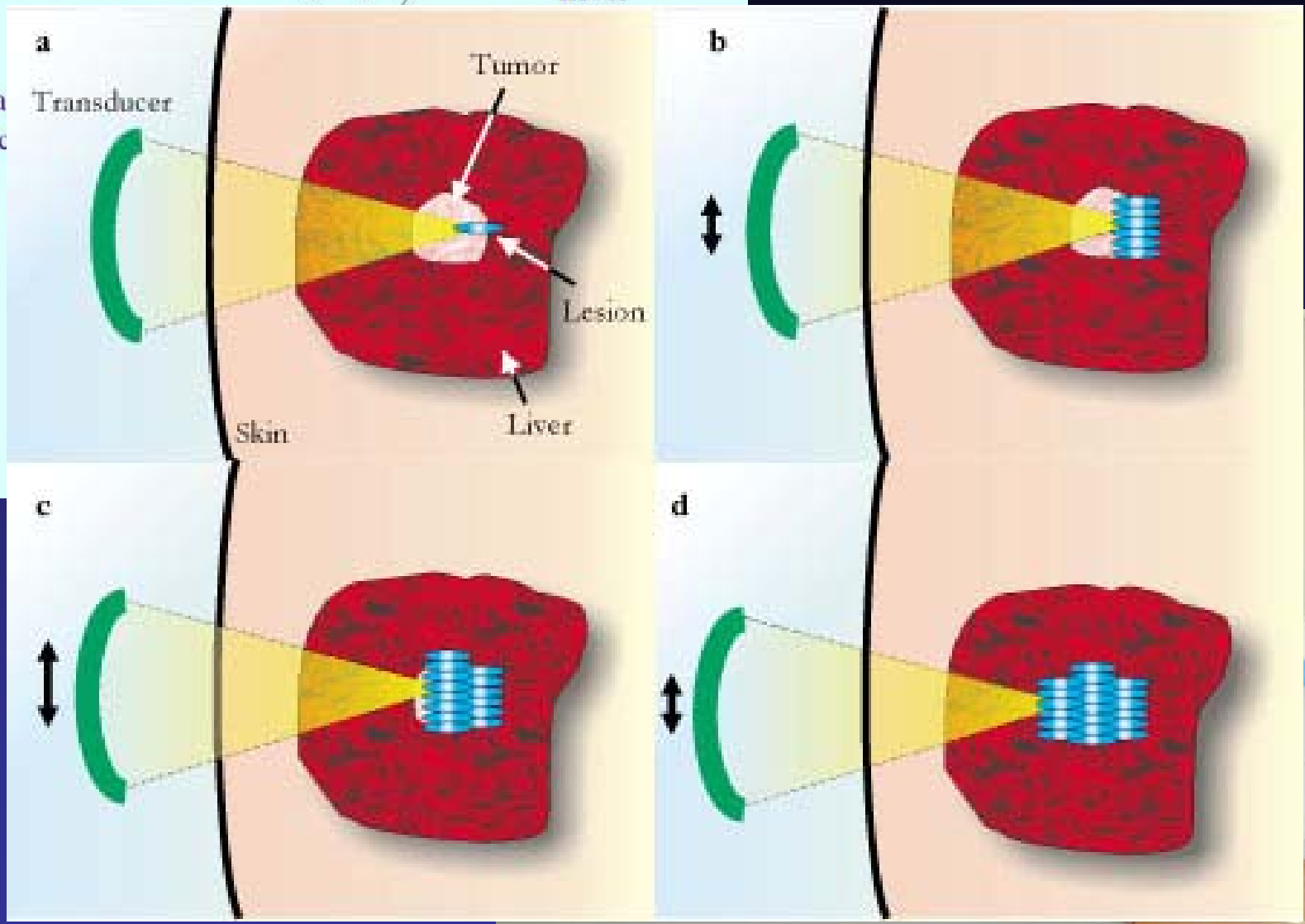
Gail ter Haar

ysics department, Institute of Cancer Research:Royal Marsden Hospita, Sutton, Surrey, SM2 5PT,

Principle of extra-corporeal high-intensity focused ultrasound surgery

Liver

Ultra
sourc



HIFU

- The technique has been demonstrated in over 2000 patients worldwide to be a safe and effective method of ablating tissue at depth without damage to intervening tissues.
- In many cases, this has been done as an outpatient technique without the need for aneasthetic or sedation.
- It now seems likely that there are a number of applications for which HIFU will become the treatment of choice.

Gt Haar, 2003. Ultrasonics International.

HIFU

- A total of 1038 patients underwent HIFU ablation in ten chinese Hospitals.
- Patological examination showed clear evidence of cellular destruction.
- Follow-up DSA, CT, MR and color Doppler US showed that there was no blood supply in the treated tumors.
- Among patients treated with HIFU an extremely low major complications rate was observed.
- It is concuded that HIFU ablation is a safe, effective and feasible modality for the ablation of liver carcinoma.

WU F: 2003. Ultrasonics International.