HCC su cirrosi: terapia delle forme avanzate con farmaci bersaglio. C'è ancora spazio per l'ablazione percutanea?

Paestum 15 Maggio 2014

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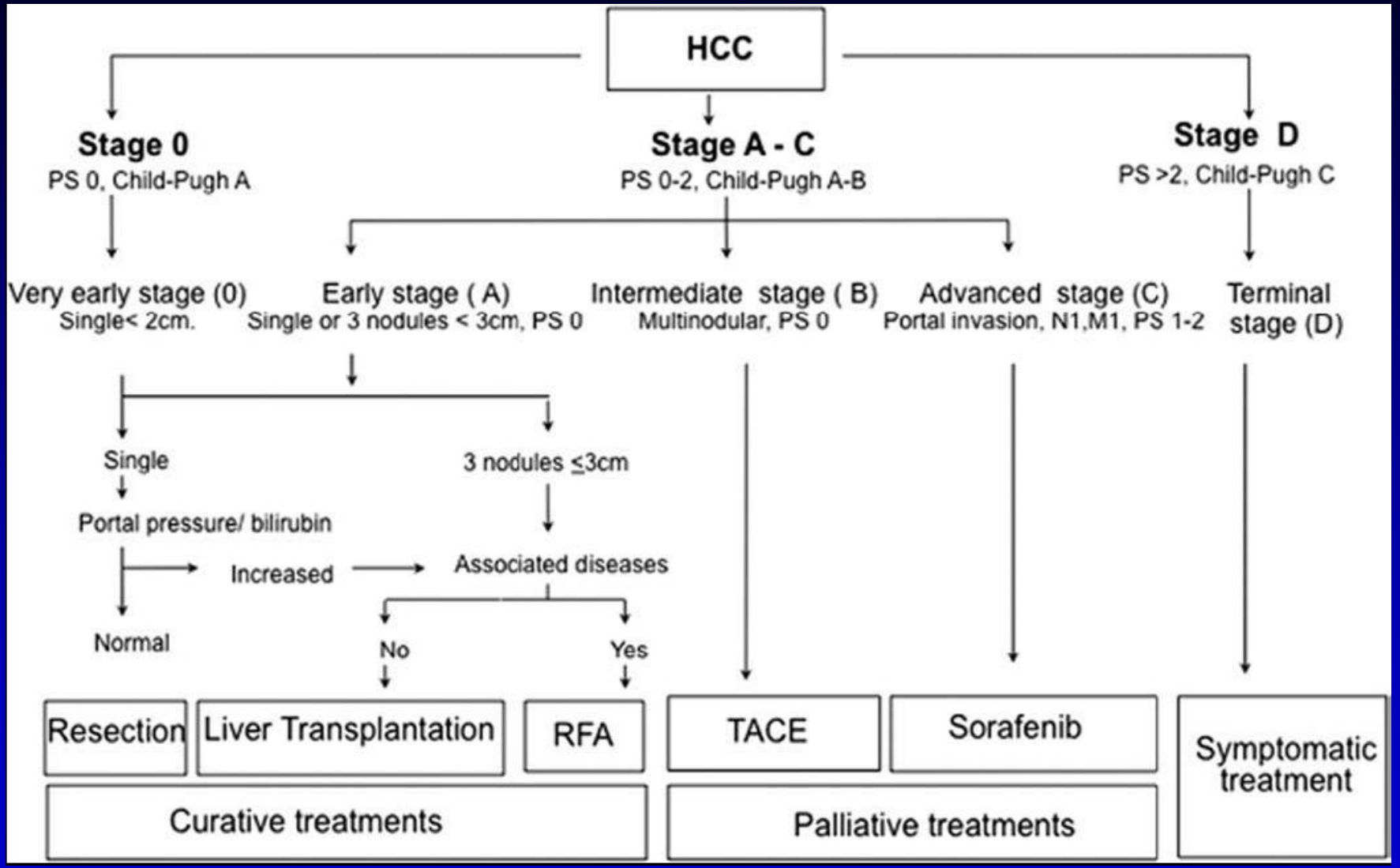
- ✓ Prognosis of pts with HCC and portal vein tumor thrombus (PVTT) is poor if left untreated, a median survival time of 2.7- 4.0 months is reported

Treatment of HCC accompanied by portal vein tumor thrombus

Minagawa M, Makuuchi M. World J Gastroenterol 2006


HCC
Stage 0
PS 0, Child-Pugh A
Stage A - C
PS 0-2, Child-Pugh A-B
Stage D
PS >2, Child-Pugh C
Very early stage (0)
Single< 2cm.
Early stage (A)
Single or 3 nodules < 3cm, PS 0
Intermediate stage (B)
Multinodular, PS 0
Advanced stage (C)
Portal invasion, N1,M1, PS 1-2
Terminal stage (D)
Single
3 nodules ≤3cm
Portal pressure/ bilirubin
Increased
Associated diseases
Normal
No
Yes
Resection
Liver Transplantation
RFA
TACE
Sorafenib
Symptomatic treatment
Curative treatments
Palliative treatments

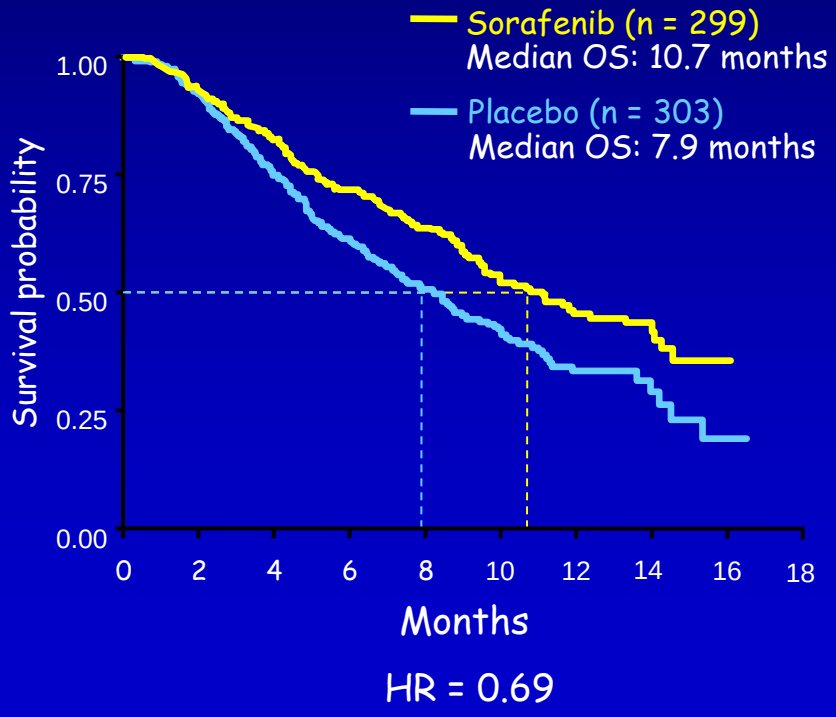
COSA E' SORAFENIB

Sorafenib è un inibitore delle multichinasi, capace di inibire la proliferazione cellulare e la neoangiogenesi, agendo sulle tirosin-chinasi presenti sulla superficie delle cellule tumorali e delle cellule dell' endotelio vascolare.

Sorafenib is the first systemic targeted therapy to show significant survival benefits and has shifted the HCC treatment paradigm

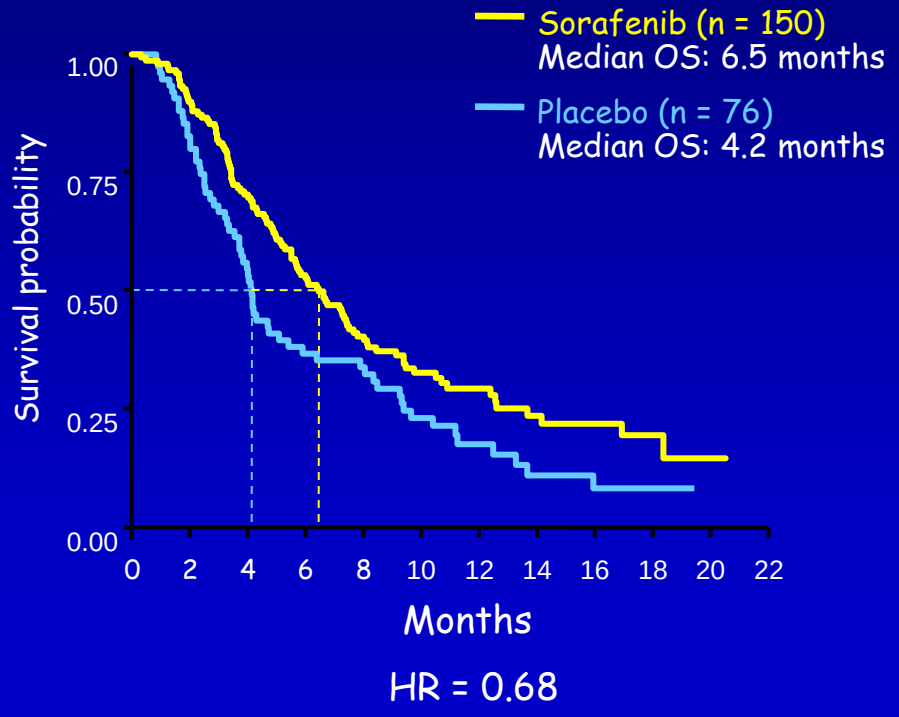
Results from pivotal trials demonstrated that sorafenib consistently increased overall survival in different patient populations across geographic regions and etiologies[1,2]

SHARP[1]



HR = 0.69

Asia-Pacific[2]



HR = 0.68

1. Llovet JM, et al. N Engl J Med. 2008;359:378-90.
2. Cheng A, et al. Lancet Oncol. 2009;10:25-34.

Many treatment options for HCC invaiding the main portal vein are been proposed: as first chance surgery with surgical remition of portal vein tumor thrombus has beeen proposed, mainly by asian surgeons. Further option include chemoembolization, interferon and recently radioembolization or, finally medical treatment with antiangiogenetic drugs as Sorafenib.

Effects of location and extension of portal vein tumor thrombus on long-term outcomes of surgical treatment for HCC

Chen XP et al, Ann Surg Oncol 2006

438 pts

Group A: 286 pts → PVTT not extended in PV/hepatic resection

Group B: 152 pts → PVTT extended in PV
hepatic resection + thrombectomy

6 months recurrences

Group A: **11.3%**

Group B: **76.9%**

Effects of location and extension of portal vein tumor thrombus on long-term outcomes of surgical treatment for HCC

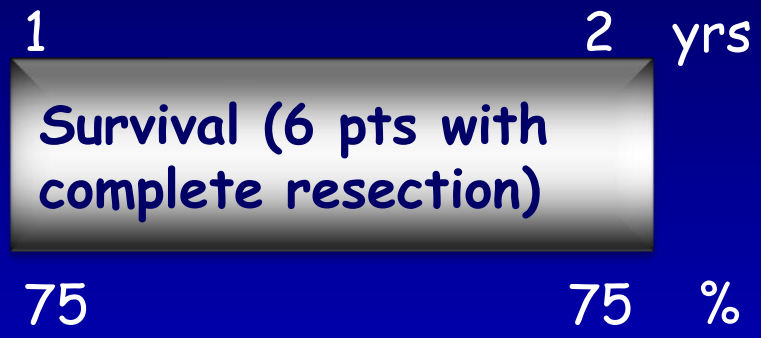
Chen XP et al, Ann Surg Oncol 2006

CONCLUSIONS

Liver resection with thrombectomy yielded better outcomes in the HCC patients with PVTT confined to the first or second branch of the main portal vein compared with PVTT extending into the main portal vein

Surgical treatment of hepatocellular carcinoma with direct removal of the tumor thrombus in the main portal vein

Konishi M et al Hepatogastroenterol 2001



In the 3 of 5 pts who died within 90 postoperative days, incomplete removal of the tumor thrombus in the portal vein caused early recurrence and death

Up to now, to our knowledge, no report has been published on Percutaneous RF ablation of both HCC and portal vein tumor thrombus

A. Giorgio
Recent Pat Anti-Cancer Drug Discov, 2010

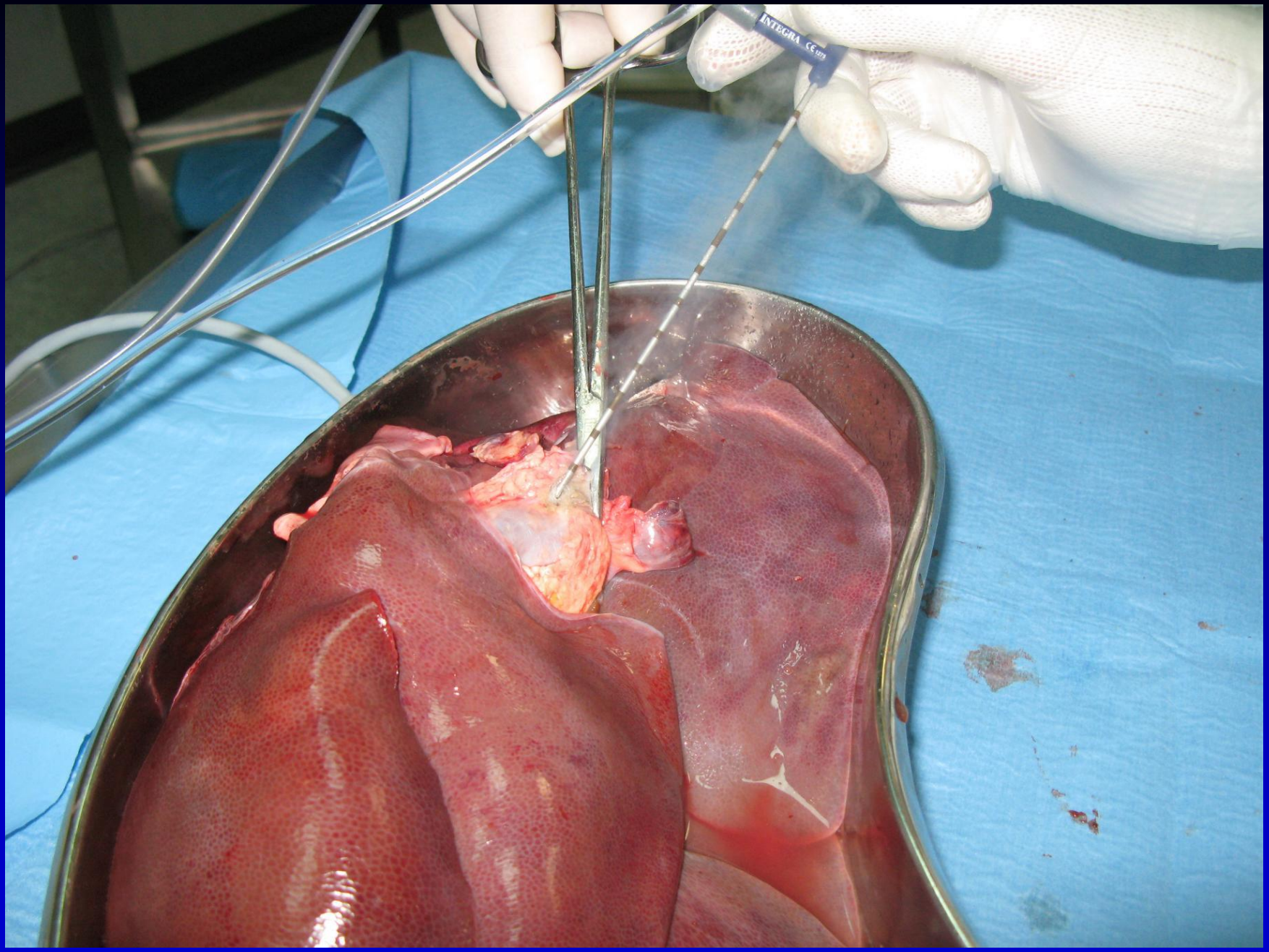
On the basis of our experience in the treatment of neoplastic thrombus of right/left branch of portal vein with One Shot PEI

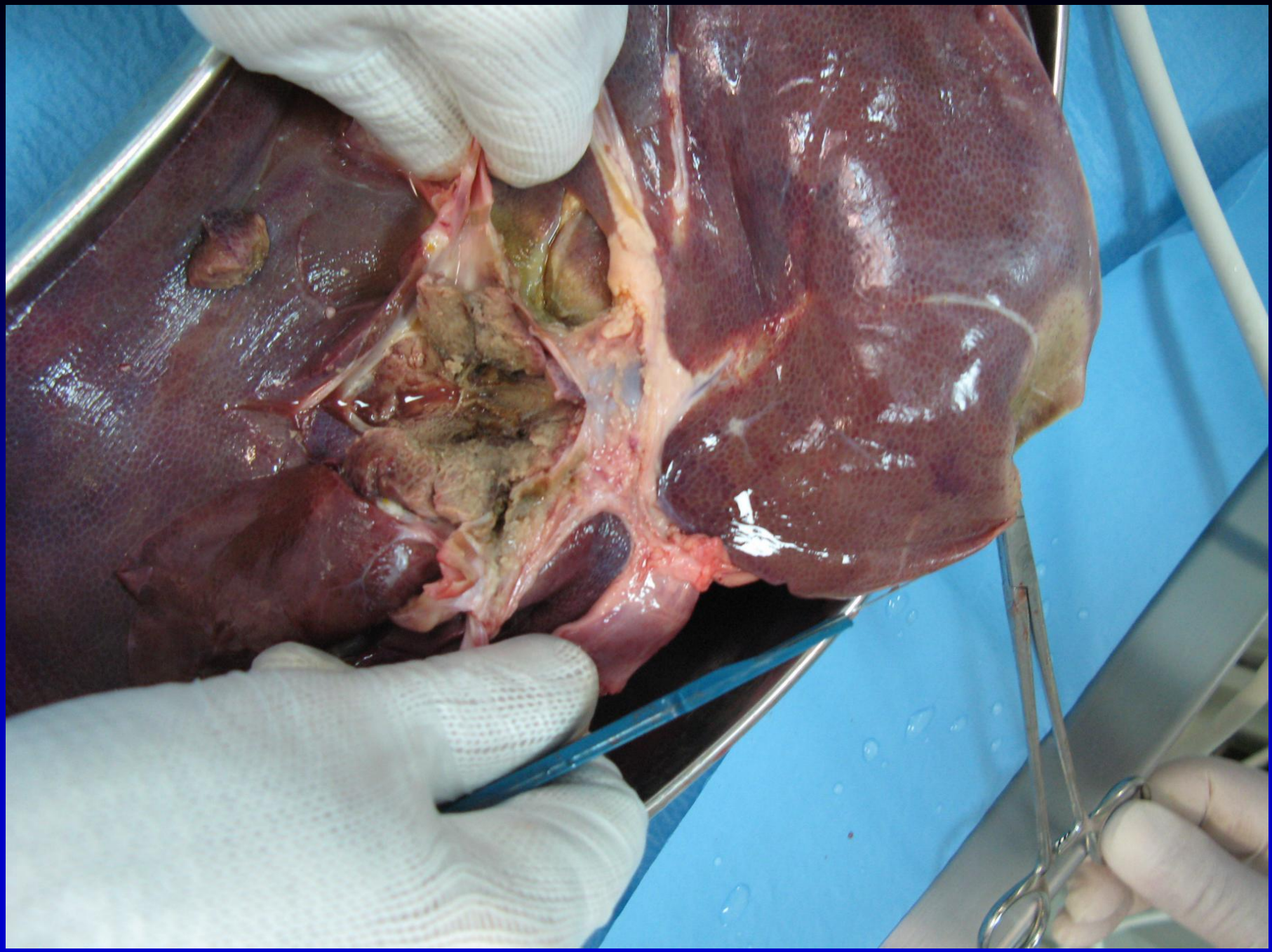
we speculated

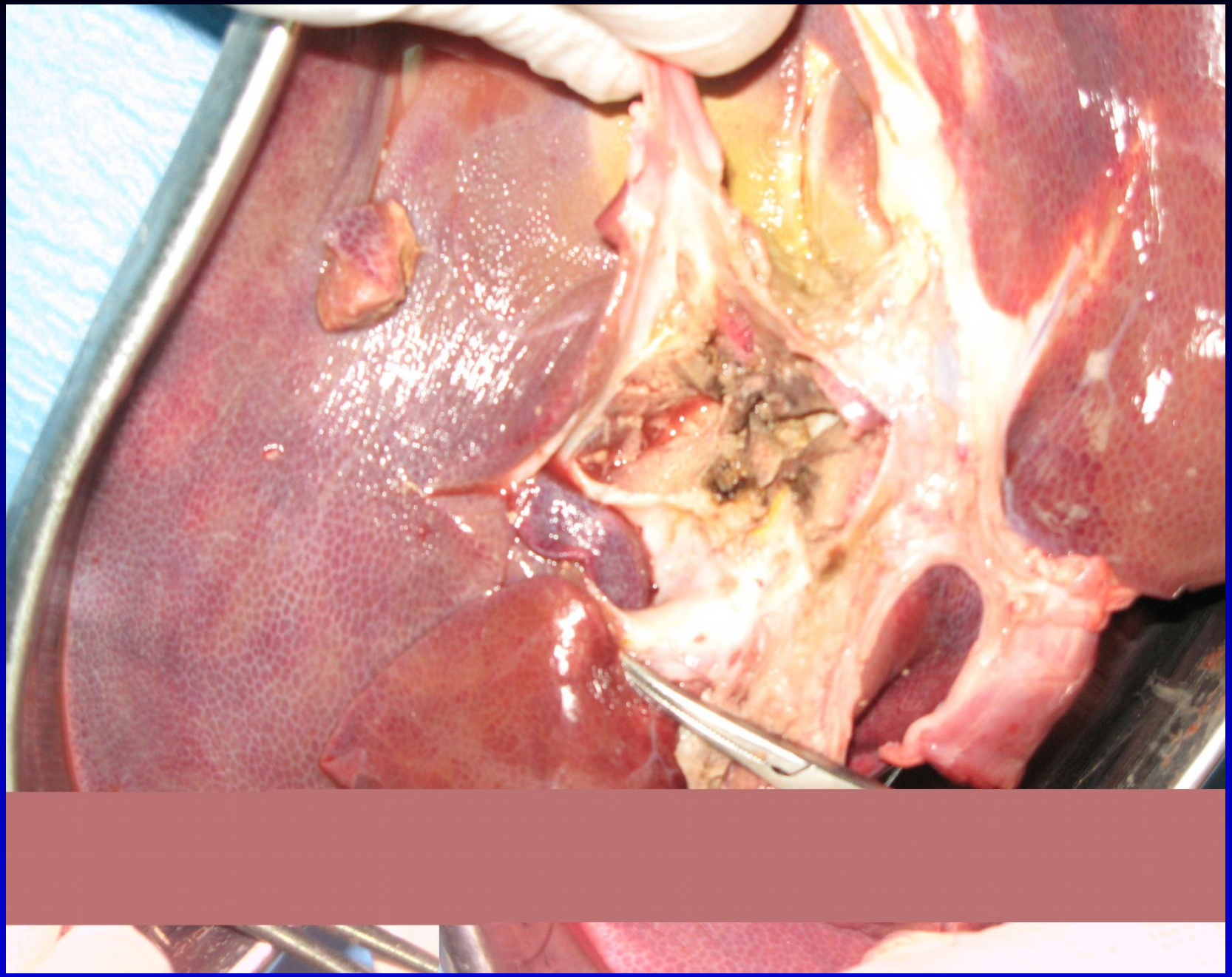
to treat both the HCC and the neoplastic tissue extended in the MPV with heat, using RF ablation in alternative to other treatment options

Ultrasound – guided percutaneous ethanol injection under general anaesthesia for the treatment of HCC on cirrhosis: long-term results in 268 patients

A. Giorgio et al, Eur J Ultrasound; 2000


INTEGRA





Hepatocellular carcinoma with cirrhosis: are patients with neoplastic main portal vein invasion eligible for percutaneous radiofrequency ablation of both the nodule and the portal venous tumor thrombus ?

A. Giorgio et al. AJR 2009; 193:948-954

patients and methods

January 2005/January 2008

1837 pts with HCC → 412 portal vessel invasion

in all cases diagnosis of neoplastic thrombus was achieved by fine-needle biopsy

27 pts had a single HCC and main portal vein tumor thrombus (**MPVTT**)

13 pts (10 males, 66-74 yrs) with 13 HCC (3.7 – 5 cm) extended in the MPT **underwent RF (group 1)**

14 matched pts with 14 HCC (3.6 - 4.8 cm) extended in MPT **refused RF (group 2: control group)**

A. Giorgio et al. AJR 2009; 193:948-954

materials and methods

Efficacy of procedure

Complete efficacy was defined when complete necrosis of HCC and complete recanalization of main portal vein and their branches were achieved

HCC necrosis was evaluated using enhanced triphasic CT

Recanalization of portal vessels was analyzed using color Doppler

A. Giorgio et al. AJR 2009; 193:948-954

results

group 1

10 pts (77%)

complete necrosis of HCC nodules
and recanalization of MPT

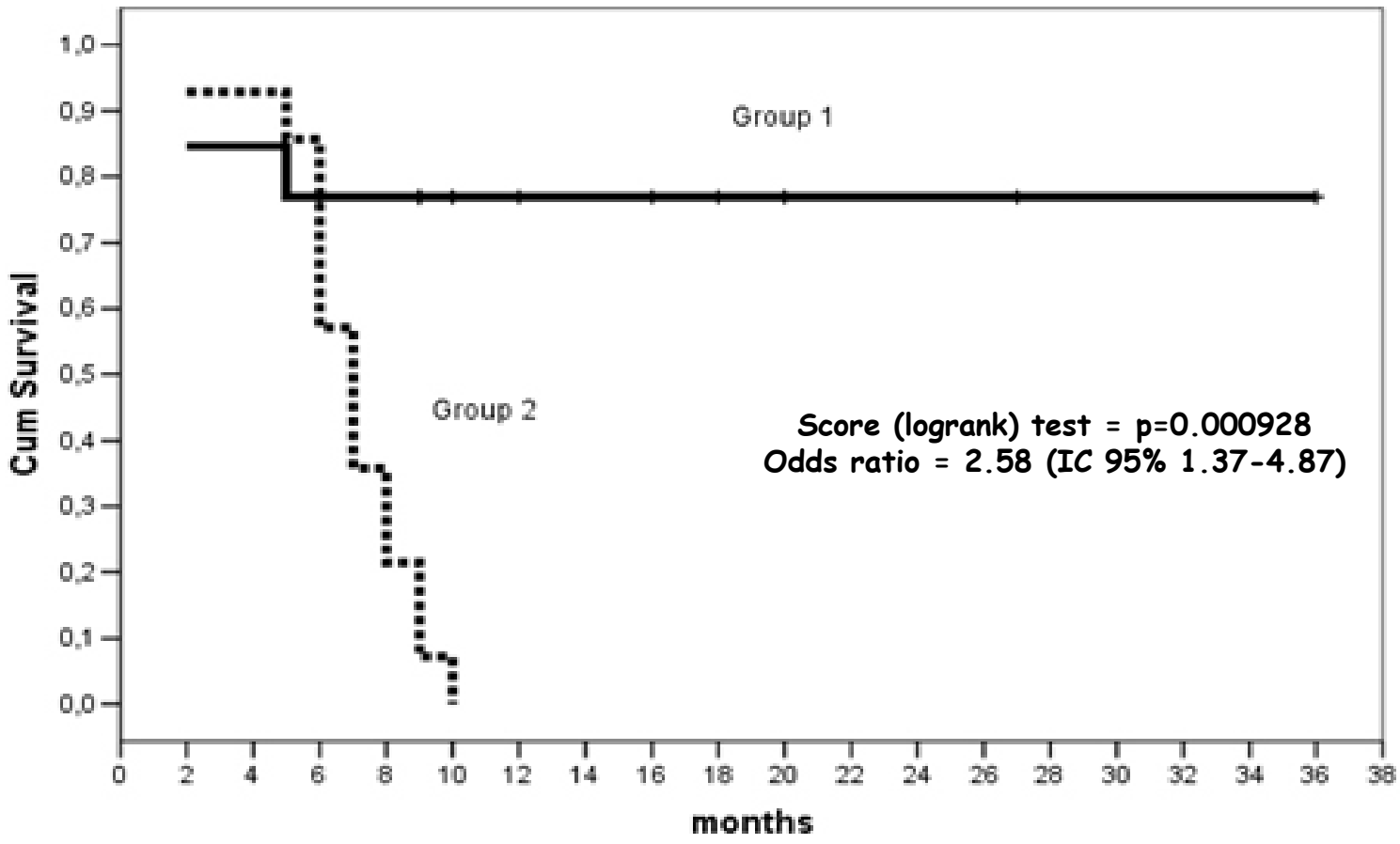
3 pts (23%)

incomplete necrosis of HCC nodules
(70-90 % on CT)
recanalization of MPT was not complete

A. Giorgio et al. AJR 2009; 193:948-954

results

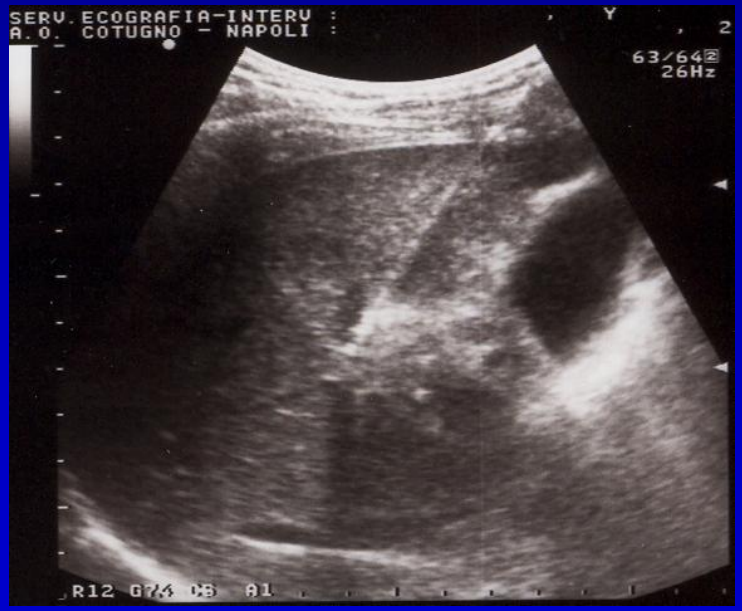
cumulative survival curves of group 1 and 2



A. Giorgio et al. AJR 2009; 193:948-954


SERV. ECOGRAFIA-INTERV :
A.O. COTUGNO - NAPOLI :
18-04-'07
12:27:20
ALOKA
89/90
24Hz
DVA: 90%
R15 G63 C5 A1
1:Addome


SERV. ECOGRAFIA-INTERV :
A.O. COTUGNO - NAPOLI :
314/315
25Hz
R15 G63 C5 A1
1:Addome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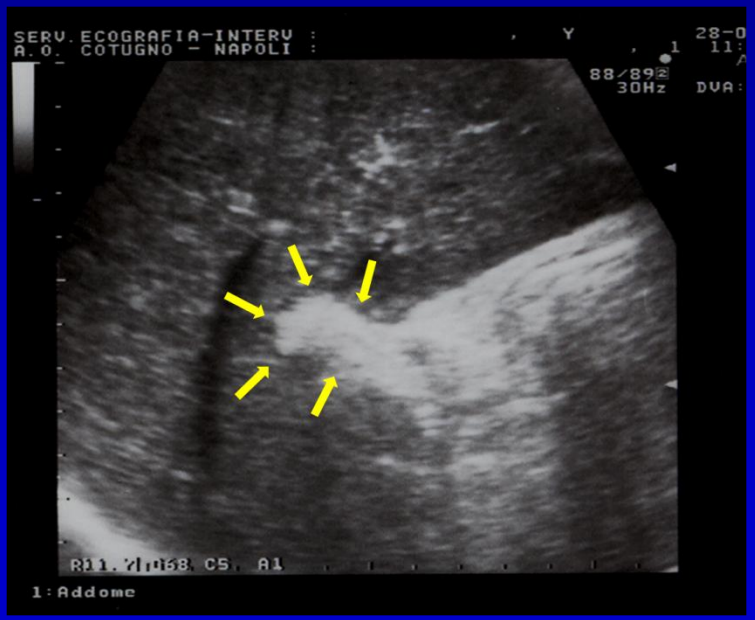
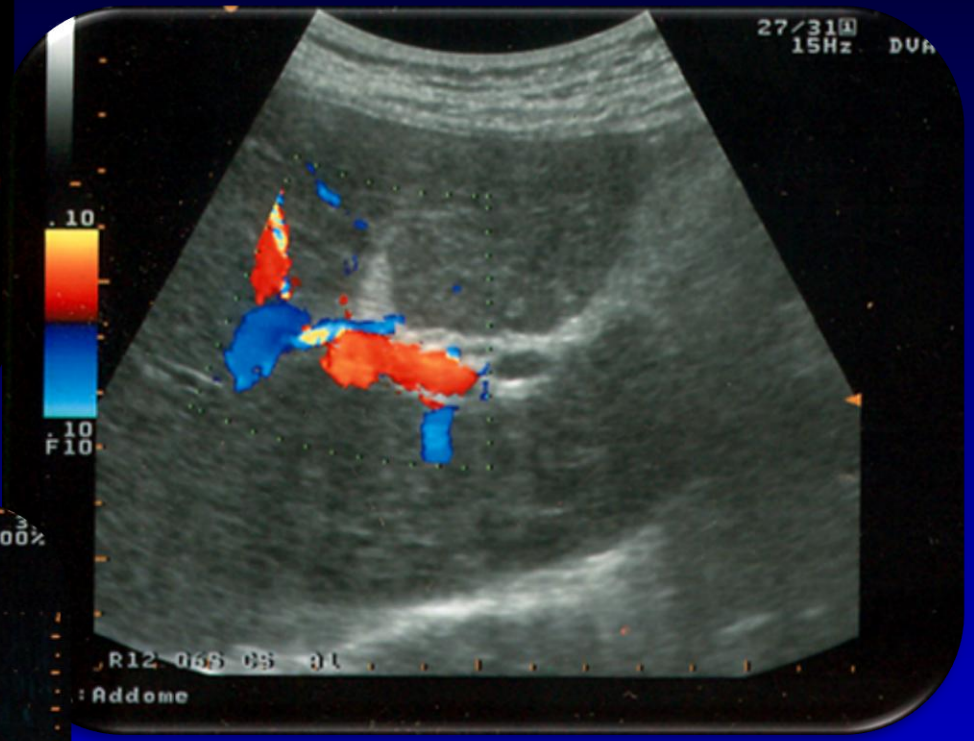
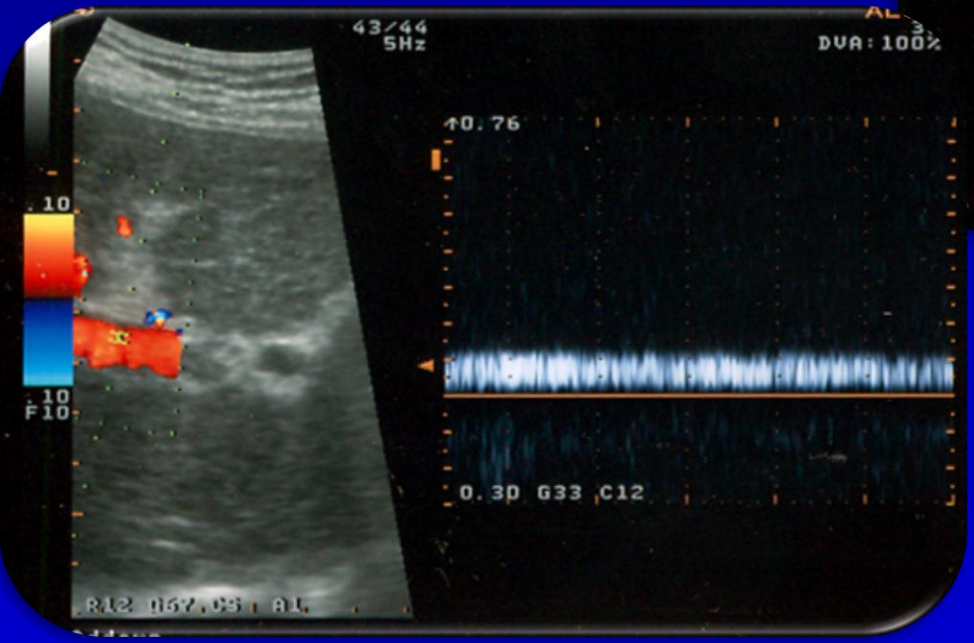
63/64
26Hz
R12 G74 C8 A1

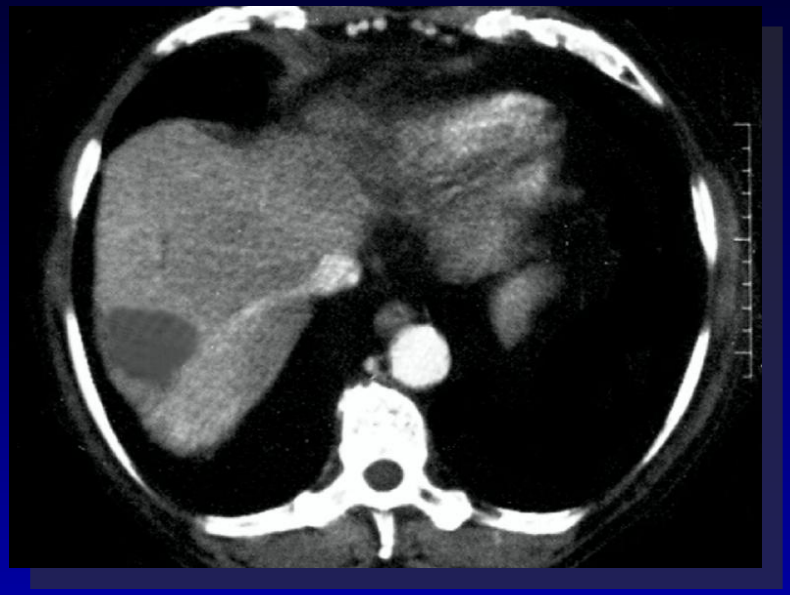

SERV. ECOGRAFIA-INTERV :
A.O. COTUGNO - NAPOLI :
88/89
30Hz
DVA:
1:Addome


.49
F09

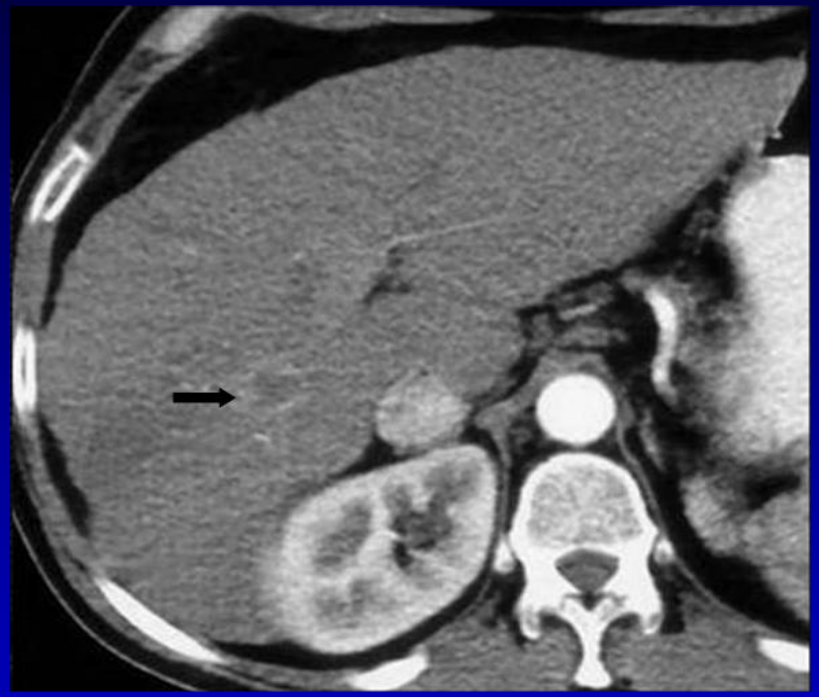

27/31
15Hz
DVA
.10
.10
F10
:Addome


43/44
5Hz
DVA:100%
0.76
.10
.10
F10
0.3p G33 C12

CT images of successful treatment during 3 year follow-up



CT images of unsuccessful treatment during 3 year follow-up



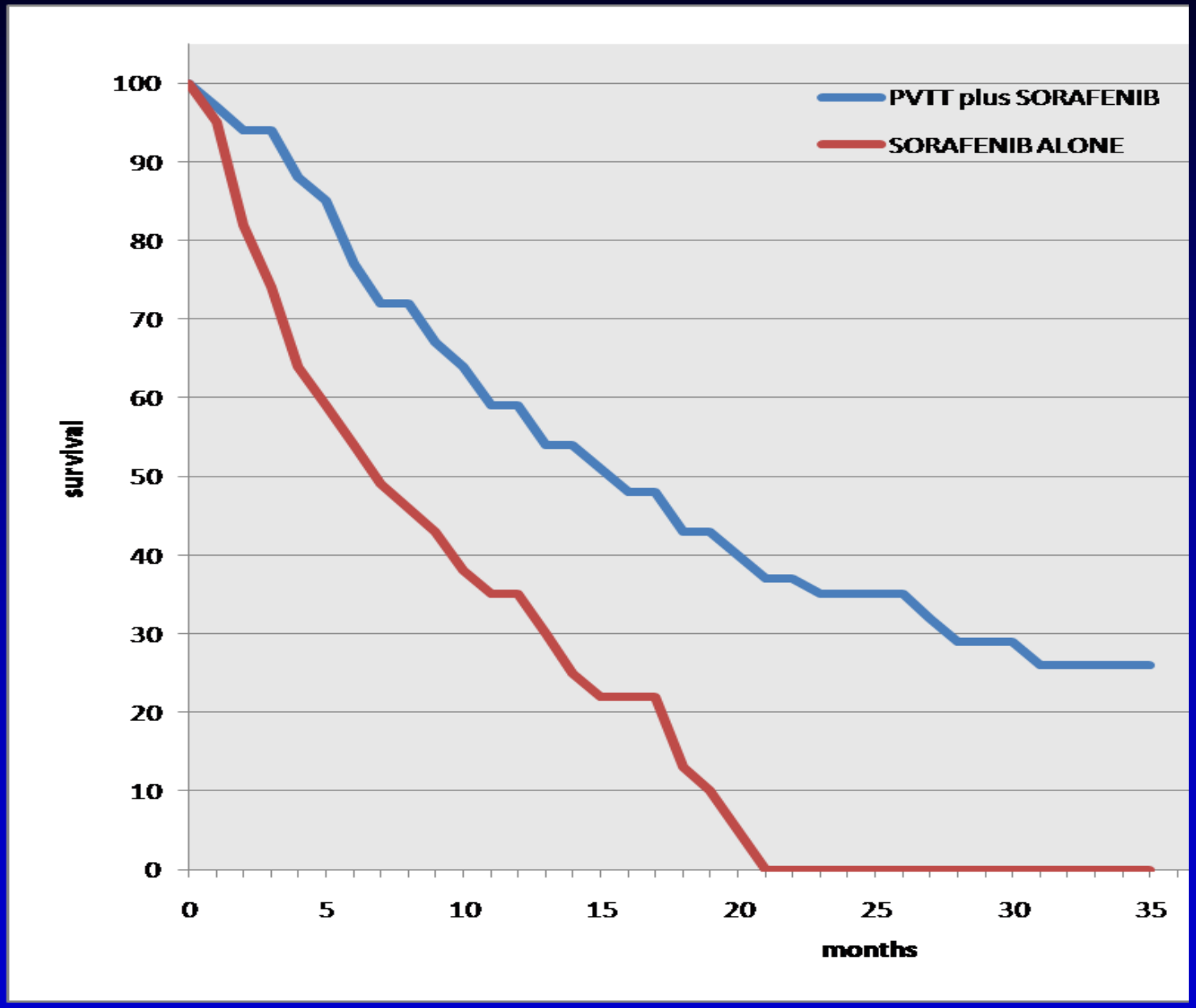
A western trial comparing percutaneous RF of both HCC and the portal venous tumor thrombus plus sorafenib with sorafenib alone

A Giorgio et al
Infectious Disease and Interventional Ultrasound Unit, "D. Cotugno" Hospital, Naples

ILCA 2011
HONG KONG

patients and methods

- ✓ from february 2009 to janaury 2011, 79 Child-Pugh A *naïve consecutive* cirrhotic pts with HCC and PVTT were randomly assigned to receive RFA of both HCC and PVTT plus sorafenib (n.39) or sorafenib alone (n.40)


PVTT plus SORAFENIB
SORAFENIB ALONE
survival
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
months

complications

RF-thrombectomy plus sorafenib

✓ADVERSE EVENTS : **37%**

✓ **abdominal pain, diarrhea, weight loss, asthenia, hand foot syndrome**

spinocellular haepitelioma,acute pancreatitis in one case

✓DROPPED-OUT : **25%**

complications

sorafenib alone

- the dropped-out were 29%

- adverse events in 39%

  - abdominal pain, diarrhea, weight loss, asthenia, hand foot syndrome,

conclusions

✓ the combination between RFA of both HCC and PVTT plus sorafenib significantly increases 3-year survival compared to the sorafenib alone

✓ our data seems to suggest that RFA of both HCC and PVTT represent a significant factor for increased survival

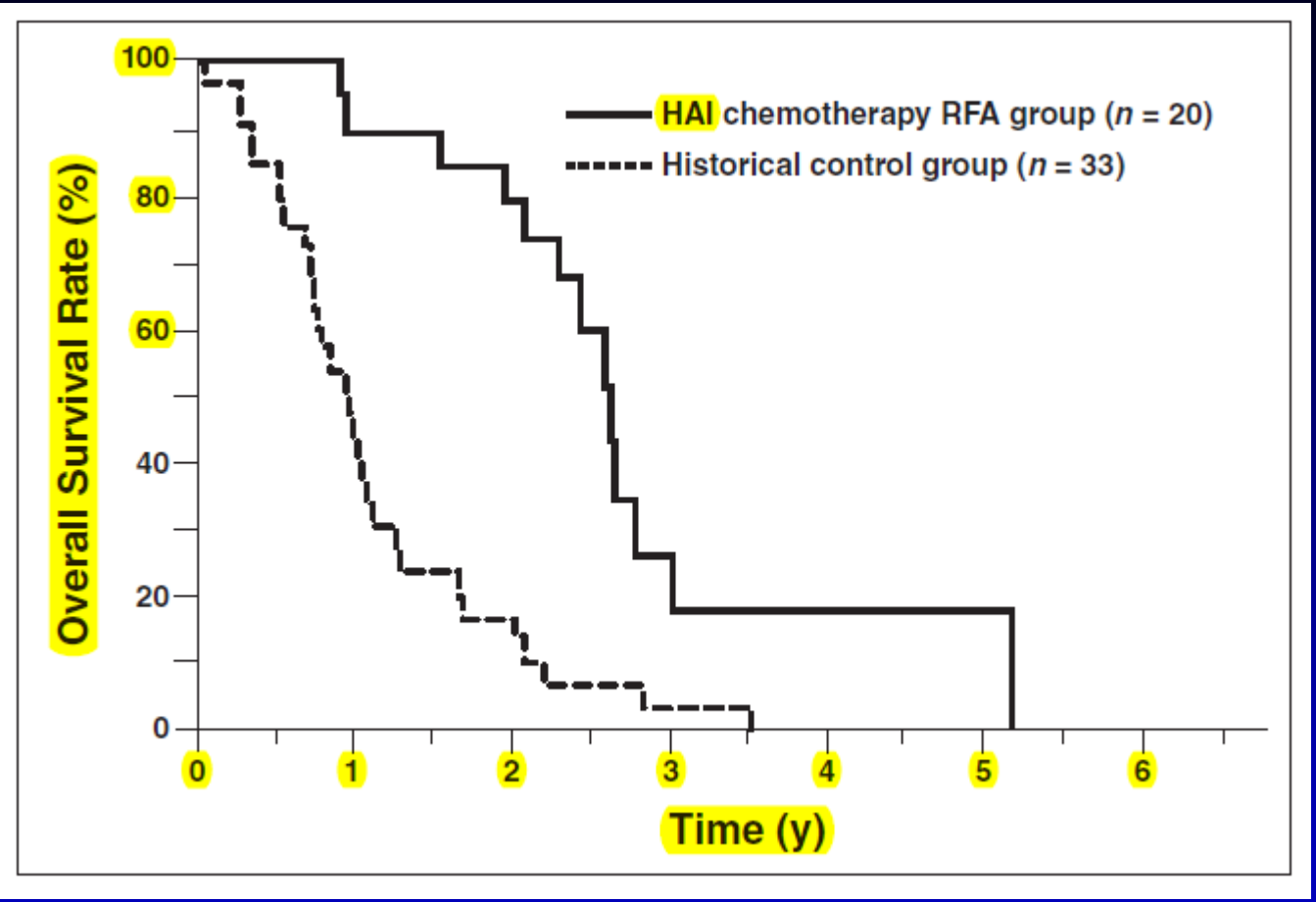
AJR Am J Roentgenol. 2010 Feb;194(2):W221-6. doi: 10.2214/AJR.09.2852.

Mass reduction by radiofrequency ablation before hepatic arterial infusion chemotherapy improved prognosis for patients with huge hepatocellular carcinoma and portal vein thrombus.

Hirooka M[1], Koizumi Y, Kisaka Y, Abe M, Murakami H, Matsuura B, Hiasa Y, Onji M.

SUBJECTS AND METHODS:

HCC with PV tumor thrombosis was diagnosed in 20 patients between April 2004 and December 2008, and treatment was performed using mass-reduction therapy by RFA before HAI chemotherapy. For comparison, 33 patients treated with HAI chemotherapy without RFA were retrospectively selected as historical control subjects under the same conditions. Prognosis in each group was evaluated.



In the mass-reduction group, the cumulative survival rates at 6, 12, and 24 months were 100%, 89.7%, and 78.8%, respectively.

CONCLUSION

For patients with huge HCC and PV tumor thrombosis, mass-reduction treatment by RFA before HAI chemotherapy is safe and can improve prognosis.

HCC on cirrhosis invading main portal vein: long-term results of percutaneous RFA

Giorgio A et al J. Hepatol 2011

aim

to report 5-year survival of percutaneous RF ablation of both medium-sized HCC accompained by portal venous tumor thrombus (PVTT) in cirrhotic pts

patients and methods

✓ 2847 pts with HCC, 672 had HCC and PVTT;
57 of 672 had a single HCC with portal vein tumor thrombus (PVTT)

✓ 35 pts with 35 HCC (3.7-5 cm) extending into the main portal trunk (MPT) underwent RFA (treated group)
22 matched pts with 22 HCC (3.6-5 cm) extending into the MPT refused RFA (control group)

✓ diagnosis of PVTT was made with fine needle biopsy in all cases

results

complete necrosis of the HCC with complete recanalization of MPV was achieved in 67% of cases (follow-up 8-68 months)

1	2	3	4	5	yrs
cumulative survival *(treated group)*					
63	41	30	20	20	%

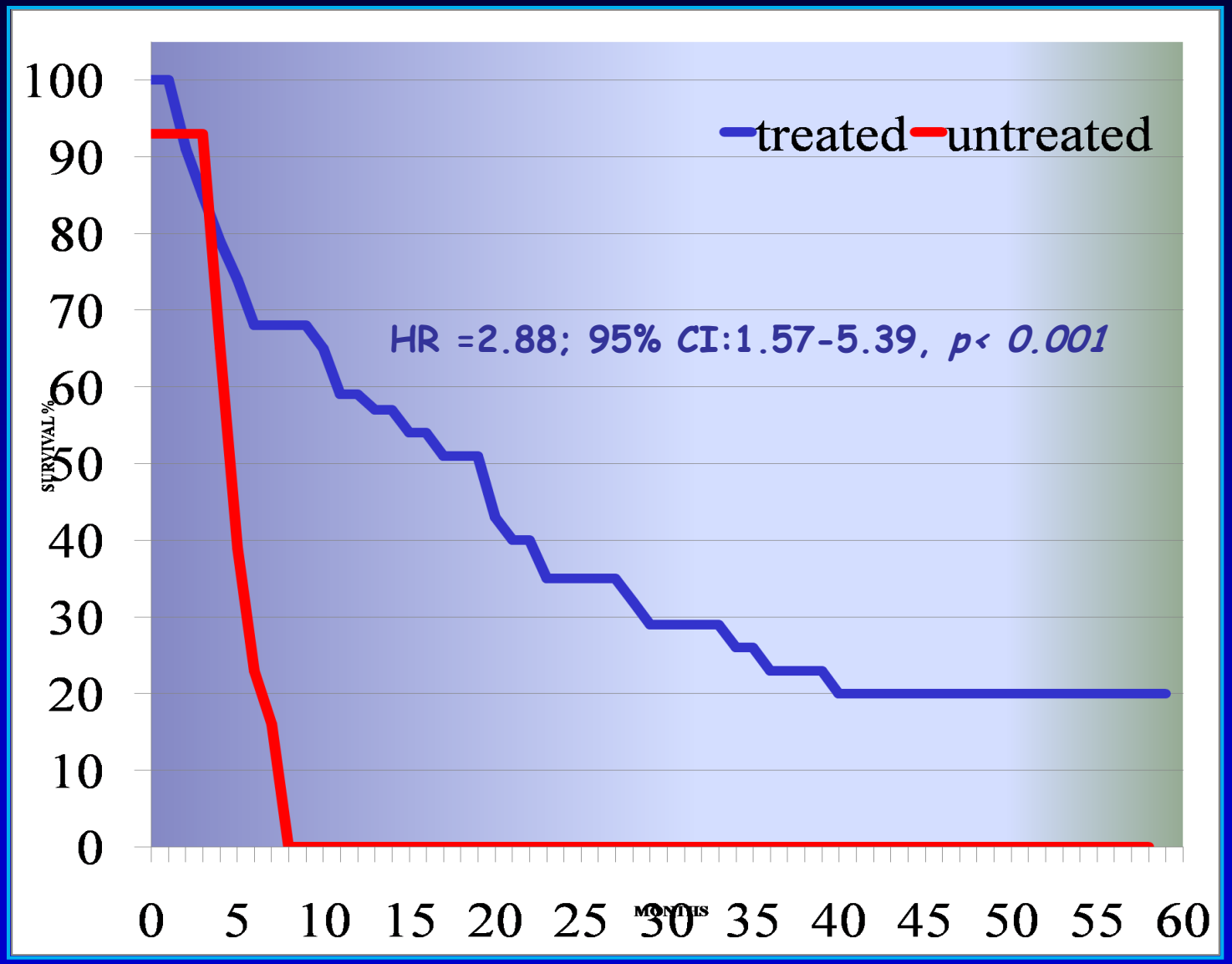
1	yr
cumulative survival *(untreated group)*	
0	%

P< 0.001

results

cumulative survival curves

treated *vs.* untreated groups



complications

- ✓ no patient died
- ✓ one patient had haemoperitoneum that healed spontaneously
- ✓ seven patients presented with ascites and 9 with increased transaminases: both these complications resolved within 7 days

conclusion

- ✓ percutaneous RFA of both single intraparenchymal medium-size HCCs with MPVTT, significantly prolongs long-term survival of cirrhotic pts compared with no treatment

- ✓ the procedure is safe, with low rate of major complications and should be considered as a new and effective tool in the treatment of advanced HCC

Recently the use of Yttrium-90 radioembolization for the treatment for advanced HCC accompanied by PVTT was introduced.

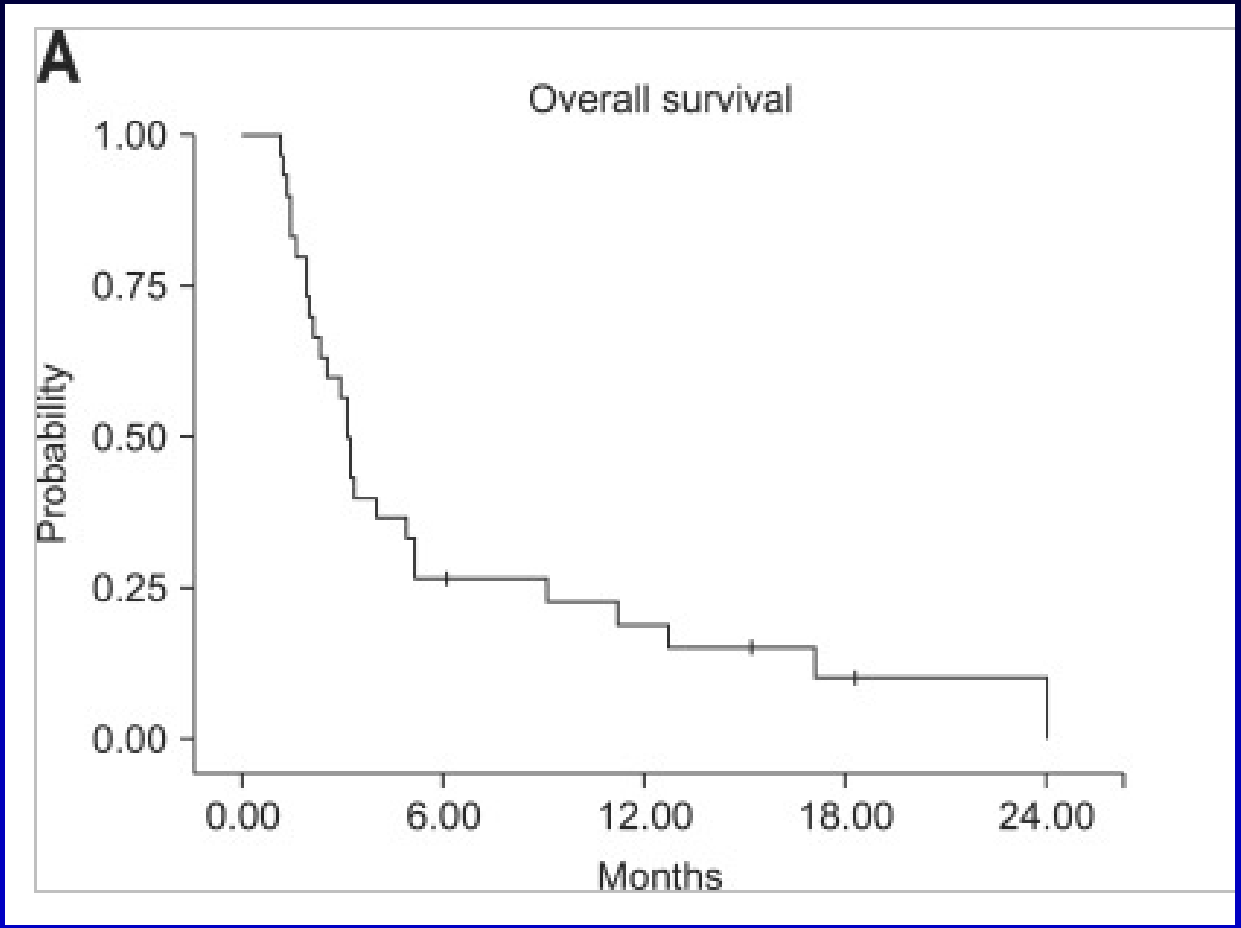
In the study by Mazzaferro et al **58 treatments were performed on 52 patients**. Median follow-up was 36 months.
Median survival was 15 months (95% confidence interval 12-18) with a non-significant trend in favor of non-PVT vs. PVT patients (18 vs. 13 months). Five complete responses occurred (9.6%) and the 2-year progression rate was 62%

Tsai et al conducted a retrospective review of HCC with main (n = 10) or first-branch (n = 12) PVT treated with (90) yttrium microspheres (N = 22) [14]. Median survival for patients with CLIP scores of 2/3 was 7 months, versus 1.3 months for those with scores of 4/5 (P = .04)

Practical Effect of Sorafenib Monotherapy on Advanced Hepatocellular Carcinoma and Portal Vein Tumor Thrombosis

Soung Won Jeong, Jae Young Jang, Kwang Yeun Shim, Sae Hwan Lee, Sang Gyune Kim, Sang-Woo Cha, Young Seok Kim, Young Deok Cho, Hong Soo Kim, Boo Sung Kim, Kyoung Ha Kim, Jung Hoon Kim

Gut Liver 2013


A
Overall survival
1.00
0.75
0.50
0.25
0.00
Probability
0.00
6.00
12.00
18.00
24.00
Months

HPB
THE OFFICIAL JOURNAL OF THE
International Hepato-Pancreato-Biliary Association
Americas Hepato-Pancreato-Biliary Association
European-African Hepato-Pancreato-Biliary Association
IHPBA

HPB (Oxford). Apr 2012; 14(4): 247–253.
doi: 10.1111/j.1477-2574.2011.00436.x
PMCID: PMC3371211

Factors linked to longterm survival of patients with hepatocellular carcinoma accompanied by tumour thrombus in the major portal vein after surgical resection

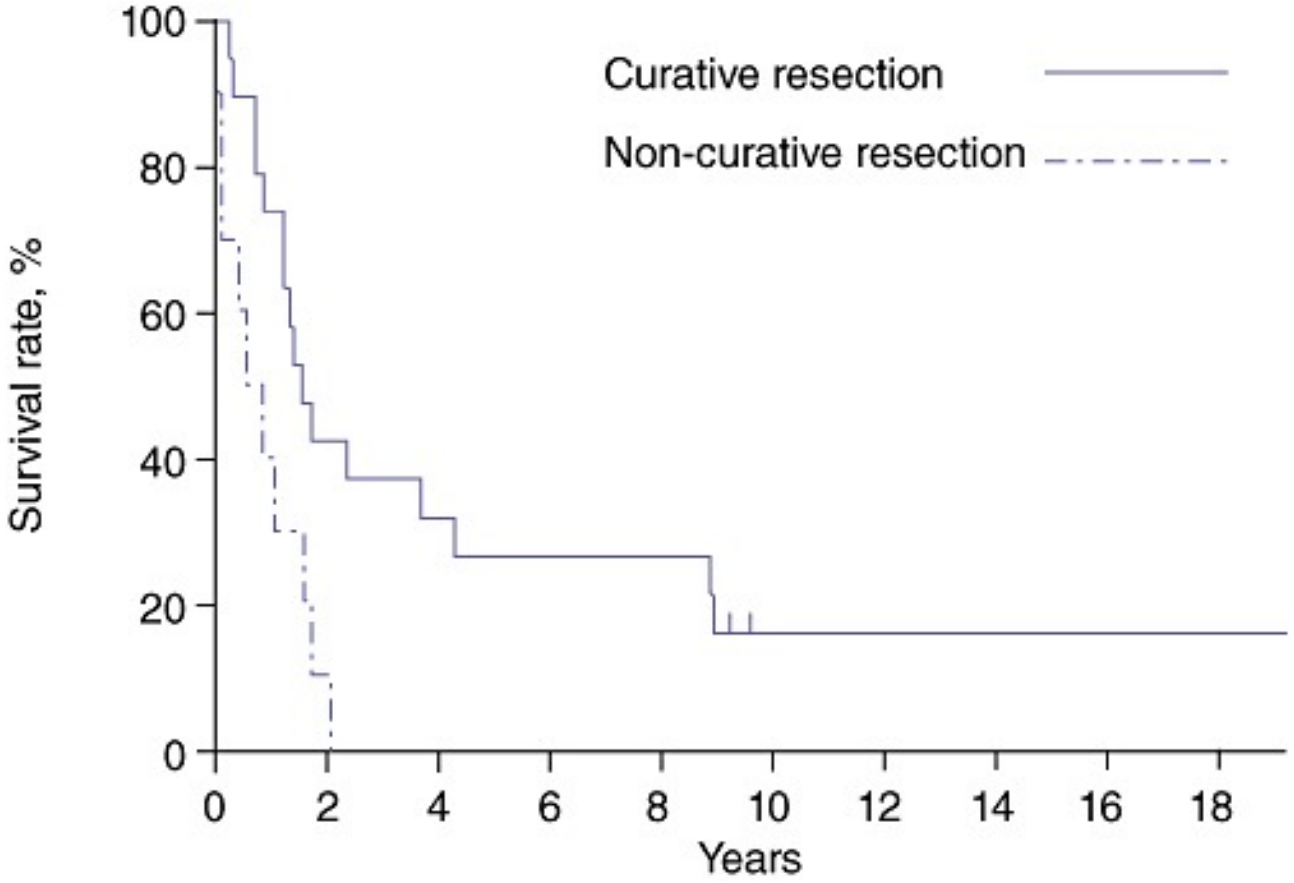
Rumi Matono, Shohei Yoshiya, Takashi Motomura, Takeo Toshima, Hiroto Kayashima, Toshiro Masuda, Tomoharu Yoshizumi, Akinobu Taketomi, Ken Shirabe, and Yoshihiko Maehara

Author information ► Article notes ► Copyright and License information ►

Methods

Twenty-nine HCC patients with MPVTT were divided into two groups comprising, respectively, patients who survived >5 years after hepatectomy (survivors, *n* = 5) and those who did not (non-survivors, *n* = 24). The two groups were compared.

Figure 2

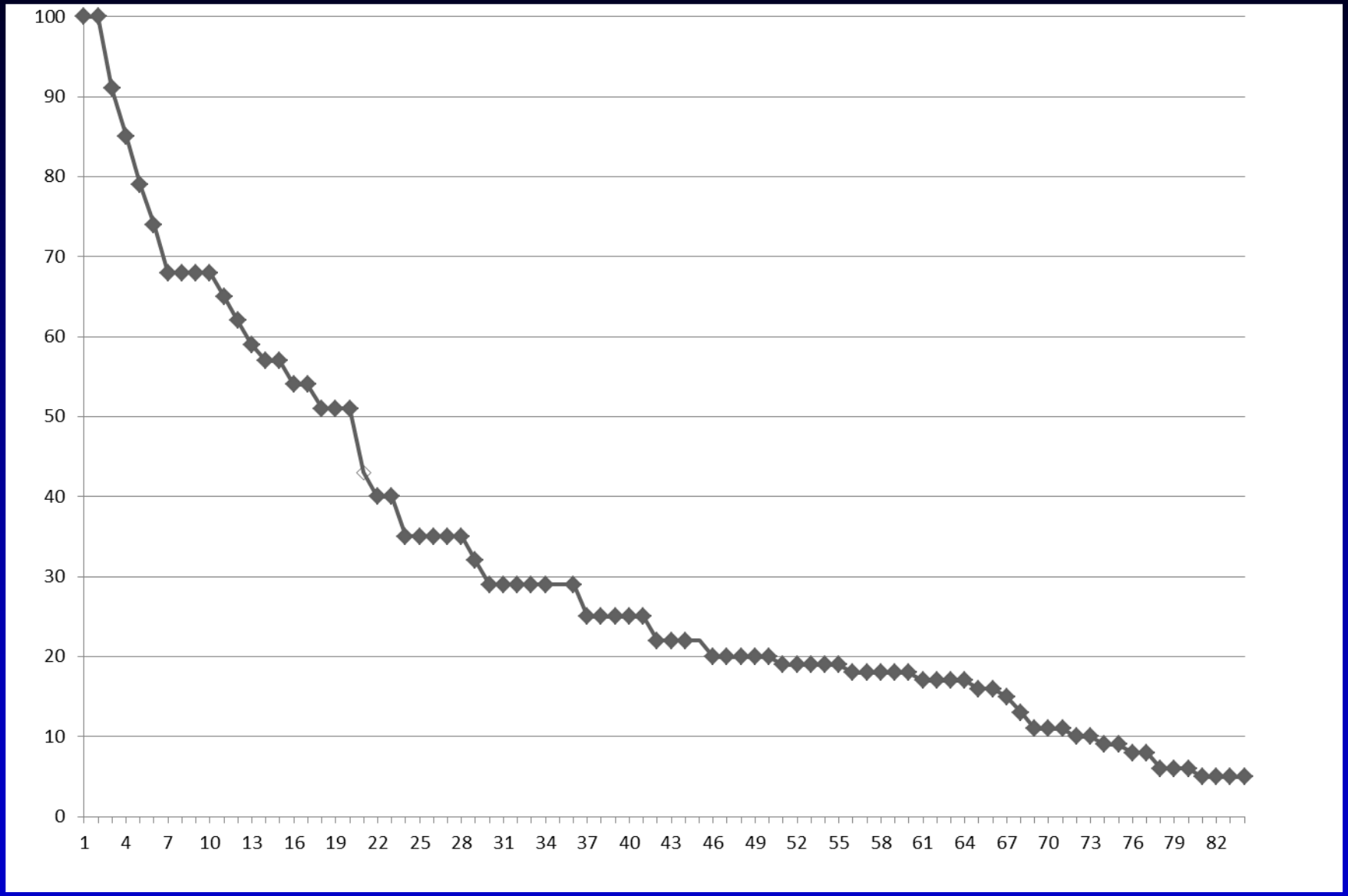

Curative resection
Non-curative resection
Survival rate, %
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
18
Years

Hepatocellular carcinoma (HCC) invading portal venous system in cirrhosis: 7 years results of Percutaneous Radiofrequency Ablation of both HCC nodule and main portal vein tomor thrombus (MPVTT). A case control study

A. Giorgio et al
Naples , Italy

J Hepatol , 2014

- **SUBJECTS AND METHODS:**
- From January 2005 to January 2012 , among 3144 consecutive cirrhotics , 772 had HCC and MPVTT ; of these ,**70** had a single HCC with MPVTT . **48 patients** (38 men; mean age, 69 years)with 48 HCC nodules 3.7-5 cm in diameter invading main portal trunk (MPT) underwent RFA.
- **22** matched patients (18 men; mean age, 69 years) with 22 HCC nodules 3.6-4.8 cm in diameter extending into the MPT refused RFA and composed the control group. Efficacy of RFA was defined complete when both complete necrosis of HCC and complete recanalization of the MPT and its branches was achieved .


100
90
80
70
60
50
40
30
20
10
0
1
4
7
10
13
16
19
22
25
28
31
34
37
40
43
46
49
52
55
58
61
64
67
70
73
76
79
82

- **RESULTS:**
-
- The 1, 3 ,5 and 7- year survival rates of treated patients were 62 , 29 , 18 and 5 % , respectively. None of the patients in the untreated group survived at 1 year.
- The difference was statistically significant ($p < 0.001$; hazard ratio, 2.88; 95% CI, 1.57– 5.39). The disease free survival rates in the treated group was 52 ,38 ,35 , and 23 % at 1 ,3 , 5 , and 7 years ,respectively. No deaths occurred .
- As far as major complications is concerned no deaths occurred after RFA.

- ***CONCLUSIONS:***

- ***RFA of HCC with MPVTT significantly prolongs long-term survival compared with no treatment. The procedure is safe and should be considered as a new and effective tool in the treatment of advanced HCC***