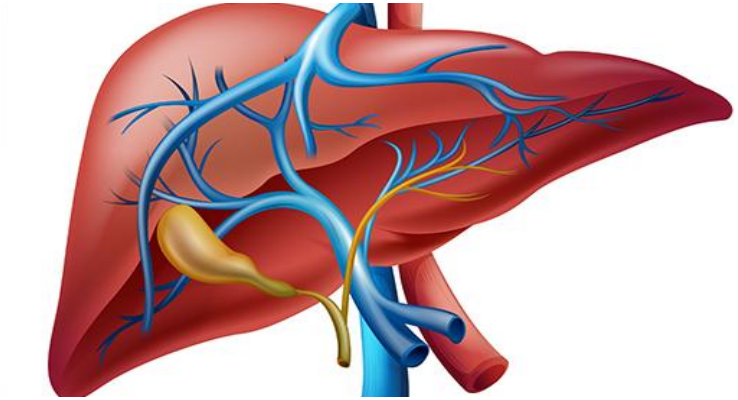

HCC e Virus Epatitici

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Clinica Tortorella -Salerno

Significance of hepatitis virus infection in the oncogenic initiation of hepatocellular carcinoma

Caecilia HC Sukowati, Korri E El-Khobar, Susan I Ie, Beatrice Anfuso, David H Muljono, and Claudio Tiribelli 2016 Jan 28; 22(4): 1497–1512

Hepatocellular carcinoma is the most common type of primary liver cancers, it accounts for around 90% of all cases.

It is the fifth most common cancer in men and the ninth in women, and the second most common cause of cancer-related death, estimated to be responsible for around 9% of all cases in 2012.

The global distribution of HCC is associated with the prevalence of its dominant risk factors.

Infection of endemic hepatitis B virus (HBV) is the major cause of HCC in eastern Asia and sub-Saharan Africa for around 70%.

In Europe and North America countries, hepatitis C virus (HCV) infection ranges from 50%-70% while excessive alcohol consumption leading to alcohol steatohepatitis (ASH) contributes for around 20% of all cases.

El-Serag HB. Hepatocellular carcinoma. *N Engl J Med*. 2011;**365**:1118-1127.

In its development, HCC usually emerges from a long-term chronic disease course with underlying liver cirrhosis (around 80%)

Caldwell S, Park SH. The epidemiology of hepatocellular cancer: from the perspectives of public health problem to tumor biology. *J Gastroenterol*. 2009;**44 Suppl 19**:96-101

HEPATITIS VIRUS INFECTION

HBV infection

HBV-related HCC development is mainly associated with risk factors such as male gender, persistently high HBV DNA levels, hepatitis B *e* antigen (HBeAg) positivity, presence of liver cirrhosis, older age, persistently high ALT levels, family history of HCC or chronic infection from perinatal transmission, and co-infection with HIV and/or HCV

Sukowati,WJG;2016

Male gender has hazard ratio (HR) 2-8 times more for HCC development compared to female

Similarly, higher HBV DNA levels is associated with higher incidence of HCC compared to HBV DNA levels lower than 10000 copies/mL.

HBeAg positivity and ALT levels ≥ 45 U/L have HR 4.3 and 4.1, respectively, while liver cirrhosis is associated with 10.8-33.3 increased risk of HCC development compared to chronic hepatitis B patients without cirrhosis.

- *Bosh, Gastroenterol 2004 ; Chen, JAMA 2006*
- *Kim , J Hepatol 2015*

Since hepatitis B is endemic mainly in the Asia Pacific regions with HBV genotype B and/or C domination, most reports on the relation between genotype and HCC development concerns these two genotypes

Most reports propose HBV genotype B to be more lenient than genotype C, with some exception

In general, HBV genotype C is commonly associated with later HBe seroconversion, more severe liver diseases, as well as faster progression of liver fibrosis and HCC development, although the life-long risk remain similar between genotype B and C

- **Liu S,** Zhang H, Gu C, Yin J, He Y, Xie J, Cao G. Associations between hepatitis B virus mutations and the risk of hepatocellular carcinoma: a meta-analysis. *J Natl Cancer Inst*. 2009;**101**:1066-1082.
-]

HBV genotype B is associated with better response to treatment, enhancing the prognosis and reducing the risk of advanced disease progression.

Vice versa even compared to other genotypes, genotype C appeared to have worse prognosis in term of severe advanced liver disease development, with HR 2.05-2.34 times more than HBV genotype B or A and D, the four major HBV genotypes associated with HCC development.

This might be because HBV genotype C has higher tendency to induce DNA double-strand breaks and accumulate reactive oxygen species (ROS) that causes endoplasmic reticulum (ER) stress, in addition to more efficient cellular homologous-recombination events that increase the risk of chromosomal rearrangements and DNA damage, stimulating the formation and development of HCC.

Cheung KK, Meta-analysis: The association of hepatitis B virus genotypes and hepatocellular carcinoma. *Aliment Pharmacol Ther*. 2013;**37**:517-526.

Datta S, Distinct distribution pattern of hepatitis B virus genotype C and D in liver tissue and serum of dual genotype infected liver cirrhosis and hepatocellular carcinoma patients. *PLoS One*. 2014;**9**:e102573.

HBV/HDV coinfection

Super-infection often manifests in a rapidly progressive disease leading to cirrhosis within 2 years in 10%-15% of patients.

HBV/HDV co-infected patients usually have higher ALT and bilirubin levels as well as a higher prevalence of liver cirrhosis and HCC.

HDV co-infection is considered as a risk factor for HCC (HR 1.4-6.0 fold compared to HBV mono-infection), with lower survival rate

Rizzetto M. *Hepatitis D: clinical features and therapy. Dig Dis. 2010;**28**:139-143*

- .

High serum level of HDV RNA can be used as a predictor of cirrhosis and liver *cancer in patients with chronic HDV infection*

-

Romeo R, *. High serum levels of HDV RNA are predictors of cirrhosis and liver cancer in patients with chronic hepatitis delta. PLoS One. 2014*

HCV infection

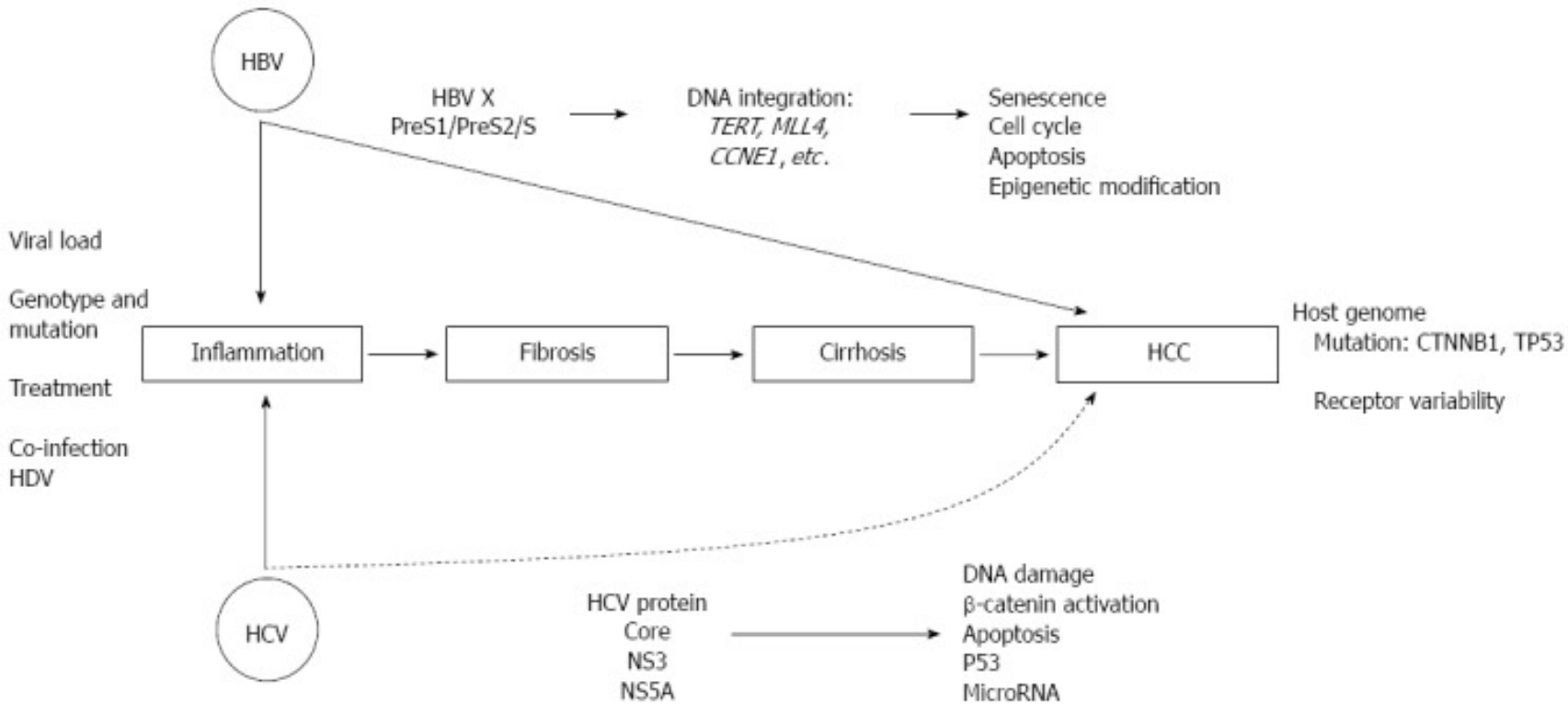
Early study showed that genotype 1b patients have a significantly higher risk of developing HCC.

This early observation was supported by the result of a seventeen-year prospective cohort study, which showed 44 out of 104 genotype 1b followed-up patients developed HCC.

A meta-analysis study that calculated age-adjusted risk estimated genotype 1b patients had almost double the risk of developing HCC in comparison with patients infected with other genotypes

- **Bruno S,** Crosignani A, Maisonneuve P, Rossi S, Silini E, Mondelli MU. Hepatitis C virus genotype 1b as a major risk factor associated with hepatocellular carcinoma in patients with cirrhosis: a seventeen-year prospective cohort study. *Hepatology*. 2007;**46**:1350-1356.
- **Raimondi S,** Bruno S, Mondelli MU, Maisonneuve P. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. *J Hepatol*. 2009;**50**:1142-1154.

ONCOGENICITY OF HEPATITIS VIRUS


HBV
HBV X
PreS1/PreS2/S
DNA integration:
TERT, MLL4,
CCNE1, etc.
Senescence
Cell cycle
Apoptosis
Epigenetic modification
Viral load
Genotype and
mutation
Treatment
Co-infection
HDV
Inflammation
Fibrosis
Cirrhosis
HCC
Host genome
Mutation: CTNNB1, TP53
Receptor variability
HCV
HCV protein
Core
NS3
NS5A
DNA damage
β-catenin activation
Apoptosis
P53
MicroRNA

HBV infection causes immunological response that may lead to oxidative stress and successive DNA damages of the cells

Higgs MR, Chouteau P, Lerat H. 'Liver let die': oxidative DNA damage and hepatotropic viruses. *J Gen Virol*. 2014;**95**:991-1004

Direct oncogenic property of HBV sequence by integration of its DNA into human genome can explain the incidence of non-cirrhotic HCC

This insertion might involve deletions, cis/trans-activation, translocation, production of fusion transcripts and generalized genomic instability

Ringelhan M, O'Connor T, Protzer U, Heikenwalder M. The direct and indirect roles of HBV in liver cancer: prospective markers for HCC screening and potential therapeutic targets. *J Pathol*. 2015;**235**:355-367

- **HBV DNA integration is present in majority of HBV-related HCC, even though it is also found in non-tumor tissue and chronic hepatitis B without HCC**

- ***HBV DNA integration is considered as a strong oncogenic effect in hepatocarcinogenesis***

- ***Tsai WL,*** *Chung RT. Viral hepatocarcinogenesis. Oncogene. 2010;**29**:2309-2324*

HCV and oxidative stress

Since HCV RNA cannot integrate into human genome, at the beginning, the mechanism in HCV-related HCC pathogenesis is *thought majorly to be indirect pathways via the effects of chronic inflammation and oxidative stress*

Subsequently, it leads to fibrosis and eventually cirrhosis as observed in the other HCC etiologies such as ASH, NASH, and obesity-related disorder.

However, current literatures also showed a direct oncogenic effect of the viral proteins

- **Oxidative stress has been implicated as one of the mechanisms of HCV-induced hepatocarcinogenesis**.
- Oxidative stress occurs when there is imbalance in the production and clearance of ROS. ROS is a normal by-product of numerous cell processes including proliferation, apoptosis, and cell senescence.
- In the liver, ROS is mainly produced by mitochondria in hepatocytes, and from nicotinamide adenine dinucleotide phosphate oxidase and xanthine oxidase reactions in Kupffer cells and inflammatory cells.
- ***Long-term oxidative stress may induce DNA damage, and since ROS can also functions as second messenger in cellular signaling, increased ROS level may trigger the activation of oncogenic signaling pathways***

- **Arzumanyan A,** Reis HM, Feitelson MA. Pathogenic mechanisms in HBV- and HCV-associated hepatocellular carcinoma. *Nat Rev Cancer*. 2013;**13**:123-135.

Increased oxidative stress in chronic hepatitis C patients has been shown through elevated levels of several oxidative stress biomarkers, including 8-hydroxydeoxyguanosine (8-OHdG), malondialdehyde, and thioredoxin in both sera and liver biopsy samples

Chronic hepatitis C patients have also been shown to have higher expression of 8-OHdG, also an indicator for DNA damage, in comparison with chronic hepatitis B patients; suggesting that hepatic oxidative DNA damage is more common in chronic hepatitis C

.

Mahmood S, Kawanaka M, Kamei A, Izumi A, Nakata K, Niiyama G, Ikeda H, Hanano S, Suehiro M, Togawa K. Immunohistochemical evaluation of oxidative stress markers in chronic hepatitis C. *Antioxid Redox Signal*. 2004;**6**:19-24

Further, some clinical studies have shown that addition of antioxidant agent could improve oxidative stress-caused liver injury and maybe important for treatment management of HCV patients

.

Fujita N, Sugimoto R, Ma N, Tanaka H, Iwasa M, Kobayashi Y, Kawanishi S, Watanabe S, Kaito M, Takei Y. Comparison of hepatic oxidative DNA damage in patients with chronic hepatitis B and C. *J Viral Hepat*. 2008

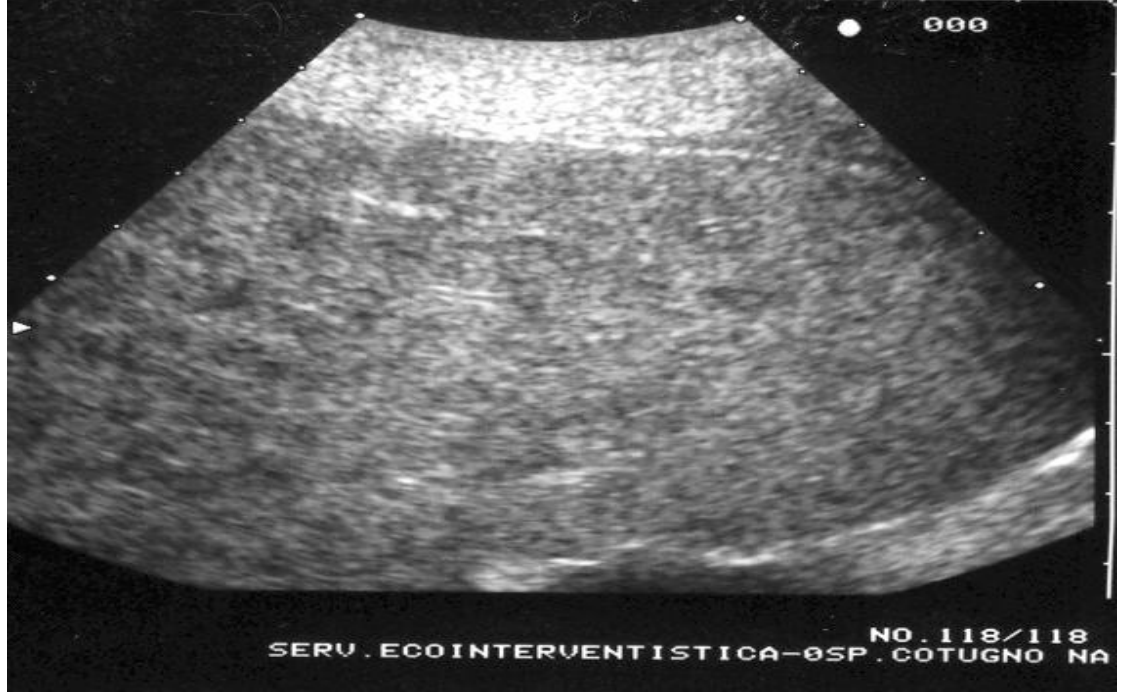
CHE FARE?

- J Hepatol. 2015 Apr;62(4):956-67. doi: 10.1016/j.jhep.2015.01.002. Epub 2015 Jan 13.

Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy.

Papatheodoridis GV[1], Chan HL[2], Hansen BE[3], Janssen HL[4], Lampertico P[5].

- *In the treatment of chronic hepatitis B (CHB), the ultimate goal is preventing hepatitis B virus (HBV)-associated liver disease, including hepatocellular carcinoma (HCC).*
- Recently published studies show that in **CHB patients treated with the currently recommended first-line nucleos(t)ide analogs (NAs) entecavir or tenofovir, annual HCC incidences range from 0.01% to 1.4% in non-cirrhotic patients, and from 0.9% to 5.4% in those with cirrhosis**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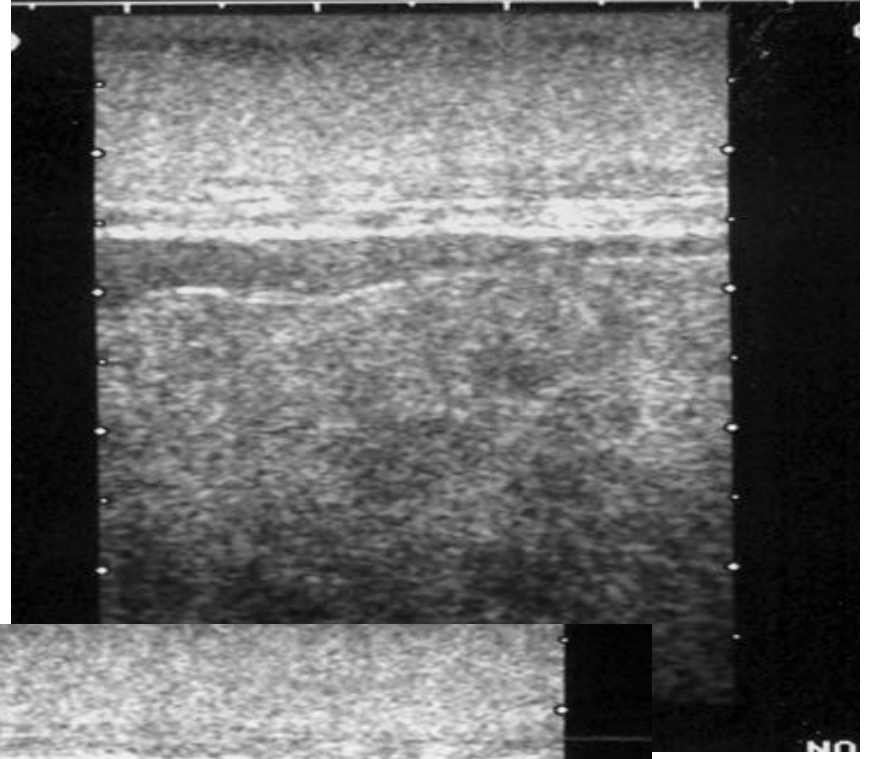
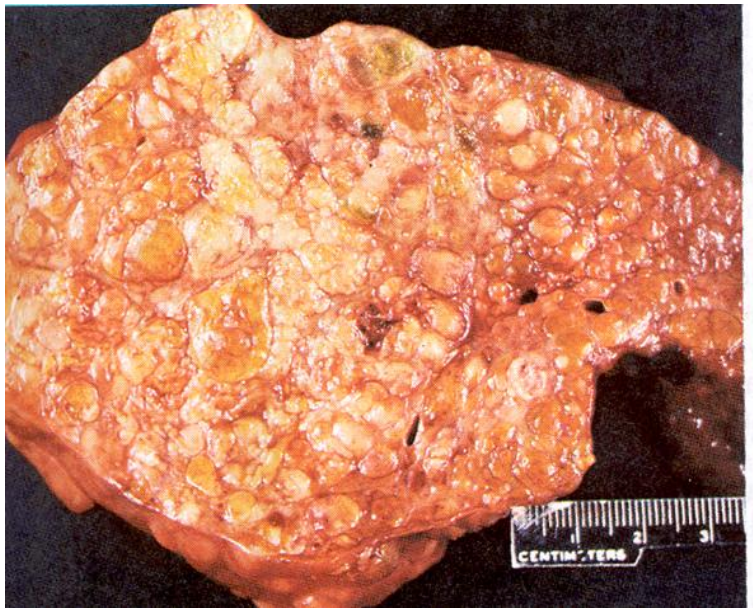
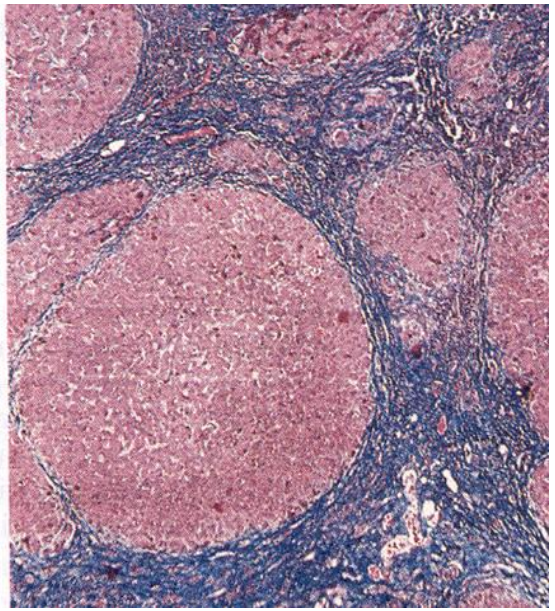
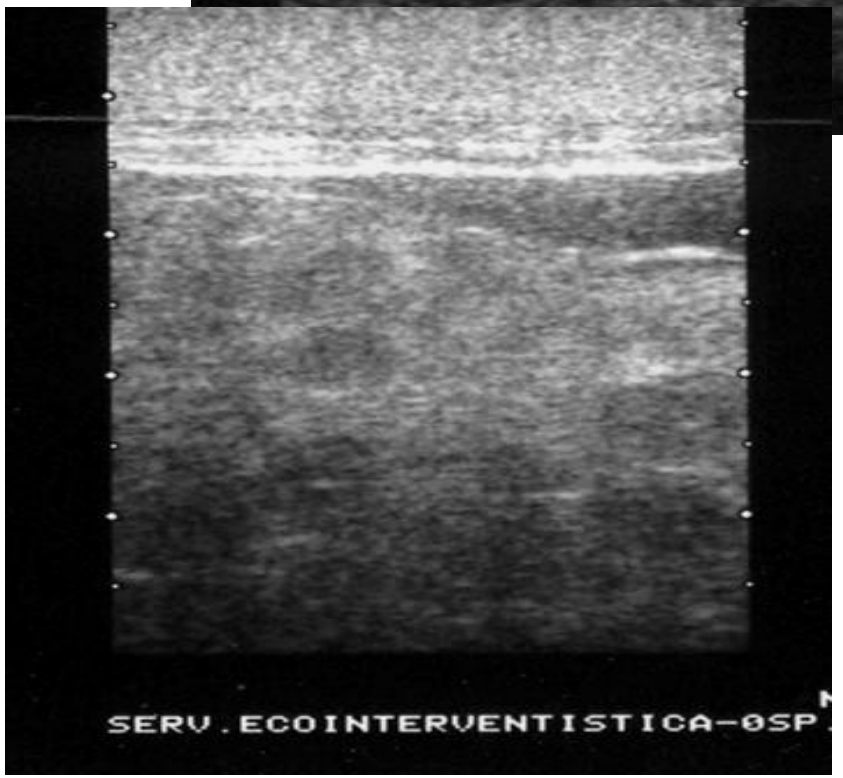



CENTIMETERS

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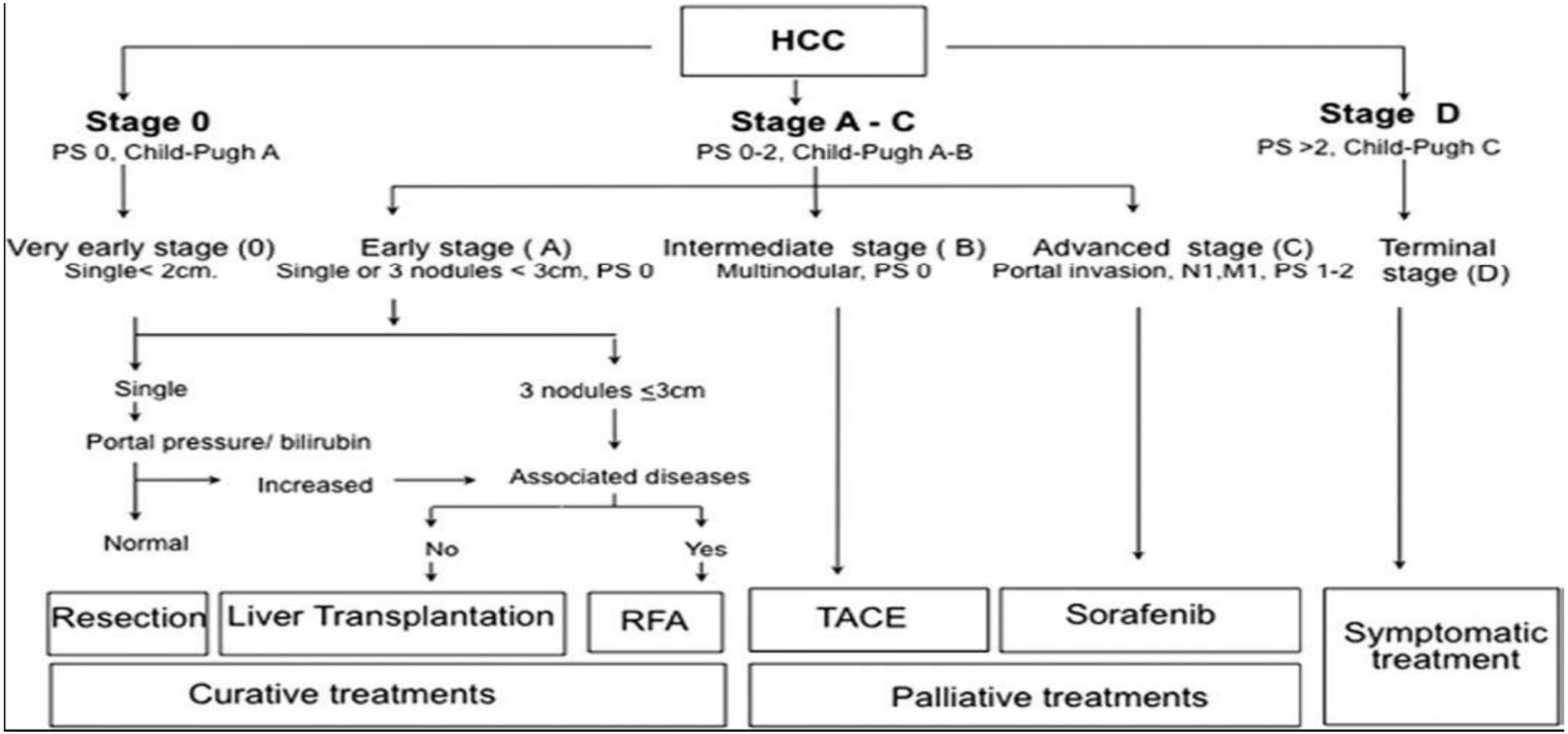

HCC
Stage 0
PS 0, Child-Pugh A
Stage A - C
PS 0-2, Child-Pugh A-B
Stage D
PS >2, Child-Pugh C
Very early stage (0)
Single< 2cm.
Early stage (A)
Single or 3 nodules < 3cm, PS 0
Intermediate stage (B)
Multinodular, PS 0
Advanced stage (C)
Portal invasion, N1,M1, PS 1-2
Terminal stage (D)
Single
3 nodules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

J Clin Exp Hepatol. 2014

Role of local ablative therapy for hepatocellular carcinoma

Thandassery RB, Goenka U, Goenka MK

Radiofrequency ablation (RFA) *is considered as the first line treatment in some centers*, though most of the guidelines recommend it for small HCCs, where surgical resection is not feasible.

Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice?

Hepatology Jan 2008 - Livraghi T. et al

218 pts with single HCC <or= 2.0 cm (very early or T1 stage) underwent RFA.

After a median follow-up of 31 months, sustained complete response was observed in **216 patients (97.2%)**

Peri-operative mortality, major complication, and 5-year survival rates were 0%, 1.8%, and 68.5%, respectively Af

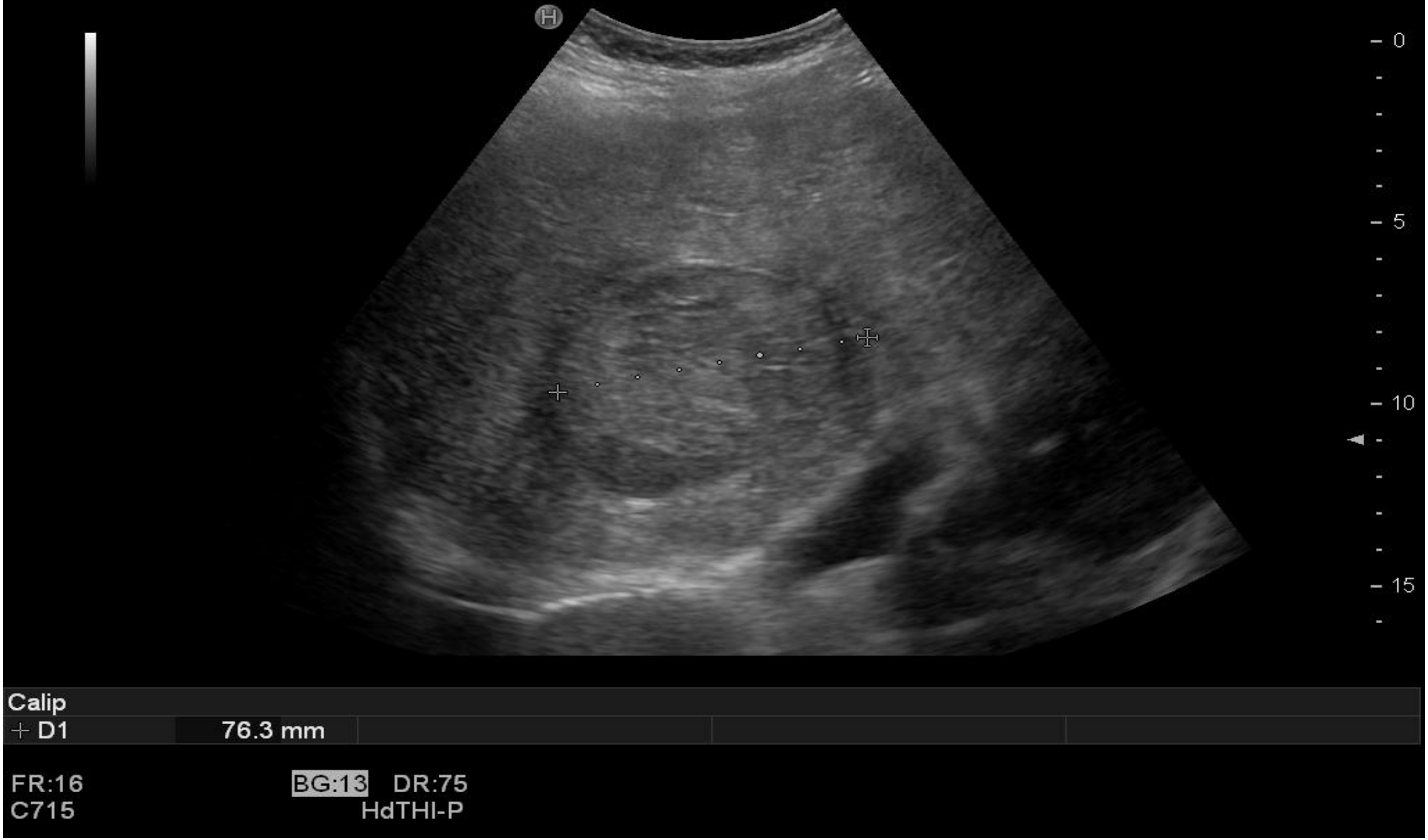
J Hepatol. 2013 Jul;59(1):89-97.

Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤3 cm. Results of a multicenter Italian survey.

Pompili M[1], Saviano A, de Matthaeis N, Cucchetti A, Ardito F, Federico B, Brunello F, Pinna AD, Giorgio A, Giulini SM, De Sio I, Torzilli G, Fornari F, Capussotti L, Guglielmi A, Piscaglia F, Aldrighetti L, Caturelli E, Calise F, Nuzzo G, Rapaccini GL, Giuliante F.

544 cirrhotics; 246 resection – 298 radiofrequency

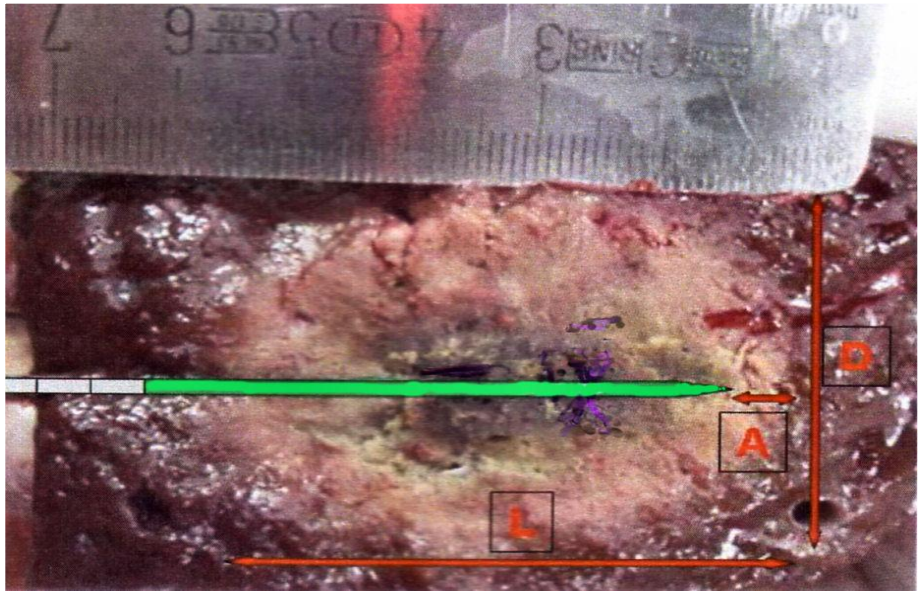
In spite of a higher rate of local tumor progression, ***radiofrequency ablation can provide results comparable to liver resection in the treatment of single hepatocellular carcinoma ≤3 cm occurring in compensated cirrhosis.***


H
0
5
10
15
Calip
D1
76.3 mm
FR:16
C715
BG:13
DR:75
HdTHI-P

BCLC Sub-Stage	B1	B2	B3	B4
CPT score	5-6-7	5-6	7	8-9*
Beyond Milan and within Ut-7	IN	OUT	OUT	ANY
ECOG (Tumor Related) PS	0	0	0	0-1
PVT	NO	NO	NO	NO
1st option	**TACE**	TACE or TARE		**BSC**
Alternative	LT TACE + ablation	SOR	Research trials TACE SOR	LT**

Bolondi l et al, Sem Liv Dis -2012

microwaves



electromagnetic waves ~~rotate H_2O~~ ~~heat~~

coagulative necrosis indipendent by impedance

Clin Radiol. 2015 Jul 25.

High-powered microwave ablation of larger hepatocellular carcinoma: evaluation of recurrence rate and factors related to recurrence.

Zhang NN[1], Lu W[2], Cheng XJ[1], Liu JY[1], Zhou YH[1], Li F[1].

The complete ablation rates were 85.71% for the second ablation for 5-8 cm lesions.

.

The 1-year and 2-year survival rates were 95.56% (43/45) and 86.67% (39/45), respectively.

No procedure-related mortality was observed and no major bleeding, liver rupture, or liver abscesses occurred.

High-powered microwaves ablation of intermediate Hepatocellular Carcinoma in cirrhosis: a multicenter, prospective study

215 pts

Mean age 70

Child A 149, Child B 66

Group A 109; one nodule; range 5,3-8,2, mean 6.4 cm

Group B 70; two nodules; range 3.6; at least one > 5cm

Group C 36; three-five nodules; range 1,5-6,7; at least one >5cm

1 , 3 and 5-year survival rates were 89 , 81 , 60 , 40 and 21% , respectively .

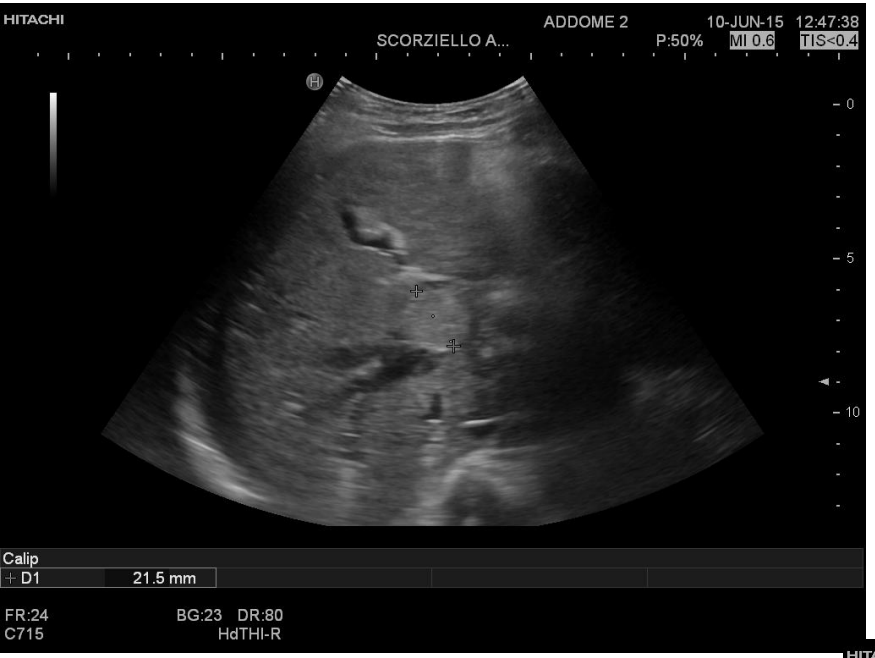
A Giorgio et al Dig Liv Dis, february 2016

• Jpn J Radiol. 2015 Jul;33(7):424-32

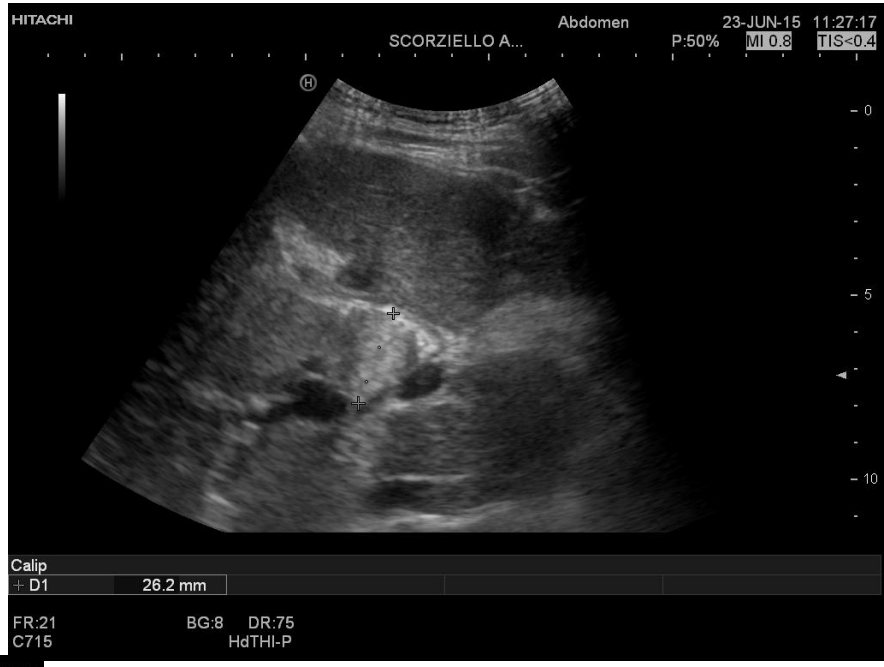
Irreversible electroporation for nonthermal tumor ablation in patients with hepatocellular carcinoma: initial clinical experience in Japan.

• Sugimoto K[1], Moriyasu F, Kobayashi Y, Saito K, Takeuchi H, Ogawa S, Ando M, Sano T, Mori T, Furuichi Y, Nakamura I.

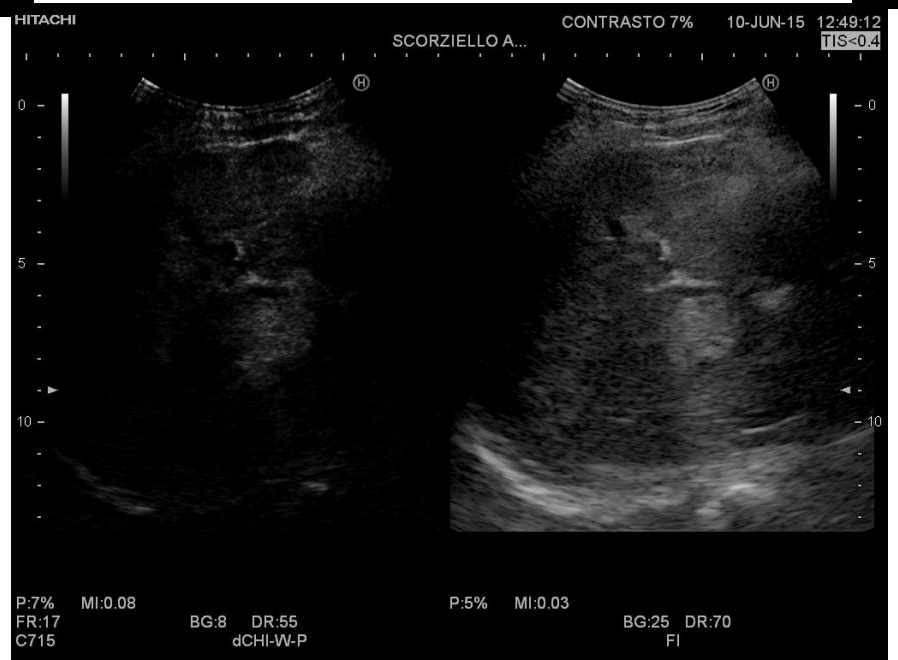
IRE OF UNRESECTABLE and not -suitable for RF HILAR HCC



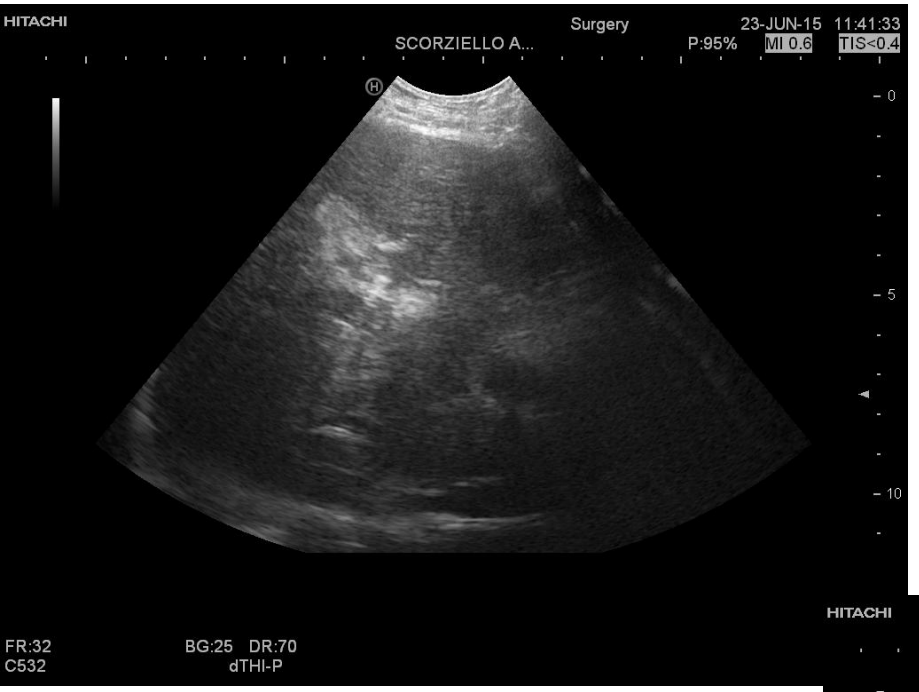
Conventional US



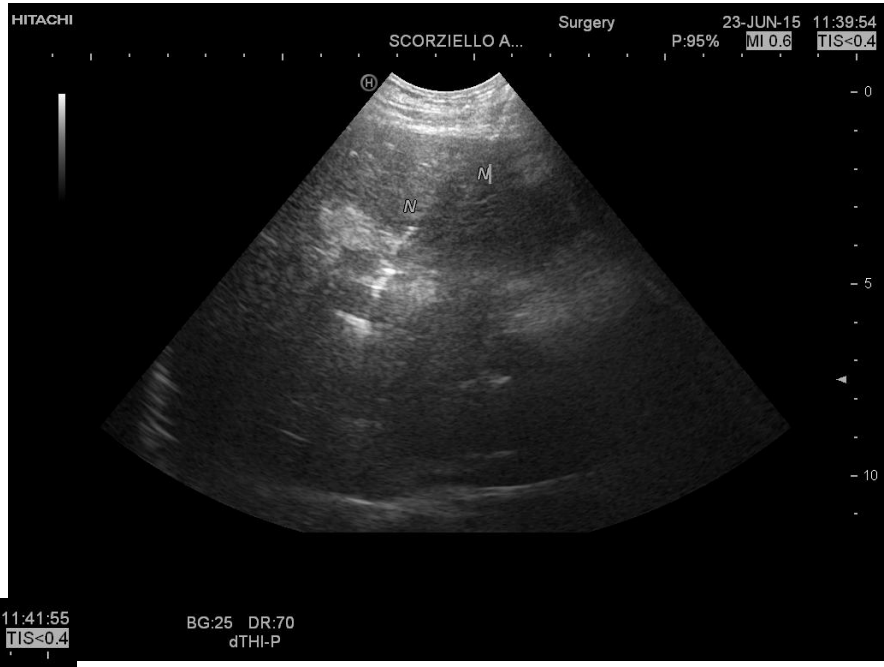
CEUS

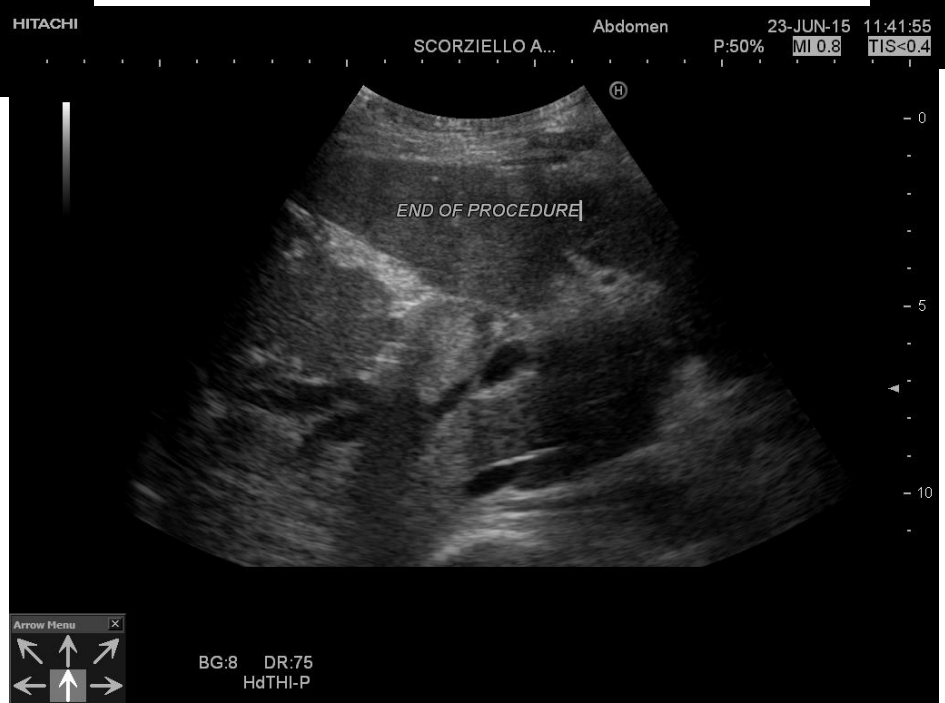


IRE OF UNRESECTABLE, UNABLATABLE HILAR HCC, WITHOUT CIRRHOSIS

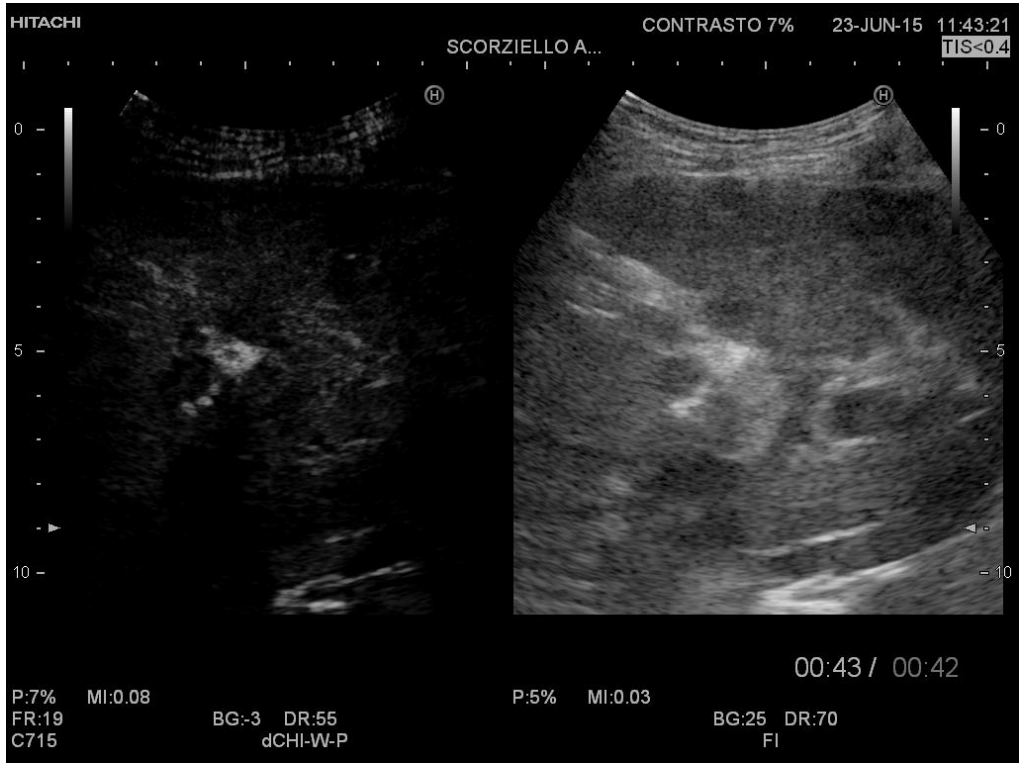


PROCEDURE

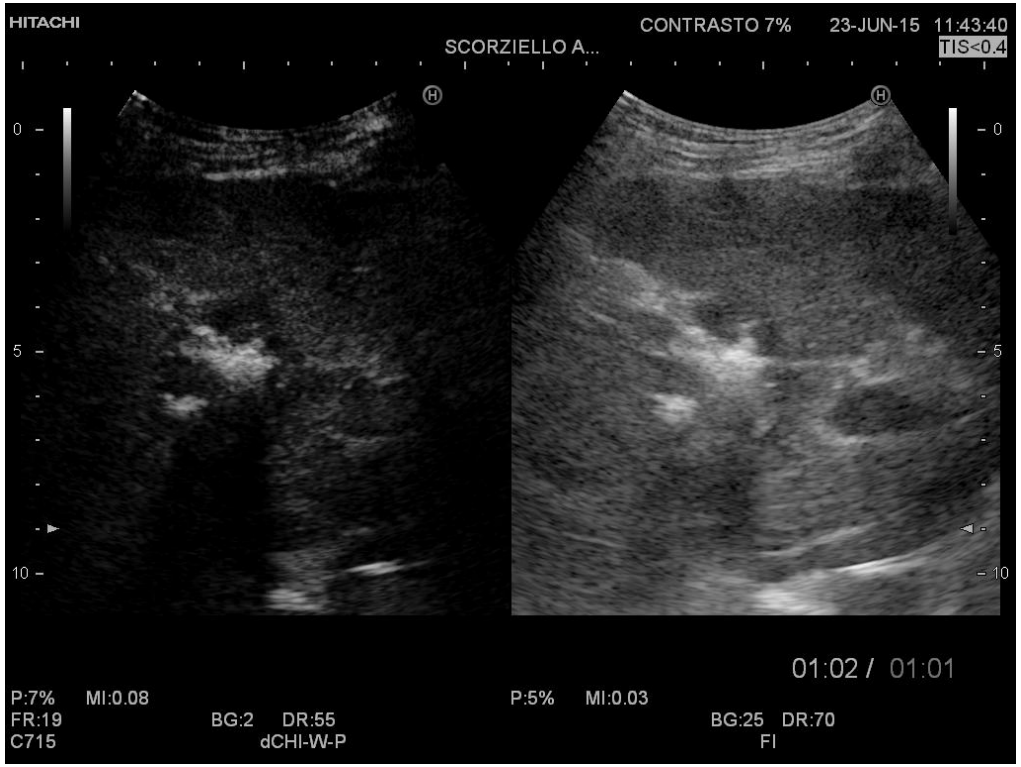


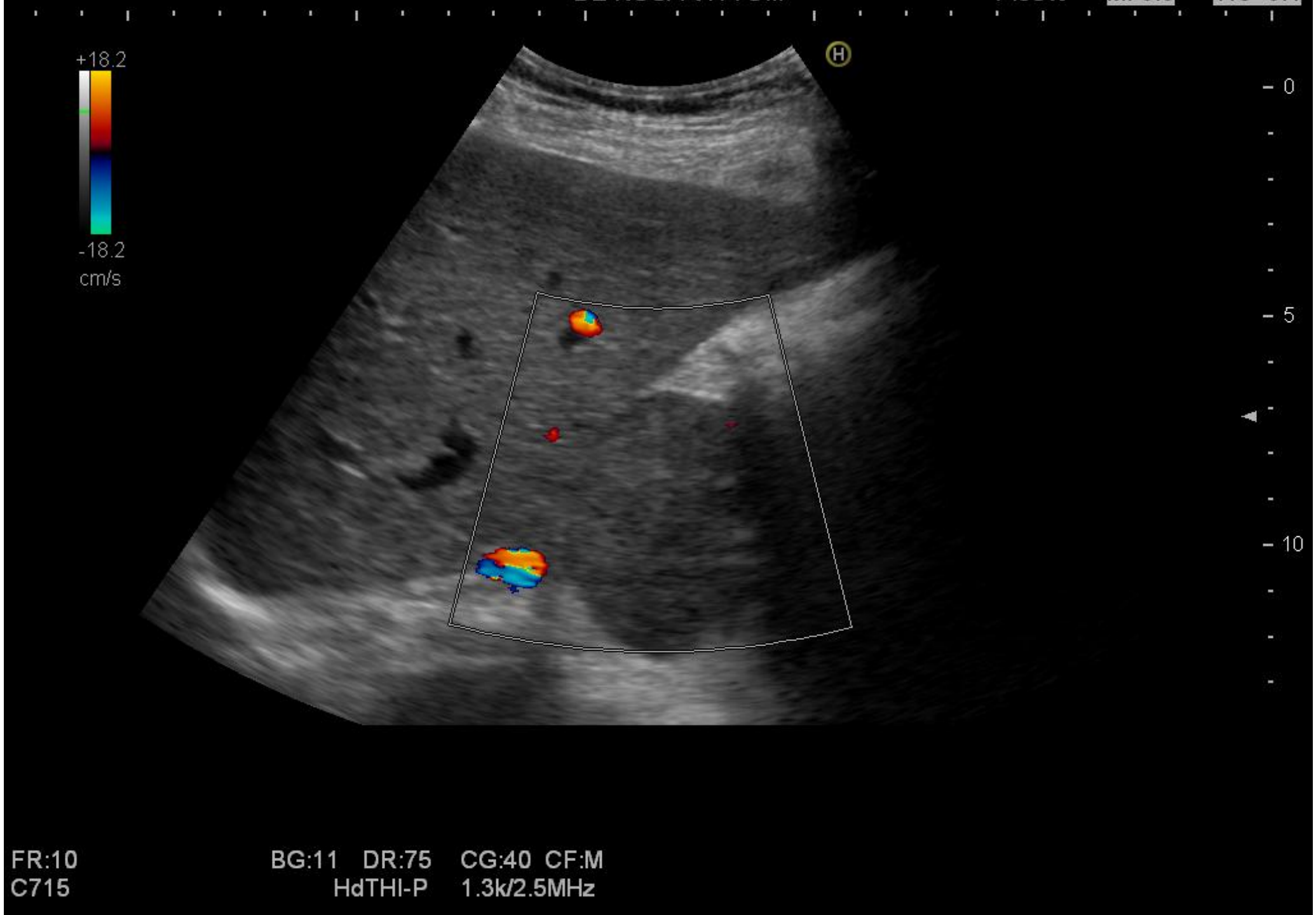


IRE OF UNRESECTABLE, UNABLATABLE HILAR HCC



CEUS SHOWS AVASCULAR HCC AFTER IRE




+18.2
-18.2
cm/s
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5
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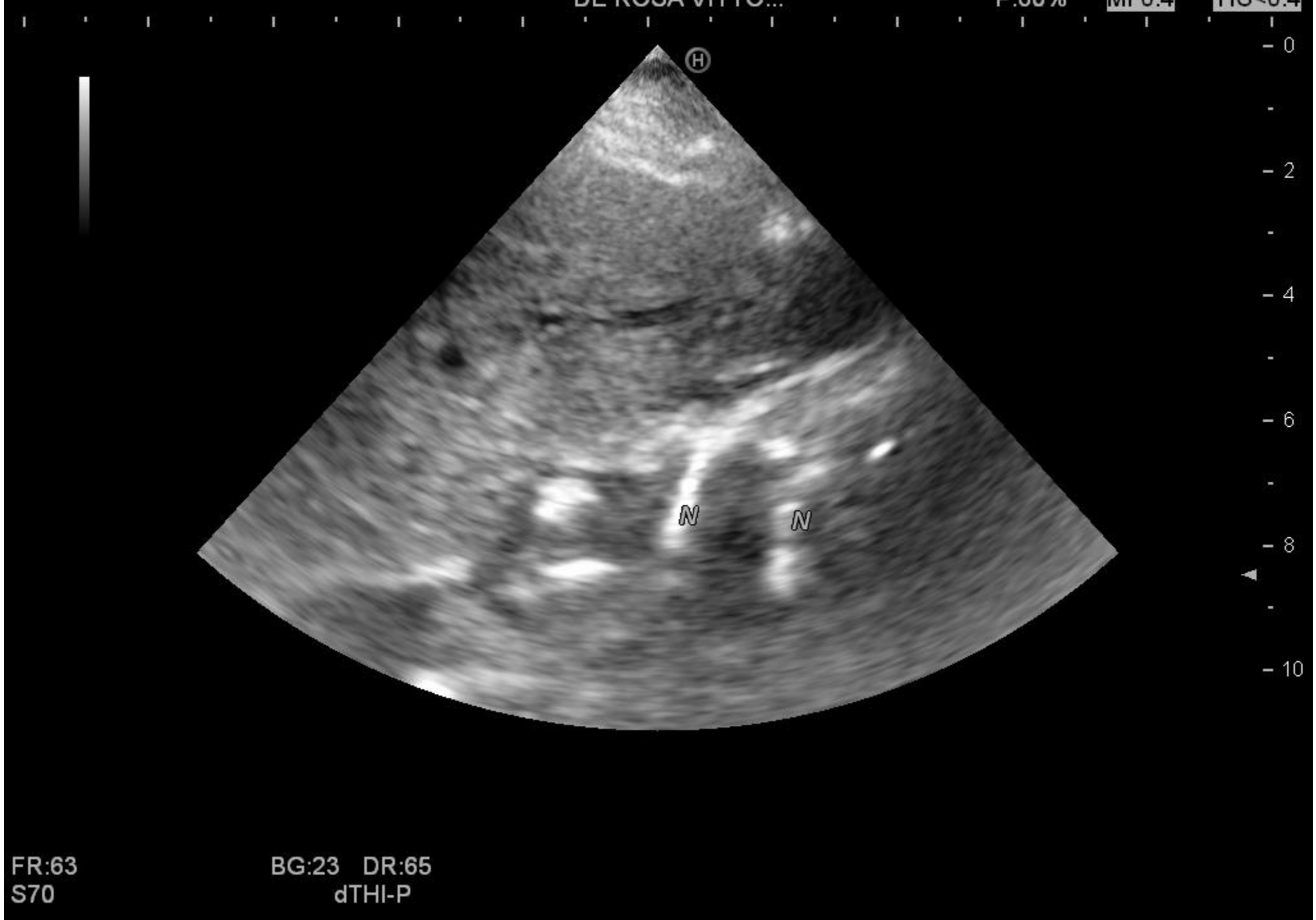
FR:10
C715
BG:11 DR:75 CG:40 CF:M
HdTHI-P 1.3k/2.5MHz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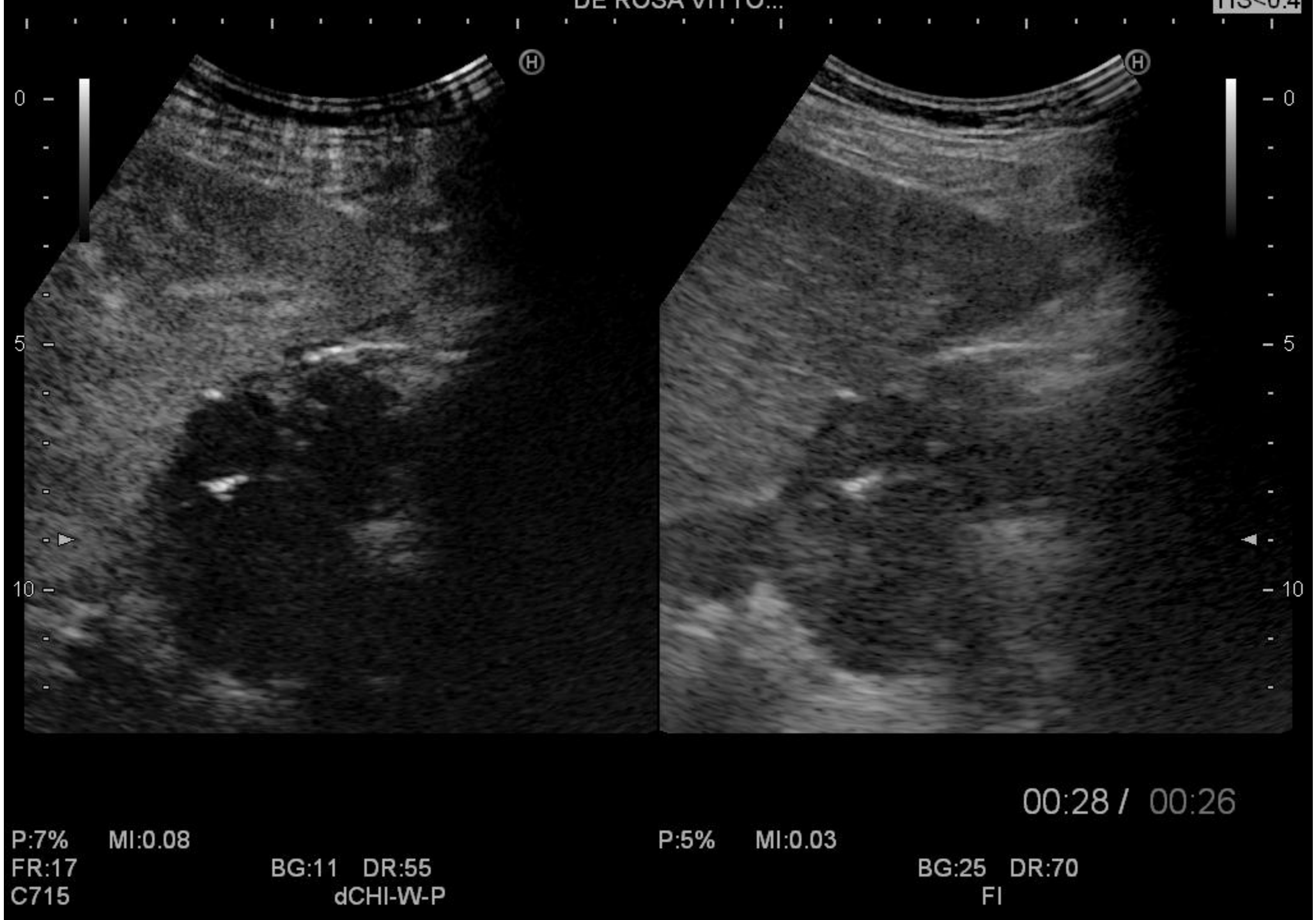
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00:28 / 00:26
P:7% MI:0.08
FR:17
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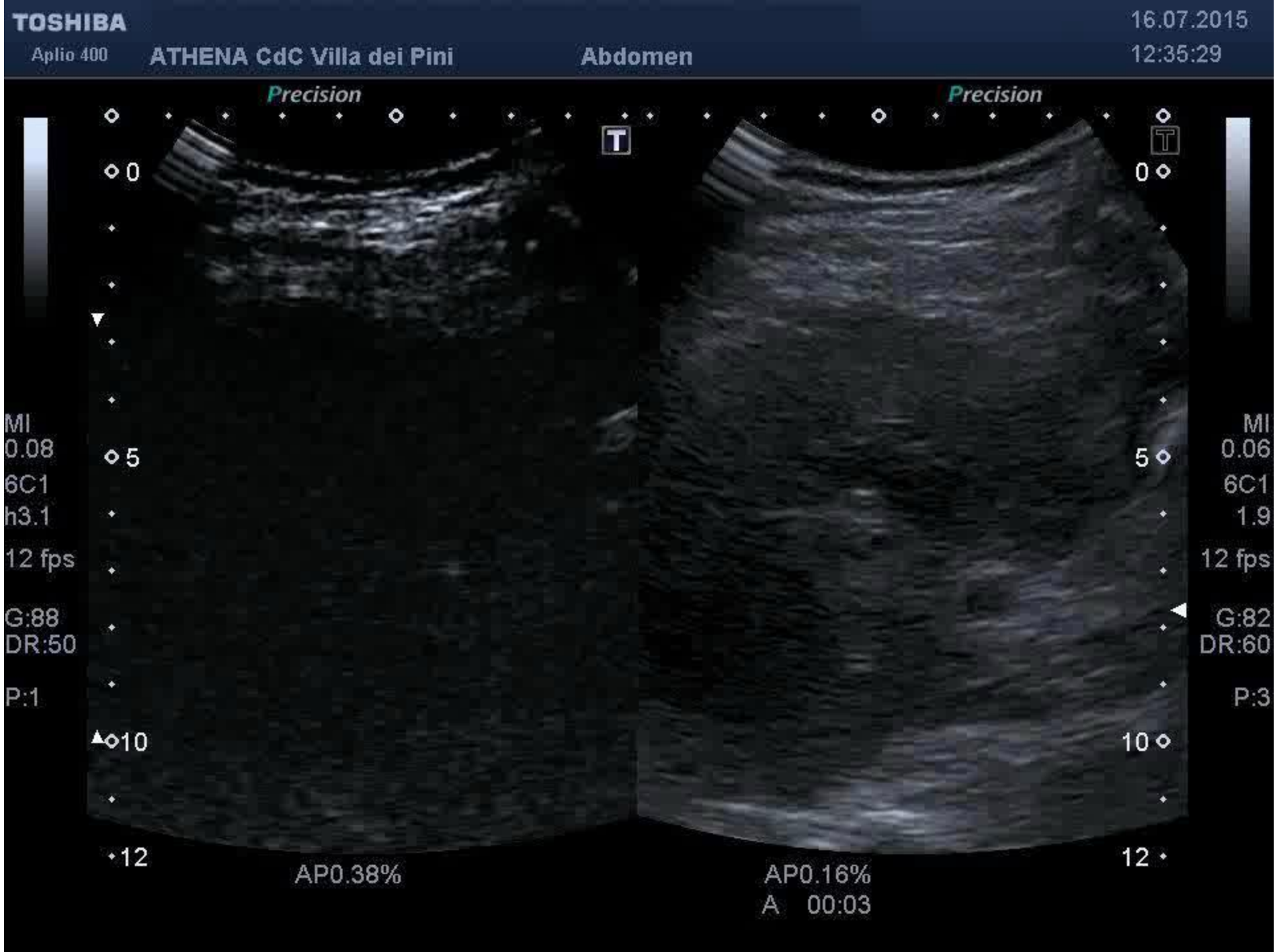
BG:11 DR:55
dCHI-W-P
P:5% MI:0.03
BG:25 DR:70
FI

Advanced HCC

What possibilities for interventional ultrasound?

Hepatocellular Carcinoma on cirrhosis: are patients with neoplastic main portal vein invasion eligible for percutaneous Radiofrequency ablation of both nodule and portal vein tumor thrombus?

A. Giorgio et al, AJR October 2009


TOSHIBA
Aplio 400
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Abdomen
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Precision
Precision
MI
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h3.1
12 fps
G:88
DR:50
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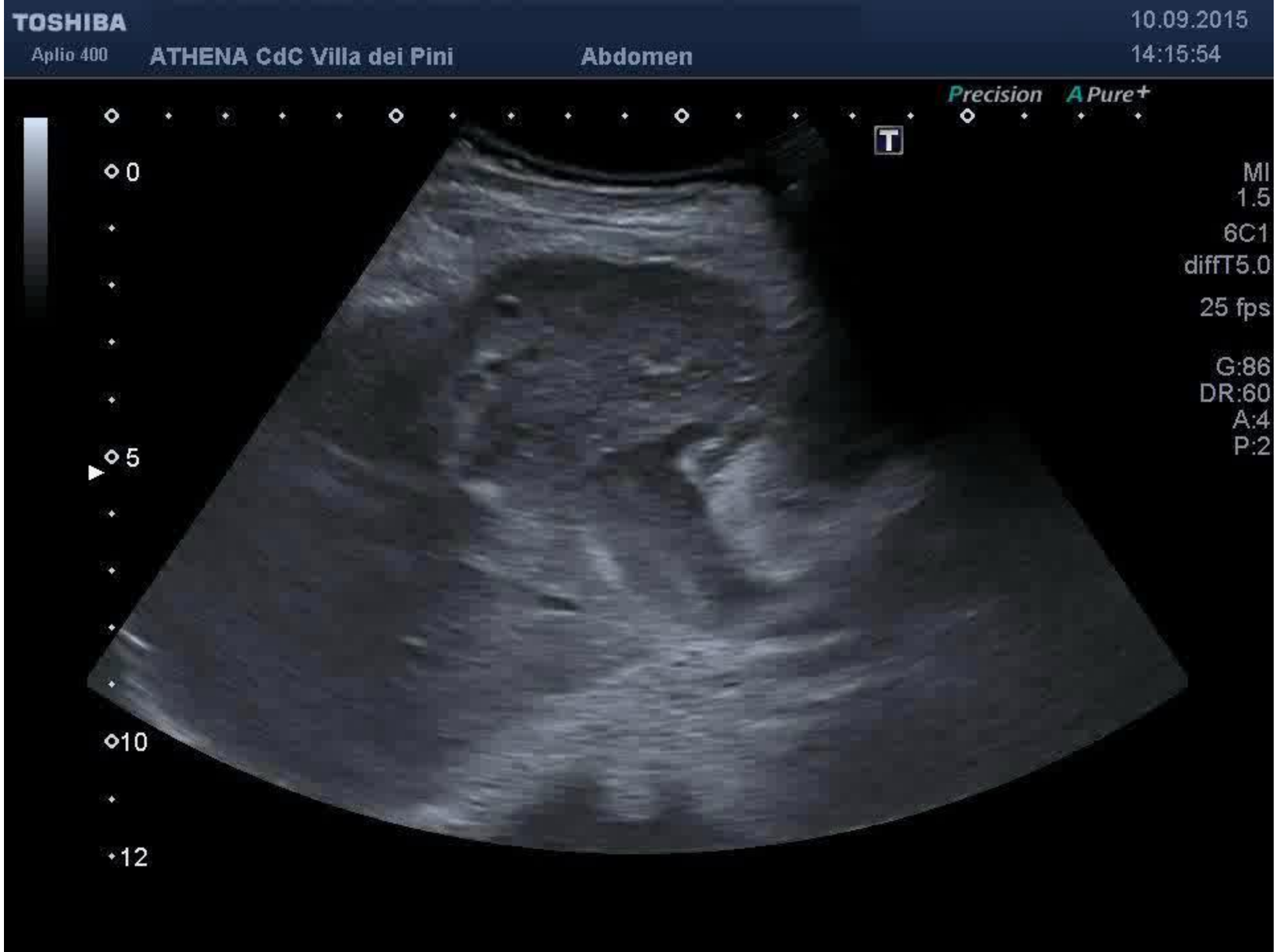
DR:60
P:3
AP0.38%
AP0.16%
A 00:03


TOSHIBA
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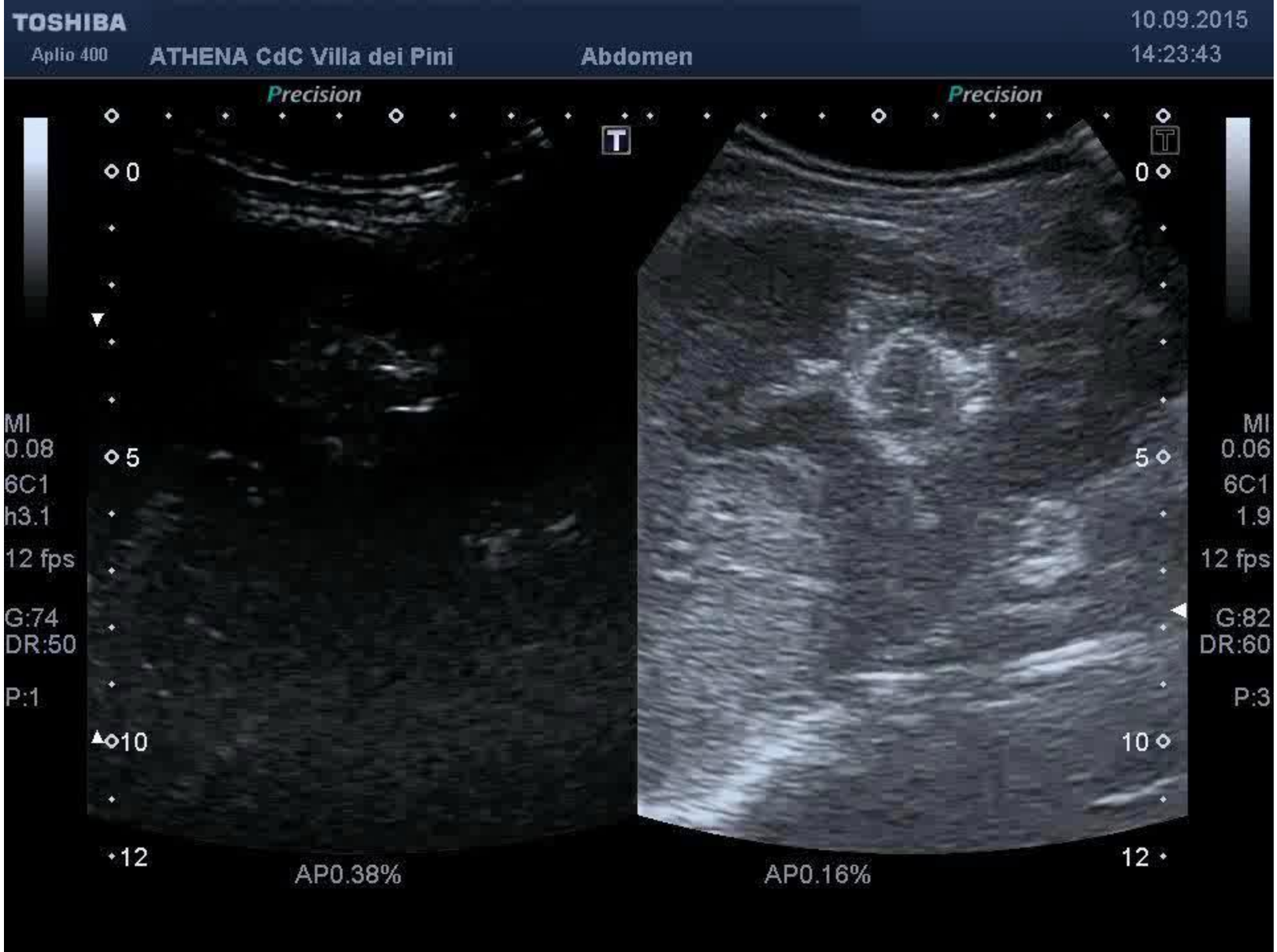
TOSHIBA
Aplio 400
ATHENA CdC Villa dei Pini
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Precision
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h3.1
12 fps
G:74
DR:50
P:1
MI
0.06
6C1
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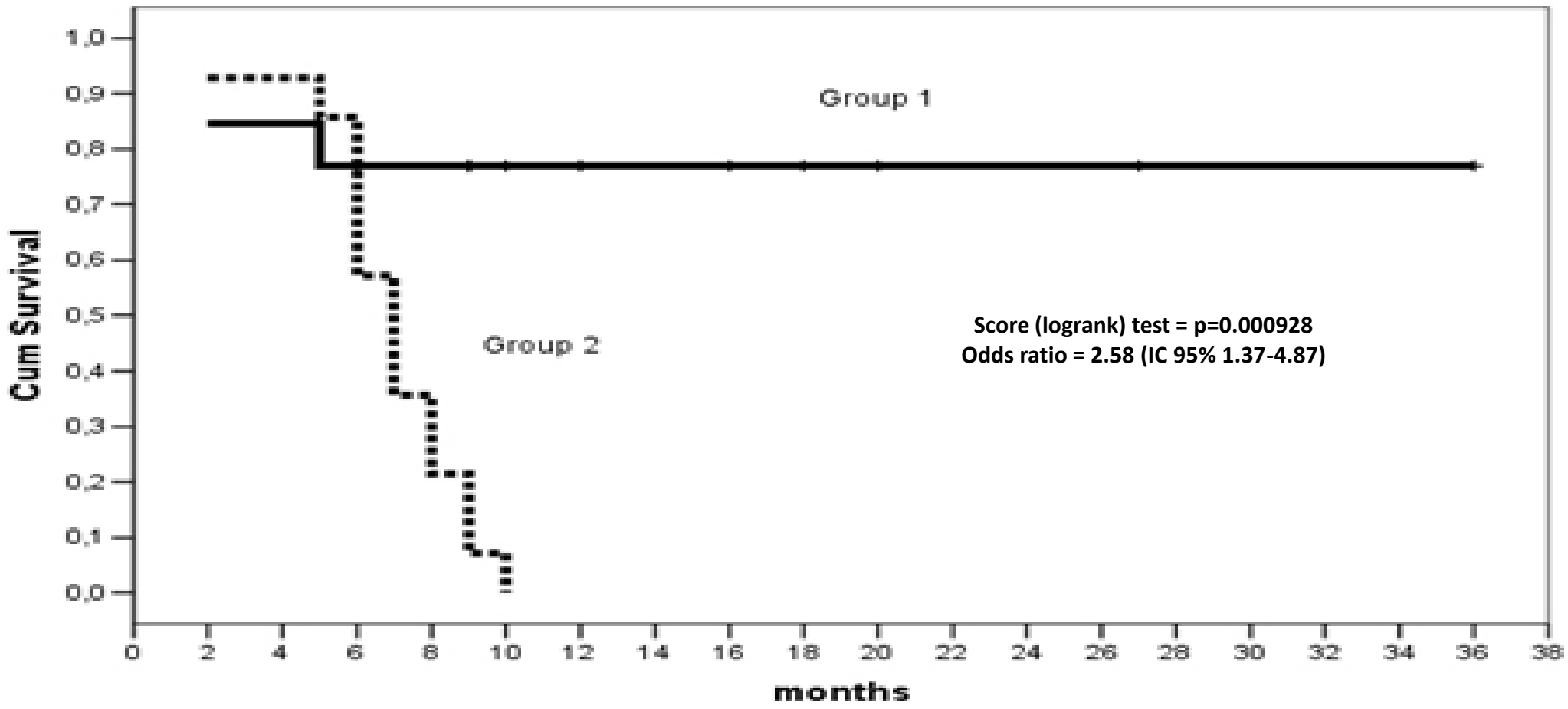
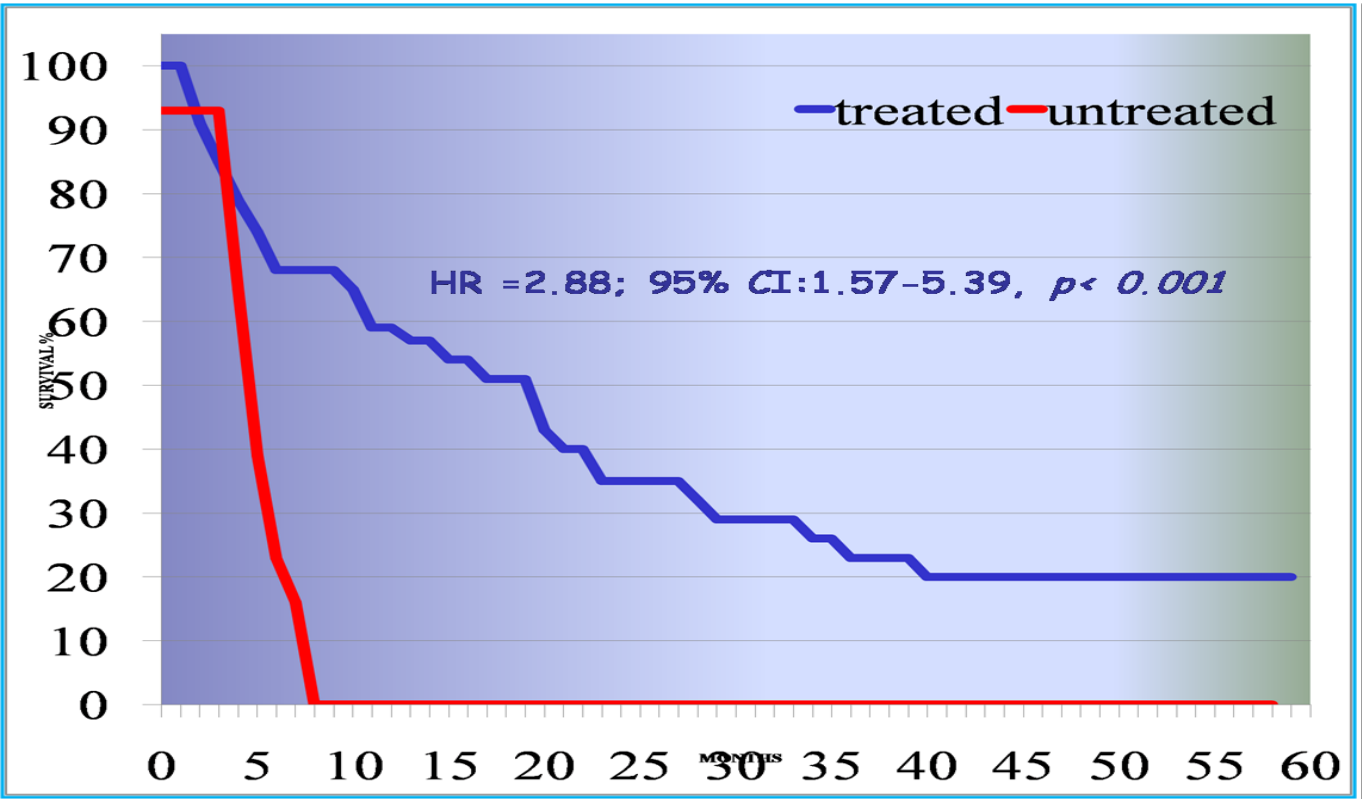
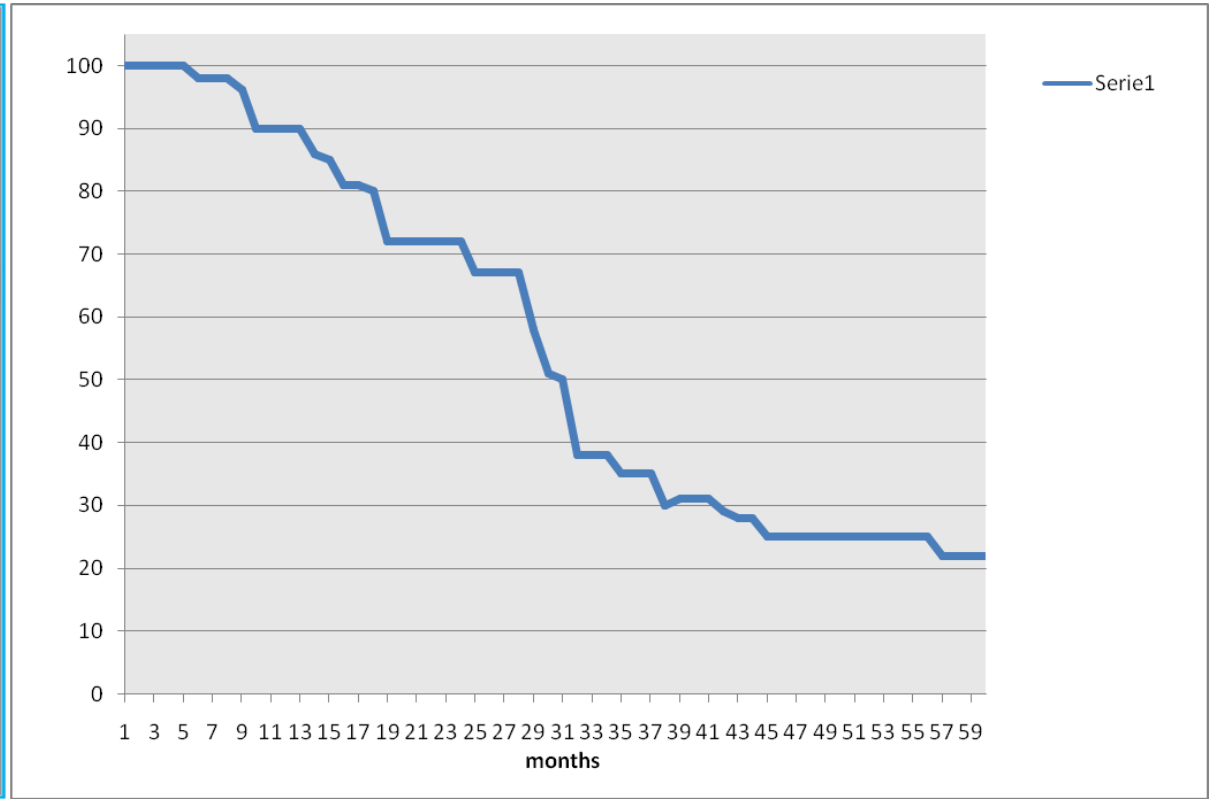
12 fps
G:82
DR:60
P:3
AP0.38%
AP0.16%

results


Cum Survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
Group 1
Group 2
Score (logrank) test = p=0.000928
Odds ratio = 2.58 (IC 95% 1.37-4.87)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
months





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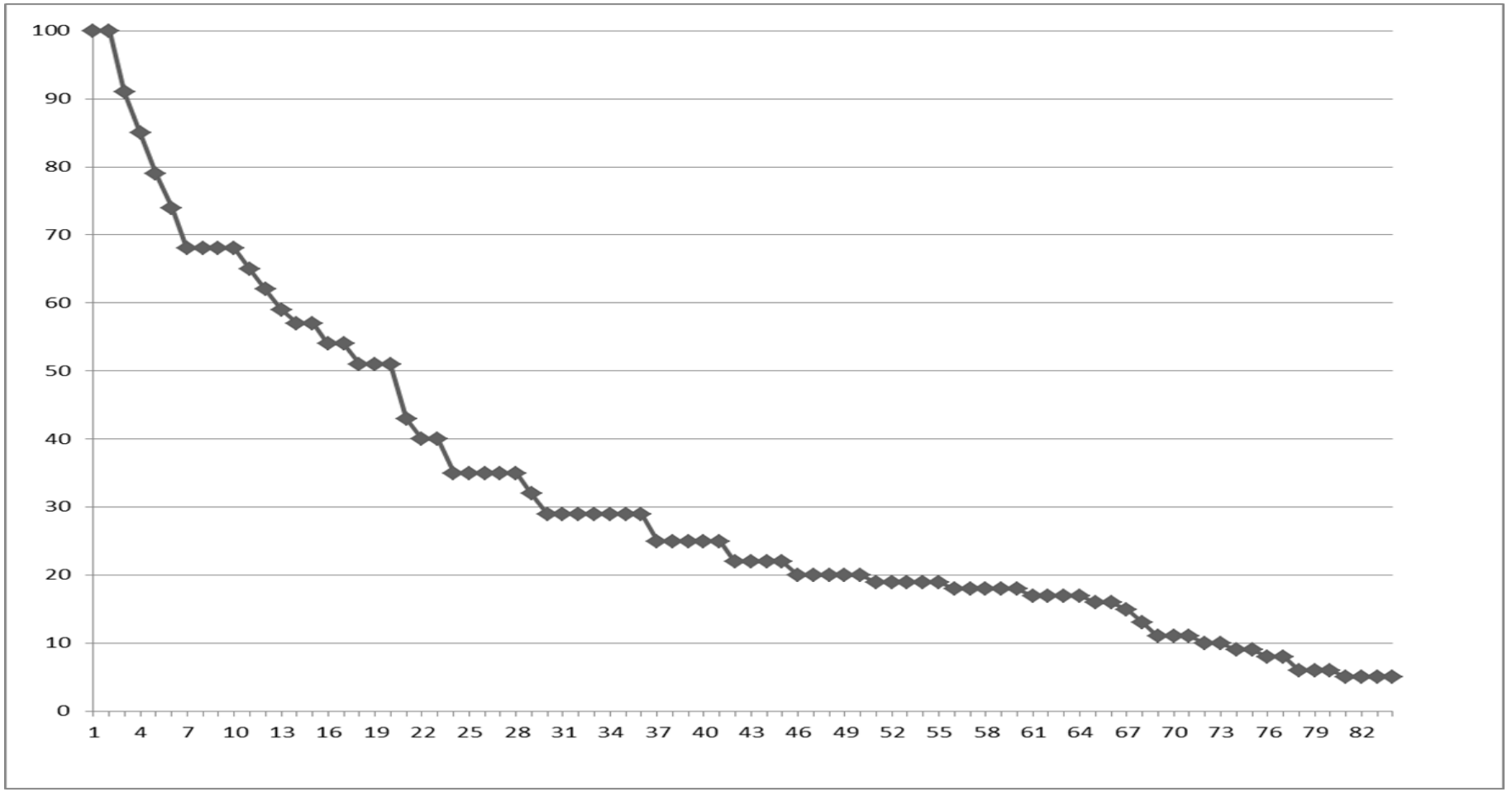

Cumulative 7-year survival rates of treated patients
(1 , 3, 5 and 7-year survival rates: 62, 29, 18 and 5%)

Hepatocellular carcinoma (HCC) invading portal venous system in cirrhosis: 7 years results of Percutaneous Radiofrequency Ablation of both HCC nodule and main portal vein tumor thrombus (MPVTT)

The 1, 3 ,5 and 7- year cumulative survival rates of treated patients were 62 , 29 , 18 and 5 % , respectively. The 12-months cumulative survival rate of untreated patients was 0%. The difference was statistically significant ($p < 0.001$; harzard ratio, 2.88; 95% CI, 1.57– 5.39).

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

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III Corso residenziale di ECOGRAFIA ed ECO-INTERVENTISTICA

Direttore **Prof. Antonio Giorgio**

Congresso di Apertura

19 - 20 maggio 2016

Lloyd's Baia Hotel
Vietri sul Mare - Salerno