Treatment with Stem Cell Differentiation Stage Factors of Hepatocellular Carcinoma in Intermediated -Advanced Stage (up-to-date findings) * slides selection *

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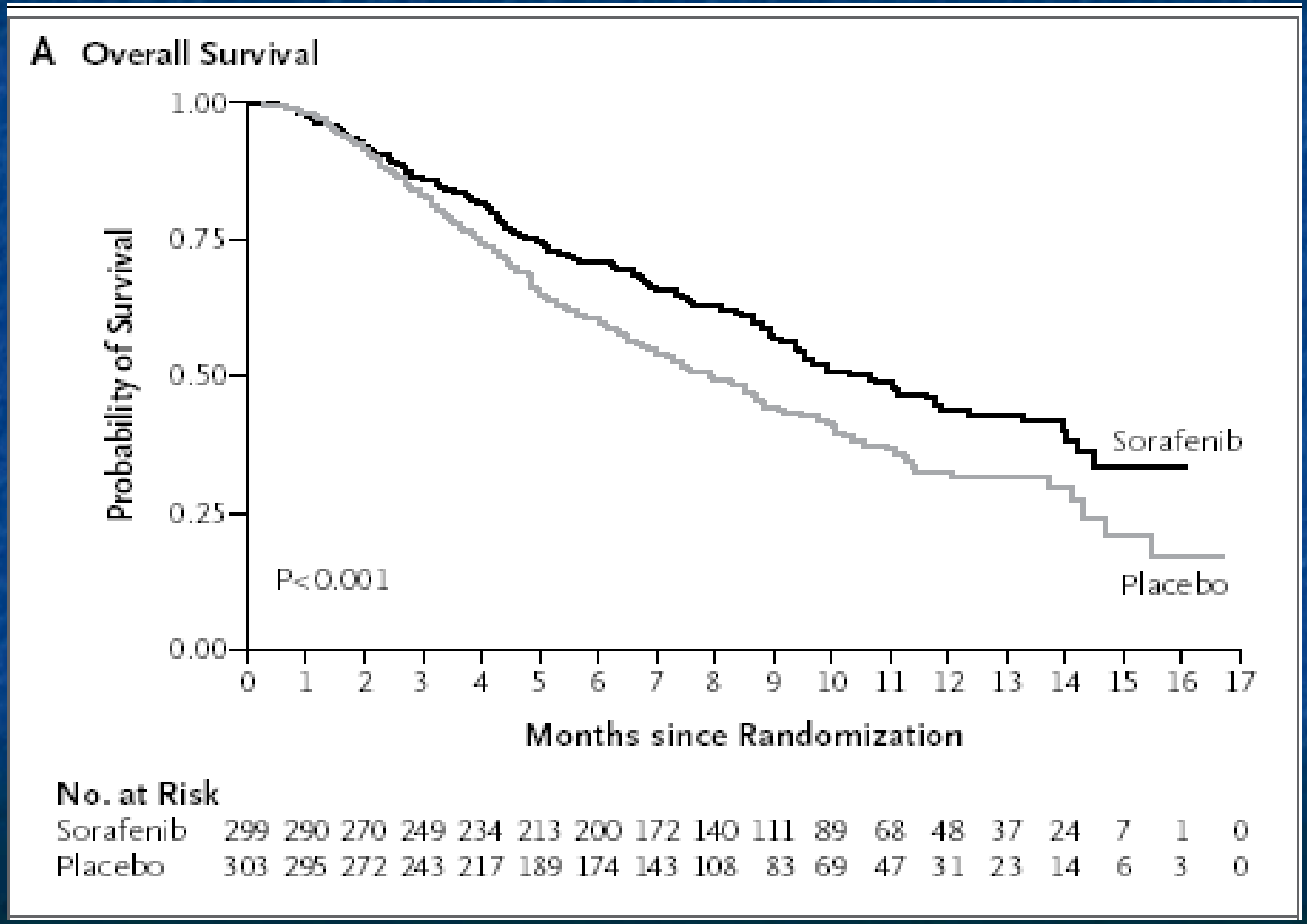
MOLECULAR - TARGETED THERAPIES

- Such strategies are targeted at inihibition of growth factors or interruption of signalling pathways that are essential for tumor growth and expantion, such angiogenesis or activation of telomerases

- Significant progress on the treatment of **HCC** has been made by sorafenib, a signal transduction inihibitor

Sorafenib: median survival = 10.7 months
Placebo = 7.9 months

Llovet JM et al. - NEJM 2008



Sorafenib is not well tolerated

- **Hand-foot skin disease**
- **Alopecia**
- **Diarrhea**
- **Anorexia**
- **Abdominal pain**
- **Voice changes**
- **Hypertension**
- **Risk of bleeding ?**
- **Liver disfunction ?**

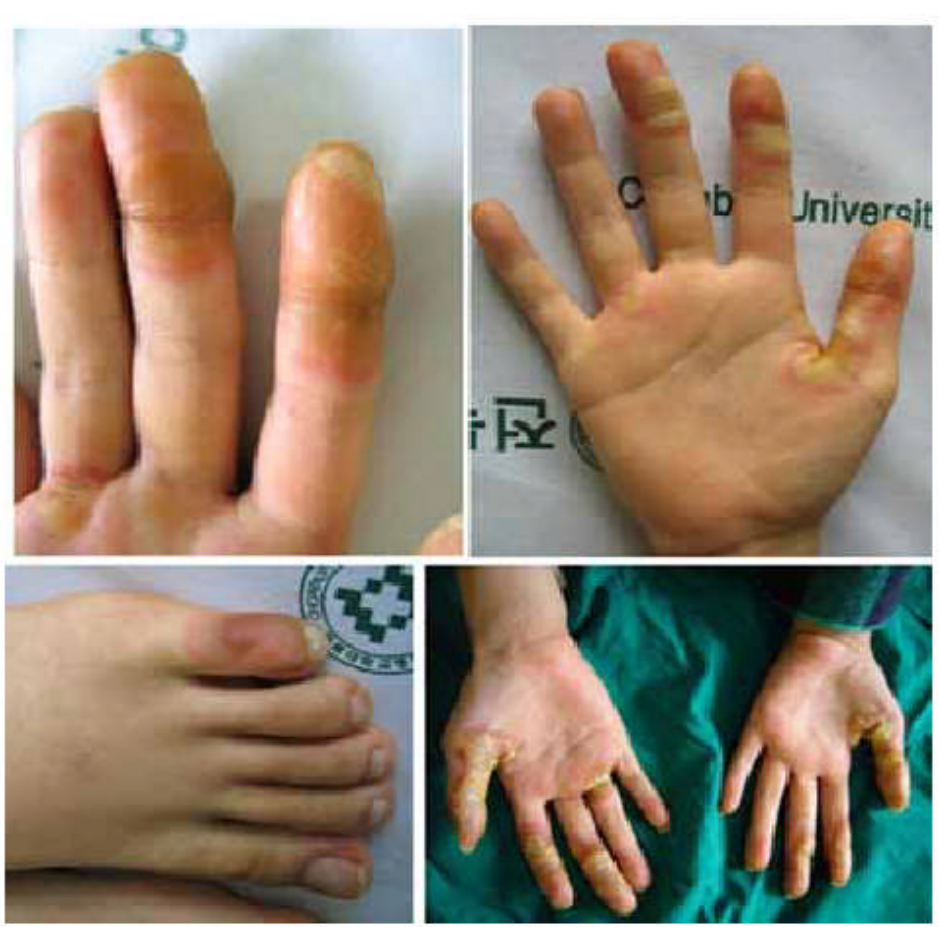


Fig. 3. Acral erythema and hyperkeratosis in the hand and foot of a patient treated with sorafenib.

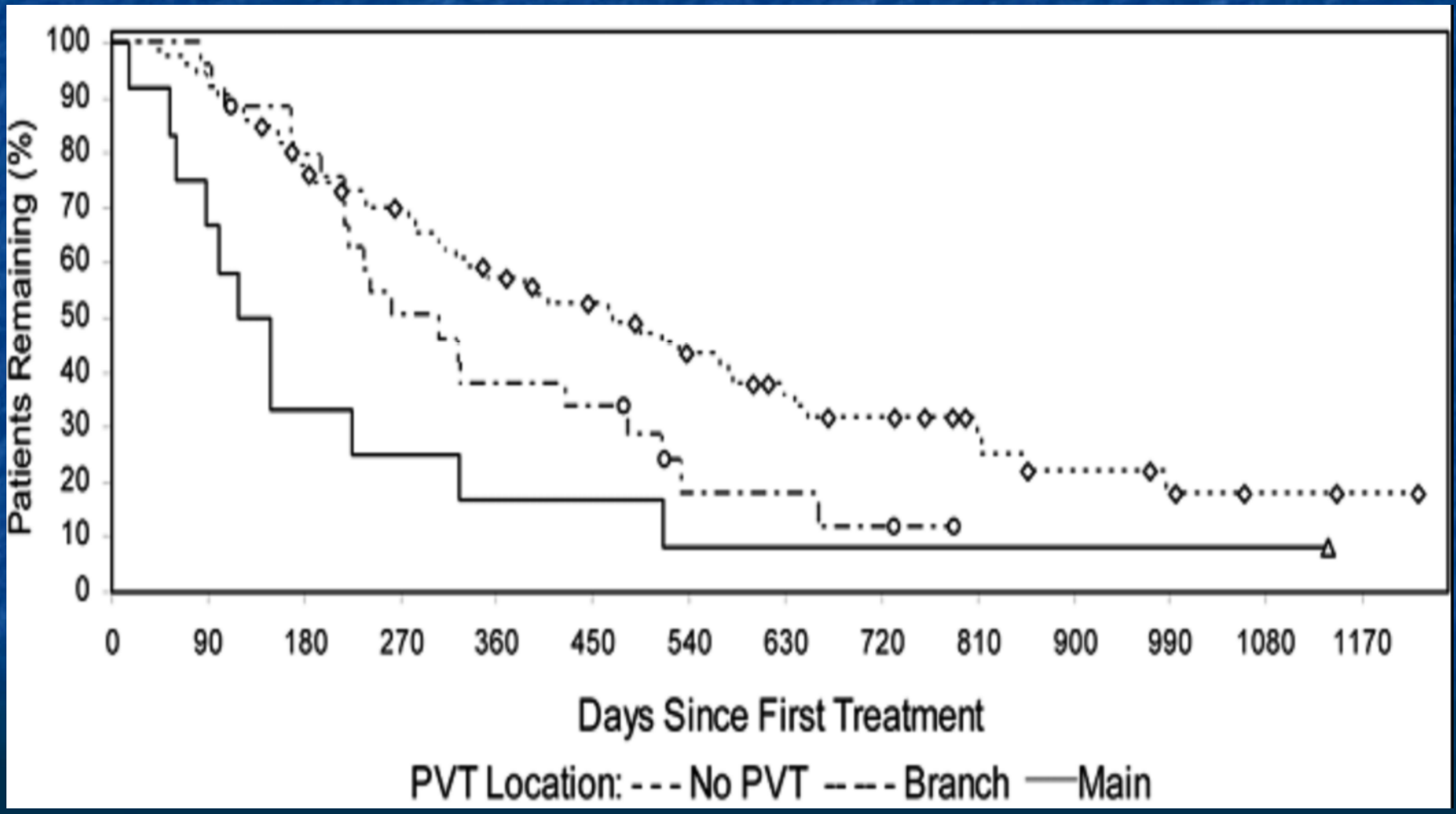
Radioembolisation with ^{90}Y microspheres

- Unlike chemoembolisation (TACE), 90Y microspheres do not occlude the blood vessels (hepatic artery) and can be applied irrespective of the presence of portal vein thrombosis
- No controlled studies
- Response rates quite high, around 50% and even more
- Survival curves vary consistently depending on presence and location (extension) of portal thrombosis (PVT) and presence of cirrhosis

→ Portal Thrombosis of a branch and cirrhosis = 261 days (8.7 months) survival

Kulik LM et al. Hepatology 2008

^{90}Y MICROSPHERES
Kaplan-Meier:
patients with cirrhosis, stratified for PVT location



Kulik et al. Hepatology, 2008;47(1):71-81

BACKGROUND OF OUR RESEARCH

1) The administration of known carcinogens in the course of cell differentiation in embryo causes some malformations in the offspring, but no tumor induction

2) Once organogenesis is completed, the frequency of tumor induction rises with a concomitant decrease in the rate of malformations

3) Embryonic networks are responsible for gene expression in leading totipotent stem cells to complete differentiation

4) In terms of complexity, information depends on the frame of the network not on a single bit. Biological networks are auto organizing, self repairing and able to create order

AIMS

On the basis of this background some experiments in vitro and in vivo were performed.

Factors taken from different embryos during the stage in which totipotent stem cells are differentiating into pluripotent stem cells were used for treatment of different human tumor cell lines in vitro and on Lewis Lung carcinoma in C57BL/6 mice.

The aims of these experiments were:

1. Studying the efficacy in vitro and in vivo of these factors
2. Studying the biological pathways they involve in the regulation of tumor growth (Biava PM, Bonsignorio D, Hoxha M, Impagliazzo M, Frosi A, et al. *Mother-Embryo Cross-Talk: The anti-Cancer Substances Produced by Mother and Embryo During Cell Differentiation. A Review of Experimental Data.* Journal of Toumor Marker Oncology 2002;17:55-58)
3. Preparing a product for clinical purpose. This product was named Stem Cell Differentiation Stage Factors (SCDSF)

In an experiment, by another research group, human metastatic melanoma cells were transplanted into zebrafish blastula-stage embryos

RESULTS:

- The melanoma cells placed in the zebrafish embryo survive, exhibit motility and divide
- They do not form tumors
- Become scattered throughout the embryo, reflecting the de-differentiated state of cancer cells
- Zebrafish embryo contains possible homing cues that can be interpreted by normal human cells
- Zebrafish microenvironment appears to suppress the tumorigenic phenotype of malignant melanoma cells

Lee LMJ and al. 2005 →
http://onlinelibrary.wiley.com/doi/10.1002/dvdy.20471/full

CLINICAL TRIAL ON HEPATOCELLULAR CARCINOMA

A product containing a very low concentration (3micrograms/ml) of Stem Cell Differentiation Stage Factors (SCDSF) was used in an open randomized clinical trial for 40 months on 179 patients with hepatocellular carcinoma in intermediate-advanced stage. The doses of SCDSF were 9 micrograms/daily in sublingual administration

RESULTS OF CLINICAL TRIAL ON HEPATOCELLULAR CARCINOMA

20% of regression and 16% of stable disease were observed in treated patients, with a significant increase of survival.

It was also observed a significant improvement of performance status

(in 81% of the patients) with a negligible rate of adverse effects.

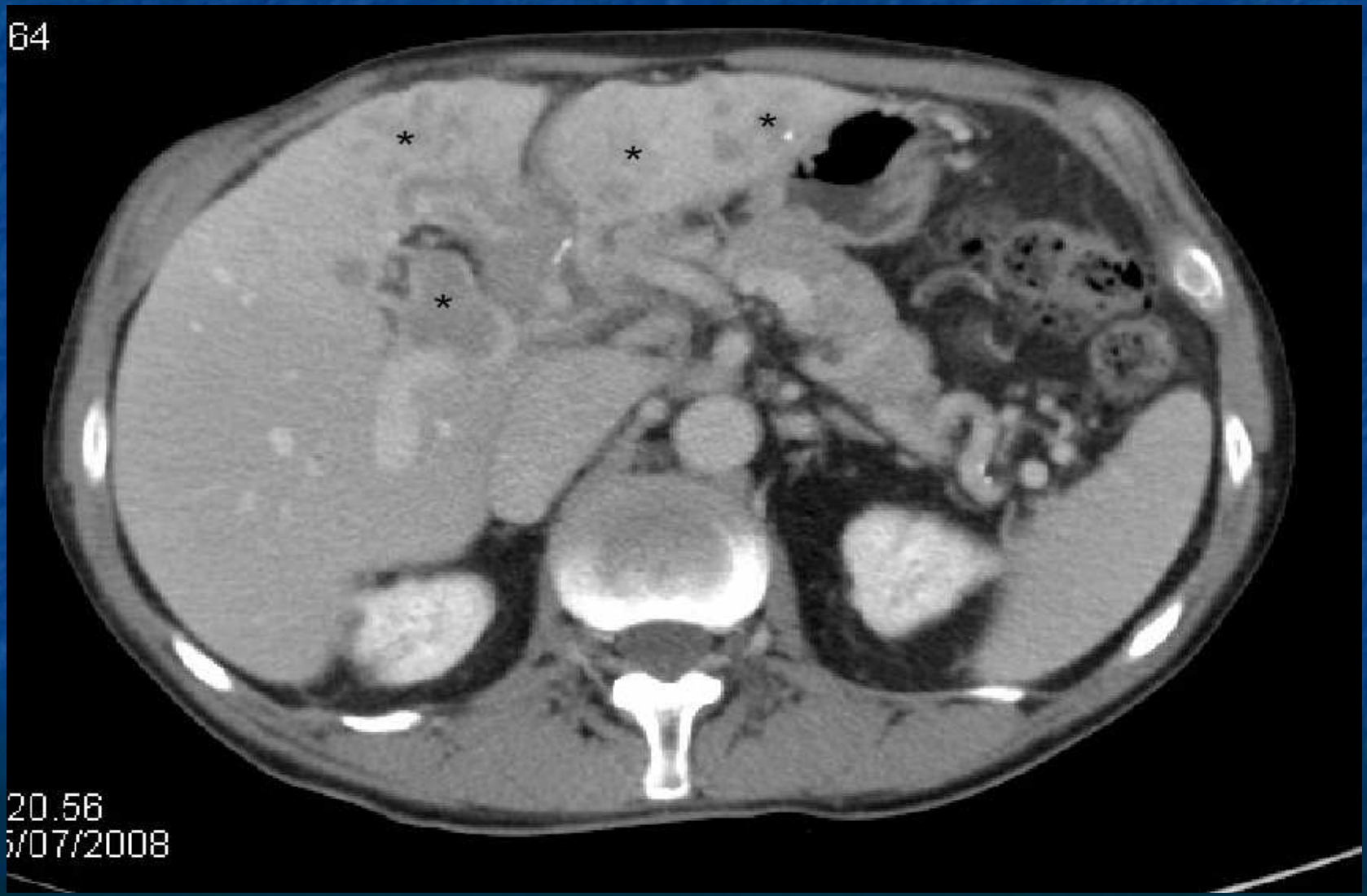
Oncology Research 2005

A recent retrospective cohort study, aimed to validate the efficacy of SCDSF for advanced HCC, demonstrated:

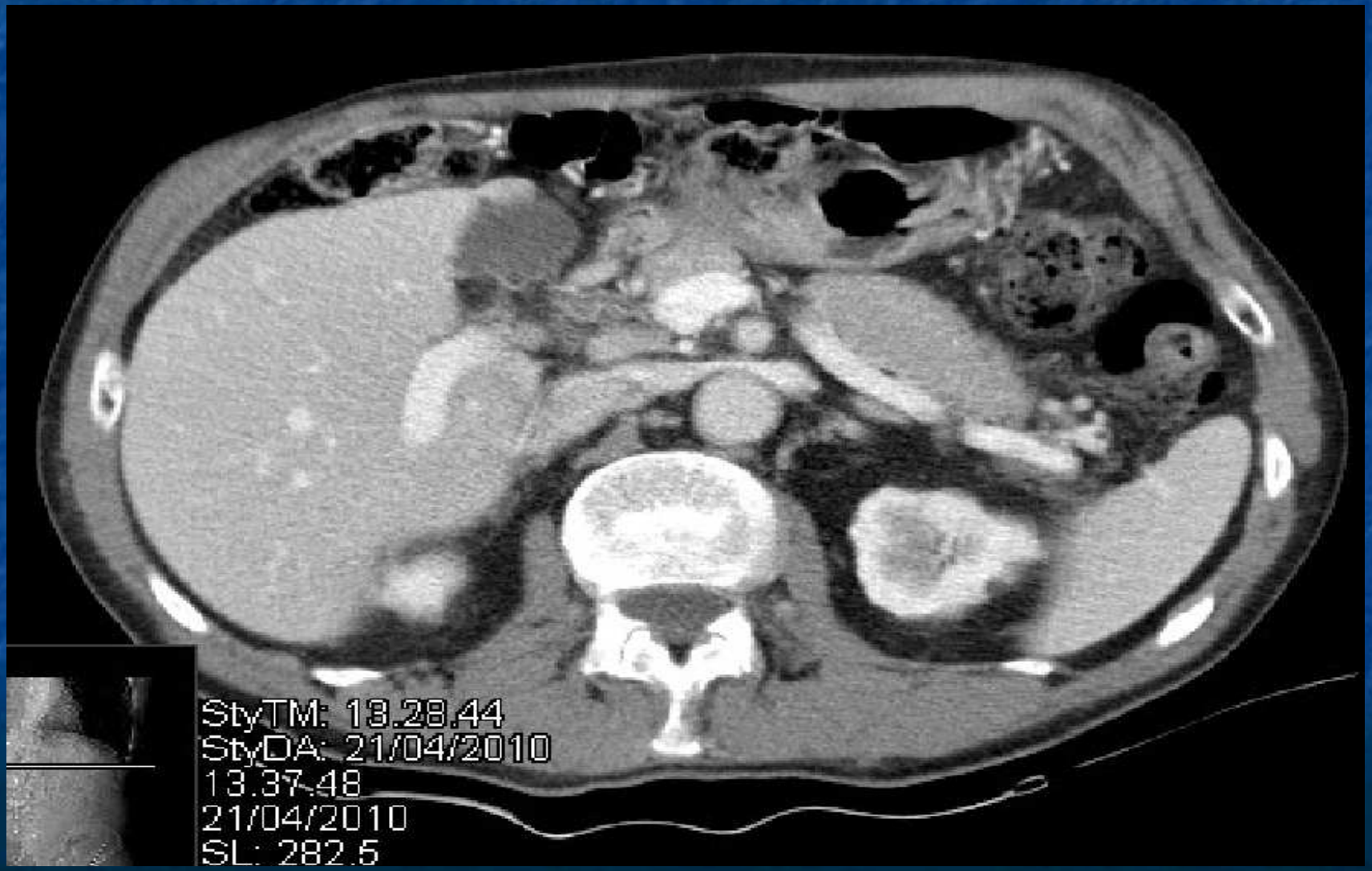
- complete response in 5 out of 38 patients, all of them alive and free of disease at the end of study, after 53,29,27,26,26 months
- overall improvement on performance status in 17 patients (34.6%)

Livraghi, Curr Pharm Biotechnol 2010

CT during the portal phase performed prior to treatment with SCDSF shows diffuse neoplastic thrombosis occupying all the portal system



CT during the portal phase performed after therapy shows disappearance of neoplastic thrombosis and patency of portal system.



BARCELONA CLINIC LIVER CANCER STAGING AND TREATMENT APPROACH

MODIFIED and CONCLUSIONS:

We propose SCDSF as a safe and effective option treatment for INTERMEDIATE-ADAVANCED HCC