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# FUNCTIONAL EVALUATION OF HEPATIC PARENCHYMA WITH DYNAMIC TESTS (INDOCYANINE GREEN AND HIPPURATE RATIO) IN PATIENTS WITH HCC


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**ABSTRACT**

Our aim was to assess hepatic functionality in patients with HCC and candidate for liver resection. We used dynamic tests of liver functionality Indocyanine green (ICG) and Hippurate ratio, for the evaluation of surgical risk and postoperative clinical course.
The clinical and predictive value of the tests has been compared with each other and with routine tests. Tests have been performed on 11 patients with HCC, in 8 before surgery and after 6 months, in 1 before TACE and after 6 months. The results showed a significative correlation with the endpoints: survival, liver failure, general condition of the patients, and parallelism in the clinical assessment of patients. ICG and Hippurate ratio are useful in patients undergoing liver resection and in the follow up.

## Introduction

Hepatocellular carcinoma (HCC) is the most common liver malignancy. It is in fifth place among malignant tumors and the third cause of death for cancer *rfr. Altckrose S.F., Reichman M.E. (2009),* with a male/female ratio 7/1. The worldwide incidence is 714,600 cases per year *rfr. Jong-Wook L. (2003)*, 71% in men. The incidence is also increasing in developed countries; in the United States in the last two decades there has been an increase of 80%, greater in blacks than in whites *rfr. Montaldo G.et al. (2002); El-Serag H.B., Mason A.C. (1999).*

80% of cases affects China, Africa and South East Asia; HCC is responsible for 600,000 deaths every year *rfr. Kerstin S., et al. (2009); Gomaa A.I. et al. (2008)* .

In Italy incidence is 5,800 cases in 2002, prevalence 4,300; the trend of incidence in 2007 is 5,500-6,000 cases, prevalence 4,000; in 2012, 6,600 and 4,230 cases respectively *rfr. Bosetti C., et al. (2009)*; mortality rate is 5.7 /100,000 in males, 1.9 /100,000 in females *rfr. Bosetti C., et al. (2009)*.

In the majority of cases (80-90%), HCC develops on the basis of liver cirrhosis. HCC can also develop in the presence of pre-cirrhotic liver diseases or even in healthy liver. Risk factors include: HCV infection, which represents the major risk factor in Western World and USA, and HBV infection; combined HCV and HBV infections; combined HBV and HDV infections; the association of HCV and schistosomiasis; alcoholism, nonalcoholic steatohepatitis, obesity, exposure to exogenous toxic subsances, in particular aflatoxin-B1 and pesticides; metabolic syndrome, diabetes *rfr. Gomaa A.I. et al. (2008)*. In patients HBV+ predictors of HCC are: HBe Ag positivity, high viral load and genotype C. *rfr. Altckrose SF, Reichman ME (2009).*

An additional factor is exposure to aflatoxin B-1, that can be an independent cause of hepatic damage and hepatocellular carcinoma *rfr. Dufour JF, Johnson P. (2009)*

The disease that most frequently develops into HCC is HCV-related chronic hepatitis, usually through the evolution into cirrhosis. It is estimated that 10-30% of HCV-related hepatitis develops into HCC, with an increased annual risk of 1-2% . In many countries 30% of HCC is HCV+, while positivity in general population is 1%. *rfr. Dufour JF, Johnson P. (2009)*. The genotype 1b is the most frequently associated to HCC *rfr. Bruno S. et al. (2007)*.

The suspicion of HCC arises from ultrasound image of one or more intrahepatic nodules especially in patients with liver cirrhosis, and from increased alpha-fetoprotein. The diagnosis is established with the following investigations: ultrasound, CT angiography, volumetric CT, MRI with specific contrast. In doubtful cases ultrasound-guided liver biopsy.

The choice of the treatment depends on the size of the tumor, the presence of a single nodule or multiple nodules, the localization of the hepatic functional reserve, the patient's general conditions, the stage of the disease, Child and Meld's evaluation *rfr Capussotti L. Child and Meld (2005), Poon R.T.P. (2007)*.

Surgical resection is the treatment of choice in patients with HCC not suitable for transplantation; only single nodules with maximum diameter less than 5 cm or three nodules with diameter ≤ 3 cm each are resectable. According to EASL / AASLD guidelines nodules with maximum diameter more than 5 cm are resectable in patients with good liver function *rfr. Bruix J., Sherman M. (2005); Bruix J., et al. (2001)*. For the execution of surgical resection is necessary an adequate hepatic functional reserve, ≥ 40% *rfr. Bege T. (2007); Liapi E., Geschwind JF (2006)*.

For large lesions or multinodular tumors with more than 3 unresectable nodules, TACE can be practiced *rfr. Bruix J., Sherman M. (2005); Liapi E., Geschwind JF (2006)*; **www.exvascular.com**; Sofarenib has been proposed as palliative chemotherapy in unresectable and non-transplantable patients *rfr. Llovet JM., Et al. (2008).*

## Aim of the research

We intended to evaluate the hepatic functional capacity using dynamic tests (Indocyanine green and Hippurate ratio) in patients with HCC, candidates for major liver resection; the perioperative mortality and the risk of liver failure after surgical resection in relation to the extension of resection; the risk of liver failure in treatments with portal embolization in preparation for major resection; *rfr. Purcell, R., et al. (2006)* any differences in functional activity in relation to the etiology of the liver disease evolved into HCC; to compare the predictive value of the two dynamic tests.

## Materials and methods

The research, conducted with the approval of the research project by the Ethics Committee (July 10, 2008), has been implemented in the following structures: Sapienza University of Rome-Policlinico Umberto I: UOC of Internal Medicine E, Medical Therapy and Thermal Medicine, Department of Internal Medicine and Medical Specialties, UOC of Gastroenterological and Hepatobiliary Surgery, Department of Surgery "Pietro Valdoni"; UOC of Anesthesiology and Intensive Care of the Department of Cardiovascular, Respiratory and Morphological Sciences; Department of Chemistry, "Sapienza" University of Rome; National Institute of Health, Department of Veterinary Public Health and Food Safety-Department of Methodology and Indicators for the Chemical Safety in Food Chains.
We enrolled 11 patients with HCC, M 6 – F 5, mean age 73, range 65-89. 7 of them were HCV+, 2 HBV +, 2 negative for HBV and HCV. None of the patients reported alcohol abuse, 10 patients were classified as Child A and 1 as Child B; 8 patients showed Meld from 3 to 6, 1 Meld 9, 1 Meld 8, 1 Meld 7; moreover catheterization of hepatic veins and hepatic biopsy were also performed in 3 cases. According to Multidimensional Geriatric Assessment (MGA 1-3) 8 patients were MGA 1, 3 MGA 2. According to the Evaluation of the Association of Anesthesiologists (ASA 1-5), 8 patients were ASA 1, 2 were ASA 2, 1 patient, not undergoing surgery, was ASA 3. All patients underwent endoscopy to assess the presence and / or the size of esophageal varices, and / or the presence of gastropathy / ulcers.
The diagnosis of HCC was performed by ultrasonography, CT angiography, volumetric CT, MRI with specific contrast. For diagnosis and treatment, guidelines of the European Ass. Study of Liver were followed *rfr. Bruix J., et al. (2001)* and of the American Ass. of Liver Disease (AASLD 2005) *rfr. Bruix J., Sherman M. (2005)*
The patients were classified according to the Cancer of the Liver Italian Program (CLIP) *rfr (2000)*, United Intern. Consensus Committee (UICC), modified according to AHPBA, Barcelona Clinic Liver Cancer (BCLC) *cfr. Grieco A., et al. (2005), Llovet JM., et al. (1999)*.
For the evaluation of diagnostic and prognostic significance, we considered the following criteria: perioperative mortality, liver failure, general condition of patients and survival. We enrolled 11 patients: 8 underwent liver resection, 1 TACE, 2 died of intercurrent causes.
Dynamic tests were performed before surgery and then six months after in 6 of the 8 operated patients, 2 operated patients are waiting for check up; in 1 patient they were performed before and six months after TACE.
The ICG, administered intravenously at a dose of 0.5 mg/kg, was measured as PDR percentage-minute of elimination of indocyanine green from plasma (v.n.>14%) after 15' with Limon equipment at the UOC of Anaesthesia and Intensive Care. *rfr. R. Purcell et al. (2006); Sheng QS. et al. (2004).*
Hippurate Ratio was determined after intake of PABA orally, mg 5/Kg dosed as the percentage of transformation of p-amnobenzoic acid (PABA-vit. B10-) into p-aminohippuric

acid (Hippurate Ratio v.n.>20%), a sample was taken (time T0) before PABA intake, and after 30' (tempo T1) *rfr. Hemming AW, et al. (2001), Linda LY, et al. (1988)*.
Samples were assayed by high-resolution chromatographic method (HPLC) at the National Institute of Health, Department of Veterinary Public Health and Food Safety; synthesis and control of the purity of a precursor of PABA, p-acetamid hippuric acid, were performed by chemical analysis of the elements, mass spectrometry and MRI at the Department of Chemistry.

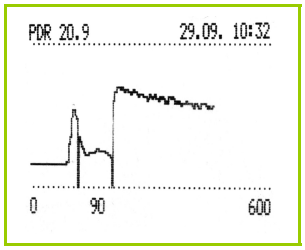
## Analytical list of patients

Table. 1

| PT | BD | SEX | VIRUS B-C | ANGIO CT MRI WITH SPECIFIC CONTRAST | VOLU METRIC TC | CHILD | MELD | ICG PRE TREAT | PABA PRE TREAT | SURGERY TACE | ICG POST TREAT | PABA POST TREAT | ECO/CT/MRI CHECK UP | SIX MONTHS FOLLOW UP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RF | 30/07/30 | M | HCV+ | NODULE HCC SEG VI/VII SIZE 5CM | | A | 6 | PDR 20.4 | 33.00% | RESECTION SEG VII | | | | APR 2011 |
| PMA | 06/08/45 | F | HBV+ | NODULE HCC SEG V/VI SIZE 4CM | | A | 6 | PDR 25.5 | 35.00% | RESECTION SEG VI | | | | DEC 2010 |
| GF | 02/08/40 | M | HCV+ | NODULE HCC IRREGULAR MARGINS SEG VII/VIII SIZE 5CM | | A | 6 | PDR 15.3 | 35.00% | RESECTION SEG VII/VIII | PDR 21.1 | 36.00% | OUTCOME OF RESECTION IN SEG VII/VIII | JAN 2010 |
| CF | 11/07/42 | M | NEG | NODULE HCC SEG VIII V+IV SIZE 11CM | VOL 570.89CC H 10.80CM | A | 7 | PDR 35.5 | 40.00% | RIGHT HEPATECTOMY TO SEG IV | PDR 21.6 | 37.00% | COMPENSATORY HYPERTRPHY OF THE LOBE ON WIDELY HOMOGENEOUS PARENCHYMA | APR 2010 |
| DMC | 15/07/30 | F | HCV+ | NODULE HCC EXOPHYTIC SEG IV SIZE 4CM | | A | 8 | PDR 26.8 | 40.00% | RESECTION SEG IV B | PDR 26.2 | 40.00% | COMPENSATORY HYPERTRPHY OF RESIDUAL WIDELY HOMOGENEOUS PARENCHYMA | MAY 2010 |
| CI | 31/05/21 | F | HCV+ | NODULE HCC EXOPHYTIC SEG III SIZE 4CM | | A | 9 | PDR 11.2 | 18.00% | RESECTION SEG III | PDR 5.4 | 15.00% | FINELY NON-HOMOGENEOUS ECHOTEXTURE FREE FROM IMAGES OF FOCAL PATHOLOGY | SEPT 2010 |
| GV | 31/03/34 | F | HCV+ | NODULE HCC EXOPHYTIC SEG III SIZE 4CM | | A | 6 | PDR 12.8 | 18.00% | RESECTION SEG III | PDR 10.6 | 18.00% | FINELY NON-HOMOGENEOUS ECHOTEXTURE REGULAR V8P AND PORTAL VEIN | SEPT 2010 |
| RA | 27/06/42 | M | HCV+ | NODULE HCC SEG V SIZE 4CM | | A | 6 | PDR 17.8 | 30.00% | RESECTION SEG V + WEDGE | PDR 20.6 | 34.00% | SLIGHT HEPATOMEGALY FIBROTIC SCARS FROM PREVIOUS SURGERY | OCT 2010 |
| DUS | 08/12/22 | F | HBV HCV+ | NODULE HCC SEG VII/VII SIZE 7..5CM | | A | 4 | PDR 10.9 | 20.00% | | | | | DEAD |
| VG | 30/07/37 | M | HCV+ | NODULE HCC SEG VII/VIII SIZE 8CM | VOL 261.68CC H 8.90CM | A | 6.5 | PDR 20.9 | 40.00% | | | | | DEAD |
| BG | 15/05/39 | M | HBV+ | NODULE HCC SEG VI/VII SIZE 5.5CM | | B | 8 | PDR 5.3 | 18.00% | CHEMOEMB | PDR 4.6 | 15.00% | | MAY 2009 |

1) V.G., M, age 71, HCC of cm8 in segment VII and VIII in HCV+. ICG-PDR 20.9, PABA 40%, indicative of good hepatic compensation; Child A, Meld 6.5, MGA 1, ASA 2. The patient died for bone metastases.

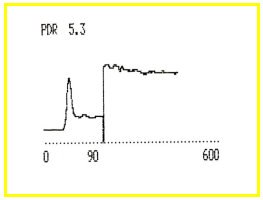
Table.2 ICG before treatment




2) D.S., F, 87 years, HCC of 7.5cm in segment VII and VIII in HBV and HCV negative; ICG-PDR 10.9, PABA 20%, indicative of modest hepatic compensation; Child A, Meld 3, MGA 2, ASA 3.
The patient died for brain metastases.

3) BG, M, 70 years, HCC of 5.5 cm in segment VI and VII in HBV +, ICG-PDR 5.3, PABA 18%, indicative of reduced hepatic compensation. Child B, Meld 8, VMG 2, ASA 2. The presence of portal hypertension, underlined by catheterization of the hepatic veins, indicated the chemoembolization of the lesions. Six months after treatment ICG-PDR 4.6, 15% PABA showed no significant changes.

Table.3 ICG before treatment




4) GF, M, 69 years, 5cm HCC in segment VII in HCV+, ICG-PDR 15.3, PABA 35%, indicative of good liver compensation. Child A, Meld 6, VMG 1, ASA 1. Six months after surgical resection of the segment VII adjusted for saving and small resection of the diaphragm ICG-PDR 21.1, PABA 36%, data indicative of improved liver function.

Table. 4 trabecular HCC

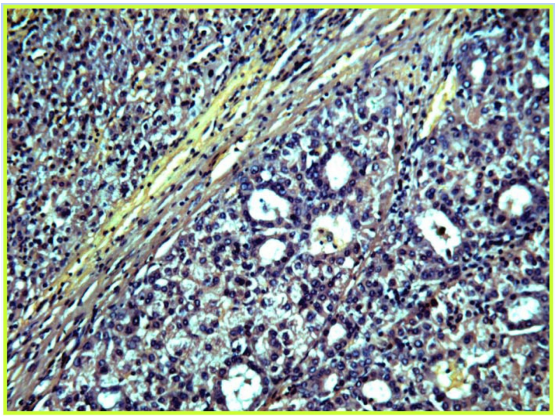
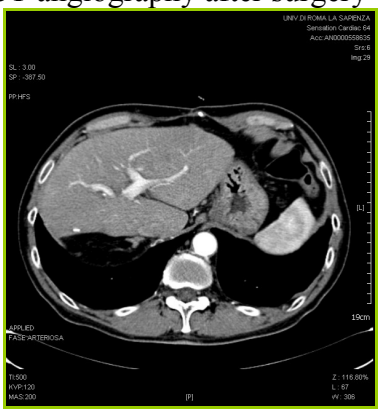


Table.5 CT angiography after surgery



5) CF, M, 67 years, 10cm HCC in segment VII and VIII; ICG-PDR 35.5, PABA 40% indicative of good liver compensation. Child A, 7 Meld, MGA 1, ASA 1. Six months after right hepatectomy (segments V and VIII) extended to IV b and I 9 ICG-PDR 21.6, PABA 37%, data indicative of *preserved* liver function

Table.6 CT volumetric study

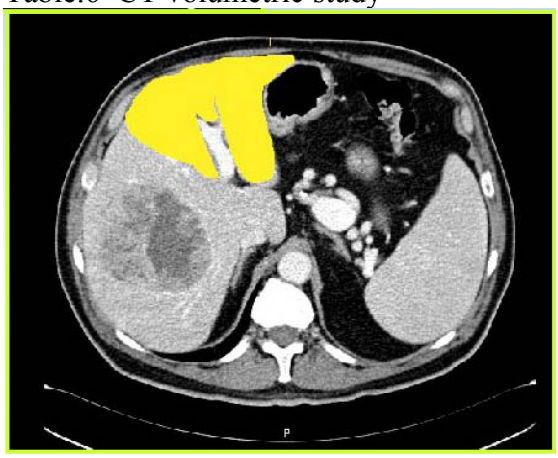
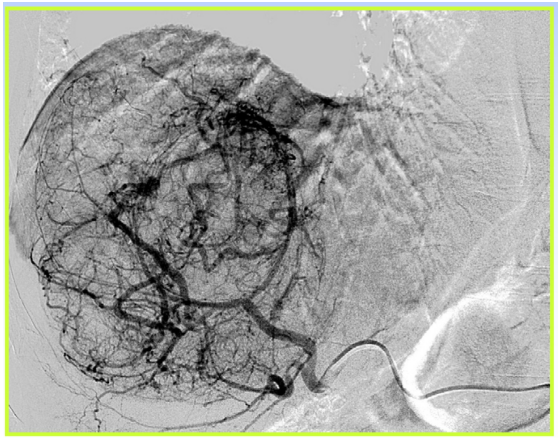


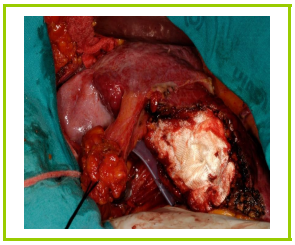
Table.7 Arteriography pre-chemioemb.



6) Di MC, F, 69 years, 3.5 cm HCC in segment IV in HCV +, ICG-PDR 26.8, PABA 40% indicative of good liver compensation. Child A, Meld 6, MGA 1, ASA 1. 6 months after surgical resection of segment IV ICG-PDR 26.2, PABA 40%, data indicative of *preserved* liver function

7) CJ, F, 89 years, HCC of 4cm in segment III in HCV+; ICG-PDR 11.2, PABA 18% indicative of moderate liver function. Child A, 9 Meld, MGA 1, ASA 1. After 6 months from the resection of segment III ICG-PDR 5.4, PABA 15%, data indicative of decreased liver function.

Table. 8



8) GV, F, 75 years, HCC of 4 cm in segment III in HCV+; ICG-PDR 12.6, PABA 18%, indicative of moderate liver activity. Child A, Meld 6, MGA 2, ASA 1. After six months from the resection of segment III, ICG-PDR 10.6, PABA 15%, data indicative of *preserved* liver function.

9) RA, M, 68 years, 4cm HCC in segment V in HCV+; ICG-PDR 17.8, PABA 30% showing good liver function. Child A, Meld 6, MGA 1, ASA 1. After six months from the wedge resection of the segment V ICG-PDR 20.6, PABA 34%, data indicative of very good liver function

10) PMA, F, 65 years, 4cm HCC in segment V and VI in HBV +, ICG-PDR 25.5, PABA 35% indicative of good liver function. Child A, Meld 6, MGA 1, ASA 1.
She underwent resection of segment VI on June 15, 2010, and is waiting for check up after 6 months.

11) RF, M, 80 years, HCC of 5cm in segment VII in HCV+; ICG-PDR 20.4, PABA 33%, showing good liver function. Child A, Meld 6, MGA 1, ASA 1. ALT 33, AST 29, gamma-GT 33, PT 107%, alpha-fetoprotein 489. He underwent resection of segment VII on October 12, 2010, and is waiting for check up after 6 months.

Table. 9 Pre-surgery CT angiography

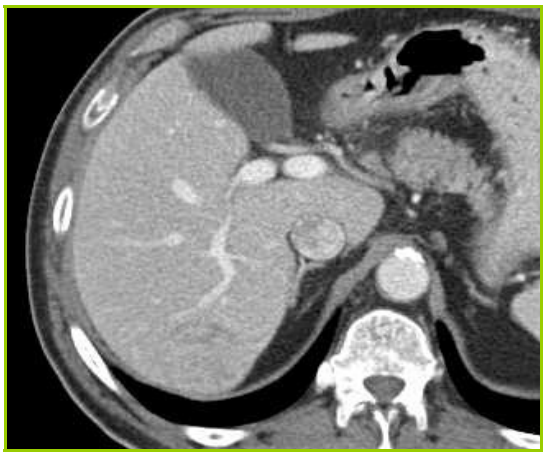
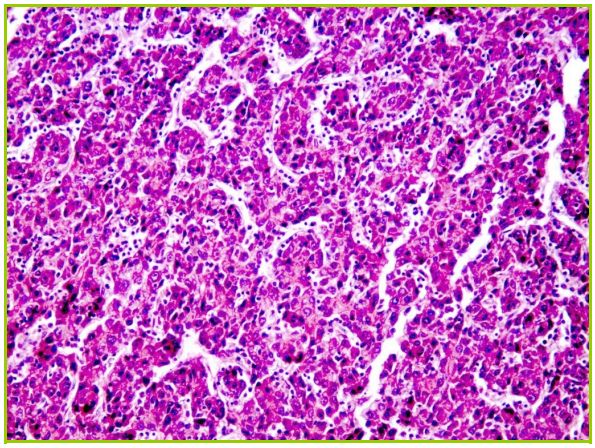


Table. 10 Trabecular HCC



## Results

Dynamic tests, ICG and Hippurate ratio, were outside the normal range in 3 out of 9 treated patients; 8 patients underwent surgical resection, 1 TACE. Mean pre-treatment values in operated patients were: ICG - PDR 19.9, range 11.2 - 35.5, PABA 19.9 range 18% - 40%; in the patient undergoing TACE: ICG-PDR: 5.3, PABA 18%. Mean post-treatment values in operated patients: ICG - PDR 19.2 range 5.4 - 26.2; PABA 17.6%, range 15% -37%. Post-TACE treatment: ICG - PDR: 4.6, PABA 15% .

## Discussion

Dynamic tests have proved to correlate well with the considered end points: perioperative mortality, survival, liver failure, general conditions of patients, and the results of routine tests: blood count, GOT, GPT, bilirubin, total protein, albumin, compared to which they have a higher predictive value. A strong correlation between the two tests has been underlined, without significant differences in the occurrence of liver failure, in contrast to what reported by Hemming et al. in favour of Hippurate ratio. The correlation shown by dynamic tests with the event "death" in the perioperative period (normal test, except one, no deaths), confirms what was highlighted in the cases studied by Hemming et al; the good correlation with Child classifications *rfr. Child CG. , Turcotte JG. (1964)* and Meld classifications *rfr Meld. Kamath PS., et al. (2001)* confirms what stated in other studies *rfr. Lao XM, et al. (2004); Sheng QS., et al. (2004.)*
Finally, the favorable course of the studied patients must be noticed, although advanced age is considered as a risk factor in major liver resection *rfr. Fan ST (2002)*; *Capussotti L. (2005)*. Therefore, we recommend the execution of dynamic tests in elderly patients with HCC suitable for surgery; ICG and Hippurate Ratio tests are useful in the evaluation of patients with HCC undergoing liver resection and follow-up. The patient who underwent TACE showed no significant changes in testing 6 months after treatment.

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