THE POSSIBILITIES AND PERSPECTIVES OF THE SURGICAL TREATMENT IN THE PRIMITIVE MALIGNANT LIVER TUMORS

PhD THESIS

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Project co-financed from the European Social Fund by the Sectoral Operational Program Human Resources Development 2007 – 2013. „Education and professional training supporting the economic growth and the society development based on knowledge” primary axis
Main intervention field: 1.5 „Doctoral and post-doctoral program supporting the research”
Project title: „Doctoral fellowships for the increase of competitiveness in the medical and pharmaceutical field”
Contract Identification Number: POSDRU/88/1.5/S/58965
Beneficiary: “Gr. T. Popa” University of Medicine and Pharmacy of Iasi
Partner : “Iuliu Hatieganu” University of Medicine and Pharmacy of Cluj Napoca

Write so as not to lose the flowers of your mind, otherwise the wind takes them away!
Nicolae Iorga

**KEYWORDS:** PRIMITIVE LIVER TUMORS; HEPATOCARCINOMA; CHOLANGIOCARCINOMA; FIBROLAMELLAR CARCINOMA; DIAGNOSTIC; TREATMENT; HEPATIC RESECTION; LIVER TRANSPLANT; FOCAL DESTRUCTION; CURATIVE TREATMENT; HISTOLOGICAL TYPE; COMPLICATIONS; TUMORAL RELAPSE; PROGNOSTIC; SURVIVAL.
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<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AFP</td>
<td>Alpha-fetoprotein</td>
</tr>
<tr>
<td>CHA</td>
<td>Common hepatic artery</td>
</tr>
<tr>
<td>RHA</td>
<td>Right hepatic artery</td>
</tr>
<tr>
<td>PHA</td>
<td>Proper hepatic artery</td>
</tr>
<tr>
<td>LHA</td>
<td>Left hepatic artery</td>
</tr>
<tr>
<td>SMA</td>
<td>Superior mesenteric artery</td>
</tr>
<tr>
<td>CGDSHT</td>
<td>Centre for General, Digestive Surgery and Hepatic Transplant</td>
</tr>
<tr>
<td>ICC</td>
<td>Intrahepatic cholangiocarcinoma</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized tomography</td>
</tr>
<tr>
<td>FD</td>
<td>Focal destruction</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>HBP</td>
<td>High blood pressure</td>
</tr>
<tr>
<td>ALF</td>
<td>Acute liver failure</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>AKF</td>
<td>Acute kidney failure</td>
</tr>
<tr>
<td>MODS</td>
<td>Multiple organ dysfunction syndrome</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>NASH</td>
<td>Non-alcoholic steatohepatitis</td>
</tr>
<tr>
<td>HR</td>
<td>Hepatic resection</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic resonance</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard error of mean</td>
</tr>
<tr>
<td>TD</td>
<td>Thermodestruction</td>
</tr>
<tr>
<td>HT</td>
<td>Hepatic transplant</td>
</tr>
<tr>
<td>PMHT</td>
<td>Primitive malignant hepatic tumor</td>
</tr>
<tr>
<td>TNRF</td>
<td>Termonecrosis by radiofrequency</td>
</tr>
<tr>
<td>TNWVP</td>
<td>Termonecrosis by water vapors under pressure</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior vena cava</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>RHV</td>
<td>Right hepatic vein</td>
</tr>
<tr>
<td>MHV</td>
<td>Middle hepatic vein</td>
</tr>
<tr>
<td>LHV</td>
<td>Left hepatic vein</td>
</tr>
<tr>
<td>VP</td>
<td>Vena porta</td>
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</table>
1. INTRODUCTION

The incidence of the primitive malignant hepatic tumors and mainly that of the hepatocellular carcinoma, is ever-growing worldwide [1]. Even though HCC prevails in Asia and Africa, its incidence has also increased lately in Europe and USA [2]. The hepatocellular carcinoma is the fifth carcinoma according to the frequency, having an estimative value of about 442,000 new cases each year [3]. The most frequent carcinoma of this type develops in the presence of a chronic viral hepatitis type B or C, which have a high prevalence inclusively in Romania [4,5]. The morbidity caused by HCC is high and it depends on several factors, the most important being connected to the diagnostic and treatment [6].

The treatment methods in the liver tumors have evolved a lot over time. The first attempts of surgical treatment for the malignant liver tumors were carried out in the '50s. These were solitary cases of hepatic resection successfully practiced and published in that period [7]. After the description of the liver segmentation by C. Couinaud, the hepatic resections started being practiced more and more frequently, including for malignant liver tumors. Initially, anatomic resections were practiced, being subsequently followed by non-anatomic resections [8,9]. Starting with the '90s, various instruments and devices were introduced, performing a easier dissection and hemostasis at the level of the hepatic parenchyma, shortening in a significant manner the operation time. In the past 10 years, the place of the classical surgical resections was gradually took over by the laparoscopic
resections, carried out including for the liver carcinomas [10,11]. With regard to the robotic liver carcinomas, they are at the beginning and they present no advantage as compared to the laparoscopic resections [12]. The novelty with regard to the hepatic resections in the analyzed patients consisted of the use of the radiofrequency Habib tuck for the performance of the liver transection.

The liver transplant as treatment method of the liver tumors was introduced in the '80s. One noticed that not all the patients with malignant liver tumors can benefit from liver transplant. In order to obtain favorable post-operative results and a long-term survival opportunity for the patients, it is necessary to treat by this method only the patients who observe certain criteria. These criteria were formulated by V. Mazzaferro and subsequently enforced in the selection of the patients with primitive hepatic tumors for transplant [13]. Due to a low number of cadaver donors and to the increased necessities of liver transplant, the transplant methods with liver from a living donor perfected [14,15]. When the relatives agree to donate a part of the liver for the patient with HCC, the transplant can be carried out even though the Milano criteria are exceeded [16,17]. Another problem for the performance of the transplant is the existence of a well-trained medical team and of a center equipped accordingly. At present, there is one transplant center in the country.

The methods of termodestruction by hyperthermia of the hepatic tumors have developed lately. Different proceedings of obtaining hyperthermia are employed. In our clinic, we promoted and developed the
termodestruction proceeding, using the water vapors under pressure. This termodestruction method proved its effectiveness in the patients with secondary liver tumors [18]. In HCC, we used it both for curative purpose in the small tumors and for palliative purpose in the patients with non-resectable tumors. All these patients were included in the study in order to compare them to the ones who benefited from termodestruction by radiofrequency. At the same time, the focal termodestruction methods are used as neo-adjuvant treatment for the patients included on the waiting list of the hepatic transplant or are associated to the hepatic resections [19-21].

In order to increase the resecability of the liver tumors, one can resort to the means of reconversion of the tumor from advanced stages into operability stages. The techniques employed for this conversion are the local neo-adjuvant chemotherapy (in the hepatic artery), the selective ligation or embolization of the hepatic artery, the portal selective ligation or embolization, local ablation „in situ” and radiotherapy [22]. With all these progresses, the resecability rate in the primitive malignant liver tumors is of 40% only.
2. PURPOSE AND OBJECTIVES OF THE STUDY

The main purpose of this study is to analyze and optimize the surgical treatment methods existing in the patients with primitive malignant liver tumors and to reduce to the maximum the operative risks and the post-operative complications, without influencing in a negative manner the prognostic of the disease.

The objectives at the beginning of the study were the following:

✓ the analysis of the ethiopatogenetic data of the patients with primitive malignant liver tumors and their importance in choosing the treatment method;
✓ the analysis of the clinical data, of the laboratory and imagistic data, but also their influence in the post-operative evolution of the patients;
✓ the assessment of the surgical treatment methods practiced and the comparison of the data obtained with the ones from literature;
✓ the analysis and comparison of the intra-operative data according to the surgical method practiced;
✓ the monitoring of the post-operative complications and the determination of the risk factors of these complications;
✓ the analysis of the histopathological data of the tumors and of the non-tumor liver tissue, but also their reflection on the relapses.
✓ the analysis of the distance survival according to the treatment method practiced;  
✓ the creation of a diagnostic and treatment guide of the patients with primitive liver tumors, enforceable in the conditions of the Romanian sanitary system.
3. MATERIAL AND METHOD

SELECTION OF THE PATIENTS

In order to achieve the purpose and the objectives aimed at, we carried out a retro-prospective study over a 8-year period. The study was carried out on the casuistry of the Clinic I Surgery of the “Sf. Spiridon” Hospital of Iași, but also on a part of the casuistry of the Center of General, Digestive Surgery and Hepatic Transplant (CGDSHT) of the Croix-Rousse Hospital of Lyon, France. The patients with primitive malignant hepatic tumors treated over the period from January 2009 to December 2012 in Clinic I Surgery were analyzed prospectively, and the patients treated in the same clinic over the period from January 2005 to December 2008, but also some of the patients treated in the center of Lyon over the period from January 2005 to December 2011, with hepatocellular carcinoma associated to the metabolic syndrome, were treated retrospectively. I mention that I performed a three-month training stage in the center of Lyon and I had partial access to their database. This explains the existence of certain differences with regard to the laboratory analyses, imagistic data, technical conditions, but also the treatment possibilities.

The study included all the patients diagnosed with primitive malignant liver tumors and who benefited from one of the treatment methods mentioned above. Three groups of patients resulted, according to the treatment enforced.

I. The first group included the patients who benefited from hepatic resection.
The inclusion criteria in this group were the following:

- age $\geq$ 18 years old;
- primitive malignant hepatic tumor, histopathologically confirmed;
- unique hepatic tumor $> 3$ cm;
- multiple hepatic tumors located in the same lobe;
- condition of the non-tumor liver parenchyma: normal or Child-Pugh A or B chronic hepatopathy
- volumetry of the remaining liver $> 40\%$;
- absence of the distant metastases.

According to the technique carried out for the liver transection, the patients were divided into two subgroups. Subgroup IA included the patients who benefited from transection by means of the radiofrequency device (Habib 4X tuck), and the subgroup IB included the patients who were subject to other methods for transection (the ultrasound dissector, Ligasure tuck, the electrocauter, the finger fracture technique).

II. The second group included patients who were subject to focal destruction by hyperthermia. The inclusion criteria in this group were the following:

- age $\geq$ 18 years;
- primitive malignant liver tumor confirmed by hepatic biopsy;
- unique hepatic tumor located deeply in the parenchyma $< 3$ cm;
- multiple hepatic tumors located in both lobes;
non-resectable hepatic tumors;
- the tumor does not make contact with the supra-hepatic veins or with the hilar plate.

According to the destruction method by applied hyperthermia, the patients were classified into two subgroups. Subgroup IIA included the patients with thermo-necrosis by water vapors under pressure and subgroup IIB included the patients with thermo-necrosis by radiofrequency.

III. The third group included the patients who benefited from liver transplant (all these patients were operated in the Center of General, Digestive Surgery and Hepatic Transplant (CGDSHT) of the Croix-Rousse Hospital of Lyon, France).

The inclusion criteria in this group were the Milano criteria:
- HHC developed on cirrhosis;
- unique tumor which does not exceed 5 cm in the largest diameter;
- multicentric tumor, with 2 or 3 nodules of maximum 3 cm each;
- absence of the macroscopic vascular invasion;
- absence of the extra liver tumor extension.

The study excluded the patients who refused the surgical treatment aimed at, but also the patients who only benefited from intratumoral ethanol injection, intra-arterial embolization or symptomatic treatment. Moreover, the study excluded the patients surgically treated, whose histopathological result highlighted a
benign hepatic tumor or a secondary malignant hepatic tumor. We obtained from all the patients the written consent of participating in this clinical study, by signing the informed consent (addendum 1 and 2).

ASSESSMENT CRITERIA USED SO AS TO EVALUATE THE RESULTS
We carried out a non-randomized retrospective observational study, in which we analyzed the patients with primitive malignant hepatic tumors, surgically treated. In the first stage of the study, we analyzed the pre-, intra- and post-operative data in the three groups. In the second stage, we analyzed the occurrence of relapses and the distant survival. We tried to establish the preoperative risk factors which favor the occurrence of relapses and diminish the survival so as to be reduced in the future.

Analysis of the pre-, intra- and post-operative data
The data in the medical files (medical records, operative protocols, imagistic and histopathological reports) of the patients of the two clinics, were managed within a MF Excel, Office 2007 database. The variables included in this database were of qualitative and quantitative type. The quantitative ones were continuous and categorical. Therefore, the personal, anamnesis, clinical, paraclinical data, those regarding the operative technique, evolution, complications, adjuvant treatments were numerically coded or as alpha numerical expressions. The values of different biometrical parameters (waistline, body mass, tumor dimension,
concentration of the serum hemoglobin, of the bilirubin, serum proteins, AFP, intervention duration, quantity of blood lost during the surgery, etc.) were numerically introduced, and coded fields were created for the categorical values, according to the requirements of the statistical analysis (the surgical clinics were noted with 0 respectively, 1, the male / female gender with 0, respectively 1, the rural / urban background with 0 respectively 1, the blood transfusion with 1 (yes) or 0 (no)). Certain fields had several variables: the Child-Pugh classification from 1 to 3, tumor localization in the segments of the liver from 1 to 8, the ASA anesthetic-surgical risk from 1 to 4.

We mention that the assessment of the operative risk was performed by the re-evaluation of the medical documents of the patients.

In order to ensure the homogeneity of the study, we re-assessed the intra- and post-operative complications, using the following definitions:

✓ The intra-operative hemorrhage was taken into consideration when we had a blood loss higher than 500 ml.

✓ The biliary fistula was defined as the persistence of a biliary drainage of more than 50 ml/day or the radiological identification of a fistula tract which communicates with the biliary tract.

✓ The post-operative death was considered as the death occurred during the first 30 days following the surgery.

✓ The tardy complications included the complications occurred a month after the surgery and which were connected to the surgical
intervention, excepting however the tumor relapses.

Distant assessment and diagnostic of the post-operative tumor relapses

In order to analyze the occurrence of the post-operative tumor relapses, the patients who were subject to a radical surgical treatment at a post-operative time period of 3 and 60 months were analyzed. For this purpose, a clinical-paraclinical investigation and post-operative monitoring protocol was created (addendum 3). The clinical-paraclinical investigation protocol included the clinical examination, the biological sampling, the AFP graduation and the imagistic investigations. The CT examination was performed for all the patients whose ultrasound suspected local relapse or metastases. The liver ultrasounds were performed by the same physician and this allowed a much more accurate assessment of the changes occurred at the level of the liver parenchyma.

In order to assess the survival rate, we contacted the Computerized Population Register of Iaşi, which informed us on the death date. In the case of the death patients, we contacted the family in order to establish the cause of death.

STATISTICAL ANALYSIS

The database was processed in MS Excel and the statistical analysis was performed by means of the SPSS program, version 20.0, for Windows (Statistical Package for the Social Sciences, Chicago, Illinois). The tests employed were: the t Student test, Pearson-$\chi^2$, the Fisher exact test, the ANOVA test, the logistic regression, the
Pearson correlation, the Spearman correlation, the Kaplan Meier survival curves and the Cox regression model. The threshold of significance was p<0.05. For the continuous variables, the average values were expressed as: average value ± standard deviation. When the standard deviation had very high values, because the study group is non-homogenous and little numerous, we used the standard error of mean (SEM), specifying this aspect.

4. RESULTS AND DISCUSSIONS

PATIENTS’ DISTRIBUTION IN THE TWO SURGICAL CENTERS

Over the period from 2005 to 2012, 106 patients with primitive malignant liver tumors were admitted in the Clinic I Surgery of the “Sf. Spiridon” Hospital of Iasi. Of all these patients, the study included 74 (69.81%) patients. The other 32 (30.19%) patients were excluded for the following reasons: 8 (7.55%) patients refused the proposed treatment; 4 (3.78%) patients were subject to percutaneous ethanol injection, without sampling tumor biopsy; 10 (9.43%) patients benefited from intra-arterial embolization with Lipiodol and they did not come back for the hepatic resection; on the admission date, 7 (6.6%) patients were out of the therapeutic resources and had symptomatic treatment only; in other 3 (2.83%) cases, the histopathologic result at paraffin highlighted benign tumor in 2 (1.89%) cases, and in one case (0.94%) secondary hepatic tumor (non-differentiated tumor metastasis), even though the result at the extemporaneous examination was of primitive malignant liver tumor.
The study group was complemented by 31 patients with HCC associated to the metabolic syndrome, treated in the Center of General, Digestive Surgery and Hepatic Transplant of the Croix-Rousse Hospital of Lyon, France over the period from 2005 to 2011.

The definitive study group comprised 105 patients with PMHT, surgically treated over the period from 2005 to 2012. Of them, 74 (70.48%) patients were operated in the Clinic I Surgery and 31 (29.52%) patients in CGDSHT of Lyon.

The dynamics of the surgical interventions in the two clinics is represented in figure 7.1.

![Figure 7.1 Annual distribution of the surgical interventions in the two centers](image)

This chart shows that most of the patients with PMHT were operated in 2011 in both centers.
DEMOGRAPHICAL DATA

The analysis and interpretation of the demographical features of the groups of patients always represent the first step in the performance of a clinical study. In the case of the prospective studies, the groups are defined according to the demographical data; for the retrospective studies, the statistical analysis of the demographical data (uni- and multivariated) allows the assessment of the risk, prognostic factors for a certain disorder or type of intervention (treatment).

Gender characteristics

Of the total number of patients with PMHT, men represented 70.48% (n=74), and women 29.52% (n=31). This distribution is shown in Figure 7.2.

Fig. 7.2 Distribution according to gender of the patients with primitive malignant liver tumors
The distribution of the patients with PMHT according to the gender and the type of surgical treatment enforced does not show statistically significant differences ($\chi^2=5.702; \text{df}=2; p=0.058$).

**Age characteristics**

The average age (Aa) for the entire group of 105 patients was of 62.84±9.26 years (median of 61 years old), with extremes between 26 and 88 years old. The variation coefficient (VC=14.74%) showed an average dispersion of the age in the general group. The average age of the patients belonging to the three study groups is represented in Table X.

**Table X. Average age of the patients belonging to the three groups**

<table>
<thead>
<tr>
<th>Study group</th>
<th>No. Of patients</th>
<th>Average age (years old)</th>
<th>Standard deviation</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (HR)</td>
<td>64</td>
<td>63.53</td>
<td>10.18</td>
<td>1.27</td>
</tr>
<tr>
<td>Group II (TD)</td>
<td>29</td>
<td>62.79</td>
<td>8.73</td>
<td>1.62</td>
</tr>
<tr>
<td>Group III (HT)</td>
<td>12</td>
<td>59.33</td>
<td>2.81</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Comparing the average age between the three groups of patients by means of the t Student test, we noticed the following: between group I and group II (t(91)=0.338, $p=0.736$), but also between group II and group III (t(39)=1.909, $p=0.064$) there were no statistically significant differences; and between group I and group III (t(74)=2.783, $p=0.007$) there were
statistically significant differences. The ANOVA test shows the existence of a significant difference between the three groups ($F(2.102)=4.355; p=0.013$).

**Background**

The patients of the studied groups belong to two different countries, with different food and cultural peculiarities. Those from Romania come mostly from the Moldavian counties, near the Iasi University Center. In these conditions, we can consider that this study can represent a regional study (mainly for the North of Moldavia) regarding PMHT (Fig. 7.4).

![Fig.7.4 Cases distribution per counties](image)

The distribution of the patients operated in the CGDSHT of Lyon shows that most of the patients belong to the Rhône-Alpes region.

Analyzing the background of the patients, we notice that 60 cases (57.14%) come from the urban area, and 45 (42.86%) from the rural area. The distribution
according to the background in the two centers is represented in Figure 7.6.

![Figure 7.6 Distribution per centers according to the background](image)

In our country, the patients from the urban area represented 59.46% (n=44), and the ones from the rural area 40.54% (n=30), and in France the distribution was almost equal: urban area 51.61% (n=16), rural area 48.39% (n=15). Even though at first sight it seems like we had more patients from the urban area, the statistical analysis does not ascertain it ($\chi^2=0.549; df=1; p=0.459$). The exact Fisher test confirms that the distribution per centers according to the background is uniform ($p=0.52$).

**Waistline and weight**

The waistline of the patients was between 1.5 and 1.87 m with the average value of Aw=1.69±0.08 m (median 1.7 m). The analysis of the average waistline in the patients of the two centers was the following: the patients of Romania had the Aw=1.68±0.077 m, and
those from France – \( \text{Aw}=1.0 \pm 0.096 \) m. This difference was insignificant \((t(103)=-1.018, p=0.311)\).

The body mass of the patients in the study varied between 48 and 115 kg, the average weight being of \( \text{Aw}=75.47 \pm 13.93 \) kg (median 76 kg, module 78 kg).

BMI in the three study groups had the following values: \( \text{aBMI}=26.62 \pm 4.98 \) kg\(\text{m}^2\) (group I), \( \text{aBMI}=25.19 \pm 3.52 \) kg\(\text{m}^2\) (group II), \( \text{aBMI}=27.93 \pm 3.6 \) kg\(\text{m}^2\) (group III). A significant difference of the BMI was noticed between groups II and III \((t(39)=-2.24, p=0.037)\), and between group I and II \((t(91)=1.592, p=0.116)\) and group I and III \((t(74)=-1.083, p=0.292)\) there was no significant difference. The ANOVA test does not highlight significant differences of the BMI in the three groups \((F(2.102)=1.842, p=0.164)\).

Fig. 7.9 BMI distribution in the patients included in the study
FEATURES OF THE ANAMNESIS AND CLINICAL EXAMINATION DATA

The analysis of the anamnesis and clinical examination data raised certain problems because of the large number of variables. In the patients analyzed retrospectively, certain clinical and anamnesis data were absent. Certain data could be mathematically quantified and expressed and statistically processed and another could not be analyzed from a statistical point of view.

Symptoms analysis at admission

On the admission date in the hospital, most of the patients had one or more symptoms. Some of the patients were asymptomatic and the liver tumor was diagnosed accidentally, by means of a routine examination. The symptoms presented by the patients on the admission date were grouped in 6 categories: pain, jaundice, fever, weight loss, physical asthenia and anorexia. Separate fields were created in the database for each symptom and the presence or absence of pain in the patient was noted with 1 and respectively 0.

On the admission date, 94 (89.52%) patients were symptomatic, and 11 (10.48%) were asymptomatic. The distribution of these patients according to the surgical treatment practiced is presented in Table XIII and was statistically insignificant ($\chi^2=2.678; \text{ df}=2; p=0.262$).

The graphic distribution of symptoms in the three groups is represented in Figure 7.10.
Analysis of the personal pathological clinical record and of the etiological factors

100 (95.24%) patients presented associated diseases, being uniformly distributed in the three groups ($\chi^2=0.892; \text{df}=2; p=0.64$).

The chronic viral hepatitis was present in 45 (42.86%) patients, and in 60 (57.14%) patients the serology for hepatitis B and C was negative. With regard to the presence of the viral chronic hepatitis in the patients from Romania ($n=43, 58.11\%$) and those from France ($n=2, 6.45\%$) there was a statistically significant difference ($\chi^2=24.293; \text{df}=3; p<10^{-3}$). The distribution of the chronic viral hepatitis B and C in the patients of the three groups is shown in Figure 7.12.
Fig. 7.12 Distribution of the chronic viral hepatitis in the three groups

Even though the visual analysis shows a different distribution of the patients with chronic viral hepatitis in the study groups, it was statistically insignificant both for the ones with hepatitis B ($\chi^2=1.839; \text{df}=2; \text{p}=0.399$), and for the ones with hepatitis C ($\chi^2=5.813; \text{df}=2; \text{p}=0.055$).

The hepatic cirrhosis of diverse etiology was present in 62 (59.05%) patients of the general group. The distribution in the three study groups of the patients with cirrhosis (Table XXVII) was non-uniform, this difference being statistically significant ($\chi^2=13.424; \text{df}=2; \text{p}=0.001$).
Table XXVII. Distribution of the patients with cirrhosis according to the treatment enforced

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>Intervention type</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hepatic resection</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (46.87%)</td>
<td>62 (59.05%)</td>
</tr>
<tr>
<td>No</td>
<td>34 (53.13%)</td>
<td>43 (40.95%)</td>
</tr>
<tr>
<td></td>
<td>Focal destruction</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (68.97%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9 (31.03%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver transplant</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (100%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>105</td>
</tr>
</tbody>
</table>

The chronic alcohol consumption higher than 20 g/day, confirmed by the patient and by the family was present in 63 (60%) patients. The distribution of the patients chronic alcohol consumers in the study groups was non-uniform, existing statistically significant differences ($\chi^2$=10.6; df=2; $p=0.005$). The alcohol quantity consumed every day could not be established. The chronic alcohol consumers from the group of France were fewer (41.94%, n=13) than those from the group of Romania (67.7%, n=50). This difference was statistically significant ($\chi^2$=5.981; df=1; $p=0.014$). The exact Fisher test confirmed this difference ($p=0.017$).

The general distribution of the etiological factors involved in the occurrence of PMHT in the three study groups is presented in Figure 7.16.
Objective clinical examination

In the PMHT pathology and the determination of the treatment indication, the data of the clinical examination are relatively limited. A part of them has already been presented at the admission reason section (jaundice).

The clinical examination analyzed the following signs and clinical modifications: hepatomegaly, ascites presence (clinically detectable), presence of the portal high blood pressure syndrome, signs of portal encephalopathy. These clinical signs were compared in
the three study groups (Table XXVIII). The clinical signs developed in a different manner at the patients from the three groups, existing a significant statistic difference.

Table XXVIII. Presence of the clinical signs in the three groups

<table>
<thead>
<tr>
<th>Present clinical sign</th>
<th>Hepatic resection (Group I)</th>
<th>Focal destruction (Group II)</th>
<th>Liver transplant (Group III)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly</td>
<td>23 (35.94%)</td>
<td>15 (51.72%)</td>
<td>1 (8.33%)</td>
<td>0.031</td>
</tr>
<tr>
<td>Ascites</td>
<td>14 (21.87%)</td>
<td>12 (41.38%)</td>
<td>8 (66.67%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Portal high blood pressure syndrome</td>
<td>10 (15.62%)</td>
<td>12 (41.38%)</td>
<td>11 (91.67%)</td>
<td>&lt;10^{-3}</td>
</tr>
<tr>
<td>Portal encephalopathy</td>
<td>2 (3.12%)</td>
<td>1 (3.45%)</td>
<td>6 (50%)</td>
<td>&lt;10^{-3}</td>
</tr>
</tbody>
</table>

PARACLINICAL EXPLORATION DATA

The determination of the PMHT diagnostic was performed by a range of biological and imagistic explorations. They were performed in the following order: biological tests, including the tumor markers (AFP), abdominal ultrasound focused mainly on the liver, computer tomography examination and/or examination by nuclear magnetic resonance, exploratory laparoscopy and liver puncture-biopsy. Because of the technical facility conditions of the “Sf. Spiridon” Hospital and of the deficiencies in the Romanian sanitary system, we did not succeed to perform all these explorations in all the patients and in certain cases the diagnostic was determined only based on the ultrasound, the resecability being assessed by laparoscopy.
Alpha-fetoprotein is the most important tumor marker used in the HCC diagnostic. This marker was sampled before the surgery in 104 (99.05%) patients of our study group. Its average value was of 116.47±41.26 ng/ml (median of 14 ng/ml) with extremes between 1 and 3086 ng/ml. The AFP value in the three groups is presented in table XXXIII. The difference existing among the three groups was statistically insignificant (F(2.101)=0.833; p=0.438). We consider suggestive for the HCC diagnostic the AFP value higher than 10 ng/ml, and certain a value higher than 100 ng/ml.

Table XXXIII. AFP value in the three groups

<table>
<thead>
<tr>
<th></th>
<th>AFP (Av)</th>
<th>Standard deviation</th>
<th>SEM</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>156.09</td>
<td>530.67</td>
<td>66.33</td>
<td>1</td>
<td>3,086</td>
</tr>
<tr>
<td>Group II</td>
<td>72.32</td>
<td>85.01</td>
<td>16.06</td>
<td>2</td>
<td>324</td>
</tr>
<tr>
<td>Group III</td>
<td>8.17</td>
<td>5.9</td>
<td>1.7</td>
<td>2</td>
<td>20</td>
</tr>
</tbody>
</table>

Imagistic explorations
The determination of the PMHT diagnostic and the establishment of the surgical treatment variant was performed by imagistic methods.

*The abdominal ultrasound* was the simplest imagistic investigation, which allowed a first assessment of the liver disorder (Fig.7.23).
The ultrasound localization of PMHT in the patients treated in Iași was of 90.54% (n=67), and in the ones treated in Lyon was of 64.52% (n=20). This difference was statistically significant ($\chi^2=10.417; \text{df}=1; \ p=0.001$). The exact Fisher test confirmed the statistic significance of these data ($p=0.003$).

The computed tomography (CT) exploration is a routine examination in the assessment of a patient with PMHT proposed for surgical treatment. This exploration is necessary for the evaluation of the neoplasia extension (adenopathies, metastases), the assessment of the resecability possibilities, but also the hepatic volumetric analysis (Fig. 7.26). Because of the particular conditions of the sanitary system, CT was performed only in 98 (93.33%) patients: 60 (93.75%) in the first group, 26 (89.66%) in the second group and 12 (100%) in the third group ($\chi^2=1.506; \text{df}=2; \ p=0.471$). The CT exploration was performed in 67 (90.54%) patients of Clinic I Surgery and in 31 (100%) patients of the CGDSHT of Lyon. The existing difference was statistically insignificant ($\chi^2=3.142; \text{df}=1; \ p=0.076$). The exact Fisher test confirms this aspect ($p=0.102$). The computed
tomography can determine the localization, size, extension and type of the tumor. The average dimension of the tumor, determined by CT was available in 98 (93.33%) patients, having the value of $59.86 \pm 32$ mm. The tumor dimensions in the three groups had the following values: 60.03±28.85 mm (between 19 and 173 mm) in the patients with hepatic resection, 74.35±34.22 mm (between 17 and 129 mm) in the patients with focal destruction, 27.67±16.7 mm (between 11 and 61 mm) in the patients with liver transplant. This difference was statistically significant ($F(2.95)=10.436; p<10^{-3}$).

The magnetic resonance (MR) was performed in 35 (33.33%) patients. This imagistic exploration was non-uniformly performed in the patients of the three groups. MR was performed for 96.77% (n=30) of the patients with PMHT treated in France and only 6.76% (n=5) of the patients treated in our country. This difference is statistically significant ($\chi^2=79.665; \text{df}=1; p<10^{-3}$). The exact Fisher test shows the same thing ($p<10^{-3}$).

The puncture-biopsy was performed in 54.84% (n=17) of the patients treated in France and in 29.73% (n=22) of the patients treated in our country. The difference with regard to the puncture-biopsy in the patients with PMHT in the two centers was statistically significant ($\chi^2=5.9; \text{df}=1; p=0.015$), being also confirmed by the exact Fisher test ($p=0.026$).

The diagnostic laparoscopy was performed in 21 (20%) patients of the global group of patients with PMHT (Fig. 7.32).
Fig. 7.32. The HCC diagnostic developed on cirrhosis (laparoscopic image)

It was performed for the assessment of the liver, diagnostic determination by the exploration of the abdominal organs and the exclusion of the metastasis nature of the liver tumor, sampling of tumor biopsy with histological confirmation of the diagnostic and last but not least for the assessment of tumor resecability. The laparoscopy was performed more frequently in the Clinic I Surgery Iaşi (25.68%, n=19) than in the CGDSHT of Lyon (6.45%, n=2). This difference was statistically significant, being calculated by the chi square test ($\chi^2=5.046; \text{df}=1; p=0.025$) and by the exact Fisher test ($p=0.031$).
Tumor localization

Tumor localization in the 105 patients was the following: in the right liver lobe in 66 (62.86%) patients, in the left liver lobe in 24 (22.86%) patients and in both lobes in 15 (14.8%) patients. The analysis of the segmental localization of the tumors was a little bit more difficult, given that the tumors with higher dimensions covered two or even three segments and some of the patients had several tumors. So as to avoid confusions, I mention that the 154 tumors determined in the 105 patients included in the study correspond to 198 hepatic segmental localizations. For this reason, the statistical analysis was performed for each liver segment separately. Analyzing these data, we noticed that tumors were most frequently located at the level of segment VII (21.2%) and most rarely at the level of segment I (1.5%). The selection of the treatment method according to the segmental localization of the tumors is presented in table XLIII. The analysis of the tumors with uni-segmental, bi-segmental and tri-segmental localization highlighted that tumors were uni-segmental in 65.71%, bi-segmental in 23.81% and tri-segmental in 10.48% of the total number of patients. With regard to the distribution of the uni- bi- and tri-segmental tumors in the three study groups, there were no statistically significant differences ($\chi^2=5.947$; df=4; p=0.203).
Table XLIII. Treatment method practiced according to the segmental localization of the tumors

<table>
<thead>
<tr>
<th>Tumor localization</th>
<th>Hepatic resection</th>
<th>Focal destruction</th>
<th>Liver transplant</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segment I</td>
<td>1 (0.92%)</td>
<td>1 (1.49%)</td>
<td>1 (4.55%)</td>
<td>0.423</td>
</tr>
<tr>
<td>Segment II</td>
<td>11 (10.09%)</td>
<td>4 (5.97%)</td>
<td>1 (4.55%)</td>
<td>0.712</td>
</tr>
<tr>
<td>Segment III</td>
<td>13 (11.93%)</td>
<td>4 (5.97%)</td>
<td>1 (4.55%)</td>
<td>0.512</td>
</tr>
<tr>
<td>Segment IV</td>
<td>12 (11.01%)</td>
<td>7 (10.45%)</td>
<td>2 (9.09%)</td>
<td>0.796</td>
</tr>
<tr>
<td>Segment V</td>
<td>16 (14.68%)</td>
<td>9 (13.43%)</td>
<td>4 (18.18%)</td>
<td>0.746</td>
</tr>
<tr>
<td>Segment VI</td>
<td>18 (16.51%)</td>
<td>14 (20.9%)</td>
<td>6 (27.27%)</td>
<td>0.099</td>
</tr>
<tr>
<td>Segment VII</td>
<td>22 (20.18%)</td>
<td>17 (25.37%)</td>
<td>3 (13.63%)</td>
<td><strong>0.046</strong></td>
</tr>
<tr>
<td>Segment VIII</td>
<td>16 (14.68%)</td>
<td>11 (16.42%)</td>
<td>4 (18.18%)</td>
<td>0.428</td>
</tr>
</tbody>
</table>

HEPATIC RESECTION

Nowadays, the surgical resection is a first intention treatment option for the patients with PMHT. Whenever possible, we resorted to the tumor resection. We practiced this treatment method in 60.95% (n=64) of the patients included in the study.

For the hepatic transaction technique we used the bloodless liver resection variant performed by means of the Habib tuck (Fig. 8.2) and the variant with the use of other devices (the ultrasound dissector, the Ligasure tuck, the electrocautery, the finger fracture technique).
According to it, the patients were classified in two subgroups: IA and IB. Group IA included 29 (45.31%) patients and group IB - 35 (54.69%) patients. There were no differences in the selection of the liver transaction variant connected to the gender ($\chi^2=0.067; \text{df}=1; p=0.796$) and the background ($\chi^2=1.891; \text{df}=1; p=0.169$), and the development of PMHT on the cirrhotic liver influenced the selection of the liver transaction variant, the existing differences were statistically significant ($\chi^2=10.392; \text{df}=1; p=0.002$; determined by the exact Fisher test).

The average sizes of the tumors determined before the surgery by ultrasound and CT in the group IA were of $64.89\pm20.24$ mm respectively $62.26\pm19.06$ mm,
and in group IB of 67.33±35.33 mm respectively 58.21±35.09 mm. The existing differences between the two groups, from the point of view of the tumor sizes, were statistically insignificant (t(52)=-0.312; p=0.757 respectively t(58)=0.568; p=0.573).

Tumor localization in the two groups is shown in figure 8.5. The existing differences from the point of view of the segmental localization were statistically insignificant ($\chi^2=2.767$; df=7; p=0.251).

Fig. 8.5. The hepatic resection technique according to the segmental localization of the tumors

Group IA included 15 (51.72%) minor hepatectomies and 14 (48.28%) major hepatectomies, and group IB included 14 (40%) minor hepatectomies and 21 (60%) major ones.
The existing difference between the two groups with regard to the hepatic extension resection was statistically insignificant ($\chi^2=0.88; \ df=1; \ p=0.451$; determined by the exact Fisher test).

The average duration of the intervention in group IA was of 121.03±51.22 minutes, and in group IB of 181.52±82.1 minutes (Fig. 8.11). The time difference existing between the two groups was statistically significant (t(62)=-3.577; $p=0.001$).

Analyzing the intra-operative blood losses, we noticed that in group IA the average value was of 344.48±293.21 ml, and in IB – of 1015.71±1210.76 ml. These data show that in the first group blood losses were significantly lower than in the second one (t(62)=-3.169; $p=0.003$).

The average width of the surgical resected sample in the patients with hepatic resection was of 8.52±8.18 mm with limits between 0 and 35 mm. The surgical resected sample in group IA was of 7.03±5.89 mm, and in group IB of 9.74±9.59 mm. The difference between the width of the surgical resected sample in the two groups was statistically insignificant (t(62)=-1.326; $p=0.19$).

**FOCAL TUMOR DESTRUCTION**

The focal tumor destruction represented the destruction of the hepatic tumors by hyperthermia. We used two different physical methods of raising the temperature at tumor level: the radiofrequency and the water vapors under pressure. According to the thermo-destruction technique employed, these patients were classified in two subgroups: IIA (destruction by water
vapors under pressure) and IIB (destruction by radiofrequency). Group IIA included 25 (75.76%) patients and group IIB - 8 (24.24%) patients. The number of tumors destructed in one session only varied between 1 and 4 tumors. There were no differences with regard to the number of destructed tumors, according to the termonecrosis method enforced ($\chi^2=0.187; \text{df}=3; p=0.98$).

The average sizes of the tumors of the two groups were $77.6\pm35.05$ mm (extremes between 30 and 140 mm) in group IIA and of $59.5\pm27.22$ mm (extremes between 18 and 95 mm) in group IIB. The difference between the diameter of the tumor of the two subgroups was statistically insignificant ($t(31)=1.332; p=0.192$).

The localization of the tumors destructed by termonecrosis is presented below (Fig. 8.18). The difference existing in the lobar distribution of the termonecrosis tumors by the two methods was statistically insignificant ($\chi^2=2.248; \text{df}=2; p=0.325$).

Fig. 8.18 Localization of the tumors destructed by termonecrosis
The intra-operative ultrasound was performed in 14 (42.42%) patients with focal destruction.

HEPATIC TRANSPLANT

The hepatic transplant is the most recent surgical treatment method included in the curative arsenal of the PMHT. The hepatic transplant offers the theoretical possibility of completely removing the PMHT, regardless of the number and size of the tumors, but also of eliminating the non-tumor pathological hepatic tissue.

All the patients with hepatic transplant included in the study were treated in the CGDSHT of Lyon. For all the patients, the Rio Branco incision was used, which has a median xipho-umbilical tract and it subsequently leaves under an acute angle towards the right costal margin. In all the patients, the orthotopic hepatic transplant re-allied with the liver from a cadaver donor, according to the „pyggy back” technique (Fig. 8.22).
The waiting period on the transplant list is a very important criteria for the patients with PMHT developed on cirrhosis. The average waiting duration for the patients included in the study was of 177.5±138.14 days (median of 122 days), with limits between 29 and 456 days.

The average value of the MELD score in these patients was of 19.37±7.13 (median of 16), with limits between 12 and 36 (Fig. 8.25).
The average duration of the surgery in the patients with liver transplant was of 405±102.36 min (median of 405 min) with limits between 250 and 630 min. The duration was much longer as compared to the two surgical techniques ($t(103)=11.605; p<10^{-3}$).

The average blood quantity lost intra-operatively was of 1850±1560 ml (median of 1450 ml), with limits between 600 and 6000 ml. There was a statistically significant difference with regard to the quantity of blood lost intra-operatively in the patients with transplant, as compared to the rest of the patients ($t(103)=2.841; p=0.015$).

**Intra-operative accidents**

The intra-operative accidents were noticed in 36 (34.29%) patients of the general group. Their distribution
in the three groups is shown in the table below (Table LXII).

<table>
<thead>
<tr>
<th>Intra-operative accidents</th>
<th>Intervention type</th>
<th>Hepatic resection</th>
<th>Focal destruction</th>
<th>Liver transplant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
<td>25 (39.06%)</td>
<td>6 (20.69%)</td>
<td>5 (41.67%)</td>
<td>36 (34.29%)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>39 (60.94%)</td>
<td>23 (79.31%)</td>
<td>7 (58.33%)</td>
<td>69 (65.71%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>64</td>
<td>29</td>
<td>12</td>
<td>105</td>
</tr>
</tbody>
</table>

The fewer intra-operative accidents were in group II (20.69%) and the difference existing in the three groups was statistically insignificant ($\chi^2 = 3.318; \text{df}=2; p=0.19$).

PATHOLOGICAL ANATOMY OF THE TUMORS

Of the 105 patients included in the study, 100 (95.24%) patients had hepatocellular carcinoma (Fig. 9.1), 3 (2.86%) patients had fibrolamellar carcinoma and 2 (1.9%) patients intrahepatic cholangiocarcinoma.
The global group included 44 (41.9%) patients with well-differentiated tumors (1\textsuperscript{st} degree, according to Edmondson), 44 (41.9%) patients with moderately differentiated tumors (2\textsuperscript{nd} degree, according to Edmondson) and 17 (16.2%) patients with poorly differentiated tumors (3\textsuperscript{rd} degree, according to Edmondson). We noticed that the difference existing among the three differentiation degrees and tumor diameter was statistically significant (F(2.102)=5.388; p=0.006).

We included the tumor capsule, the satellite nodules, the tumor necrosis and the tumor vascular
embolies in the detailed histopathological analysis of the tumors. These data could only be analyzed for the patients in group I and group III and are presented in the thesis.

All the patients were subject to biopsy at the level of the non-tumoral liver, being histopathologically examined. At the non-tumoral liver, we analyzed the steatosis degree, the fibrosis degree, hepatocytes balonization, the lobular inflammation, the presence of Mallory corpuscles and of the hepatosiderosis.

**POST-OPERATIVE COMPLICATIONS**
The global post-operative morbidity was of 48.57%, 51 patients presenting different types of complications (respiratory, renal, hepatic, infections, fistules, etc.). The distribution of the patients who developed post-operative complications in the three groups is presented in Table LXXVII. Even though the complication rate is higher in the patients with transplant, the difference is statistically insignificant ($\chi^2=0.533$; df=2; p=0.766).

| Table LXXVII. Distribution of the post-operative complications in the three groups |
|---------------------------------|------------------|------------------|------------------|--------|
| Post-operative complications | Intervention type |                  |                  | Total  |
|                               | Hepatic resection | Focal destruction | Liver transplant |       |
| Yes                            | 30 (46.88%)       | 14 (48.28%)      | 7 (58.33%)       | 51 (48.57%) |
| No                             | 34 (53.12%)       | 15 (51.72%)      | 5 (41.67%)       | 54 (51.43%) |
| Total                          | 64                | 29               | 12               | 105    |
The distribution of all the post-operative complications in the study groups, according to the percentage, is shown in the figure below (Fig. 10.2).

![Graph showing post-operative complications]

**Fig. 10.2. Post-operative complications in the three groups (%)**

**REINTERVENTIONS**

Reinterventions in the global group represented 8.57% (n=9). Their distribution in the three groups was the following: 6 (9.37%) cases in the first group, 1 (3.45%) case in the second group and 2 (16.67%) cases in the third group. The existing difference had no statistic significance ($\chi^2=2.027; df=2; p=0.363$).
EARLY POST-OPERATIVE MORBIDITY

In the early post-operative morbidity we included the patients who died in the first 30 days after the surgery. 7 (6.67%) patients of the global group died over this period. Other 37 (35.24%) patients died at an interval longer than 1 month following the surgery. At the end of the study there were 61 (58.09%) patients alive. The analysis of the early post-operative deaths according to the surgery type shows a death rate of 6.25% (n=4) in the group with hepatic resection and 10.34% (n=3) in the group with focal destruction, and in the group with hepatic transplant, the early post-operative morbidity rate was zero. The existing difference was statistically insignificant ($\chi^2=1.506; \text{df}=2; p=0.471$).

TUMOR RELAPSE

The tumor relapse represented the reappearance of the tumor after the surgery at the level of the liver. This aspect was analyzed in 95 patients (7 patients died in the first month following the surgery, and 3 patients did not attend the periodic examination). Relapses were identified in 32 (33.68%) patients in the global group. Relapses distribution according to the type of treatment enforced is presented in the table below (Table C).
Table C. Relapses appearance according to the type of treatment enforced

<table>
<thead>
<tr>
<th>Tumor relapse</th>
<th>Intervention type</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hepatic resection</td>
<td>Focal destruction</td>
<td>Liver transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (31.67%)</td>
<td>13 (56.52%)</td>
<td>0</td>
<td>32 (33.68%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41 (68.33%)</td>
<td>10 (43.48%)</td>
<td>12 (100%)</td>
<td>63 (66.32%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>23</td>
<td>12</td>
<td>95</td>
<td></td>
</tr>
</tbody>
</table>

The difference of relapses appearance in the three study groups was statistically significant ($\chi^2=11.575; \text{df}=2; \ p=0.003$). The average period of relapse appearance was of $13.25\pm7.96$ months (median of 11 months) with limits between 3 and 33 months. The average period of relapse appearance in the patients with hepatic resection was of $16.37\pm8.41$ months, and in those with focal destruction of $8.69\pm4.44$ months. The existing difference between relapse appearance according to the two treatment methods used was statistically significant ($t(30)=3.354; \ p=0.002$). Over the first two years after the surgery, the relapse appeared in 29 (90.63%) patients and only in three 3 (9.37%) patients the relapse appeared at an interval longer than two years following the surgery.

The distant metastases represented the appearance of the primitive malignant liver tumors in other organs than the liver. The metastases appeared in 12 (12.63%) patients. According to their localization, the metastases were pulmonary in 6 (50%) patients, osseous in 4 (33.4%) patients, osseous and pulmonary in 1 (8.33%) patient and parietal abdominal in 1 (8.33%) patient.
SURVIVAL

The statistical analysis of the survival data was performed in all the patients. For the survival study we used the Kaplan-Meier method and the log-rank test. The average global survival was of 49.99 months (41.61 – 58.39 months; 95% Confidence Interval) (median of 38 months).

The average survival in the patients with hepatic resection was of 58.69 months (47.98 – 69.40 months; 95% CI), in those with focal destruction – of 21.53 months (12.90 – 30.16 months; 95% CI), and in those with hepatic transplant of 72.80 months (59.41 – 86.19 months; 95% CI) (Fig. 10.5). The comparison of the three survival curves shows the existence of certain statistically significant differences ($p<10^{-3}$; log-rank test).

**Fig. 10.5. Survival according to the intervention type**

(Kaplan Meier)
5. CONCLUSIONS

After the analysis of the pre-operative data of the study group, we can sum up the following:

- PMHT are more frequent in men than in women;
- These tumors appear more frequently in the sixth decade of life;
- The patients in the urban area and those in the rural area are affected in equal proportions;
- Most of the patients with PMHT were overweight;
- The clinical manifestations in PMHT are non-specific, prevailing the pain at the level of the right hypochondrium, asthenia and weight loss
- PMHT etiology is determined by the viral hepatitis, the chronic alcohol consumption, obesity, diabetes mellitus type II and the metabolic syndrome.
- The hepatic cirrhosis is an important etiological factor, but not compulsory for the appearance of HCC.
- The hepatic cirrhosis was in a more advanced stage in the patients who benefited from hepatic transplant;
- The analysis of the biological data highlighted more important modifications in the patients of group III, because of the more advanced stage of the cirrhosis;
- The alpha-fetoprotein is important in the determination of the hepatocellular carcinoma diagnostic, but it is not a certainty marker;
✓ The hepatic ultrasound performed by an experienced professional remains a basic imagistic method in the PMHT diagnostic;
✓ CT and MR have a higher sensitivity and specificity for the primitive hepatic tumors, performing a differentiated diagnostic.
✓ The pre-operative tumoral puncture-biopsy is useful, but not strictly necessary for the PMHT diagnostic;
✓ The solitary tumors prevailed, but the proportion of the multicentric hepatic tumors is big enough;
✓ From a topographical point of view, there is no preferential segmental localization of the PMHT.
✓ The Child-Pugh, MELD and ASA scores can anticipate the intra-operative risks and the post-operative evolution in the patients with PMHT;
✓ The neo-adjuvant treatment is useful in the patients who require an extended hepatic resection and in those included on the waiting list for the transplant.

Our conclusions related to the analysis of the operative factors in the patients with PMHT are the following:
✓ The hepatic resection is the basic method in the PMHT treatment;
✓ The approach method depends on tumor localization, being as direct as possible and offering a good possibility of liver mobilization;
✓ The intra-operative ultrasound is very useful in the assessment of the hepatic resection limits, but also for the diagnostic of other existing tumor nodules;
The liver transection by means of the Habib tuck is very useful in the patients with PMHT developed on cirrhosis, because it reduces the operative time and the quantity of lost blood;

The oncological safety is necessary in the hepatic resections of the PMHT, so as to prevent relapses;

The intra-operative hemorrhage has an increased risk in the patients with PMHT developed on cirrhosis, and the use of the bloodless liver transaction techniques is welcome;

The liver transplant is the ideal treatment method for the patients with PMHT who meet the Milano criteria and are associated to an advanced degree of hepatic cirrhosis;

The focal destruction is an alternative treatment method of the small PMHT, but it can be also used in the patients with great tumors, which cannot be resected, improving the survival rate.

The hepatocellular carcinoma is the most frequent histopathological form of PMHT, exceeding 95% of the cases;

After the analysis of the post-operative data, we obtained the following conclusions:

The overall post-operative morbidity in the patients with PMHT is of about 50%;

The intra-operative factors which influenced the post-operative morbidity were: surgery duration, quantity of lost blood, blood transfusion and the intra-operative accidents;

The most frequent post-operative complications are the respiratory complications, the acute liver failure and the ascitis;
The reintervention rate after the hepatic resections for PMHT is of about 10%, and it increases significantly over the post-operative hospitalization period;

The average post-operative hospitalization duration depends on the type of surgical treatment used and it is significantly longer in the patients with hepatic transplant;

The overall post-operative death rate was of 6.67%, as compared to the data from literature;

The patients operated in emergency for burst liver tumor have a much higher post-operative death rate (60%), as compared to the ones operated as scheduled (4%);

The post-operative death rate is influenced by the quantity of blood lost during the surgery and it does not depend on the surgery period;

Tumor relapse appeared in a tierce of the patients, being much more frequent after the focal destruction than after the hepatic resection and null after the liver transplant.

Relapses appear the most frequently between 6 and 24 months, the maximum pick being of 13 months;

The liver tumor relapse is significantly influenced by the tumor reminiscence;

The distant metastases appeared in 12.67% cases, being located at pulmonary and osseous level;

The overall average survival was of 50 months, and it significantly depends on the treatment method used;
The best distant survival for the patients with PMHT is ensured by the liver transplant; even the focal destruction in the patients with PMHT ensures a survival rate which has to be taken into consideration (21.5 months). All the three treatment methods used for the patients with PMHT are welcome, and their selection depends on several pre-operative factors.

**FINAL DATA**

The thesis comprises 116 tables, 136 figures and 480 bibliographic indexes. The tables and figures in the abstract kept the numbering from the thesis.

**LIST OF SCIENTIFIC PAPERS ISSUED DURING THE PhD STUDIES**


4. Vlad N, Lupaşcu C, Dănilă N, Georgescu Şt, Moldovanu R, Târcoveanu E. Atypical hepatic resection technique for hepatocellular carcinoma
using radiofrequency Habib 4x. *Chirurgia* 2013; 108 (1): 51-55. (Factor de impact - 0,375)

**LIST OF PAPERS PRESENTED IN NATIONAL AND INTERNATIONAL CONGRESSES**

1. „*REZECTIILE HEPATICE IN CANCERUL HEPATOCELULAR - REZULTATE PRELIMINARE*” - Al XI-lea Congres al Asociației Chirurgilor „Nicolae Anestiadi” din Republica Moldova, Chișinău/R. Moldova; *September 27-30, 2011.* (prezentare orală)

2. „*CANCERUL HEPATOCELULAR DEZVOLTAT PE STEATOZA NON-ALCOOLICĂ (NAFLD)*” - Al XXVI-a Congres Național de Chirurgie, Timișoara/România; *May 23-26, 2012.* (prezentare orală)

3. „*HEPATIC RESECTION FOR HEPATOCELULAR CARCINOMA USING A RADIOFREQUENCY ABLATION DEVICE*” - 10 World Congress of the International Hepato-Pancreato-Biliary Association, Paris/France; *July 1-5, 2012.* (prezentare orală)

4. „*IMPACTUL ȘTIINȚIFIC ȘI PROFESIONAL AL UNUI STAGIU DOCTORAL DE MOBILITATE EXTERNĂ*” - Zilele UMF „Gr.T.Popa” Iași; *November 22, 2012.* (oral exposure)
REFERENCES


