is difficulty in predicting their biological behavior This study was designed to review the clinical characteristics of surgically treated gastrointestinal stromal tumors at our institution and evaluate their immuno histochemical and pathologic features and correlate finding with surgical management and prognosis.

Patients and Methods : Patients and disease characteristics were studied in a group of 11 cases (9 gastric, one jejunal and one ileal). In addition, the pathologic features, surgical management, and treatment outcome were evaluated.

Results: A preoperative diagnosis was suspected in eight using endoscopy and endo sonography while CT defined local extra gastric spread in one patient. The median diameter of the tumors was 6.6 cm and no liver metastases were detected in any case. Planned cold surgery was possible in 8 of the 11 cases and excision was successful in all. Three cases were operated upon emergency basis. Histological and immunohisto-pathological evaluation confirmed the preoperative diagnosis in all cases. In half of the c-kit positive tumors the lesions were high grade malignant

Conclusion: GISTs are underdiagnosed in Egypt due to their vague presentations, but should be incorporated in the list of causes of GI bleeding. Surgical removal is feasible in most cases and the prognosis is strictly related to tumor size and number of mitoses.

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Trefoil factor family 2 stimulates cell proliferation via epidermal growth factor receptor

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Cholangiocarcinoma (CCA) is a malignancy of bile duct epithelium. The trefoil factor family (TFF), consisting of TFF1, TFF2 and TFF3, plays an important role in restitution and repair of the epithelium and is rapidly up-regulated in response to mucosal injury. However, TFF peptides are overexpressed in several human solid tumors. Our study in CCA patients demonstrated that TFF2 is rarely expressed in normal bile ducts and non-malignant stage but expressed highly in tumor stage and that TFF2 acts in concert with TFF3 for tumor progression. The present study aimed to investigate the effect of TFF2 peptide (rTFF2) on cell proliferation in human CCA cell line, KMBC, which shows no TFF2 expression and to explore the signaling pathway by which rTFF2 induced proliferation. Cell Proliferation in the presence of rTFF2 or epidermal growth factor (EGF) was performed by determining cell viability using Trypan blue reagent. EGFR tyrosine kinase inhibitor, PD130353 was used to abrogate EGF receptor. The result showed that rTFF2 increased the proliferation of KMBC starting at concentration of 5-500 μg/ml and EGF increased proliferation of KMBC by dose dependence. Both rTFF2 and EGF promoted cell proliferation and this effect was abrogated by EGFR tyrosine kinase inactivation. In conclusion, TFF2 stimulates cell proliferation via epidermal growth factor receptor signaling pathway.

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Dependence of some molecular-biological peculiarities of breast cancer cells on the blood plasma homocysteine level

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Background. It is known, that estimation of features of malignant process and choice of adaptive tactic of treatment of patients with breast cancer takes place on the basis of clinical and morphological characteristics (size of tumor, histological type, degree of malignant, presence of metastases, age of patient etc.). Besides this, possibilities of the use of different molecular-biological markers are widely studied for providing of authenticity of prognosis of features of flowline of malignant process. Now the mechanisms of malignant cell transformation are studied in detail. They attract attention of researchers on the physiological mechanisms of adjusting of altered pathways and metabolic processes in tumour cells. The amino acid Homocysteine is a one of such natural factors, influence of which on development of oncologic pathology is only studied.

Objectives: 1) to describe the molecular profile of malignant cells of patients with breast cancer; 2) to detect the methylation status promoters of genes, associated with drug resistance; 3) to define the level of homocysteine in plasma of blood; 4) to set the associative communications between clinical, laboratory and molecular-biological parameters.

Methods. Clinical investigations of 117 patients with breast cancer, immunohistological, methylation-specific PCR (MSP), statistical methods.

Results. It is shown, that methylation status of mdr1 gene promotor correlates with expression of P-glycoprotein (r=-0,69, P=0,01), GSTp – with expression of glutation-S-transferase (r=-0,76, P=0,001), tp53 – with p53 expression (r=-0,57, P=0,05), CDH1 – with E-cadherin expression (r=-0,63, P=0,02). Methylation status of bcl-2 gene promotor doesn't correlate with bcl-2 expression. The main level of homocyteine in blood plasma was 9,75±3,67 (SD). Homocystein level correlates with the age of patients (r=0,31, P=0,009), expression of metallothioneins (r=0,26, P=0,03), E-cadherin (r=0,27, P=0,03) and methylation status of promotor of CDH1 gene (r=-0,69, P=0,002).

Conclusions. Summarizing everything mentioned above, let's emphasized on the following: 1) expression of P-glycoprotein, glutation-S-transferase, p53 and E-cadherin depends on methylation status of promoters of encodings genes; 2) increased homocysteine level stipulated the expression of metallothioneins and E-cadherin, which have independent prognostic value and characterize sensitivity to some antineoplastic drugs and tumor invasive and metastatical potential.

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Thermal injury associated with the genesis of esophageal epidermal carcinoma

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Background: Esophageal squamous cell carcinoma is one of the most common and lethal cancers. Some areas from South America present a high incidence of this kind of cancer. Many etiological factors are associated with this disease in these areas such as alcohol, tobacco and hot maté consumption, causing a thermal injury in the esophagus. However, there is no study on the effect of hot maté on experimental carcinogenesis.

Materials and Methods: The effect of thermal injury caused by hot water adiministration at 70ºC by gavage three times/week either with or without N-nitrosodiethylamine (NDEA) at 1 or 10 ppm in the drinking water of female Balb/C mice (8 weeks-old(was analysed during nine months. The control group received cold water at room temperature. Each group was composed by 5 animals. The evaluation was done histologically with hematoxylin-eosin and molecular analysis was done using gene array.

Results: The animals that received cold water or only NDEA did not present tissue alterations. The group that received only water at 70ºC presented an initial epithelial necrosis that caused an acute inflammation that became almost undetected after 8 weeks. However, with the animals that were treated with water at 70ºC and NDEA, the initial inflammatory process became chronic and resulted in a hiperplasia-displasia-carcinoma sequence. Gene array expression analysis revealed that NDEA, even at 1 ppm, altered the profile of cytokines induced or repressed by the thermal injury.

Conclusion: Our results suggest that the concomitant ingestion of low doses of NDEA and water at 70ºC leads to a chronic inflammation from the thermal injury caused by hot beverage administration, and this resulted in esophageal tumors.

Supported by: CNPq / FAPERJ / SR2 UERJ

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Study of kinetic hepatic regeneration after partial hepatectomy by radioisotopic method

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Background: Liver regeneration (LR) after partial hepatectomy (PH) is now defined as an orchestrated response induced by specific external stimuli and involving sequential changes in gene expression, growth factors production, and morphologic structure. Much of the research on mechanisms and kinetic of hepatic growth has been done only in partially hepatectomized animals and in hepatocytes primary cultures. The study of the hepatic extraction fraction (HEF) by radioisotopic methods gives

information about physiological mechanism of uptake and transport and allows the quantification of the 99mTc-IDA derivatives excretion by hepatobiliary system. Based on these we studied the HEF as an indicator of human LR of patients with hepatic tumors underwent PH.

Material and Methods: 33 patients (13 W and 20 M; 61,3±11,3 years old) with colorectal metastases (n=25), hepatocellular carcinoma (n=4) and other tumors (n=4) were included. Eight patients (24%) were submitted to a major hepatectomy (MAH) and the others (76%) to a minor hepatectomy (MIH). LR was assessed after intravenous bolus injection of 99mTc-N-(3-bromo-2,4,6-trimethylphenylcarbamoilmethyl 1-iminodiacetic acid (Mebrofenin) that was uptaked by the hepatocytes and eventually excreted via billiary pathway without any change to its chemical structure. The HEF is calculated using deconvolution analysis of first pass curve coming from scintigraphic data. We evaluated the pre-operative HEF (T0) and in the 5th day (T5) and one month after PH (T30). We considered the HEF values of 98.8 ± 0.4% (MED ± SD) as normal. For statistical analysis: t-Student test was used.

Results: 1) The mortality and morbility rates were 0% and 15% respectively; 2) the HEF was 98.33±3.36% at T0, 98.7±2.7% at T5 and 97.9±5% at T30 (no significant differences); 3) the HEF values of the patients submitted to a MAH were 98.2 ± 3.1% at T0, 98.7 ± 2.3% at T5 and 97.1 ± 5% at T30, and for those submitted to a MIH were 98.4 ± 3.1% at T0, 98.9 ± 3.3% at T5 and 98.1 ± 5% at T30 (no significant differences).

Conclusion: These results allows to say that the human LR is early enough to normalize the HEF at day 5 after PH, being this evaluation of undoubtedly interest to know the function kinetics and indirectly knowledge about human LR. Additionally, this fast functional liver recovery has high clinical importance, because more aggressive adjuvant chemotherapy can start much early after surgical treatment.

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Estrogen-associated genes expression in uterine leiomyomas

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Uterine leiomyomas are benign smooth muscle tumors and the most common type of gynecological tumor, representing a significant public health problem. It is generally accepted that these tumors are estrogen dependent because they have the ability to enlarge during pregnancy and to shrink during menopause, ovariectomy, and other hypoestrogeneic conditions. There are only a few studies in the literature regarding hormone regulation and steroid hormone receptor status in uterine leiomyomas. Previous studies suggested that the AHR gene, involved in cell proliferation regulation, is a potential marker involved in uterine leiomyomas. AHR gene codifies the dioxin receptor, which forms dimers with another receptor, the ARNT. The complex AHR-ARNT binds DNA sequences to modulate transcription rates of some genes, including the estrogen receptor. The aims of the present study was investigate the ESR1, ESR2, PGR and AHR mRNA expression in 46 uterine leiomyomas and in normal myometrium using quantitative real time PCR to explore the hormonal molecular basis of these tumors. It was detected a down-expression of all genes: 72% of cases for ESR1, 43% for ESR2, 35% for PGR, and 76% for AHR. In addition, in the 46 cases studied, 63% showed an increased ratio of ESR2/ESR1. The expression pattern was compared to clinical-pathological data, including patient age, age at menarche, number of pregnancies, age at first pregnancy, cycle reproductive phase, race, body mass index features, number of myomas, and localization. It was detected that ESR1 and ESR2 expression levels were statistically associated with race (non-white versus white patients) and that PGR gene expression was higher in patients that presented early menarche. These results suggest that ESR1 and ESR2 may play an important role in the development of leiomyoma and that an imbalance in expression of these receptors may contribute to the pathogenesis of the disease. In addition, AHR gene can be assessed as putative marker in the growth and development of uterine leiomyomas.

Both authors (Reis-Rosa, L.A. and Cirillo, P.R.) have contributed equally.

Supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) and Conselho Nacional de Pesquisa (CNPq), Brazil.

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Proliferation-associated genes correlated to hormonal receptors and Ki-67 status in breast carcinomas

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The determination of estrogen and progesterone receptors expression status is crucial for the decision on therapeutic strategies. However, the routine evaluation of ESR1 and PGR status by immunohitochemistry shows large interlaboratory variability, particularly when these genes are expressed at low levels. The stratification of breast cancer patients based on characteristic patterns of gene expression associated with ESR1/PGR status is important to improve clinical management and useful to overcome these limitations. Recently, our group reported that breast carcinomas with high Ki-67 expression were significantly associated with tumors exhibiting low levels of mRNA and undetectable protein levels of ESR1 and PGR. In the present study, global gene expression analysis was performed in 68 invasive ductal carcinomas (29 cases: training set; 39 cases: validation set) using the CodeLink Human Whole Genome BioArray (GE HealthCare) platform. The samples were grouped according to ESR1 and PGR expression status measured at both the transcript and protein level as well as to their proliferative index (< 25% and > 25% immunopositivity to discriminate Ki-67- and Ki-67+ tumors, respectively) to explore the implications of the Ki-67 status in defining proliferation gene expression signatures. Using signal-to-noise ratio with permutation and leave-one-out cross-validation, 68 sequences differentially expressed ($p<0.001$) were identified between ESR1-/Ki-67+ and ESR1+/Ki-67- tumor samples. A similar analysis comparing PGR-/Ki-67+ versus PGR+/Ki-67- tumor samples showed 83 sequences differentially expressed ($p<0.001$). A set of 17 genes involved in cell proliferation was identified as differentially expressed in both analyses. A subset of these genes was investigated by quantitative real time PCR (qRT-PCR) in an independent group of samples confirming the oligoarray expression data. Moreover, a significant statistical correlation was observed between gene expression and histologic grade. These data point to a set of genes with a role in increasing the proliferative rate of breast tumor cells, revealing novel potential biomarkers involved in breast carcinogenesis.

Supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) and Conselho Nacional de Pesquisa (CNPq), Brazil.

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Identification of a gene expression signature correlated to breast cancer prognosis

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Breast carcinoma is a heterogeneous disease with different molecular subtypes being characterized by distinct morphological appearances, genetic alterations, and clinical presentation. This heterogeneity poses a major challenge in its diagnosis and treatment. Breast cancer can also display notorious distinct clinical characteristics in different patient and ethnic populations, having divergent clinical courses despite having similar histopathologic histopathology appearances. Brazilians form one of the most heterogeneous populations in the world, the result of five centuries of interethnic crosses between peoples from three continents: the European colonizers and immigrants; African slaves; and the autochthonous Amerindians. For this reason, molecular signatures of breast carcinomas from Brazilian patients can contribute to identify new molecular markers common at several ethnicities. To this end, global gene expression profiles of a a set of 43 primary breast tumors samples were evaluated using high-density oligoarrays (Platform CodeLink Human Whole Genome BioArray, GE HealthCare). Multiple statistical methods (signal-to-noise ratio with permutation, leave-one-out, t-test) were applied, combining the prognostic information and clinical outcome. Based on clinical criteria and traditional markers used in clinical practice two subgroups of patients were defined: a group of 25 patients were evaluated as “good prognosis”, of which 5 of them presented metastasis; and a group of 18 patients considered of “poor prognosis”, from which 4 of them showed metastasis. The comparison between all patients with metastasis (9 cases) with the group of good and poor prognosis identified an expression signature comprising 52 genes (leave-one-out, $p<0.001$) able to distinguish good prognosis patients without metastasis from patients who had metastasis independent of the molecular prognosis. We also identified an expression signature comprising 134 genes (t-test, $p< 0.02$) able to differentiate patients with poor prognosis that showed no metastasis (for more than five years after the surgical procedure), from patients who developed metastasis. This gene expression signature correctly stratified patients into good prognosis group or poor prognosis group. Differential expression of a subset of these genes was independently confirmed in a larger set of tumor samples using quantitative RT-PCR. Cross-reference of these signature with available breast cancer prognosis signatures such as Oncotype DXtradeTM (Genomic Health Inc.) and MamaPrintTM (Agendia Inc.) showed a limited overlap. These results point to a novel gene expression signature of breast