MEETING ABSTRACTS

A1
Adriamycin-Cyclophosphamide (AC) followed by Paclitaxel-Cisplatin (PC). A highly active neoadjuvant regimen in locally advanced breast cancer
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Background: Locally Advanced Breast Cancer patients require neoadjuvant chemotherapy (NACT), surgery and radiation therapy to optimize the chance of a cure. Pathological responses to NACT, are strongly associated with long-term outcome. Cisplatin has shown antitumor activity in breast cancer, shows synergy with paclitaxel and antitumor activity in anthracycline-resistant breast tumors. As NACT, Paclitaxel-Cisplatin (PC) achieves high pathological responses. On the other hand, dose dense chemotherapy has improved free and overall survival in early breast cancer. This phase II trial was set to evaluate the pathological complete response (pCR) of this regimen based on 4 cycles of adriamycin/cyclophosphamide (AC) followed by weekly (dose dense) PC. Secondary endpoints were to evaluate the safety profile and recurrence-free survival.

Materials and methods: Patients with histological confirmation of breast cancer in stage IIB-IIIC and aged 18–75 years. Patients also had good performance status [ECOG] score ≤2, adequate hematological, cardiovascular, renal, and hepatic functions. Patients were excluded if they were pregnant or breast feeding or if they had other malignant tumors. Patients received 4 cycles of AC at 60/600 mg/m² every 21 days followed by weekly PC at 80/30 mg/m² respectively, at the end of chemotherapy patients underwent surgery.

Results: A total of 33 patients were included and were evaluable for toxicity and response; the analysis was done in the intention-to-treat. One patient showed paclitaxel hypersensitivity and was removed from the study. Three patients remained inoperable after chemotherapy, hence, received preoperative radiation. Median age was 48 years-old (26–73), 66.7% of cases were in stage IIIA and IIIB, tumor median size was 6 cm (2.5–16), node median size was 3 cm (2–16), all patients had clinical positive nodes. ER or PgR were positive in 60.6%, HER2 was positive in 36.4% (determined by IHC or FISH). The pCR rate was 30%, the complete nodal response was 52%. At 18 months of follow-up 2 patients had distant relapse for a 91% of recurrence free-surival. The regimen was well tolerated with grade III-IV toxicity observed in 6% of cases.

Conclusion: The addition of cisplatin to paclitaxel is well tolerated with no significant increase in toxicity. Interestingly, the 30% of pCR observed seems superior to other regimens without cisplatin.

A2
Breast cancer vaccines: maximizing peptide-based vaccines by regulatory T cell depletion and toll-like receptor 9 activation
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BMC Cancer 2007, 7(Suppl 1):A2

Background: Breast cancer is the most prevalent cancer in the world due to high incidence and favorable prognoses. Relapse is the major cause of mortality and will occur in up to 65% of patients with node-positive disease. Thus, effective long-term protection strategies are needed for preventing relapse. One approach that has generated interest in recent years is cancer vaccines. One of the problems with the translation of cancer vaccines is that multiple boosters are required in order to generate high-avidity memory immunity that is able to recognize naturally processed antigens. Our goal in this study was to determine if the need for boosters could be eliminated by preconditioning the immune system with anti-CD25 antibodies, which is known to deplete regulatory T cells, the latter of which are known to regulate the development of high-avidity memory T cells.

Materials and methods: We first developed a single peptide vaccine to generate neu-specific CTL immunity in the Neu-T mouse. Neu-T mice have targeted expression of the activated rat neu antigen, which is known to deplete regulatory T cells, the latter of which are known to regulate the development of high-avidity memory T cells. We then tested the efficacy of a single peptide vaccine

Results: The vaccine peptide, TYYPANASL (p66–74), was pre-

(page number not for citation purposes)
CD25 monoclonal antibodies were used to deplete Tregs prior to immunization. Following depletion, a single vaccination administered at week 10 following birth, when diffuse atypical hyperplasia is already evident in the mammary glands, vaccination induced a sufficient CTL response that has kept 100% of Neu-T mice tumor free until week 31. Immune monitoring revealed that Treg depletion resulted in lower avidity T cells following a single immunization.

**Conclusion:** Our results show that by combining a strong adjuvant (CpG) and an immunogenic peptide, we can induce an immune response capable of preventing spontaneous tumors when repetitive vaccinations are administered. Importantly, the need for boosters is reduced when Tregs are depleted prior to immunization. Removing or reducing the need for booster immunizations may facilitate the clinical translation of cancer vaccines for prevention of breast cancer development and relapse.

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**A3 Surveillance in surgery prevents infections and ensures good quality of care**

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3Department of Infectious Diseases, INCAN Mexico

**Background:** Breast and ovarian cancer are the most frequent malignancies in women. The purpose of the current study was to determine which imaging features suggest either benignity or malignancy.

**Materials and methods:** The clinical and imaging history of 86 women treated for Phyllodes tumor (histologically proven) at our institution was retrospectively reviewed and analyzed.

**Results:** The mean age at diagnosis was 42.2 years (17–86 years). 59 (67.8%) were classified as low grade, 11 (12.6%) intermediate and 16 (18.4%) high grade. The tumor size range was 1 – 25 cm. Imaging features more characteristic were: high breast density (92.8% high grade, 90% intermediate, and 77.2% low grade); breast distortion (26.6% high grade, 24.4% low grade, and 10% intermediate); circumscribed borders (70% intermediate, 53.3% high grade, and 48.8% low grade); indistinct borders (57.7% low grade, 57.2% high grade, and 50% intermediate), 3 low grade Phyllodes had spiculated borders. With US examination, an hypoechoic mass was the main feature (61.1% low grade, 55.5% high grade, and 20% intermediate); other features were heterogeneous echographic pattern (80% intermediate, 44.5% high grade, and 28.8% low grade); necrosis within the tumor (27.2% intermediate grade, 25% high grade, and 10.1% low grade); architectural breast distortion (13.5% low grade, 11.1% high grade); circumscribed borders (62.1% and 33.3% high grade). All patients had follow-up after 1 – 2 years. In the 1 year follow-up, 2.3% of the patients had locally recurrent tumor (n = 2; 1 intermediate; 1 high grade). At the 2-year follow-up, 4.6% of the patients had recurrence (n = 4; 2 low grade; 1 intermediate grade; 1 high grade).

**Conclusion:** Necrosis within the tumor was the main feature of malignant Phyllodes tumor (p = 0.059), however pathologic correlation is mandatory.

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**A4 Imaging evaluation of phyllodes tumor at the National Institute of Cancerology: 86 patient series**

Nestor Villafáñez 1,2, Yolanda Villasénor 1, Adolfo Fuentes-Alburu 1 and Diana Vilar-Compte 3

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**BMC Cancer 2007, 7(Suppl 1):A4**

**Background:** Phyllodes tumor is a rare female breast neoplasm, it resembles fibroadenoma but frequently occurs in older women. The purpose of the current study was to determine which imaging features suggest either benignity or malignancy.

**Materials and methods:** The clinical and imaging history of 86 women treated for Phyllodes tumor (histologically proven) at our institution was retrospectively reviewed and analyzed.

**Results:** The mean age at diagnosis was 42.2 years (17–86 years). 59 (67.8%) were classified as low grade, 11 (12.6%) intermediate and 16 (18.4%) high grade. The tumor size range was 1 – 25 cm. Imaging features more characteristic were: high breast density (92.8% high grade, 90% intermediate, and 77.2% low grade); breast distortion (26.6% high grade, 24.4% low grade, and 10% intermediate); circumscribed borders (70% intermediate, 53.3% high grade, and 48.8% low grade); indistinct borders (57.7% low grade, 57.2% high grade, and 50% intermediate), 3 low grade Phyllodes had spiculated borders. With US examination, an hypoechoic mass was the main feature (61.1% low grade, 55.5% high grade, and 20% intermediate); other features were heterogeneous echographic pattern (80% intermediate, 44.5% high grade, and 28.8% low grade); necrosis within the tumor (27.2% intermediate grade, 25% high grade, and 10.1% low grade); architectural breast distortion (13.5% low grade, 11.1% high grade); circumscribed borders (62.1% and 33.3% high grade). All patients had follow-up after 1 – 2 years. In the 1 year follow-up, 2.3% of the patients had locally recurrent tumor (n = 2; 1 intermediate; 1 high grade). At the 2-year follow-up, 4.6% of the patients had recurrence (n = 4; 2 low grade; 1 intermediate grade; 1 high grade).

**Conclusion:** Necrosis within the tumor was the main feature of malignant Phyllodes tumor (p = 0.059), however pathologic correlation is mandatory.

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**A5 Molecular characterization of BRCA1 and BRCA2 genes in breast cancer patients under 40 years-old or with familiar cancer history**

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**BMC Cancer 2007, 7(Suppl 1):A5**

**Background:** Breast and ovarian cancer are the most frequent causes of death in women, generating an important problem. A
small proportion of these tumors results from alterations in cancer susceptibility genes. Two of these genes are BRCA1 and BRCA2, which are described as hereditary breast and ovarian cancer genes. BRCA1 mutations have been identified in 15 to 20% of women with familiar breast cancer, and in 60 to 80% of women with familiar breast and ovarian cancer; to date over 500 sequence variants have been reported for this gene. It is estimated that mutations in BRCA2 cause approximately 35% of hereditary breast cancer cases, besides, is associated with breast cancer in men, ovarian, pancreas and prostate cancer. Specific mutations to particular ethnic groups have been described. There are no known mutations for the Mexican population. The purposes of this work were to determine the mutation frequency of BRCA1 and BRCA2 genes in breast cancer patients under 40 years old or patients with familiar breast and/or ovarian cancer history, through DHPLC analysis and, to establish genotype-phenotype correlations. Those families with mutations will be followed-up for an early detection, and will receive genetic counseling.

Materials and methods: Forty breast and/or ovarian cancer patients were included. DNA was obtained from peripheral leukocytes, and was amplified for the 24 exons of BRCA1 using 31 pairs of oligonucleotides, and for the 26 exons of BRCA2 with 39 pairs of primers. The primers were designed to include each exon flanked by a small portion of the corresponding introns. The amplifications were analyzed in a DHPLC (Transgenomics).

Results: We have analyzed the entire BRCA2 gene for the 40 patients, and found 1 polymorphism at exon 4 in 4 patients and 4 different polymorphisms at exon 11 in 24 patients. We identify a patient with a mutation in exon 11 already reported at Breast Cancer International Core (BIC), which was also present in her father, for this reason the rest of the family will be analyzed and receive the appropriate genetic counseling. Regarding BRCA1, we have completed the amplifications, and we are now performing the DHPLC analysis.

Conclusion: We have found an elevated percentage of patients with polymorphisms (up to 30%). Until now we have found only one mutation, which has been reported only three times in the BIC. It seems that mutations in BRCA2 are not frequent in our hereditary breast cancer patients.

A6
Metaplastic carcinoma of the breast: a clinical and pathological study of 40 cases
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BMC Cancer 2007, 7(Suppl 1):A6

Background: Metaplastic carcinoma of the breast (MCB) is a rare neoplasm, described in approximately 1% of all breast carcinomas. MCB is associated with poor prognosis and correlated with a high recurrence rate and visceral metastases. MCB is generally hormonal receptor-negative; specific treatments are not well defined. The objective of this study was to describe the clinical and pathological features of MCB.

Materials and methods: We included all the patients with diagnosis of MCB, treated in Instituto Nacional de Cancerología (INCan) of Mexico City during the period from 1995 to 2005; all cases had histopathological confirmation by two pathologist. Clinical information, pathological features of the tumor and survival information were collected; descriptive analysis was done.

Results: From 1995 to 2005 the Instituto Nacional de Cancerología attended 6,610 breast cancer cases; during this period we found 40 (0.6%) cases of MCB, all of them were female with a mean age of 47.9 years old (24–74). Based on the WHO classification, 20 cases were purely epithelial and 20 were mixed. Of purely epithelial cases, 8 (20%) were squamous, 9 (22.5%) spindle cell and 3 (7.5%) adenosquamous. Mixed cases with chondroid metaplasia, osseous metaplasia and carcinosar-

Table 1 (abstract A6) Clinical and pathological features between purely epithelial and mixed epithelial MCB

<table>
<thead>
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<th>All cases</th>
<th>Purely epithelial</th>
<th>Mixed epithelial and mesenchymal</th>
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<td>Mean age (years) (n = 40)</td>
<td>47.9</td>
<td>49.4</td>
<td>46.4</td>
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<tr>
<td>Breast side (n = 38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>22 (58%)</td>
<td>10 (52.6%)</td>
<td>12 (63.1%)</td>
</tr>
<tr>
<td>Left</td>
<td>16 (42%)</td>
<td>9 (47.3%)</td>
<td>7 (36.8%)</td>
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<tr>
<td>Mean tumor size (cm)</td>
<td>7.16 (1.8–40)</td>
<td>5.79 (2–11)</td>
<td>8.31 (1.8–40)</td>
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<tr>
<td>Clinical stage</td>
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</tr>
<tr>
<td>I</td>
<td>2 (5%)</td>
<td>0</td>
<td>2 (10.5%)</td>
</tr>
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<td>II</td>
<td>14 (35%)</td>
<td>8 (42.1%)</td>
<td>6 (31.5%)</td>
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<td>III</td>
<td>21 (52.5%)</td>
<td>10 (52.6%)</td>
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<td>Non-classifiable</td>
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<td>Outcome (n = 33)</td>
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<td>No relapse</td>
<td>20 (60.6%)</td>
<td>1 (20%)</td>
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<td>Relapse</td>
<td>10 (30.3%)</td>
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<td>Progression of disease</td>
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<tr>
<td>Recurrence site</td>
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<tr>
<td>Local</td>
<td>2 (20%)</td>
<td>1 (20%)</td>
<td>1 (20%)</td>
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<tr>
<td>Distant</td>
<td>8 (80%)</td>
<td>4 (80%)</td>
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<td>Overall survival (months)</td>
<td>45.2</td>
<td>49.9</td>
<td>40.5</td>
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Role of HPV18 E6 in PKB signal transduction pathways

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BMC Cancer 2007, 7(Suppl 1):A7

Background: The etiological role of Human Papillomavirus (HPV) in cervical cancer development has been clearly demonstrated, it is known that only a minority of cervical lesions infected with high risk HPVs evolve to higher grade lesions or cervical cancer. It is thought that intratype HPV variations may play an important role in differences in viral biological behaviour. It has been recently reported that E6 protein of high risk HPVs degrades proteins such as p53, Bak, Myc and hDlg which are involved in cellular processes such as proliferation, apoptosis and maintenance of cytoarchitecture possibly by the PKB pathway. The objective of this study was to determine the differential contribution of E6 from variants of HPV18 in cell proliferation through the Akt/PKB pathway.

Materials and methods: C33, cervical cancer cell line HPV negative (mutated in p53), and MCF-7 breast cancer cell line (wt p53), were transfected with different E6 genes from HPV18 – Asian American, -European, and -African variants. Protein levels of p53, hDlg, PI3K, PTEN, PKB and activated forms were determined by Western Blot. Proliferation was analyzed by methylene blue and flow cytometry assay. Immunohistochemistry was performed in cell lines and cervical cancer tumor biopsies.

Results: Proliferation was significantly diminished in cells transfected with African E6 in relation to -European or -Asian American clones. This fact is correlated to an increase in hDlg protein levels in cell lines harboring the E6 African variant; as well as an increase in PI3K and PKB activated forms in cells with the E6 European and -Asian American clones. hDlg was found abnormally localized in these cell lines.

Conclusion: Cell proliferation is induced by E6 of HPV18 independent of p53, this effect may be probably related to its effect over certain elements of the akt/PKB pathway. This work could help us to identify possible E6 targets in signal transduction and cell architecture, as well as biological differences between HPV18 variants.

A8

MTHFR (C677T) polymorphism determination in patients with metastatic colon cancer and its effect on the treatment with 5-fluorouracil and folinic acid

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BMC Cancer 2007, 7(Suppl 1):A8

Background: Fluoropyrimidine-based chemotherapy is the most common treatment for colon cancer, especially the combination of 5-fluorouracil (5FU) and folinic acid (FA). Despite the existence of other treatment choices, more than 50% of the patients in Mexico cannot afford their cost, and the regimen used is still 5FU/FA. However, not every patient responds to this treatment, and it will be useful to have a biological marker that helps to predict the response to 5FU/FA giving the basis for treatment selection. The enzyme called Methylene tetrahydrofolate Reductase (MTHFR) plays an important role in the metabolism of folates. The MTHFR substrate is needed for the synthesis of a tertiary complex with 5FU and thymidylate synthase, which inhibits thymine synthesis. A mutation in MTHFR has been identified as one of the most common polymorphisms in the Mexican population (thymine instead of cytosine in gene position 677). This genetic variation has been correlated with a reduction in the enzymatic activity and increases substrate levels, which increases the activity of 5FU. The aim of this study was to evaluate the presence of C667T MTHFR polymorphism and its relation with progression-free survival in patients with metastatic colon cancer treated with 5FU and FA.

Materials and methods: We studied 29 patients with metastatic colon cancer treated with 5FU/FA at the Instituto Nacional de Cancerología, in Mexico City. Healthy mucosa from paraffin blocks were used to obtain DNA and determine C667T polymorphism by PCR and allele specific digestion.

Results: The following proportions were found: 27% CC homozygous, 52% CT heterozygous and 21% TT homozygous. There was no difference regarding gender, functional status, tumor differentiation, site and number of metastases between the three groups. The median time for progression was: CC 3.43, CT 4.77 and TT 4.80 months, respectively (p = 0.047 log rank). When comparing the non-polymorphic (CC) and polymorphic groups (CT and TT), we observed a greater time to progression (4.80 vs. 3.43 months) in the polymorphic group (p = 0.031 log rank).

Conclusion: Our findings are the first to suggest that the C677TT MTHFR polymorphism plays a role as a predictive marker of progression-free survival in patients with metastatic colon cancer treated with 5FU/FA.
A9  
**Study of the polymorphism Mad1 G558A in a Mexican population and its relationship with the generation of aneuploidy**  
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BMC Cancer 2007, 7(Suppl 1):A9

**Background:** Chromosomal segregation in eukaryotic cells is controlled by a group of proteins that constitute the mitotic spindle checkpoint (MSC). Any alteration in this checkpoint causes chromosomal instability, mainly aneuploidy. MAD1 is one of the MSC proteins, which has structural and regulatory functions that influence the cell cycle progress. MAD1 regulates positively MAD2, attracting it to the active kinetochore, and promoting its interaction with CDC20. This complex inhibits progression of the cell cycle towards anaphase until all chromosomes have the adequate alignment. Recently, it was reported a polymorphism at codon 558 of Mad1 gene that replaces a G for an A, promoting the change towards anaphase until all chromosomes have the adequate alignment. The treatment with agents that alter the chromosomal segregation. This polymorphism was only observed in cancer cells, but not in cells from healthy donors. Even though, preliminary studies in our laboratory have detected the polymorphic variant in healthy donors. The aim of the present work was to determine the frequency of the G558A polymorphism in Mad1 gene of a Mexican population, as well as its influence on the MSC activation.

**Materials and methods:** Whole blood samples were obtained from 140 Mexican healthy donors. DNA isolation was performed by the standard protocols (phenol-chloroform-isoamyl alcohol) and precipitated with ice-cold ethanol. Genotyping of Mad1 polymorphism (G558A) was performed by PCR and restriction-enzyme digestion. After digestion, wild type genotype generates five fragments (12, 42, 43, 50 and 136 bp), while the polymorphic variant generates four fragments (12, 43, 50 and 94 bp). In order to investigate activation of the MSC in the polymorphic individuals, cells from 27 donors were cultured and exposed to nocodazole (0.2 μg/ml) for 2 and 6 h. Cells were fixed and stained to detect cell cycle progression. This complex inhibits progression of the cell cycle towards anaphase until all chromosomes have the adequate alignment.

**Results:** Of the 140 studied donors, 34 had GG genotype, 74 GA and 34 AA, with a genotypic frequency of 24.3, 51.4 and 24.3 respectively, and a frequency of 50% for both alleles. Treatment with nocodazole induced a higher mitotic index in lymphocytes with GG genotype, followed by the heterozygous (GA) and finally by the homozygous AA.

**Conclusion:** This study demonstrates that the polymorphic variant A558 of Mad1 gene is very frequent in healthy Mexican individuals, and therefore is not a result of the malignant transformation process as had been proposed. The Mad1 polymorphic variant has an influence in the cellular response to the treatment with agents that alter the chromosomal segregation. The fact that cells of the individuals of the AA variant do not stop in metaphase after treatment with nocodazole makes cells more sensitive to present errors in the chromosomal segregation, which may eventually result in the generation of aneuploid cells.

A10  
**Signaling induced by PAR1 on breast cancer cell lines is correlating with its invasive potential**  
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BMC Cancer 2007, 7(Suppl 1):A10

**Background:** PAR1 (Protease-Activated Receptor 1) is an oncogene that has long been proposed to be involved in the invasive and metastatic process of breast cancer. PAR1 activates Mitogen-Activated Protein Kinases (p44 and p42 also called ERK1/2) leading to cell proliferation. It has been suggested hyperexpression of the MAP Kinases may be a key process in the metastatic potential of breast cancer. PAR1 signaling mechanisms are not completely understood. The aim of this study was to determine ERKs activation in relation to PAR1 expression leading to tumor progression on breast cancer cell lines.

**Materials and methods:** We assayed by immunoblot PAR-1 and ERKs expression and activation on a highly invasive MDA-MB-231 and minimally invasive MCF-7 breast cancer cell lines. We also determined PAR1-induced cell proliferation and invasion. To determine ERKs specific contribution to tested activities, we used U0126 MEK inhibitor. Additionally we evaluate their ability to growth on 3D cultures. Two tailed Student’s test was used to compare data. p values = 0.05 were considered significant.

**Results:** We found invasive cells overexpressed PAR1, and when stimulated with thrombin (1 nM), we observed a selective and time independent ERK1 activation (p < 0.05). Cell proliferation and invasion were also significantly increased (83% ± 0.05% stimulation above media control, p < 0.02; and 87% ± 0.05% cell invasion compared with media control, p < 0.05 respectively). All activities were blocked significantly when assayed in the presence of U0126 (p < 0.0001). Spheroid’s size was elevated upon thrombin stimulation and elongated in shape. In contrast in the low invasive cell line we found very low levels of PAR1. We observed thrombin-induced an up-modulation of ERKs activation. ERK1 showed a maximal activation at 30 minutes, while ERK2 was barely activated in a time independent way. No significant increase was found on cell proliferation or invasion. Neither between spheroid’s sizes, and they were all round.

**Conclusion:** Our data suggest different modulation of signaling pathways induced by PAR1 leading to tumor progression in breast cancer.

**Acknowledgement:** This work was supported by CONACYT (Salud-2003-C01-003).

A11  
**Apoptosis induced by cisplatin but not by 5-FU in colon cancer cells depends on Omi/Htra2 protein**  
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BMC Cancer 2007, 7(Suppl 1):A11

**Background:** The most frequent cause of treatment failure in patients with advanced cancer is chemotherapy resistance. One
of the mechanisms of chemotherapy resistance is failure to trigger apoptosis of cancer cells. Apoptosis can be induced by two pathways, intrinsic and extrinsic. The intrinsic pathway is activated by mitochondrial release of apoptotic proteins secondary to genomic stress. Omi/HtrA2 is one of the released mitochondrial proteins. It is a serine protease which inactivates the family of Inhibitor of Apoptosis Proteins (IAPs).

**Materials and methods:** In this study, the participation of Omi/HtrA2 in cell death induced by the chemotherapeutic agents Cisplatin and 5-Fluorouracil (5-FU) was assessed in human colon cancer cell lines SW480. 5-FU and Cisplatin induced apoptosis in this cell line as shown by cell morphology and further confirmed by showing cleavage of caspase 3. Both drugs induced apoptosis via the intrinsic pathway as shown by mitochondrial release of cytochrome C.

**Results:** 5-FU and Cisplatin promoted the release of Omi/HtrA2 from the mitochondria to the cytosol, as demonstrated by immunofluorescence and western blot assays of subcellular fractions. When cells were exposed to an Omi/HtrA2 serine protease inhibitor, UCF-101, cell death was significantly suppressed of cells exposed to Cisplatin, but not to 5-FU. Additionally, Omi/HtrA2 inhibition partially prevented reductive cell death measured by clonogenic assays of cells exposed to Cisplatin but not to those exposed to 5-FU.

**Conclusion:** This study shows that Omi/HtrA2 participates in cell death induced by CDDP but not by 5-FU in colon cancer cells. In addition, our findings suggest downstream differences in the intrinsic pathway of apoptosis triggered by diverse antineoplastic drugs.

**A12**

Up-regulation of HLA class I antigen expression and antigen-specific CTL response in cervical cancer cells by the demethylating hydralazine and the histone deacetylase inhibitor valproic acid

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**BMC Cancer 2007, 7(Suppl 1):A12**

**Background:** DNA hypermethylation and histone deacetylation are epigenetic events that contribute to the absence or downregulated expression of different components of the tumor recognition complex. These events affect the processing and presentation of antigenic peptides to CTLs by HLA class I molecules. In this work we evaluated the effect of the DNA hypomethylating agent hydralazine (H) and the histone deacetylase inhibitor valproic acid (VA), on the expression of HLA class I molecules and in the antigen-specific immune recognition of cervical cancer cells.

**Materials and methods:** Cell lines C33A (HPV-), CaSkI (HPV-16+) and MS751 (HPV-18+) were treated with hydralazine and valproic acid to assess cell proliferation and to evaluate the expression of HLA class I molecules on cell surface by flow cytometry. Primary cervical tumors of five HLA-A*0201 allele patients were typed for HPV and their CTLs stimulated in vitro with the T2 cell line previously loaded with 50 µM of the HPV peptides. Cytotoxicity of stimulated CTLs was assayed against Caski and MS751 cells pre-treated with hydralazine and valproic acid.

**Results:** The combination of HV acid had antiproliferative effect in C33 and CaSkI cells. VA and VA+H up-regulated the constitutive HLA class I expression as evaluated by flow cytometry. In addition, the antigenic immune recognition of Caski and MS751 cells by CTLs specific to HPV-16/18 E6 and E7-derived epitopes, was more prominent on cells treated with VA + H+VA than cells treated with either H or IFN-α.

**Conclusion:** These results support the potential use of H and VA as an adjunct for immune intervention in cervical cancer patients whenever clinical protocols based on tumor antigen recognition is desirable, such as in those cases where the application of E6 and E7 based therapeutic vaccines is used.

**A13**

Prediction of the recurrence probability in patients with parotid gland cancer

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**BMC Cancer 2007, 7(Suppl 1):A13**

**Background:** Parotid gland carcinoma is an infrequent tumor, and series which report on these neoplasms are relatively scarce in the literature. Our aim is to identify prognostic factors in parotid gland carcinoma and develop a method to define the probability of recurrence.

**Materials and methods:** Patients with parotid gland carcinoma who attended our institution from January 1981 to December 2004 and completed treatment constitute our study group. Disease-free survival was calculated using the Kaplan-Meier method. Logistic regression analysis was used to define the prognostic factors associated to recurrence.

**Results:** One-hundred and twenty seven patients were included (64 male and 63 female). Mean age was 53 years. Mucoepidermoid carcinoma was found in 34.6%, adenoid cystic 15.7%, adenocarcinoma 14.3% and acinic cell carcinoma 9.4%. Median disease-free survival was 8.3 years (95% CI 4.3–12.2). Logistic regression analysis confirmed that T classification, facial nerve palsy, differentiation grade, age and surgical margins as factors associated to recurrence (p < 0.00001). Using this model, we defined three postoperative risk groups: high, intermediate and low risk with recurrence frequency of 71.4%, 43.1% and 8.8%, respectively (p = 0.0001). Five-year disease-free survival for these groups were 18.7%, 53.9% and 99.9%, respectively (p = 0.00001).
Conclusion: Our study identifies several significant prognostic factors. Consequently, a prognostic score categorization is proposed, which allows a straightforward calculation of the recurrence risk for a given case, to define therapeutic strategies, for counseling of patient and to design future trials.

A14
Expression of MMPs and TIMPs in different tumor progression stages of oral cavity squamous cells carcinoma (experience of 30 cases in Instituto Nacional de Cancerología, México 1999–2004)

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BMC Cancer 2007, 7(Suppl 1):A14

Background: Squamous cells carcinoma constitutes 90% of malignant tumors of the oral cavity. Typically, it has a high potential of invasion, reinicidence and lymphatic metastasis. Metalloproteinases (MMPs) AND tissue inhibitors of metalloproteinases (TIMPs) are considered the main molecules involved in invasion and metastasis. The purpose of this study was to establish through immunohistochernistry the expression of MMP1, 2, 3, 7, 9, 11 and 13, and TIMP-1 and 2, in different selected areas reporting tumor progression stages in oral cavity squamous cells carcinoma (OCSCC).

Materials and methods: Out of 412 patients from the Institute National de Cancerología with a histological diagnosis of OCSCC and treatment with primary tumor surgery and neck dissection from 1999 to 2004, 30 cases were selected with material for immunodyeing of representative areas of tumor progression (in situ carcinoma, primary tumor, tumor front, invasive carcinoma distant to the primary tumor and metastatic node) and control tissue (normal mucous membrane to the tumor). Immunohistochemical reactions were appraised in five representative fields in each area (40× objective). Cases considered positive were those with more than 20% neoplastic cells and/or peritumoral stromal cells with mild, moderate or intense expression. Statistical analysis included Fisher’s exact test to contrast the different appraised areas.

Results: Expression of seven out of nine MMP and TIMP enzymes was observed both in neoplastic cells and peritumoral stromal cells.

Conclusion: Expression of MMP-2, 3, 7, 9, 11 and TIMP-2 was observed in different stages of tumor progression, both in neoplastic cells as in peritumoral stromal cells in OCEC. This allows us to consider them invasion facilitators, and their joint action may confer to them a more aggressive behavior in neoplastic growth.

A15
Prevalence of human Papillomavirus in head and neck cancer in Mexico: a case-control study

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BMC Cancer 2007, 7(Suppl 1):A15

Background: Smoking or chewing tobacco and alcohol consumption are the major risk factors for development of Head and Neck Squamous Cell Carcinoma (HNSCC). However, studies suggest that a subset of these cancers could be associated with HPV infections. This association is reinforced by the fact that the most prevalent HPV types found in cervical carcinoma are those most frequently detected in Head and Neck Cancer. The prevalence of HPV in this type of cancer is highly variable with detection rates varying from 0 to 100% depending on the study and the anatomic location of the neoplasm. Few studies have been made in Mexican populations to determine prevalence of HPV in HNSCC. The aim of this study is to determine the prevalence of HPV in samples of patients with HNSCC and healthy individuals in a Mexican Population and to establish the types of HPV and HPV16 variants present in these samples.

Materials and methods: We conducted a case-control study in 100 samples of HNSCC and 100 control subjects. DNA from samples of exfoliated cells and biopsies was extracted using the salting out method, amplification of β-globin gene by PCR was used to assess DNA quality. HPV presence was evaluated by PCR with MY09/MY11 and GP5+/GP6+ primers. DNA sequencing was used to determine HPV types and variant types.

Results: So far we had evaluated 50 samples of case patients. 46 were β-globin positive. HPV was detected in 72% (33/46) of the samples: 61.5% of carcinomas of the oral cavity, 74% of larynx and 100% of oropharynx. HPV type 16 was the most prevalent one (47%). Some variants of HPV type 16 have been determined and European (E) variants had been the most frequent ones.

Conclusion: HPV DNA was found in a high percentage of HNSCCs. HPV may preferentially infect certain anatomic sites of the Head and Neck because prevalence was greater in the samples of the oropharynx than any other site, although analysis of a greater number of samples is needed to confirm these observations. As previously documented for Cervical Cancer, the most frequent type found was HPV type 16 and the variant type was European (E).

A16
Outcomes of radiotherapy in patients with glottic larynx cancer T1 and T2

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BMC Cancer 2007, 7(Suppl 1):A16

Background: Early Larynx Cancer (ELC) has been historically treated with radiotherapy and the outcomes reported vary considerably. We analyze the patient and treatment related...
parameters that may influence the frequency of local control, overall and disease free survival; and voice preservation.

**Patients and methods:** Thirty patients were treated with radiation therapy between 1996–2002. We use the AJCC 2002 classification for the patients and also they were stratified according to the extent of disease. Variables like age, clinical stage, tumor extension, involvement of anterior commissure, Karnofsky index, total dose, field size, protraction, beam energy and others were used for the statistical analysis.

**Results:** We found 30 male patients with a median age of 64 years (range 55 – 85). Twelve patients were T1a, 10 patients T1b and 8 patients had T2 tumor; according to the tumor extension, 11 (37%) had affected one vocal cord, 13 (43%) one vocal cord and anterior commissure and 6 (20%) had affected two cords and the anterior commissure. The median follow up was 53.2 months and a range between 5 and 114 months. All patients were treated with a continuous course of radiotherapy with a fraction size of 2 Gy per day, the median dose was 68.7 Gy (56 – 81 Gy). The median of protraction was 53 days (range 42 – 77), Co60 was used in 25 patients and 6 MV in 5 patients, the field size was equal to or smaller than 7 × 7 cm² with a larynx box technique for all. In 27 patients the dose calculation was made with a Cadplan® system to an isodose curve of 95% to the tumor. Local control rates at five years were as follows: T1a 100%, T1b 75% and T2 37.5%. The overall survival to 5 years for the entire group was 73.3%. Voice preservation was reached in 25 patients (83%) until the last visit. The reported toxicity was mucositis in 27 patients (90%), 3 of them required a nasogastric tube, no surgical treatment was required. Radiotherapy was not the cause of death in any patient. There were 8 recurrences, 3 of them were rescued with total laryngectomy, one patient was treated with partial laryngectomy and presented a new recurrence, 4 patients did not accept any further therapy. Only those variables like stage (p = 0.008), tumor extension (p = 0.009) Karnofsky index 90 Vs 100 (p = 0.008), and anterior commissure involvement (p = 0.04) had a significant association with local control in univariate analysis.

**Conclusion:** Radiation therapy cures a high percentage of patients with T1 glottic carcinoma and has a low rate of severe complications. For T2 glottic carcinoma an adequate selection and staging for the election of the best treatment option is necessary. The major tumor-related parameter that influences the likelihood of local control is T stage and extension of disease.

**A17 Concurrent chemoradiation with carboplatin for locally advanced cervical cancer at high-risk for developing cisplatin-induced renal dysfunction**

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**Background:** Chemoradiation based on weekly cisplatin is the standard treatment for locally advanced cervical cancer; however, the nephrotoxic potential and the requirement for hydration of cisplatin somewhat restrains its use. We previously reported that the recommended dose of carboplatin to be used weekly with radiation was 133 mg/m² (IJROBP 2003). Hence, we wanted to analyze our results of treatment with carboplatin chemoradiation which was adopted as routine treatment in our Institution for patients having high risk conditions to develop renal dysfunction by cisplatin.

**Materials and methods:** We reviewed the files of 85 patients with locally advanced cervical cancer who received radiation plus weekly carboplatin. The three main conditions that dictated the use of carboplatin instead of cisplatin in the patients analyzed were diabetes mellitus, high blood pressure and/or >70 years old. Treatment compliance, response rate and survival were analyzed.

**Results:** A total of 85 patients who received radiation and carboplatin were analyzed. Mean age was 58 years (range, 27–79 years). The majority of cases were squamous cell carcinoma (94%), and distribution according to International Federation of Gynecology and Obstetrics (FIGO) stage was as follows: IB2, 4.7%, IIA, 8.2%; IIB, 41.1%, IIIA, 4.7% and IIIB, 38.8%; there were only two IVA cases (2.5%). Overall, 93% of patients completed external beam, and intracavitary low-dose rate brachytherapy. The majority of patients received five and six courses of weekly carboplatin, 40% and 38.8% respectively. Complete responses were achieved in 72 (84.7%) patients, whereas 5 patients (5.8%) had persistent and 8 (9.4%) progressive disease. At median follow-up (20.8 months; range, 5–45 months) overall survival is 81.7%.

**Conclusion:** Our results support the use of chemoradiation with six weekly applications of carboplatin at 133 mg/m² during external radiation for routine management of locally advanced cervical cancer in patients who present high risk factors to develop renal dysfunction.

**A18 Synergistic effects of mifepristone on the cytotoxicity of cisplatin in cervical carcinoma cell lines and tumors grown in athymic mice**

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**Background:** Cisplatin and its derivatives are important drugs in cancer therapy. It has been widely used for its potent cytotoxic effects upon a variety of tumors types including cervical carcinoma. However, the administration of cisplatin is associated with serious side effects, including nephrotoxic and neurotoxic events. There have been several studies aimed at finding drugs able to potentiate the antiproliferative effects of cisplatin without increasing the already serious side effects, but the search has not been successful. In this work we investigated the ability of a progesterone antagonist, mifepristone, to modulate the cytotoxic effects of cisplatin in cancer cell lines and in a model of cervix cancer in athymic mice.

**Materials and methods:** The effect of cisplatin alone and cisplatin combined with mifepristone on cellular death was
studied using an assay based on a tetrazolium dye, XTT. Before and after treatment with mifepristone, the intracellular accumulation of cisplatin in cancer cells and tumors of mice receiving treatment was evaluated by HPLC, the expression of Bcl-2 gene was assessed by RT-PCR and western blotting. Tumors measurements were performed weekly using vernier calipers.

**Results:** Analysis of the data by the isobologram method shows that the combination of mifepristone and cisplatin produced a synergistic effect in cervical cancer cells. The effect of mifepristone on the cytotoxicity of cisplatin could be mediated, at least partially, by increase of intracellular cisplatin accumulation and the down-regulation of the Bcl-2 expression. The in vivo studies showed that the combination of these agents had a significant antitumor activity against xenograft tumors.

**Conclusion:** Our results suggest that mifepristone can improve the efficacy of cisplatin in cancer cells and this anti-hormonal drug therapy may be a candidate for further evaluation in combination with antineoplastic drugs in the treatment of cancer.

**Acknowledgements**

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**A19 Chemoradiation with cisplatin followed by either brachytherapy or radical hysterectomy. A non-randomized comparison in FIGO stages IB2-IIA**

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**BMC Cancer 2007, 7(Suppl 1):A19**

**Background:** The current standard of treatment for locally advanced cervical cancer consists of external radiation plus brachytherapy concurrent with weekly applications of cisplatin. On the other hand, current evidence suggests that preoperative chemoradiation is at least as effective as the standard treatment. Because limitations in the availability of brachytherapy in Mexico and many other developing countries, it is of major interest to determine whether a radical hysterectomy after external chemoradiation has superior or at least equivalent results in terms of survival to chemoradiation and brachytherapy. In FIGO stages IB2-IIA patients.

**Patients and methods:** This is a non-randomized comparison of both treatment modalities. The data of preoperative chemoradiation modality was taken from the cisplatin arm of a randomized phase II study we performed comparing preoperative chemoradiation with cisplatin against cisplatin/gemcitabine (JROBP 2005). These forty patients were paired against a cohort of 40 patients treated with external radiation and cisplatin plus brachytherapy. In both groups, the dose of external radiation was 50 Gy in 2 Gy fractions and cisplatin was dosed at 40 mg/m² for six weekly applications. Survival was analyzed with the Kaplan-Meier method and curves compared with the Log-rank test.

**Results:** There were no significant differences in the clinicopathological characteristics of the patients. Mean age was 45 years (range 24 – 70). In both groups the histologies were squamous cell carcinoma (70%), adenocarcinoma (20%), and adenosquamous (10%). Stage distribution according to the FIGO was as follows: IB2, 22.5%; IIA, 10%; IIIB, 67.5%, in both groups. Overall, 100% of patients completed external beam, and surgery or intracavitary brachytherapy. The majority of patients received the planned six courses of weekly cisplatin. At median follow-up (28 months; range 2–58 months), overall survival is 78% and 75% (p > 0.05) for the surgical and brachytherapy groups of patients.

**Conclusion:** The results of this non-randomized comparison suggest that these treatment modalities are equivalent in terms of survival. A randomized study is ongoing to confirm these results.

**A20 Differential expression of HaCaT cells transfected with E6 oncogen from the HPV18**

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**BMC Cancer 2007, 7(Suppl 1):A20**

**Background:** In Mexico cervical cancer is the first cause of death in women. The causal of high risk human papillomavirus in all cancers of uterine cervix has been firmly established biological and epidemiologically. HPV 16 and 18 account for about 70% of all cervical cancers. In both HPV types intra type variants with differences in their pathogenic potentials have been found. HPV 18 variants have shown differences in viral transcription, as well as differences in relation to E6 oncogene expression and their interaction with important cellular proteins such as p53, hDlg, Bax, etc. European (E) and Asian-American (AsAi) HPV 18 variants have been associated with a worse prognosis because they are predominantly found in cervical cancers and infrequently in premalignant lesions. However, most of the HPV18 positive cancers contain the European variant. These facts suggest that HPV18 European variant could have a biological advantage over the AsAi isolate. The aim of this study was to determine if human immortalized keratinocytes cells (HaCaT) transfected with HPV18 E6 variants (E and AsAi) have different genomic expression patterns.

**Materials and methods:** RNA from HaCaT cells transfected with E6 oncogen from the HPV18 European and AsAi isolates were tested twice through hybridization on 10 KB Human microarrays. Statistical analysis was done with GenArise software. Microsoft Access data base was used to match genes with a differential expression ratio. Biological process was studied with Fatigo data base.

**Results:** Our results show that within cells transfected with the different E6 variants, 165 genes were differentially expressed; 95 were up-regulated and 70 down-regulated. Even global expression differences seem to be minor, particular
Expression of viral and cellular cycle proteins and proteinases in cervical carcinoma cell lines as possible immunochemical markers of malignant phenotype

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A21

Background: Cervical cytology has been used extensively as a screening procedure for cervical cancer. Recent molecular developments increase its sensitivity and sensibility including HPV assessment, and the use of molecular biomarkers such as p16 protein. The aim of this study was to explore the pattern of expression of proteins from HPV, cell cycle and proteinases in various cell lines to determine the best candidates to serve as cytological biomarkers of malignancy.

Materials and methods: The following cell lines were used: Hela (HPV-18), Caski (HPV-16), Siha (HPV-16), C33-A (HPV-negative); MCF-7 (Breast cancer) and SW480 (Colon cancer) as negative controls. Slides were prepared from cultured lines and incubated with the following primary antibodies: E6, E7, Rb, p53, p16NK4A, p14ARF, E2F1, Cyclins A, E and B1, MMP2, 9, 10, 11 and 12; Cathepsins B, D and F; and PCNA and Ki-67. Immunoreactivity was evaluated after staining with the DAKO-peroxidase system recording its cellular localization and intensity.

Results: All HPV positive cervical cell lines showed an intense nuclear staining for p16, except in C33-A that stained in the cytoplasm. Expression of p14 was intensely positive in the nuclei of cervical carcinoma cell lines with or without HPV. Expression of replication proteins PCNA and Ki-67 was intensely positive in the nucleus of all cell lines. Proteases were found intensely positive in the cytoplasm of all cells except for MMP12. Cell cycle proteins A, B1, E and E2F1 varied in intensity and cell location. Viral proteins E6 and E7 were found in low intensity and percentage in HPV positive cells. Rb and p53 were detected in the cytoplasm or nucleus of HPV positive cells.

Conclusion: Expression of p16 in the nucleus and p14 in the nuclei of the most constant histochemical biomarkers in malignant cervical cell lines. Replication proteins PCNA and Ki-67 and proteinases Cathepsin B and MMP are good markers of the malignant phenotype in dependent of the presence of HPV. The use of these biomarkers in conjunction might improve the sensitivity and diagnostic accuracy of cervical cytology.

A22

Frequency and follow-up of cytological studies diagnosed as atypical squamous cell (ASC) at Instituto Nacional de Cancerologia from 2000 to 2004

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A22

Background: ASC is the most frequent abnormal diagnosis in the interpretation of cervicovaginal cytology (CVC), it represents from 1 to 9%. There is not much known about its frequency or proportion in groups of high risk, such as the ones that are seen at Instituto Nacional de Cancerologia, center of reference for cancer treatment.

Materials and methods: A total of 64,602 CVC were retrieved from files at the Cytology Department of the Instituto Nacional de Cancerologia, conventional Papanicolaou slides were reviewed, and all cases from patients without previous cytologic, histologic or surgical diagnosis of epithelial abnormalities were included. Data related with age, gynecobstrategic background, type and time of observations were obtained from clinical files.

Results: 565 ASC cases from patients without previous cytologic, histologic or surgical diagnosis of epithelial abnormalities were identified during a period of five years (2000 to 2004). They constituted 6.6% of abnormal diagnosis, with an ASC: Squamous intraepithelial lesion (SIL) relation of 0.06:1; 316 cases were excluded, and 229 patients were the study group. 69% were premenopausal, 42.4% of them were observed and followed by cytology, colposcopy and biopsy. Coppelson I (31.9%) was the main colposcopic diagnosis, whereas in 51.4% an inflammatory cytologic diagnosis was done, and in 41.9% a low grade squamous intraepithelial lesion was the histological diagnosis.

Conclusion: The combination of cytology, colposcopy and biopsy is recommendable for detection of cervical abnormalities, as well as the correlation of the three methods permits to avoid aggressive and unnecessary invasive procedures.

A23

A proof-of-principle study of epigenetic therapy with hydralazine and magnesium valproate plus doxorubicin cyclophosphamide as neoadjuvant therapy for locally advanced breast cancer

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http://www.biomedcentral.com/bmccancer/supplements/7/S1
Background: Aberrant DNA methylation and histone deacetylation participate in cancer development and progression, hence their reversal by inhibitors of DNA methylation and histone deacetylases (HDACs) is undergoing clinical testing in cancer therapy. As epigenetic alterations are common to breast cancer, in this proof-of-concept study, the demethylating hydralazine plus the HDACs inhibitor magnesium valproate were added to neoadjuvant doxorubicin and cyclophosphamide in locally advanced breast cancer to assess their safety and biological efficacy.

Materials and methods: Patients were typed for acetylator phenotype and then treated with hydralazine at 182 mg for rapid or 83 mg for slow-acetylators, and magnesium valproate at 30 mg/Kg, starting from day -7 until chemotherapy ended, which consisted in four cycles of doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m², every 21 days. Core needle biopsies were taken from the primary breast tumors at diagnosis and at day 8 of treatment with hydralazine and valproate.

Results: Sixteen patients were included and received treatment as planned. All were evaluated for clinical response and toxicity and 15 for pathological response. Treatment was well-tolerated. The most common toxicity was drowsiness grades 1–2. Five (31%) patients had clinical CR and eight (50%) PR for an ORR of 81%. No one progressed. One out of 15 operated patients (6.6%) had pathological CR and 70% had residual disease <3 cm. There was a statistically significant decrease in global 5⁰C content and HDAC activity. Hydralazine and magnesium valproate up and down-regulated at least 3-fold, 1091 and 89 genes respectively. Among up-regulated genes there were several tumor suppressor genes including p53.

Conclusion: Hydralazine and magnesium valproate produce DNA demethylation, HDAC inhibition and gene reactivation in the primary tumors. This treatment associated with doxorubicin and cyclophosphamide is safe, well-tolerated and seems to increase the efficacy of chemotherapy. A randomized phase III study is ongoing to support the efficacy of the so called epigenetic or transcriptional cancer therapy.

A24
Pericentromeric demethylation and chromosomal instability induced by chemicals
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Background: Chromosomal instability, aneuploidy in particular, plays an important role in the initiation, progression and aggressiveness of cancer cells. However, the mechanisms implicated in the formation of aneuploid cells are still not fully understood. DNA methylation is critical for condensation of chromatin and for determination of patterns of genetic expression in somatic cells. Pericentromeric heterochromatin form highly methylated chromosome regions, which sometimes are altered inducing different forms of chromosomal instability, including ruptures, centromere decondensation, formation of isochromosomes and other chromosomal aberrations. However, the role of pericentromeric heterochromatin methylation in the formation of aneuploid cells and the mechanisms implicated in this alteration are not known. In this work we evaluated the role of pericentromeric methylation in the formation of aneuploid cells induced by chemical substances.

Materials and methods: Whole blood lymphocytes were cultivated and exposed to 5-azacytidine (10 µM) during 24, 48 and 72 h. Formation of micronuclei (MN), patterns of methylation of metaphasic chromosomes, fluorescent in situ hybridization, and DNA methylation using MSP (methylation-specific PCR) technique after bisulfite treatment, were analyzed on every period of study.

Results: 5-azacytidine induced MN formation, being more evident at 72 h of treatment. A high proportion of MN was positive to chromosome 1, a chromosome with a high degree of pericentromeric chromatin methylation. We found a progressive loss of pericentromeric methylation of chromosomes 1, 9 and 16 by immunodetection. This loss of methylation was corroborated by MSP, which showed intense demethylation of non-CpG cytosines.

Conclusion: This would be the first report of association between chromosomal instability and pericentromeric demethylation induced by chemical substances, especially in non-CpG cytosines.

A25
The effects of DNA methylation and histone deacetylase inhibitors upon the human papillomavirus early genes expression in cervical cancer. An in vitro and clinical study
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BMC Cancer 2007, 7(Suppl 1):A25

Background: Epigenetic aberrations such as alterations in DNA methylation are a common hallmark of cancer. HPV genome methylation profiling in normal, precursor, and invasive lesion smears has shown that as lesion severity increases, there is progressive hypomethylation on the LCR and E6 gene regions, suggesting that neoplastic transformation can be suppressed by gene hypermethylation, whereas hypomethylation accompanies or causes cervical cancer progression. Because of that, some are argued on caution against the use of epigenetic therapy for HPV-related malignancies as it may act as a tumor promoter by enhancing the expression of HPV oncoproteins. To address this issue, herein we analyzed the effects of DNA methylation and histone deacetylase inhibitors upon the human papillomavirus early genes expression in cervical cancer cell lines and patients.

Methods: CasKi, HeLa, CaLo, SiHa cell lines were studied. Cell proliferation was assayed by MTT assay. E6/E7 expression by RT-PCR, chromatin immunoprecipitation by ChiP and methylation profile by PCR after McBC digestion. Clinical
samples were taken from clinical studies performed with hydralazine, valproate and both (BMC2005, Mol Cancer 2005, in preparation). P53 expression and p53/E6 interaction were analyzed by western blot and immunoprecipitation assays.

**Results:** Our results demonstrate that hydralazine and valproate induce growth inhibition in cervical cancer cells without causing significant changes in the expression level of E6/E7 transcript. Likewise, chromatin immunoprecipitation assays demonstrate that hydralazine and valproate induced no major changes in the acetylation status of H4 at the LCR of the HPV. The lack of significant changes at the expression levels of viral E6/E7 viral oncogenes occurs despite epigenetic drugs induced some degree of hypomethylation at the viral LCR. E6/E7 expression changes were minor and heterogenous in the posttreatment biopsies of patients treated with hydralazine, valproate or both. On the contrary, hydralazine and valproate induce a strong increase in p53 at the protein level which resulted from p53 protein acetylation which protects its degradation by E6 leading to transactivation of p53 targets such as the pro-apoptotic gene bax.

**Conclusion:** Hydralazine and valproate treatment not only fail to increase HPV E6/E7 viral oncoprotein expresion but leads to accumulation of p53 levels by its acetylation which increases the transactivation function of p53. These data suggest that hydralazine and valproate may increase the efficacy of current cervical cancer treatments.

**A26 Analysis of the methylation status of HPV DNA in human cell lines**

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BMC Cancer 2007, 7(Suppl 1):A26

**Background:** DNA methylation is an important epigenetic process that regulates gene expression mainly through its effect on chromatin conformation. It involves the stable maintenance of methylated cytosines at CpG dinucleotides (meCpGs) which in turn can regulate gene expression by two mechanisms: by direct interference with transcription factors binding to their target sequences, or by binding MeCP2 proteins, which recognize methylated DNA and recruit histone deacetylases, resulting in a highly compact chromatin structure. Human Papillomavirus (HPV) E2 protein controls various viral processes, including gene transcription and DNA replication. These activities rely upon its ability to bind as an homodimer to its target sequences (5'-ACCGN4CGGT-3') in the viral DNA. Since these sequences contain CpG dinucleotides, they are potential targets for DNA methylation, and, in fact, it has been demonstrated that E2's ability to bind to its cognate sequence is inhibited by methylation. Different studies have shown that the methylation patterns of HPV DNA, in the long control region (LCR) and the 3' region of the L1 gene, are heterogeneous in human cell lines and clinical samples. The objective of this study was to determine the methylation status of HPV type 18 and 16 DNA in different human-derived cell lines.

**Materials and methods:** DNA from HeLa, ViPa and CaLo cell lines (with integrated HPV type 18 DNA) was extracted and modified with sodium bisulfite. The 5' region of the L1 gene, the complete LCR (divided in three regions) and the 5' region of the E6 gene, were amplified using specific primers designed for modified DNA. These PCR fragments were cloned in TOPO A vector and 10 clones from each cell line were sequenced for analysis.

**Results:** DNA methylation patterns observed in three different cell lines containing HPV type 18 DNA showed great similarity. No methylation of CpG dinucleotides was observed in the complete LCR and the 5' region of the E6 gene in CaLo cell line. Similarly, the enhancer and promoter regions within the LCR, and the 5' region of E6 were unmethylated in HeLa and ViPa cell lines. However, the 5' region of the L1 gene, although mostly hypermethylated in HeLa and CaLo, exhibited an heterogeneous pattern in ViPa cells. Interestingly, the E6 at position 7318 (within the 5' region of the LCR) was consistently found methylated in two cell lines (HeLa and ViPa), as opposed to CaLo where it was found unmethylated.

**Conclusion:** The methylation patterns of HPV 18 DNA in these three cell lines are very similar, with the LCR generally unmethylated. The heterogeneity of the methylation patterns in the 5' region of the L1 gene reported in previous studies was confirmed in the present work. Further studies are needed in order to determine if these patterns are consistent in tumor samples, and how they correlate with various stages of the carcinogenic process and the viral life cycle.

Further analysis using methylation-specific and Headloop suppression PCRwill be useful to establish the CpG methylation patterns of the viral genome in different types of lesions (low and high grade) and during different stages of the viral life cycle.

**A27 A phase II study of epigenetic therapy with hydralazine and magnesium valproate to overcome chemotherapy resistance in refractory solid tumors**

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BMC Cancer 2007, 7(Suppl 1):A27

**Background:** Chemotherapy resistance, either innate or acquired requires for its development, expression changes on a large number of genes therefore, it has been hypothesized that epigenetic-mediated changes could be the driving force for chemotherapy resistance. Abrerrant DNA methylation and histone deacetylation are the main epigenetic alterations in cancer, hence we hypothesized that hydralazine, a DNA
methylation inhibitor and valproate, a histone deacetylase inhibitor may overcome resistance in refractory solid tumors.

**Methodology:** This is a MinExpSize 2-stage phase II open-label, single- arm study in which patients with advanced solid tumors who were progressing at the second or third cycle of first, second, third, fourth or fifth line of palliative chemotherapy were included. Patients were typed for acetylator phenotype and then treated with hydralazine at a daily dose of 182 mg for rapid or 83 mg for slow-acetylators, and magnesium valproate at 40 mg/kg. Both drugs were started at day -7 and continued until chemotherapy ended. Chemotherapy consisted of the same pre-study protocol regimen on which patients progressed. Response and toxicity were evaluated.

**Main findings:** From a total of 27 patients that signed informed consent, 17 patients were evaluable for toxicity and 15 patients for response. The primary sites in the 15 evaluable patients were cervix (3), breast (3), lung (1), testis (1) and ovarian (7) carcinomas. A clinical benefit (complete response, partial response or disease stabilization) was observed in 12 (80%) patients, 4 partial responses and 8 stable disease. The treatment was well tolerated even though the studied population was heavily pretreated. The most significant toxicity was hematological. Grade 3 and 4 toxicities were anemia, neutropenia, leukopenia and thrombocytopenia in 23.5%, 41.1%, 47% and 35.2% respectively. The main non-hematological toxicity was drowsiness, mostly grade 2. The median survival was 6 months.

**Conclusion:** Hydralazine and magnesium valproate are able to overcome chemotherapy resistance in a heavily treated patient population. The obtaining of partial responses and disease stabilization regardless of the tumor type and chemotherapy schedule strongly supports the concept that epigenetic agents can erase the epigenetic mark associated with the chemoresistant phenotype of cancer cells. These results are in line with our observations in breast and cervical cancer patients that hydralazine and valproate can up-regulate a huge number of tumor suppressor genes. Thus, epigenetic therapy with hydralazine and valproate can be added to the armamentarium for cancer therapy.

**A28**

**Epigenetic therapy with hydralazine and valproate associated to cisplatin chemoradiation in FIGO stage IIIB. A phase II study**

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**BMC Cancer 2007, 7(Suppl 1):A28**

**Background:** Standard chemoradiation with cisplatin has improved the results of treatment, however, newer therapeutic modalities are needed. DNA demethylating and histone deacetylase inhibitors have shown radiosensitizing effects as well as potentiation of chemotherapy drugs. This study was set to evaluate hydralazine and valproate as epigenetic therapy added to chemoradiation with cisplatin in cervical cancer.

**Materials and methods:** Eligibility criteria included untreated disease, histological diagnosis and adequate bone marrow, hepatic and liver function. Patients were typed for acetylator phenotype and then oral hydralazine at 182 mg/day or 83 mg/day for rapid and slow-acetylators respectively. Oral magnesium valproate was used at 30 mg/kg/day. Treatment started 7 days before commencing chemoradiation. Chemoradiation consisted on EBRT 50 Gy in 2G fractions plus cisplatin at 40 mg/m² weekly × 6. Brachytherapy was scheduled after EBRT. Response, toxicity and survival were evaluated as well as the biological effects of hydralazine and valproate in blood and primary tumor samples.

**Results:** Twenty one patients were included. Mean age was 50.4 years (range: 28–69 y). Overall, 85% of patients completed both phases, external beam and intracavitary therapy. Three patients did not receive brachytherapy: two abandoned treatment during EBRT and one died after the first cycle of chemotherapy. Mean + SD dose administered to point A was 84.6 ± 2.2 (range: 79.6 – 87 for point A). Median number of cisplatin cycles administered was five (range 1–6). The 18 patients evaluable for response achieved complete clinical response after EBRT. The most frequent grade 3/4 hematological toxicity was neutropenia (45%), followed by thrombocytopenia (10%) and anemia (10%). Non-hematological toxicity was mild in most cases. Three out of 18 cases have relapsed (16.6%): one local, one had local/systemic relapse and one systemic, at a median follow-up of 11 months (range: 1 – 13.4 m). The hydralazine/valproate-induced changes in the expression of genes analyzed by microarrays will be presented in the meeting.

**Conclusion:** Epigenetic therapy with hydralazine and valproate associated to chemoradiation in cervical cancer is well-tolerated and seems effective as all evaluable patients achieved clinical complete response during the external radiation.

**A29**

**Lung cancer mortality in Mexico**

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**BMC Cancer 2007, 7(Suppl 1):A29**

**Background:** Lung cancer (LC) is the cause of the highest cancer-related rate in the world for both sexes (1,179,000 deaths). In Mexico, the raw mortality rate for LC was 5.01 per 10⁵ inhabitants in 1979. Tobacco is its most important risk factor. The purpose of this study was to analyze lung cancer...
mortality in Mexico, in each of the Mexican Republic States, from 1998 to 2004.

Materials and methods: Data was obtained from the National Institute of Statistics, Geography and Informatics (INEGI) for deaths by LC from 1998–2004. The annual mortality mean rate (AMMR) was established for each of the 32 Mexican Republic States. The “world standard population” was used. AMMR was standardized by age (SRA) through direct method, and the standard error was calculated by Poisson approximation with a 95% reliability interval. Excess of mortality risk was calculated from standardized mortality ratios (SMR) of SRA for each state, using the national rate as reference, with 95% and 99% reliability intervals. SPSS, version 10.0 for Windows, was used.

Results: From 1998 to 2004, 397,400 deaths by malign tumors were registered, out of which 45,578 (11.5%) were due to LC.

Conclusion: The highest mortality rates by LC were seen in the north of Mexico for both sexes, restricted to women in the central area. Although tobacco is the main risk factor for LC, other factors, such as environmental pollution or exposure to toxic substances, may be associated with this cancer. The cities with the highest rate of air pollution are found in states in northern and central Mexico (according to monitoring from 1994 to 2001). According to the Histopathologic Register of Malign Tumors (HRMT), years potentially lost by LC for both sexes were 258,550 for men and 133,315 for women, or a total of 391,865. Studies focused on characterizing and measuring polluting agents will be the first step to establish any contribution to lung cancer. Source: INEGI, 1998–2004 * Age Ratio Standard.

A30
PM10 from Mexico City (MC) induce senescence-like phenotype and ATM, γH2A.X and p53 activation linked to oxidative stress

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BMC Cancer 2007, 7(Suppl 1):A30

Background: Urban air particulate matter (PM) relates to adverse health effects including lung cancer. Previous work from our group demonstrated that the PM10 produce DNA damage, although the mechanisms involved are not known. DNA double-strand breaks (DSBs) are the most deleterious DNA lesions. DSBs arise from exogenous agents such as metals and hydrocarbons, or endogenous agents, such as reactive oxygen species (ROS). We explore the cellular response that senses DNA damage after cell exposure to PM10, evaluating markers such as phosphorylation of ATM (ser1981), γH2A.X (ser139) and p53 (ser15), and senescence-like induction, as well as the identification of ROS co-participation in the response.

Materials and methods: A549 cells were exposed 24 h to 10 μg/cm² of PM10 from an urban-commercial zone from MC. ROS induction was evaluated by DCFH-DA assay. Senescence was determined by the β-galactosidase assay. ATM, γH2A.X and p53 activation and their co-localization on DNA damage foci were done by immunofluorescence. Experiments in the presence of Trolox as an OH· scavenger were done in parallel.

Results: Senescence-like was induced by PM10. ATM, H2A.X and p53 were activated by PM10 and co-localize in DNA damage foci. Both cellular responses were prevented by Trolox.

Conclusion: Cells exposed to PM10 had a cellular response directly involved in sensing DSBs. There was a strong correlation with the presence of ROS that suggests the participation of oxidative stress in the deleterious effects induced by PM10. Senescence-like phenotype and ATM, γH2A.X and p53 activation conform an early cellular response that could evolve into the signaling and recruitment of repair factors, and the activation of enzymes of cell cycle checkpoints in cells exposed to PM10. Further studies must be done to confirm that.

Acknowledgements
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A31
Effect of the all-trans retinoic acid on neural growth factor serum levels (NGF) and chemotherapy induced neuropathy in patients with advanced lung cancer

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BMC Cancer 2007, 7(Suppl 1):A31

Background: Peripheral neuropathy is a common adverse event in patients treated with chemotherapy. The development of peripheral neuropathy observed in chemotherapy is similar to the diabetic patients where there is reduction of the expression and transport of Neural Growth Factor (NGF). Retinoic acid (RA) regulates genes related to cellular proliferation and the expression of NGF. Phase 1 and in vitro studies suggested that retinoic acid may synergize the therapeutic effect of chemotherapy, in particular paclitaxel and cisplatin. We conducted a phase II randomized double blind clinical trial to determine the effect of all-trans retinoic acid on the development of chemotherapy induced neuropathy based on the combination of paclitaxel and cisplatin in patients with advanced lung cancer; in addition we analyzed the therapeutic effect of retinoid with chemotherapy.

Methods: Thirty four patients with advanced Non Small Cell Lung Cancer (NSCLC) were included in this study to receive chemotherapy based on the combination of paclitaxel 175 mg/m² and cisplatin 80 mg/m² every three weeks. The patients’ characteristics were median age of 58.9 ± 12 years in the control group and 58.4 ± 12 in the RA (p = 0.914). Prior to chemotherapy and after two cycles of treatment neurophysiology studies, clinical examination and serum NGF levels were performed. The patients were randomized to receive all-trans retinoic acid 20 mg/day or placebo 1 week before treatment and after completing 2 cycles.

Results: Grade I and II neuropathy was increased in the control group after 2 cycles (2C) of chemotherapy (66% vs.
A32
The diagnostic utility of immunohistochemical and electronic microscopy in distinguishing between pleural mesothelioma and adenocarcinoma
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BMC Cancer 2007, 7(Suppl 1):A32

Background: The mesothelioma is a mesodermic tumor localized in the pleura in 70–90% of the cases, with an incidence of 2 × 100,000 habitants per year in women and 10–30 × 100,000 habitants per year in men. The diagnosis is realized by cytology, guided biopsy by computed tomography and electronic microscopy which is the gold standard where we can observe several nodes in the visceral and parietal pleura where are produced effusion pleural. The objective of this trial was to realize the immunohistochemical and structural study of the effusion pleural in patients with lung tumors in which we suspect the presence of mesothelioma versus adenocarcinoma to show an adequate diagnosis method.

Materials and methods: The material utilized in this trial was obtained in the cytopathology and pathology department of the respiratory disease institute. We studied thirty effusion pleural fluids of ten patients with the diagnosis of mesothelioma and ten patients with the diagnosis of adenocarcinoma during the period between August and November. We realized the determination of calretinina and keratin (CK) and the ultrastructural study with the electronic microscopy.

Results: The patients with mesothelioma diagnosis were calretinina positive which confirms the histological diagnosis. We observed in the electronic microscopy profusion of microvilli in the surface cells. The adenocarcinoma fluids were CK positive and negative for the rest of the test.

Conclusion: We demonstrate that we can distinguish between pleural mesothelioma and adenocarcinoma by immunohistochemical test and electronic microscopy, these diagnosis methods may be an option for patients in whom are contraindicated the biopsy realization, besides they may be cheaper and quicker than the biopsy.

A33
Clinical and pathologic factors associated with development of hepatocellular carcinoma in patients with hepatitis virus-related cirrhosis: a long-term follow-up study
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BMC Cancer 2007, 7(Suppl 1):A33

Background: Hepatocellular carcinoma (HCC) represents >90% of primary liver neoplasms and develops mainly in patients with liver cirrhosis. Risk factor identification for development of HCC in patients with cirrhosis possesses great clinical relevance due to its high incidence and poor prognosis when detected at advanced stages. The aim of our study was to identify HCC development-associated risk factors in a cohort of patients with hepatitis virus-related chronic liver disease and cirrhosis.

Materials and methods: Patients with a diagnosis of hepatitis virus-related cirrhosis from January 1980 to January 2000 were included. Patients were followed with abdominal ultrasound and determination of alpha-fetoprotein levels, physical examination, and routine biochemical tests every 3–6 months. The endpoint in this study was defined as development of HCC. Liver histology was evaluated according to the French METAVIR Cooperative Study Group (METAVIR) score.

Results: Two hundred and eighty two patients met the inclusion criteria: the majority of these (86%) had a serologic diagnosis of hepatitis C virus, and only 14% had hepatitis B virus at the time of diagnosis of cirrhosis, while 56 and 37% were classified as Child A and B, respectively, and only 7% as Child C. Histological activity was mild in 59% of patients, and moderate and severe in 41%. Mean annual incidence was 1.87%, and 22 and 35% of patients developed HCC at 10 and 15 years of follow-up, respectively. Diagnosis of HCC was made by histopathology in 37% and by tumoral lesion-associated alpha-fetoprotein elevation confirmed by imaging studies in 63%. In multivariate analysis, we found three variables associated with HCC: platelet count <105 × 10^3/mm^3, and alpha-fetoprotein >5 ng/mL (see Table 1). We

Table 1 (abstract A33) Variables with independent predictive value for HCC in the multivariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>Coefficients (log rank)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>3.7 (1.2–11)</td>
<td>1.3</td>
<td>0.025</td>
</tr>
<tr>
<td>Alpha-fetoprotein</td>
<td>5.41 (1.86–15.7)</td>
<td>1.23</td>
<td>0.02</td>
</tr>
<tr>
<td>Histological activity</td>
<td>7.6 (1.7–33)</td>
<td>2.03</td>
<td>0.007</td>
</tr>
</tbody>
</table>
divided patients into two groups according to regression coefficient: low and high-risk; patients assigned to the low-risk group showed 5-, 10-, and 15-year HCC incidences of 3.4, 6.4, and 6.4%, respectively, in contrast to patients from the high-risk group, who showed incidences of 17.8, 33.5, and 56.8%, respectively.

**Conclusion**: We found three HCC-associated variables: histological activity; platelet count and alpha-fetoprotein levels. Patients with high risk for developing hepatocellular carcinoma must be considered candidates for closer follow-up.

**A34**

**Magnification endoscopy to detect dysplastic aberrant crypt foci in Mexican patients with high risk for colorectal cancer**

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**BMC Cancer 2007, 7(Suppl 1):A34**

**Background**: The sequence of adenoma-cancer has been broadly documented, being accepted as the aberrant crypt-adenoma concept. These lesions are detected early in colonic carcinogenesis, but only a minority presents dysplasia. The objectives of the study are: 1) to identify and measure FAC in patients with different levels of risk to develop colorectal cancer; 2) to correlate FAC with magnification endoscopy and histopathological study, and 3) to correlate FAC histopathologically confirmed with over-expression of Ki-67 and p53.

**Materials and methods**: We made a cases-controlled study at the endoscopy service of the Instituto Nacional de Cancerología-Mexico from March to June 2006. We selected patients with different indications for colonoscopy according to the potential risk for colorectal cancer. We made chromoendoscopy with magnification in the last 10 cm of the rectum and we took biopsies on the FAC sites; the samples were analyzed for a blind-test pathologist and we realized immunohistochemistry for p53 and Ki-67.

**Results**: We selected 24 patients, 10 male, 14 female, which were separated in groups according to the risk:

- Group 1: n = 8, mean age 52.3 years-old, ED 15.61. The most common indications for colonoscopy were chronic diarrhea, anemic syndrome digestive tract bleeding. The mean FAC were 2.5(0–8), in all cases corresponding to Kudo’s types I, II, and III.
- Group 2: n = 16, mean age 45.3 y-o, SD 16.91. Of them 7/16 had CRC at the moment of the study, 7/16 just operated for CRC and 2/16 with familiar adenomatous polyposis (FAP). The mean FAC were 6.25(0–22) that shows a statistical difference p < 0.001 with the mild risk group. In all cases corresponded to Kudo’s patterns II, and III. The sensitivity and specificity of chromoendoscopy with magnification to detect FAC were 83% and 56%, respectively (p =< 0.00021), predictive positive value 31, predictive negative value 98. The observed concordance for presence or absence of FAC was 64%. The frequency of FCA-D for group 1 was 1.35%, group 2 18% (p < 0.00021). With respect to sporadic CRC and FAP-related CRC were 11.7% and 6.3%. The high risk patients with FAC had an odds-ratio (OR) 4.91, CI 95% (2.53, 9.74) (p =< 0.0000001). On group 2 with FCA-D the OR 8.58, CI 95% (2.82, 36.2) (p =< 0.000051). The over-expression of p53 was detected in only 6% of patients with FAC-D and high risk (p = 0.58). Ki-67 was positive in 100% of FAD-D, FAC-H and FAC NH-ND.

**Conclusion**: The frequency and intensity of FAC are higher in high risk population for CRC. The presences of FAC-D increase the risk 8-times more than in medium population. Chromoscopy with magnification has a low specificity and high sensitivity to detect FAC. The Ki-67 over-expression in FAC is present in almost all the cases; disregard to p53 which is over-expressed in a minority of FAC-D, which means deorganized hyperproliferation and that probably p53 is not present on FAC of sporadic CRC patients.

**A35**

**Prediction of morbidity after gastrectomy for gastric adenocarcinoma using logistic regression analysis**

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**BMC Cancer 2007, 7(Suppl 1):A35**

**Background**: Surgical morbidity after gastrectomy remains high in some institutions. In a recent report, we reported a simple method to predict the probability of complications after gastrectomy. However, we did not stratify the severity of surgical morbidity. Therefore, the aim of this study was increase the sample size, to define the major determinants of surgical morbidity and to develop a computer model to predict the probability of complications after gastrectomy for GC.

**Methods**: A retrospective cohort of patients with GC who underwent gastrectomy in a 18-year period was studied. Analysis of those factors associated to surgical morbidity and mortality were performed using logistic regression methodology.

**Results**: A total of 331 patients were included, 161 females and 170 males (mean age 56.5 years, SD 13.1). Surgical morbidity was recorded in 126 (38%) patients. Surgical morbidity requiring a medical or surgical intervention was reported in 81 cases (24.4%), including 21 cases (6.3%) of operative mortality. Serum albumin, age more than 40 years, male gender, total gastrectomy and operative bleeding were significant determinants of surgical morbidity. Estimators of this model are shown in Table 1

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>CI 95%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total gastrectomy</td>
<td>3.21</td>
<td>1.17 - 8.86</td>
<td>0.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.73</td>
<td>1.09 - 2.72</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum albumin &lt; 3.5 g/L</td>
<td>3.43</td>
<td>1.16 - 10.32</td>
<td>0.02</td>
</tr>
<tr>
<td>Total gastrectomy</td>
<td>3.21</td>
<td>1.17 - 8.86</td>
<td>0.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.73</td>
<td>1.09 - 2.72</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum albumin &lt; 3.5 g/L</td>
<td>3.43</td>
<td>1.16 - 10.32</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Conclusion**: The event of surgical mortality should be regarded as a complex phenomenon associated with the interaction of various events. We are proposing to use a simple
Table 1 (abstract A35) Multivariate analysis of factors associated to the event of surgical morbidity (p = 0.00001)

<table>
<thead>
<tr>
<th>Factor</th>
<th>S.E.</th>
<th>p</th>
<th>(exp)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Albumin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.9 g/dL or less</td>
<td>0.772</td>
<td>0.307</td>
<td>0.034</td>
<td>1.19–3.95</td>
</tr>
<tr>
<td>3 to 3.49 g/dL</td>
<td>0.063</td>
<td>0.309</td>
<td>0.012</td>
<td>1.655</td>
</tr>
<tr>
<td>3.5 g/dL or more</td>
<td>-</td>
<td>-</td>
<td>0.84</td>
<td>0.58–1.95</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>subtotal</td>
<td>0.956</td>
<td>0.255</td>
<td>0.0001</td>
<td>2.6</td>
</tr>
<tr>
<td>total</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39 or less</td>
<td>0.847</td>
<td>0.394</td>
<td>0.032</td>
<td>2.333</td>
</tr>
<tr>
<td>more than 40</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>0.447</td>
<td>0.245</td>
<td>0.069</td>
<td>1.563</td>
</tr>
<tr>
<td>Male</td>
<td>0.001</td>
<td>0.0001</td>
<td>0.031</td>
<td>1.001</td>
</tr>
<tr>
<td>Surgical bleeding (ml)</td>
<td>0.966</td>
<td>0.25</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

S.E. = standard error; p = probability value of the odds ratio; (exp) = beta exponent or odds ratio; CI = confidence interval

A36
Adaptation of the questionnaire EORTC QLQ-STO22 to measure quality of life from Mexican patients with gastric carcinoma
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BMC Cancer 2007, 7(Suppl 1):A36

Background: The gastric cancer (GC) is the most common gastrointestinal tumor and it is the second cause of death in Mexico. Recently new agents chemotherapeutic, combinations and multimodal treatments have been developed. Traditionally your outcomes assessment is for clinical answers, tumor size, toxicity, survival free of disease or global survival. However, recently attention has been called to the assessment of quality of life, which OMS defines as the state of complete well-being, not only physique but also emotional and social. The quality of life implies the global evaluation that a person makes of his life with basis in his personal (demographic, value, personality, emotions, interpersonal relationships) characteristics and in external factors, provoked for illnesses and the treatment, includes the spheres physical, psychological and social health seen as different areas that are influenced by experiences, beliefs, expectations and people's perceptions. Each one can be measured in two dimensions: an objective evaluation and the individual's subjective perception. This last one can explain that two people with similar state of health can have very different quality of life. The assessment of the Quality of life has had a wide development, through generic questionnaires designed for patient with cancer, the EORTC has developed a module for patient with gastric cancer that evaluates the quality of life with related to the disfagia, feeding restrictions, reflux, and abdominal pain, as well as specific symptoms of the chemotherapy or radiotherapy the questionnaire QLQ STO-22. The objective of this study was to adapt and validate of the instrument EORTC QLQ-STO22 in a Mexican population from Instituto Nacional de Cancerologia (INCan).

Materials and methods: Sample: Ten patients with Gastic Cancer, the mean age is 54.5 years old (35 to 73 years). Seven were female and three men. Their occupations were: one merchant and six are devoted at the home. All three male patients were car drivers. All patients were Mexican, and Mexican-born and their maternal language was Mexican Spanish, and all can read and write Mexican Spanish. Five patients were married, one was separate, one was bachelor, one was free union and two were widows.

Procedure: The process of adaptation follow the norms pointed out by the European Organization for the Study and Treatment of Cancer (EORTC), which has been contacted with this organization and it is had their supervision and authorization.
2. Content validity by a group of the experts in Gastroenterology and psychooncology.
3. Test pilot in a described sample. Each patient answered the questionnaire EORTC QLQ STO-22 and immediately they were interviewed to search questions difficult, confusion, offensive, words difficult to understand.
4. Convenient adjustments to the Instrument taking into account the frequency of difficulties, and patients' suggestions.

Results: Pilot Testing: The items 32, 33, 34, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51 and 52, were not associated with any difficult to answer, confusing, difficult to understand, upsetting, neither offensive, nor any patient asked the question in a different way.

Question 31. Five patients did not understand what the word “sólidos” (solids) means or the expression “alimentos sólidos” (solid food), two patients proposed examples of solid food as “¿Ha tenido problemas con al comer carne, pan, tortilla?” (Had you have trouble to eat meat, bread, tortilla?). The research team suggests changing the expression “alimentos duros” (hard food) for the alternative expression...
“alimentos sólidos” (solid food). Therefore, the definite form of the question is: Have you had problems eating hard food? This is the only question that requires modification. Question 49 The question 49 provoked a reaction of embarrassment in some patients; however, the research team decided this should remain unchanged.

Conclusion: In Mexico, there is a lack of instruments to measure quality of life in GC, standardized and adapted to the Mexican culture that allow an appropriate assessment of the quality of life, and serve as additional tools of the clinical: the patient's integral evaluation with GC and the conduction of clinical trials. For this reason, it is required of translation, adaptation and validation of instruments of common use in the rest of the world, with the purpose of evaluating the impact of the oncological treatments for the GC from the patient's perspective in the physical, psychological, and social area. At the same time to help in the physician and patient's decision about the treatments and their administration, to identify the patient's needs, and the way that support services can collaborate during the treatment process.

A37 Major complications following exenteration in cases of pelvic malignancy: an 18-year experience
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BMC Cancer 2007, 7(Suppl 1):A37

Background: Despite radical surgery, up to 33% of patients with rectal cancer will develop locoregional relapse. The management of these patients is particularly challenging. Surgery is the mainstay of treatment for those with a mobile recurrence. However, the majority of patients develop recurrence involving the pelvic wall. In these patients, multimodality therapy including radical surgery and intraoperative radiotherapy have been reported with 5-year survival of up to 31% and local control rates of 50–71%. The most important factor for obtaining long-term local control and survival is R0 resection. Objective: To analyze the major complications after exenteration of colorectal and anal malignancies.

Materials and methods: Fifty nine patients with colorectal and canal anal malignancies underwent pelvic exenteration (PE) between 1984 and 2002. 48 patients underwent posterior pelvic exenteration PPE, 8 total pelvic exenteration and 3 posterior supralevator exenteration were performed.

Results: Major complications in the operative field involving the urinary tract infection or the wound dehiscence occurred in 29 patients (49.15%). The mortality rate was 3.3%. Major complications often occurred in advanced primary colorectal cancer affecting those with recurrent malignancies.

Conclusion: PE is more beneficial to patients with colorectal and canal anal cancer recurrence than to those with recurrent cancer. Knowledge of the inherent complications and morbidity of PE is essential.

A38 Pancreatoduodenectomy, fifteen years of experience
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BMC Cancer 2007, 7(Suppl 1):A38

Background: Pancreatoduodenectomy or Whipple’s procedure is still the treatment of choice for periampullary and head of pancreas tumors, as well as distal coledochal neoplasms. The effectiveness of this procedure is related to the clinical stage of the disease, the conditions of the patient in addition to the experience and the skill of the surgical institutional equipment. The objective was to evaluate morbidity and mortality after the accomplishment of Whipple’s technique.

Materials and methods: A retrospective analysis was performed with the database of patients submitted to Whipple’s procedure from January 1990 to May 2006 in the Instituto Nacional de Cancerología.

Results: From 69 patients submitted to surgery, 35 were women (%) and 34 men (%). The average age at the time of diagnosis was 52.8 years (rank 18–73). Out of 69 patients 59 had a neoplasm of the biliary three, finding 23 pancreatic tumors (%), 25 of Vater’s ampulla (37.5%) 8 of the duodenum (12.5%) and 3 coledochal tumors (%). We also found two patients with neuroendocrine tumors, four patients with Papillary and cystic tumors of the pancreas, one patient with an adenoma of Vater’s ampulla and three patients with chronic pancreatitis. In 7 patients pylorus preservation surgery was carried out (10.93%), in the rest classic Whipple was performed (87.5%). Average surgery time was 7 hours and 20 min, with an average bleeding time of 1293 ml (200–6000). The average hospital stay was 21 days, only 3 patients did not require ICU. Fourteen patients developed abdominal sepsis (18.2%), thirteen suffered respiratory complications (noseosomical pneumonia, pulmonary embolism) (20.3%), nine patients presented biliary fistula (14.06%) and eight more an intestinal fistula (12.5%). Twenty patients received adjuvant treatment for the neoplasm in turn (31.25%). Of 18 patients who developed recurrence of the disease (28.12%), 13 of which was alive without evidence of disease. We splitted the series into two different periods of 7.5 years each.
During the first period (January 1990–June 1997) 18 classic Whipple’s surgery and one pylorus preservation surgery were performed; we had a morbidity of 52.63% and a mortality of 31.57% (6 patients). During the second period (July 1997–September of the 2005) 44 patients were submitted to classic Whipple and 6 patients to pylorus preservation surgery; with a morbidity of 35.3% (16 patients) and a mortality of 8%.

Conclusion: Pancreatoduodenectomy is the election procedure for patients with pancreatobiliary tumors. In spite of the advances and variations to the technique, it remains a hazardous procedure. Surgery outcome is importantly related with the greater training and experience of the surgical team as we observed in our series.

A39 Polymorphisms of the thiopurine methyl transferase gene in healthy and acute lymphoblastic leukemia mestizos

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BMC Cancer 2007, 7(Suppl 1):A39

Background: Polymorphisms at the thiopurine S-methyltransferase coding gene (TPMT) determine enzyme activity and as a consequence the development of toxicity to thiopurines.

Materials and methods: A total of 108 DNA samples from volunteer donors and 39 from patients with acute lymphoblastic leukemia (ALL) were analyzed. Genomic DNA from peripheral blood leukocytes was isolated by standard methods. Known (wild type and polymorphic) sequenced PCR fragments of the TPMT gene were used as controls. TPMT gene fragments were amplified for exons 5, 7 and 10. PCR products were then analyzed by denaturating high performance liquid chromatography (DHPLC) for the most frequent TPMT alleles, according to the method developed by Schaeffeler et al. on an analysis system from Transgenomics.

Results: No elution profiles at the DHPLC analysis were different to those already reported. The frequency of gene polymorphisms was 53.7% in healthy and 38.4% in the ALL population. However, only 17.6% of all polymorphisms found are considered as functional, being the most frequent the *3A (n = 13, 8.8%), followed by *3B (n = 5, 3.47%), *3C (n = 5, 4.6%) and *2 (n = 3, 2.7%).

Conclusion: DHPLC is a highly sensitive, rapid and efficient method to identify relevant TPMT gene mutations which allows the screening for genetic variability in the TPMT gene. This is the first analysis of the polymorphisms at this gene in a Mestizos population. The frequency of known silent polymorphisms was higher than those reported in other regions worldwide, but although the frequency of functional polymorphism in healthy population is within the range found in other reports, the frequency of such polymorphism was higher in the patients. All together, the routine typing of TMPT polymorphisms in the patients with ALL is being set in our Institution.

Acknowledgements

The donation of DNA’s controls from Dr. Margaret Fischer-Bosch Institute of Clinical Pharmacology, is greatly appreciated. This project was supported by CONACYT (SALUD 2004-01-05/A-I), and Psicofarma S.A. De C.V., Mexico.

A40 Survival among AIDS patients with and without non-Hodgkin’s lymphoma, and NHL-HIV-negative patients

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BMC Cancer 2007, 7(Suppl 1):A40

Background: The risk of non Hodgkin’s lymphoma (NHL) is 150–250 times higher among HIV infected patients. In developed countries with open access to highly active antiretroviral therapy (HAART), the prognosis of these patients appears to be impacted positively, and survival in some groups can be similar to non-HIV infected patients. Recent data has shown improved survival among NHL-HIV+ patients receiving standard chemotherapy (QT) HAART, with acceptable range of toxicity.

Objective: To analyze the median survival of patients with AIDS with and without NHL and NHL-HIV negative patients.

Materials and methods: We retrospectively reviewed all medical records of patients with NHL-HIV+ seen from January 1990 to December 2005 at the Instituto Nacional de Cancerología in Mexico City, Mexico. We used as control groups patients with AIDS

| Table 1 (abstract A40) Mean survival for NHL/HIV+, NHL/HIV negative and AIDS groups |
|---------------------------------|----------------|----------------|
| NHL/HIV+ (n = 69) | AIDS (n = 93) | p |
| No-HAART (months ± SD) | 5.01 ± 7.7 (n = 27) | 25.9 ± 25.12 (n = 40) | 0.001 |
| HAART (months ± SD) | 15.75 ± 19.4 (n = 42) | 50 ± 37.9 (n = 53) | <0.0001 |
| Total (months ± SD) | 11.5 ± 16.7 | 39.7 ± 35 | <0.0001 |
| NHL/HIV | | |
| Incomplete chemotherapy (months ± SD) | 4.32 ± 5.5 (n = 40) | 1.84 ± 1.66 (n = 22) | 0.04 |
| Complete chemotherapy (months ± SD) | 21.3 ± 20.26 (n = 29) | 29.07 ± 36.27 (n = 68) | 0.286 |
| Total (months ± SD) | 11.5 ± 16.7 | 22.41 ± 33.61 | 0.01 |
(defining-event non-lymphoma related), and patients with NHL treated as well at our institution, diagnosis made ± 3 years, with same gender and age ± 5 years. We recorded clinical, laboratory and pathology data; survival or follow-up time was calculated from date of diagnosis to death or to the date when the patient was last seen.

Results: Sixty-nine patients were diagnosed with NHL-HIV. AIDS control patients (n = 93) were divided into no-HAART and HAART; and NHL/HIV negative control patients (n = 90) were divided into incomplete (<3 cycles or <100% of total dose), and complete chemotherapy (Table 1).

Conclusion: Survival in patients with AIDS is better than in NHL/HIV+ and NHL/HIV-. The use of HAART has significantly improved the prognosis. Mean survival with the use of a complete chemotherapy regime is similar in patients with NHL and in patients with NHL/HIV+.

A41
Clonal evolution in a patient with CML detected by FISH precedes imatinib treatment failure
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2Hospital Angeles del Pedregal, México, D.F
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BMC Cancer 2007, 7(Suppl 1):A41

Background: Imatinib (IM) inhibits the TK protein from chromosome Philadelphia (Ph). However, less than 10% of IM-treated patients become resistant. Second generation TK inhibitors are on active clinical research aimed to overcome most, but not all, important mutations.

Case report: A 61 year-old male was diagnosed on Sep/98 with CML chronic phase, he was treated with hydroxyurea, interferon and Ara-C. On July/01 the patient was on complete hematological response (CHR), but Ph positive in karyotyping (Ky) and fluorescence in-situ hybridization (FISH), there were not additional abnormalities. Patient began IM treatment, 400 mg/day. After 4 months of treatment, +der(22) was detected, but the patient was still on CHR. On subsequent visits, the patient had an increased frequency of chromosomal abnormalities, and after 2 years he lost CHR, regardless of the increase IM dose and the concomitant use of Ara-C. The patient was included on a dasatinib phase II protocol. 2 weeks after he had a profound cytopenia and 2 months after had CHR. Table 1 shows clinical and hematological and Ky and FISH follow-up.

Conclusion: Additional abnormalities found on Ky and FISH could precede treatment failure. Molecular monitoring is required to guide treatment decisions. The role of second generation TK inhibitors needs to be defined.

A42
Hematopoietic stem cell transplantation in Multiple Myeloma. Experience of the Instituto Nacional de Cancerología, Mexico
Magdalena Bahena-Garcia, Silvia Rivas-Vera, Pedro Sobrevilla-Calvo, Juan Labardini-Mendez, Eduardo Cervera-Ceballos and Ernesto Calderon-Flores
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BMC Cancer 2007, 7(Suppl 1):A42

Background: The failure of conventional therapy to cure multiple myeloma has led investigators to test the effectiveness of high dose chemotherapy and hematopoietic stem cell transplantation. The objective of this study was to determine the mortality and morbidity in patients with multiple myeloma treated with hematopoietic stem cell transplantation at our institution.

Materials and methods: We reviewed the charts of patients with multiple myeloma, who received high dose chemotherapy

<table>
<thead>
<tr>
<th>Sample</th>
<th>Date</th>
<th>Ky</th>
<th>FISH</th>
<th>Treatment &amp; clinical condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jul/01</td>
<td>Only Ph</td>
<td>Only Ph 35%</td>
<td>Began IM 400 mg/d CHR</td>
</tr>
<tr>
<td>2</td>
<td>Nov/01</td>
<td>Ph plus double Ph</td>
<td>Not enough material</td>
<td>IM 400 mg/d CHR</td>
</tr>
<tr>
<td>3</td>
<td>Jan/02</td>
<td>No growth</td>
<td>Only Ph 26%</td>
<td>IM 400 mg/d CHR</td>
</tr>
<tr>
<td>4</td>
<td>Sep/02</td>
<td>Hipodiploid plus Ph</td>
<td>Only Ph 22% Clone BCR amplified without Ph</td>
<td>IM 400 mg/d Leucocytosis</td>
</tr>
<tr>
<td>5</td>
<td>Jun/03</td>
<td>Only Ph</td>
<td>Only Ph = 28% Clone BCR amplified without Ph = 1% Clone ABL and/or BCR amplified with Ph = 28% Clone ABL and/or BCR amplified and double Ph = 51% Clone ABL and BCR amplified with triple Ph = 11% Clone ABL lost with Ph = 5%</td>
<td>IM 600 mg/d</td>
</tr>
<tr>
<td>6</td>
<td>Nov/03</td>
<td>Ph plus lost Y, marker chromosome, trisomy chr 19, double Ph and trisomy chr 8</td>
<td>Only Ph = 4% Clone ABL amplified without Ph = 1% Clone ABL and/or BCR amplified with Ph = 18% Clone ABL and/or BCR amplified with double Ph = 74% Clone ABL and BCR amplified with triple Ph = 1% Trisomy chr 8 = 72%</td>
<td>IM 600 mg + Ara-C</td>
</tr>
<tr>
<td>7</td>
<td>Jul/04</td>
<td>No growth</td>
<td>Only Ph = 44% Clone ABL amplified with Ph = 6% Clone ABL and/or BCR amplified with double Ph = 17%</td>
<td>IM 800 mg/d</td>
</tr>
<tr>
<td>sample</td>
<td>Jan/05</td>
<td></td>
<td>Only Ph = 18%</td>
<td>Began with dasatinib</td>
</tr>
<tr>
<td>8</td>
<td>Dec/05</td>
<td>No growth</td>
<td></td>
<td>Dasatinib</td>
</tr>
</tbody>
</table>
and hematopoietic stem cell transplantation, at the Instituto Nacional de Cancerología from 1991 to March 2006. We recorded the demographic variables, the type of transplant, the conditioning regimen, number of CD34+ cells transfused, number of platelets and red blood cells transfusions, neutropenia and thrombocytopenia duration. We also analyzed the adverse events related to the procedure.

**Results:** We did 18 peripheral blood stem cell transplants in 14 patients with MM, from 1991 to March 31, 2006. Nine were female and five male. Median age was 51.5 years (range 38 to 63 years). Regarding the monoclonal protein, 10 cases were IgG (5 lambda and 5 kappa), 2 IgA (1 kappa and 1 lambda), and 2 cases light chain (1 lambda and 1 kappa). Ten patients had stage II. Treatment before the transplant consisted in 1 to 4 chemotherapy regimens, mainly VAD, melphalan-prednisone and thalidomide-dexamethasone. In 3 patients the transplant was allogeneic and in 11 autologous, 4 patients had a second transplant (tandem). We used filgrastim for stem cell mobilization, and in 1 patient filgrastim and cyclophosphamide. The cells were collected with a standard apheresis procedure. Median CD34+ cells transfused were 2.04 × 106/Kg. In the autologous setting we used Melphalan 200/m² (po) and in the case of the allotransplant 2 cases were conditioned with Busulfan-cyclophosphamide and 1 patient with BEAM and Alemtuzumab. The median time to achieve >500/mm³ neutrophils in the patients with tandem transplants was 4 days for the first procedure and 7 for the second, in the patients with 1 autologous transplant the median time was 13 days and for the patients with allogeneic transplant was 21 days. Median time to >20 000/mm³ platelets were, 8 and 9 days for the tandem procedures, 14 days for the single autologous transplant and 22 days for the allogeneic transplant. The patients with autologous transplant received form 0 to 3 pack red cells and from 1 to 4 platelets transfusions. The most frequent significant adverse event was infection. One patient died of cerebral hemorrhage on day +6, in the allotransplant group. No transplant related deaths occurred in the autotransplant group.

**Conclusion:** Autologous transplant conditioned with oral melphalan in patients with MM is a very safe procedure when performed at the INCAN. Infections are frequent and commonly related to the venous access. Allotransplants have a high mortality.

**A44**

Management of post-radiotherapy hemorrhagic cystitis refractory to conventional treatment

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BMC Cancer 2007, 7(Suppl 1):A44

**Background:** In the treatment of pelvic cancer such as rectum, bladder, prostate, cervix and others, the use of radiation therapy as primary or adjuvant cancer treatment is a common practice; however, complications and side effects could occur, the most common urological complication present in about 5.7 to 11.5% of the cases is the post radiation hemorrhagic cystitis (PRHC). We present the clinical evolution of all the patients with PRHC who did not respond to the standard management of the hemorrhagic cystitis.

**Materials and methods:** From January 2006 to August 2006, thirty seven patients with diagnosis of PRHC were evaluated including: sex, age, oncology diagnostic cystoscopic findings, clinical features, blood transfusion required, and failure to treatment, alternative treatment and clinical evolution.

**Results:** In a period of 8 months, 37 patients from the urology department of the Instituto Nacional de Cancerología, were evaluated, 36 female and 1 male, median age 62 years old (43 – 72 years), diagnosis of cervix cancer stage IIb and IIIb in the
females and prostate cancer in the male, all of them treated with radiotherapy as primary therapeutic technique. The main symptoms were: pelvis pain in 34 cases, dysuria in 25 and gross hematuria in 37, all the patients underwent cystoscopic evaluation, which develop inflammatory changes and hemorrhagic lesions in bladder walls in 100% of the patients. All the cases were treated with 50 cc intravesical instillations of 50% solution of dimethylsulfoxide (DMSO) in saline solution weekly for 6 weeks.

Four cases presented therapeutic failure with gross hematuria and required prolonged hospitalization and blood transfusion of 3 units. The 4 cases were treated with urinary diversion only (ileal conduit) in 3 and urinary diversion and cystectomy in the other. One female treated only with urinary diversion due to intense desmoplasic reaction secondary to RT which makes cystectomy not possible, presented persistent hematuria and must be treated with instillation of 10% of formaldehyde solution under IV sedation. The evolution was satisfactory after the procedure and the hematuria stopped.

**Conclusion:** The PRHC must be treated according with the standard procedures however, the surgical management must be considered as the definitive procedure in patients with no response to the inra-vesical therapy.

### A45

**Retroperitoneal soft tissue sarcoma**
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**BMC Cancer 2007, 7(Suppl 1):A45**

**Background:** Retroperitoneal sarcomas are rare malignant tumours with aggressive course of disease and high local recurrence rate. The evaluation and treatment of retroperitoneal sarcomas are challenging because the tumours are relatively rare and frequently present with advanced disease in an anatomically complex location. We analyzed the treatment and survival in 96 patients with primary or recurrent retroperitoneal sarcoma (RPS).

**Materials and methods:** Between 1991 and 2003, 98 patients with RPS were treated at the Instituto Nacional De Cancologı´a de Méxi-co. We retrospectively evaluated clinicopathological data from 96 patients in a single institution. We examined the treatment and outcome. Survival curves were generated using the Kaplan-Meier and the log rank test.

**Results:** The median age at diagnosis was 47 years (range 17–81). 57 women and 41 men. The mean time following was 30 month (m). At diagnosis 30 patients had metastasis with hepatic metastasis in 14% of all cases, followed by lung (9%). Liposarcoma was the most common type of histology (34%), followed by leiomyosarcoma (20%). The mean size of tumor was 17 centimeter. We removed surgically in 87 patients and 11 patients were treated in other institutions. 42% multisviscerale resection. Only in 62 patients were valuable status of the surgical margins. R0 resection was made in 24 patients, R1 resection in 14 and R2 in 24 patients. 37 patients we treated with adjuvant radiotherapy (RT). The local recurrence was present 36%. The overall survival (OS) was 39 m for low grade vs 29 m by high grade (p = NS). The patients treatment with RT surviving 41 m vs 33 m (p = 0.03) The OS in patients treated with surgery in the institution was 42 m vs 10 m in patients treated outside (p = 0.01). At following 47 patients were lost.

**Conclusion:** The treatment of patients with RPS remains unsatisfactory. Aggressive surgery is recommended in the majority of the cases. The adjuvant RT seems to be that impacts in the overall survival. Our results indicate that the patients with RPS should be treated in institutions specialized and with a high experience in the multidisciplinary management.

### A46

**Germ-cell tumors with sarcomatous components. A clinicopathologic and immunohistochemical study of 48 cases**
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**BMC Cancer 2007, 7(Suppl 1):A46**

**Background:** The presence of sarcomatous components (SC) in gonadal or extragonadal germ cell tumors (GCT) is an infrequent phenomenon whose clinical outcome and biological significance remains unsettled. It may cause diagnostic pitfalls and treatment failure. In order to define the clinical and pathological characteristics, prognosis and biological behavior of these tumors, a clinicopathologic study of 48 cases of GCT/SC was undertaken, with immunohistochemical studies (IHCs) in 34 of them to define the phenotype of SC.

**Materials and methods:** Forty-eight cases of GCT with SC were retrieved from the files of the Instituto Nacional de Cancologı´a, Armed Forces Institute of Pathology and Mount Sinai Medical Center (23 gonadal, 23 mediastinal and 2 retroperitoneal tumors). Routine H&E slides were reviewed and IHCs were done in 34 cases, with antibodies against actin, desmin, vimentin, CAM 5.2, S-100 protein, CD34, CD31, and ulex eurpeaeus lectin. A group of 25 cases of GCT without sarcomatous component (GCT/NS) were retrieved for comparison. Survival of both groups was compared.

**Results:** Germ cell component was pure teratoma in 27 cases, teratoma mixed with other components in 17, pure seminoma in 2, intratubular GCT in 1 and hepatoid yolk sac tumor in 1. SC was: embryonal rhabdomyosarcoma in 30, angiosarcoma in 6, leiomyosarcoma in 4, undifferentiated sarcoma in 4, myxoid liposarcoma in 1, malignant peripheral nerve sheath tumor in 1, malignant triton tumor in 1 and epithelioid hemangoendothelioma in 1. IHCs supported the diagnosis in all cases. Metastases with combined GCT and SC were observed in 6 cases and metastases with the SC alone in 5. Metastatic tumor showed only GCT elements in 3 cases. Follow-up data was available in 40 cases of the GCT/SC group, 25 patients (62.5%) died of tumor; 7 (17.5%) were alive with disease from 1 to 84 months (mean 24 months), and 8 patients (20%) were alive and free of disease.
Management of osteosarcomas over one decade: the INCAN experience
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Background: Osteosarcoma is the most common primary malignant bone tumour in children and young adults. Survival has improved from historic rates of <20% to current rates of 50–75% with multimodality therapy. Despite advances in the diagnosis and management of osteosarcoma, there have been few recent studies describing the experiences of tertiary referral centers. We aim to describe and discuss the clinical features, management and outcomes of these patients in a single institution.

Materials and methods: Retrospective study of 100 consecutive patients managed for osteosarcoma at Instituto Nacional de Cancerología (Distrito Federal, México) between 1985 and 1995. Survival curves were generated using the Kaplan-Meier and the log rank test.

Results: Median age at diagnosis was 21 (range, 13–70) years. Gender distribution was: 59 male and 41 female patients with a relation male-female 1.4:1. Pain was the most common presenting symptom in fifty-five patients (55%). Median tumor size was 15 cm. 55 patients (55%) had osteosarcoma in the femur, 22 in tibia, in the humerus 9 and others 14. At the diagnosis, 33 patients had metastatic disease, the highest rate was lung metastasis (79%) followed of bone metastasis (12%) The surgical resection was realized in 93 patients, with radical surgery in 62 patients and limb sparing 31 patients. All but twenty-four patients received chemotherapy; of patients who were administered chemotherapy, 33 patients received neoadjuvant chemotherapy and 43 adjuvant chemotherapy. In five patients received radiotherapy.

The median follow-up time for surviving patients was 44 months (range, 2–240) for the 10-year periods. Following initial therapy, over fifteen percent of patients remained relapse-free during the follow-up period. The median of survival for the patients with stage I of the American Joint Committee on Cancer (AJCC) was 103 months, II (72 months), III (92 months), IV (17 months) (p = 0.0019). The median of survival for the patients without or with metastasis was of 71 months vs 16 months (p = 0.001).

Conclusion: Patient outcomes can be optimized through a multidisciplinary approach in a tertiary referral centre. In the Instituto Nacional de Cancerología survival and relapse rates of patients managed for osteosarcoma compare unfavourably with the published literature actually. A poor survival in this period of study reflected the lack of effective treatment as the chemotherapy. Our results in this period are comparable to the results of it period pre chemotherapy.

A48
Skin-sparing mastectomy in breast cancer
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Background: Breast cancer is one of the main health problems in women in Mexico. Breast cancer treatment needs to be multidisciplinary. Surgical treatment has presented dramatic changes. Skin-sparing mastectomy (SSM) greatly enhances the aesthetic results of breast reconstruction, is not yet a standard technique for breast cancer treatment, although it is shown as an advanced and promising procedure. The objective of this study was to present the experience of the National Cancer Institute of Mexico in skin-sparing mastectomy in patients with breast cancer.

Materials and methods: A retrospective review was performed in patients who underwent SSM and immediate breast reconstruction from April 1997 to December 2004. Records were analyzed for each patient, including type of tumors and treatment, overall survival, disease free survival and aesthetic results.

Results: During April 1997 and December 2004, SSM with immediate reconstruction was performed in 91 patients (4 patients with bilateral cancer and 10 underwent prophylactic mastectomy in the other breast). The mean age was 40 years (22–58 years). Most patients were pre-menopausal (77%). Five patients (5.5%) have contralateral breast cancer. The histological diagnoses was invasive ductal carcinoma in the most patients (74.7%). Systemic neoadjuvant chemotherapy was performed in 32.9% (30 patients) and radiotherapy preoperative in 7.7% (7 patients). Most of half of patient (58) underwent adjuvant chemotherapy (63.3%) and 27 patients received adjuvant radiotherapy (29.6%). In most of the patients (50) TRAM flap was the reconstruction method employed, tissue expander-implant in second place (27 patients), implant in 23 patients and latissimus flap and implant in 5 patients. The complication rate was 36% (38 cases in 105 procedures), 28 minor and 9 majors. Of 7 patients with preoperative radiotherapy 6 underwent complications (3 majors) and 11 of 27 patients with adjuvant radiotherapy have any type of complication (4 majors). The aesthetic result was in 63.3% this was excellent or good; 14.4% regular; 7.7% poor and 14.4% not reported. The follow-up mean was 66 months (13–100 months), four recurrences were detected (4.4%); 3 systemic and 1 local-regional and systemic.

Conclusion: SSM is an oncological safety procedure in breast cancer early with recurrence rates similar to non-SSM, the complication rates were comparable to conventional mastectomy, being mostly associated to radiotherapy.
A49  
**Who are the best candidates for multiorgan resection among patients with T4 gastric carcinoma?**  
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**Background:** The indications for gastrectomy in T4 gastric carcinoma (GC) remain controversial. Our aim was to develop a method for the selection of patients with T4 GC with the best chances to receive a benefit from multiorgan resection.  
**Materials and methods:** We study a cohort of patients with T4 GC treated from January 1987 to December 2005. Relevant clinical, pathological and therapeutic variables were recorded. Prognostic factors associated with survival were defined by Kaplan-Meier and Cox’s methods. Factors associated to surgical morbidity were selected by Logistic Regression analysis.  
**Results:** 718 patients were included (gastrectomy performed in 169). The clinical and pathological characteristics of the cohort depending on the residual status after the surgery was recorded. Presence of metastasis (Hazard ratio = 1.68 [HR], 95% confidence interval [CI] 1.19–2.36), albumin <3 g/dL plus lymphocytes <1000 cells/mm<sup>3</sup> (HR = 2.9, 95% CI 1.8–4.6), presence of ascites (HR = 2.1, 95% CI 1.06–4.2), 50 years old or more (HR = 1.37, 95% CI 1.02–1.8) and absence of surgical resection (HR = 2.6, 95% CI 1.7–4.1) define patients with the worst prognosis (model p = 0.00001). Including only patients underwent surgical resection, presence of metastases, extent of gastrectomy, serum albumin level and R1–R2 residual were determinants of poor survival (model p = 0.00001). Surgical morbidity and mortality were 39% and 10.7%, respectively. The significant determinants of surgical morbidity were extent of gastrectomy, age, serum albumin and lymphocyte count (model p = 0.0001).  
**Conclusion:** The decision to perform a curative gastrectomy in patients with T4 GC must be balanced between the chances of long-term survival and the chances of surviving a potentially fatal operation. We propose a simple method to select those patients with high probability of benefiting from the procedure.

A50  
**Complete pathological response in patients with locally advanced cancer of breast and positive Her2/neu with neoadjuvant chemotherapy**  
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**Background:** This retrospective study was made with the purpose of evaluating the rate of complete pathological response (CPR) of the tumor and CPR of the axillary lymph nodes in patients with Her2/neu treated with neoadjuvant systemic treatment.  
**Materials and methods:** We retrospectively reviewed thirty-three (n: 33) clinical records of females with diagnosis of locally advanced breast cancer with positive Her 2/neu receptors, which was treated with neoadjuvant chemotherapy in the Institute from January 2004 to December 2005. The median of age was of 58 +/- 14 years (range: 36–91 years). The initial clinical stages were: IIA, n: 1 (3%); IIB, n: 3 (9%), IIIA, n: 19 (58%) and IIIB, n: 10 (30%). The initial nodal stage were: N0, n: 5 (15%); N1, n: 9 (27%), and N2, n: 19 (58%). Twenty-one (64%) patients had both hormonal ER and PR negatives. The combination of Anthracyclines and Taxanes was prescribed in n: 17 (52%) and n: 8 (24%) received in addition neoadjuvant Trastuzumab (Herceptin). A breast conservative surgery was performed in four (n: 4) patients, the rest of patients a modified radical mastectomy was made. The median number of dissected nodes was of 13 +/- 7 nodes (range: 3–32) and median of the percentage of metastatic nodes was of 15 +/- 24% (range: 0–72%).  
**Results:** The rate of tumor CPR was achieved in 9/33 patients (27%) and the rate of nodal CPR was noted in 11/33 patients (33%). The patients who received neoadjuvant Trastuzumab had same tumor CPR and axillary lymph node CPR of 38% (3/8). An 18% (6/33) of the patients presented total CPR (tumor and nodal). The tumor or axillary lymph nodes CPR was not associated with age, histology, menopause status, initial clinical or nodal stage, use of neoadjuvant Trastuzumab or the scheme of chemotherapy or the state of ER/PR. Sixty-six percent of complete pathologic responders had negative axillary lymph nodes compared to 21% of patients who did not have a complete pathologic response (p = 0.013).  
**Conclusion:** The rate of tumor and nodal CPR is within of the reported in the literature. It is important to emphasize the promising benefit and the controversial role of neoadjuvant Trastuzumab in these patients. Others molecular biological factors must be studied like favorable predicting of pathological response.

A51  
**GIST in a reference cancer center in México**  
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**Background:** Gastrointestinal stromal tumours (GIST) are rare malignancies characterised by their association with KIT oncogene mutations. Until now, population-based reports of the incidence or survival of kit-confirmed GIST have been rare, and none have originated in México.
Materials and methods: We reviewed the files in the Instituto Nacional de Cancerologia to identify malignant mesenchymal tumours of the digestive tract between 1995 and 2005, and performed c-kit testing in the tumour samples. Results: Seventeen cases were found with 88% of GIST localised in the stomach, 5.8% in small intestine, and 5.8% in esophagus. Fifty-eight percent were classified as high risk of an aggressive behaviour and 42% as low or very low risk. Only one patient received treatment with imatinib mesilate and three had radiotherapy. The relative 3-year survival rate was 29.4% for the entire cohort.

Conclusion: We report the first review of incidence in a referral cancer center in México. The incidence rate is low and comparable with that of cancer registries from Northern America and Europe. Survival was favourable in our pre-imatinib population although it was low in high-risk cases. Prognostic discrimination of the cases with intermediate, low, or very low risk is inadequate, and these categories should be considered jointly in the future. Our results will help researchers in establishing baseline values against which they can compare in the future, the impact of imatinib and other Kit tyrosine inhibitors on survival.