EUROPEAN JOURNAL OF CANCER 48, SUPPL. 2 (2012) S13–S16

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# Non-Invited Publications

## Hepatobiliary Cancer

**01** SCIENTIFIC POSTER ABSTRACT

**The risk level of liver cancer cases among smokers in developing countries**

E.O. Odiase. *Tobacco/Cancer Control, University of Ibadan/SmokeFree Foundation, Abuja, Nigeria*

**Introduction:** Tobacco use is a rising concern for the developing world. It causes about 5 million deaths yearly and is projected to cause 10 million deaths yearly by 2025 with 80% of these deaths from the developing countries if current trends continue. Tobacco is also a major risk factor for all kinds of cancer including Liver cancer.
**Goal:** To help determine whether the risk of liver cancer from smoking was less or greater than other forms of cancers caused by tobacco.
**Methods:** In this study, we ascertained retrospectively the smoking habits of 24,000 adults who had died from liver cancer (cases) in 10 Chines cities, 7 Indian Cities and 5 Nigerian Cities. These areas were chosen for reasons of high population. Smokers from these three countries constitute 40% of smokers worldwide. Calculations of the smoker risk ratios (RR) for liver cancer mortality were standardized for age and locality. We used Cox proportional hazard regression models to adjust for confounding variables. We conducted analysis on the entire study population, among male and females who had smoked for at least 20 years separately for each country.
**Results:** Among adult men (aged 35+) there was a 36% excess risk of death from liver cancer (smoker standardized risk ratio [RR] = 1.36, with 95% confidence interval [CI] 1.29–1.43, $2p < 0.00001$; attributable fraction 18%). In the general male population, this indicates absolute risks of death from liver cancer before age 70 of about 4% in smokers (in the absence of other causes). The RR was approximately independent of age, was similar in urban and rural areas, was not significantly related to the age when smoking started but was significantly ($p < 0.001$) greater for cigarette smokers than for smokers of other forms of tobacco. Among men who smoked only cigarettes, the RR was significantly ($p < 0.001$ for trend) related to daily consumption, with a greater hazard among those who smoked 20/day (RR = 1.50, 95% CI 1.39–1.62) than among those who smoked fewer (mean 10/day: RR = 1.32, 95% CI 1.23–1.41). Smoking was also associated with a significant excess of liver cancer death in women (RR = 1.17, 95% CI 1.06–1.29, $2p = 0.003$; attributable fraction 3%), but fewer women (17%) than men (62%) were smokers, and their cigarette consumption per smoker was lower. Among women who smoked only cigarettes, there was a significantly greater hazard among those who smoked at least 20/day (mean 22/day: RR = 1.45, 95% CI 1.18–1.79) than among those who smoked fewer (mean 8/day: RR = 1.09, 95% CI 0.94–1.25).
**Conclusion:** This study goes to show that even though liver cancer from tobacco use kills about 200,000 people yearly in these three developing countries, the deaths from lung cancer (1.5 million yearly worldwide) is still higher than liver cancer deaths.

**02** SCIENTIFIC POSTER ABSTRACT

**miRNA network dysregulation in hepatocarcinogenesis**

V.A. Halytskiy. *Molecular Immunology Department, Palladin Institute of Biochemistry of the National Academy of Sciences of Ukraine, Kiev, Ukraine*

**Goals:** Tumor growth is tightly associated with regular shifts in microRNA (miRNA) expression pattern. More than 50% of miRNA genes are located in fragile chromosomal regions that are susceptible to various damages during the carcinogenesis. Usually, expression of miRNAs miR-22, miR-29, miR-122a, miR-124, miR-126, miR-148, miR-152, miR-203, miR-223, miR-375 is down-regulated in hepatocellular carcinoma (HCC) cells whereas expression of miRNAs miR-19a/b, miR-21, miR-31, miR-20a, miR-106a, miR-125a, miR-221, miR-222, miR-224, miR-301, miR-454, miR-483−5p is up-regulated. This investigation aims to identify how abnormalities in miRNA network contribute to the hepatocarcinogenesis.
**Methods:** miRNA targets within gene transcripts were predicted in silico using TargetScan software.
**Results:** Down-regulated miRNAs miR-22 and miR-148/152 silence WNT1 gene. miR-223 targets transcripts of genes encoding proliferative signal pathway components RASA1 and E2F1. Transcript of another oncogene N-Ras carries sites of miR-22, miR-29, miR-124 and miR-148/152. miR-124 and miR-203 target transcript of gene encoding antiapoptotic pathway component Akt2. Also, miR-203 silences gene of transcription factor E2F3 as well as gene BIRC5 encoding survivin. miR-124 silences E2F3, E2F5, E2F6 genes as well as gene of cyclin-dependent kinase CDK4. miR-148/152 targets E2F3, E2F7, CDK6, CDK8 gene transcripts. miR-22, miR-29 and miR-122a silence gene LAMC1 encoding laminin g1. Also, miR-148/152 and miR-29 target LAMA4 and, respectively, LAMA2 and LAMC2 gene transcripts. Up-regulated miRNAs miR-221 and miR-222 silence genes encoding cell cycle inhibitors p27 and p57. miR-19 inhibits gene encoding tumor suppressor protein pTEN and thus derepresses PI-3K/Akt antiapoptotic signaling pathway. miR-20a as well as miR-106a target transcripts of genes encoding pTEN, cell cycle inhibitors p21 and Rb1. Also, transcript of gene encoding p21 carries miR-301/454 target.
**Conclusion:** miRNA network is intertwined with signal transduction pathways. HCC cells down-regulate expression of miRNAs that silence proliferative and antiapoptotic genes. Moreover, down-regulation of some miRNAs can allow the ectopic expression of laminins that are heteroorganic antigens. Up-regulated miRNAs suppress genes encoding cell cycle inhibitors. Therefore, shifts in miRNA expression pattern can themselves cause reactivation of cell oncogenes and antiapoptotic genes as well as repression of cell cycle inhibitor genes. Furthermore, as each miRNA impairs the expression of many genes, including genes of other miRNAs, illegitimate activation or repression of some miRNA genes can be the first event in carcinogenesis, leading to the reorganization of epigenetic pattern in transforming cells through the RNAi-dependent DNA methylation. As a result, cancer cells proliferate and accumulate, forming a tumor.

## Gastric Cancer

**03** SCIENTIFIC POSTER ABSTRACT

**Extracapsular lymph node spread: not-so-well known but important prognostic factor in gastric cancer**

A. Picchetto[1], P. Aurello[1], V. Catracchia[1], N. Petrucciani[1], F. D'Angelo[1], S. Uccini[2], G. Ramacciato[1]. *[1]Department of Surgery, University of Rome "La Sapienza", Rome, Italy, [2]Department of Clinical and Molecular Medicine, University of Rome "La Sapienza", Rome, Italy*

**Goals:** Current AJCC and JCGC pN staging system of gastric cancer are both based on the number of metastatic lymph nodes. Instead, little has been done about the histopathological characteristics of the metastatic lymph node itself, specially for the prognostic impact of tumor penetration through the nodal capsule in metastatic lymph nodes, also called extracapsular lymph node involvement. Aim of this study is to evaluate the significance of extracapsular lymph node involvement as a prognostic factor and its correlation with clinicopathological parameters.
**Methods:** We took account of 96 patients underwent curative gastrectomy for gastric adenocarcinoma. In the present study, number of metastatic lymph nodes with capsular and/or extracapsular lymph node involvement was also evaluated. Extracapsular lymph node involvement was defined as invasive cancer extending through the nodal capsule into the perinodal adipose tissue. The deposits of invasively growing cancer cells without a recognizable lymph node were considered extracapsular lymph node involvement, unless these deposits were associated with perineural and/or vessel involvement.
**Results:** Extracapsular lymph node involvement was associated with higher nodal status ($P = 0.037$), with higher TNM stages ($P < 0.001$).

Extracapsular lymph node spread was strongly associated with poor overall survival ($P < 0.001$) and disease free survival ($P < 0.001$).
**Conclusion:** The results of this study seem to confirm the role of extracapsular spread as a negative prognostic factor of patients with gastric cancer, by means of statistical analysis. Our results suggest that extracapsular spread is more sensitive than the total number of metastatic lymph nodes to identify classes of patients with similar life expectancy.
In conclusion, randomized multicenter studies are needed in the future to confirm these preliminary results; possibly including extracapsular spread in a more complete and accurate staging system, in order to reduce differences between the groups, trying to find the best treatment option and identify the correct prognosis for patients with gastric cancer and to compare results worldwide.

**04** SCIENTIFIC POSTER ABSTRACT
**Effect of one year adjuvant imatinib on gastric stromal tumors**

A. Bensalem[1], K. Bouzid[2]. [1]*Medical Oncology, CHU, Mentouri's University, Constantine, Algeria,* [2]*Medical Oncology, CPMC, Algiers, Algeria*

**Goals:** Though recurrence is high, local excision is the preferred approach for dealing with gastric stromal tumors. Achieving negative margins is mandatory, sometimes requiring subtotal gastrectomy. Adjuvant imatinib is essential for advanced cases and prolonging survival.
**Methods:** The study included 12 patients (7 males, 5 females, median age 46 years) presenting with gastrointestinal stromal tumors (GISTs). The schedule was imatinib (400 mg/day) for 1 year after surgery, in adjuvant setting. Clinical and radiological evaluation was at 4 months of treatment.
**Results:** All patients had abdominal discomfort, while 50% had epigastric pain, and 10% had hematemesis, in the beginning of the treatment.
**Conclusion:** Imatinib has an acceptable safety profile and can be considered as an adjuvant and why not as a neoadjuvant therapy in GISTs. More clinical data are needed to confirm this hypothesis.

**05** SCIENTIFIC POSTER ABSTRACT
**Methylation of MLH1, MGMT, DAPK genes in the cancerous and adjacent non-cancerous stomach tissues**

R. Kupcinskaite-Noreikiene[1], E. Juozaityte[1], S. Grižas[2], R. Markelis[3], L. Venclauskas[2], V. Baltrėnas[3], L. Sakavicius[2], I. Semakina[3], R. Venclovaite[2], J. Skieceviciene[2]. [1]*Oncology Institute, Lithuanian University of Health Sciences (LUHS), Kaunas, Lithuania,* [2]*Lithuanian University of Health Sciences, Lithuania,* [3]*Lithuanian University of Health Sciences Hospital Kaunas Clinics, Lithuania*

**Goals:** To assess the profile of the expression of methylated genes in the cancerous tissue and adjacent non-cancerous stomach tissues.
**Methods:** Genetic analysis of the cancerous and non-cancerous tissues (assessed by pathologist) sampled 2 cm away from the edge of the tumor was accomplished. Samples were acquired from patients who underwent surgeries for gastric cancer in LUHS Oncology Institute during 2009–2011 and who agreed to participate in the study. DNA extraction was accomplished according to protocol using commercial set, DNA was converted according to instructions provided by manufacturer using bisulfite kit. Bisulfitic DNA was amplified during methylation-specific PCR by using gene-specific primers for methylated and non-methylated alleles. PCR products were separated using agarose gel electrophoresis and were visualized in ultraviolet illuminator after staining with ethidium bromide. Statistical analysis was performed using SPSS software.
**Results:** Results of our research have shown that the methylation of MLH1 gene occurrence rate is 66.6% (24 from 36) in cancerous tissue, and 58.3% (21/36) in adjacent non-cancerous tissue; the rates of DAPK were 9.7% (3/31) and 29% (9/31) respectively, and for MGMT rates were 7.1% (2/28) and 10.7% (3/28) respectively. A strong relationship between the expressions of gene methylation in cancerous and adjacent non-cancerous tissue was determined (MLH1 $\chi^2 = 4.6$; $p = 0.031$), (MGMT $\chi^2 = 17.9$; $p < 0.0001$). No statistically significant relationship between the expressions of methylation of DAPK was found ($\chi^2 = 2.28$; $p = 0.131$).
**Conclusion:** A strong relationship between the expressions of gene methylation in cancerous and adjacent non-cancerous tissue was determined (MLH1, MGMT). No statistically significant relationship between the expressions of methylation of gene DAPK was found.

## Oesophageal Cancer

**06** SCIENTIFIC POSTER ABSTRACT
**Postoperative chemotherapy and disease-free survival in esophageal and gastric adenocarcinoma**

T. Alcindor[1], L. Ferri[2], S. Ades[3], M. Thirlwell[1]. [1]*Oncology and Medicine, McGill University Health Centre, Montreal, Canada,* [2]*Surgery and Oncology, McGill University Health Centre, Montreal, Canada,* [3]*Vermont Cancer Center, Burlington, United States of America*

**Goals:** Perioperative chemotherapy is used in the management of esophageal and gastric adenocarcinoma. Randomized studies have shown that it improves disease-free and overall survival in comparison with surgery alone. However, because of toxicity, inconvenience, or surgical complications, many patients do not receive the postoperative part of treatment. We have previously reported the efficacy and safety data of a phase II trial of docetaxel/cisplatin/5-FU perioperative chemotherapy. The current study specifically examines the impact of postoperative chemotherapy on disease-free survival.
**Methods:** From May 2007 to September 2009, we enrolled 43 patients with operable adenocarcinoma of the esophagus or stomach on a phase II clinical trial. Patients were to receive 3 cycles of chemotherapy (docetaxel/cisplatin/5-FU) before and after surgical resection. We performed a retrospective analysis to compare disease-free survivals between Group A (at least 1 postop cycle given) and Group B (no postop chemotherapy given). The log-rank test was used for univariate analysis, and the Cox regression model for multivariate analysis. P value is double sided. Median follow-up is 808 days, disease-free survival calculated from time of surgery.
**Results:** Surgery was not performed in 2 subjects (disease progression in one, and withdrawal of consent, for the other). One patient was excluded from analysis as her tumor was a neuroendocrine tumor. Grade 3/4 toxicity was observed in 47% of patients before surgery. Of 40 patients, 29 received postoperative chemotherapy (3 cycles/2 cycles/1 cycle: 24/26/29), and 11 did not (personal preference 4, postoperative complications 2, other reasons 5). Only 56% of study subjects completed the 6 cycles of chemotherapy planned in the protocol. After a median follow-up of 808 days, the median survival of patients in Group B is 455 days, while it has not been reached in Group A ($p = 0.076$). Similar results were found by multivariate analysis, after adjustment for radiological, pathologic and metabolic response to preoperative chemotherapy.
**Conclusion:** Previous episodes of severe toxicity and occurrence of surgical complications probably contribute to relatively low rates of chemotherapy completion in the postoperative period. The small number of patients in this trial and a retrospective analysis do not allow us to draw definitive conclusions about the impact of postoperative chemotherapy on the risk of recurrence in patients with esophageal and gastric adenocarcinoma treated with a perioperative chemotherapy protocol. However, our results show a strong trend in improvement of disease-free survival in favor of postoperative chemotherapy, suggesting that, outside of a clinical trial, this part of therapy should not be discarded.

## Colorectal Cancer

**07** SCIENTIFIC POSTER ABSTRACT
**Serum tryptase as a new biomarker in colorectal cancer patients**

M. Ammendola[1], R. Patruno[2], E. Ruggieri[2], M. Coviello[3], V. Di Lecce[2], A. Vacca[4], R. Sacco[1], S. Montemurro[2], C.D. Gadaleta[5], G. Ranieri[5]. [1]*Chair of General Surgery, Magna Graecia University, Catanzaro, Italy,* [2]*National Cancer Institute Giovanni Paolo II, Surgery Unit, Bari, Italy,* [3]*Department of Experimental Oncology, National Cancer Institute Giovanni Paolo II, Bari, Italy,* [4]*Department of Internal Medicine and Infectious Diseases, University of Bari, Bari, Italy,* [5]*Interventional Radiology Unit with Integrated Section of Medical Oncology, National Cancer Institute Giovanni Paolo II, Bari, Italy*

**Goals:** Data from experimental tumour models suggest that mast cells (MCs) accumulate near tumour cells before the onset of angiogenesis and that they are required for the macroscopic expansion and metastatic spread of primary tumour cells. Tryptase is a serin protease stored in mast cell granules that plays a role in tumour angiogenesis. Mast cells (MCs) can release tryptase following c-Kit receptor activation. On the other hand colo-rectal cancer (CRC) is a well-established angiogenesis dependent tumour and anti-angiogenic based therapy is a standard treatment in metastatic CRC. This preliminary study aims to assess tryptase serum levels in 54 CRC patients before and after radical surgery resection.
**Methods:** In this study patients with stage B and C CRC (according to Astler and Coller staging system) were selected. Samples of blood were taken from CRC patients between 7 and 9 a.m.1 day before and 1 day after