- R05 -

**Invited Lecture**

Hereditary colorectal cancer syndromes : an update.

M. Novelli. University College London Hospitals, London, Great Britain (UK)

Until relatively recently our knowledge of hereditary colorectal cancer was limited to the autosomal dominantly inherited syndromes Familial Adenomatous Polyposis (FAP) and Lynch syndrome (formerly HNPCC). However, it has become increasingly apparent that the hamartomatous polyp syndromes Juvenile polyposis and Peutz-Jegher syndrome are actually cancer syndromes and over the last ten years or so a number of new colorectal cancer syndromes have also been described (including MYH-associated polyposis, Hereditary mixed polyposis, Polymerase proofreading-associated polyposis, serrated polyposis and congenital mismatch repair deficiency). These syndromes include a couple of autosomal recessively inherited conditions (MYH-associated polyposis and congenital mismatch repair deficiency) and serrated polyposis where the mode of inheritance remains unclear. The clinical features, genetics and histopathology of these syndromes will be described.

- R06 -

UNDIFFERENTIATED PLEOMORPHIC SARCOMA OF THE LIVER DEVELOPING IN THE CONTEXT OF LYNCH SYNDROME. H. Djedaimi (1), G. Delvaux (1), J. De Greve (1), A. Hoorens (2). (1) UZ Brussel, Brussels, Belgium ; (2) UZ Brussel, Brussels, Belgium.

**Aim** : To report the occurrence of an undifferentiated pleomorphic sarcoma of the liver that developed on the basis of Lynch syndrome (HNPCC).
**Methods and results** : A 36-year-old man presented with right upper quadrant pain. This patient had previously been shown to harbour a germ-line mismatch repair gene mutation. Since almost 10 years he had an annual screening colonoscopy, that each time revealed the presence of adenomatous polyps. His last colonoscopy dated back to 9 months before. At that time a flat adenomatous polyp had been removed from the colon. Radiological examination identified a large mass (9x7x6cm) pendulating from segment 6 of the liver, penetrating the liver capsule and infiltrating the parietal peritoneum and mesocolon. An en bloc resection of the liver mass was performed together with a right hemicolectomy and parietal peritoneal resection. The histological features, immunohistochemical profile and complementary molecular pathology findings of this liver mass were consistent with the diagnosis of an undifferentiated pleomorphic sarcoma. Immunohistochemistry in addition showed loss of expression of the MMR proteins MLH1 and PMS2. Expression of MSH2 and MSH6 appeared preserved. A peritoneal washing demonstrated the presence of tumour cells in the abdominal cavity
**Conclusions** : Lynch syndrome was originally described as a genetic syndrome predominantly causing colorectal cancer. Numerous other neoplasms however may be associated with HNPCC, mainly located in the endometrium, stomach, ovary, hepatobiliary and urinary tract. Sarcomas have only rarely been reported in Lynch syndrome. This case emphasis that sarcomas indeed may develop in the context of Lynch syndrome and be caused by the underlying genetic defect as indicated by the loss of expression of MMR proteins in the liver sarcoma in this patient. It makes clear that sarcomas may not be disregarded when analysing pedigrees in the context of HNPCC, especially if they occur at an early age. Like for colorectal cancer, the prognosis compared to sporadic sarcomas might be more favourable.

- R07 -

ORGANIZED PROTEOMIC HETEROGENEITY IN COLORECTAL LIVER METASTASES AND IMPLICATIONS FOR THERAPIES. A. Turtoi (1), A. Blomme (1), D. Debois (1), J. Somja (2), E. De Pauw (1), P. Delvenne (2), O. Detry (2), V. Castronovo (1). (1) University of Liege, Liège, Belgium ; (2) Centre Hospitalier Universitaire de Liège, Liège, Belgium.

**Introduction** : Tumor heterogeneity is a major obstacle for developing effective anti-cancer treatments. Recent studies have pointed at large stochastic genetic heterogeneity within cancer lesions, where no pattern seems to exist that would enable a more structured targeted therapy approach.
**Aim** : Because to date no similar information is available at the protein (phenotype) level, we aimed at characterising the proteomic heterogeneity in human colorectal carcinoma (CRC) liver metastases.
**Methods & Results** : We employed MALDI imaging-guided proteomics and explored the heterogeneity of extracellular and membrane sub-proteome in a unique collection of eight fresh human CRC liver metastases. Monitoring the spatial

distribution of over 1000 proteins we found unexpectedly that all liver metastasis lesions displayed a reproducible, zonally delineated, pattern of functional and therapeutic biomarker heterogeneity. Peritumoral region featured elevated lipid metabolism and protein synthesis, the rim of the metastasis displayed increased cellular growth, movement and drug metabolism whereas the center of the lesion was characterized by elevated carbohydrate metabolism and DNA-repair activity. From the aspect of therapeutic targeting zonal expression of known and novel biomarkers was evident, reinforcing the need to select several targets in order to achieve optimal coverage of the lesion. Finally we highlight two novel antigens, LTBP2 and TGFBI, whose expression is a consistent feature of CRC liver metastasis.
**Conclusions** : In the current work we studied human CRC liver metastases and demonstrated for the first time that their proteome heterogeneity has a distinct, organized, pattern. This particular hallmark can now be used as a part of the strategy for developing rational therapies based on multiple sets of targetable antigens.

- R08 -

T-CELL INFILTRATION ON LIVER COLORECTAL METASTASES RESECTED AFTER TREATMENT IS PROGNOSTIC. M. Van Den Eynde (1), B. Mlecnik (2), J.P. Machiels (3), D. Debetancourt (3), C. Sempoux (1), A. Jouret-Mourin (1), J.F. Gigot (1), C. Hubert (1), Y. Humblet (1), N. Haicheur (2), F. Marliot (2), F. Pages (2), J. Galon (2). (1) Cliniques universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium ; (2) Hôpital Européen Georges Pompidou, Paris, France ; (3) Clin universitaires St-Luc, UCL, Brussels, Belgium.

**Background** : Colorectal cancer T-cell infiltration (TCI) is a strong prognostic factor for survival after primary tumor resection. Curative surgery of liver colorectal metastases LCM is the only hope for cure of metastatic patients (pts). Nevertheless, 70% of them will relapse. TCI analysis of LCM is poorly characterized and could be a prognostic factor for disease-free survival (DFS) and overall survival (OS) as in primary tumor.
**Material and methods** : pts engaged for curative liver surgery after preoperative treatment with available FFPE blocks for all resected LCM, were included. An immunoscore (IS), defined by the TCI in the center (CT) and the invasive margin (IM) for each LCM, was determined using whole-slide quantitative immunohistochemistry (markers : CD3, CD8, CD45RO). The mean value of the 3 most infiltrated fields (0.8 $mm^2$) for each markers was defined in the CT and IM for all LCM. The total number of high densities (Hi, above the cut-off at the median density) in CT and IM for each marker was used to stratify pts for the IS. The markers were combined 2 by 2 in CT and IM (CD3-CD8, CD3-CD45RO, CD8-CD45RO) and finally regrouped to an IS of 0-2 Hi (IS 0-2 : low TCI) or 3-4 Hi (IS 3-4 : high TCI). For pts with multiple LCM ; the median value of all densities, the less and the most infiltrated LCM/pt were analyzed. Cumulative DFS/OS analyses were performed using the Kaplan-Meier estimator. OS/DFS analyses were made using univariate Cox regression and compared by log-rank tests (IS0-2 vs 3-4).
**Results** : 59 patients (M/F 1.1, 203 LCM, mean 3.4 /pt, synchr/metachr 5.4) were included. IS 3-4 in the less infiltrated metastasis is significantly associated with OS and DFS for all markers combinations.

| LCM/pt | Markers | Survival | HR (IS 0-2 vs 3-4;95%IC) | logrank p-value | months (IS 0-2 vs 3-4) |
|---|---|---|---|---|---|
| **Median of all** | **CD3-CD8** | **DFS** | 1.2 (0.7-2.3) | 0.48 | |
| | | **OS** | 2.2 (0.7-6.9) | 0.14 | |
| | **CD3-CD45RO** | **DFS** | 1.5 (0.8-2.9) | 0.16 | |
| | | **OS** | 2.2 (0.8-5.9) | 0.11 | |
| | **CD8-CD45RO** | **DFS** | 1.0 (0.6-2.0) | 0.82 | |
| | | **OS** | 1.0 (0.4-2.8) | 0.93 | |
| **Less infiltrated** | **CD3-CD8** | **DFS** | 1.8 (1.0-3.4) | **0.05** | 8.0 vs 14.9 |
| | | **OS** | 8.8 (2.0-39.1) | **0.0007** | 27.9 vs NR |
| | **CD3-CD45RO** | **DFS** | 2.9 (1.5-5.7) | **0.0008** | 8.0 vs 17.0 |
| | | **OS** | 4.5 (1.2-14.2) | **0.009** | 31.8 vs NR |
| | **CD8-CD45RO** | **DFS** | 2.3 (1.2-4.4) | **0.006** | 8.4 vs 16.0 |
| | | **OS** | 2.9 (1.0-8.4) | **0.04** | 47.8 vs NR |
| **Most infiltrated** | **CD3-CD8** | **DFS** | 1.0 (0.6-1.9) | 0.93 | |
| | | **OS** | 2.1 (0.7-6.6) | 0.17 | |
| | **CD3-CD45RO** | **DFS** | 1.7 (0.9-3.2) | 0.12 | |
| | | **OS** | 3.7 (0.8-16.2) | 0.06 | |
| | **CD8-CD45RO** | **DFS** | 1.6 (0.8-3.2) | 0.16 | |
| | | **OS** | 2.4 (0.7-8.4) | 0.16 | |

**Conclusions** : The T-cell infiltration determined in the less infiltrated LCM/pt after resection is a prognostic factor.