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A cura di: M. Frego e M. Iacobone

Fast track rehabilitation in elective colorectal surgery. Early experience and preliminary results in a non specialized hospital.

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INTRODUCTION: Fast Track Rehabilitation (FTR) programs in patients undergoing elective colorectal surgery have been shown to accelerate recovery, reduce general morbidity and decrease hospital stay. To establish FTR as the standard perioperative treatment in a non specialized hospital requires a great effort in organization. This study analyses enforcement of a FTR protocol and reproductibility of the reported benefits in a non specialized hospital, comparing a prospective group of selected patients undergoing elective colorectal resections above the peritoneal reflection within an enhanced recovery program with a retrospectively studied historic cohort that received conventional care.

PATIENTS AND METHODS: In December 2007 fourty four patients (Group 1 – G1) out of 64 treated between January and October 2007 were reviewed and retrospectively considered eligible for the FTR program after meeting the inclusion/esclusion criteria. Between January 2008 (first performed) and March 2009 twenty four patients (Group 2 – G2) out of 71 undergoing a colorectal resection were treated with a FTR program including 15 of the 17 FTR elements as defined in the literature (no synbiotics and liber-

al use of drains). Surgery was performed via a transversal laparotomy for right colon and laparoscopically for left colon. Data were collected prospectively in a database. They include demographics, ASA class, anesthesia procedure, length of postoperative analgesia, type of operation, length of i.v. regimen, first solid food intake, first evacuation, mobilization, drains and urinary catheter removal, general and surgical morbidity, reoperation rate, mortality, postoperative length of stay and readmission rate. Patients in G2 were examined for anxiety and depression (AD/R) and for quality of life (SF-12) preoperatively and postoperatively at day 4, and (together with the surgical follow-up) at day 10 and 30. On discharge from hospital patients who did not drop out of protocol were given a health-related quality of life questionnaire to fill in daily until day 10 and then weekly until day 30.

RESULTS: Baseline clinical data were similar in both groups apart from sex (50% males in G1 vs 75% in G2). Laparoscopic surgery has been performed more frequently in G2 (50% vs 16%). Thoracic epidural analgesia (EPA) has been used for 2 days in 87.5% in G2, while EPA at a lower level in 39% in G1. Significant results are listed as median in Table I. FTR program was completed in 15 (62.5%) of patients and 12 (50%) were discharged as expected on day 4 and 5. General morbidity was higher in G1 (16% vs 4%) while surgical complications occurred equally (G1 27% vs G2 25%). Surprisingly reoperation rate was 0% in G2 vs 16% in G1 with mortality rate 4.5% in G1 alone. Readmission has been 4% in G2. No significant change has been noticed regarding anxiety, depression and quality of life.

TABLE I

	Solid food intake (days)	First evacuation	Mobilization (days/hours)	Drain removal (days)	Urinary cath. removal (days)	i.v. regimen (days/hours)	Discharge (days)
G1 (44 p.)	4 (2-10)	4 (1-13)	1d. (1-4)	8 (2-27)	3 (1-18)	5d. (2-14)	11 (4-32)
G2 (24 p.)	1 (0-7)	2 (0-5)	5.5h. (3-23)	2.5(1-20)	1 (0-8)	6h. (2-240)	5.5 (4-21)

CONCLUSION: In our hands, after colorectal resection within a FTR program patients recovered better and were discharged safely half time earlier those treated conventionally.

Covering stoma in TME for rectal cancer in elderly patients

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INTRODUCTION: The risk of rectal cancer increases with age and achieves its maximum rate at the age of 80. In Umbria, the death rate for rectal cancer is higher than the national and global average.

Nowadays, the gold standard in rectal cancer therapy is represented by Anterior Rectal Resection with Total Mesorectal Excision (TME). Some studies have highlighted a greater frequency of anastomotic leakage in elderly patients undergone TME^{1,2}. The aim of the study is to evaluate the role of covering stoma in Anterior Rectal Resection with TME.

METHODS AND MATERIALS: A research in the databases of either Umbria Region and Terni Hospital was conducted with the aim to collect informations about patients with rectal tumours. The research allowed to identify the amount of patients with rectal cancer, the kind of intervention, and the average hospitalisation period. Specifically, all patients with rectal tumour codified as ICD-9-CM 154.0-154.1, DRG 146-147 were searched in the databases.

RESULTS: We found a 13.17% increase in rectal neoplasms, a 19% increase in surgically treated patients, and a decrease in hospitalisation period in Umbria from 1999 to 2005. From January 2001 to June 2008, 209 patients underwent surgery at General and Emergency Surgical Clinic of Terni's Hospital. Of these, 135 patients (64.59%) were submitted to an Anterior Rectal Resection with TME. The average hospitalisation period in geriatric patients does not show relevant differences compared to that of younger patients. A comparison in different age subgroups, has been promoted between patients who received a stoma and those who did not. The former have been further split up in those who had ileostomy and those with colostomy. Patients with ileostomy presented a similar hospitalisation period in all the age subgroups, while hospitalisation was much higher in geriatric patients with colostomy.

CONCLUSIONS: There is no significant difference in hospitalisation period after Anterior Rectal Resection with TME among patients with different age, probably due to proper selection before surgery. In geriatric patients a

covering stoma was associated to a higher hospitalisation only when a loop colostomy was performed.

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The Sentinel Lymph Node mapping in colon cancer.

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INTRODUCTION: Malignant tumours of the colon can metastasize along the lymphatic system in a sequential way. This means that the disease will involve a first node and from this it will progress to another node and so on. The sentinel lymph node is the first lymph node or group of nodes reached by metastasizing cancer cells. The present work aims to determine the predictive value of the sentinel lymph node procedure in the staging of non-metastatic colon cancer.

METHODS: This prospective study considers patients with adenocarcinoma of the colon T2-T3, without systemic metastases, meeting these criteria for inclusion:

- a) Minimum age: 18 years old.
- b) Staging by total colonoscopy, chest X-ray and CT scan.
- c) Patients classified as ASA 1-3.
- d) Informed consent.

Procedures:

- a) Complete inspection of the peritoneal cavity and liver surface, identification of the colonic lesion and liver intraoperative ultrasonography.
- b) Colonic resection using the standard technique with radical lymphadenectomy.
- c) Within 20 minutes the resected bowel is completely cut along the antimesenteric margin and a vital dye is injected in the submucosa at the four cardinal points within 5 mm from the lesion.
- d) Five minutes after the injection the lymph nodes marked with vital dye are identified.
- e) Then the lymph nodes are formalin fixed and sent to the pathologist: lymph nodes are histologically examined with Haematoxylin-Eosin and with the immunohistochemistry technique.

RESULTS: From January to December 2008, the ex vivo sentinel lymph node mapping was performed in 26 patients, 14 men and 12 women, ranging from 45 to

91 years of age (mean 76 years). The tumour was located at right colon in 11 cases, at the transverse colon in 2 cases, at the descending colon in 5 and at the sigma in 8 patients. The intra-operative TNM staging was: 7 cases with T2, 15 cases with T3 and 4 cases with T4 (one of these had liver metastases smaller than 5 mm). From the study were then excluded the 4 patients with T4 and M1, and 7 patients with stenotic lesions. Endly, the patients considered eligible for the study were only 14.

The histopathological examination with Haematoxylin-Eosin revealed:

- a) in 4 cases mesocolic lymph node metastases were detected.
- b) in 10 cases mesocolic lymph node metastases were not detected. In these, the mesocolic sentinel lymph nodes were searched and examined with immunohistochemical technique: micrometastases were found in 2 cases. Particularly, an aberrant lymphatic drainage pattern was identified in one case, but the sentinel lymph node was negative also at immunohistochemical technique.

CONCLUSION: The examination of the sentinel node is feasible with the ex vivo method. Using the immunohistochemical technique we detect micrometastasis in 20% of otherwise negative cases at the classical Haematoxylin-Eosin examination. The study of sentinel lymph node with multilevel microsections and immunohistochemical techniques allows a better histopathological staging.

Physiopathological changes after rectal resection: results of minimally invasive surgery

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INTRODUCTION. Low and ultra-low rectal resections often imply important changes in defecatory, urinary and sexual function. These are due not only to the resection itself but also to the damage to perirectal and hypogastric nerves. Particularly, the dissection of the hypogastric plexus may be difficult because of its closeness to the rectum and the narrow pelvic space. Laparoscopic surgery may help in rectal dissection thanks to the magnified vision of the camera and the accuracy of the instruments. Recently robotic surgery has been proposed to solve laparoscopic limits of bidimensional view and dexterity of the surgical instruments. This study evaluates the results of laparoscopic (VLS) and robotic (ROB) rectal resection performed in our Surgical Department.

PATIENTS AND METHOD. From 1998 to 2007, 160 patients underwent VLS surgery and 21 ROB for rectal tumor. Patients were divided in 3 groups according to the tumor site (proximal, medium or distal rectum) and the data were collected in a perspective maintained data base. All patients had a fol-

low up control 6 months after surgery, then every year.

RESULTS. No difference was registered in the operation time (mean VLS/ROB $285 \pm 76 / 283 \pm 98$ min), oncological resection (length of specimen VLS/ROB $27 \pm 8 / 24 \pm 8$ cm, number of lymph nodes VLS/ROB $12 \pm 7 / 13 \pm 2$), recover of bowel function and oral intake, hospital stay (VLS/ROB $12 \pm 7 / 11 \pm 5$ days). Postoperative complication rate was lower in robotic group, with 11% of anastomotic leak in VLS group and 5% in ROB. At a mean follow-up of 38 months, cancer related survival was 87%. Concerning physiopathological changes there was no difference in urinary function between the two groups. Modifications in intestinal functions were reported by 38 VLS patients with a prevalence in males (males/females 24/14) and by 2 ROB ones. Symptoms were usually transient. All male patients who underwent robotic resection had a normal sexual function, while in VLS group sexual function was normal in 81% of patients. **CONCLUSIONS.** Our study found no difference in operative and oncological results between VLS and ROB rectal resections for cancer. Post-operative urinary, intestinal and sexual functions seem to be better in robotic group, but in VLS group more patients underwent neoadjuvant radiotherapy. These data need to be confirmed by randomized studies.

Utility of the vacuum assisted closure (VAC) therapy in the treatment of enterocutaneous fistula.

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INTRODUCTION: Anastomotic dehiscence is one of the most dangerous and feared early complications following surgical resection. Anastomotic dehiscence occurs in 2 to 19% of patients, with a mortality rate up to 25- 50% in the different series. The present case focuses on new technologies for the non invasive treatment of a recurrent fistula after several operations. The aim is to demonstrate that local negative pressure is able to promote healing of these lesions, often associated with considerable morbidity and mortality, with an appropriate cost-benefit ratio. Indeed the VAC increases local circulation, reduces edema, promotes formation of granulation tissue, reduces bacterial growth and approximates the borders of the lesion.

MATERIALS AND METHODS: A 65 years old woman was observed for an external iliac node at PET scan during follow-up for a colonic adenocarcinoma treated elsewhere two months before. After an ileal resection, the patient developed an anastomotic fistula. This recurred and was unsuccessfully resected again. The complication was then successfully treated with VAC therapy.

CONCLUSIONS: The use of VAC for enterocutaneous fistula can be safely performed. In absence of large randomized studies, the use of this technique mainly depends upon surgical experience. Multicentric studies are necessary to standardize the technique and identify patients that really benefit from this conservative therapy.

Endoscopic ablation of Barrett's esophagus with high energy laser therapy: lower risk of buried glands?

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INTRODUCTION: Persistence of buried glands under the restored squamous epithelium is a limit of endoscopic ablation of Barrett's esophagus (BE)¹. As high energy laser-therapy causes a deeper tissue damage with respect to other ablative techniques, such as APC, this treatment could present less risk of buried glands and of recurrences². Aim of this study was to analyse the long term results of laser therapy for BE with particular attention to risk of recurrences.

PATIENTS AND METHODS: All the patients treated by laser-therapy for BE and followed up for at least 2 years were considered for enrollment in this study. After histology of intestinal metaplasia all the patients underwent laser treatment with Nd:YAG or diode lasers under sedation³. Those without antireflux surgery received also high dose proton pump inhibitors. Sessions were scheduled every three months the first year and then every 6 months until complete endoscopic ablation was obtained. Follow-up endoscopies with multiple biopsies were scheduled yearly. Length and circumferential extension of BE were reported during each endoscopic exam.

RESULTS: A total of 20 patients with intestinal metaplasia underwent endoscopic laser-therapy and presented a follow-up longer than 2 years. From them 13 presented long segment Barrett and 7 short Barrett. After a total of 173 sessions, in mean 8 per patient, no complications were recorded.

Stable complete endoscopic and histologic remission was obtained in 11 patients (55%). In the other 9 patients a mean reduction of 54% of the metaplastic area was obtained. Complete ablation was obtained in 6/7 short Barrett and 5/13 long Barrett ($p=0,05$). After a mean follow-up of 66 months, no cases of degeneration or recurrences were observed.

CONCLUSIONS: According to our experience, ablation of BE with laser therapy is a safe method, effective in most cases of short BE, though its efficacy is minor in the long form. This ablative technique, with deep tissue penetration, presents a low risk of recurrence.

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High energy laser therapy combines ablation and haemostasis during treatment of gastro-duodenal polyps in cirrhotic patients.

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INTRODUCTION: Gastro-duodenal polyps in cirrhotic patients can be a source of chronic bleeding^{1,2}. In these patients standard diathermic polypectomy presents a high risk of bleeding. Laser therapy has both ablative and haemostatic effects, thus seems more indicated for these subjects. For this reason we wanted to analyse the effects of laser-therapy for the treatment of gastro-duodenal polyps in cirrhotic patients.

PATIENTS AND METHODS: Laser-therapy was offered to all the patients with liver cirrhosis and hyperplastic polyps found with endoscopy in the stomach and duodenum and confirmed by histology. Patients were treated with Nd:YAG or Diode lasers under sedation with propofol [3]. Sessions were scheduled every three months. Endoscopic follow-up was performed every six months.

RESULTS: 23 patients (15 males and 8 females), mean age 58 years (range 40- 73 years) were enrolled in this study. The number of treated polyps was 76, in mean 2.8 per patient. The polyps were in 43% in the antrum, 21% in the corpus, 18% in duodenum, 9% respectively in fundus and pylorus. Mean diameter of polyps was 12 mm (range 5-30 mm). After 194 sessions, in mean 7.2 per patient, no complications were reported. In 17/23 (74%) patients a complete ablation of the polyps was obtained, in the other 6 a reduction of 60% of polyps' dimension was achieved. In all the cases a remission of gastrointestinal bleeding was observed.

After a mean follow-up of 31 months, 3 recurrences were seen (18%) and treated again with laser-therapy.

CONCLUSIONS: Laser therapy of hyperplastic gastro-duodenal polyps in cirrhotic patients is safe and effective. Endoscopic follow-up is suggested for the risk of recurrence.

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Current role of surgery and imatinib mesylate in the treatment of GISTs

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INTRODUCTION: In patients with localized GISTs, surgery remains the elective treatment. Nowadays Imatinib (imatinib mesylate, ST1571, Gleevec or Glivec) is an established therapy in advanced GISTs and has shown continue improvement in progression-free and overall survival. A combination of imatinib therapy and surgery may also be effective in a subset of patients with unresectable or metastatic GIST. In this study we analyzed the role of Imatinib mesylate associated with surgery in unresectable and/or metastatic GISTs.

PATIENTS AND METHODS: We searched for all published and unpublished RCTs and controlled clinical trials, and we conducted the review according to the recommendations of the Cochrane Collaboration. The statistical analysis was done using Review Manager 5 software.

RESULTS: We didn't find RCTs or controlled clinical trials on this issue. A subgroup analysis in the patients preoperatively treated with Glivec showed a lower incidence of recurrent or metastatic GISTs,

and a higher incidence of locally unresectable GISTs in responsive patients ($P=0,001$). Furthermore, the same patients group presented a better 12 and 24 months DFS (disease free survival) after complete resection (respectively $P=0,06$ and $P=0.003$) and a better 24 months OS (overall survival, $P=0,04$). Moreover, small bowel GISTs presented a greater rate of progressive or stationary disease after Imatinib treatment; while gastric GISTs showed a complete or partial response more frequently ($P=0.008$).

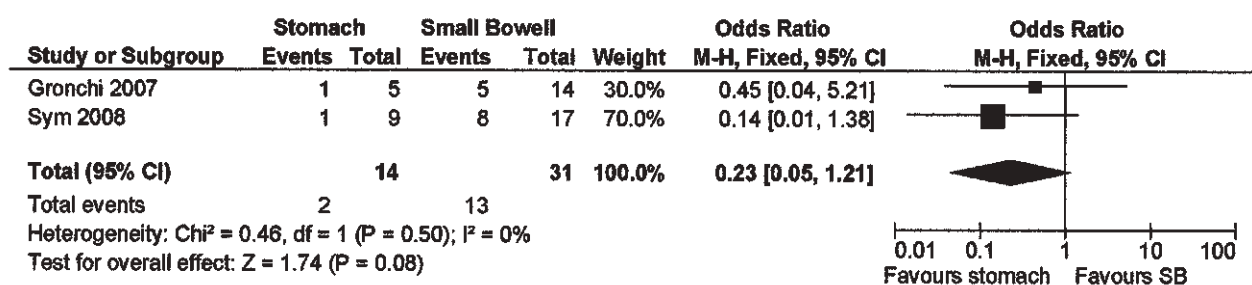
CONCLUSION: No randomized controlled clinical trials analyze the role of surgery in advanced disease. Imatinib mesylate represents the standard preoperative treatment for locally unresectable and/or metastatic GISTs and a trial is not required to compare this approach versus surgery alone. For patients responding to Imatinib or patients with prolonged stable disease, resection of residual disease should be considered. Moreover, surgery is to be considered for patients at higher risk of complications during pharmacological debulking. In advanced GISTs the advantages of the integrated treatment are significant in the complete or partial response disease group, in term of more complete resection, and better disease free and overall survival.

Preoperative methylprednisolone administration maintains coagulation homeostasis in patients undergoing liver resection: importance of inflammatory cytokine modulation

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BACKGROUND: Alterations in hemostatic parameters are a common finding after major hepatic resection. There is growing evidence that inflammation has a significant role in inducing coagulation disarrangement that follows major surgery. This study was aimed to determine



whether preoperative methylprednisolone administration has a protective effect against the development of coagulation disorders; we evaluated the effect of preoperative steroids administration on changes in hemostatic parameters and plasma levels of inflammatory cytokines in patients undergoing liver surgery.

PATIENTS: Seventy-three patients undergoing liver resection were randomized to a steroid group or to a control group. Patients in the steroid group received 500 mg of methylprednisolone preoperatively. Serum levels of coagulation parameters (prothrombin time, platelets, fibrinogen, plasma fibrin degradation products [D-dimer], antithrombin III) and inflammatory mediators (IL-6 and TNF) were measured before and immediately after the operation and on postoperative days 1, 2, and 5. Multivariate analysis was performed to identify factors related to the characteristics of the patients and surgery affecting coagulation parameters between the two groups.

RESULTS: Decreases in antithrombin III, platelet count and fibrinogen levels, prolongation of prothrombin time, and increases in the plasma fibrin degradation products were significantly suppressed by the administration of methylprednisolone. Cytokines production was also significantly suppressed by the administration of methylprednisolone, and there was significant correlation between plasma levels of cytokines and coagulation alterations.

CONCLUSIONS: These findings suggest that preoperative methylprednisolone administration inhibits the development of coagulation disarrangements in patients undergoing liver resection, possibly through suppressing the production of inflammatory cytokines.

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Prevention of small for size syndrome: liver compensatory hypertrophy induced by portal vein occlusion techniques

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BACKGROUND: The extent of liver resection is limited by the functional reserve of the remnant liver. The introduction of preoperative portal vein occlusion techniques (portal vein embolization-PVE- and portal vein ligation-PVL) to induce a compensatory hypertrophy of the future remnant liver (FRL) has reduced postoperative complications, “small for size syndrome” above all. PVE and PVL block the portal venous flow to the side of the liver ipsilateral to the lesion and redirect portal flow to the intended FRL. This paper was aimed to assess the efficacy of right PVE and right PVL for induction of volumetric increase of the left lateral liver lobe before extended right hepatectomy. It has moreover remained a matter of debate whether PVE or PVL during exploration is the preferred technique, so we made a comparison between the two techniques in order to evaluate their effectiveness and rate of complication.

PATIENTS: Between January 2006 and December 2008, 47 patients, affected by primary or secondary liver neoplasms, underwent portal vein occlusion to induce hypertrophy of FRL at Department of Surgery – Liver Unit at Scientific Institute H. San Raffaele. 35 patient underwent PVE (PVE group) and were retrospectively compared to 12 patient who underwent PVL during a first time laparotomy (PVL Group). Groups were compared in terms of demographic data, concomitant diseases, stage of disease, extent of liver resection and use of previous chemoradiotherapy. The outcome was evaluated in terms of effectiveness of the procedure (liver volume increase), complications associated to vascular occlusion technique and postoperative stay, mortality and morbidity.

RESULTS: Patients were homogeneously distributed into groups. There were no complications related to PVE or PVL. There was no significant difference between the two groups in the increase of the left liver volume. After PVE and PVL, right hepatectomy was performed in 28 and 7 patients, respectively. In the remnant number of patients liver resection was not carried out mainly because of disease spreading. Mortality was nil in both groups, and morbidity rates were not significantly different.

CONCLUSIONS: Preoperative PVE and PVL are safe and effective methods of increasing the remnant liver volume before extended liver resection. During the first laparotomy of a two-stage hepatectomy, PVL can be efficiently and safely performed.

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Liver redox status induced by ischemia-reperfusion injury during hepatic surgery: analysis of hematic and tissutal parameters.

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INTRODUCTION: Strategies to reduce intraoperative bleeding during liver resections include temporary occlusion of blood inflow by hepatic pedicle clamping (Intermittent Pringle manoeuvre).

When oxygen supply to cells becomes insufficient as a direct result of a too long period of hepatic vasculature clamping, hepatic “ischemia reperfusion” (IR) injury may result: this is a phenomenon whereby cellular damage in a hypoxic organ is accentuated following the restoration of oxygen delivery. The main source of damage are reactive oxygen species that can affect the result of the surgical procedure, altering the “oxidative balance” with a prevalence of oxidant species. This paper was aimed to investigate the alterations of the redox status induced by Pringle manoeuvre on plasma and liver tissues, in patients undergoing liver surgery for benign and malignant pathology. Glutathione is the main thiol involved in antioxidant cellular defence: its active site is represented by SH group. Redox status depends mainly on relative amount of reduced and oxidized forms of this molecule.

PATIENTS AND METHODS: From December 2004 to May 2006, 43 patients undergoing liver resection at Department of surgery – Liver Unit at Scientific Institute H. San Raffaele were enrolled in the study. In thirty-six patients hepatic resection was performed under portal clamping (Pringle manoeuvre, group P). In seven patients the Pringle manoeuvre was not used because not necessary, and considered as a control group (group NP). The study consisted in collection of liver tissue samples (before the ischemic period, after the first ischemic period and after 20 minutes of the last reperfusion) and plasmatic samples (before surgery, at the end of surgery, in POD 1 and 4).

RESULTS: In P group we can see a significant reduction of tissue cysteine, cysteinyl-glycine, and glutathione, after the ischemic phase, compared to basal values. This reduction continues also during the reperfusion phase. In the NP group, in the absence of ischemic phase, these modifications are less important. Plasmatic concentration of cysteine and cystenyl-glycine increases in postoperative days, reaching higher values than at basal conditions in

both groups, while total glutathione is lower than normal values in all patients. There's moreover a low activity of glutathione peroxidase (lacking of substrate to peroxide), and an increased activity of glutathione reductase.

CONCLUSIONS: Thiol redox status, expressed as a ratio between their reduced and total concentration, and the postoperative trend of detoxifier enzymes (glutathione peroxidase and glutathione reductase) revealed to be specific and sensitive markers of cellular homeostasis, showing that the lack of their substrate (glutathione) and its presence in a prevalent oxidized form, caused a block in α -glutamyl cycle, and inhibits enzymatic activity. Since oxidative stress is accompanied by alteration in these parameters, closely linked each other, they could be used to design a dynamic profile of redox status. This study also noticed a correlation between systemic and response “in situ”, showing that circulating factors reflect local hepatic situation, and can be used as surrogated marker of oxidative stress.

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Interpretation of Maspin expression in pancreatic tumors

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INTRODUCTION: Maspin (Mammary Serine Protease Inhibitor) was initially isolated as a protein expressed in normal mammary epithelial cells and absent in breast carcinomas¹. Further research led to maspin characterization as a serpin with tumor suppressive properties, based on inhibition of cell invasion and angiogenesis, and promotion of apoptosis^{2,3}. Most normal epithelial cells express maspin and the loss of its expression appears to be involved in human carcinogenesis⁴. Paradoxically, some human cancers such as ovarian, lung and pancreatic acquire maspin expression properties⁵⁻⁸. Maspin expression is controlled through the epigenetic state of its promoter that involves cytosine methylation and histone acetylation. Maspin is aberrantly methylated and epigenetically silenced in most carci-

noma cells compared to their cells of origin⁹⁻¹¹. Otherwise, maspin gene is not expressed in normal human pancreatic cells, but its expression is acquired during carcinogenesis. The gain of expression is regulated by the same epigenetic mechanisms, but in the opposite direction¹². Maspin-negative pancreatic cells have a methylated maspin promoter, and the associated histones are hypoacetylated, whereas pancreatic carcinoma cells display activation of maspin expression linked to demethylated promoters and hyperacetylation of the histones. This study was aimed to investigate maspin expression in a series of different pancreatic tumors.

MATERIALS AND METHODS: A series of 66 surgically treated pancreatic tumors between 1996 and 2008 was evaluated for maspin expression. 39 patients were men and 27 were women, with a mean age of 67 years (range 39-78 years). All pathological slices were reviewed to confirm the diagnosis, considering the following different histological types: 41 ductal adenocarcinomas; 5 ampullary adenocarcinomas; 3 peri-ampullary carcinomas; 3 papillary carcinomas; 3 mucinous cystadenocarcinomas; 1 mucinous cystadenoma; 2 cases of intra-ductal papillary mucinous carcinomas; 4 choledocal carcinomas; 2 biliary duct tumors; 2 neuro-endocrine tumors. Five-micrometer sections of formalin fixed neoplastic tissue were used for immunohistochemical staining: they were placed in a 99°C oven and deparaffinized, then placed in citric acid solution (pH 6.0) to perform the antigen. The slices were quenched in a hydrogen peroxide solution to block for endogenous peroxidase and incubated with the antihuman maspin monoclonal antibody G167-70 (PharMingen International, San Diego, CA, USA; diluted 1:500). The detection system used was based on the application of an antibody linking enzyme and a chromogen substrate. The maspin immunostaining was graded as negative (<5%) and positive (>5%).

RESULTS: All epithelial malignant pancreatic tumors showed maspin expression. Maspin was not detected in epithelial benign tumors, in neuro-endocrine tumors and in peri-tumoral pancreatic tissue. In the mucinose cystadenoma, maspin expression was associated only with the cystic dysplastic areas. Moreover, immunohistochemical staining showed two different sub-cellular localizations (cytoplasmic and nuclear) and therefore three possible labeling patterns (greater cytoplasmic, greater nuclear, equal). The cytoplasmic localization and pattern were the most frequent, while only a sporadic antibody positivity was found for the nuclear localization and only one case could be considered a greater nuclear pattern.

CONCLUSIONS: Our results show that maspin expression hardly characterizes a malignant degeneration of the pancreatic epithelial tumors. Maspin presence discriminates between carcinomas and epithelial benign tumors, and between carcinomas and non-epithelial

malignant tumors. Moreover, positivity only in dysplastic areas of the mucinous cystadenoma inner side may suggest an early biological relevance of maspin in carcinogenic process. Furthermore, the immunohistochemical staining for maspin may be helpful in differentiating malignant lesions from peri-tumoral tissue in cases of inflammatory cytological and architectural atypia. Different labeling patterns of maspin suggest that the protein may have different functions depending of its sub-cellular localization.

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The Abdominal Compartment Syndrome and the decompressive laparotomy in patients with severe acute pancreatitis.

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INTRODUCTION: The Abdominal Compartment Syndrome (ACS) is an increasingly recognized complication in medical and surgical patients. The World Society of the Abdominal Compartment Syndrome defined Intra Abdominal Hypertension (IAH) as a mean Intra Abdominal Pressure (IAP) ≥ 12 mm Hg and the ACS as IAP ≥ 20 mmHg (with or without an Abdominal perfusion pressure < 60 mm Hg) that is associated with dysfunction or failure of one or more organ systems that was not previously present. The IAH contributes to organ failure in patients with abdominal trauma and sepsis and leads to the development of ACS. The true prevalence of IAH in patients with severe pancreatitis is not known. A study of 297 patients treated for Severe Acute Pancreatitis (SAP) in China showed that the overall incidence of IAH was 36%¹. In a study comparing patients treated for SAP with or without ACS the hospital mortality rate for patients with ACS was 50% compared with 15% in patients without ACS². The clinical impact of IAH/ACS on pancreatic infection and organ failure in SAP patients needs to be investigated. This study aims to investigate the clinical significance of IAH in patients with SAP, the prevalence of ACS and the importance of abdominal decompressive laparotomy.

PATIENTS AND METHODS: The study included 6 patients, 2 men and 4 women with an average age of 68 years (range, 45-87) operated for SAP between January and December 2008. SAP was defined as attacks of acute pancreatitis associated with the development of organ failure and/or local complications. Patients with chronic pancreatitis were excluded from the study. According to gold-standard methods, we indirectly measured the IAP using the transvesical route via Foley bladder catheter. **RESULTS:** Among 6 patients with SAP, 3 patients (50%) developed an IAH > 16 mm Hg and they reported no significant organ dysfunction. Other 3 patients (50%) developed an IAH > 27 mm Hg associated with organ dysfunction. For this reason, the last three patients underwent a decompressive re-laparotomy with temporary closure. Two (66,7%) of them died in the early postoperative course.

CONCLUSION: IAH and ACS are frequent in patients with SAP and are frequently associated with impairment in organ function. Mortality is high in patients with IAH for the relationship between IAH/ACS and organ dysfunction. The laparotomy with temporary closure, necrosectomy and drainage may improve survival in patients with SAP.

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A signal detection analysis of medical decision

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BACKGROUND: In the medical practice, making a decision means using and combining different information, answering as soon as possible to emergencies and selecting the most effective decisional strategies in a state of uncertainty. This study was aimed to examine the role of The Signal Detection Theory on medical decision. The Signal Detection Theory enables us to estimate the decisor's attitude, and in particular, as proposed by Primi¹, the optimal parameter allows to assess his position along a continuum gambler-conservative, where:

$$\beta_{opt} = \frac{p(N)(V_{CR} + C_{FA})}{p(I)(V_H + C_M)}$$

Here p(N) is the probability to being not ill, p(I) the probability to be ill, V_{CR} and V_H the benefits of a correct rejection or of a Hit, C_{FA} and C_M the costs of a false alarm or of an omission.

MATERIALS AND METHODS: In our research, we created a questionnaire that has been administered to 82 physicians, in which they had to rate how serious were 10 diseases, and how frequently they were met in their practice. They had also to assess costs and benefits of respectively hits, correct rejections, false alarms, and omissions for each disease.

RESULTS: The results show a significant propensity to act as gamblers (that is, to establish the presence of the disease even if it could create false alarms) in serious illnesses, and to act in a conservative way in slight illnesses.

CONCLUSIONS: The proposed experiments showed that Signal Detection Theory can play a fundamental role in the study of decision making, and that optimal β is a reliable parameter in cost-benefit evaluation.

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Evaluation of stability and instability of advanced carotid plaques with a panel of circulating inflammatory markers

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INTRODUCTION: Recent studies suggest that inflammation plays an important role on the pathogenesis and evolution of atherosclerotic plaques complications, but usually studies compared atherosclerotic patients with healthy controls subjects. Nevertheless, the pathophysiologic mechanisms linking together inflammation and atherosclerosis still remain unclear. From the clinical point, in addition to the well recognised risk factors for thromboembolic complications such as degree of the stenosis, ultrasonography structure of the plaque, previous symptoms, it would be useful to be able to discriminate stable from unstable plaques. The purpose of this study is to verify if an association exists between a systemic inflammatory status and the biological activity of advanced carotid plaques, classified as stable and unstable on the basis of a histopathologic and immuno-histochemical examination after carotid endarterectomy.

PATIENTS AND METHODS: Twenty-eight symptomatic and asymptomatic patients that were candidates to carotid endarterectomy conforming ECST¹ criteria were enrolled. Pre-operative measurements of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor alpha (TNFα), fibrinogen, von Willebrand factor (vWF), D-dimer and homocysteine were performed. After endarterectomy plaques were classified as stable or type V conforming AHA², and unstable or type VI by two blind, independent pathologists. Statistical analysis was performed with the bivariate and multivariate logistic regression.

RESULTS: At least one marker was abnormally higher in 26 of the 28 patients. Fifteen plaques were classified as type V and thirteen as type VI. The two groups of patients identified in relationship with the type of plaque presented similar clinical characteristics. According to the Student t test and the Mann-Whitney U test only the TNFα concentration was significantly different ($p < 0.05$) between the two groups. At multivariate analysis the evaluation of the markers that were positive at least in ten patients correctly identifies the type of plaque in 86 % of the cases; an exploratory model, that considered significant only TNFα and homocysteine, permits to correctly diagnose 80% of cases.

CONCLUSIONS: High levels of TNFα are significantly associated with the presence of unstable carotid plaques. The contemporary assessment of several markers allows to correctly identify the type of plaque in 84% of cases, but TNFα only associated with homocysteine also retains a high predictive value (80 %).

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Cervico-mediastinal goiters: physiopathological aspects and choice of surgical treatment.

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INTRODUCTION: Different surgical classifications have been proposed for the topographic evaluation of cervico-mediastinal goiters, particularly for the mediastinal involvement and vascular connections. Ultrasounds and other radiological exams are very important to evaluate the relationship between thyroid increase in volume and mediastinal structures. Goiters that expand at least 3 cm below the thoracic outlet are – according to several Authors – suitable to surgical treatment, sometimes more invasive. In selected cases a sternal split or even sternotomy is required in addition to cervicotomy.

MATERIALS AND METHODS : Our experience from January 1999 to December 2008 is presented. Among 331 patients with mediastinal lesions, 53 had a goiter. Twelve of these were cervico-mediastinal (22.6 %) and 4 ectopics. In all these cases a surgical treatment was performed, with the exception of a patient with severe ischemic cardiomyopathy. The classic cervicotomy was sufficient in 9 cases, while a sternotomy (4 pts) and a thoracotomy (2 pts) was necessary in 6 patients, considering the depth of the goiter, vascular relationships and tracheal dislocation.

DISCUSSION: Patients with mediastinal goiter treated via a cervicotomy had an average stay in-hospital of 3 days; those treated via a sternotomy or toracotomy stayed 6 days. Two patients presented clinical signs of hypocalcemia that required medical therapy. Other 2 patients presented hypophonia due to monolateral cord hypomobility seen at tracheoscopy. Mediastinal and dyspnoic

symptoms disappeared after surgical treatment in patients with tracheal dislocation.

CONCLUSIONS: Cervico-mediastinal goiters require always a surgical removal, often through the classic Kocher cervicotomy, but sometimes through a partial or total sternotomy. Their treatment is related to surgeon's experience.

Parafibromin expression, single-gland involvement and limited parathyroidectomy in Familial Isolated Hyperparathyroidism

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INTRODUCTION: Familial Isolated Hyperparathyroidism (FIHP) is a rare inherited syndrome with a variable extent of parathyroid involvement. Extensive Parathyroidectomy is usually indicated, but limited excisions may be performed because a single-gland involvement is often reported¹. FIHP is caused by inactivating mutations of HRPT2, a suppressor oncogene coding for the Parafibromin, an intracellular protein. Biallelic mutations may inactivate HRPT2 and Parafibromin production; subsequently, loss of Parafibromin expression may be considered a distinctive feature of FIHP². This study was aimed to evaluate the extent of parathyroid involvement and Parafibromin expression in parathyroid tissues in FIHP patients.

PATIENTS AND METHODS: Twelve consecutive patients (median age 31 years, range 11-58) from 3 FIHP families with confirmed HRPT2 mutations underwent bilateral neck exploration, selective excision of the grossly enlarged glands and, when necessary, biopsies of the apparently normal parathyroids. Parafibromin expression was evaluated by immunohistochemical staining in FIHP tissues and compared to 18 adenomas from sporadic hyperparathyroidism and 10 normal parathyroids accidentally removed after surgery for thyroid disease.

RESULTS: Pathology confirmed a single-gland involvement in all cases of FIHP (11 adenomas and 1 parathyroid carcinoma) and the presence of normal tissue in all grossly normal parathyroids. The selective excision of macroscopically enlarged glands achieved the cure of hyperparathyroidism in all cases, except a persistent disease in 1 case of parathyroid carcinoma. After a mean follow up of 10,2 years (range 2-27), all the remaining patients are disease-free, although 3 patients underwent successful reoperations for single-gland recurrence after 5, 9 and 27 years. In specimens from FIHP patients, Parafibromin was absent in all cases of grossly and histopathologically affected glands while it was strongly stained in 100% of cases of normal parathyroid tissue. Parafibromin was also

strongly evident in all adenomas from sporadic-Hyperparathyroidism patients and in normal glands ($p < 0,01$).

CONCLUSIONS: The loss of Parafibromin expression is the distinctive marker of parathyroid involvement in FIHP. A single-gland involvement may occur often; limited and focused parathyroidectomy may be effective and achieve long-term disease-free periods

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HRPT2 mutations, Parafibromin and PGP 9.5 expression in sporadic parathyroid carcinoma

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INTRODUCTION: Parathyroid carcinoma (PC) is a rare disease; its definitive diagnosis may be challenging, especially in case of absence of unequivocal diagnostic criteria (histopathological vascular and extracapsular invasion of the adjacent tissues; distant metastases), with subsequent under-recognition and possibly under-treatment. In these cases a prolonged and strict follow up is required to assess the diagnosis. Recently, somatic inactivating mutations of HRPT2 (a gene encoding the Parafibromin, a nuclear protein with antiproliferative effects) have been described in most cases of sporadic PC¹; furthermore, an increased expression of PGP 9.5 (a protein produced by the oncogene UCHL-1) has been recently described in Parathyroid Carcinoma. This study was aimed to assess the role of HRPT2 mutations and the usefulness of Parafibromin and PGP 9.5 immunostaining in the diagnosis of sporadic PC.

PATIENTS AND METHODS: Somatic and germ-line mutations of HRPT2 gene and immunohistochemical evaluation of nuclear Parafibromin and PGP 9.5 was assessed in 3 unequivocal PC, in 20 sporadic adenomas and 10 normal parathyroids (control group).

RESULTS: Germ-line HRPT2 mutations were absent in all patients. Somatic HRPT2 mutations were absent in 100% of cases in the control group and in 2 PC patients, while a novel inactivating mutation of HRPT2 was found only in 1 PC. Nuclear Parafibromin staining was strongly evident in all cases in the control group; it was

weakly and variably present in 2 PC and absent in the remaining case. PGP 9.5 expression was positive in all cases of the control group while it was strongly expressed in the case of Parathyroid Carcinoma with absent Parafibromin staining and variably expressed in the remaining 2 cases.

CONCLUSIONS: Loss of nuclear Parafibromin staining may be a useful tool for the diagnosis of PC in most cases. However, since HRPT2 mutations may not be involved in a subset of PC, its negative predictive value may be limited. PGP 9.5 may be a useful diagnostic tool, but further studies are needed.

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