in the highest income areas were less likely to die from colorectal cancer (MRR 0.77; 95% CI:0.65-0.89). Divergence in colorectal cancer mortality among individuals living in different income areas increased over time, with rising colorectal cancer mortality observed in the lowest income areas and declining colorectal cancer mortality observed in the higher income areas. Conclusions: Individuals living in lower income neighborhoods are continuing to experience rising colorectal cancer mortality, despite residing in a jurisdiction with universal health care and should receive increased efforts to reduce colorectal cancer mortality.

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Race and Colorectal Cancer Stage in an Equal Access Medical System

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Background: Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States. In the past decade, there has been tremendous progress in reducing colorectal cancer incidence and death rates largely through prevention and early detection. Overall, colorectal cancer incidence and mortality rates are highest in black men and women. In general, blacks have also been diagnosed at a later stage compared to non-blacks. This disparity may be due to a number of factors, such as disproportionately limited access to medical care for blacks. The military health care system is unique in that equal access is available to all patients. The aim of this study is to evaluate if there is a difference in patient age and colorectal cancer stage at diagnosis between blacks and non-blacks in an equal access medical system. Methods: We conducted a retrospective cohort study examining data from patients diagnosed with colorectal cancer in an academic tertiary military health system from 2007-2012. Data including age, race, and stage of cancer at diagnosis were reviewed. Results: Data were available for 192 patients. The average patient age diagnosed with colorectal cancer was 60.5 years and the majority of patients were male (70%). Blacks comprised 8% of the total patient population diagnosed with CRC. The average age of CRC diagnosis of non-blacks was 60.3 years and 64.1 years for blacks (p=0.508). There was no difference in the stage of CRC at diagnosis between blacks and non-blacks (p=0.915). Furthermore, 47% of blacks were diagnosed at advanced CRC stage compared to 55% of non-blacks (p=0.614). Conclusion: In an equal access medical system, there was no difference between blacks and non-blacks with regard to patient age and stage of CRC at diagnosis.

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Bile Acid Malabsorption is a Very Common Cause of Diarrhoea Secondary to Different Cancer Therapies for a Whole Range of Different Cancer Types

Frank Phillips, Jervoise Andreyev

Introduction In the UK, approximately 16,000 patients per year are left with a chronic change in bowel function and gastrointestinal symptoms following treatment for cancer. This can have a significant impact upon quality of life and even compromise on-going cancer therapy. Previous small studies focusing on patients with gynaecological cancers suggest that bile acid malabsorption (BAM) may be an important cause of radiotherapy-induced diarrhoea. This retrospective study aims to elucidate the true prevalence of BAM in all patients referred to a specialist gastroenterology clinic which specialises in treating patients with consequences of cancer treatments. Methods Patients referred to our clinic are managed using a peer reviewed algorithm. If they report diarrhoea, defined as Bristol Stool Charts type 6-7, a routine referral for a SeHCAT (75-selenium homocholic acid taurine) scan is made to diagnose possible BAM. BAM is diagnosed when the SeHCAT 7 day retention is <15% and is graded mild (10-15%), moderate (5-10%) and severe (<5%). Results During a four year period between 2009-2013, 506 consecutive patients were referred for a SeHCAT scan. 276 (54.5%) were male (median age 66) and 230 (45.5%) female (median age 61). The graphs below show the proportion of patinets with each type of cancer who have BAM, with mild, moderate and severe grades indicated accordingly. Conclusions This study has several new and important findings, and the BAM seen is likely to be caused by a variety of reasons. Some of the stand-out findings include: 1) Cancers lower down in the pelvis generally have much lower rates of BAM than those higher in the pelvis. This is likely due to reduced collateral damage to the terminal ileum. 2) Notwithstanding this, there are significantly lower rates of BAM in prostate cancer, which is treated with radiotherapy alone and may therefore lack a sensitising effect from chemotherapy. 3) The high rates of BAM and severe BAM after colon cancer treatment is associated with right hemicolectomy, which removes the terminal ileum. 4) The high rates of BAM and severe BAM after pancreatic cancer treatment is associated with the Whipple's procedure. Subsequent fat malabsorption likely interferes with bile acid reabsorption. 5) The high rates of BAM seen after myeloma treatment is exclusively caused by the use of lenalidomide. It is notable that the majority have severe BAM. Overall, this landmark study with significant patient numbers establishes BAM as a very frequent cause of diarrhoea secondary to cancer treatments. Given the effectiveness of dietary fat manipulation combined with a new generation of bile acid sequestrants for BAM, SeHCAT scanning should be a first line investigation for patients with diarrhoea after cancer therapies.

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Protective Effects of Beta-Cn(94-123), a Bioactive Peptide Present in Fermented Milk, in Inflammation and Stress-Related Gastrointestinal Disorders

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Background : beta-CN(94-123) is a recently discovered casein-derived bioactive peptide found in yogurt, targeting goblet cells. Our aims were to determine whether this peptide was able to reinforce the intestinal barrier function in two animal models of epithelial barrier breakdown: neonatal maternal deprivation (NMD) and indomethacin-induced intestinal inflammation (Indo). Methods: Male Wistar rats were submitted to NMD three hours a day, from postnatal days 5 to 20. Beta-CN (94-123), or its vehicle, was administered by gavage from day 10 to day 20, at the concentration of 0.01, 1 and 100 µM (10µL/g of body weight). Animals were thereafter euthanized either at day 24 or at 12 weeks-old. Portions of jejunum and colon were collected and (i) mounted in Ussing chambers to evaluate paracellular permeability to FITC-dextran 4kDa, (ii) fixed for mucin Muc2 immunohistochemistry. In a second study, adult male Wistar rats were orally treated with beta-CN(94-123) for 8 days, then injected twice with 10 mg/kg indomethacin (s.c.) to induce intestinal inflammation, and euthanized at day 12. Jejunum were collected to determine macroscopic and microscopic damage scores, cytokine expression, myeloperoxydase activity and Muc2 and mucus layer labeling. Finally, we determined whether the peptide was able to stimulate wound healing on HT29 cells. Results: beta-CN(94-129) abolished NMD-induced jejunal paracellular hyper-permeability (0.87 ± 0.16 vs 2.61 ± 0.51 [p<0.01] and 1.65 ± 0.13 vs 0,59 ± 0,20 nmol.h^{-1}.cm^{-2} [p<0.01] at day 24 and 12 weeks-old, respectively) and goblet cell depletion, at the dose of 0.01µM. Similar observations were made in the colon, but at a concentration of 100 µM. In the second study, beta-CN(94-129) 100 µM prevented inflammation-induced increase of MPO activity, as well as TNFα and IL-1β expression [p<0.001]. Indomethacin induced severe epithelial erosion, neutrophil infiltration and goblet cell depletion associated with mucus thickening. All these parameters were ameliorated upon pretreatment with beta-CN(94-123) 100 µM, but not at lower concentrations. Wound healing experiments showed a stimulation of epithelial restitution of wounded HT29 monolayers, which was inhibited by pretreatment with anti-CCR6 neutralizing antibody. Conclusions: Beta-CN(94-123) given orally, prevents intestinal barrier alterations triggered by stress or chemically-induced inflammation in rats. The mechanism of action would include a CCR6-dependent pathway. This peptide may represent a novel therapeutic approach for intestinal diseases therapies.

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Lanreotide Autogel 120 mg As a Treatment for Chronic Idiopathic Refractory Diarrhea : A Multicenter Prospective Trial

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Introduction Lanreotide has an inhibitory effect on gastrointestinal secretions and motility. We evaluated the efficacy and safety of the prolonged-release somatostatin analogue lanreotide Autogel 120 mg for the treatment of persistent idiopathic diarrhea in a multicenter, prospective, open label study. **Materials & Methods** The study was performed in 10 centers between July 2009 and August 2012. The study protocol was approved by the Ethics Committee of UZ Leuven, Belgium (ClinicalTrials.gov NCT00891371; EudraCT 2009-009356-20). Male or female adult patients with refractory diarrhea (mean of > 3 stools/24 h) for at least 1 month after workup to rule out inflammatory, infectious causes, and rectum disorders, and insufficient /non-response to standard anti-diarrheal were treated for 8 weeks with lanreotide autogel 120 mg deep s.c. every 4 weeks. Patients' stool frequency and consistency (Bristol Stool Form Scale) were recorded in a daily diary. Quality of life (QOL) was assessed using the SF-36 and IBS-QOL questionnaires. Responders were patients with a ≥50% decrease or a normalization of the mean number of stools. Adverse events (AEs) were recorded during the entire study. **Results** In total, 36 patients (24 women, 12 men) with chronic refractory diarrhea were studied. The mean age was 55.2 ± 16.4 years. Four weeks after the first injection (Day 28), 44.4% of patients were responders, which increased to 54.3% at Day 56. Response rates were higher in male patients (58.3%) compared to females (37.5%). Overall, the mean number of stools decreased significantly from 5.5 ± 2.3 at baseline to 3.6 ± 2.2 at Day 56 (-30.7%) (p = 0.0006). In the responder subgroup at Day 56 this number changed significantly from 5.3 ± 2.4 to 2.2 ± 0.8 (p < 0.0001). The median percentage of days per week with less than 3 stools/day increased from 7.1% at baseline to 57.1% at Day 56. At Day 56, the mean change from baseline for the IBS-QOL score was +16.3. Similarly, the SF36-QOL scores improved at Day 56, especially in the domains of social functioning (+14.0), physical role (+11.8) and mental health (+10.1). In the responder subgroup at Day 56, the mean stool consistency score dropped significantly from 6.4 ± 0.7 to 5.2 ± 1.2(p = 0.0005). In total, 93 treatment emergent AEs were reported, of which the majority (79) were mild to moderate and only 9 were serious. The most frequently reported AEs were gastrointestinal disorders (abdominal pain, 25% of patients; nausea, 11.1% and steatorrhea, 8.3%), injection site reactions (16.7%) and asthenia/fatigue (11.1%). **Conclusion** This study showed improvement of diarrheal symptoms and QOL during therapy with lanreotide autogel 120 mg treatment, which suggest it is effective for the management of persistent refractory idiopathic diarrhea. Confirmatory studies are needed.

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Diamine Oxidase Activity As a Serum Biomarker for Intestinal Mucosal Damage, Appearance of Diarrhea and Malnutrition Due to Anticancer Drugs

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Aim:Intestinal mucosal damage due to anticancer drugs which induces QOL impairment and malnutrition is one of major problems for cancer treatment. However, there is no method to evaluate objectively intestinal mucosal damage and malnutrition due to anticancer drugs. Diamine oxidase(DAO) is an enzyme which exists specifically in villi tips of enterocytes of the small intestine. Since DAO activity decreases as intestinal mucosa is damaged, it is expected that DAO activity is a good indicator which reflects sharply damage of small intestinal mucosa. The aim of this study is to investigate whether DAO activity is useful as an indicative marker for intestinal mucosal damage, appearance of diarrhea and malnutrition in patients with chemotherapy. Method:The subjects are 20 patients with unresectable advanced gastric cancer who received docetaxel, CDDP and S-1(DCS) combination chemotherapy (Takayama et al, Br J Cancer, 2008) as a first line chemotherapy. DCS therapy is a modified regimen of docetaxel, CDDP and 5-FU combination chemotherapy, in which 5-FU was replaced by S-1. DAO activity was measured according to the methods of Takagi et al. (Clin Chim Acta, 1994) before, during and after chemotherapy. Mucosal atrophy is characterized by diminished intestinal function as well as morphological changes including decreased villous height, surface area(Shaw et al, World J Gastroenterol, 2012) and reduction in the number of goblet cells(Chang et al, World J Gastroenterol, 2005). Therefore, damage

of small intestinal mucosa was evaluated by villous height, villous surface area and the number of goblet cells by endoscopic duodenum biopsies before and during chemotherapy. Degree of diarrhea was evaluated by NCI-CTC V4.0. Nutrition was evaluated by serum albumin and serum total protein before, during and after chemotherapy. Results:The mean DAO activities(± SD) in 20 patients were 4.88±2.06U/L before chemotherapy, 2.96±1.62U/L during chemotherapy(day14) and 3.66±1.27U/L after drug holiday(day21). The DAO activity decreased significantly during chemotherapy and recovered significantly after drug holiday. Diarrhea(Grade1-3) appeared in 19 patients in the 10 to 18 day after administration of anticancer drugs and followed decrease in DAO activity. Villous height, villous surface area, the number of goblet cells were all significantly reduced by anticancer drugs and followed decrease in DAO activity. Serum albumin and serum total protein were significantly reduced by anticancer drugs and significantly increased after drug holiday. The DAO activity reduction rate between day1 and day14 was significantly correlated with albumin and total protein reduction rate between day1 and day21. Conclusion:Our results suggested that the DAO activity was useful as an indicative marker for intestinal mucosal damage, appearance of diarrhea and malnutrition in patients with chemotherapy.

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Occludin Limits Epithelial Survival by Inducing Caspase-3 Expression

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BACKGROUND & AIMS: Knockout (KO) of the tight junction protein occludin (ocln) has been reported to have no impact on intestinal barrier function ex vivo. However, in vivo and in vitro studies have implicated ocln in cytokine-induced paracellular barrier loss. Further, ocln expression is downregulated in human and experimental inflammatory bowel disease (IBD). Thus, ocln function remains enigmatic. Our aim was to define the contributions, if any, of ocln to intestinal epithelial homeostasis and pathogenesis of intestinal disease. METHODS: Ocln KO and transgenic mice, caspase-$3^{+/-}$ mice, ocln knockdown (KD) Caco-2 cells, and human biopsy samples were studied. RESULTS: Ocln KO mice were resistant to DSS-induced mucosal damage and colitis relative to wild type (WT) mice (weight loss WT 9±2%, KO 1±0.4%, P<0.01). Disease sensitivity could be restored by intestinal epithelial-specific ocln expression in ocln KO mice (weight loss increased to 7±2%, P<0.01 versus ocln KO), showing the importance of epithelial ocln in promoting DSS colitis. Further analyses showed that, while epithelial proliferation was not affected, epithelial apoptosis was markedly reduced in ocln KO, relative to WT, mice after DSS treatment. Ocln KO mice were also protected from intestinal epithelial apoptosis induced by 5-fluorouracil (5-FU) or tumor necrosis factor-α (TNF), indicating that ocln promotes both intrinsic and extrinsic pathways of apoptosis. TNF-induced caspase-8 and -9 activation were unaffected by ocln KO, but caspase-3 activation was reduced. Consistent with this, cytochrome C and dATP failed to efficiently activate caspase-3 in cytosolic extracts of Ocln KD Caco-2 cells. Moreover, caspase-3 protein and mRNA expression were reduced in ocln KO colonocytes (to 47±9% and 46±5% of WT colonocytes, respectively) and olcn KD Caco-2 cells, and caspase-3 promoter activity was decreased in ocln KD Caco-2 cells (to 45±7% of control), indicating that ocln promotes caspase-3 transcription. Similar to ocln KO mice, DSS- or 5-FU-induced intestinal epithelial apoptosis were reduced in caspase-$3^{+/-}$ mice (caspase-3 expression decreased to 54±6% of WT) relative to WT mice, suggesting that caspase-3 expression decrease is responsible for the protection afforded by ocln KO. Analyses of colon biopsies from ulcerative colitis patients and control subjects showed a direct correlation between ocln and caspase-3 expression, indicating ocln downregulation may promote epithelial survival to limit IBD disease progression. CONCLUSION: Ocln expression enhances caspase-3 promoter activity and sensitivity to intrinsic and extrinsic apoptotic stimuli. Conversely, reduced ocln expression increases epithelial survival. Thus, in addition to reducing paracellular barrier function, decreased ocln expression in colitis may limit intestinal epithelial apoptosis, reduce damage, and promote mucosal homeostasis.

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Chemotherapy Induced Diarrhea in Colorectal Cancer: A Retrospective Analysis of Clinico-Pathological and Radiological Features

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Background Chemotherapy induced diarrhea (CID) is a common and debilitating side effect of cancer treatment. Aims and Methods The aim was to ascertain the incidence of CID in a single tertiary centre, to identify risk factors for the development of CID and to determine it impact on overall survival in our patient cohort. Colorectal Cancer (CRC) patients who received adjuvant chemotherapy during the period 2006-2009 were identified from a prospectively maintained database. Demographics, pathology, surgery type and details of chemotherapy were recorded. The incidence and severity of CID and other toxicities were graded using Common Terminology Criteria for Adverse Events (CTCAE v4.0). Body composition was analyzed by measuring cross sectional area of skeletal muscle and body adiposity based on Computerized Tomography (CT) performed at staging. All patients were followed up to study completion or death. Results 105 patients (61 males) underwent surgery with curative intent for CRC and subsequently received adjuvant chemotherapy. The mean age at diagnosis was 62.5 years (Range=30.5-83.8). 75.2% of CRC were left sided lesions. 57 patients (54.26%) had node positive disease at pathology. These patients received chemotherapy totaling 807 cycles with a completion rate of 85.7 %. 126 episodes of CID were reported in 57 patients; giving a CID incidence rate of 54.2%. 16 patients (15.2%) experienced severe CID during adjuvant chemotherapy; resulting in delay of treatment cycle (n= 10), dose reduction or alteration (n= 12), hospitalization (n=3) and early termination of chemotherapy (n=2). Females had a significantly higher risk of developing CID (68.1% v 44.2%, Chi Squared p=0.018) and chemotherapy regimens containing both oxaliplatin and fluorouracil (5FU) had a higher rate of CID compared with 5FU alone (62.8% v 35.8%, Chi Squared p=0.03). There was no association between CID with any surgical or pathological characteristics of the patients. Development of severe CID (Grade 3 or 4) was significantly associated with female sex (25% v 8.1%, p=0.027) and not with the type of chemotherapy regimen. Males with severe CID had significantly lower skeletal muscle mass on CT compared with those without severe CID (148.0 cm2, (IQR=140.5 to 165.5) v 186.0 cm2, (IQR=169.0-196.5) p=0.034)[Fig 1]. Patients who develop CID during treatment have a significantly higher overall survival (OS) at 3 years compared with patients without CID (92.9% vs 81.25%, p=0.047). However OS at 5 years were similar in both groups. Conclusion CRC patients frequently suffer CID that limits treatment. Female sex and use of oxaliplatin are associated with increased risk of CID. In male patients the occurrence of severe CID is associated with lower skeletal muscle mass. The development of CID was associated with better outcome (OS) at 3 years, a finding that merits further study.

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A Multi-Transcript Blood Signature Outperforms Chromogranin a for Detecting Gut Neuroendocrine Tumors

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Background: A key issue in the management of gut neuroendocrine tumors (NETs or "carcinoids") is the need for a specific and sensitive biomarker panel to accurately detect disease and provide a sensitive tool to assess treatment efficacy. The current general biomarker, Chromogranin A (CgA) (a constitutive neurosecretory peptide), has limitations in terms of sensitivity, specificity and reproducibility NET and imaging is relatively insensitive in respect of detection of change. We therefore developed a PCR-based 51 transcript peripheral blood signature (NETest) for the detection of gut neuroendocrine tumors (NETs or "carcinoids") and evaluated it in comparison to CgA. Methods: The NET signature was validated in two sets (n=115; n=120) using a 2-step qPCR method. We then prospectively collected two additional independent blood sets: 1): NETs (n=120: gastric; n=8, pancreatic: n=31, small intestinal: n=66, appendiceal: n=4, colorectal: n=6, and unknown site: n=5) and 2) non-NET patients taking PPIs who underwent ERCP or EUS for upper GI symptoms (n=29: pancreatic cysts: n=19, pancreatitis: n=6, GERD: n=4). An accuracy detection comparison was undertaken between the NETest and plasma CgA (DAKO-ELISA). Results: The NETest was robust (reproducibility: Coefficient of Variation<2%). It detected NETs with high sensitivity (85-98%) and specificity (93-97%) and was significantly ($p<0.0005$) more accurate than CgA. The NETest identified pancreatic and gastrointestinal NETs with similar efficacy (>85%). The accuracy for both metastatic and non-metastatic lesions was>90%. In subset analysis, the test detected poorly differentiated tumors (100%) as well as individuals with MEN-1 (100%). In the prospectively collected NET group (n=120), the NETest tumor detection sensitivity was 95.8% (95% CI: 90.5-98.6%) versus 51.3% (95% CI: 43.1-59.5%) for CgA. When CgA was in the normal range NETest was elevated in 94%. This was particularly useful in pancreatic NETs (<20% elevated CgA). In the prospectively collected non-NET group (n=29) taking PPIs (>1 month) CgA was increased in 80% of patients whereas 0% increase in NETest was evident. Conclusions: This study demonstrates that a multi (51)-gene NET panel is robust and efficient for detecting gastroenteropancreatic NETs, including high grade lesions and MEN1. The test is significantly more sensitive than plasma CgA measurement and is elevated in ~95% of patients when CgA is normal. In addition, in contradistinction to CgA the NETest is unaffected by long-term PPI use. NETest provides an accurate and sensitive measure of NET disease that is not limited by site or grade and is not affected by acid inhibitory therapy.

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Factors Influencing the Development of Toxicity After Peptide Radio-Receptor Therapy for NETs: an Evaluation of 807 Patients

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Background: Peptide Receptor Radionuclide Therapy (PRRT) using 90Y-octreotide (Y) and 177Lu-octreotate (Lu) has been utilized for ~two decades in inoperable/metastasized neuroendocrine tumors (NETs). Tumor responses are 15-35% and PFS>30 months. Generally, PRRT is well-tolerated and acute/sub-acute side-effects, e.g. hematologic toxicity, are mild and transient. Long-term toxicity may involve kidney and bone marrow. Our aim was to identify clinical parameters predictive of long-term renal and hematological toxicity in a large cohort of NETs at the Institute of European Oncology-Milan (1997-2013). Methods: 807 patients were treated with PRRT: 793 (98%) received Lu, Y or the combination (Lu: 278, 34.4%, Y: 358, 44.4%, Lu+Y: 157, 19.5%), 14 (2%) combinations of PRRT+ other agents. Median cumulative activity for Y was 272 mCi (30-715), 621 mCi (46-860) for Lu, and 174 mCi (10-856) + 344 mCi (50-978), for Y+Lu, respectively. An adjunctive "salvage" PRRT treatment was given to 93 (median 95 mCi [Y in 26], 350 mCi [Lu in 55] and 74 mCi [Y] and 150 mCi [Lu] in 11). Parameters analyzed included kidney toxicity risk factors (age, diabetes, hypertension, chemotherapy, renal disease), bone marrow toxicity (myelotoxic chemotherapy), and PRRT features. Data analysis was by multiple regression and Recursive Partitioning and Analysis. Results: Both Y (33.6%) and Y+Lu (23.6%) exhibited greater nephrotoxicity than Lu alone (13.1%, $p<0.0001$). Nephrotoxicity of any grade occurred in 279 (34.6%), only 42% of which could be predicted by the clinical data (F=73.4, p=2.2x10-90). The main variable was Hb toxicity, followed by age and hypertension. Persistent toxicity occurred in 196 (24.3%), only 33% of which could be modeled by clinical data (F=56.8, p=4.9x10-66). The relevant variables were Hb toxicity (co-efficient 0.16, p=1.97x10-5) and Y therapy (±Lu, co-efficient 0.22-0.26, $p<0.001$). Persistent toxicity was associated with a shorter exposure to PRRT (mean 387 vs. 658 days, $p<0.004$). Myelodysplastic syndrome (MDS) occurred in 2.6%, only 29% of which could be modeled by clinical data (F=56.3, p=4.7x10-58). The main related variable was acute leukemia (AL, co-efficient 0.67, p=4.78x10-40), as a consequence of MDS. MDS patients had higher PLT toxicity (2.05±1.23 vs. 0.58±0.78, $p<0.0001$) and longer duration of PRRT (22.6±24.1 months vs. 15.5±8.9, p=0.01). AL occurred in 1.1%, only 22% of which could be modeled by clinical data (F=47.96, p=1.9x10-43). The only related clinical variable was MDS (co-efficient: 0.29, p=3.5x10-42). Conclusion: PRRT, particularly with Lu, is safe in the majority of cases. Although known risk factors are informative in prediction of PRRT tolerance they only provide a partial (<45%) estimate of risk. Our data suggests the existence of unidentified individual susceptibility to radiation-associated disease, which is likely to have a genetic basis.