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## TREATING ACUTE MYELOID LEUKEMIA IN YOUNG ADULT PATIENT WITH END-STAGE RENAL DISEASE AND CONGESTIVE HEART FAILURE

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**Background:** Acute myeloid leukemia (AML) is the most common acute leukemia in adults and accounts for approximately 80% of cases. Reported estimated five-year overall survival is 26% (range=0-53). Standard induction chemotherapy for eligible fit patients is 7+3 regimen (cytarabine + anthracycline). However, there is no data or guidelines on AML treatment recommendations for patients with end-stage renal disease (ESRD) and congestive heart failure (CHF). **Case Presentation:** Our patient is a 36-year-old male with ESRD from glomerulonephritis now on hemodialysis, dilated cardiomyopathy/CHF with EF 20-30%, pulmonary hypertension and kidney transplant in 1994 with graft failure in 2006. He was found to have worsening anemia (hemoglobin (HB) 6 gm/dl) and leukopenia (white blood cells (WBC) 2,000/microliter, absolute neutrophil count (ANC) 200/microliter). Bone marrow biopsy revealed 90% cellular marrow involvement by AML with 95% myeloblasts. Fluorescence *in situ* hybridization (FISH) showed deletion 9q. Flow cytometry revealed 68% myeloblasts; CD33- and CD7-positive. Based on pharmacokinetic and anecdotal cases we decided on giving him fludarabine and cytarabine induction chemotherapy (FLAG). Fludarabine 25% dose reduction was based on report of sickle cell patient with ESRD receiving it pre-stem cell transplant. Our patient received fludarabine 24 mg/m<sup>2</sup> day 1-5, cytarabine 1.5 g/m<sup>2</sup> day 1-3 and 2 g/m<sup>2</sup> day 4-5 and tbo-filgrastim. He was dialyzed daily during chemotherapy. The patient had appropriate cytopenic response to chemotherapy with severe pancytopenia. He did develop neutropenic fever; which was managed successfully. Unfortunately, repeat bone marrow biopsy revealed 50% cellular marrow involvement by AML with 63% myeloblasts. The patient was not stem cell transplant candidate. With limited options, given his comorbidities, currently he is being treated with azacitidine with palliative intent. **Discussion:** Despite having appropriate cytopenic response to chemotherapy and successful management of side-effects, our patient had residual leukemia post-induction chemotherapy. Further studies are needed to delineate treatment options for AML patients with ESRD and CHF.

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## A RARE CASE OF AN UNDIFFERENTIATED EMBRYONAL SARCOMA OF THE LIVER IN A YOUNG ADULT

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**Background:** Undifferentiated embryonal sarcoma of the liver (UESL) is a rare malignant hepatic tumor of the mesenchymal origin seen in the pediatric population with a peak incidence between the ages 7-10 but extremely uncommon in adults. Being an aggressive tumor with poor prognosis, early diagnosis is key to treatment and survival. **Case Presentation:** Patient is a 25-year-old white male with no significant past medical history and was admitted with the chief complaints of intractable abdominal pain. On examination, patient's vitals were within the normal limit but noted to be in mild distress along with diffuse abdominal tenderness on palpation and hepatomegaly. Laboratory studies revealed slightly elevated transaminase levels. Computed tomography (CT) scan of the abdomen revealed a large well-circumscribed lesion in the right lobe of the liver measuring 16.8x20.2x20.3 cm. The patient underwent radical *en bloc* resection with right partial hepatectomy. Histopathology revealed malignant pleomorphic spindle cells in a fibromyxoid stroma, consistent with UESL. Patient was started on chemotherapy with adriamycin, ifosfamide and mesna, receiving a total of 6 cycles. Follow-up surveillance revealed good control of the patient's tumor burden. **Discussion:** Patients with UESL usually present with nausea, vomiting, abdominal pain, jaundice, weight loss and fatigue. Serum alpha-fetoprotein and cancer antigen (CA)-125 levels may be deranged. Histologically, cells have a sarcomatoid appearance in a myxoid background. Cytogenetic studies have revealed multiple mutations, including overexpression of *p53* and alterations in chromosome 19. Radiological studies can be misleading with a primarily cystic appearance on CT/magnetic resonance imaging (MRI) in comparison to the predominantly solid appearance on ultrasonogram. Surgical resection followed by chemotherapy is the preferred treatment of choice. Neoadjuvant and adjuvant systemic chemotherapy with combinations of doxorubicin, cisplatin or cyclophosphamide is often used. Though liver transplantations have been performed in the pediatric population, no documented benefit of it in adults have been noted.

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**PRIMARY SQUAMOUS CELL CARCINOMA OF THE RECTUM: VERY RARE BUT CURABLE CANCER**Neha R. Patil<sup>1</sup> and Mohamad A. Younes<sup>2</sup><sup>1</sup>University of Alabama at Birmingham - Huntsville Campus, Huntsville, AL, U.S.A.;<sup>2</sup>The Cancer Center of Huntsville, Huntsville, AL, U.S.A.

*Background/Aim:* Squamous cell carcinoma (SCC) of the rectum is very rare with incidence ranging from 0.10 to 0.25 per 1,000 colorectal neoplasms reported. The first case of SCC of the rectum was reported in 1933. Between 1933 and 2009, a total of 73 cases of rectal SCC have been reported. Median age at diagnosis is 57 years with female predominance (66%). Overall, five-year survival rate reported is 32% with tumor stage being the most important prognostic factor. We present here a very rare case of rectal SCC with our experience of treating it with neoadjuvant chemoradiation therapy. *Case Presentation:* A 57-year-old white female with hypothyroidism, hyperlipidemia and depression presented to clinic in 2014 with rectal bleeding. She postponed recommended colonoscopy for over one year. In July 2015, colonoscopy revealed non-obstructing mass in rectum 10 cm from anal verge. Biopsy showed poorly differentiated SCC of rectum. Obstetrics and Gynecology (OB/Gyn) assessment revealed vaginal wall invasion. Computed tomography (CT) of chest, abdomen, pelvis showed 2.4×5×3.8 cm symmetric mass with multiple enlarged perirectal lymph nodes. Magnetic resonance imaging (MRI) showed mass extending to perirectal fat with 2.5 cm nodule abutting the low rectum and periaortic lymphadenopathy. Rectal ultrasound revealed T3 disease with three areas of adenopathy. Positron emission tomography (PET)/CT did not show any distant disease. Patient was treated with 5-fluorouracil (5-FU) and mitomycin C chemotherapy and radiation therapy (RT) followed by surgery. Patient is currently following up with our clinic regularly and there is no evidence of cancer per pelvic examination, colonoscopy and imaging. *Conclusion:* Diagnosis of SCC of rectum is often delayed. Treatment options include surgery, chemotherapy and RT. However, no definite approach has been described to date. Recent reports suggest that neoadjuvant chemoradiation therapy does improve survival.

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**SURVIVAL TRENDS IN MULTIPLE MYELOMA: A US POPULATION-BASED STUDY**Nibash Budhathoki<sup>1</sup> and Binay K. Shah<sup>2</sup><sup>1</sup>Interfaith Medical Center, Brooklyn, NY, U.S.A.;<sup>2</sup>North Puget Cancer Center, Sedro-Woolley, WA, U.S.A.

*Background/Aim:* Since 2000 AD, novel treatment molecules like thalidomide, lenalidomide and bortezomib have been used in the treatment of multiple myeloma (MM). There is limited information on ethnic and gender variation in the treatment response to these agents. We conducted this study to evaluate the ethnic and gender differences in relative survival in pre- and post-novel treatment era. *Patients and Methods:* We selected elderly MM patients ( $\geq 65$  years) from the Surveillance, Epidemiology, and End Results (SEER) 18 database. We analyzed one- and five-year relative survival (RS) rates of MM patients by ethnicity and gender during pre-novel treatment (1992-2000) and post-novel treatment (2001-2011) time periods. We used Z-test to compare survival rates. *Results:* There was a total of 8,880 patients in pre-novel treatment era and 20,982 patients in post-novel treatment era with median survival of 22 months and 18 months, respectively. Overall five-year relative survival improved in post-novel treatment era (N=8,880, RS=24.50%±0.50%) compared to pre-novel treatment era (N=20,982, RS=32.80%±0.50%) with Z score of 10.58. Stratification of study population revealed relative survival improved in white (N=7,032 vs. 16,085; RS=24.00±0.60% vs. 32.70%±0.50%; Z score=9.53) and black population (N=1,279 vs. 3,423, RS=26.30%±1.50% vs. 33.40%±1.20%) and the results reciprocated for both genders within the race. However, in other races, the relative survival in males (N=281 vs. 640; RS=25.80%±3.00% vs. 24.50±2.50%; Z score=0.28) did not significantly improve compared to pretreatment era. In patients of 65-74 years age group, significant improvement in relative survival was seen among white (Z score=6.15), black (Z score=2.88) and other females (Z score=2.13); however, amongst males, significant improvement in relative survival was found only among whites. In patients aged 75 years or more, relative survival significantly improved among white males (N=1,742 vs. 4,247, RS=18.40%±1.20% vs. 26.80%±1.10%; Z score=5.17) and white females (N=1,942 vs. 4,249, RS=19.70%±1.10% vs. 25.00%±1.00%; Z score=2.50). In black patients or in patients of other races, no significant improvement in relative survival was found in either sex. There was a significant improvement in one-year survival of white males in post-novel treatment era (N=3,600 vs. 8,619, RS=66.40%±0.90% vs. 70.20%±0.50%; Z score=3.77). The results were consistently reproduced among patients of 65-74 years age group and among patients above 75 years age group. In white females and in patients of races other than white, no significant improvement in relative survival was detected. *Conclusion:* Relative survival showed variation based on race, gender and age group when compared between pre- and post-novel treatment era.

\*Other races refers to American Indian/AK Native, Asian/Pacific Islander.

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## IS HPV A CULPRIT FOR BREAST CARCINOMA? A RETROSPECTIVE STUDY

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*Background/Aim:* It is well known that there are genetic, hormonal, environmental and lifestyle risk factors associated with breast cancer development. Nonetheless, in 50-80% of cases, known risk factors have not been identified. Recent studies have investigated the potential links between breast cancer and viral infections, including human papillomavirus (HPV) infection. Unfortunately, the results are rather controversial. The purpose of this study was to examine the association between breast cancer and HPV-related cervical dysplasia by means of a retrospective chart review. Breast cancer and cervix cancer are number 1 and 2 respectively in women in Nigeria. Some reports have suggested that incidence of triple-negative breast cancer (TNBC) in Nigeria is up to 65% (compared to 15% in USA). The role of viruses in most common cancers is undoubtedly important, yet highly underestimated. HPV has been implicated with 99.7% of cervical cancers and its oncogenic mechanism has been clearly identified. Finding of breast cancer with up to 65% of TNBC cases in African countries creates an intriguing possibility of HPV being a candidate oncovirus for breast cancer. In fact, numerous recent tissue studies conducted throughout the world detected HPV DNA in breast cancer tissues of patients with cervical cancer, while high-risk HPV types were present in invasive ductal carcinomas. Prevalence of HPV varied from 4% in Mexican to 86% in American women. The virus was noted to be present in tumor tissue only with the exception of one study, which identified lower concentration of HPV in normal tissue. Although substantial evidence exists supporting involvement of HPV in breast cancer, no clinical studies have been conducted to elucidate this relationship. The goal of our retrospective chart review was to examine the association of breast cancer and HPV-related cervical dysplasia in a cohort of women in an urban setting. *Patients and Methods:* We retrospectively reviewed and analyzed the breast cancer type, grade, estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor 2 (HER2) status, Pap smear and HPV test results in 462 patients with diagnosis of breast cancer in their electronic medical chart between 1/1/2009 and 4/10/2015. Since not every patient had all the aforementioned information available, the comparisons of Pap smear abnormality and HPV positivity among the groups in each of the following categories were performed independently: breast cancer types (ductal, including invasive ductal

carcinoma (IDC) and ductal carcinoma *in situ* (DCIS) vs. lobular, including invasive lobular carcinoma (ILC) and Lobular carcinoma *in situ* (LCIS) vs. both ductal and lobular), breast cancer grade (I vs. II vs. III) and receptor ER/PR/HER2 status (luminal vs. non-luminal; double-negative vs. luminal A vs. luminal B vs. triple-negative; double-positive vs. non-double-positive). *Results:* Fifteen percent (39/260) of the patients had abnormal Pap smear and 8% (16/198) of the patients were tested positive for HPV. No statistically significant differences of Pap smear abnormality were detected among the groups in all categories. Similarly, no statistically significant differences of HPV positivity were detected among the groups in all categories. However, we observed an interesting tendency that patients with non-luminal breast cancers (double-negative and triple-negative) tended to have higher rate of HPV positivity (13.3% vs. 6.3% of luminal breast cancers). More specifically, 12.5% of double-negative breast cancers and 11.5% of triple-negative breast cancers were HPV-positive, while only 6.4% of luminal A breast cancers and 6.3% of luminal B breast cancers were HPV-positive. *Conclusion:* Our analysis suggests that HPV might be associated with more than 50% increase of incidence rates of non-luminal breast cancers (double-negative and triple-negative), although no statistically significant difference has been detected yet likely due to the low patient number with positive HPV test. Given the poorer prognosis of non-luminal breast cancers, especially the triple-negative cancers, larger-scale retrospective/case-control studies or prospective/cohort studies are needed to confirm the possible association between HPV positivity and non-luminal breast cancers. It will also be interesting to examine the effect of wide-spread HPV vaccine administration on the change of incidence rates of non-luminal breast cancers in the future.

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## EXTERNAL VALIDATION STUDY OF THE NEW MAGEE EQUATIONS IN PREDICTING ONCOTYPE DX RECURRENCE SCORE

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*Background/Aim:* Decision-making for adjuvant chemotherapy in hormone receptor-positive, node-negative breast cancer is routinely done by Oncotype DX, a commercial 21-gene assay used to predict 10-year recurrence risk. Although it correlates with distant recurrence, it is extremely expensive. New Magee Equations 1, 2 & 3 were derived based on histopathological variables by Klein *et al.* (1). that predicted the actual

Oncotype DX recurrence score. This study was conducted to analyze the concordance of prediction and compare the results with the study by Klein *et al.* *Patients and Methods:* Data of 122 patients with estrogen receptor (ER)/progesterone receptor (PR)-positive, lymph node-negative breast cancer at Abington Jefferson Health were reviewed. Variables for calculation of the equations included Nottingham's score, ER immunohistochemistry (IHC) score, PR IHC score, Her2-Neu status, tumor size and Ki67 index. Cases were categorized as low-, intermediate- and high-risk using the same cut-offs as the actual recurrence score. Pearson's correlation and concordance was calculated between the predicted score and the actual Oncotype Dx recurrence score with respect to categorization. *Results:* The mean predicted scores±standard deviation (SD) for New Magee Equations 1, 2 & 3 were 17.3±6.7, 18.2±7 and 16.4±6.4, respectively. The mean actual Oncotype DX score was 20.8±13. Pearson's correlation coefficients were 0.713, 0.677 and 0.698. The concordance between actual Oncotype DX recurrence score and predicted recurrence scores for New Magee Equations 1, 2 & 3 were 68%, 68.9% and 65.6%, respectively. One-step discordance was 30.3%, 30.3% and 33.6%, while two-step discordance was 1.6%, 0.82% and 0.82%. With intermediate categories removed, the concordance improved to 97%, 98.5% and 98.5%. *Conclusion:* This study demonstrated comparable results to the original study with overall concordance in the range of 65%-69%. Even though concordance improved to >95% with elimination of intermediate categories, it requires further elucidation since a majority of patients fell into this category. Further validation of these equations may potentially provide accurate risk assessment, particularly in low- and high-risk groups, and result in significant healthcare cost savings.

1 Klein ME, Dabbs DJ, Shuai Y, Brufsky AM, Jankowitz R, Puhalla SL and Bhargava R: Prediction of the Oncotype DX recurrence score: use of pathology-generated equations derived by linear regression analysis. *Mod Pathol* 26: 658-664, 2013.

## 7 EPENDYMOMA-SUBEPENDYMOMA: A RARE CULPRIT BENEATH A COMMON GUISE

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*Background:* Ependymomas are rare tumors, accounting for 2-3% of primary brain tumors and 25% of spinal cord tumors, rarely seen in adults and usually present with severe neurological deficits. Subependymomas are even rarer in occurrence, occurring mostly in the fourth ventricle. *Case Presentation:* A 73-year-old female patient with past medical

history of renal cell carcinoma status post-nephrectomy presented to the emergency room with nausea alone for the past 6 weeks, which had not responded to outpatient medical therapy. Patient denied vertigo, vision changes, focal weakness, tinnitus, numbness, tingling or dysphagia. Physical exam revealed no neurological deficits. Magnetic resonance imaging (MRI) of the brain showed a mass in the fourth ventricle 2.4×2.2×2.8 cm in size. The patient underwent suboccipital craniotomy for tumor resection and was diagnosed with combined ependymoma-subependymoma, WHO grade II. Post-surgically, the patient developed severe neurological deficits and became hypoxic, which required re-intubation. In a surprise turn of events, the patient made the decision to pursue hospice care and she passed away 30 minutes post-extubation. *Discussion:* Ependymoma/subependymomas are slow-growing tumors, primarily associated in children less than 5 and in adults around the age of 35. Around 75% of cases reported in the adult population presented in the spinal canal. They are rarely seen in the elderly population. They carry a good prognosis, which is directly related to the age at presentation. This rare intracranial neoplasm in a 73-year-old female patient, with both location and age being atypical and under the sole presentation of nausea alone, represents an unusual occurrence with an unexpected grave outcome.

## 8 BETWEEN THE DEVIL AND THE DEEP BLUE SEA: CLOPIDOGREL-INDUCED ACQUIRED HEMOPHILIA A

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*Aim:* We described a rare case of clopidogrel-induced acquired hemophilia. *Case Presentation:* An 87-year-old male with a history of coronary artery disease, chronic kidney disease and peripheral arterial disease presented with easy bruisability and left hip pain after sustaining a fall. Four months ago, clopidogrel was initiated after primary angioplasty with stent placement for left lower extremity arterial disease. Vital signs were normal. Physical examination demonstrated upper extremity ecchymoses and profound tenderness to passive movement at left hip but intact distal pulses. Laboratory investigations showed hemoglobin of 7.8 g/dl (baseline 10 g/dl), platelet count of 251,000/μl, fibrinogen of 443 mg/dl, bleeding time of 1 minute, international normalised ratio (INR) of 1.1, activated partial thromboplastin time (aPTT) of 60-seconds (documented normal value prior to clopidogrel) and thrombin time of 21.8 seconds. Computed tomography revealed 8×5 cm left iliacus hematoma. 1:1 mixing study partially corrected the aPTT to 42 seconds that prolonged progressively to 44 and 46 seconds at 30 and 60 minutes

respectively, indicating presence of a clotting factor inhibitor. Factor VIII assay showed a markedly depressed activity (4%). Workup for von Willebrand disease, antiphospholipid syndrome, autoimmune diseases, hematological and solid-organ malignancies was negative implicating clopidogrel as the suggested cause of factor VIII inhibitor. Immunosuppression with corticosteroids and intravenous immunoglobulin was commenced. After 3 weeks of intensive recombinant factor VIII and activated factor VII replacement, aPTT normalized. However, management was complicated by venous thromboembolism and a massive ischemic stroke culminating in his death; these being consequences of hypercoagulable state induced by factor replacement. *Conclusion:* Acquired hemophilia A in non-hemophiliacs is a rare disorder caused by autoantibodies against factor VIII. Etiology includes autoimmune disorders, malignancies, pregnancy and drugs. Clopidogrel-induced acquired hemophilia has rarely been described. Prudent mechanism is immunological as in clopidogrel-associated thrombocytopenia and microangiopathic hemolytic anemia. The presented case is not only extremely rare but also presented a management dilemma. Hemophilia caused major bleeding on one hand, whereas its treatment caused hypercoagulability on the other; hence the title.

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**A MASSIVE UNILATERAL PLEURAL EFFUSION:  
NO ASBESTOS EXPOSURE DOES  
NOT EQUAL NO MESOTHELIOMA**

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*Background:* Malignant mesothelioma (MM) of pleura was rare prior to the widespread use of asbestos in industries (1). Eighty percent of cases of MM are associated with asbestos exposure (2). The Incidence rate of mesothelioma with minimal or no asbestos exposure is as low as 1.14 and 0.94 per million for men and women, respectively (3). *Case Presentation:* A 70-year-old Hispanic male with no significant past medical history presented to the Emergency Department (ED) with shortness of breath. His symptoms started two months prior, when he was in Mexico. He underwent thoracentesis twice in Mexico; however, he was unaware of the fluid analysis results. He had a twenty pound weight loss in 3 months but denied fever, night sweats or cough. He worked as a furniture upholsterer for forty years and never smoked tobacco. His vitals were within normal limits. Oxygen saturation was 94% in room air. Chest X-ray (CXR) showed a massive right-sided pleural effusion. Two liters of amber fluid was removed in ED *via* thoracentesis. Fluid

analysis was exudative per Light's criteria. Cytology, acid-fast bacillus (AFB) smear and gram stain of fluid were negative. Computed tomography (CT) scan showed thickening of right parietal pleura and a few peripheral pulmonary nodules, largest measuring 4 mm. QuantiFERON®-TB Gold was positive. Bronchial washing was negative for AFB. Thoracoscopy showed extensive pleural plaquing around the entire pleural space, including the diaphragmatic surface. Biopsy confirmed malignant epithelioid mesothelioma. He was started on palliative chemotherapy. We did not try exploring other possible etiologies for MM, such as Simian Virus 40 (SV40) and genetic causes. *Conclusion:* Pleural MM with no occupational exposure to asbestos is rare but should be considered in the differential diagnosis of massive unilateral effusions. The sensitivity of cytology for diagnosis of MM is only 32%. Pleural biopsy should be performed in all suspected cases with negative cytology.

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2 McDonald J and McDonald A: The epidemiology of mesothelioma in historical context. *Eur Respir J* 9(9): 1932-1942, 1996.

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**THE IDENTIFICATION OF SOLID TUMORS  
IN PATIENTS WITH KNOWN DIAGNOSIS  
OF MYELOYDYSPLASTIC SYNDROMES  
AND POPULATION-BASED DATA ANALYSIS:  
A POTENTIAL AID IN EARLY  
DETECTION OF MALIGNANCY**

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*Background:* Secondary myelodysplastic syndromes (MDS), as a delayed complication of cancer treatment, is a known phenomenon; however, the concomitant diagnosis of primary solid tumors and MDS has not been well studied. While there have been clinical reports indicating an association between paraneoplastic syndrome and *de novo* MDS, there is no population-level data on the association between MDS and primary solid tumors. *Patients and Methods:* We selected adult patients diagnosed with non-treatment-related MDS

from National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) 18 database. We calculated the risk of primary solid tumor malignancies in those patients using a primary standardized incidence ratio (MP-SIR) analysis in the SEER\*Stat software. A confidence level of  $\alpha=0.005$  was used. *Results:* A total of 40,780 patients with a diagnosis of 'MDS and other myeloproliferative diseases' were reported in the SEER 18 registry during 2001 to 2011. The mean age at diagnosis of MDS was 76.37 years (range=0-98) and mean follow-up duration of patients was 15.80 months (range=0-120). In this population, a total of 2,111 primary solid tumors were diagnosed with an observed/expected (O/E) ratio of 1.16 and an absolute excess risk of 26.86 per 10,000. Malignancies of the esophagus (O/E=1.74), ascending colon (O/E=1.63), liver (O/E=3.13), lung and bronchus (O/E=1.43), urinary system (O/E=1.22) and kidney (O/E=1.81) were more likely after a diagnosis of MDS at a significance level of  $p<0.005$ . Patients were significantly more likely to be diagnosed with solid tumors immediately (0-month latency) after diagnosis of MDS (O/E=2.30) or within 1 year of diagnosis (1- to 5-month latency O/E=1.51; 6- to 11-month latency O/E=1.22). Similar results were found when broken down by sex. *Conclusion:* The risk of primary solid tumor malignancies in adult patients with MDS is significantly increased compared to the general population and may represent an opportunity for early detection.

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### THE PERCEIVED RELATIONSHIP BETWEEN LUNG CANCER AND CARBON DIOXIDE EMISSIONS: A LONGITUDINAL ANALYSIS OF COUNTRIES

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*Background:* Air pollution leads to an increase in carbon dioxide (CO<sub>2</sub>) emissions and has long been suspected as a contributing factor to rising lung cancer rates. Although a biological rationale exists, the relationship has never been proven to any great degree empirically and little is known about its true strength, specifically when controlling for other risk factors. *Materials and Methods:* Panel data was gathered from the International Agency for Research on Cancer to determine lung cancer incidence and carbon dioxide levels were gathered from the Carbon Dioxide Information Analysis Center. Lung cancer rates were lagged by 20 years in relation to the predictors of interest. A fixed-effects multivariate linear regression model was then developed in which lung cancer incidence was the dependent variable and the covariates of interest included CO<sub>2</sub> levels, age, smoking and gross

domestic product (GDP) per capita. *Results:* In an unadjusted analysis of cross-sectional data from a given year, there is a highly statistically significant positive relationship between lung cancer and CO<sub>2</sub> emissions in which each additional unit of increase in CO<sub>2</sub> (measured in tones per person) is associated with an additional 3.2 cases of lung cancer (per 100,000 individuals) among men ( $p<0.001$ ) and 1.4 cases of lung cancer among women ( $p=0.01$ ). A fixed-effects model, adjusting for all covariates of interest, was then employed and any relationship between lung cancer and CO<sub>2</sub> emissions was no longer evident. *Conclusion:* Research has suggested that a direct relationship exists between CO<sub>2</sub> emissions, particulate matter size and lung cancer. However, this has never been substantively proven. This analysis suggests that, while such a relationship may exist, it is more likely a function of high smoking rates and older age (in countries with elevated levels of CO<sub>2</sub> emissions). In countries that are reported to have high CO<sub>2</sub> emission rates, this suggests that other variables must be considered when estimating lung cancer risk.

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### A CASE REPORT OF RENAL FAILURE AND SEVERE SYSTEMIC INFLAMMATION CAUSED BY HHV-8-NEGATIVE MULTICENTRIC CASTLEMAN DISEASE SUCCESSFULLY TREATED WITH TOCILIZUMAB, AN ANTI-IL-6 RECEPTOR MONOCLONAL ANTIBODY

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*Background:* Human herpesvirus-8 (HHV-8)-negative multicentric Castleman disease is a very rare illness. One of the central mediators of this disease is interleukin-6 (IL-6) production and several therapies targeting IL-6, including tocilizumab, have shown activity in this disease. *Case Report:* We describe the case of a young man with HHV-8 -negative multicentric Castleman disease successfully treated with tocilizumab. *Results:* A 23-year-old man of Indian descent presented with 2 week history of increasing fatigue, dyspnea on exertion, diarrhea, leg swelling and 15 pound weight gain. Laboratory testing was notable for white blood cells (WBC) of 14,000 with 80% polymorphonuclear leukocytes (PMNs), hemoglobin 8.5 g/dl, platelet count 80,000, hyponatremia, hyperkalemia, azotemia, hypoalbuminemia, erythrocyte sedimentation rate (ESR) of 82 mm/hr and markedly elevated C-reactive protein (CRP) of 238 mg/l. Computed tomography (CT) scan showed diffuse lymphadenopathy. Imaging also demonstrated bilateral pleural effusions, ascites, anasarca, edematous kidneys and splenomegaly. An axillary lymph node biopsy revealed Castleman disease with features of both plasma cell and hyaline cast variance. An HHV-8 test was negative. The patient's kidney function worsened and he

required hemodialysis. He was treated with 2 cycles of rituximab and then cyclophosphamide and etoposide, but continued to require dialysis with additional need for platelet and red blood cell transfusions. Treatment was then changed to tocilizumab at a dose of 8 mg/kg and he had dramatic clinical improvement within 48 hours. Dialysis was discontinued 6 days after the first tocilizumab infusion. Tocilizumab was continued for 10 more cycles every 2 weeks and was eventually discontinued as symptoms waned and CT scan showed no evidence of lymphadenopathy with resolution of splenomegaly. The patient made a full recovery and continues to have no evidence of recurrence more than 30 months since his initial presentation. *Conclusion:* Increased production of IL-6 is an important driver of Castleman disease and tocilizumab, a monoclonal antibody against the IL-6 receptor, provides an effective treatment option for human immunodeficiency virus (HIV) and HHV-8 negative multicentric Castleman disease as demonstrated in this case.

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#### TAKOTSUBO CARDIOMYOPATHY IN CARCINOMA OF THE CECUM

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*Background/Aim:* Colon carcinoma and Takotsubo cardiomyopathy are uncommon among young people. We report a case of signet ring cell adenocarcinoma of the cecum that was complicated by Takotsubo cardiomyopathy. *Case Presentation:* A 22-year-old female presented to the emergency department with abdominal pain for two and a half weeks. The pain was associated with abdominal bloating and three episodes of vomiting on the day of presentation. On examination, a 2x2 cm mass was palpable in the right iliac fossa. A computed tomography (CT) scan showed moderate wall thickening in the right colon. The patient underwent colonoscopy that showed an edematous cauliflower like growth in the cecum near ileo-cecal valve. On the third day of admission, the patient developed sudden onset of shortness of breath with retro-sternal chest pain, 8/10 in intensity, associated with nausea and vomiting. Pulmonary embolism was ruled out by CT angiogram. Electrocardiogram (EKG) did not reveal any significant ST- T wave changes but her troponin was 1.3 ng/ml. Her troponin peaked to 4.3 ng/ml. EKG revealed hypokinesia of lateral and infero-basal walls. Cardiac catheterization revealed patent coronaries. Based on Mayo's criteria, Takotsubo cardiomyopathy was diagnosed. Biopsy of the cecal mass showed primary signet ring cell adenocarcinoma. The patient underwent right hemicolectomy

and was diagnosed with stage T4N3M1 tumor. A follow-up study on patients with Takotsubo cardiomyopathy showed that 38.8% of deaths was due to malignancies. A comparative study between Takotsubo cardiomyopathy and myocardial infarction patients showed significantly higher incidence of malignancies amongst the Takotsubo group. *Conclusion:* Takotsubo cardiomyopathy in our patient could be cancer-related and a plausible explanation for it could be a paraneoplastic syndrome. We recommend considering cancer as a possible precipitant of Takotsubo cardiomyopathy besides the traditional risk factors.

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#### ANEMIC OUTCOME REPORTING CONSISTENCY: EVIDENCE OF SELECTIVE REPORTING BIAS IN LEADING HEMATOLOGY JOURNALS

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*Background/Aim:* Selective outcome reporting is a significant methodological concern leading to potential bias in clinical trial results. Comparisons between outcomes reported in trial registries and Journal publications allow investigators to examine the frequency of selective reporting occurrences among trialists. We examined selective outcome reporting in randomized controlled trials (RCTs) published in high impact factor hematology Journals and whether outcome reporting favored statistically significant results. *Materials and Methods:* A PubMed search identified RCTs published in five hematology Journals from 2010-2015. After screening, primary and secondary outcomes were recorded for each trial and then compared to outcomes pre-specified in the trial's registration. We compared whether pre-specified trial registry outcomes were changed in the publications, primary outcomes had been downgraded to secondary outcomes, secondary outcomes had been upgraded to primary outcomes or primary outcomes had been omitted, added or changed. *Results:* A total of 93% (143/154) of included RCTs were registered prior to the completion of the trial and further analyzed. Fifty-eight percent (83/143) demonstrated major outcome discrepancies between registry and publication. Fifty-four percent (59/109) of included RCTs published in Blood, 75% (12/16) in Arteriosclerosis Thrombosis and Vascular Biology (ATVB), 56% (5/9) in Circulation Research, 75% (6/8) in Leukemia and 100% (1/1) in Stem Cells included at least one major discrepancy. A total of 37 (21%) major discrepancies from 19 RCTs reported *p*-values and were evaluated for selective outcome reporting. Seventy

percent (26/37) of these major discrepancies favored a statistically significant result. *Conclusion:* We observed a high rate of discordance between pre-specified and published outcomes in high impact factor hematology Journals, suggesting need for continued improvement. Among outcomes, which reported *p*-values, many outcome discrepancies favored publication of statistically significant results, further suggesting selective outcome reporting bias.

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### COEXISTENCE OF MYELOPROLIFERATIVE AND LYMPHOPROLIFERATIVE NEOPLASMS: A REPORT OF TWO CASES

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*Background/Aim:* Myeloproliferative neoplasms (MPNs) are characterized by clonal proliferation of one or more myeloid lineages. Study shows that MPN patients have a three-fold increased risk of developing lymphoproliferative neoplasm (LPN) compared with the general population (1). Here we report two cases of concurrent MPN and LPN, which is extremely rare. *Case Presentations:* (i) Ms. L is an 87-year-old female who was diagnosed with stage 0 chronic lymphocytic leukemia (CLL) in 2006. She has been on surveillance without requiring any intervention except for intermittent intravenous (*i.v.*) immunoglobulin due to hypogammaglobulinemia secondary to CLL. Since 2007, she was noted to have persistent thrombocytosis of  $600\text{--}700 \times 10^9/l$ . Fluorescence *in situ* hybridization (FISH) analysis was negative for *BCR-ABL*, *JAK2V617F* mutation, *JAK2* exon 12 mutation and *MPL515* mutation. After exclusion of reactive thrombocytosis, the diagnosis of essential thrombocythemia (ET) was made. Patient was started on hydroxyurea with good response. She has been clinically stable. (ii) Ms. P is an 88-year-old female with newly diagnosed non-small cell lung carcinoma of the left lower lobe, stage IV, positive for epidermal growth factor receptor (*EGFR*) exon 19 mutation. She was given Tarceva® with excellent response. Meanwhile, she was noted to have leukocytosis, erythrocytosis and thrombocytosis, indicating MPN. *JAK2V617F* mutation was positive. Erythropoietin level was low. Patient was started on hydroxyurea. Intriguingly, she had an acute increase in her white count with lymphocytosis and smudge cells. Flow cytometry analysis of peripheral blood revealed B-cell lymphoproliferative disorder. Bone marrow aspirate showed 28% of monoclonal kappa B cells, with no evidence of increase in blasts or abnormal myeloid maturation. *Conclusion:* Concurrence of MPN and LPN is extremely rare. The underlying molecular pathogenesis is unclear. Genetic abnormalities may occur in the pluripotent stem cell, which lead to unchecked

proliferation of both myeloid and lymphoid lineages. A better understanding of the pathogenesis may open up new opportunities for screening, early diagnosis and novel therapeutics for these disorders.

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### BINAYTARA HOME HOSPICE CARE IN NEPAL: INITIAL EXPERIENCE

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*Background/Aim:* Home hospice is relatively a new concept in Nepal. Up to 90% of approximately 60,000 cancer patients diagnosed in Nepal every year die within a year. In this report, we share our initial experience with the home hospice program in Nepal. *Materials and Methods:* The Binaytara home hospice (BHH) program was established in January 2016. This program serves patients in Kathmandu, Nepal, a city with a population of around 4 million. This is a joint collaborative program of Binaytara Foundation (BTF), USA and Cancer Care Nepal (CCN) with technical support from National Hospital and Cancer Research Center, Jawalakhel, Kathmandu, Nepal. The BHH services are provided free of cost to the patients and their families. From January to April 2016, a total of 21 patients were enrolled in the hospice program. *Results:* Among 21 patients, 15 were women and 6 men. Median age was 61 years (range=27-85). Majority of the patients had lung cancer (38.69%) followed by gastrointestinal (23.80%), hepatobiliary (14.28%), glioblastoma (9.52%), cervix (4.76%), ovary (4.76%) and acute myeloid leukemia (AML) (4.76%). Commonest symptoms included nausea (85.71%), pain (76.19%), cough (66.69%) and constipation (57.14%). Patients were treated with morphine and tramadol. Nineteen of the 21 patients treated with this regimen reported that their moderate to severe pain reduced to mild. Average dose of morphine was 40 mg (range=20-60). Among 12 patients who died, 10 died at home and 2 at the hospital. The average length of stay in hospice care from admission until death was one month. *Conclusion:* The Binaytara home hospice program, though in very early stage, has helped many patients with terminal cancer, as well as their families. Free services, such as our program, may encourage enrollment of patients in resource-poor countries.

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## TISSUE MATRIX SCAFFOLD FOR BREAST TUMOR MODELING AND DRUG SCREENING

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**Background:** A better understanding of human cancer development requires mechanistic examination of cancer cell biology in systems that closely resemble those tissues in which tumors originate. The current cell culture systems using planar substratum, synthetic polymer support and single extracellular matrix (ECM) component do not meet the tissue-mimicry requirements. There is an urgent need for an experimental system, which closely mimics the tumor tissues and enables the studies of cancer development that are difficult to achieve with the current models. **Materials and Methods:** Three-dimensional (3D) tumor construction using synthetic biomaterials has not been successful to date because of their failure in mimicking native-like environment to the cells. To advance the field, we have developed a “next generation” biocompatible and biodegradable tissue matrix scaffold (TMS) system using animal tissues containing the full spectrum of native ECM. While the porous TMS facilitates the supply of nutrients, oxygen and migration of cancer cells in culture, its combination with the hydrogel form of TMS allows compartmental co-culture with additional cell types and tissues. MCF10A ( $1 \times 10^5$ /scaffold) and MDA-MB-231 cells ( $1 \times 10^5$ /scaffold) were cultured and the potentiality of this scaffold was compared with other different types of scaffolds prepared from the available biomaterials (collagen, matrigel, polycaprolactone (PCL), poly(lactic-co-glycolic) acid (PLGA), PCL:PLGA) for cell attachment, proliferation and migration. Cells were cultured for different time points (3 days to 3 weeks). Proliferation and cellular activity of the cells were evaluated with the Cell Counting Kit-8 (CCK8), live and dead cell assay; and hematoxylin and eosin (H&E) staining. Both cells were immunostained with human epidermal growth factor receptor 2 (HER2) (positive for MCF10A) and Ki-67 (positive for MDA-MB-231) after cryosectioning of scaffolds. Each group had six scaffolds and each experiment was repeated three times. TMS scaffolds supported the cell growth significantly better ( $p$ -value=0.5) than others. *In vivo* experiments also showed the largest tumor formed by TMS than other scaffolds. Briefly, the scaffolds were implanted into the mammary-fatty pads of mice (six weeks old NU/NU Nude Female mice from Charles river; a control group-only scaffold; and an experimental group-scaffold seeded with MDA-MB-231,  $1 \times 10^5$  cells/scaffold). After three weeks, tumors were harvested, fixed, sectioned and stained with routine H&E and immunostains (HER2, Ki-67 and 4',6-

diamidino-2-phenylindole (DAPI)). It was observed that TMS scaffolds not only supported better attachment and migration of the cells but also maintained their structures' integrity maintaining porous architecture for the supply of nutrients and oxygen to the inner active cells. **Results:** The TMS system supported the cell growth significantly more than other similar kind of scaffolds for tumor formation both *in vitro* and *in vivo* ( $p$ -value <0.5). Cancer cells seeded in TMS showed robust growth and tumor induction in animals (approximately 5 times more) over the other 3D model systems currently available. Mimicking native tissue microenvironment is the greatest advantage of this system assisting *in vitro* tumor formation. The use of animals for pre-clinical trials, therefore, would be greatly reduced. The cell-cell/ECM interactions, multiplex cell population for tumor formation would be studied easily both in normoxic and hypoxic conditions. **Conclusion:** TMS, as a native mimicking systemic platform, will help to study the key mechanisms of tumor formation, angiogenesis and metastasis, and explore the efficacies of the system in screening biomarkers and anticancer drugs.

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## PERIANAL SWELLING: IS IT ABSCESS OR SOMETHING ELSE?

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**Background:** Plasmablastic lymphoma (PBL), first described in 1997, is a rare and highly aggressive form of non-Hodgkin's lymphoma. Ninety percent of patients die within 2 years from the date of diagnosis. Commonly described with human immunodeficiency virus (HIV), PBL typically affects the oral cavity. Our case of PBL presents as perianal swelling. **Case Presentation:** A 36-year-old male presented to the emergency room with a 4-week history of painful, progressively enlarging left perianal swelling. Patient also had blood in stool but denied fever, chills, night sweats or weight loss. He was a former smoker and a homosexual. Anal examination revealed few areas of mucosal breakdown but no exophytic lesions were seen in the anal canal. Initially, a diagnosis of perianal abscess was made and patient was scheduled for an incision and drainage. **Results:** Incision did not reveal an abscess; instead a necrotic mass was encountered. Tissue pathology demonstrated Ki-67 score of 100%, suggesting aggressive malignancy. Computed tomography (CT) scan demonstrated a 5.8x8.8 cm mass abutting the rectum. Differential diagnosis included Burkitt's lymphoma or granulocytic sarcoma. Pathology showed tumor cells positive for CD79a, CD45, CD10, CD138, multiple myeloma oncogene-1 (*MUM-1*) with a 100% Ki-67-positive rate; negative for pancytokeratin, CD34,

c-kit, MPO, CD3, CD5, CD20, CD30, CD99, TdT, PAX-5, EBV-LMP, HHV-8, BCL-2 and BCL-6. Starry-sky pattern was noted. Final diagnosis was PBL and the patient was scheduled to begin high intensity chemotherapy. *Conclusion:* Although, PBLs are post-germinal center B-cell tumors, they do not demonstrate B-cell markers. However,

plasma cell markers are universally expressed. These tumors were initially considered a subset of diffuse large B-cell lymphoma but are now a distinct diagnostic entity. The overall incidence of PBL is approximately 2% of all HIV-associated non-Hodgkin lymphomas with a still very rare extra-oral presentation.