In CT-based lung cancer screening and incidentally detected indeterminate pulmonary nodules, radiomics has shown value in improving diagnostic accuracy to discriminate cancer from benign pulmonary nodules. We have analyzed data from the National Lung Screening Trial, NLST, to identify subjects with cancerous and benign nodules, and have organized them into cohorts based on their screening history. Patients who are diagnosed with cancer following a prior nodule-negative screen have significantly worse outcome than patients who develop cancer following a prior nodule-positive/cancer-negative screen. In cohorts of patients with nodules not diagnosed as cancer in the first screen, we have identified significant radiomic features that can discriminate those who will subsequently develop cancer from those that remain benign with an accuracy of 80%, and this can be the basis for a “radiomics risk score” to predict subsequent cancer development. However, even the seemingly large “big data” NLST data set is underpowered once cohorts are assembled with similar histories, and co-variates are accounted for. Solutions to the problem of generating sufficiently powered data sets include capturing the radiomic data at the point of care (i.e. by the radiologists) and inter-institutional sharing of images, data, features and algorithms, which have yet to be reliably implemented.

From bench to bedside to beam: Hippocampal-sparing during cranial irradiation

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Whole-brain radiotherapy either therapeutically for brain metastases or prophylactically for small-cell lung cancer has been associated with cognitive toxicity, in the form of decline primarily in list-learning recall as well as patient-reported cognitive functioning. Emerging evidence suggests that the pathogenesis of radiotherapy-induced cognitive deficits may involve radiation-induced injury to proliferating neural stem cells in the subgranular zone of the hippocampus. Conformal avoidance of this hippocampal neural stem cell compartment during whole-brain radiotherapy using intensity-modulated radiotherapy has been proposed as an approach to preserving hippocampal neurogenesis and thus preventing or mitigating radiotherapy-related cognitive toxicity.

Promising results as compared to historical controls were observed in RTOG 0933, a phase II study of hippocampal avoidant WBRT for patients with brain metastases. Validation of these results in a phase III setting is being pursued through NRG CC001, a phase III trial of memantine plus whole-brain radiotherapy with or without hippocampal avoidance for brain metastases. Extrapolation of these results to the setting of prophylactic cranial irradiation for small cell lung cancer is being explored through NRG CC003, a randomized phase II/III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small cell lung cancer. Both trials are currently activated and accruing patients.

This presentation will review the biology and radiosensitivity of the hippocampal neural stem cell compartment and prior and ongoing clinical studies to corroborate these preclinical observations using advanced radiotherapy techniques.

Primary and adaptive resistance to checkpoint blockade in lung cancer

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The incorporation of immunotherapies, and most notably immune checkpoint inhibitors, into the management of non-small cell lung cancer (NSCLC) has led to a paradigm shift in the management of patients with advanced disease. While PD1 antagonists have been shown to be superior to standard chemotherapy for subjects with progressive advanced disease many other immunomodulatory agents are currently under investigation as single agents or in combination with other therapies.

While the lung cancer community has made great strides in identifying genomic alterations in cancers which are associated with specific therapeutic vulnerabilities, our knowledge regarding predictive biomarkers for immunotherapies is limited. It remains the case that only a minority of patients respond to PD1:PDL1 antagonists, and for those who do, resistance to therapy develops over time.

Here, I will present data describing our efforts in profiling mouse models and patient specimens to describe two modes of resistance to PD1:PDL1 therapy. The first centers on primary non-response in patients with KRAS mutated lung cancers, tumors which typically display high rates of somatic mutations. I will present data demonstrating that within KRAS mutated lung adenocarcinoma tumors with concurrent loss of STK11/LKB1 display an adverse immune microenvironment for PD1:PDL1 therapy. I will discuss specific features of this immune microenvironment and suggest strategies to overcome primary resistance.
Tobacco smoke toxicant and carcinogen biomarkers and lung cancer susceptibility in smokers

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Lung cancer is the leading cause of cancer death in the United States, with more than 158,000 deaths expected in 2015, approximately 90% of which will have been caused by cigarette smoking. World Wide Web in 2012, there were 1,589,800 deaths from lung cancer. Cigarette smoking accounts for 80% of the worldwide lung cancer burden in males and at least 50% in females. Our approach to lung cancer prevention is based on an understanding of the carcinogens in tobacco smoke and their mechanisms of action. This leads to carcinogen and toxicant biomarkers that have the potential to identify susceptible individuals at a young age so they can be targeted for intensive smoking cessation therapy and surveillance. We have developed a panel of urinary tobacco smoke carcinogen and toxicant metabolites that can be used to quantify exposure in cigarette smokers. The panel consists of nicotine metabolites comprising nearly 90% of the nicotine dose (nicotine, cotinine, 3'-hydroxycotinine and their glucuronides, and nicotine-N-oxide), total NNAL (comprised of free NNAL and its glucuronides – metabolites of the tobacco-specific lung carcinogen NNK), total NNN (comprised of free NNN and its glucuronides – metabolites of the tobacco-specific carcinogen NNN), phenanthrene tetraol and 3'-hydroxyphenanthrene (metabolites of the representative polycyclic aromatic hydrocarbon phenanthrene), mercapturic acid metabolites of the volatile toxicants and carcinogens 1,3-butadiene, acrolein, crotonaldehyde, and benzene, 8-iso-PGF2α (a representative F2-isoprostane resulting from oxidative damage), and PGEM, a prostaglandin E2 metabolite related to inflammation. Multiple studies by our group and others have clearly demonstrated that this panel of metabolites is related to exposure to tobacco smoke. Thus, most of these metabolites decrease upon cessation of cigarette smoking. We have participated in collaborative prospective epidemiologic studies to determine whether these urinary biomarkers are also related to lung cancer risk. The Shanghai Cohort Study of 18,244 Chinese men collected and stored urine samples in the 1980s. We analyzed urine samples from 325 lung cancer cases and 356 controls, all smokers from this study, and found that the smoking-adjusted odds ratios (95% CIs) for lung cancer for the highest relative to the lowest quartile of urinary total nicotine, total cotinine, total 3’-hydroxycotinine, total nicotine equivalents and total NNAL were 3.03 (1.80-5.10), 4.70 (2.61-8.46), 4.26 (2.37-7.68), 4.71 (2.61-8.52), and 3.15 (1.86-5.33), respectively (all P trend <0.001). We have also found that phenanthrene tetraol, but not the mercapturic acid metabolites of the volatile toxicants and carcinogens, is independently related to lung cancer risk among smokers in this study. These results demonstrate that these urinary metabolites are risk biomarkers as well as exposure biomarkers.

We have also used these biomarkers to investigate potential explanations for differing risks of lung cancer among ethnic groups. The Multiethnic Cohort Study demonstrated that, for the same number of cigarettes smoked, African Americans and Native Hawaiians have a higher risk for lung cancer than Whites while Latinos and Japanese Americans have a lower risk. We analyzed urine samples from 300-700 subjects per group for total nicotine equivalents, total NNAL, phenanthrene tetraol, 3'-hydroxyphenanthrene, and the mercapturic acids of acrolein, crotonaldehyde, and benzene. The results demonstrated that African Americans, although smoking fewer cigarettes per day than any of the other groups except Latinos, had significantly higher levels of total nicotine equivalents, total NNAL, phenanthrene tetraol, 3'-hydroxyphenanthrene, and the benzene metabolite S-phenylmercapturic acid compared to Whites while Japanese Americans had significantly lower levels of total nicotine equivalents, total NNAL, and 3'-hydroxyphenanthrene than Whites. The relatively low levels of total nicotine equivalents in the urine of the Japanese American smokers was related to low activity polymorphisms in CYP2A6, the major enzyme responsible for nicotine metabolism. These results partially explain the differing susceptibilities to lung cancer among these ethnic groups, but further research is necessary to fully understand the relatively high risk of Native Hawaiians (which may be related to their acrolein levels) or the low risk of Latinos.