Translational Science and Policy and Health Outcomes

Data Science Biostatistics/Informatics

00003

Volumetric assessment of cervical cancer tumor volume during definitive chemoradiation and the risk of early distant metastasis

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ABSTRACT IMPACT: This study assesses patient and volumetric risk factors for distant recurrence within 6 months of completion of curative chemoradiation with brachytherapy in locally advanced cervical cancer. OBJECTIVES/GOALS: Initial tumor volume and tumor shrinkage velocity are prognostic of cure and survival after curative chemoradiation (CRT) for cervical cancer. We explored whether local tumor volumetric changes influence time to distant recurrences outside the radiation field. METHODS/STUDY POPULATION: We performed a retrospective cohort study of patients with FIGO Stage IB-IVA cervical cancer treated with curative CRT and brachytherapy at a tertiary academic center with minimum 3 months follow up and standard post-treatment FDG-PET. Patients received 6 weekly fractions of brachytherapy interdigitated with external beam radiation and cisplatin. Tumor volumes were assessed by MRI at brachytherapy planning. Patients who developed distant metastasis were classified as earliest (3-6 months), early (6-24 months) or late (>24 months) following completion of CRT. Absolute and percent decrease in tumor volume for each fraction were calculated with respect to first brachytherapy volume. Fisher's exact and Mann Whitney-U tests were used for comparison of categorical and continuous variables. RESULTS/ANTICIPATED RESULTS: 143 of 574 (25%) patients developed distant metastasis. Distribution of age, histology, FIGO 2018 stage, primary tumor SUV_{max}, treatment length, and pre/post treatment squamous cell carcinoma antigen levels were not associated in each group. Para-aortic lymph metastases were more common in patients with earliest distant recurrence (33% earliest, 26% early, 12% late, p=0.03). Median initial tumor volume in the earliest (n=24), early (n =29) and late (n=9) groups was 57, 28 and 40 mL, respectively (p=0.08); 57 (earliest) vs 30mL (early+late groups), p=0.04. Average mid treatment (fraction 4) and end of treatment (fraction 6) percent shrinkage was 80 (earliest) vs 73 (early+late), p=0.84 and 94 vs 92, p=0.95, respectively. Neither absolute nor percent tumor shrinkage differed between early vs. late groups. DISCUSSION/SIGNIFICANCE OF FINDINGS: Tumor volumetric changes during definitive chemoradiation were not associated with the timing of developing distant metastasis, which is linked to presence of lymph node metastasis and tumor volume at diagnosis.

00004

Accuracy of the PREP2 algorithm for predicting Three Month Upper Limb Functional Capacity within a United States population of Persons with Stroke

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ABSTRACT IMPACT: Evaluate the accuracy of applying a predictive algorithm using clinical measures only in persons with stroke in the US. OBJECTIVES/GOALS: PREP2 is an algorithm, that predicts UL functional capacity at 3 months post stroke from measures taken within the first week.(1, 2) Despite its accuracy and ease of use, challenges arise of applying PREP2 in the US. The objective of this study was to evaluate the accuracy of PREP2 using only clinical measures in persons with stroke in the US. METHODS/STUDY POPULATION: Individuals with first-ever stroke were recruited from a local hospital and followed longitudinally, as part of an ongoing observational cohort. Variables captured within two weeks of stroke and entered into the algorithm were: age, SAFE score(1-3) and NIH Stroke Scale(4) total score. The algorithm classifies individuals into one of four expected categories: excellent, good, limited, or poor. The dependent variable was the predicted category of UL functional capacity as defined by ranges of the 3-month Action Research Arm Test score.(5) Accuracy, specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) of the algorithm, were calculated using a 4x4 contingency table. Other statistics analyzed include demographic characteristics and a weighted kappa for the algorithm. RESULTS/ANTICIPATED RESULTS: Data from 49 individuals were analyzed (57% male, 88% ischemic stroke, age = 65±8.56 years). Expected categorization matched observed categorization in 29/49 subjects, with the overall accuracy of the algorithm of 59% (95% CI = 0.44-0.73). The sensitivity of the algorithm was low except for the excellent category (0.95). Specificity was moderate to high for good (0.81), limited (0.98), and poor (0.95) categories. PPV was low for all categories and NPV was high for all categories except the good category. Additional results including weighted kappa and inaccuracy of predictions to be presented. DISCUSSION/SIGNIFICANCE OF FINDINGS: PREP2 algorithm, with clinical measures only, is better than chance (chance = 25% for each of the 4 categories) alone at predicting a category of UL capacity at 3 months post stroke. PREP2 is a simple tool that facilitates evaluation of eventual UL outcome from measures routinely captured after a stroke within most healthcare settings in the US.

Precision Medicine

00005

Urine tumor DNA detects minimal residual disease in muscle-invasive bladder cancer treated with curative-intent radical cystectomy*

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ABSTRACT IMPACT: Urine tumor DNA non-invasively detects minimal residual disease and infers tumor mutational burden in locally advanced bladder cancer prior to radical cystectomy, which may potentially enable the selection of patients for bladder-sparing treatment or facilitate personalized adjuvant immunotherapy. OBJECTIVES/GOALS: Standard-of-care treatment for muscle-invasive bladder cancer (MIBC) is radical cystectomy. The inability to assess minimal residual disease (MRD) non-invasively limits our ability to offer bladder-sparing treatment. We sought to develop a liquid biopsy solution via urine tumor DNA (utDNA) analysis. METHODS/STUDY POPULATION: We applied uCAPP-Seq, a targeted sequencing method for detecting utDNA, to urine cell-free DNA samples acquired on the day of radical cystectomy from 42 patients with bladder cancer. utDNA variant-calling was performed

https://doi.org/10.1017/cts.2021.690 Published online by Cambridge University Press

non-invasively without prior tumor mutational knowledge. The overall utDNA level for each patient was represented by the non-silent mutation with the highest variant allele fraction after removing germline variants. Urine was similarly analyzed from 15 healthy adults. Tumor mutational burden (TMB) was inferred from the number of non-silent mutations detected in urine cell-free DNA by applying a linear relationship derived from TCGA whole exome sequencing of 409 MIBC tumors. RESULTS/ANTICIPATED RESULTS: utDNA levels were significantly higher in patients with residual disease detected in their surgical pathology compared to those who achieved a pathologic complete response ($P = 0.002$). Using an optimal utDNA threshold to define MRD detection, positive utDNA MRD significantly predicted the absence of pathologic complete response with a sensitivity of 81% and specificity of 81%. Positive utDNA MRD also portended significantly worse progression-free survival ($HR = 7.4$; $P = 0.03$) compared to negative utDNA MRD. Furthermore, we applied a linear relationship (Pearson $r = 0.84$; $P < 0.0001$) to identify patients with high inferred TMB who may have been candidates for early immune checkpoint blockade. DISCUSSION/SIGNIFICANCE OF FINDINGS: utDNA MRD analysis prior to surgery correlated significantly with pathologic response and progression-free survival, which may help select patients for bladder-sparing treatment. utDNA can also non-invasively infer TMB, which could facilitate personalized adjuvant therapy for patients in the future.

00006

Yield of routine PET/CT surveillance imaging after primary surgical treatment for asymptomatic patients with high-risk stage II/III melanoma

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ABSTRACT IMPACT: The results of this research may influence NCCN guidelines on PET/CT surveillance for this population of patients for whom the guidelines are currently vague. OBJECTIVES/GOALS: We aim to quantify and describe the yield of surveillance PET/CT for detecting asymptomatic recurrence of melanoma after primary surgical treatment for stages IIB, IIC, and IIIA. Our goal is to provide evidence to inform appropriate guidelines for scheduling surveillance PET/CT for this population. METHODS/STUDY POPULATION: This is a retrospective study of patients who have undergone a PET/CT at Barnes-Jewish Hospital. Data will be collected in our Research Electronic Data Capture (REDCap) database. The sample size is 158. Data analysis will be explanatory for the yield of imaging and description of false positives and additional unnecessary workup. Survival endpoints will be reported and multivariate analysis with subgroups will be performed for predictors of PET/CT results. Cost-efficiency analysis will be conducted in collaboration with the Center for Health Economics and Policy (CHEP), with emphasis on a patient-oriented perspective. RESULTS/ANTICIPATED RESULTS: To date, we have collected data for 158 patients, with approximately equal numbers of each stage (56 IIB, 54 IIC, 48 IIIA). Due to lack of clear guidelines for this population, there is significant variation of imaging schedules and results between similar patients or groups of patients. This makes it difficult to anticipate results. Based on clinical experience, literature review, and preliminary data, we may anticipate lower yield of routine PET/CT for the detection of asymptomatic recurrence, with frequent false negatives and occasional false positives, in addition to detection and further workup of benign processes. DISCUSSION/SIGNIFICANCE OF FINDINGS: The high-risk stages IIB, IIC, and IIIA currently occupy a gray area where surveillance PET/CT remains controversial. For this group of patients, it is important to weigh the benefits of early detection and risks of false positives, unnecessary workup and anxiety, and cost.

Basic Science

24780

Investigating the role of mycobacterial lipid antigens and CD1-restricted T cells in host-protective tuberculosis immunity using a guinea pig model*

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ABSTRACT IMPACT: Examining lipid immunity for Mycobacterium tuberculosis in a translatable Guinea pig model may serve as a critical foundation for the creation of an efficacious human lipid based vaccine against tuberculosis. OBJECTIVES/GOALS: CD1 is a group of glycoproteins on antigen-presenting cells (APCs) that present lipid antigens to T cells. Mycobacterium tuberculosis (Mtb) has a lipid-rich cell wall which is essential for the pathogenesis of tuberculosis. Our goal is to determine the frequency, phenotypes, and functionality of CD1 T cells against Mtb using the guinea pig model. METHODS/STUDY POPULATION: Guinea pigs serve as the best translational model for CD1 immunology as they have both group 1 and group 2 CD1 complexes, comparable to human CD1. We performed ex-vivo and in-vivo experiments to analyze lipid antigen-specific CD1 T cell responses with Mtb infection. Assays to detect lipid-specific CD1 T cell activation include cellular proliferation, cytotoxicity assays, and interferon-gamma (IFNγ) release assay (Elispot) using both synthetic and Mtb-derived lipids. We isolated and characterized CD1 T cells using tetramerized CD1 complexes loaded with specific Mtb lipids. Spatial interaction between lipid loaded CD1 APCs with CD1 T cells were demonstrated by immunohistochemistry (IHC). Lastly, we will investigate the impact of lipid-based immunology via knockdown and overexpression of CD1 complexes. RESULTS/ANTICIPATED RESULTS: The cytotoxicity assay demonstrated that the CD1b1 and CD1b3 complexes play roles in the presentation of Mtb lipids, specifically glucose monomycolate, and mycolic acid, as noted by T cell killing of fibroblasts that express specific CD1 complexes that can present Mtb lipids. Similarly, cellular proliferation exhibited lipid specific T cell proliferation. IFNγ production by the stimulated CD1-restricted T cells (Elispot) was weak indicating CD1 T cells may not produce IFNγ. IHC successfully showed CD1 APCs in lungs and spleens of infected guinea pigs. It is anticipated that knocking out CD1 expression will lead to impaired immunity, and increase severity of disease as noted by pathologic lesions/bacterial burden, and systemic spread; in contrast, CD1 enhancement will limit the severity of tuberculosis. DISCUSSION/SIGNIFICANCE OF FINDINGS: We characterized

https://doi.org/10.1017/cts.2021.690 Published online by Cambridge University Press