Eight Best Posters – Oral Presentations

OP 54

A genomic-based signature of response to chemotherapy in ovarian cancer fails to predict clinical outcome in two independent cohorts.

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Background: The development of numerous genomic signatures, from either pre-clinical assays or archived biospecimen, has suggested their potential clinical utility as biomarkers in cancer. However, due to (a) the technical precision of assays, (b) the potential for false discovery in high-dimensional data, and (c) tumor heterogeneity derived from multiple etiologies or from other key clinical factors; it is necessary to independently validate signatures in additional cohorts. Herein, we evaluate a previously-derived gene expression signature of response to chemotherapy (Dressman et al, 2007) in two ovarian cancer datasets.
Materials and Methods: The genomic signature for response to platinum-based therapy was evaluated in (1) 47 banked biospecimen at Duke University with known clinical response, and (2) 402 samples publicly available through The Cancer Genome Atlas (TCGA) project. Differences in labeling procedures and platform (Affymetrix U133a versus U133plus2.0 versus HT array) required normalization by gene standardization prior to validation. The association of genomic predictions to complete clinical response was evaluated using receiver operator characteristics and based on an a priori defined threshold. Time-to-death was evaluated by Kaplan–Meier plots and the logrank test. Differential expression within each cohort was evaluated using the empirical Bayes method, LIMMA. Signatures are evaluated using the resampling-based process, SAFE.
Results: The genomic prediction of chemosensitivity was not associated with response to treatment in the Duke ovarian cancer patients (AUC = 0.52, p = 0.8), nor in the TCGA samples (AUC = 0.48, p = 0.9). No difference in overall survival is observed (HR = 0.95, p = 0.7). Genes in the predictive signature do not show comparable levels of differential expression in the validation cohorts (SAFE p-value = 0.65 and 0.82) relative to the original test set (SAFE p = 0.004). A Venn diagram demonstrates almost no overlap in the patterns of differential expression within each cohort.
Conclusion: These results demonstrate the genomic signature of response to platinum-based therapy from Dressman et al (2007) failed to predict clinical outcome in two independent cohorts. Further, evaluation of differential expression from the three cohorts suggests the global patterns of gene expression from Affymetrix platforms are not supportive of developing a robust signature of chemo-responsiveness in ovarian cancer using untargeted approaches.

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Initial experience with the EANM accreditation procedure of FDG PET/CT devices

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Background: Quantitative FDG PET/CT studies in a multicenter setting are hampered by large variability in applied PET methodology, resulting in an up to 2 fold differences in results between centres. Therefore, in 2010 the European Association of Nuclear Medicine (EANM) published the European procedure guideline for PET tumour imaging with FDG. The guideline specifically aims at harmonizing quantification in multi-center studies. As SUVs are lesion size dependent, QC experiments measuring SUV as function of 'lesion' size are defined along with harmonizing criteria. To our best knowledge the European guideline is the first and only guideline with harmonizing performance standards and the EARL (EANM Research Ltd) accreditation program is the first initiative for implementation into practice.
Materials and Methods: A pilot accreditation program was launched by EARL from October 2010 till April 2011 in collaboration with and endorsed by the European Organisation for Research and Treatment of Cancer (EORTC). Eleven FDG PET/CT imaging sites (12 systems) that participated in an EORTC trial were included in the program. Accreditation QC included: (1) verification of PET/CT system calibration and uniformity using a uniform cylinder and (2) assessment of SUV recovery and image quality using a modified NEMA NU2 2007 phantom. After 3 months calibration QC was repeated to assess repeatability of calibration accuracy.
Results: After initial minor technical issues, e.g. related to data transfer, data entry errors and clock synchronization, all imaging sites met calibration accuracy requirements, i.e. global scanner calibration was within 10% without (visible) image artifacts. QCs for assessing SUV recovery allowed for harmonizing scanner performance to within the lower and upper (harmonizing) standards. Initially only for 2 imaging sites, recalibration or adjustment of reconstruction parameters was needed to achieve harmonized scanner performance.
Conclusion: The pilot study has shown the feasibility and successful execution of the EARL FDG PET/CT accreditation program in a multi-center setting. Retrospective analysis of clinical data collected in a Dutch trial demonstrated good correspondence in baseline SUV results between sites that were performing PET studies in accordance with the guideline, while SUV differed substantially (2 fold) for an imaging site that did not comply with the harmonizing standards. The results encourage to further spread the accreditation initiative across Europe.

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The co-development of a folate receptor molecular diagnostic imaging agent (99mTc-EC20) and folate receptor targeted drug conjugate (EC145) in the treatment of ovarian cancer patients

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Background: Molecular imaging provides a unique approach to assessing molecular markers for cancer treatment. Folate receptor (FR) is over-expressed in ovarian, breast, lung and colorectal cancers. Folate is required for cellular division and folate receptor expression is implicated as a negative prognostic marker for cancer. This study evaluates the potential use of a folate targeting SPECT imaging agent 99 mTc-EC20 to select ovarian cancer patients with high FR expression to be treated with EC145, a FR targeted-cytotoxic drug conjugate.
Materials and Methods: Women with platinum resistant ovarian cancer were scanned with 99mTc-EC20 to determine FR status and each measureable lesion was scored as either FR positive or FR negative. Patients were then randomized 2:1 to receive EC145 (2.5 mg IV t.i.w. weeks 1 and 3) + pegylated liposomal doxorubicin PLD (50 mg/m2 Ideal Body Weight (IBW) IV q 28 days) or PLD alone (50 mg/m2 IBW IV q 28 days). Progression free survival (PFS) was the primary endpoint. Exploratory analyses of the FR+ and FR− patient subgroups evaluated the use of 99 mTc-EC20 to select the patient population most likely to benefit from the treatment with EC145. The reproducibility of the EC20 reads was evaluated in an inter-reader agreement study.
Results: The majority of patients (80%) scanned with 99 mTc-EC20 were folate receptor positive. The final results on the reproducibility of the EC20 reads will be presented at the meeting. In the overall ITT patient population, PFS was statistically significant different in favor of the combination arm, 21.7 weeks compared with 11.7 weeks for patients treated with PLD alone (HR 0.626; 2-sided log-rank p value 0.031). The HR was improved to 0.547 (p value 0.044) in patients with at least one FR+ lesion and even further to 0.381 (p value 0.018) in patients with 100% FR+ lesions.
Conclusion: Women with platinum resistant ovarian cancer have very poor prognosis. No approved treatments have demonstrated an improvement in PFS or OS. 99 mTc-EC20 provides a reliable and reproducible imaging technology to select FR+ ovarian cancer patients that benefit most from the treatment with EC145. Statistically significant increase in PFS was seen in the combination of EC145 + PLD versus PLD alone, with increased benefit seen in patients with FR+ tumors. 99 mTc-EC20 and EC145 are the first folate receptor molecular imaging and drug combination to demonstrate a statistically significant improvement in PFS in platinum resistant ovarian cancer.

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Development of a genomic-clinical classifier model for predicting clinical recurrence in patients with localized prostate cancer

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Background: The efficient delivery of adjuvant and salvage therapy after radical prostatectomy in patients with prostate cancer is hampered by a