alleles are low, the combined effects are sufficiently large to be important in risk prediction, targeted screening and prevention.

Special Session (Thu, 24 Sep, 11:15−12:15)
Established and emerging imaging applications

341 INVITED

PET-CT: has sensitivity and specificity improved for staging and response monitoring?

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FDG-PET-CT has established itself as an important cancer staging and therapy monitoring imaging modality in the last decade and has replaced CT in many questions. While FDG-PET mostly adds sensitivity to the combined exam, CT offers mostly specificity. However, not infrequently FDG-PET adds specificity and CT sensitivity. As a result, FDG-PET-CT is a more accurate staging modality than either of its two parts and several publications also demonstrate that it is better than FDG-PET and CT read side by side. The value of PET-tracers other than FDG is much less well elucidated. Some data are available on F-choline-PET-CT in recurrent prostate cancer, in F-DOPA and F-DOTATOC and others for staging and therapy monitoring of neuroendocrine tumors and FLT is considered useful in therapy monitoring.
Outcome studies on diagnostic imaging are difficult to perform because the imaging specialists do not control the ensuing therapy path. Therefore, the best current measure is the impact on management, where the researchers look at the percentage in which adding a PET-CT results in a relevant change in patient management. Many studies on different cancers have appeared which demonstrate that PET-CT results in such changes in 20−50% of the cases. Furthermore, in therapy monitoring a number of studies have appeared which demonstrate that after therapy, patients who show persistent FDG uptake will have a decreased survival when compared to those in which FDG-uptake has either been reduced or has disappeared. These data therefore suggest that PET (-CT) may serve as a surrogate endpoint for the evaluation of therapy in many cancers. FDG-uptake much more strongly correlates with successful therapy than the morphological imaging modalities.
In summary, FDG-PET-CT has considerably improved staging and therapy monitoring in the last few years justifying the worldwide growth of the number of examinations performed.

Special Session (Thu, 24 Sep, 11:15−12:15)
Trial methodology

342 INVITED

The role of randomised trials and surrogate biomarkers in early clinical development

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Phase II trials in cancer patients are essentially a screen to reject treatments having insufficient activity to warrant further study. The primary end-point of phase II trials is often the response rate, i.e. the proportion of patients with measurable lesions in whom a substantial tumour regression is observed. Often phase II trials are uncontrolled, and consist of treating one group of patients with the experimental drug. The major drawbacks of this approach are that the results of these trials may depend more on the patient selection than on the drug's true activity, and that cytostatic agents may control the tumor growth rather than cause it to shrink in the vast majority of patients. The first of these drawbacks can be addressed by randomizing patients between the experimental arm and a control group receiving standard of care. The second drawback can be addressed by using a more statistically sensitive endpoint than the response rate, for instance repeated measurements of the tumor or, if possible, specific biomarkers (e.g. prostate-specific antigen in prostate cancer, functional imaging, etc.) Even though these biomarkers are seldom validated surrogates for long-term clinical endpoints, they may better reflect the anti-tumor activity of new therapies than a mere response rate. The traditional approach to phase II design, which is to demand that the response rate of the new therapy exceed some pre-defined threshold, may then be replaced by a suitably powered statistical comparison of repeated measures of the biomarker between the randomized groups.

343 INVITED

Integration of diagnostic markers into the development process of targeted agents

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New technology and biological knowledge make it increasingly feasible to predict which patients require systemic therapy and which are most or least likely to benefit from a specific treatment. Using genomic classifiers to target treatment can greatly benefit patients, reduce societal medical costs and improve the chance of success in new drug development. There are, however, many challenges in effectively co-developing new drugs with predictive classifiers.
Much of the conventional wisdom about how to develop and utilize predictive biomarker classifiers is flawed. The data used to develop a predictive classifier should be distinct from the data used to test hypotheses about treatment effect in subsets determined by the classifier. Developmental studies are exploratory, but studies on which treatment effectiveness claims are to be based should be definitive studies that test pre-specified hypotheses (33). This presentation will describe phase III clinical trial designs for utilizing biomarker classifiers in new drug development. The presentation will cover randomized enrichment designs (20,21) that utilize predictive biomarkers for selecting patients as well as randomized stratification designs (72−75) that do not restrict eligibility but permit evaluating the treatment overall for all randomized patients as well as for one pre-defined biomarker determined subset of patients. The adaptive signature design of Freidlin and Simon (38) and the adaptive threshold design of Jiang et al. (53) will also be presented. Reprints of the above citations are available at http://brb.nci.nih.gov using the specified citation numbers. Interactive software for designing clinical trials with predictive biomarkers is also available at that website.

Special Session (Thu, 24 Sep, 11:15−12:15)
Sarcomas in adolescents

344 INVITED

Managing sarcomas in teenagers and young adults

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Sarcomas account for 10% of cancers occurring in 15−24 year olds. Within this group there is considerable clinical and biological heterogeneity and incomplete understanding of optimal treatments.
Most clinical research attention has focused on the management of bone sarcomas, particularly osteosarcoma and Ewing's tumours. Several factors have been studied which consistently identify patient groups with differing outcomes. Age at diagnosis appears to affect prognosis in Ewing's tumours but less obviously in localised extremity osteosarcoma. Any underlying biological or treatment delivery variables which may explain these observations have yet to be elucidated. Whether different treatment approaches for bone sarcomas should be adopted for teenagers and young adults (TYA) is unclear and will require systematic prospective evaluation.
Soft tissue sarcomas affect all ages. The numerous histiotypes are not evenly distributed across all age ranges. In the progression from childhood through adolescence to adulthood, rhabdomyosarcoma is replaced as the commonest subtype by the many different subtypes recognised by adult oncologists. There is little guidance about appropriate management of 'adult-type' soft tissue sarcomas occurring in TYA and this group have not been systematically studied. Their representation within clinical trials may be biased towards those with adverse features. There is considerable variation in practice particularly regarding the use of adjuvant chemotherapy. Few studies address whether specific approaches to treatment are appropriate for TYA with soft tissue sarcoma.
In the future, biologists and clinicians familiar with sarcomas affecting TYA and adults need to work together to share understanding and to design rational treatment programmes aimed at improving outcomes for TYA.

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Hot topics in sarcoma of adolescence

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Sarcomas of adolescence encompass malignant bone sarcomas, such as osteosarcoma and Ewing sarcoma, and soft tissues sarcomas, such as rhabdomyosarcoma, synovial sarcoma and Kaposi sarcoma.
The focus of this lecture will be put on difference in outcome between children and adolescents in tumors with similar diagnosis, of which