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

J. Whelan[1]. [1]*University College London, Oncology, London, United Kingdom*

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.

345 INVITED

Hot topics in sarcoma of adolescence

W.T.A. Van der Graaf[1]. [1]*Radboud University Nijmegen Medical Center, Medical Oncology, Nijmegen, The Netherlands*

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

data from the literature and results from our own Dutch study in rhabdomyosarcoma will be used as illustration.
In addition promising new ways of treatment in sarcoma of adolescents will be addressed, of which the focus will be on IGF-1R in Ewing sarcoma.
Data from the literature suggest that adolescents and young adults (AYA) with cancer do badly compared with children. The reasons are poorly understood. Whereas improvement in the survival of children with pediatric malignancies has been shown over the last decades, this is less the case for sarcomas when occurring in adolescence. The question remains whether this is due to “nature or nurture”. For rhabdomyosarcoma, Ewing sarcoma and osteosarcoma reasons for different outcome will be discussed. Do these tumors have a different biology when presenting in childhood or at AYA age? Evidence suggests that adolescents with rhabdomyosarcoma present with a more advanced stage of disease, which might be related to tumor biology, but also to patient factors. Is the chemosensitivity different between children and adolescents or are adolescents underdosed when being treated for sarcoma as compared to children?
In the second part of the talk aspects of new treatment options in sarcoma of adolescence will be discussed, with special focus on the intruiging results of IGF-1R antibodies in Ewing sarcoma patients. The difficulties of response prediction on IGF-1R in Ewing sarcoma will be addressed, which will be illustrated with new data from our own series of Ewing sarcoma patients.
Finally also other potential targets of treatment of sarcomas in adolescents, such as mTOR, will be addressed briefly.

Special Session (Thu, 24 Sep, 11:15−12:15)
Career development opportunities after your degree

346 INVITED

Grant opportunities in the United States: funding for oncology research

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Many professional societies and private foundations within the United States fund international oncology research. These programs include training and career development grants targeted for young oncologists. This session will provide an overview of the different funding opportunities for cancer research that are available to early-career oncologists outside of the United States. Helpful hints on how to successfully compete for international funding will also be discussed.

Special Session (Thu, 24 Sep, 11:15−12:15)
Lymphadenectomy for GI cancer − does it make a difference?

347 INVITED

Lymhphadenectomy in cancer of the oesophagus and gastro-oesophageal junction (GOJ). Does it matter?

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Up to 85% of patients with cancer of the esophagus or GOJ first present with dysphagia and weight loss caused by obstruction of the oesophageal lumen by the tumour. Within this subset of patients another 80% have lymph node involvement.
Surgery is the mainstay of therapy in absence of systemic metastasis. During the last three decades technical modifications and improvements in perioperative care substantially reduced mortality and morbidity figures even in the case of the more extended, mostly transthoracic, oesophagectomy and lymphadenectomy.
Yet, in contrast to gastric and colorectal cancers where the extent of lymphadenectomy has been shown to be important for both staging and survival, controversy persists regarding the benefits of lymphadenectomy in cancer of the oesophagus and GOJ.
At this point there is only one published randomized controlled trial on adenocarcinoma of the oesophagus and gastrooesophageal junction (GOJ) assessing the potential impact of lymphadenectomy. This trial failed to show a difference between the transthoracic extended lymphadenectomy versus the transhiatal resections without lymphadenectomy. Although, a net trend toward improved survival with the extended approach was observed. A subsequent subanalysis showed in adenocarcinoma of the distal esophagus a significant 17% survival benefit after transthoracic oesophagectomy with two field lymphadenectomy.
Moreover there is an increasing number of publications both from Asia and the Western hemisphere indicating that more extensive lymphadenectomy results in a survival benefit. Indeed nowadays overall 5-year survival figures after extended lymphadenectomy often exceed 40% and reported 5-year survival figures for stage III disease vary between 25% and 35%, survival figures rarely obtained after resection without such lymphadenectomy.
However it remains unclear what constitutes optimum lymphadenectomy. Using random forests multivariable regression models it is concluded that to maximize 5-year survival a minimum of 10 nodes should be resected for T1 cancers, 20 nodes for T2 cancers and 30 or more nodes for T3-T4 cancers [1].
From a recent published multicenter international study [2] it appears that the number of removed nodes is an independent predictor for survival. The optimal threshold for this survival benefit was the removal of minimum 23 nodes and survival continued to improve as the number of nodes removed increased. Comparing 5 year survival figures of patients who had 23 or more nodes removed to those with less than 23 nodes removed indicated a significant survival benefit in all stages I, II and III in favour of 23 or more removed nodes.
Conclusion: Although for cancer of the oesophagus and gastrooe-sophageal junction the final proof is lacking there is from literature data a growing body of evidence indicating that extended lymphadenectomy has a beneficial impact on survival without an increase in postoperative morbidity and mortality. The survival figures obtained after such type of surgery are the gold standard to which other therapeutic regimens are to be compared.

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348 INVITED

Lymphadenectomy and strategies for regional control in gastric cancer

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Gastric cancer recurs predominantly in regional nodes and the peritoneal cavity; isolated distant recurrence is infrequent. Treatment of recurrent gastric cancer only rarely generates long-term survival. Appropriate initial treatment of gastric cancer minimizes lymphatic/regional recurrence, and data indicate that improved regional control significantly improves survival. Appropriate initial surgical and adjuvant strategies for minimizing regional recurrence will be reviewed. Examples include “low Maruyama Index” surgery, and adjuvant chemo-radiation. Current and future trials incorporate both strategies.

349 INVITED

Lympadenectomy in colorectal cancer – does it make a difference?

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Current results of meta-analyses and prospective randomized trials comparing radical versus limited lymphadenectomy in colorectal cancer will be presented. As a consequence lymphadenectomy can be considered rather predictive than prognostic. In particular in rectal cancer Total Mesorectal Excision (TME) and a negative Circumferencial Resection Margin (CRM-neg.) are of more relevance for prognosis than the total number of excised lymph nodes. Furthermore, the lymph node ratio of excised/metastatic lymph nodes is a negative prognostic marker. Since prognosis in node positive colon cancer patients can be improved by adjuvant chemotherapy, in the histopathological work up a more accurate and simple lymph node staging is mandatory. For colon cancer this probably can be achieved by sentinel lymph node biopsy with multisection and immunohistochemical examinations. This results in lymphonodal upstaging in about 20−25% even in patients who underwent extended conventional lymphadenectomy in colon cancer. In the future molecular marker analysis or pre operative tumor biopsy may tailor the indication for radical lymphadenectomy or even make it history in most of the colorectal cancer surgeries.