enhancement, biological cooperation, temporal modulation and normal tissue protection are proposed as the five main exploitable mechanisms for rational combination of drugs and radiation in cancer therapy. The large number of novel molecular targeted or cytotoxic agents that are in pre-clinical development will require hypothesis-driven trials to ensure efficient identification of treatments with the most favorable risk:benefit ratio.
In this perspective innovative approaches combining altered fractionation to chemotherapy will be discussed as potential avenues of research to enhance the therapeutic index in the management of locally advanced HNSCC.

130 INVITED

The impact of the cetuximab trial on the treatment of head and neck carcinoma

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Results of numerous phase III clinical trials have demonstrated that, depending on the presence of co-existing illnesses, the preferred treatment for patients with locally advanced head and neck carcinoma (HNC) is one of the established altered fractionation (AF) or concurrent radiotherapy and chemotherapy (CRTC) regimen, or surgery followed by CRTC in the presence of high-risk features. However, both AF and CRTC intensify acute toxicity and CRTC also appears to increase late morbidity relative to the conventional daily radiotherapy. These findings along with advances in cancer biology inspired the search for selective enhancers of tumor response. Motivated by preclinical findings showing a consistent association between high EGFR expression with resistance of HNC to radiation and enhancement of tumor radiation response by EGFR antagonists (e.g., cetuximab or kinase inhibitors), a phase III trial was launched to compare the efficacy of radiotherapy plus cetuximab relative to radiotherapy alone in patients with locally advanced HNC. This trial showed that the addition of cetuximab to radiotherapy significantly improved local-regional control and survival without increasing mucositis or other radiation-related side effects. Cetuximab did induce acneiform rash in most patients and occasionally hypersensitivity reactions.
The cetuximab trial provided thus an important proof of principle that targeting a pertinent signaling pathway can selectively enhance the radiation response of tumors with a given biological feature and established a new treatment option for locally advanced HNC. However, the improvement in the local-regional control rate has been modest (within the range achieved with CRTC) and more than half of patients receiving radiotherapy plus cetuximab still experienced local-regional relapse. Therefore, there is a need to further improve outcome. Ongoing clinical efforts are devoted to address whether the addition of cetuximab to CRTC can yield a better outcome. Preclinical studies are being undertaken to develop rational strategies and assess the relative merits of inhibiting a given signaling pathway at several transduction levels or targeting multiple signaling pathways. Examples of clinical and preclinical studies will be briefly reviewed.

Scientific Symposium
Soft tissue sarcoma – no longer one disease?

131 INVITED

Soft Tissue Tumors: pathology and genomics

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During the last decade, rapid scientific progress has been made in soft tissue tumor pathology. A significant conceptual advance is certainly represented by the publication of the new WHO classification of bone and soft tissue tumors [1]. Its main strength is represented by the integration of morphology with immunofenotypic, genetic, and prognostic data. Many new entities have been included and several conceptual changes have been introduced, among which the definition of the concept of borderline neoplasia; the settlement of the atypical lipomatous tumour/well differentiated liposarcoma controversy; the reappraisal of the concepts of MFH, hemangiopericytoma and fibrosarcoma. In addition the use of the FNCLCC grading system is advocated because of better discrimination between low and high-grade sarcomas, improved reproducibility [2]. Immunohistochemical characterization becomes a key factor in the diagnostic workup of STS, allowing not only proper classification, but also providing prognostic and/or predictive information. Although traditional morphological and immunohistochemical assessment still represents the mainstay of clinical decision-making, data from genetic studies can improve diagnostic accuracy and help predicting behaviour and response to therapy Genetic aberrations have been described in many benign and malignant soft tissue and bone tumours. Of particular importance, a number of sarcomas have consistent specific translocations which have proved diagnostically and prognostically helpful. Mutational analysis is proving particularly relevant in clinicopathological assessment of GIST wherein the type of KIT or PDGFRA genes determines the response to inhibitors of tyrosine kinases [3]. Further advances may be provided by gene expression profiling studies, that may reveal further useful markers for diagnosis and prognosis as well as identify possible targets for molecular therapy [4].

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132 INVITED

Soft tissue sarcomas: from cytogenetics to genomics and expression profiling

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Soft tissue sarcomas represent a heterogeneous group of tumors with over 50 histotypes. Resolution of this histopathological complexity is being facilitated by data from chromosomal and molecular characterization. Identification of specific translocations and mutations associated with these tumors, which seems to be central to their pathogenesis, has been widely incorporated as diagnostic criteria. Integration of sequencing of the human genome and rapidly evolving microarray technology provide the ability for the analysis of genomic changes and global expression patterns of the variety of sarcoma subtypes, illuminating aberrant signaling pathways that cause the diseases, and determining the biologic behavior and possible therapeutic targets. Distinctive expression profiles have been found in gastrointestinal stromal tumors (GISTs), synovial sarcomas, malignant peripheral nerve sheath tumors, and in subsets of liposarcomas. Subgroups with distinctive expression profiles can be identified also among more pleomorphic tumor types, such as high-grade variants of leiomyosarcomas, fibrosarcomas, pleomorphic undifferientiated sarcomas, and subtypes of liposarcomas. In some sarcoma types, explicit genetic alterations lead to activation of specific tyrosine kinase growth-factors receptors, and these have been successfully treated with drugs that specifically inhibit the activated kinase receptor. The success of imatinib mesylate in treatment of GISTs provides important lessons for development of new therapeutics from targets identified in other sarcomas. The GISTs response to imatinib therapy has been shown to be highly dependent on the presence and the nature of the activating mutations of targeted genes. To date, the molecular mechanisms responsible for the differences in the effect of different mutations on tumor sensitivity to imatinib remain only partially understood. Unstable genomes may lead to the evolution of resistance mechanisms, definition of which may yield identification of other therapeutic targets.

133 INVITED

Modulating radiotherapy approaches for sarcoma heterogeneity

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Contemporary techniques permit very exact radiotherapy delivery to the intended target. This presentation will describe research efforts in this area including on-line cone beam CT imaging with volumetric reconstruction and how these may be applied to soft tissue sarcomas (STS) in the base of skull, paraspinal regions and limb. The latter includes an ongoing clinical trial at our centre designed to delivery very selective radiotherapy volumes to protect tissues with the intent of reducing wound complications. The anatomic, clinical, and technical issues governing this approach will be outlined including a unique method of collaboration between surgical and radiation oncologists tailored to individual patient indications. Myxoid liposarcoma, a distinctive STS having a t(12:16) translocation has an unusual predilection for soft tissue metastases; it is extremely radiosensitive and evidence for this will be presented and the impact this has on management discussed. The role of radiotherapy will also