Results: Literature data clearly demonstrate, that combination of different prognostic factors in a given patient cohort can have a significant impact on biochemical and clinical outcome. Treatment decision should be influenced not only by outcome results, but also by individual preferences of the patients. This decision often includes preferences in possible side effects and psycho-oncological factors.
Conclusions: In lack of prospective randomized trials the outcome analysis of different experiences is the only method to learn more on optimal patient selection to different treatment methods. Good functioning interdisciplinary teams with high workload of patients could be the solution finding the optimal tailored treatment method for the individual patient.

Scientific Symposium
Chemo-radiotherapy or modified fractionation in head and neck cancer: two sides of the same coin

126 Abstract not received

127 INVITED

Chemo-radiotherapy in head and neck squamous cell carcinomas: an update

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In the recent years, the role of chemotherapy in HNSCC has been extensively studied in HNSCC, especially through the constitution of the MACH-NC data base which has been recently up-dated. It was based on the collection of up-dated individual patients data, the gold standard method for meta-analysis of randomized trials. For head and neck squamous cell carcinomas, the MACH-NC data base of randomized trials has been generated (17,858 patients), evaluating the effect of adding chemotherapy (CT) to local treatment. The main results were that the benefit associated with the use of CT depended on the timing of CT, concomitant RT-CT being more effective than adjuvant or neo-adjuvant CT. The overall improvement in survival at 5 years in favor of adding CT concomitantly to RT was 8%, and more pronounced when CDDP alone was used (11%) (100 mg/m^2 day 1, 22, 42 during the course of radiotherapy). The effect of poly or mono chemotherapy were not found to be statistically different, when given concomitantly to RT. The benefit associated with the use of concomitant CT was decreasing significantly with age, and more pronounced in younger patients. The effect of concomitant CT was found relatively unchanged, whether RT was conventional, altered fractionnated RT or adjuvant RT after surgery. In conclusion, the addition of CT to local treatment and especially to radiotherapy significantly improved survival.
More recently, and not included in the MACH-NC data base, a taxane-based induction chemotherapy (taxotere-5FU-CDDP) schedule was randomly compared to induction 5FU-CDDP a large series of patients with advanced HNSCC. A benefit in terms of loco-regional control, toxicity and survival was observed in favor of the taxotere-based chemotherapy, suggesting that this new combination may eventually lead to revisit the issue of induction chemotherapy in this type of cancer (Vermorken et al., ASCO 2004).
As mentioned above, the addition of CT, concomitantly to RT improves survival but has also been shown to increased both acute and late toxicity (Denis et al., IJROBP, 2003). Given this increase in toxicity, optimization is needed in order to improve efficacy and decrease toxicity, perhaps by using different schedules (ex: split dose CDDP) or new drugs and new radiation techniques such as Intensity Modulated RadioTherapy, IMRT). A new generation of cytotoxic agents is currently being tested in combination with ionizing radiation, including Taxotere, Taxol, Gemcitibine, or novel agents which are cytotoxic in hypoxic conditions (tirapazamine, Rishin et al., Proc. ASCO 2004). Whether these drugs may provide superior results, as compared to more conventional cytotoxic agents remains to be studied.
In addition, new generation of molecular targeting drugs have shown promizing results in pre-clinical studies and recently, a proof of principle have been obtained in a randomized trial, showing a benefit associated to the targeting of the Epidermal Growth Factor receptor concomitantly to irradiation (Bonner et al., ASCO 2004).
In conclusion, the updated MACH-NC data base has confirmed the benefit associated with the use of concomitant RT-CT. Optimization is needed to further increase the anti-tumor effect, while decreasing the toxicity.

128 INVITED

Modified fractionation in head and neck cancer – implication for current radiotherapy practice?

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One of the most investigated areas in the last ten years has been the importance of modifying the fractionation schedules in order to achieve an improved therapeutic ratio in radiotherapy. Especially in squamous cell carcinomas and most importantly in head and neck cancer we have gained a substantial amount of information due to the large number of randomized trials recently performed.
From a principal point of view one can manipulate the fractionation schedules by modifying the number of doses, reducing the overall treatment time, and modifying the dose per fraction. The limitation is both acute and late morbidity.
Three principles have been addressed in the randomized trials where the control arm normally has been conventional fractionation. One being the issue of hyperfractionation where more fractions with smaller dose per fraction are given to a higher total dose; accelerated fractionation where the same dose and number of fractions are given in a shorter overall treatment time, and a combination of the two. The results have shown that such a modification involving both acceleration and an increased total dose is likely to give a better tumour control, but at the same time the window for performing such a modification is limited when normal tissue morbidity is taken into account.
Not all patients are likely to benefit from the same modifications and recent research is about to identify patients which may have more benefit of one principle than another. Previous studies have indicated that poor histopathological differentiation and low expression of EGFr may compromise the ability of tumour to express accelerated regeneration. This problem was therefore addressed in a subset of the DAHANCA fractionation protocols. The study clearly indicated that the response to accelerated fractionation is heterogeneous and that tumour repopulation may be linked with factors influencing control of tumour differentiation and proliferation. Poor histopathological differentiation and lack of EGFr expression may indicate that such mechanisms are not functioning. This hypothesis, however, requests confirmation prior to application as a predictive factor.
With the background in the large randomized trials recently published and a subsequent meta-analysis will an overview and update of the fractionation principles for head and neck cancer be presented with special focus on the biological heterogeneity and its therapeutic implications.

129 INVITED

Chemo-radiotherapy or modified fractionation: exploitable mechanisms for new trends

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In radiotherapy, altered fractionation was investigated for two main "families" of schedules: hyperfractionation and accelerated fractionation. The former modality uses to deliver higher doses than conventional regimens through multiple daily sessions, delivering less than 1.5 Gy each. Declared target for hyperfractionation: to increase cell killing without enhancing toxicity in normal tissues. Accelerated fractionation also uses multiple daily sessions in order to shorten significantly the overall treatment time. The objective of this approach is to counterbalance tumour cell repopulation during treatment, especially in patients with fast growing tumors as Head and Neck carcinomas (HNSCC). Various mono-institutional and multicentric trials comparing conventional regimens to altered fractionation schedules show that patients with locally advanced disease draw a significant benefit – mainly in terms of loco-regional control – from hyperfractionation or acceleration, with some price to pay in terms of acute and late complications, the severity of which is shown to vary widely according to type of altered fractionation applied.
In the early 1980's a flurry of chemoradiation trials have been conducted in HNSCC. This approach was based on the implementation of four main mechanisms: (i) spatial cooperation; (ii) toxicity independence; (iii) protection of normal tissues; (iv) enhancement of tumor response. These concepts have been widely used in the literature and there is no doubt that they have influenced the development of combined modality strategies. While this has created a substantial body of empirical data, the drug-radiation schedules tried have often been selected without an underlying scientific hypothesis. In parallel with this, progress in molecular and cancer biology has generated a large number of non-cytotoxic drugs with new molecular targets and these are now in various stages of pre-clinical or clinical development. There is therefore a need for developing new mechanistic models to help investigators radiotherapy and cytotoxic or non-cytoxic compounds: spatial cooperation, cytotoxic

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