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