of recurrent disease). Moreover, molecular imaging can aid in the different steps of the drug development process speeding up drug development and validation.
In disease staging for instance, PET has been proven to have high accuracy in detecting unsuspected but pathological lymph nodes and other metastases, and this has been further improved with the use of integrated PET/CT systems. Precise and accurate target delineation is the first step in delivering curative doses of radiation while sparing surrounding normal tissue. Images from specific tracers can assist normal treatment planning and allow dose painting of radioresistant foci to improve biological dose conformality. In addition to selectively targeting subregions within the tumor with higher doses, tumor specific therapies including molecular targeted therapeutics may be incorporated into treatment. This approach is currently being pioneered using specific tracers to image hypoxia, but has broader implications, such as targeting rapidly proliferating areas within tumors or areas expressing other forms of molecular heterogeneity. As a response indicator, volume measurement is known to lack specificity and significance. PET/CT/MRI of functional parameters can assist in assessing outcome and can also help differentiate viable tumor from treatment-induced effects such as fibrosis, atelectasis, and radiopneumonitis. The best tracers and optimal timing of these exams before, during and after treatment is still under experimental investigation and before PET/CT/MRI imaging enters into the clinical routine of the oncology department, several methodological issues need to be addressed. For example, PET-based target volume definition using different PET tracers needs to be studied. Finally there is an urgent need for controlled studies to establish the impact of PET/CT/MRI on the final outcome of patients treated by molecular imaging guidance.

40 INVITED

Targeting tumour cells

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Radiotherapy is highly effective to inactivate clonogenic tumour cells. While untreated tumours contain a large number of clonogenic tumour cells, recurrences after high dose radiotherapy originate from a few surviving clonogenic tumour cells. Based on radiobiological considerations, additional cell kill among the survivors would result in a substantial increase in local tumour control probability. Additional cell kill can be achieved by different approaches including radiation dose escalation, combination with cytotoxic chemotherapeutics and biological targeting compounds. In the clinical situation, radiation dose escalation and intensification of chemotherapy is often limited because of normal tissue complications. Biological targeting compounds in the context of radiotherapy are specifically designed to modify functions relevant for radiation response in either malignant (direct targeting) or non-malignant (indirect targeting) cells in tumour tissues. As a monotherapy these targeting compounds have only a modest anti-tumour efficacy but in combination with radiotherapy results from preclinical and clinical investigations are very promising. Important examples for direct targeting compounds are EGF receptor inhibitors and for indirect targeting anti-angiogenic agents. In principle, both targeting approaches were shown to be effective in combination with fractionated radiotherapy. However, further investigations into molecular and cellular mechanisms of interaction are necessary to better define and exploit the potential of biological targeting of tumour cells to improve outcome after radiotherapy.

41 INVITED

Imaging of the microenvironment

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New strategies that have improved the outcome of head and neck cancer include altered radiotherapy schedules, combination of radiotherapy with chemotherapy, hypoxic sensitizers and, more recently, with EGF receptor inhibitors. These treatments target one or multiple of the major radiation resistance mechanisms: intrinsic radiosensitivity, tumor cell proliferation and hypoxia. Notwithstanding their succes, only a minority (15% at best) of the head and cancer patients profit from each of these new treatment strategies whereas all of them experience the increased toxicity which often is not insignificant. Furthermore, head and neck cancer is a heterogeneous disease and patient selection based on the traditional clinical and histopathological characteristics is not successful. Methods for qualitative and quantitative assessment of functional microenvironmental parameters such as hypoxia and tumor cell proliferation have identified several candidate markers for future use in predictive assays. Before these molecular markers qualify for application in routine clinical practice, they must be validated against reference tests of proliferation and hypoxia and their potential should be demonstrated in well-designed prospective studies. This overview will address the progress in this field of research and discuss a number of promising markers and marker profiles currently under investigation. In conclusion, there have been important gains in the treatment of head and neck cancer in the last decade but there is a need to apply the new treatments more effectively. Identification of biological tumor characteristics may allow a better selection of patients for intensified treatments. The ultimate aim is to provide the best attainable quality of life for individual patients and the cancer patient population as a whole and to apply new therapies in a cost-effective manner.

42 INVITED

Targeting the microenvironment

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Seminal publications in the early 1950s by Gray, Thomlinson and colleagues alerted the scientific community to the possibility that solid tumors contained cells at low oxygen concentrations and that, because of their resistance to killing by radiation, these hypoxic cells could adversely affect the curability of patients by radiotherapy. These predictions have proven correct: Today it is widely accepted that the majority of human tumors have viable hypoxic cells, and that these affect sensitivity to radiotherapy and to chemotherapy, provide a major angiogenic stimulus and increase the probability of metastasis. However, despite more than 50 years of clinical experimentation, we still do not have a proven, effective solution for overcoming the radiation resistance conferred by tumor hypoxia. This is the problem of tumor hypoxia. But there is also a opportunity: Tumor hypoxia could be an advantage in cancer treatment: It is a unique feature that can be targeted by appropriate hypoxia-activated drugs. Will this become a clinical reality with hypoxia activated cytotoxins such as tirapazamine, and PR-104? Meanwhile we are now much more aware of the fact that tumors comprise large numbers of normal, host-derived cells, and that this so-called tumor stroma, particularly the vasculature, is a crucial requirement for tumor growth and a potential target in cancer treatment. Indeed recent data from several groups have suggested that hypoxia confers tumor resistance to radiation by protection of the vasculature by hypoxia inducible factor (HIF-1) mediated pathways distinct from the classical oxygen effect of radiobiology. How much do these pathways contribute to tumor radiation resistance, and can the HIF-1 pathway be exploited by making the tumor vasculature more vulnerable in radiotherapy? In this lecture I will attempt to shed light on these questions.

Symposium (Mon, 24 Sep, 14:45−16:45)
Invasion and metastases

43 INVITED

Genome and transcriptome analysis of single disseminated cancer cells

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Background: It is obvious that later arising metastases are derived from one or several tumor cells that disseminated prior to surgical resection of the primary tumor. Indeed, single disseminated cancer cells residing in various organs after so-called “curative” surgery can be detected by sensitive molecular and immunocytochemical assays. Clinical follow-up studies have established the prognostic significance of disseminated tumor cells for many types of carcinomas, although they are detected in bone marrow or lymph nodes at a frequency of only 10−5 to 10−6. Materials and Methods: The prognostic impact of disseminated tumor cells (DTC) suggests that they are likely candidates for metastatic progenitor cells and that they are important target cells of adjuvant therapies. Unfortunately, only circumstantial knowledge about these cells is currently available. Therefore, we started to develop techniques for the study of single cells and to investigate the early stages of systemic tumor progression. Thus far, we succeeded in establishing protocols for the isolation of DTCs by micromanipulation as well as single cell genome and transcriptome analysis. Results: Results obtained from the genome analysis of several hundred samples of cancer patients demonstrate that dissemination is an early event in the genomic development of a tumor and suggest a parallel evolution of the primary tumor and its metastases. Phenotypic characterization of single disseminated cancer cells identified several subsets of disseminated cancer cells. A comparative analysis of primary tumors and DTCs revealed that important therapy target genes are not equally expressed and genetically activated in local and systemic disease. Conclusions: Metastatic precursor cells are genetically heterogeneous and