2005 were managed with emerging ablative techniques, in contrast to 22%, 17%, 33% and 18% having laparoscopic partial nephrectomy, open partial nephrectomy, laparoscopic or open radical nephrectomy, respectively.

References

[1] Hollingsworth JM, Miller DC, Daigneult S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. JNCI 99: 569–570, 2007.
[2] Remzi M, Ozsoy M, Klingler HC, et al. Are small renal tumors harmless? Analysis of histopathological features according to tumors 4 cm or less in diameter. J Urol 176: 896–899, 2006.
[3] Hafez KS, Fergany AF, Novick AC. Nephron sparing surgery for localized renal cell carcinoma: impact of tumor size on patient survival, tumor recurrence and TNM staging. J Urol 162: 1930–1933, 1999.
[4] Gill IS, Matin SF, Desai MM, et al. Comparative analysis of laparoscopic versus open partial nephrectomy for renal tumors in 200 patients. J Urol 170: 64−86, 2003.
[5] Volpe A, Panzarella T, Rendon RA, Haider MA, Kondylis FI, Jewett MA. The natural history of incidentally detected small renal masses. Cancer 101: 650, 2004.
[6] Remzi M, Memarsadeghi M. small incidental renal tumors: evaluation and biological parameters. Urologe A 46: 478–484, 2007.
[7] Marberger M. Ablation of renal tumours with extracorporeal high-intensive focused ultrasound. BJU Int 99: 1273–1276, 2007.
[8] Marberger M, Mauermann J. Ablative therapy of renal tumors. In: Campbell-Walsh Urology, 9th Edition, Eds. LR Kavoussi, AA Novick, AW Partin, CA Peters. Vol. II, Ch. 52, pp. 1810–1818, 2006.
[9] Klingler HC, Marberger M, Mauermann J, Remzi M, Susani M. Skipping is still a problem with radiofrequency ablation of small renal tumours. BJU Int 99: 998–1001, 2007.
[10] Chosy SG, Nakada SY, Lee FT Jr, Warner TF. Monitoring renal cryosurgery: predictors of tissue necrosis in swine. J Urol 159: 1370–1374, 1998.
[11] Silverman SG, Tuncali K, vanSonneberg E, et al. Renal tumors: MR imaging-guided percutaneous cryotherapy – initial experience in 23 patients. Radiology 236: 716–724, 2005.

36 INVITED

Novel targeted and signalling pathway inhibitors: an overview

T. Eisen. *UK*

Abstract not received.

37 INVITED

Novel targeted and signalling pathway inhibitors – ongoing studies

C. Sternberg. *San Camillo Forlanini Hospitals, Medical Oncology, Rome, Italy*

Global investigators have combined their efforts in groundbreaking landmark trials which have changed our perception of metastatic RCC.
AVOREN study: AVOREN is an international European phase III double blind randomized placebo control trial which included 649 pts with advanced clear cell carcinoma in >50% of the specimen after nephrectomy. Pts were randomized between IFNα and placebo and the combination of Bevacizumab and IFNα. Although OS survival was to have been the primary endpoint, the trial was stopped by the IDMC after an improvement in PFS was seen and pts were offered Bevacizumab. A similar study is ongoing in the US cooperative groups.
PAZOPANIB Trial: Pazopanib is a potent, multi-target receptor TKI of VEGFR-1, -2, -3, PDGFR-a and -b and c-kit. A Phase III randomized global study has compared Pazopanib to matching placebo, in a 2:1 ratio, in pts with locally advanced or metastatic RCC. Of 435 pts entered, approximately 1/2 had prior cytokines and 1/2 had no prior therapy. The 1º objective is to evaluate PFS. The 2º objectives are OS, objective RR, adverse events and QOL.
RECORD-1 Trial: RAD 001 (Everolimus) is an oral mTOR pathway inhibitor, an active Rapamycin derivative, not a prodrug. Renal Cell Cancer Oral RAD 001 given Daily (RECORD-1) is a multicenter international phase III trial in 362 pts with progressive metastatic disease. RAD 001 plus BSC compared to BSC and placebo in pts who have progressed after antiogenesis TKIs (Sunitinb and Sorafenib). PFS is the primary objective. Secondary objectives include: OS, response and duration, safety, disease related symptoms and QOL. Exploratory evaluation of serum and tissue biomarkers will be evaluated.
BEST Trial: The BEST ECOG trial is designed for 360 pts with untreated advanced RCC and will randomize pts to 1 of 4 treatment arms: Bevacizumab, Bevacizumab plus Temsirolimus, Bevacizumab plus Sorafenib and Sorafenib plus Temsirolimus. This trial may be criticized for not including a Sunitinb arm, which is at the moment considered to be a new standard of therapy in the 1st line setting.
AMGEN trial: Angiopoietin-2 (Ang-2) is a regulator of angiogenesis. An inhibitor (AMG386) to Ang-2 is being evaluated. Because this represents an alternative pathway to VEGF-mediated angiogenesis, the potential exists for combining inhibitors of this pathway with current anti-VEGF approaches.
EFFECT trial: This phase III will evaluate the combination of Sunitinib plus IFNα. The planned multicenter phase III study will evaluate 3 treatments. Sunitinib, 50 mg/day orally, 4 weeks on 2 weeks off (the intermittent, FDA-approved dosing), Intermittent Sunitinib plus IFNα and Sunitinib continuous dosing. Planned accrual is 499 pts.
TROVAX Trial: TroVax delivers a novel tumor associated antigen (5T4) using Modified Vaccinia Ankara vector An international, randomized, double blind study to investigate whether TroVax, added to 1st-line standard of care, prolongs survival: sc IL-2, sc IFNα or Sunitinib. The 1º endpoint is OS. 700 pts will be enlisted.
Many trials of novel combinations are underway, vertical combination therapy targeting the same pathway (i.e. Sorafenib and Bevacizumab), horizontal targeting of different pathways (i.e. Sunitinb and Erlotinib) and other combinations which target distinct mechanisms of action (i.e. high-dose IL-2 plus Bevacizumab or IFN + Sunitinib).
It is extremely likely that combinations of agents will emerge as important approaches to treatment. Since direct comparisons of these agents have not yet been made, they have all emerged as promising and viable options. It is unknown to what degree these agents are cross-resistant and whether combination therapies or sequential therapy with cytokines or with Bevacizumab or with TKI will improve prognosis. It will be important to evaluate how these therapies work through analysis of patients with both responsive and resistant tumors

38 INVITED

Is there still a place for immunotherapy?

P. Mulders. *University Hospital Nijmegen, Department of urology, Nijmegen, The Netherlands*

Immunotherapy has been used for decades for the treatment in RCC. In an adjuvant setting it did not show clinical benefit. For mRCC in randomized studies, IFN-alpha has proven superiority for survival over hormonal therapy in patients with mRCC. The patients who benefited were of good WHO status (0−1) and were treated for at least 12 weeks and up to 1 year with an improved survival of several months. Interleukin-2 (IL-2) has been used in mRCC since 1985 with a substantially higher toxicity than that of IFN-alpha. Several studies have shown responses ranging from 7−27%. The optimal IL-2 regimen is not clear, but long-term (>10 years) complete responders have been achieved with high-dose bolus IL-2. However, no randomized study has been done against best supportive care. It seems that only clear cell type RCC responds to immunotherapy.
Several randomized studies have been performed to investigate the efficacy of combinations of cytokines. Patient survival was not better than survival achieved with monotherapy. No other combinations with cis-retinoic acid or 5FU have shown a clinical significant benefit, although some survival advantage has been seen. It can be concluded that immunotherapy can be beneficial in good risk mRCC patients with clear-cell type histology. This has to be seen in the era of new targetted drugs. These chronic drugs have a high stabilizing capacity, were the significance of survival benefit is still under discussion. This had to be seen against the immunotherapy strategies

Symposium (Mon, 24 Sep, 14:45−16:45)
Biological targeting for radiotherapy

39 INVITED

Imaging of the biological target

K. Haustermans. *U.Z. Gasthuisberg, Department of Radiotherapy, Leuven, Belgium*

Molecular imaging allows molecular and cellular events to be tracked in a living organism. Powerful new targeted imaging technology has become available including fMRI and PET for which specific tracers have been developed for tumor cell proliferation, metabolism, apoptosis, angiogenesis, receptor and gene expression. The long term goal of these studies is to use this new technology to stage the disease, to select the treatment for the patient (treatment individualisation), to plan treatment volumes that compensate for volumes of radioresistant disease, and to evaluate treatment efficacy (early response prediction and early detection

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

D. Zips, M. Baumann, M. Krause. *TU Dresden, Radiation Oncology OncoRay, Dresden, Germany*

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

J.H.A.M. Kaanders[1], J. Bussink[1], A.J. van der Kogel[1], O.C. Boerman[2], W.J.G. Oyen[2]. *[1]UMC St Radboud, Department of radiation oncology, Nijmegen, The Netherlands; [2]UMC St Radboud, Department of nuclear medicine, Nijmegen, The Netherlands*

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

M. Brown. *Stanford University Medical Center, Department of Radiation OncologyCCSR South Room 1255, Stanford, USA*

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

C. Klein. *University of Regensburg, Abteilung für Onkogenomik, Regensburg, Germany*

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