Patients with Lymph node positive disease are at high risk for tumor relaps and thus are potential candidates for adjuvant chemotherapy.
Materials and Methods: Publications of major journals and abstracts form major scientific meetings were reviewed.
Results: Several randomised trials comparing observation vs. 5-FU based treatment all reported that adjuvant chemotherapy results in an about 30% reduction of the risk of death and 6 months as compared to 12 months treatment duration are sufficient. Infusional 5-FU with leucovorin does not increase the results achieved with bolus 5-FU/FA but is less toxic. The oral fluoropyrimidines such as UFT/LV and capacitabine are alternatives to intravenous applications. The most promising data are reported with the use of capecitabine. Infusional 5-FU in combination with leucovorin and oxaliplation has further improved the efficacy by significantly prolonging the time to progression and as recently reported also the overall survival by about 4% in patients with stage III disease. The FOLFOX4 regimens is therefore the reference regimen and standard of care for this gorup of patients. Interestingly, the use of bolus 5-FU plus oxaliplatin (FLOX) confirms these results and indicates that oxaliplation is an important drug in the adjuvant setting. Long term neurotoxicity in about 12% of patients event after 4 years and in 75% within the first year has to be considered as a sequelae which ma ynot be acceptable for some patients. Irinotecan based regimens either with 5-FU given as a bolus or as an infusion have failed to improve over 5-FU/LV alone. Ongoing trials investigate the role of VEGF and EGFr antagonists.
Conclusions: Adjuvant chemotherapy should be offered to patients with stage III colon cancer. If FOLFOX4 can not be administered oral or intravenous fluoropyrimidies are second best options.

Symposium (Mon, 24 Sep, 14:45−16:50)
What is new in renal cancer

34 INVITED

An update on the molecular genetics of (hereditary) renal cancer: novel families, novel genes, novel diagnostic opportunities . . .

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Renal cell carcinomas (RCCs) represent ~90% of all primary renal tumors in adults. In recent years its incidence has been increasing worldwide. As yet there is no long term effective therapy for RCC, but if detected early and without metastases the tumors can be removed surgically. Such patients have a relatively good prognosis.
Besides sporadic RCCs also familial cases have been reported. Both share the presence of anomalies involving chromosome 3, suggesting a primary role for this chromosome in RCC development, particularly the clear cell type. Previously we, and others, have identified a number of families in which the occurrence of RCC co-segregates with constitutional chromosome 3 translocations. Based on allele-segregation, loss-of-heterozygosity and mutation analyses in these families, a multi-step RCC model was generated in which the occurrence of the chromosome 3 translocation acts as the primary step. Since then, this step-wise model was corroborated by several other investigators. As a corollary, we evaluated a cohort of ~100 Dutch families (Dutch Intergroup Study) known to segregate constitutional chromosome 3 translocations. Among these, several novel RCC families (as also families with other cancer syndromes) were detected. Additionally, we have collected an extensive series (~30) of RCC families without overt cytogenetic anomalies.
Aiming at the identification of additional RCC susceptibility genes, we initiated the positional cloning of the translocation breakpoints in these families. By doing so, we previously identified two novel genes, DIRC2 and DIRC3. Using similar approaches others identified FHIT, TRC8, DIRC1 and, more recently, LSAMP, NORE1 and TRC8. Interestingly, there appears to be a functional overlap between at least some of these genes. For the rapid mapping of additional familial chromosomal breakpoints and the identification of its corresponding genes, we developed a novel highly efficient microarray-based approach. In this approach chromosome flow sorting (FACS) and genomic microarray (arrayCGH) technologies have been integrated. In addition, we have developed a whole genome tiling-resolution BAC array (32K) for high-resolution detection of DNA copy number changes in cases lacking any apparent cytogenetic anomalies. Through the application of these array technologies we have been able to (i) precisely map novel translocation breakpoints and (ii) identify novel microdeletions/microduplications and their corresponding (onco-/tumor-suppressor) genes. Identification of these genes does not only provides us with relevant information for familial risk assessment, genetic counseling, and early detection, but also with clues with regard to alternative pathogenetic routes. Our ultimate goal is to establish an integrated model for (familial) RCC development, including the nature and role of its predisposing genes.

35 INVITED

Energy ablative therapy of renal cancer: new option or wrong track?

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Renal tumours <4 cm in diameter and detected incidentally in asymptomatic patients represent up to 50% of all solid renal lesions diagnosed today [1]. Although ~20% of them prove benign on histological examination and the majority grow slowly, 79% are renal cancers and of these 14% are multifocal, 15% Fuhrman grade 3−4, 22% >pT3a and 6% have metastasized at the time of diagnosis [2]. Nephron-sparing surgical excision is the standard therapy and achieves 10-year cancer-specific survival rates of up to 96%, with the rare recurrent tumour diagnosed after a median 5.4 years [3]).
Regardless of whether performed by open or laparoscopic partial nephrectomy, this carries a complication rate ~15% [4]. With the largest increase in incidence seen in the age group over 70 years of age with inherently high comorbidity, less invasive treatment options appear attractive. Based on small, retrospective series which suggest a low progressive rate, a watchful waiting strategy has been advocated for these tumours in infirm patients [5]. With at present no way to reliably identify the less aggressive tumours by imaging or percutaneous biopsy [6] and in view of the dominant histology of these tumours [2] this comes at considerable risk. Targeted destruction with less invasive energy based ablation appears safer. Small renal tumours are good targets, as they often have a spherical shape, are unifocal, located peripherally in the renal cortex and easy to locate by imaging. Ideally, the tumour is destroyed by an extracorporeal 'no touch' approach. The only non-radiation based technique theoretically capable of doing this is high-intensity focused ultrasound ablation. In clinical practice, problems with acoustic interphases from ribs and abdominal wall, ultrasonic inhomogeneity of the tumour and respiratory movement of the kidney have so far caused disappointing results with this technique, so that it remains strictly experimental at present [7]. Heating >60ºC causes instantaneous coagulative necrosis of all tissues, even in highly perfused organs like the kidney, and this is achieved by radiofrequency using either monopolar or bipolar electrodes. Under CT or MRI guidance, the electrodes can be placed percutaneously, even in local anaesthesia. Radiofrequency ablation's (RFA) main problems stem from the fact that tissue destruction cannot be visualised in real time, but has to be monitored by thermometry or changes in impedance. As a result, a recent metaanalysis of published data revealed a residual/recurrent tumour rate of 14% after percutaneous RFA of small, biopsy proven renal cell cancers, in spite of a mean follow-up of only <15 mos [8]. Even with state-of-the-art RFA equipment and technique and visual control of electrode placement, skipping of the area of necrosis and residual vital tissue has been demonstrated histologically after RFA ablation in 22% of tumours [9]. Skipping also seems to be the reason for late urinary fistula and ureteric strictures, which have been observed after percutaneous RFA [9].
After laparoscopic exposure of the kidney, cryoablation using needle cryoprobes and multiple freeze–thaw cycles under ultrasonic control has been utilised extensively. The objective is to freeze all tissues to be ablated below a minimum −20ºC [10], yet avoid all other structures. The ice ball, which is generated during the process, is not representative for this temperature, but can be monitored by laparoscopic ultrasonography. Clinical experience has shown that with an overlap of 6−10 mm beyond the tumour margin, reliable tumour destruction is achieved. With follow-up now reaching 5 years in some series, 92% of small peripheral tumours are completely ablated, as documented by a complete loss of contrast enhancement, progressive shrinking of the lesion and negative follow-up biopsies [8]. With the recent development of thinner cryoprobes ('cryoneedles') of 1.5 mm diameter and real time monitoring of needle placement and ice ball formation by open access, interventional MRI percutaneous cryoablation has come into the realm of clinical practice. Morbidity with the latter technique has proven low, but with retreatment needed in about 15% of tumours because of incomplete tumour destruction, results are still problematic [11, 12]. The keys to successful energy ablative therapy are correct patient selection and surgical technique, state-of-the-art technology and meticulous follow-up by serial cross-sectional imaging.
Patients with exophytic peripheral tumours <3 cm in diameter are ideal and complete ablation can be achieved in 95%, especially using laparoscopc cryoablation. Larger multifocal or central tumours have a high failure rate and a potentially significant complication rate, especially with RFA. Tumours on the anterior aspect of the kidney are difficult to reach percutaneously and the laparoscopic approach is definitely preferable. Complete loss of contrast enhancement and progressive shrinkage of the lesion on repeat CT or MRI studies are mandatory criteria for success. If this does not occur, follow-up biopsies are mandatory. If these guidelines are adhered to, energy ablative therapy definitely has a place in the management of renal cancer: it may be the therapy of choice in a high-risk surgical patient with a solitary, small and peripheral renal tumour. At this institution, using these criteria, 10% of 394 kidneys with tumours treated surgically 2002–

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.

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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

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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?

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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

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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