The role of surgery in EPP remains controversial. Less invasive methods are available for diagnosis and symptom control. Comparative survival benefits have been recorded from chemotherapy regimes alone.
Mesothelioma surgery can be complex and of high risk and should therefore be concentrated in specialized centres. There remiains a problem with equity of access to specialist skills, however. Well designed clinical trials are the best solution to these problems and the future aspiration of surgical enthusiasts.

Scientific Symposium (Wed, 23 Sep, 14:45−16:45)
What are the side-effects of therapy in mRCC and how to handle them?

254 INVITED

Tyrosine kinase inhibitors

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The tyrosine kinase inhibitors have a range of side-effects which are only now becoming familiar to oncologists. Many of the toxicities are understated in their severity by use of the CTC. These criteria were developed for use with intermittent chemotherapy and it has become apparent that even grade 2 toxicities may significantly impair the quality of a patient's life. Often toxicities reported in studies are only really noticed if they are grade 3 or worse.
The main toxicities of TKI therapy are fatigue, rash, diarrhoea, hypertension, stomatitis, hypothyroidism and of particular importance in the neo-adjuvant or adjuvant setting, a potential to reduce healing. In addition there are emerging toxicities such as cardiac toxicity, the exact incidence and severity of which is still a matter for debate. Whilst most multi-targeted tyrosine kinase inhibitors exhibit most of the side-effects noted above, each tyrosine kinase inhibitor has its particular profile. For example, stomatitis and fatigue tend to be more marked with sunitinib. Rash tends to be more marked with sorafenib. Liver function disturbances tend to be more marked with pazopanib. Most of the side effects can be handled by patients, such that the large majority of patients are able to stay on treatment. Particular interventions may be useful to minimise the effect of side-effects and these interventions are often best used early in the course of a side-effect's natural history or even as preventative measures. The measures include using children's toothpaste and children's toothbrushes for stomatitis. Avoiding strong spirits or curries also for stomatitis. Diarrhoea may be handled by standard techniques such as loperamide. Hypertension should be rigorously controlled as evidence is accumulating that this reduces the risk of other cardiac toxicities. Standard agents may be used although care should be taken in choosing concomitant medications to use with tyrosine kinase inhibitors. Rash and hand/foot syndrome are often best managed preventatively by keeping the skin moist and supple with the use of emollient creams and occasionally urea-containing creams particularly where there is hyperkeratosis.
These side-effects, their severity and management will be discussed in the session. Mention will also be made of the possible future benefits of more precisely targeted tyrosine kinase inhibitors.

255 INVITED

mTOR inhibitors, bevacizumab

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Therapy of metastatic RCC has changed a lot in the past 3 years with approval of many new targeted agents. Due to the number of approved agents, and to the fact that very few patients (if any) are cured with these agents, side effects have to be taken into account both in terms of helping to choose the best drug to provide in each individual patient and in terms of management. In addition, toxicity should be considered differently when given chronically, since grade 1−2 toxicity is dramatically different when occurring for a few days or permanently.
Among targeted agents used in mRCC, mTOR inhibitors (temsirolimus and everolimus) and bevacizumab are very selective targeted agents, for which side effects are directly linked to the mechanism of efficacy, which might be different from tyrosine kinase inhibitors.

1. mTOR inhibitors mainly produce fatigue, skin rash and stomatitis. However, some less common side effects such as pneumonitis and algodystrophia should be known. Interestingly, most of these side effects are rapidly reversible when the drug is stopped. Metabolic dysregulation is directly due to mTOR inhibition. Usually mild, hyperglycemia, hyperlipemia might require adequate measures
2. bevacizumab has been used in oncology for more than 6 years and toxicity profile is well characterizes. VEGF inhibition induces hypertension, glomerular damages which can induce proteinuria and increased risk of bleeding and thrombosis. In RCC in addition, bevacizumab is given with interferon (IFN), and classical toxicity of IFN might be slightly increased by the addition of bevacizumab. However, specific side effects of bevacizumab appear similar to those observed without IFN, in other tumor types

In conclusion, a better knowledge of the side effects of the available drugs in RCC should help the physician to determine whether the benefit of a drug is large enough to justify its use in an individual patient.

256 INVITED

Do combination and sequential therapies have increased side-effects?

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Since 2005 the panorama of metastatic renal cell carcinoma (mRCC) treatment has radically changed, with four molecularly targeted agents (Sorafenib, Sunitinib, Temsirolimus and Bevacizumab – the latter in combination with Interferon) currently registered and available in European Union Countries, and two more (Everolimus and Pazopanib) presently under evaluation. Despite these dramatic improvements, no individual agent will benefit all mRCC patients, who should still be regarded as incurable; it is therefore mandatory to design rational clinical trials to try to further improve the results obtained so far. Two treatment strategies can be followed: to combine these agents, or to sequence them. Both strategies leave some questions open (do the mechanisms of action matter? does the target matter? in sequencing treatments, does the agent sequence matter? in combining treatments, is a 'horizontal' or a 'vertical' blockade better? and many more), but the issue of the tolerability of combination and sequential therapies appears to be key. Currently, available data are scarce and somehow biased. As for sequential treatments, we can mainly rely on retrospective series, while data relative to the safety of combinations come mainly from phase I trials, even though some of these combinations have already entered phase III development! Sequential therapies appear feasible, with a predictable and manageable adverse events profile and no signs of increased toxicity (except, probably, for fatigue and hypertension). Differently, combination treatments, while possibly providing increased activity, appear to be poorly tolerated, especially at full doses, and to cause even completely new toxicities (e.g. microangiopathic hemolytic anemia for the Sunitinib plus Bevacizumab combination). Furthermore, the choice of the agents to combine and the design of phase I studies proved to be extremely relevant when toxicity profile is taken into account. While waiting for the results of several phase II and III trials currently underway, we can say that the safety profile of combination treatments is somehow worrying (though there are some exceptions), while there is less concern for the safety of sequential treatments. To clarify not only activity but also safety issues, specific and well designed studies are badly needed.

257 INVITED

Cytokines and vaccines

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In mRCC the standard of care in Europe has, until the recent introduction of the targeted agents, been interferon alpha 2a (IFNα-only) based on the results of several randomised trials. In particular, the MRC RE01 study which showed a modest but clinically and statistically significant overall survival advantage for IFNα over MPA.
Interleukin-2 (IL2) when given intravenously at high dose by bolus injection results in response rates of 14−23% (13−15) but more importantly, about 7% of patients obtain a durable complete remission lasting over three years and some of these have been maintained for ten years. However, no randomised trial has ever shown a survival advantage for this treatment over a control group.
The toxicity profile of immunotherapy with IFN and IL2 is related to the aspecific nature of the treatment. In the largest trial in RCC, randomising IFNα versus INF, interleukin 2 (IL2) plus fluorouracil (FU) (IIF) in patients with previously untreated mRCC, no differences in PFS and overall survival exist. The toxicity is however different: during treatment there was significantly more grade 3/4 toxicity associated with IIF compared to IFNα-only (56% versus 38%, $p < 0.001$). Fatigue was significantly worse for IIF patients with 22%, 45% 24% and 2% experiencing grade 1, 2, 3 and 4 fatigue respectively, compared to 34% 39% 17% and <1% in IFNα-only patients. There was no evidence of significant differences between treatment arms in terms of worst quality of life score for tiredness, lack of appetite, shivering or lack of energy. Serious adverse events were reported in 6% and 5% of patients receiving IFNα-only and IIF, respectively.

Vaccines can be considered as so called specific immunotherapy. This is the reason why the above mentioned toxicities are not seen. Vaccines strategies like dendritic cells loaded with tumorproteins/peptides/RNA, GMCSF manipulated tumorcells or heatshock proteins have been explored in mRCC and in an adjuvant setting after tumornephrectomy for localized RCC. Only grade 1 toxicities were seen in about 30% of the patients.
In conclusion the side-effective profile of immunotherapy and vaccines is dependent on nature and the specificity of the approach and should be handled accordingly.

258 INVITED

Adjusting therapy in the elderly patient with metastatic renal cell cancer (mRCC)

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We know that the average age at presentation of renal cancer is 62 years in both men and women. Given that the number of elderly people is rapidly rising and that cancer incidence increases with age, we must expect an escalating burden of renal cell cancer in the coming years. The treatment of metastatic renal cancer has changed completely over the recent years with the introduction of different targeted therapies which have demonstrated a benefit in terms of both overall and progression-free survival. However, these new drugs induce toxicities which complicate the management of elderly patients. We know that older cancer patients have comorbidities which may affect treatment tolerability, as well as patient general prognosis and quality of life. No specific trial has been conducted in this particular population; the main results available come from clinical trials including only a limited number of patients older than 65 years. The six randomized trials testing sofafenib, sunitinib, bevacizumab, temsirolimus or everolimus had no upper age limit for recruitment. However, the average age of patients entered in these trials was quite similar and younger (58−62 years) than in the general population. In addition, subgroup analyses to assess the relationship of age to treatment benefit have limitations and should be regarded as hypothesis-generating and not as definitive evidence. Obviously, all these treatments have demonstrated efficacy in the elderly and the results obtained seem to be in the same range as in younger patients. Although it appears difficult to analyse the side-effects induced in the elderly population, some well-known toxicities from targeted therapies may have a more significant impact in this subgroup: hypertension, cardiac impairment, thromboembolism, asthenia and digestive symptoms, especially diarrhoea. In addition, elderly patients use a variety of drugs for managing comorbidities and these drugs may interact with targeted therapies. For these reasons, patients with several comorbidities and treatments may require an oncogeriatric evaluation before making a treatment decision. Stricter management with more frequent consultations may also be useful to avoid severe adverse events as well as major impairment in their quality of life.

Scientific Symposium (Wed, 23 Sep, 14:45−16:45)
Targeting in radiotherapy

259 INVITED

Targeting the tumour stroma

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Background: The tumour stroma plays an essential role in malignant transformation, tumour progression and development of resistance to conventional radio- and chemotherapy. It consists of different cell types such as fibroblasts, immune and inflammatory cells and endothelial cells and the connective-tissue framework/extracellular matrix (ECM). Although histological distinguishable, the tumour stroma and the tumour cells are functionally inevitable linked. On top of e.g. tumour cell-specific gain-of-function mutations, these interactions further promote the survival, growth and spread of the tumour cells via production of growth factors, extracellular matrix remodeling and by provoking a tumour-friendly microenvironment. Owing to these various prosurvival effects, targeting strategies against the tumour stroma might be reasonable and clinically achievable in modern radiochemotherapy. One of these potent strategies is the inhibition of integrin cell adhesion molecules. Integrins facilitate interactions between the cells of the tumour stroma and ECM and between cells of the tumour stroma and tumour cells.
Material and Methods: Different tumour cell lines, particularly head and neck squamous cell carcinomas, have been investigated under conventional monolayer and three-dimensional growth conditions and in vivo with regard to radio- and chemoresistance. Moreover, the results of targeting approaches against integrins and associated molecules evaluated in additional preclinical models and clinical trials will be discussed.
Results: Inhibition of integrins on both tumour stroma and tumour cells shows promising results. Other approaches against integrin associated signaling molecules such as Focal adhesion kinase or Rho-GTPases or ECM remodelling matrix metalloproteinases further underscore the relevance of these signaling pathways for therapy resistance and tumour progression. The findings also highlight dramatic effects of radiochemotherapy and particularly molecular therapeutics on the tumour stroma, at which the exact benefits and consequences in terms of cancer cure remain to be clarified. For example, the optimal sequence of antiangiogenic compounds in combination with radiotherapy is currently unclear.
Conclusions: The tumour stroma and the tumour microenvironment are integral functional parts in tumourigenesis, tumour progression and resistance to radio- and chemotherapy. Besides specific targeting of molecules essential for tumour cell survival and proliferation, targeting strategies against the tumour stroma have shown to be promising, powerful adjuvants for conventional anticancer treatment. Nevertheless, further efforts are warranted to understand the underlying molecular mechanisms that drive tumour growth in dependence on the tumour stroma for the development of more efficient molecular therapeutics.

261 INVITED

Improving radiotherapy by targeting the bone marrow derived stroma

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Tumor blood vessels can derive from two sources: by angiogenesis, or the sprouting of endothelial cells from nearby blood vessels, and by vasculogenesis, which is produced by circulating cells. We have recently proposed that the radiation doses given in radiotherapy, which produce very high local cell killing in and immediately surrounding the tumor, will abrogate local angiogenesis and thereby forcing tumor regrowth to rely on vasculogenesis. This alternative pathway involves the recruitment of proangiogenic circulating cells many of which are derived from the bone marrow. To investigate this hypothesis, we used the subcutaneously implanted FaDu human head and neck tumor and an orthotopic brain tumor using human U251 GBM cells that were retrovirally transduced with the luciferase gene in order to monitor tumor growth in real-time.
To examine the influence of irradiation on the influx of bone marrow derived cells (BMDCs) into the tumors, we sacrificed tumor-bearing nude mice containing GFP-expressing bone marrow when the tumors grew back to their pre-irradiation size following either 8 or 15 Gy. We found that irradiation induced BMDC influx in a dose-dependent manner with most of this increase reflecting influx of CD11b+ myelomonocytes. We postulated that this influx of BMDCs was stimulated by increased tumor hypoxia and HIF-1 levels caused by radiation damage to the tumor vasculature. To determine HIF-1 activity in real-time in our brain implanted U251 GBM, we stably expressed the HIF-1 reporter construct 5HRE-luc in U251 cells and monitored luciferase activity in control and irradiated tumors. HIF-1 activity paralleled tumor growth in non-irradiated tumors but increased more rapidly than tumor growth starting at about two weeks following 15 Gy, indicating increase in HIF-1 levels parallel to the increase in tumor hypoxia that we observed at this time.
To test our hypothesis that the increased HIF-1 levels were responsible for the increased influx of CD11b+ cells into the tumors, we used the HIF-1 inhibitor NSC-134754. When this inhibitor was given daily for 2 weeks, starting immediately following irradiation, the increased tumor levels of CD11b+ monocytes observed after 15 Gy was abrogated. This treatment also prevented recurrence of the irradiated tumors following irradiation even when we ceased administration of the drug.
As a further test of our hypothesis we determined the effect of inhibiting the interaction of stromal derived factor-1 (SDF-1) with its receptor CXCR4 using the clinically approved drug AMD3100. It has been shown that BMDCs are retained in hypoxic normal tissues and in tumors by the hypoxia-dependent secretion of SDF-1, which binds to its receptor, CXCR4, on BMD monocytes thereby promoting angiogenesis. To prevent this interaction we infused tumor-bearing mice with AMD3100 starting immediately following irradiation. This had no significant effect on the growth of unirradiated tumors in the brain but completely inhibited the recurrence of the irradiated tumors following either a single dose of 15 Gy or the more clinically relevant scheme of 5 daily doses of 2 Gy.
We also showed that the recurrence of FaDu tumors locally irradiated with 20 Gy is prevented using a monoclonal neutralizing antibody against CD11b+ monocytes. This treatment does not increase the radiosensitivity of normal skin. In fact we observed a consistent protection of the skin when the irradiated mice were treated with the antibody starting 4 days after irradiation