of translational repression and/or induction of the different genes varied widely. Global analysis using microarray technology indicated that as many as 5% of all genes may be differentially affected during hypoxia through regulation of mRNA translation.

Scientific Symposium
What is new in renal cancer

38 Abstract not received

39 Abstract not received

40 INVITED

Systemic therapy and novel targeted therapies in renal cancer

M. Gore. *Royal Marsden Hospital, London, United Kingdom*

Renal cell carcinoma has always been considered a chemo-resistant disease and data from the 1980s suggests that response rates are very low. There have however, only been limited data on the newer cytotoxic agents and more recently, non randomised trials have suggested that some patients may respond to combination treatments such as gemcitabine plus capecitabine. It is becoming increasingly recognised that renal cell carcinoma is not a single disease entity. Histology subtype and specific molecular abnormalities may not only define the behaviour of individual tumours but may also have therapeutic relevance. This is best exemplified in relation to targeted therapies. Hormone treatments have for many years been used as second-line treatment in patients who have failed first–line immunotherapy or as initial therapy in those unfit for immunotherapy. They are associated with low response rates and randomised trials suggest that at least, at first-line these treatments confer little or no benefit.

Standard therapy involves immunotherapy with either interferon or interleukin 2. There are randomised data that support the use of interferon and non-randomised data that suggest high dose bolus interleukin 2 is associated with durable complete remissions in a small percentage of patients. There is no evidence that combination immunotherapy is associated with an overall survival benefit. Case-controlled studies and a recent randomised trial from the French cooperative group show that immunotherapy is of no benefit to patients with intermediate or poor prognosis disease.

There is something of a revolution taking place in the treatment of renal cell carcinoma and a number of new targeted agents have shown activity in this disease. The most notable activity and best data produced so far involves Sutent and Sorafenib, the multi targeted tyrosine kinase inhibitors and Avastin, the monoclonal antibody directed against VEGF.

Sutent has shown response rates of nearly 40% in two consecutive phase 2 trials. These studies have involved 160 patients and this makes these data of great interest. Similarly, Sorafenib has shown significant activity in second-line with a doubling of progression-free survival. These are particularly impressive data as the trial was randomised; patients with stable or responding disease were randomised to continue on Sorafenib or placebo. Avastin has an overall response rate of 10% and at higher doses, a statistically significant prolongation of progression-free survival in a randomised trial against placebo. Other targeted agents that have shown activity include Temsirolimus and infliximab.

Trials in the first-line setting are currently underway with Sutent, Sorafenib and Temsirolimus being compared to interferon. Avastin has been combined with interferon and is being compared to single agent interferon. These agents and other targeted compounds are being combined and further data are awaited. Within the next 12–24 months we will have a clearer picture of the precise efficacy of these novel agents, particularly in comparison to interferon. Positive results from these studies will beg many questions: will these new agents replace interferon or will they be given in combination with it? Which targeted agents should be combined and will that be a better strategy than administering them sequentially? Do these compounds with their relatively good toxicity profile, open up therapeutic options for those patients with poor prognostic features who are currently considered unfit for active treatment? Can we now start developing maintenance strategies? We are entering a new therapeutic era in renal cell carcinoma and it is imperative that we now conduct a series of well-designed trials to precisely define how these new compounds can best be utilised.

41 Abstract not received

Scientific Symposium
Laparascopic surgery versus conventional surgery in colorectal cancer

42 INVITED

Laparoscopic versus open surgery for colon cancer: short-term outcomes of a randomised trial – COLOR Trial

H.J. Bonjer[1,2]. *On behalf of the COLOR Study Group.* [1]*Dalhousie University, Surgery, Halifax;* [2]*Capital Health, Surgery, Halifax, Canada*

Background: Oncological safety and short term benefits of laparoscopic colectomy for cancer remain under debate. To investigate these outcomes, a multicenter study randomizing patients with colonic cancer for either laparoscopic or open resection was performed.

Patients & Methods: Twenty-nine European hospitals participated in the COlon cancer Laparoscopic or Open Resection trial (COLOR trial). Patients with a solitary cancer of the right or left colon were randomly assigned to either laparoscopic or open surgery as curative treatment. Cancer free survival at three years after surgery was the primary outcome. Clinical characteristics, operative findings and postoperative outcome are presented.

Results: Of the 1248 patients randomly assigned to one of the two surgical procedures, 153 were excluded and 13 could not be analyzed due to missing data.

Blood loss was significantly less during laparoscopic than during open surgery ($p < 0.001$). Laparoscopic surgery took half an hour longer to perform than open surgery ($p < 0.001$). In 17% of the laparoscopic procedures conversion to open resection was necessary. Radicality of resection assessed by number of removed lymph nodes and length of resected oral and aboral bowel segments was similar after laparoscopic and open surgery. During the postoperative course, laparoscopic colectomy was associated with earlier recovery of bowel function ($p < 0.001$), fewer analgesics requirements ($p < 0.001$) and one day shorter hospital stay ($p < 0.001$). Rates of morbidity and mortality within 28 days after colectomy did not differ between arms.

Interpretation: Laparoscopic surgery allows safe and radical resection of colonic cancer of the right, left and sigmoid colon. Although laparoscopic colectomy requires more operating time, it is associated with less blood loss, earlier restoration of bowel function, fewer analgesic requirements and shorter hospital stay.

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43 INVITED

The CLASICC trial

P. Guillou. *St James's University Hospital, Academic Surgical Unit, Clinical Science Building, Leeds, United Kingdom*

The CLASICC Trial is a randomised clinical trial of laparoscopic-assisted versus conventional surgery in colorectal cancer. Between 1996 and 2002 794 patients from 27 UK centres were allocated to undergo laparoscopic-assisted (n = 526) or open (n = 268) surgery for cancer of the colon (n = 413) or rectum (n = 381). All surgical resection specimens were treated identically and centrally reviewed for circumferential resection margins (CRM) positivity. In the lap-assisted group overall 29% underwent conversion to open surgery but this fell from 38% in year 1 to 16% in year 6 of the trial. Tumour stage was equivalent between the two arms of the trial and the proportions of Dukes stage C_2 tumours did not differ between the lap-assisted (7%) and open (6%) groups. Duration of operation was shorter in the open (135 [100–180] min) than in the lap-assisted (180 [135–220] min) group. Rates of CRM positivity were similar between groups except for those undergoing laparoscopic anterior resection for rectal cancer where CRM positivity was 12% ($^{16}/_{129}$) compared with 6% ($^{4}/_{64}$) in the group undergoing open anterior resection ($p = 0.19$). Lymph node yield was high in both arms (13.5 open, 12 lap-assisted). In the lap-assisted group average hospital stay was 2 days shorter than in the open group. Overall 30-day complication rates were identical in the two arms but in those who underwent conversion from laparoscopic to open surgery the complication rates were higher and this was reflected in a higher in-hospital mortality (open 5%, lap-assisted 1%, converted 9%, $p = 0.34$). Up to 3 months postoperatively quality of life scores (EORTC QLQ-C30, and QLQ-CR38) showed similar patterns between the two surgical groups. All patients have now been followed up for at least 3 years.

For cancer of the colon there seems to be little difference between laparoscopic-assisted and open resection and on the basis of the pathological data there is no reason to suspect that cancer-related outcomes will be different. Preliminary analysis of the 3-year overall and disease free survival bears this out. For rectal cancer the data might suggest that a higher local recurrence rate might be expected in those

undergoing lap-assisted anterior resection (but not abdomino-perineal resection) but this is not currently supported by the 3-year disease free survival data.

44 Abstract not received

Scientific Symposium
Brain tumours in childhood – problems and new concepts

45 INVITED

Hyperfractionated radiotherapy for PNET

R.D. Kortmann[1], L. Gandola[2], U. Ricardi[3], R. Taylor[4], C. Carrie[5]. *On behalf of the SIOP Brain Tumour Subcommittee Working Group for PNET.* [1]*Clinic for Radiation Therapy and Radiooncology University of Leipzig, Germany;* [2]*Radiotherapy, Istituto Nazionali dei Tumori, Milan, Italy;* [3]*Radiation Therapy Department, University of Turin, Italy;* [4]*Cookridge Hospital, Leeds, UK;* [5]*Department of Radiotherapy, Centre Leon Berard, Lyon, France.*

Background: In children with standard risk PNET (medulloblastoma) hfx-RT may allow a higher local total dose (68–72 Gy) in order to improve tumour control within the posterior fossa (PF) and reducing long-term toxicity in normal brain compared with conventionally fractionated RT (36 Gy). In high risk PNET hfx-RT (40 Gy CSA/68–72 Gy tumour site) results in increased tumour cell kill without increasing normal tissue toxicity. The rationale for hyperfractionated radiotherapy (hfx-RT) is to try to reduce delayed effects of radiation injury and to prevent tumour repopulation by giving more than one radiation fraction per day in smaller doses per fraction.allowing a redistribution of proliferating tumour cells with some cells entering a radiosensitive stage. Other non-proliferating or dose-limiting tissue, such as normal brain, will potentially be spared.
Methods: Results from retrospective and prospective series and present observations of ongoing phase II trials were analysed.
Results: *In standard risk disease* 5 year PFS was 76 and 79% (Ricardi et al., 1997, Prados et al., 1993). In the recent SFOP study (1.0 Gy bid. 36 Gy CSA/68 Gy tumour) the 3 year PFS was 81% (overall survival 89%) without chemotherapy. No decrease in intelligence was observed in 22 children tested during the first 2 years (Carrie et al., 2005). The SIOP–HIT PNET IV study is currently investigating this concept in a prospective randomized study and compares hfx-RT (1.0 bid./CSA 36 Gy/PF 60 Gy tumour 68 Gy) with conventionally fractionated RT (CSA 23.4 Gy/PF 54 Gy) followed by 8 courses Cisplatin, CCNU, VCR. *In high risk disease* 14 of 15 patients (93%) remained disease free for a median of 68 months (Allen et al., 1997). In the Milan study, hyperfractionated-accelerated RT (1.3 Gy bid. 39 Gy CSI/1.5 Gy bid. 21 Gy PF boost) was delivered to 31 pts (median age 9 yrs) combined with high-dose sequential postoperative CT. 5 yrs PFS, EFS, and OS were 75%, 72%, and 76% respectively. The UKCCSG phase 1study investigates hyperfractionated accelerated RT (HART) with cisplatin, vincristine and CCNU chemotherapy. In the ongoing HIT 2000 study (intensive chx. followed by hfx-RT 1.0 Gy bid. CSA 40 Gy, boost, 60–68 Gy) only 18/110 patients (16.4%) (0–51 months) showed progressive disease. Data on late effects are not yet available.
Conclusion: Hfx-RT is a novel approach to improve tumour control and survival in standard and high risk PNET. Results of phase II studies are promising. In standard risk PNET a preservation of neurocognitive function might be possible. Quality of life as an endpoint is of increasing importance.

46 INVITED

Treatment of PNET in children without radiotherapy

J. Grill[1], D. Ashley[2], D. Walker[3], S. Rutkowski[4]. [1]*Institut Gustave Roussy, Paediatric Department, Villejuif, France;* [2]*Royal Children's Hospital, Paediatric Oncology, Melbourne, Australia;* [3]*Queens Medical Centre, Paediatric Oncology, Nottingham, United Kingdom;* [4]*Children's Hospital, Paeditric Oncology, Wurzburg, Germany*

Young children with medulloblastoma have a dismal prognosis and morbidity is high with standard therapy including craniospinal irradiation (CSI). Two recently published national trials (one from Germany and one from France) have shed some light on the possibility to treat some children without using CSI. To analyse these results, three groups of patients can be defined a priori: R0M0 (no residue, no metastasis), R1M0 (radiological residue only) and RXM+ (presence of metastasis whatever the residue). Despite the use of completely different chemotherapy regimens and salvage strategy, both trials have shown that more than 70% of children with R0M0 disease can be cured without craniospinal irradiation. In the German trial, these results were obtained after an intensive methotrexate-containing chemotherapy while in the French trial two third of the survivors required a salvage regimen with high-dose chemotherapy. Patients with RXM+ and R1M0 diseases have a poorer prognosis when treated with conventional chemotherapy only. In both trials, desmoplasia was an indicator of better prognosis. In addition, in the French trial, a poorer outcome was observed for patients with subtotal resection (ie surgical report indicating microscopic tumor remnants despite the absence of radilogic residue on early postoperative scans). Both trials claimed an improved intellectual outcome albeit different scales were used for neuropsychologic assessment. Concurrent trials still ongoing or recently completed in the USA and in UK seem to have similar results for R0M0 patients with protocols including early posterior fossa irradiation together with conventional chemotherapy.The brain tumor comittees of the International Society of Pediatric Oncology (SIOP) and the Children's Oncology Group (USA, Canada, Australia) have started the process to build up a common randomized trial in this category of patients (localized medulloblastomas) to compare the different strategy both in terms of survival and in terms of cognitive outcome. The progresses of this endeavour will be presented at this meeting.

47 INVITED

Modern approach to childhood low grade glioma

G. Perilongo. *Neuro-oncology Program, Department of Pediatrics, University Hospital of Padua, Padua, Italy*

The treatment of childhood low grade glioma (LGG), if not amenable to complete resection, quite often is a relevant clinical challenge. LGG in many instances are indeed slow growing tumours, which, if not controlled, can cause severe morbidity and ultimately jeopardize life. Most of the time children bearing an unresectable LGG can be considered affected by a chromic disease, deserving protracted cures. The treatment philosophy, which has dictated the treatment of malignant cancers, has also inspired the therapeutic concepts for managing childhood LGG. However, it is getting more and more evident that different strategies are needed for them. LGG represent a highly heterogeneous group of neoplasm and comprehensive treatment concepts rarely meet the individual patient's needs. After more than 20 years of clinical research it can be stated with confidence that for unresectable, progressive LGG, chemotherapy (CT) represents an effective treatment modality. It delays tumour growth and postpones the use of radiotherapy (RT), thus sparing the deleterious effects of irradiation on a developing brain. However, CT rarely cures LGG and definitively obviates the need of RT or aggressive surgery. Furthermore, little is known on the actual impact of CT on patients' overall health status. Recent progresses in RT delivering techniques, which allow reducing the safety margins, are tempering the concerns related to the use of this treatment modality in children. While waiting for more biological based therapeutic approaches, CT and RT (other than surgery) are the present tools for treating childhood LGG, which seems to be working best if guided by expert and dedicated multidisciplinary neuro-oncology teams

48 INVITED

New approaches for high-grade gliomas

J. Wolff. *M.D. Anderson Cancer Center, Houston, USA*

High grade glioma are characterized by there heterogenic molecular and histological appearence, and their poor prognosis. With the improvement of radiation and with more radical surgery, survival times have increased. In addition, large phase II studies have shown significant but limited survival benefits with chemotherapy in high grade glioma with temozolomide and nitrosurea. However, numerous clinical trials have been published previously with smaller patient numbers and no control groups. A small positive effect could be missed this way resulting in premature rejection of possible beneficial treatment.
Expanding our former database (Hauch 2005), we analyzed the glioma literature 1997 to 2005 in order to compare treatment results. In this database, one record represents a cohort of patients treated in the same way. Various patient cohort characteristics such as median age, and outcome measures such as median overall survival times (mOS), were documented. Patient population factors influencing the outcome of a cohort were analyzed. Based on those, a predicted outcome for each cohort was calculated. The measured outcome was compared with the predicted outcome to calculate the survival gain archived by the treatment, and treatments were ranked according to their survival gain.
24023 patients are reported in 503 cohorts in 362 publications. The male to female ratio was 1.55 to 1. The median age was 45 years, 9% of the studies included children only. The grade IV to grade III ratio was 3.3 to 1. Supratentorial to infratentorial: 7.1 to 1. Newly diagnosed to recurrent tumors: 1.9 to 1. The median overall survival was 14.5 months.