**2015** POSTER DISCUSSION

**Pharmacological inhibitors of heat shock protein 90 can overcome radioresistance of tumor vasculature**

V. Kudryavtsev[1], Y. Makarova[1], Y. Malyutina[1], A. Kabakov[1]. [1]*Medical Radiology Research Center, Department of Radiation Biochemistry, Obninsk, Russian Federation*

**Background:** Progression of solid tumors and their resistance to therapy strongly depend on the tumor vasculature delivering oxygen, nutrients and growth factors. Therefore, besides invasive tumor cells, the tumor vasculature cells are also a significant target for chemo- and radiotherapy. The aim of the present work was to study how 17-N-allilamino-17-demethoxygeldanamycin (17AAG) and 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (17DMAG), known as anticancer agents inhibiting heat shock protein 90 (HSP90), modifies responses of human vascular endothelial cells (EC) to growth factors and gamma-photon irradiation.
**Material and Methods:** EC cultured from human umbilical veins were exposed to vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) or/and gamma-irradiation (3−6 Gy) while some EC samples were pretreated with 17AAG or 17 DMAG (10–500 nM). The postirradiation cell death/survival and morphogenesis were assessed in TUNEL, annexin V-staining, clonogenic and tube formation assays. The drug-affected phosphorylation and expression of certain signaling- and apoptosis-related proteins were explored by Western blotting. Transient transfection with plasmids expressing dominant negative or constitutively active mutant Akt constructs was used to manipulate the Akt activation/expression levels in the EC cultures.
**Results:** It was found that nanomolar concentrations of 17AAG or 17DMAG inhibit the chaperone function of HSP90 in EC. Importantly, pretreatments with 17AAG or 17DMAG repressed a capability of the growth factor-stimulated EC to form capillary-like tubular structures (tubes) in Matrigel. Moreover, both the drugs were able to radiosensitize EC and fully abolish the radioprotection conferred by VEGF and bFGF. As it appears from the transfection experiments, these effects can be due to the drug-induced prevention of HSP90-dependent phosphorylation (activation) of Akt that resulted in blockade of the PI3K/Akt pathway; the latter is known to contribute to proliferation and radioresistance of vascular EC.
**Conclusions:** Clinically achievable (nanomolar) concentrations of 17AAG or 17DMAG can abrogate both the high radioresistance intrinsic to human vascular EC and the angiogenic and radioprotective action of tumor-derived growth factors such as VEGF and bFGF. This finding gives additional rationale for combining anticancer radiotherapy with pharmacological inhibition of HSP90.

**2016** POSTER DISCUSSION

**Stereotactic body radiation therapy: a potential treatment option for colorectal liver metastases**

A.E.M. van der Pool[1], A. Méndez Romero[2], W. Wunderink[2], P.J. Nowak[2], J.H.W. de Wilt[1], A.M.M. Eggermont[1], J.N. Ijzermans[3], B.J. Heijmen[2], P.C. Levendag[2], C. Verhoef[1]. [1]*Erasmus University MC-Daniel den Hoed Cancer Center, Surgical Oncology, Rotterdam, The Netherlands;* [2]*Erasmus University MC-Daniel den Hoed Cancer Center, Radiation of Oncology, Rotterdam, The Netherlands;* [3]*Erasmus University MC, Transplantation and Hepatobiliary Surgery, Rotterdam, The Netherlands*

**Background:** Most of the patients with colorectal liver metastases are not eligible for surgery because of unfavourable tumor factors or due to patients' general condition. The introduction of stereotactic body radiation therapy (SBRT) has allowed physicians to add another local therapy to the treatment armamentarium of liver metastases. Local control, patient survival and toxicity were determined in our experience with stereotactic body radiation therapy for colorectal liver metastases.
**Materials and Methods:** SBRT was delivered with curative intent to 20 consecutive patients with colorectal hepatic metastases who were neither candidates for resection nor for radiofrequency ablation (RFA). Generally, the radiotherapeutic regimen consisted of 3 courses of 12.5 Gy with a prescription isodose of 65%. Median number of metastases was 1 (range, 1−3) and median size of metastases was 2.3 (0.7−6.2) cm. Toxicity was scored according to the Common Toxicity Criteria 3.0 (CTC). Local control rates were defined on tumor-based analysis.
**Results:** From December 2002 to July 2008, SBRT was given with curative intent to 20 patients with 31 colorectal liver metastases. In all patients the primary tumor was resected and liver metastases were irresectable and not amenable for radiofrequency ablation. Median follow-up was 26 months (range, 6−57 months). Local failure was observed in 9 out of 31 lesions after a median time interval of 22 months (range, 12−52 months). The actuarial two year local control and survival rate were 74% and 83%, respectively. Median overall survival was 34 months. Hepatic toxicity grade $\leqslant$2 (CTC) was reported in 18 patients. Two patients had an episode of hepatic toxicity grade 3 (CTC). No grade 4, 5 (death) or stomach, bowel, kidney or spinal cord toxicity was found.
**Conclusions:** SBRT has demonstrated to be a treatment option for patients with colorectal liver metastases, who were neither candidates for resection nor for RFA, with encouraging local control rates. The method seems to be safe concerning toxicity, if restrictions to normal tissue and patient selection are respected.

**2017** POSTER DISCUSSION

**Results from a phase I partial liver radiotherapy for patients with unresectable colorectal liver metastases**

M.A. Hawkins[1], C. Coolens[1], C. Ockwell[1], D. Tait[1]. [1]*Royal Marsden Hospital – NHS Trust, GI/Radiogtherapy Department, London, United Kingdom*

**Purpose:** To report preliminary toxicity and response data from a phase I study of partial liver irradiation using highly conformal radiotherapy (CRT) for unresectable colorectal liver metastases (CRLM). Study has research and ethics committees approval REC: 06/Q0801/43.
**Methods**: Eligible patients have unresectable or medically inoperable CRLM and received all standard chemotherapy options, Childs score A and KPS >60 and signed informed consent. CRT is delivered hypofractionated in 10 fractions over 2 weeks. Planning target volume is patient specific according to tumour motion characterized on 4DCT and cine MRI. Dose is individualized according to volume of uninvolved liver treated in 3 dose bins: <30% = 40 Gy, 30−50% = 35 Gy, 50−70% = 30 Gy and to keep the estimated risk of liver toxicity <5%. Six patients to be entered in each dose bin. The endpoints are feasibility and toxicity using CTCv3 criteria. Radiation induced liver disease (RILD) grade 4 will stop recruitment. The trial sponsor is: Royal Marsden Hospital.
**Results**: From Nov 2006 to April 2009, 12 patients were recruited and all completed CRT. Mean age 67.9 years (range 44−85). All patients had chemotherapy median 2 cycles (range 1−4), 3 patients also had hepatic resection and 5 also had radiofrequency ablation. The tumor size ranged from 2.8cc to 395cc (mean 118cc). The CRT tumour dose ranged from 30 Gy to 40 Gy (average 34.6 Gy). Median follow-up was 8.4 months (range 1.5 to 28 months). No grade 3/4/5 related toxicity was observed at any time in follow up. No radiation-induced liver disease (RILD) was observed. Other toxicity within 3 months following CRT included grade 2: anaemia (1), pain (1), fatigue (2) and skin toxicity (1). In 11 evaluable patients, in-field response assessed using CT at 3 months was: partial response = 3, marginal response/stable disease = 6, progressive disease = 2.
**Conclusion**: In a heavily pretreated population this approach of individual dose CRT appears safe, and recruiting is continuing. Further dose escalation will be attempted. Longer follow up is required for assessment of late toxicity and efficacy.

**2018** POSTER DISCUSSION

**Benefit of radiotherapy dose escalation in localized prostate cancer with respect to expression of intrinsic markers of hypoxia**

G.P. McVey[1], S.C. Morgan[1], R. Vergis[1], C. Cooper[2], R. Huddart[1], C. Corbishley[3], A. Horwich[1], D.P. Dearnaley[1], C.C. Parker[1]. [1]*Institute of Cancer Research, Department of Radiotherapy, Sutton, United Kingdom;* [2]*Institute of Cancer Research, Department of Molecular carcinogenesis, Sutton, United Kingdom;* [3]*St Georges Hospital NHS Trust, Department of Histopathology, London, United Kingdom*

**Background:** Dose escalation improves the efficacy of prostate cancer radiotherapy (RT) at the cost of increased toxicity. Tumor hypoxia causes radioresistance, so the benefit of RT dose escalation may be greater in more hypoxic cancers.
**Methods:** Cases had localized prostate cancer treated with neo-adjuvant androgen deprivation and radical RT at the Royal Marsden in two randomized trials of dose escalation (64 vs 74 Gy). Tumour expression of three markers (vascular endothelial growth factor (VEGF), hypoxia inducible factor-1Î± (HIF-1Î±), and osteopontin) was assessed immunohistochemically using a semi-quantitative scale by a uro-pathologist, and analyzed with respect to freedom from biochemical failure (FFBF) using the Phoenix definition. Expression of each marker was dichotomised about the median for analysis of the impact of dose-escalation on outcome.
**Results:** 201 cases with a median follow-up of 7 years were evaluable. Seven-year FFBF was 67% vs 40% (HR: 0.42, 95% CI 0.26−0.7, p = 0.001) for 74 Gy versus 64 Gy, respectively, among cases with high osteopontin expression, and 70% vs 82% (HR: 1.41, 95% CI 0.53−3.76, p = 0.49) for 74 Gy vs 64 Gy among cases with low osteopontin expression. The benefit of RT dose escalation was similar regardless of VEGF or HIF-1Î± expression.
**Conclusion:** These data generate the hypothesis that osteopontin expression could inform RT dose individualisation. If validated, patients

with low tumor expression of osteopontin could elect to receive less toxic, standard dose RT.

**2019** POSTER DISCUSSION

**Early clinical outcome of simultaneous modulated accelerated radiation therapy (SMART) intensity modulated radiotherapy (IMRT) for nasopharyngeal Carcinoma (NPC) in Queen Elizabeth Hospital (QEH), Hong Kong**

F. Cheung[1], S.F. Liu[2], K.C. Ngan[1], F. Lee[2], C.L. Chan[2], K.H. Wong[1], S.K. Au[1], C.K. Law[1]. *[1]Queen Elizabeth Hospital, Clinical Oncology, Hong Kong, Hong Kong; [2]Queen Elizabeth Hospital, Medical Physics, Hong Kong, Hong Kong*

**Background:** Radiotherapy is key component of NPC standard treatment. IMRT dosimetric advantage is observed by various authors. SMART escalates the physical dose in tumor without prolonging treatment thereby conferring radiobiological advantages. IMRT was introduced in QEH for NPC in 2003 for either as boosting or full course treatment. This retrospective review on whole course SMART IMRT treated NPC patients analyzed clinical endpoints of local control (LC), regional control (RC), metastasis-free survival (MFS), overall survival (OS), and progression free survival (PFS), as well as complications. Dose prescribed to NP is 66 Gy in 33fractions in 6 1/2 weeks.
**Material and Methods:** Total 94 patients (pts) from 2003 to 2006 were stratified according to age, sex, T, N and stage. Overall 15, 4, 15, 23 and 37 pts had stage T1, T2a, T2b, T3, and T4 cancers respectively. 58, 13, 20, and 3 pts had N0, 1, 2 and 3 diseases respectively. 13, 4, 13, 26, 35, and 3 pts had stage I, IIa, IIb, III, IVa and IVb disease respectively. 30.8%, 26.6% and 8.5% pts had neoadjuvant, concurrent and adjuvant platinum based chemotherapy respectively.
**Results:** Median age was 52 (range: 13−77). Median of mean dose to GTV NP and GTV neck nodes was 72.7 Gy and 70.5 Gy respectively. 22.3% and 4% pts experienced grade 3 mucosa and skin acute toxicity. 4 and 1 pts had locally and regional persistent disease respectively. At a median follow-up of 30.4 months, 3 year (3 yr) LC, RC, MFS, PFS and OS were 91.2%, 97.7%, 90.5%, 78.7% and 83.8% respectively. Altogether, 9 (9.6%) and 2 (2.1%) pts had local and regional relapses respectively. 3 yr LC for T1, T2, T3 and T4 were 84.6%, 100%, 95.5%, and 82.8% respectively. 3 yr MFS for stage I to IVb was 100%, 100%, 73.8%, 92%, 86.8% and 66.7% respectively; 3 yr PFS for stage I to IVb was 75.5%, 100%, 73.8%, 84.4%, 64.5% and 66.7% respectively; 3 yr OS for stage I to IVb was 92.3%, 100%, 87.5%, 92.3%, 76%, and 50% respectively. 3 pts had choking or dysphagia during and after treatment and needed tube feeding. 2 T4 pts without active cancer died of massive epistasis within 6 months after RT completed. One T4 pts had temporal lobe necrosis 3 yrs after chemoradiation. 3 had noticeable hearing loss and 1 developed hypothyroidism. T4 stage was the only significant factor in univariate analysis of OS and PFS.
**Conclusion:** This report demonstrated SMART IMRT treatment results were on par with conventional RT results of our institute and IMRT results in published series. The lower T1 LC can be explained by the small number of cases in the group. Improvement in metastasis control in stage IVb is a major challenge.

**2020** POSTER DISCUSSION

**Is 18F-FDG a surrogate tracer to measure tumor hypoxia? Comparison with the hypoxic tracer 14C-EF3 in animal tumour models**

N. Christian[1], S. Deheneffe[1], A. Bol[1], M. De Bast[1], D. Labar[1], J.A. Lee[1], V. Gregoire[1]. *[1]Université Catholique de Louvain, Center for Molecular Imaging and Experimental Radiotherapy, Bruxelles, Belgium*

**Background:** Fluorodeoxyglucose (FDG) has been reported as a surrogate tracer to measure tumor hypoxia with Positron Emission Tomography (PET). The hypothesis is that there is an increase uptake of FDG under hypoxic conditions as a consequence of an over-expression of the glucose transporters Glut-1 and Glut-3. However, the sensitivity and specificity of FDG to measure hypoxia has never been studied. This study aimed to compare the tracers $^{14}$C-EF3 and $^{18}$F-FDG to detect hypoxia in mouse tumor models.
**Material and Methods:** C3H tumour-bearing mice (FSAII and SCCVII tumors; mean diameter of 10−12 mm) were injected with $^{14}$C-EF3, and 1 h later with $^{18}$F-FDG. Using a specifically designed immobilization device with fiducial markers, PET (Mosaic®, Philips) images were acquired one hour after the FDG injection. After imaging, the device containing mouse was frozen, transversally sliced and imaged with autoradiography (AR) (FLA-5100®, Fujifilm) to obtain high resolution images of the $^{18}$F-FDG distribution within the tumor area. After a 24 h delay allowing for $^{18}$F decay, a second AR was performed to image $^{14}$C-EF3 distribution. AR images were aligned to reconstruct the full 3D tumor volume, which could be compared with the PET images. Image segmentation with threshold-based methods was applied on both AR and PET images to derive various tracer activity volumes. A Dice matching index was then computed. The comparison was performed under normoxic (ambient air, FSAII: n = 4, SCCVII, n = 5) and under hypoxic conditions (10% $O_2$ breathing, SCCVII: n = 4).
**Results:** On AR, under both ambient air and hypoxic conditions, there was a decreasing similarity between $^{14}$C-EF3 and FDG when higher activity regions were considered. Under normoxic conditions, when comparing the 10% of tumor voxels with the highest $^{18}$F-FDG or $^{14}$C-EF3 activity, a Dice index of 0.20 and 0.19 was found for FSAII and SCCVII, respectively. Under hypoxic conditions, a DICE index of 0.31 was observed for SCCVII tumors. When comparing the AR images with $^{14}$C-EF3 with the corresponding $^{18}$F-FDG-PET images, the Dice index reached values of 0.26, 0.17 and 0.16 for FSAII and SCCVII under normoxia and SCCVII under hypoxia, respectively.
**Conclusion:** This study showed that FDG is not a good surrogate tracer for tumor hypoxia either under ambient or hypoxic conditions. Only specific hypoxia tracers should be used to measure tumor hypoxia.

## *Poster presentations* (Wed, 23 Sep, 09:00−12:00)
## Radiotherapy and radiobiology

**2021** POSTER

**Imaging tumour hypoxia: the need to combine techniques**

M.R. Horsman[1], T. Nielsen[1], L. Østergaard[2], T. Tramm[1], M. Busk[1]. *[1]Aarhus University Hospital, Department of Experimental Clinical Oncology, Aarhus, Denmark; [2]Aarhus University Hospital, Department of Neuroradiology, Aarhus, Denmark*

**Background:** Hypoxia in tumours influences radiotherapy outcome. Various non-invasive approaches are now under clinical evaluation to measure this hypoxia prior to irradiation and thus predict response. This preclinical study demonstrates that only a combination of these techniques will accurately reflect hypoxia.
**Material and Methods:** C3H mammary carcinomas (200 cubic mm) grown in the foot of female CDF1 mice were locally irradiated under normal or clamped conditions and percent tumour control determined 90 days later. Radiobiological hypoxic fraction was calculated from the dose-response curves. Additional mice were intraperitoneally (ip) injected with pimonidazole (PIMO) and then subjected to dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI) performed on a 3-tesla magnet following intravenous injection of gadolinium-DTPA. At 90 minutes post PIMO injection the tumours were excised and from histological sections the PIMO distribution determined by immunohistochemistry. All procedures were performed under control conditions or following ip injection of nicotinamide (acute hypoxia modifier) or carbogen breathing (chronic hypoxia modifier).
**Results:** The mean (with 95% confidence limits) radiobiological hypoxic fraction for control tumours was 23% (15−31). This was significantly (Chi-squared test; $p < 0.05$) reduced to 7% (3−12) by nicotinamide and 6% (3−9) by carbogen. Mean (with 1 S.E.) hypoxic fractions measured by PIMO labelling were 8.1% (6.4−9.9), 8.1% (6.1−10.2), and 1.4% (1.3−1.5) in controls, nicotinamide, and carbogen treated animals, respectively; only the carbogen group showed a significant change (Student's t-test; $p < 0.05$). Various DCE-MRI parameters were measured including IAUC, ktrans, kep, ve, and vp. The only parameters that showed significant (Student's t-test; $p < 0.05$) differences to those measured in controls were in the nicotinamide treated groups.
**Conclusions:** The radiobiological hypoxic fraction in this tumour model was reduced by both nicotinamide and carbogen, confirming that the hypoxia was both acute and chronic in nature. Changes in PIMO labelling was only seen following carbogen treatment, thus PIMO and probably other PET related hypoxia markers can only detect chronic hypoxia. Conversely, changes in DCE-MRI parameters were found only after giving nicotinamide, confirming that such "perfusion" markers primarily detect acute hypoxia. Thus, measurements of total hypoxia in tumours require combining different assays.