NW457 was assessed by Western blot, flow cytometry, caspase activity, colony formation, wound healing, viability, and transmigration assays.

**Results:** The novel small-molecule HSP90 inhibitor NW457 interferes with the radioreistant phenotype of human glioblastoma cells as it sensitized LN229 and T98G cells towards irradiation-induced clonogenic cell death and potentially induced apoptosis. NW457 provoked destabilization of critical regulators of the DNA damage response (ATM, ATR, CHK1 and CHK2) and induced activation of caspase-3 with subsequent PARP cleavage. Additionally, NW457 demonstrated potent anti-invasive activities by decreasing the inherent migration of LN229 cells as well as inhibiting irradiation-induced hypermigration.

**Conclusions:** Taken together, our data on HSP90 inhibition as a clinically relevant, novel glioblastoma treatment concept suggests that the novel small-molecule inhibitor NW457 might improve the efficacy of radiotherapy via a dual mechanism involving (i) attenuation of radioreistance through induction of apoptosis and impairment of the DNA damage response and (ii) inhibition of both inherent and radiation-induced migration.

**Proffered Papers: Physics 11: Quantifications of imaging for response prediction**

**OC-0620**  
Experimental validation of FMISO simulations on tumor xenografts: a question of O2 consumption?  
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**Purpose/Objective:** Tumor hypoxia is prognostic for poor outcome after radiotherapy (RT). A method for non-invasive assessment of hypoxia is positron emission tomography (PET) using radiotracers that accumulate in hypoxic tissue volumes. However, many factors that impact tracer accumulation are not yet fully understood. Here, mathematical simulations may help to further investigate hypoxia PET image formation. The purpose of this study is to validate a dedicated simulation model against experimental data. The model can readily be adapted to a variety of conditions, such as different human head and neck cancer (HNC) cell lines (CLs).

**Materials and Methods:** Immunohistochemically stained sections of tumor xenografts were available for nine HNC cell lines, providing information on hypoxia (pimonidazole), perfusion (Hoechst 33342), and vessel distribution (CD31). They were used to generate 2D maps of perfused blood vessels, based on which tissue oxygenation and the distribution-retention dynamics for the hypoxia PET tracer FMISO were mathematically simulated in order to generate FMISO distribution patterns four hours post injection. The model includes a Michaelis-Menten relation to describe the oxygen consumption inside the tissue. M0, representing the maximum oxygen consumption, was chosen as parameter for CL-specific optimization as this parameter strongly influences tracer distribution. Simulations were optimized for M0 on each tumor slice to reach optimum correlations between FMISO concentration and pimonidazole staining intensity.

**Results:** After optimization, very high point-to-point correlations up to $R^2 = 0.85$ were found for individual tissue sections. Experimental pimonidazole staining and simulations showed good visual agreement, confirming the validity of the approach. Mean correlations per CL varied significantly ($p'$ ranging from 0.24 to 0.53).

The derived maximum oxygen consumption rate $M_0$ differed significantly ($p'$ was found to correlate significantly with the previously published BrdU labeling index for these CL ($p$; consumption. No correlation was found with TCD50.

**Table:**

<table>
<thead>
<tr>
<th>Cell line</th>
<th>No. of tumor slices</th>
<th>M0</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAL-33</td>
<td>34</td>
<td>3.2</td>
<td>0.31 (0.06 – 0.57)</td>
</tr>
<tr>
<td>FD03</td>
<td>47</td>
<td>3.3</td>
<td>0.22 (0.03 – 0.44)</td>
</tr>
<tr>
<td>HAG</td>
<td>24</td>
<td>5.2</td>
<td>0.27 (0.07 – 0.39)</td>
</tr>
<tr>
<td>UT-DCG-14</td>
<td>55</td>
<td>2.4</td>
<td>0.43 (0.25 – 0.75)</td>
</tr>
<tr>
<td>UT-DCG-5</td>
<td>23</td>
<td>2.5</td>
<td>0.53 (0.35 – 0.72)</td>
</tr>
<tr>
<td>UT-DCG-8</td>
<td>26</td>
<td>3.5</td>
<td>0.27 (0.03 – 0.50)</td>
</tr>
<tr>
<td>UT-DCG-15</td>
<td>32</td>
<td>3.5</td>
<td>0.52 (0.26 – 0.83)</td>
</tr>
<tr>
<td>UT-DCG-65</td>
<td>33</td>
<td>4.0</td>
<td>0.34 (0.02 – 0.41)</td>
</tr>
<tr>
<td>HSC-4</td>
<td>35</td>
<td>3.1</td>
<td>0.39 (0.08 – 0.56)</td>
</tr>
</tbody>
</table>

**Conclusions:** It is technically feasible to simulate FMISO distributions that match the pimonidazole retention patterns observed in vivo. Good agreement can be obtained for multiple CLs by optimizing the individual oxygen consumption rate, $M_0$, whose optimum value differed significantly between CLs. Optimized $M_0$ correlated with the proliferation marker BrdU, but not with TCD50.

**OC-0621**

Comparison of perfusion CT parameters and [18F]-FDG uptake in head and neck cancer patients

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**Purpose/Objective:** Tumor physiology predicts response to radiotherapy. The aim of this study was to examine and correlate tumor vascularity and glucose metabolism based on [18F]-FDG uptake and perfusion maps.

**Materials and Methods:** 42 patients with head and neck cancer (15 patients T1/T2 and 27 T3/T4), who underwent [18F]-FDG PET/CT (270 - 410 MBq FDG) examination together with simultaneous perfusion CT (CTP) (40 mL of contrast, 1 s rotations time with 1 image/s, cine duration 50 s, 80 mA, 100 kV), were included in the study. A radiation oncologist contoured primary tumor (GTVPT) and lymph node metastases (GTVLN) in CTP. Using the gradient-based method GTVpet was auto-segmented. Perfusion maps were calculated using singular value decomposition method with in-house developed software. Blood volume (BV), blood flow (BF),
mean transit time (MTT) and standardized uptake value (SUV) were determined for the following structures: GTV<sub>PET</sub>, GTV<sub>T</sub>, and GTV<sub>LN</sub>, as well as 5 mm and 10 mm margins from GTV<sub>T</sub> and GTV<sub>LN</sub>. The 10 mm margin corresponds to the PTV and 5 mm margin was added to the analysis to study the signal changes in the PTV periphery. Voxel-wise Spearman correlations of perfusion parameters (BV, BF, MTT) and SUV were studied for each patient and each volume. Mean correlation coefficients corresponding to each structure were calculated to examine the population correlation. Moreover, correlations of mean BV, BF, and MTT with SUV<sub>mean</sub> and SUV<sub>max</sub> were tested. Differences of median values of mean BV, BF, and MTT for various volumes among the patients population were investigated using paired Wilcoxon test. The significance level chosen for correlation study was 0.05 and for Wilcoxon test 0.01.

**Results:** Based on the voxel-wise study no population-based correlation between perfusion parameters and SUV was found. A significant correlation was observed between mean MTT and SUV<sub>mean</sub> in the GTV<sub>PET</sub> of the PT (p=0.05) with a correlation coefficient of r = 0.73 for T1/T2 tumors and of r = 0.55 for T3/T4. For both PTV<sub>PT</sub> and PTV<sub>LN</sub>, significant correlations between mean BV and SUV<sub>mean</sub> were found with the same correlation coefficient r = 0.44. Such dependencies were not observed for GTV<sub>PET</sub> and GTV<sub>LN</sub>, but the similar correlation was found for alone 5 mm (r = 0.50) and 10 mm (r = 0.44) margins from GTV<sub>LN</sub>. A difference was found for median value of BV between GTV and its 5 mm margin for PT and LN for all patients. This difference was observed for GTV<sub>PET</sub> corresponding to stage T3/T4, but was not significant for stage T1/T2. The median MTT was found to be significantly higher in GTV<sub>PET</sub> in comparison to its 5 mm margin.

**Conclusions:** Tumor and surrounding normal tissue exhibit differential CT perfusion parameters. Analysis of PET and CT perfusion showed a positive correlation for SUV mean and MTT and SUV<sub>mean</sub> in the GTV PET of the PT (p=0.05) with a correlation between perfusion parameters and SUV was investigated using paired Wilcoxon test. The significance level chosen for correlation study was 0.05 and for Wilcoxon test 0.01.

**OC-0622**

Changes in FDG-PET uptake before and after chemoradiotherapy predict pathological response in esophageal cancer

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**Purpose/Objective:** Neo-adjuvant chemoradiotherapy (nCRT) followed by surgery has become the standard treatment for curative intent for esophageal cancer patients. Despite the improved overall survival compared to surgery alone, the patients’ quality of life (QoL) remains low due to the high burden of esophagectomy and high incidence of post-operative complications. QoL would be improved by postponing surgery and a wait-and-see policy for patients with a complete pathological response to nCRT. Therefore, we investigated the feasibility of FDG-PET/CT derived variables to predict this pathological response.

**Materials and Methods:** Patients with histologically proven esophageal cancer (stage IIA - IIC) that received a baseline PET/CT scan 1-4 weeks prior to the start of the nCRT were included. A pre-surgery PET/CT scan was made 5-7 weeks after the last radiation dose. Gross tumor volumes (GTVs) were delineated on the baseline diagnostic PET/CT scan or were copied from the radiotherapy planning CT scan. The volume of the GTV and the mean, maximum and peak standard uptake values (SUV<sub>mean</sub>, SUV<sub>max</sub>, and SUV<sub>peak</sub>, respectively) within the GTV were determined. The metabolic tumor volume (MTV) was defined as the region with a SUV > 40% of SUV<sub>max</sub> and SUV<sub>mean</sub>MTV was the mean SUV within this volume. The total lesion glycolysis (TLG) was defined as MTV x SUV<sub>mean</sub>MTV. Tumor response to nCRT was evaluated using the Mandard regression classification (TRG 1-5) on the pathological specimen after surgery. Patients were divided in responders (TRG 1-2) and non-responders (TRG 3-5) for statistical analysis.

**Results:** Imaging and clinical results of 25 patients treated since mid-2012 were available. In total 28% (N=7) patients showed a pathological complete response (TRG 1) at the primary tumor site, and 32% (N=8) patients had a TRG 2, these patients were identified as responders. All other patients (40%, N=10) had a higher TRG and were defined as non-responders. Looking only at the baseline or pre-surgery scan was not able to show a significant difference between both groups for any of the investigated variables. However, the relative changes between the two PET/CT scans were prognostic. Responders showed a significantly higher reduction in SUV<sub>max</sub> (50±26 vs. 16±41, P=0.017), SUV<sub>peak</sub> (-52±27 vs. -19±40, P=0.021) and SUV<sub>mean</sub>MTV (-51±30 vs. -18±43, P=0.031), also shown in figure 1. Multivariate analysis and external validation is ongoing.

**Conclusions:** The relative change in FDG-uptake at the primary tumor site before and after nCRT has a prognostic value for response assessment of esophageal cancer patients. Responders showed a significantly larger decrease in uptake than non-responders. The prediction of pathological response using two PET/CT scans could be a useful method for future treatment decisions.

**OC-0623**

Hypoxia [18F]HX4 PET imaging in patients with head and neck cancer: repeatability and stability during radiotherapy

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**Purpose/Objective:** Hypoxia imaging [18F]HX4 PET imaging in patients with head and neck cancer: repeatability and stability during radiotherapy.