registration method enabling mapping of greatly deformed and sliding tissues. In this study, we developed and report on the results of a straightforward method to translate this geometrical ground truth validation to uncertainties in the mapped dose and relevant dosimetric endpoints.

**Materials and Methods:** For 9 cervical cancer patients, T2w-MRIs acquired before EBRT and as part of the MRI-guided BT procedure (BT applicator inserted) were used. A recently developed and anatomically validated structure-wise registration with vector field integration (SW+VF) was used to map non-rigidly the EBRT and the BT scans. From the results of the anatomical validation, i.e. the residual distances after the transformation for structures and landmarks, the standard deviation of the residual vectors for each component were calculated: $\sigma_x$, $\sigma_y$, and $\sigma_z$. These standard deviations were applied in the construction of an ellipsoid with radius $\sigma_x$, $2\sigma_y$, and $2\sigma_z$, which represents the volume in which 95% of the observations occur. Next, as we mapped the dose for a given position p, we collected the doses within the ellipsoid centered at p’s mapped position. From these collected values, we calculated the 5 and 95 percentiles as measure of the uncertainty in the mapped dose per voxel. The uncertainty was calculated for mapping EBRT to BT and vice versa. To illustrate the uncertainties for clinically relevant scenarios, we summarized them using root mean squares for $D_{2\text{cc}}$ and $D_{50\%}$ for the bladder, rectum and sigmoid.

**Results:** The standard deviations of the residual vectors were $\sigma_x=2.3$, $\sigma_y=2.7$, and $\sigma_z=2.9$ mm. The uncertainties for mapping the EBRT and BT dose distribution are summarized in table 1. The mapped BT dose represents the dose of a single BT application. In general, the uncertainties in $D_{2\text{cc}}$ for mapping BT to EBRT dose distributions are higher than for mapping EBRT to BT dose. This can be explained by the high dose gradients in the BT dose distribution and the location of $D_{2\text{cc}}$ in the EBRT dose distribution. For EBRT dose mapping the uncertainties in $D_{50\%}$ are larger compared with $D_{2\text{cc}}$.

<table>
<thead>
<tr>
<th>Table 1. Mapped values and uncertainties (5 and 95 percentile) for the EBRT and BT for $D_{2\text{cc}}$ and $D_{50%}$</th>
<th>Bladder $D_{2\text{cc}}$</th>
<th>Rectum $D_{2\text{cc}}$</th>
<th>Sigmoid $D_{2\text{cc}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mapped EBRT</td>
<td>Mean over all patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 percentile</td>
<td>47.7</td>
<td>47.5</td>
<td>47.1</td>
</tr>
<tr>
<td>95 percentile</td>
<td>48.1</td>
<td>48.0</td>
<td>47.7</td>
</tr>
<tr>
<td>Mapped BT</td>
<td>7.0</td>
<td>5.6</td>
<td>6.1</td>
</tr>
<tr>
<td>5 percentile</td>
<td>5.6</td>
<td>4.3</td>
<td>3.8</td>
</tr>
<tr>
<td>95 percentile</td>
<td>9.0</td>
<td>7.0</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Conclusions: The magnitudes of the dose mapping uncertainties caused by the registration uncertainty emphasize the need of estimating these values prior to any clinical application of dose mapping. The proposed procedure gives a conservative estimate of the uncertainty by assuming the same registration uncertainty for all voxels, and by collecting all doses within the uncertainty volume. Extending this procedure to include voxel-wise registration uncertainty and its shape is part of future research.

**Purpose/Objective:** The use of high dose modulated arc techniques for stereotactic ablative radiation therapy (SABR) with flattened or unflattened beams is now common practice. With these approaches there is an increase in monitor units (MU) and in irradiation time. Consequently it is important to ensure that patient breathing, and motion, remains within acceptable limits during treatment. Here a new method, PUMA, was developed to predict the effect of motion on modulated SABR lung cancer plans (interplay effect).

**Materials and Methods:** On four-dimensional computerised tomographic (4DCT) images of 12 previously treated lung cancer patients 23 volumetric arc therapy (VMAT) plans were created using the Eclipse V.10 treatment planning system (TPS) (Varian Medical Systems, Palo Alto, USA). On six patient data sets, two plans with different level of modulation were created. Each plan was made up of four 6MV arcs of approximately 200°. Five additional plans of two 10MV FFF (flattening filter free) arcs of approximately 200° were also created. The plans were verified by irradiating radiochromic films (EBT 3, ISP Corp USA) placed within a Quasar Respiratory Motion Phantom (Quasar, Modus Medical Devices) on a Varian Silhouette and plans with FFF beams on a TrueBeam (Varian). Film Analysis was performed using the RIT 113 software (Radiological Imaging Technology, USA). Each plan was delivered twice on the Quasar phantom, the first without movement and the second with motion of 1 cm peak to peak at 12 breaths per minute (BPM). A relative comparison between the dose distributions measured and those calculated on the TPS was performed and the PUMA method used to analyse the effect of motion on the plans. The results were also compared to those obtained on the Quasar phantom. The criteria for evaluation was set to be < 5% of points with gamma 3%, 3 mm > 1% on the comparison between static and dynamic dose distributions recorded on radiochromic films and < 5% of points with > 3% difference dose between PUMA and the TPS. These were compared to the results obtained on the Quasar phantom.

**Results:** Figure 1 shows the comparison between both methods where, except for plan 7, they agree on the pass criteria. In this case PUMA, which analyses all target volumes, fails while the radiochromic film passes. This suggests that PUMA, which analyses the volumetric dose distribution, is more sensitive to interplay effect analysis than the analysis performed on one plane by using Quasar.
Preclinical evaluation of novel anticancer agents combined to Ionizing Radiation (IR) is a key step in the generation of a sound rationale for further transfer towards the early clinical phases. Animal models should allow the minimal assessment of the toxicity hazard and provide significant signs of increased anti tumor efficacy, both required to address their clinical relevance, i.e. the therapeutic ratio of a candidate future combination.

This assumption is clearly challenged by the major discrepancy between the amount of combinations suggested by preclinical data in the last decade and the fact that platinum based combinations remain the mostly widely used agents in the management of lung tumors. This not only illustrates the difficulties in funding the continuum from promising preclinical data to clinical steps, but also underscores the relatively low relevance of our preclinical models. Certainly, one of the reasons for this gap is the inactivity of our preclinical models to keep up with the changes in the mutational landscape of lung cancer. Another major aspect is that most models used so far include immunocompromised models, which fail to recapitulate the importance of the tumor stroma in the processes of radiation response. The precise correlation between the preclinical judgment criteria and the medical need is also key: while most preclinical papers focus on tumor growth delays, the onset of metastasis. Lastly, the potential deleterious impact on normal tissues, both acute and long term, should also be properly evaluated at the preclinical stage to increase the accuracy of this appraisal. Preclinical models should also try to address the current challenges of the biomarker era and suggest in which biological context, and which criteria may contribute to an improvement of the output of these murine models and eventually increase the success rates of future clinical trials while avoiding the transfer of uneffective or hazardous combinations to the patient.

Conclusions: PUMA can predict the interplay effect on SABR lung plans independently of the energy.

SP-0240
Targeted agents, systemic therapy and radiotherapy of non-small cell lung cancer: clinical evidence
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Non-small cell lung cancer (NSCLC) is a group of different histologic tumor types with diverse molecular aberrations. Lung adenocarcinomas are now classified according to driving molecular abnormalities (mutations, rearrangements or amplifications), which can be identified in more than half of tumors, leading to effective systemic therapies in many of these patients. In contrast to that, evidence for presence of such abnormalities in squamous cell lung carcinomas is less clear. Successful combination of targeted therapies, chemotherapy and radiation in early NSCLC should be taken into account in the context of molecular drivers. In oncogenic-driven stage III NSCLC, it is likely that effective systemic treatment will be combined with radical radiotherapy or radiochemotherapy as a sequential treatment, although evidence for such approach is currently lacking. RTOG 1306 phase II clinical trial is currently randomising patients with stage III non-small cell lung cancer to receive either chemotherapy alone (control arm) or 12 weeks of erlotinib (EGFR cohort) or crizotinib (ALK cohort) followed by definitive radiochemotherapy. In non-oncogene addicted NSCLC, incorporation of targeted therapies into radiochemotherapy schedules is very difficult to predict preclinically, as demonstrated by several examples, including negative results of the RTOG 0617 trial. This trial failed to show any benefit from the addition of cetuximab, a monoclonal antibody targeting EGFR, into radiochemotherapy in stage III NSCLC. Lack of good prediction of clinical data may result from complex interactions among targeted agents, chemotherapy, and radiation. One of the most promising strategies for the future is related to the success of immune checkpoint inhibitors, which should be used in the context of molecular drivers. In non-oncogene addicted stage III NSCLC, it is likely that effective systemic treatment will be combined with radical radiochemotherapy.

Optimization of combined radiation and chemotherapy programs is still a matter of ongoing discussions and investigations. Although concurrent radiochemotherapy is a standard of care in fit stage III NSCLC patients, sequential treatments with cytotoxic agents followed by either hypofractionated or hyperfractionated accelerated radiotherapy schedules are currently revisited.

OC-0241
Can dose escalation be consistently carried out in a multicentre trial? QA results for IDEAL-CRT and I-START trials
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Purpose/Objective: IDEAL-CRT and I-START are phase I/II trials investigating isotoxic dose escalation in patients with stage IIa-IIlb non-small cell lung cancer. In both trials the