Supplementary material for Lens E, et al. Probabilistic treatment planning for pancreatic cancer treatment: prospective incorporation of respiratory motion shows only limited dosimetric benefit, Acta Oncologica, **Submitted 2016**

Treatment plan optimization incorporating target motion

The optimization module in Pinnacle is based on a Quasi-Newton optimization approach. In short, the optimizer uses a cost function to calculate the total cost of a dose distribution based on predefined planning objectives. The gradient of this cost function is then calculated and the Hessian matrix is approximated using information from previous iterations to determine the search direction in the solution space towards a lower total cost.

Every predefined objective contributes to the cost function. If for example a region of interest (ROI) should receive at most/at least a certain dose level, this is expressed with the following quadratic objective function [1]:

$$f(d) = w \sum_{i \in V} \mu(d_i, d^p) \left(\frac{d_i - d^p}{d_i^p} \right)^2 v_i. \quad (1)$$

With:

$$\mu(d_i, d^p) = \begin{cases} H(d^p - d_i) : \text{min dose function} \\ H(d_i - d^p) : \text{max dose function} \end{cases}, \quad (2)$$

where *w* is the weight of the objective, *H* is the Heaviside function, d_i the dose at voxel *i*, d^p the threshold dose and v_i the relative voxel volume where the index *i* runs over the voxels within *V*, the volume to be evaluated. For regular maximum and minimum dose objectives, *V* is equal to the entire ROI in question; for DVH objectives, *V* only includes a fixed proportion of the high dose (or low dose) voxels, depending on a preset fractional threshold. The cost function is the sum of all objective functions for all ROIs of interest, with weights to assign the priority of each objective function. The

gradient of the given objective function for one voxel is obtained by taking the derivative of this objective function with respect to the dose:

$$\frac{\partial f(d)}{\partial d_i} = \mu(d_i, d^p)\frac{d_i - d_i^p}{\left(d_i^p\right)^2} \cdot 2v_i. \tag{3}$$

The gradient of the cost function is calculated and used to steer towards a new dose distribution that decreases the total cost [2]. The total cost converges to a minimum after multiple iterations. A change in dose is converted to a change in machine parameters by the optimizer, using pre-defined dose kernels. This way, the cost and its gradient are directly dependent on the machine parameters [2].

With respiratory motion present, the dose distribution with respect to the target volume will undergo blurring. This blurring of the dose is calculated by the optimizer by convoluting the dose with the probability density function (PDF) that describes the expected motion [3]. The blurred dose in a voxel *i* is the weighted sum of the dose of all voxels that contribute to voxel *i*:

$$\tilde{d}_i = \sum_{j \in Z} d_{i+j} \cdot p_j. \tag{4}$$

The dose to voxel *i* in the blurred dose distribution is denoted by $\tilde{d}_i$. *V*oxel displacement is indicated by *j* and *Z* contains all translations *j* of a voxel *i* with a non-zero probability (i.e. the motion kernel). The probability of displacement *j* is indicated by p_j, with $\sum_{j \epsilon Z} p_j = 1$. Therefore, under moving conditions the objective function of equation (1) becomes:

$$\begin{aligned} f(\tilde{d}) &= w \sum_{i \in V} \mu(d_i, d^p) \left(\frac{\tilde{d}_i - d_i^p}{d_i^p}\right)^2 v_i \\ &= w \sum_{i \in V} \mu(d_i, d^p) \left(\frac{\left(\sum_{j \in Z} d_{i+j} \cdot p_j\right) - d_i^p}{d_i^p}\right)^2 v_i. \end{aligned} \tag{5}$$

The dose at each voxel is now evaluated for the blurred dose distribution. Due to motion, the dose that is deposited as a static distribution will be spread out amongst the voxels. The gradient of the objective function for one voxel is then expressed by the following equation:

$$\frac{\partial f(\tilde{d})}{\partial d_i} = \sum_{j \in Z} \mu(d_i, d^p) \frac{\left(d_i - d^p_{i-j}\right)}{\left(d^p_{i-j}\right)^2} 2 v_{i-j} \cdot p_j. \quad (6)$$

A change in d_i influences the dose in all voxels that after blurring have some contribution from voxel *i*. So, the gradient of the cost for the blurred dose is the weighted sum of the gradients of all voxels that are affected by a change in d_i.

References

[1] Löf J, Rehbinder H, Mc Nutt T, Johnson S. P3IMRT: inverse planning optimization Pinnacle white paper Nr. 4535 983 02479, Philips 2003.

[2] Hårdemark B, Liander A, Rehbinder H, Löf J. P3IMRT: Direct machine parameter optimization Pinnacle white paper Nr. 4535 983 02483, Philips 2004

[3] Bel A, van Herk M, Lebesque JV. Target margins for random geometrical treatment uncertainties in conformal radiotherapy. Med Phys 1996;23:1537–45.

Supplementary figures

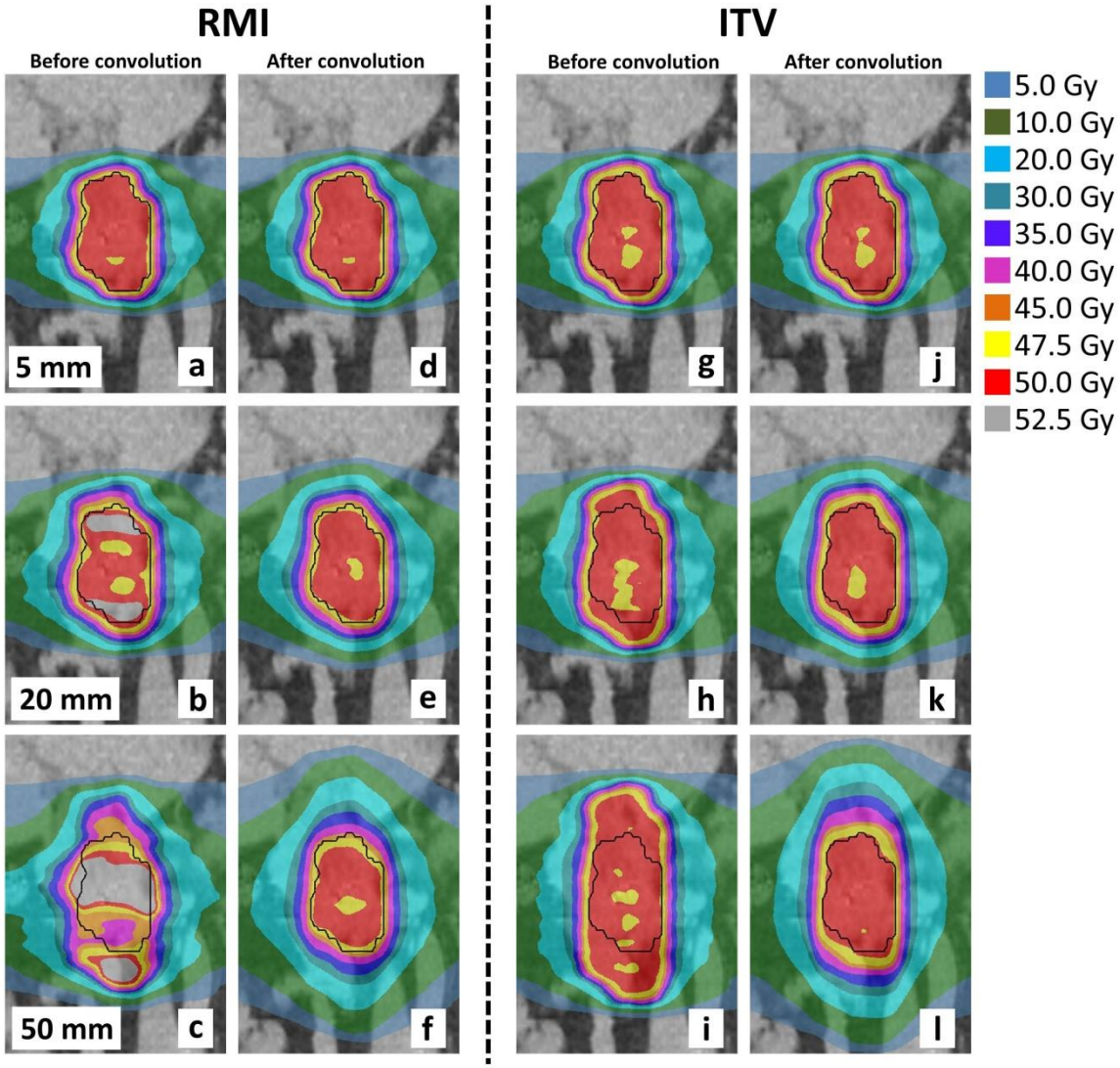

Figure B1: Examples of the optimized dose distributions before and after convolution with the expected target motion for patient 12 (i.e. smallest tumor) for three simulated respiratory motion amplitudes (5, 20 and 50 mm in the superior-inferior direction), when using the respiratory motion incorporated (RMI) approach (a--f) or the internal target volume (ITV) approach (g--l). The CTV is indicated by the black contour.

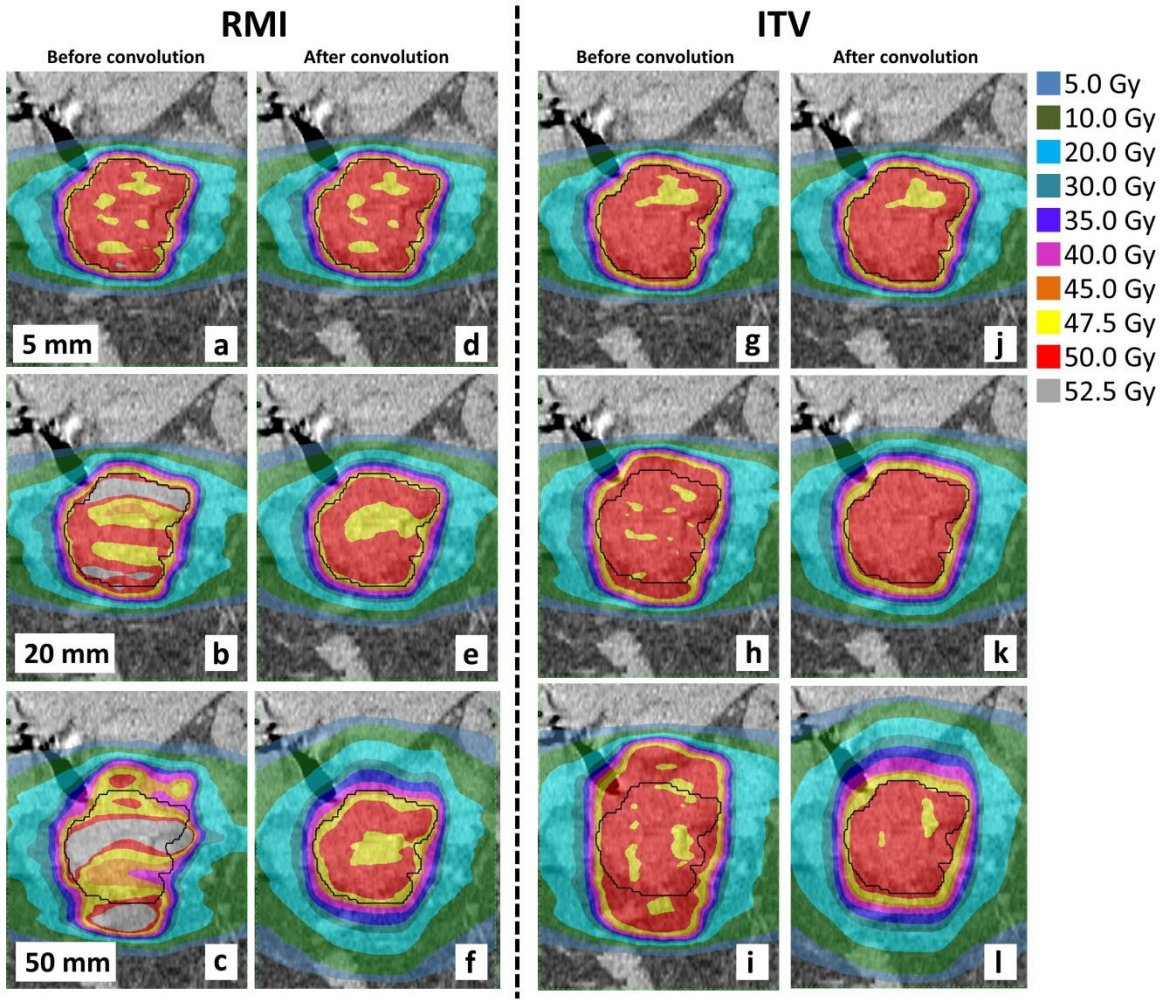

Figure B2: Examples of the optimized dose distributions before and after convolution with the expected target motion for patient 17 (i.e. largest tumor) for three simulated respiratory motion amplitudes (5, 20 and 50 mm in the superior-inferior direction), for both the respiratory motion incorporated (RMI) approach (a--f) and the internal target volume (ITV) approach (g--l). The black contour indicates the CTV.