Purpose: Uncertainties in the estimated mean excitation energies (I-value) needed for calculating proton stopping power can be in the order of 10-15%, which introduces a fundamental limitation in the accuracy of proton range determination. Previous efforts have quantified shifts in proton depth dose distributions due to I-value uncertainties in homogenous tissue phantoms. This study is the first to quantify the clinical impact of I-value uncertainties on proton dose distributions within patient geometries.

Methods: A previously developed Geant4 based Monte Carlo code was used to simulate a proton treatment plan for prostate cancer with varying tissue I-values. A total of five cases were simulated using nominal I-values as well as I-values modified by $\pm 5\%$ and $\pm 10\%$ of the nominal values. Dose volume histograms were generated for the GTV, CTV, PTV and relevant organs-at-risk (OARs).

Results: Modification of tissue I-values impacted both the proton range and SOBP width. D90 range shifts up to 4 mm from the nominal range were recorded whereas D80 range shifts reached up to 2 mm. For an increase in I-value of 10% of the nominal value, the increase in range and SOBP width resulted in a 1.4% decrease in the CTV mean dose. Inversely, decreasing the I-value by 10% increased the CTV mean dose by 0.8%. The difference in the mean dose to the OARs was relatively small except for the rectum that differed by up to 5%.

Conclusions: This study demonstrated that the impact of I-value uncertainties on patient dose distributions. Clearly, sub-millimeter precision in proton therapy would necessitate reduction in I-value uncertainties to ensure an efficacious clinical outcome.
Title: Clinical Impact of Uncertainties in the Mean Excitation Energy of Human Tissues During Proton Therapy