

Proton therapy enables lowering of the integral dose to the patient due to the finite range of protons. The basis for the reduction of integral dose is the proton's Bragg peak which increases the dose deposited in the tumour while reduces that to the normal tissue at the distal side of the target volume. Proton radiotherapy reduces the volume of normal tissue exposed to low doses, which is clinically significant with respect to the risk of second malignancies. That risk is notably more pronounced for younger patients than older ones as younger patients are more at risk to future radiation induced cancers.

However, proton therapy is less tolerant than photon therapy to uncertainties in both treatment planning and treatment delivery. For example, tissue inhomogeneity has a greater effect on proton dose distributions than on photon dose distributions. In planning proton therapy, the density of tissue along the proton path must be precisely determined and accounted for in order to obtain the required proton energy distribution to achieve the planned dose distribution in the patient. Failure to allow for a zone of higher density could result in a near zero dose in a distal segment of the target volume due to the reduced range of the protons. Conversely, neglecting to account for an air cavity upstream of the target volume would, for proton beams; result in a high dose being deposited in distal normal structures. Furthermore, motion and mis-registration of the target volume with the radiation beams have far more severe consequences in proton therapy compared to photon therapy. If the target volumes are to be adequately irradiated, and adjacent OARs are to be protected in proton therapy, it is essential: that the causes and possible magnitudes of motion and mis-registration are understood; that their possible consequences are understood; that measures are taken to minimize motion and mis-registration to the extent possible and clinically warranted.

It is almost impossible to get rid of all uncertainties in radiation therapy. Therefore, it is important to understand the sources of these uncertainties, quantify their magnitude, and develop mitigation and/or minimization strategies. In proton therapy margins are added to account for uncertainty sources that include; stopping power of tissues, dose calculation approximations, biological considerations, setup and anatomical variations, and internal movements of low and high density organs into the beam path. These margins reduce the benefit of proton therapy in treatment sites where the physical properties of protons could make a significant difference, such as lung cancer. The focus of this presentation is to; a) understand the potential sources of dosimetric uncertainties in proton therapy b) evaluate the impact of these uncertainties on the accuracy and conformity of dose delivered to patients and c) suggest potential strategies that translate physical advantage of proton therapy into a maximized dosimetric benefit in the patient.

## **Learning Objective**

1. Describe the need for knowing potential sources of treatment planning and delivery uncertainties in proton therapy.
2. Summarize strategies to mitigate both proton therapy planning and delivery uncertainties.