Lung cancer is the leading cause of cancer-related deaths worldwide. Radiotherapy is one of the main treatment modalities of lung cancer. However, the achievable accuracy of radiotherapy treatment is limited for lung-based tumors due to respiratory motion. Four-dimensional (4D) radiotherapy explicitly accounts for anatomic motion by characterizing the motion, creating a treatment plan that accounts for this motion, and delivering this plan to the moving anatomy. This thesis focuses on the current problems and solutions throughout the course of 4D radiotherapy. For characterization of respiratory-induced motion, patient tumor motion data were analyzed. It is shown that tumor motion can be significant during radiotherapy treatment, and its extent, direction, and linearity vary considerably between patients, between treatment fractions, and between respiratory cycles. After this, approaches to 4D intensity-modulated radiation therapy (IMRT) treatment planning were developed and investigated. Among the techniques to manage respiratory motion, tumor tracking using a dynamic multileaf collimator (DMLC) delivery technique was chosen as a promising method. A formalism to solve a general 4D IMRT treatment-planning problem was developed. Specific solutions to this problem accounting for tumor motion initially in one dimension and extending this to three dimensions were developed and investigated using 4D computed tomography planning scans of lung cancer patients. For 4D radiotherapy treatment delivery, accuracy of two-dimensional (2D) projection imaging methods was investigated. Geometric uncertainty due to the limitation of 2D imaging in monitoring three-dimensional tumor motion during treatment delivery was quantified. This geometric uncertainty can be used to estimate proper margins when a single 2D projection imager is used for 4D treatment delivery. Lastly, tumor-tracking delivery using a moving average algorithm was investigated as an alternative delivery technique that reduces mechanical motion constraints of a multileaf collimator. Moving average tracking provides an approximate solution that can be immediately implemented for delivery of 4D IMRT treatment. The clinical implementation of 4D guidance, IMRT treatment planning, and DMLC tracking delivery may have a positive impact on the treatment of lung cancer.

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