RISK-ADAPTIVE RADIOTHERAPY

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Currently, there is great interest in integrating biological information into intensity-modulated radiotherapy (IMRT) treatment planning with the aim of boosting high-risk tumor subvolumes – the concept has been called either 'selective boosting' or 'dose painting'. Selective boosting of tumor subvolumes can be accomplished without violating normal tissue complication constraints using information from functional imaging. However, conventional IMRT optimization utilizes physical dose-volume based objective functions, which have inherent limitations such as pursuing homogeneous dose distributions, mechanical summation of objective values, and assuming linear-dose-response curves.

In this work we have developed a risk-adaptive optimization-framework that utilizes a nonlinear biological objective function. The biological objective function we have employed is a combination of a subvolume based tumor control probability (TCP) function, and a voxel based overall normal tissue complication probability (NTCP) function, which we have termed generalized uncomplicated tumor control probability ($UTCP_{\delta}$).

Prostate cancer has been used as a model system to explore the feasibility of risk-adaptive radiotherapy. Employing risk-adaptive radiotherapy, it is possible to increase the equivalent uniform dose (EUD) by up to 35.4 Gy in tumor subvolumes having the highest risk classification without increasing normal tissue complications. Subsequently, we have studied the impact of functional imaging accuracy such as sensitivity and

specificity on risk-adaptive radiotherapy. We found on the one hand that loss in sensitivity had a large impact on expected local tumor control, which was maximal when a low-risk classification for the remaining low risk PTV was chosen. While on the other hand loss in specificity appeared to have a minimal impact on normal tissue sparing. Therefore, it appears that in order to improve the therapeutic ratio a functional imaging technique with a high sensitivity, rather than specificity, is needed.

Last but not least a comparison study between selective boosting IMRT strategies such as risk-adaptive radiotherapy and uniform-boosting IMRT strategies yielding the same EUD to the overall PTV was carried out. In order to adequately assess and compare these two radiotherapy strategies, we have developed radiobiological maps such as a voxel based iso-TCP map and voxel based iso-complication map. We found that selective boosting IMRT considerably improves expected TCP compared to uniform-boosting IMRT, especially when lack of control of the high-risk tumor subvolumes is the cause of expected therapy failure. Employing selective boosting IMRT one can increase TCP by up to 95% for high-risk tumor subvolumes. Furthermore, while on the one hand selective boosting IMRT, using physical dose-volume objectives, did yield similar rectal and bladder sparing when compared its equivalent uniform-boosting IMRT plan, risk-adaptive radiotherapy on the other hand, utilizing biological objective functions, did yield a 5.3% reduction in NTCP for the rectum when compared to its equivalent uniform-boosting IMRT plan. Hence, in risk-adaptive radiotherapy the therapeutic ratio can be increased over that which can be achieved with conventional selective boosting IMRT using physical dose-volume objectives.

In conclusion, a novel risk-adaptive radiotherapy strategy is proposed that promises increased expected local control for locoregionally advanced tumors with equivalent or better normal tissue sparing.