Radiation Dose Responses for Chemoradiation Therapy of Pancreatic Cancer: An Analysis of Compiled Clinical Data Using Biophysical models

Current survival outcomes for patients with advanced pancreatic cancer are poor, and more effective treatment modalities are needed. Given the interest by several institutions in radiotherapy (RT) dose escalations, we examined the theoretical benefits of radiation dose escalation using a biophysical model on recent clinical data resulting from chemoradiation treatment of unresectable locally advanced pancreatic cancer.

Published clinical outcomes were compared using a biologically equivalent dose (BED), and the data showed no correlation between survival and RT dose with various chemotherapy agents (Figure 1). Since treatment efficacy is also assessed via tumor local control (LC), we examined tumor LC versus BED and did observe dose dependence. However, although a useful indicator for acute treatment efficacy, tumor LC may not accurately reflect treatment effectiveness as it incorporates patients with tumor response (partial or complete) and stable disease (SD). Since most cases with pancreatic cancer are diagnosed in the advanced stages where tumor size may have reached maximal dimensions, i.e. already achieving SD before treatment, including those patients may overstate treatment effectiveness on tumor LC. Therefore, in this analysis we focused on tumor response alone versus BED.

Although no benefit to survival is apparent with increased RT dose, a correlation between tumor response and BED is clear (Figure 2). We applied a modified linear-quadratic model [1], and included a long follow-up time and delay in tumor doubling time, as well as a new factor to account for additional cell killing due to concurrent chemotherapy. The model assumes that a tumor is not controlled if the number of tumor cells is larger than a critical volume, which follows a Gaussian distribution for the patient population. The chi-square fit to the response data was good and the resulting parameters $\alpha/\beta$, $\alpha$, $T_k$, $T_d$ were then used to design fractionation schemes for potential dose escalation trials. Based on this analysis, a dose escalation trial up to 69.75 Gy in 2.25 Gy/fx is being initiated for unresectable pancreatic cancer at our institution, with at least two-fold improvement in expected tumor response rate compared to the standard fractionation RT scheme.

Figure 1: 1-year survival Vs Biologically Equivalent Dose of recently published clinical data showing no advantage to increased RT dose.

Figure 2: Response rate Vs Biologically Equivalent Dose of recently published clinical data exhibiting increased benefit to increased RT dose.