Prediction of response to preoperative chemoradiotherapy in rectal cancer by multiplex kinase activity profiling

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Study Design

In a phase II clinical trial 67 Locally Advanced Rectal Cancer (LARC) patients were treated with a chemoradiation therapy (CRT regimen consisting of radiotherapy, fluorouracil, and, where possible, oxaliplatin. Pretreatment tumor biopsy specimens were analyzed using PamChip® microarrays with kinase peptide substrates, and the resulting substrate phosphorylation profiles were correlated with tumor response to preoperative treatment as assessed by histomorphologic tumor regression grade (TRG) (figure 1). A predictive model for TRG scores from phosphosubstrate signatures was obtained by partial-least-squares discriminant analysis. Prediction performance was evaluated by leave-one-out cross-validation and use of an independent test set (figure 2).

Key Findings

Of the 67 patients, 73% and 15% were scored as good responders (TRG 1–2) or intermediate responders (TRG 3), and 12% were poor responders (TRG 4–5). In a testset of 7 poor responders and 12 good responders, treatment outcome was correctly predicted for 95%. Application of this testset model on the remaining 48 patient samples resulted in **correct prediction for 85%.** (Folkvord 2010)

"Author Quote"

Although skeptical at first we became convinced that kinase activity profiling may help predict response to preoperative radiotherapy in LARC.

Background

Locally advanced rectal cancer (LARC) comprises tumors that have grown through the rectal wall to an extent that precludes complete surgical resection and the achievement of adequate circumferential resection margin. A key objective of preoperative chemoradiotherapy (CRT) is macroscopic downstaging and control of subclinical tumor extension within the pelvic cavity, enabling complete tumor clearance after surgery.
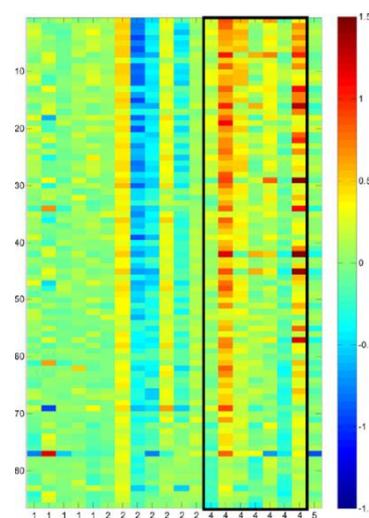

Figure 1: Color maps of 19 patient training set along horizontal axes (annotated by TRG score; TRG 4 samples are framed) and phosphosubstrates along vertical axes. Basal substrate phosphorylation levels are shown; red indicates higher phosphorylation levels, whereas blue represents lower levels. TRG = tumor regression grade
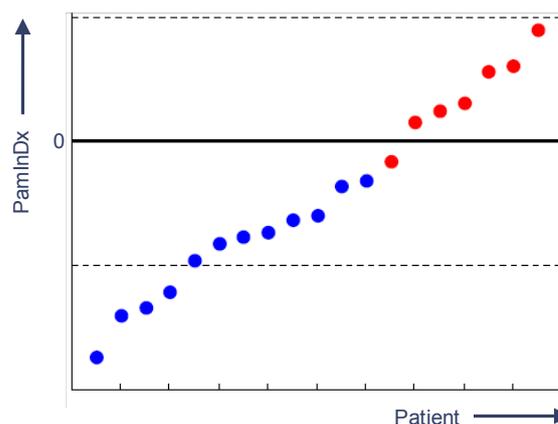

Figure 2: Prediction of tumor response from basal kinase activity profiles. Red, and blue circles represent poor-, and good-responder samples, respectively. Prediction value (PamInDx) >0 corresponds to predicted poor response, whereas value <0 corresponds to predicted good response. Results from prediction of 19 training set samples under leave-one-out cross-validation analysis are shown.

References:

Sigurd Folkvord et al. Int J Radiat Oncol Biol Phys. 2010 Jul 31

Conclusion

Multiplex kinase activity profiling may identify functional biomarkers predictive of tumor response to preoperative CRT in LARC

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