Development and Validation of a 24-gene Predictor of Response to Post-operative Radiation Therapy in Prostate Cancer

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ABSTRACT

Background: Post-operative radiotherapy (PORT) has an important role in the treatment of prostate cancer, but more personalized patient selection could improve outcomes and spare unnecessary toxicity. Our aim was to develop and validate a gene expression signature to predict which patients would benefit most from PORT.

Methods: Entry criteria were inclusion in any of five previously published studies of patients who underwent radical prostatectomy with subsequent gene expression from a single CLIA-certified microarray platform. A matched training prostatectomy cohort (N=196) was generated from the largest of the five studies, in which the 24-gene Post-Operative Radiation Therapy (PORT) Outcomes Score (PORTOS) was developed. From the remaining four studies, a matched validation cohort (N=330) was generated. Patients who received PORT were matched 1:1 with patients who had not, using Gleason, PSA, margin status, extracapsular extension, seminal vesicle invasion, lymph node invasion, and androgen deprivation therapy. The primary endpoint was the development of distant metastasis. To develop the RT predictive signature, we started with gene compilations from Gene Ontology (GO) and Gene Set Enrichment Analysis (GSEA) related to response to DNA damage and radiation which were ranked by prognostic ability. We used this ranked gene list to train a ridge-penalized Cox model, Feature selection was performed by varying the number of included features from 10 to 25 (9 to 24 genes in addition to treatment) in order to range from approximately 10 to 4 events per variable in the training cohort, minimizing the interaction p-value in the training cohort. The predictions from the model are calculated by taking the difference of the predictions without RT and with RT, and converting to binary scores using a cutoff of 0.

Results: PORTOS is able to predict response to PORT. In the training cohort, patients with high PORTOS treated with PORT have a lower metastasis rate than their untreated counterparts (5% [0-14%] vs 63% [34-80%] at 10 years; HR=0.12 [0.033-0.41], p<0.0001), whereas patients with low PORTOS treated with PORT do not have a lower metastasis rate than their untreated counterparts (57% [44-67%] vs 31% [20-41%] at 10 years; HR=2.5 [1.6-4.1], p<0.0001), with a significant treatment interaction p=0.0001. This is confirmed in the validation cohort which showed that patients treated with RT demonstrate improved outcomes only in the high PORTOS group (high PORTOS: RT 4% [0-10%] vs no RT 35% [7-54%] metastasis at 10 years; HR=0.15 [0.039-0.6], p=0.0020; low PORTOS: RT 32% [19-43%] vs no RT 32% [22-40%]; HR=0.92 [0.56-1.5], p=0.76), with a significant interaction p=0.016.

Conclusions: Patients with high PORTOS scores have selectively improved outcomes after PORT, suggesting that treatment with PORT should be strongly considered in this subgroup. PORTOS should be investigated further in additional independent cohorts.

Conflicts of Interest: MA reports employment at GenomeDx Biosciences, during the conduct of the study. HAA reports employment at GenomeDx Biosciences, during the conduct of the study. SLC reports employment at PFS Genomics, outside the submitted work. In addition, SLC has a patent PORTOS provisional filing USPTO pending. MRC reports grants and personal fees from Myriad Genetics, grants from Genomic Health, grants from GenomeDx Biosciences, personal fees from Dendreon, personal fees from Astellas, personal fees from Bayer, personal fees from Janssen, outside the submitted work. ED reports employment at GenomeDx Biosciences, during the conduct of the study. In addition, ED has a patent PORTOS provisional filing USPTO pending. RBD reports grants from GenomeDx Biosciences, during the conduct of the study. NE reports employment at GenomeDx Biosciences, during the conduct of the study. NE reports employment at GenomeDx Biosciences, during the conduct of the study. NY reports non-financial support from GenomeDx Biosciences, during the conduct of the study; grants from Varian, personal fees from Medivation/Astellas, grants and personal fees from Celgene, outside the submitted work. In addition, FYF has a patent PORTOS provisional filing USPTO pending and he is a founder and serves as president for PFS Genomics, a molecular diagnostic company aimed at personalizing radiation therapy for breast cancer. SJF reports grants and personal fees from GenomeDx, during the conduct of the study. RJK reports grants and royalties from GenomeDx Biosciences, outside the submitted work. PLN reports personal fees from Medivation, personal fees from Ferring, personal fees from GenomeDx Biosciences, outside the submitted work. AR reports grants and personal fees from GenomeDx Biosciences, during the conduct of the study. EMS reports consulting for GenomeDx Biosciences, outside the submitted work. DES reports grants from Prostate Cancer...
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