Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis.


Abstract

BACKGROUND: Postoperative radiotherapy has an important role in the treatment of prostate cancer, but personalised patient selection could improve outcomes and spare unnecessary toxicity. We aimed to develop and validate a gene expression signature to predict which patients would benefit most from postoperative radiotherapy.

METHODS: Patients were eligible for this matched, retrospective study if they were included in one of five published US studies (cohort, case-cohort, and case-control studies) of patients with prostate adenocarcinoma who had radical prostatectomy (with or without postoperative radiotherapy) and had gene expression analysis of the tumour, with long-term follow-up and complete clinicopathological data. Additional treatment after surgery was at the treating physician's discretion. In each cohort, patients who had postoperative radiotherapy were matched with patients who had not had radiotherapy using Gleason score, prostate-specific antigen concentration, surgical margin status, extracapsular extension, seminal vesicle invasion, lymph node invasion, and androgen deprivation therapy. We constructed a matched training cohort using patients from one study in which we developed a 24-gene Post-Operative Radiation Therapy Outcomes Score (PORTOS). We generated a pooled matched validation cohort using patients from the remaining four studies. The primary endpoint was the development of distant metastasis.

FINDINGS: In the training cohort (n=196), among patients with a high PORTOS (n=39), those who had radiotherapy had a lower incidence of distant metastasis than did patients who did not have radiotherapy, with a 10-year metastasis rate of 5% (95% CI 0-14) in patients who had radiotherapy (n=20) and 63% (34-80) in patients who did not have radiotherapy (n=19; hazard ratio [HR] 0·12 [95% CI 0·03-0·41], p<0·0001), whereas among patients with a low PORTOS (n=157), those who had postoperative radiotherapy (n=78) had a greater incidence of distant metastasis at 10 years than did their untreated counterparts (n=79; 57% [44-67] vs 31% [20-41]; HR 2·5 [1·6-4·1], p<0·0001), with a significant treatment interaction (pinteraction<0·0001). The finding that PORTOS could predict outcome due to radiotherapy treatment was confirmed in the validation cohort (n=330), which showed that patients who had
radiotherapy had a lower incidence of distant metastasis compared with those who did not have radiotherapy, but only in the high PORTOS group (high PORTOS [n=82]: 4% [95% CI 0-10] in the radiotherapy group [n=57] vs 35% [95% CI 7-54] in the no radiotherapy group [n=25] had metastasis at 10 years; HR 0·15 [95% CI 0·04-0·60], p=0·0020; low PORTOS [n=248]: 32% [95% CI 19-43] in the radiotherapy group [n=108] vs 32% [95% CI 22-40] in the no radiotherapy group [n=140]; HR 0·92 [95% CI 0·56-1·51], p=0·76), with a significant interaction (pinteraction=0·016). The conventional prognostic tools Decipher, CAPRA-S, and microarray version of the cell cycle progression signature did not predict response to radiotherapy (pinteraction>0·05 for all).

**INTERPRETATION:** Patients with a high PORTOS who had postoperative radiotherapy were less likely to have metastasis at 10 years than those who did not have radiotherapy, suggesting that treatment with postoperative radiotherapy should be considered in this subgroup. PORTOS should be investigated further in additional independent cohorts.

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