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Journal Club

A New Predictive Tool for Postoperative Radiotherapy in Prostate Cancer

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Abstract

The standard treatments for localized prostate cancer include surgical resection and/or radiotherapy. Recently in 2016, Zhao et al. described a tool to predict which patients will most likely gain from postoperative radiotherapy. Such a method can personalize treatment plan by maximizing benefit but minimizing harm.
Prostate cancer is a relatively indolent malignancy, and many men are diagnosed with localized disease, without any symptoms, based on high or rising prostate specific antigen (PSA) and positive needle biopsy [1]. After the possibility of metastases is ruled out by radiographic tests including bone scan, computed tomography and/or magnetic resonance imaging, appropriate candidates receive radical prostatectomy [2]. Afterwards, some patients receive adjuvant radiation based upon the presence of high risk factors, such as positive margin(s), extracapsular extension, seminal vesicle invasion or detectable PSA. For those who have not received adjuvant radiation, they get salvage radiation with rising PSA [3]. While radiation therapy is standard for disease recurrence, it exposes patients to potential side effects, such as impotence, radiation proctitis, loose stools, radiation cystitis and urinary incontinence [4]. In addition, biochemical recurrence, defined as a rise in PSA after surgery or radiation, can occur without the presence of these high risk pathological traits [5]. Therefore, a means to identify the patient population most likely to benefit from radiation, while minimizing exposure to lower risk patients, would improve the current treatment paradigm for localized prostate cancer.

Other malignancies, such as breast cancer, have risk stratification tools to help guide therapy [6]. Early breast cancer patients with estrogen receptor positive disease can receive oncotype DX, which analyzes the RNA expression of 21 genes to provide prognostic information on the likelihood of disease recurrence and predictive information regarding the potential benefit of chemotherapy. For prostate cancer, tools such as Decipher, mCCP and CAPRA-S provide prognostic, but not predictive, information on tumor aggressiveness and the probability of metastasis [7-9]. Hence, a predictive tool would complement current treatment planning, which
is formulated using a combination of imaging, histological information from biopsy, and PSA. In a study published on October 12, 2016 in *Lancet Oncology*, Zhao et al. reported a means to address this need [10]. Findings from this study may complement the current treatment paradigm by appropriately triaging patients toward or away from radiation after prostatectomy.

Five studies (four cohort or case-cohort and one case-control) performed at four U.S. medical centers from 1987 to 2010 were retrospectively analyzed. All patients received radical prostatectomy for localized prostate cancer, followed with or without postoperative radiotherapy. The patients were matched based on clinicopathological and laboratory criteria. The largest study was set aside as a training cohort, while the remaining four were pooled together to form a validation cohort. In order to construct a predictive signature, microarrays were hybridized against prostatectomy samples of matched patients from the training cohort, helping to identify candidate genes differentially regulated by radiation. Genes related to DNA damage and radiation were then ranked according to the significance of the interaction between each gene and radiotherapy. This revealed a 24-gene signature Post-Operative Radiation Therapy Outcomes Score (PORTOS). Application of PORTOS to the training and validation cohorts predicted that patients with high scores demonstrated reduced metastases in response to radiation therapy at the 10 year follow-up.

According to this study, clinicians can utilize PORTOS to limit radiation to patients who will benefit. Surprisingly, patients with low scores showed increased metastases after radiation in the training cohort. In contrast, patients with low scores in the validation cohort had a similar rate of metastases at 10 years whether or not they received radiation. While this discrepancy could be
attributed to various factors, such as statistical overfitting, it emphasizes the need for confirmation using additional cohorts. The study claimed that application of Decipher, mCCP and CAPRA-S to the validation cohort revealed no correlation to postoperative radiotherapy, while PORTOS did. However, an unbiased comparison is difficult. Decipher, mCCP and CAPRA-S are designed using different parameters, and they are prognostic not predictive signatures [7-9]. Another limitation of this study was that patients who received adjuvant and salvage radiotherapy were pooled into the postoperative radiotherapy group for analysis. Therefore, whether or not PORTOS was predictive in each subgroup was unclear.

Currently, the presence of positive margin(s), extracapsular extension, seminal vesicle invasion or detectable PSA directs patients toward postoperative radiation [2]. PORTOS can help select patients without such risk factors, but still likely to form metastases. Should PORTOS be widely adopted after validation in additional cohorts, clinicians would not have to wait until PSA rises to administer salvage radiation, but administer adjuvant radiation based upon its 24-gene signature. Consequently, adjuvant radiation may largely displace salvage radiation as the sole postoperative radiation. As we move into the era of personalized medicine, PORTOS has the potential to identify subsets of patients who will most likely gain from postoperative radiation, while saving others from unnecessary toxicity.
References


