Nature Reviews Urology **9**, 7 (2012); doi:10.1038/nrurol.2011.209

RADIOTHERAPY

PSA surrogates for survival with ADT

The addition of androgen deprivation therapy (ADT) to radiation therapy in men with localized or locally advanced prostate cancer has demonstrated clear survival benefits in several large trials. However, the slender survival advantage conferred by 3 years of ADT in comparison to just 6 months (3.8% at 5 years, according to a 2009 EORTC study) comes at an undesirable cost of treatment toxicity. In order to avoid the administration of unnecessary ADT, early identification of those men who are unlikely to be cured by radiation therapy and 6 months of ADT would be of great clinical utility. In a study published in *Lancet Oncology*, D'Amico and colleagues investigated whether PSA nadir or PSA level at the immediate end of treatment ('PSA end')—using a cut-off PSA level of 0.5 ng/ml in each case—can be used as surrogates for prostate-cancer-specific mortality (PCSM) in these men.

The authors analyzed individual patient data obtained from two randomized controlled trials: the Dana Farber Cancer Institute (DFCI) trial and the Trans-Tasman Radiation Oncology Group (TROG) trial. The results of both trials demonstrated improved overall and cancer-specific survival in men with localized or locally advanced prostate cancer treated with radiation therapy (66–70 Gy in 1.8–2.0 Gy fractions) and 6 months of ADT (comprising a luteinising-hormone-releasing hormone agonist plus anti-androgen) compared to radiation therapy alone. Patients were followed up every 3 months for the first 2 years, every 4–6 months for the next 3 years, and yearly thereafter. Overall, data from 734 men were included in the current analysis.

The utility of PSA nadir and PSA end as surrogate end points was assessed using the statistics-based Prentice criteria. Briefly, the four criteria that must be satisfied are as follows: first, patients who achieve the surrogate must have been significantly more likely to be randomized to the inferior treatment group; second, the surrogate must be a prognostic factor; third, the surrogate end point must remain prognostic for PCSM when it is included in a competing risk regression model containing the randomized treatment group as a covariate; and fourth, superior treatment must no longer be significantly associated with decreased PCSM in this statistical model.

Patients treated with radiation therapy plus ADT were significantly less likely to have PSA nadir or PSA end levels >0.5 ng/ml compared to the patients who received radiation therapy alone in both trials ($P<0.0001$ in all cases). In a competing risks regression analysis, PSA nadir and PSA end >0.5 ng/ml were associated with significantly increased risks of PCSM in both the DFCI trial ($P=0.0016$ and $P=0.017$, respectively) and the TROG trial ($P<0.0001$ and $P=0.0012$, respectively). In addition, PCSM was no longer significantly different between treatment groups when the surrogates were included in this model, thus completing the set of satisfied Prentice criteria.

The findings of this study indicate that PSA measurements during or immediately after treatment—and, importantly, before the point of PSA failure—can be used as early surrogates for future PCSM in men with localized or locally advanced prostate cancer receiving radiation therapy and short-course ADT. Patients who do not achieve a PSA end value <0.5 ng/ml at the conclusion of treatment might benefit from an extended period of androgen suppression; alternatively, those who fail to achieve a PSA nadir <0.5 ng/ml during treatment might be considered for enrollment into clinical trials of agents that have been shown to potentially prolong survival in patients with castration-resistant metastatic prostate cancer, such as docetaxel or abiraterone. However, the authors note that their surrogates apply only to the ADT agents used in the DFCI and TROG trials, as other androgen suppressors might affect PSA levels in a different manner. This issue will need to be addressed in future work.

Nick Warde

Original article D'Amico, A. V. *et al.* Surrogate endpoints for prostate cancer-specific mortality after radiotherapy and androgen suppression therapy in men with localised or locally advanced prostate cancer: an analysis of two randomised trials. *Lancet Oncol.* doi:10.1016/S1470-2045(11)70295-9