

Radiation dose for prostate cancer: is more better?

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In prostate cancer, a trial comparing conventional- versus high-dose conformal radiotherapy has shown that increasing the dose can improve outcome, with only slight increases in toxicity.

Major technological improvements in the treatment of prostate cancer with radiation therapy have allowed dramatically higher doses to be delivered with minimal or no additional normal-tissue toxicity. Three-dimensional treatment-planning software used in conjunction with sophisticated, computer-controlled treatment accelerators and intensity-modulated radiation therapy with or without newer radiotherapy modalities (e.g. protons, neutrons or brachytherapy) has produced unprecedented dose-delivery capabilities. These technologies have been developed according to the premise that treatment outcome can be improved as the dose of radiation to the prostate gland is escalated. A dose-response relationship in the treatment of prostate cancer is now generally accepted by most clinicians and physicists involved in the management of this malignancy. Until recently, few well-designed prospective randomised trials with

large patient numbers specifically addressing this critical issue have been published. As a result, this dose-response relationship has been extrapolated from data originating primarily from retrospective and prospective nonrandomised studies.^{1,2}

The study by Zietman et al. (see opposite), using a combination of conventional photon radiation with protons, clarifies this point by documenting that a higher dose is objectively better than a lower dose in achieving an improved 'biochemical outcome' in well-defined subsets of patients. Although the trial was optimally designed, efficiently executed and has sufficient follow-up, several critical issues related to the 'dose-response question' in particular, and to prostate cancer treatment in general, remain unresolved.

Firstly, the absolute minimum dose needed to eradicate cancer for each stage of disease is still not established. Although dose-response data such as these suggest that more

is generally better, it is difficult to determine how much of the improvement in biochemical control noted in many older dose escalation trials is simply related to better patient selection or the more optimal delivery of the radiotherapy dose (through better targeting, dose specification, and patient immobilisation or tracking). If, using modern three-dimensional techniques, a portion of the target is occasionally found to be outside the intended high-dose region, it is possible that lower doses could be sufficient with the superior targeting of off-line adaptive or on-line image-guided radiotherapy approaches.³

Secondly, it remains uncertain if the appropriate biochemical endpoint – that acts as an early surrogate for cure – to measure treatment success with all forms of radiotherapy is being used. Debate on the best biochemical definition continues.⁴

Thirdly, although protons were used very effectively in the study by Zietman et al. (some increased grade

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2 or greater morbidity was noted), the best method of radiotherapy to provide safe and economic delivery of these higher doses is debatable. While it is clear that higher energy particles and modern brachytherapy (i.e. high-dose-rate brachytherapy) can be targeted more precisely, it is uncertain whether more-expensive and more-labour-intensive technologies are any more efficacious than conventional methods applied with

more recent advances in imaging, planning software and treatment-delivery techniques.

Finally, even if higher radiotherapy doses are superior to lower doses in eradicating cancer, these new radiotherapy technologies must be directly compared with other forms of treatment (e.g. surgery) in terms of cost, quality of life, ease of administration, availability and reproducibility. Unprecedented capabilities

for radiotherapy techniques to efficiently eradicate cancer and surgical techniques to comprehensively remove cancer have been achieved. What will prove just as critical will be the long-term effects of these treatment strategies on patients' quality of life and the cost of their administration.

Details of the references cited in this article can be accessed at www.cancerworld.org/cancerworld

Synopsis

AL Zietman, ML DeSilvio, JD Slater, et al. (2005) **Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial.** *JAMA* 294:1233–1239

Background. Conventional-dose radiotherapy is unable to eradicate prostate cancer in a substantial proportion of cases. Increasing the radiotherapy dose might achieve better local tumour control, but there is a risk of higher morbidity unless the radiotherapy can be targeted accurately to avoid damage to normal tissue.

Objective. To establish whether local control of prostate cancer could be improved by the use of higher doses of radiotherapy using conformal techniques.

Design and intervention. In this randomised controlled trial, patients with localised prostate cancer received external radiotherapy at a conventional dose of 70.2 Gy or an increased dose of 79.2 Gy. All patients received the same dose of conformal photon therapy (50.4 Gy), but boost dose differed between the groups (19.8 or 28.8 Gy) and was delivered using proton-beam therapy. Men with stage T1b–T2b tumours (using the American Joint Committee on Cancer criteria), serum prostate-specific antigen (PSA) levels below 15 ng/ml and no metastatic disease according to whole-body bone scan and abdominopelvic CT scan were included. Patients were stratified according to nodal status and serum PSA levels.

Outcome measures. Biochemical failure, local control and morbidity were the endpoints for this study. Biochemical failure was assessed using the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria (i.e. 3 successive increases in PSA level), local control was estimated using a surrogate measure in lieu of biopsy (PSA levels <1 ng/ml) and morbidity was graded using the Radiation Therapy Oncology Group (RTOG) criteria.

Results. Median follow-up was 5.5 years (range 1.2–8.2 years) for all 392 patients. Five-year freedom from biochemical recurrence was 61.4% (95% CI 54.6–68.3%) in the conventional-dose group, and 80.4% (95% CI 74.7–86.1%) in the high-dose group ($P<0.001$), a 49% decrease in the risk of failure. High-dose therapy was advantageous in both low-risk disease, defined as PSA level <10 ng/ml, Gleason score of ≤ 6 , tumour stage $\leq T2a$ (51% risk reduction; $P<0.001$) and higher-risk disease (44% risk reduction; $P=0.03$). Local control at 5 years was 47.6% (95% CI 40.4–54.8%) in the conventional-dose group vs 67.2% (95% CI 60.4–74%) in the high-dose group ($P<0.01$). The overall survival rate did not differ significantly between the groups (97% vs 96%; $P=0.8$). Acute genitourinary or gastrointestinal (rectal) morbidity \geq grade 3 developed in 1% of patients in the conventional-dose group and 2% in the high-dose group, and late genitourinary or gastrointestinal morbidity of grade 3 or higher developed in 2% and 1% of patients, respectively. High-dose treatment increased acute and late genitourinary morbidity \geq grade 2, however.

Conclusion. Men who have localised prostate cancer are more likely to be free from biochemical recurrence at 5 years, and have a lower risk of locally persistent disease, if they are treated with high-dose as opposed to conventional-dose radiotherapy.

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