PROSTATE CANCER

Radiotherapy—treating patients in a fast-moving field

Two new studies comparing different radiotherapy modalities for men with localized prostate cancer highlight the difficulties associated with making treatment recommendations in such a fast-paced field. One study provides level I evidence for what might be considered an outdated technique; the other raises awareness of adopting novel treatment options before evidence from randomized controlled trials is available.

The first study, published in *The Lancet Oncology*, reports the long-term outcomes of MRC RT01—a phase III randomized controlled trial of dose-escalated 3D conformal radiotherapy, which compared the ‘standard’ dose of 64 Gy with an ‘escalated’ dose of 74 Gy. Notably, although 64 Gy was the standard dose when this trial was started in 1998, the escalated dose has been the standard of care in the UK since 2008, based on the early results of this trial.

David Dearnaley and colleagues across the UK randomized 843 men with prostate cancer (T1b–T3a, N0, M0, PSA <50 ng/ml) to receive 64 Gy ($n=421$) or 74 Gy ($n=422$) of conformal radiotherapy. Both groups received 3–6 months of neoadjuvant androgen deprivation therapy. The outcomes after a median follow-up of 10 years confirm those reported at 5 years; overall survival was 71% (95% CI 66–75) in both groups, but biochemical-progression-free survival was better in the escalated-dose group than the control group (55% versus 43%; hazard ratio 0.69, 95% CI 0.56–0.84).

In an accompanying editorial, Andrew Loblaw, a radiation oncologist at Sunnybrook Health Sciences Centre in Toronto, Canada, questions the value of trials such as MRC RT01. “Although the purists will say that randomized trials are needed to inform every decision, the pragmatist knows that there are limits to this statement,” he writes, going on to explain that—in this field in particular—although randomized trials generate level I evidence, the data might not be

clinically relevant by the time they mature. In the meantime, technological advances continue to occur and clinicians start to offer newer interventions—such as intensity-modulated radiotherapy (IMRT), stereotactic body radiation therapy (SBRT) and low-dose-rate and high-dose-rate brachytherapy—before high-level evidence has been collected.

The second study, published in the *Journal of Clinical Oncology*, compares the toxicities of SBRT and IMRT and raises the question of whether advanced treatment options that seem to offer benefits over current standards should really be recommended before high-level comparative data are available.

SBRT is a state-of-the-art radiotherapy modality, which delivers higher doses of radiation per session than IMRT. Such high doses enable a shorter treatment course and, therefore, SBRT has been touted as a cost-effective alternative to IMRT. Moreover, initial studies have reported that SBRT has an acceptable toxicity profile, leading to its adoption beyond the institutions in which it was pioneered, in the absence of randomized controlled trial data.

However, reports are now emerging that patients who have undergone SBRT experience late flares of urinary symptoms (such as urethral strictures, incontinence and haematuria), which raises some obvious concerns. To collect more information on the toxicity of SBRT at institutions across the USA, James Yu and colleagues performed a retrospective population-based analysis of Medicare data.

The investigators matched 2,670 men who received IMRT with 1,335 men who received SBRT and used procedure or diagnosis codes to assess toxicities. They found that SBRT was associated with higher rates of genitourinary toxicity than IMRT at 6 months (15.6% versus 12.6%), 12 months (27.1% versus 23.2%) and 24 months (43.9% versus 36.3%). Further analysis revealed that men who underwent

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SBRT were more likely to make claims for procedures to treat incontinence and obstruction at 6 months, 12 months and 24 months, and urethritis and urethral strictures at 12 months and 24 months, than those who received IMRT.

Although these findings are limited by the study’s retrospective nature and reliance on treatment claims data, they raise the possibility that SBRT, which is already being used across the USA, might be more toxic than the current standard of care. Accordingly, the authors imply that SBRT cannot be recommended until the results of a randomized controlled trial are reported in 2015.

These two studies reflect different viewpoints on the role of randomized controlled trials and level I evidence in the continually evolving field of radiation therapy for prostate cancer. In the words of Andrew Loblaw: “Are clinicians willing to stop innovating while they wait 20 years to design, enrol, and mature the results of each randomized controlled trial?” I’d wager the answer is no.

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Original articles Dearnaley, D. P. *et al.* Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol.* doi:10.1016/S1473-2045(14)70040-3 | Yu, J. B. *et al.* Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity. *J. Clin. Oncol.* doi:10.1200/JCO.2013.53.8562