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UROLOGICAL CANCER

For localized prostate cancer, does technology equal progress?

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Recent evolution of prostate cancer treatment reflects technological arms races driven by economic incentives rather than high-quality evidence—as exemplified by proton-beam radiation, recently found markedly inferior to far less-expensive alternatives. Another study found promise for focal treatment, but much research is required before this could become a standard option.

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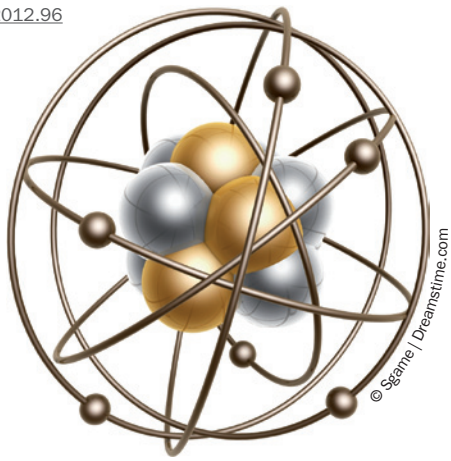

Efforts are constantly ongoing to introduce alternatives to standard treatments for localized prostate cancer that offer equivalent or better oncological efficacy, together with reduced side effects. However, the recent history of treatment evolution has been driven more by marketing hype and misaligned financial incentives than by high-quality evidence. Two studies have generated a great deal of attention in the media, and are illustrative of broader ongoing trends in the field. The first study, by Sheets *et al.*,[1] analyzed data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database to compare proton-beam treatment with other forms of external-beam radiation therapy (EBRT)—namely intensity-modulated radiation therapy (IMRT) and conventional conformal radiation—between 2002 and 2006, using both standard multivariable analysis and propensity weighting.

The growth of IMRT has been absolutely explosive: from 0.15% of EBRT cases in 2000 to 95.9% in 2008.[1] Overall, compared with conformal radiation, IMRT was associated with statistically significant, but modest clinical benefits: 9% less gastrointestinal toxicity (only on the propensity-adjusted analysis) and fewer hip fractures (which were uncommon in all groups), but no difference in urinary outcomes and 12% more erectile dysfunction. Proton-beam treatment was associated with no benefits compared to IMRT—and in fact caused 50% greater bowel toxicity, even after propensity adjustment. Proton-beam treatment was also marked by trends towards greater erectile dysfunction.[1]

The debate about proton-based versus photon-based radiation recalls similar discussions about robot-assisted versus open prostatectomy; the discussion section of the present study[1] in fact draws an explicit parallel to an earlier Medicare study focusing on this question.[2] Indeed, there are similarities in the way these technologies have been developed and marketed.[3] Both Medicare analyses are also marked by limitations in their use of administrative billing codes as proxies for quality-of-life outcomes, which ideally should be assessed via validated patient-reported questionnaires. However, important differences should be noted. The prostatectomy paper analyzed robot-assisted surgery data from many surgeons, mostly lower-volume providers early in their learning curves.[2] The proton-beam experience, conversely, was dominated by a single centre in southern California, which is an experienced, high-volume (and aggressively marketed) centre for proton-based prostate treatment; this concentrated experience should, if anything, represent a best-case for outcomes. Also, unlike the case of proton-beam treatment, many other studies have found clear benefits for robot-assisted prostatectomy compared with open prostatectomy.[4]

Furthermore, the capital and marginal costs of robot-assisted versus open surgery are utterly dwarfed by those of proton-based versus photon-based radiation. The additional costs of robotics are absorbed by hospitals, whereas the costs of novel radiation technologies are borne directly by Medicare and other payers. Costs were not directly addressed in the Sheets *et al.*[1] paper; however, another recent Medicare study found IMRT to be roughly 50% more expensive than 3D conformal radiotherapy, and about twice as expensive as brachytherapy or surgery (whether open or minimally-invasive).[5] Proton-beam therapy is twice as expensive again as IMRT. A decision analysis demonstrated in 2007 that even if decreased morbidity allowed dose escalation up to 90 Gy, proton-beam treatment still would not be cost effective.[6]

At this point, it seems very unlikely that proton-based therapy will allow such dose escalation. Indeed, while there are theoretical radiation biological advantages to proton-beam therapy, no clinical study—anywhere, ever—has shown any clinical advantage in terms of either oncological or quality-of-life outcomes. Proton-beam prostate treatment fortunately remains uncommon, but new facilities are proliferating rapidly, and because once a facility is constructed there is a major incentive to recoup a prodigious investment, local prostate cancer practice patterns tend to shift to reflect more use of proton-beam treatment.[7]

The other recent paper, from Ahmed *et al.*,[8] reported MRI-guided focal treatment with high-intensity focused ultrasound

Key point

Proton-beam therapy for prostate cancer costs two to four times as much as standard alternatives and in a recent study has been shown to yield inferior quality-of-life outcomes. Focal therapy may eventually offer a favourable alternative, but much research is needed on patient selection, workup, follow up, and outcomes assessment.

(HIFU). HIFU has been the subject of multiple series, mostly in Europe. The results have been decidedly mixed, with some series reporting excellent outcomes, and others finding low rates of cancer control, high rates of retreatment, and mediocre quality of life.[9] Given this ongoing uncertainty, the technology remains investigational in the USA.

Ahmed *et al.*[8] reported on 42 men with low-risk to intermediate-risk prostate cancer treated with HIFU targeting areas of cancer based on biopsy and imaging. The protocol allowed up to 60% ablation of the prostate, and required transperineal template prostate biopsies under anaesthesia before and after therapy. At 12-month follow up, quality-of-life outcomes were generally good, although there were certainly impacts on sexual and urinary function, particularly in the short term, and in some cases in the long term. 23% of the patients had follow-up biopsies positive for cancer, and 10% were retreated. Follow up was not sufficient for assessment of long-term oncological efficacy.

What is novel about this study[8] is not HIFU *per se,* but rather its use in a relatively well-constructed, prospective study of focal therapy. Indeed, for focal prostate cancer treatment, the ablative technology is almost irrelevant. If prostate cancer can be identified reliably, it can be destroyed by any number of modalities: HIFU, cryotherapy, interstitial laser therapy, photodynamic treatment, focal radiation, and so on. Although the results might be considered promising, many questions remain regarding patient selection, workup, imaging, and follow up, which must be answered before focal treatment could be considered for routine clinical practice. Because HIFU is not broadly available, direct cost comparisons to other treatments are not possible, although the imaging and pathology costs for an MRI-based focal protocol with before-and-after transperineal biopsies are likely to be significant.

Where do these studies leave us? Regarding proton-beam treatment the answer should be clear: at a time of increasingly constrained resources, it is completely unconscionable that we should continue to pay exorbitant premiums for a technology that has not been proven better, and may well be less effective, than competing alternatives. Proton-beam treatment should continue to be studied, but payment incentives must be revised—for both proton-beam treatment and IMRT—to provide reimbursement per patient, not per fraction, and neither should be reimbursed so richly compared to surgery or brachytherapy.

More generally, strident champions of expensive technology without supporting evidence run the risk of winning short-term, pyrrhic victories, but losing the overall war: avoidable cost and morbidity associated with overtreatment of prostate cancer is a major driver behind calls to end prostate cancer screening. Focal therapy remains an intriguing alternative, but requires much more study—and the fact remains that for most men with low-risk prostate cancer, the best treatment is active surveillance rather than any local treatment.[10]

Ultimately, what is needed in 2012 for localized prostate cancer is not new technologies, but rather new paradigms for routine, standardized assessment and reporting of both oncological and patient-centred outcomes; for risk stratification of tumours and targeting intensity of treatment to individuals' oncological risk and comorbidity; and for full engagement of patients in shared decision-making based on high-quality data on both effectiveness and cost-effectiveness of treatment alternatives.

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Competing interests
The author declares no competing interests.

1. Sheets, N. C. *et al.* Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA* **307**, 1611–1620 (2012).
2. Hu, J. C. *et al.* Comparative effectiveness of minimally invasive vs open radical prostatectomy. *JAMA* **302**, 1557–1564 (2009).
3. Cooperberg, M. R., Odisho, A. Y. & Carroll, P. R. Outcomes for radical prostatectomy: is it the singer, the song, or both? *J. Clin. Oncol.* **30**, 476–478 (2012).
4. Tewari, A. *et al.* Positive surgical margin and perioperative complication rates of primary surgical treatments for prostate cancer: a systematic review and meta-analysis comparing retropubic, laparoscopic, and robotic prostatectomy. *Eur. Urol.* http://dx.doi.org/10.1016/j.eururo.2012.02.029.
5. Nguyen, P. L. *et al.* Cost implications of the rapid adoption of newer technologies for treating prostate cancer. *J. Clin. Oncol.* **29**, 1517–1524 (2011).
6. Konski, A., Speier, W., Hanlon, A., Beck, J. R. & Pollack, A. Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? *J. Clin. Oncol.* **25**, 3603–3608 (2007).
7. Aaronson, D. S. *et al.* Proton beam therapy and treatment for localized prostate cancer: if you build it, they will come. *Arch. Intern. Med.* **172**, 280–283 (2012).
8. Ahmed, H. U. *et al.* Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. *Lancet Oncol.* http://dx.doi.org/10.1016/S1470-2045(12)70121-3.
9. Lukka, H. *et al.* High-intensity focused ultrasound for prostate cancer: a systematic review. *Clin. Oncol. (R. Coll. Radiol.)* **23**, 117–127 (2011).
10. Cooperberg, M. R., Carroll, P. R. & Klotz, L. Active surveillance for prostate cancer: progress and promise. *J. Clin. Oncol.* **29**, 3669–3676 (2011).

HAEMATOLOGICAL CANCER

Lenalidomide maintenance—perils of a premature denouement

S. Vincent Rajkumar

Of three randomized trials testing lenalidomide maintenance in myeloma, a survival benefit is apparent in one. An increased risk of second cancers is seen in all three trials. Maintenance must be considered after a review of risks and benefits, but it is premature to recommend lenalidomide maintenance for all patients.

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Three high-profile randomized placebo controlled trials of lenalidomide as maintenance therapy for patients with multiple myeloma have been published recently.[1–3] What are the implications of these studies? Do these results change the standard of care for patients with this disease? To answer these questions, we need to place the results of these studies in the context of the overall treatment strategy for myeloma.