Title
New types of radiotherapy improve cancer outcome but at what cost?

Journal
Nature Reviews Urology, 9(8)

ISSN
1759-4812

Authors
Murphy, Declan G
Williams, Scott
Cooperberg, Matthew R

Publication Date
2012-08-01

DOI
10.1038/nrurol.2012.137

Peer reviewed

With this in mind, Ahmed *et al.*[1] in their recent article in *Lancet Oncology*, studied adverse effects related to a relatively new therapeutic modality for localized prostate cancer: the ablation of prostate tumours using high-intensity focused ultrasound (HIFU).

Having previously published the initial results of a phase I/II trial on 20 patients, which reported the short-term outcomes of 'hemiablation' for *a priori* unilateral prostate cancer,[2] they report herein the preliminary results of using HIFU to treat a cohort of 42 men with prostate cancer treated focally according to their prostate cancer location, assessed by ultrasonography-guided biopsy templates and MRI. They conclude that "focal therapy of individual prostate cancer lesions, whether multifocal or unifocal, leads to low rate of genitourinary side effects and an encouraging rate of early absence of clinically significant prostate cancer".

> "...therapeutic protocols and evaluation criteria are not yet established and standardized"

Without any doubt, tumour ablation—particularly in the prostate—has to be studied, and this therapeutic modality might become a new option within the present armatorium for localized prostate cancer, which currently includes active-surveillance protocols, "watchful-waiting", radiotherapy and surgery. However, this study evaluates a new concept of treatment—tumour ablation as opposed to whole gland treatment—using a fairly new therapeutic modality, and is not so much interested in demonstrating that the therapeutic protocol is as efficient as radical surgery or radiotherapy in terms of cure, but was instead powered to demonstrate that side effects are minimized. In this sense, stating that HIFU "continues to support the proposition that tissue preservation leads to functional preservation" looks like a tautology that doesn't need such surgical experimentation, but, in fact, places the patient at risk for incomplete treatment.[3]

We are all aware of the prostate cancer conundrum that Willet Whitmore, a former chairman of the department of Urology at Memorial Sloan Kettering Cancer Center in New York, once posed: "Is cure of prostate cancer possible when it is necessary? Is cure necessary when it is possible?" Thus, either the tumour presents life-threatening

© Maksym Yemelyanov | Dreamstime.com

risk characteristics and it should be treated adequately and efficiently, and only later question how side effects can be minimized, or the tumour is considered to be possibly indolent and the question of active treatment is fundamentally erroneous and perverse.

But beyond this, and without even considering the protocol itself and the way end points were assessed, this paper seems to represent a milestone in cancer therapeutic research—to my knowledge, it represents the first attempt to consider a new cancer treatment by analysing adverse effects before efficacy has been fully established. Indeed, it is noticeable that, currently, the results of studies investigating the efficacy of HIFU published in the medical literature are particularly contradictory among different teams, probably because therapeutic protocols and evaluation criteria are not yet established and standardized.[4–6]

Nevertheless, it could be damaging for the medical community and, indeed, for our patients, that researchers might feel free to evaluate and publish studies on any kind of treatment as long as adverse effects are minimal. The risk of such a paradigm shift is to open Pandora's box to studies whose aims are no longer to establish the therapeutic roles of new therapies, and potentially serve only to add more confusion to the field of localized prostate cancer treatment.

Department of Urology, Deaconesses-Croix St Simon Medical Center, 12–18 rue du Sergent Bauchat, 75102 Paris, France.
bguillonneau@hopital-dcss.org

Competing interests
The author declares no competing interests.

1. Ahmed, H. U. *et al.* Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. *Lancet Oncol.* **13**, 622–632 (2012).
2. Ahmed, H. U. *et al.* Focal therapy for localized prostate cancer: a phase I/II trial. *J. Urol.* **185**, 1246–1255 (2011).
3. Boutier, R. *et al.* Location of residual cancer after transrectal high-intensity focused ultrasound ablation for clinically localized prostate cancer. *BJU Int.* **108**, 1776–1781 (2011).
4. Blana, A. *et al.* Complete high-intensity focused ultrasound in prostate cancer: outcome from the @-Registry. *Prostate Cancer Prostatic Dis.* doi:10.1038/pcan.2012.10.
5. Sung, H. H. *et al.* Seven years of experience with high-intensity focused ultrasound for prostate cancer: advantages and limitations. *Prostate* http://dx.doi.org/10.1002/pros.22491.
6. Ripert, T. *et al.* Six years' experience with high-intensity focused ultrasonography for prostate cancer: oncological outcomes using the new 'Stuttgart' definition for biochemical failure. *BJU Int.* **107**, 1899–1905 (2011).

PROSTATE CANCER

New types of radiotherapy improve cancer outcome but at what cost?

Declan G. Murphy, Scott Williams and Matthew R. Cooperberg

New and very expensive forms of radiotherapy, such as intensity-modulated radiation therapy and proton therapy, have taken over the localized prostate cancer market. But is there enough evidence to justify their increased utilization and if so, how can we possibly afford them?

Murphy, D. G. *et al. Nat. Rev. Urol.* **9**, 415–417 (2012); published online 3 July 2012; doi:10.1038/nrurol.2012.137

The US Institute of Medicine has identified comparative effectiveness research into treatment options for localized prostate cancer as a high priority for the coming years,[1] which reflects concerns about the large numbers of men being diagnosed with

localized prostate cancer worldwide each year, the variety of management options available to these men, and the associated costs. Management options now include active surveillance, open surgery, minimally-invasive surgery, various forms of radiotherapy, and experimental approaches such as high-intensity focused ultrasonography and focal therapy. While there has been much focus on the costs associated with the widespread adoption of robot-assisted radical prostatectomy (RARP), increasing scrutiny is appropriately being directed at newer forms of radiotherapy with their associated, and sometimes staggering, costs.

A recently published study from Sheets *et al.*[2] is therefore welcome indeed. Using Surveillance, Epidemiology, and End Results data linked to Medicare administrative claims information, the authors identified patients with localized prostate cancer who underwent radiotherapy between 2000 and 2008 and compared the morbidity and oncological outcomes of intensity-modulated radiation therapy (IMRT), proton therapy and conformal radiation therapy (CRT). The subsequent identification of condition codes that were likely to be attributable to radiation therapy were used to estimate rates of postradiation gastrointestinal, urinary and erectile dysfunction, as well as hip fractures. Cancer outcomes were approximated using the rates of additional cancer therapy.

> “...proton therapy provides no advantage over IMRT and has considerably higher gastrointestinal toxicity”

The authors documented the extraordinarily rapid adoption of costly IMRT, which increased in market share from 0.15% to 95.9% between 2000 and 2008. Using propensity-score-adjusted analysis they demonstrated that when compared with CRT, patients undergoing IMRT were less likely to have gastrointestinal morbidity (RR 0.91; 95% CI 0.86–0.96) and to suffer hip fractures (RR 0.78; 95% CI 0.65–0.93) but more likely to experience erectile dysfunction (RR 1.12; 95% CI 1.03–1.20). Patients who underwent IMRT were also less likely to require additional cancer treatment (RR 0.81, 95% CI 0.73–0.89). These relative effects, although statistically significant owing to large sample sizes, might only equate to small absolute differences of unknown clinical relevance in the absence of patient-reported quality of life measures. For example, a rate of grade ≥2 rectal toxicity of 26% was identified in one high-dose CRT prospective trial,[3] but the analysis of Sheets *et al.*[2] suggests that this toxicity would fall by just 2.3% using IMRT.

The analysis also compared IMRT with proton therapy, which is even more expensive than IMRT, and found no benefits for proton therapy in terms of either cancer control or toxicity. In fact, IMRT was associated with substantially fewer gastrointestinal adverse events than proton therapy (RR 0.66; 95% CI 0.55–0.79).[2]

The strengths of this paper include its large, population-based cohort, adjustment for baseline comorbidity, and the inclusion of proton therapy for the first time in a direct comparison against the other major forms of prostate cancer radiotherapy. Limitations include those associated with the use of administrative datasets, particularly biases inherent to treatment selection, and the use of billing codes as proxies for validated questionnaires, which are more reliable measurements of functional outcomes such as erectile dysfunction. While the propensity score and instrumental variable techniques employed are able to control for most bias related to measured covariates, elimination of bias related to unmeasured confounders would only be possible through randomization. One such missing confounder is the use of image-guided radiation therapy. Hitting the intended target is crucial for all radiation therapy, for both cancer control and toxicity avoidance. By not taking this into account, the outcomes of CRT in this study might be confounded by poor target localization.

However, even within the acknowledged limitations of this observational population-based study, it is reasonable to make three main conclusions. First, that IMRT can provide superior cancer control to CRT. Second, that IMRT is associated with a lower rate of gastrointestinal toxicity but a higher incidence of erectile dysfunction when compared to CRT, and finally that proton therapy provides no advantage over IMRT and has considerably higher gastrointestinal toxicity. The superior cancer control of IMRT is unsurprising given that the impetus for this technology came from strong evidence that dose escalation led to considerably improved survival, though at the cost of increased morbidity.[4,5] Nevertheless, although it is reassuring to see that more-sophisticated delivery techniques


© George Muresan | dreamstime.com

are associated with reduced gastrointestinal and hip morbidity, it is disappointing to discover that those undergoing IMRT are more likely to be diagnosed with erectile dysfunction than those who receive CRT. This is presumably due to the higher dose delivered to the nearby neurovascular bundles.

The increased cost associated with the wholesale switch to IMRT was not considered in this paper, an issue that is now exacerbated by the growing use of proton therapy and other novel techniques, such as stereotactic radiation, for localized prostate cancer. Furthermore, although it is noteworthy that RARP has grown to occupy 61% of the radical prostatectomy market in the USA over the past decade without any level 1 evidence to demonstrate its superiority,[6] it is even more remarkable that IMRT has grown to occupy 96% of the external beam radiotherapy market without any similar evidence.

Nguyen *et al.*[7] reported that the cost of IMRT in 2005 was US$31,574 compared to $20,588 for CRT. Similarly, brachytherapy plus IMRT cost $36,795 compared to $26,006 for brachytherapy plus CRT.[7] The cost for minimally-invasive (robotic) prostatectomy was more modest at $16,762, which was less than $300 more than the cost of open surgery. Based on these 2005 figures and the 81% adoption of IMRT at that time, Nguyen *et al.*[7] calculated that the switch to IMRT had added $341 million in costs per annum to the cost associated with CRT. Extrapolation to 2012, in light of the 96% adoption of IMRT in 2008, would clearly add enormously to this figure. At a fundamental philosophical level, these data vindicate the calls for appropriate comparative

evaluation of new technology,[8] a notion that proton advocates have deemed, quite incredibly, unethical.[9]

Another concern is the reported increase in the number of urology practices in the USA that are investing in IMRT technology, and allegations that financial incentives are driving increased utilization.[10] The impact of adopting integrated practice models on practice patterns remains controversial. Regardless, what is clear is that a combination of factors is driving the costs of managing localized prostate cancer to unsustainable levels. These include an ageing population and increasing disease incidence; expensive surgical technology; expensive radiation technology; more emerging technologies; and underutilization of active surveillance as a management option.

There is no doubt that the costs of managing localized prostate cancer will become a major challenge for health-care systems in the coming decades, and that comparative effectiveness research must become a priority to help inform doctors, patients and funders about the most sustainable strategy to manage these challenges.

*Division of Cancer Surgery (**D. G. Murphy**), Division of Radiation Oncology (**S. Williams**), Peter MacCallum Cancer Centre, East Melbourne, VIC 3003, Australia. Department of Urology, UCSF Helen Diller Family Comprehensive Cancer Center, 1600 Divisadero Street, 3rd Floor, San Francisco, CA 94143-1695, USA (**M. R. Cooperberg**). Correspondence to: D. G. Murphy*
declan.murphy@petermac.org

Competing interests
The authors declare no competing interests.

1. Sox, H. & Greenfield, S. Initial National Priorities for Comparative Effectiveness Research. *Institute of Medicine of the National Academies* [online], http://www.iom.edu/Reports/2009/ComparativeEffectivenessResearchPriorities.aspx (2009).
2. 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).
3. Pollack, A. *et al.* Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int. J. Radiat. Oncol. Biol. Phys.* **53**, 1097–1105 (2002).
4. Dearnaley, D. P. *et al.* Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol.* **8**, 475–487 (2007).
5. Zietman, A. L. *et al.* Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95–09. *J. Clin. Oncol.* **28**, 1106–1111 (2010).
6. Trinh, Q. D. *et al.* Perioperative outcomes of robot-assisted radical prostatectomy compared with open radical prostatectomy: results from the nationwide inpatient sample. *Eur. Urol.* **61**, 679–685 (2012).
7. 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).
8. Zietman, A. L. The Titanic and the Iceberg: prostate proton therapy and health care economics. *J. Clin. Oncol.* **25**, 3565–3566 (2007).
9. Goitein, M. & Cox, J. D. Should randomized clinical trials be required for proton radiotherapy? *J. Clin. Oncol.* **26**, 175–176 (2008).
10. Carreyrou, J. & Tamman, M. A device to kill cancer, lift revenue. *Wall Street Journal* [online], http://online.wsj.com/article/SB10001424052748703904804575631222900534954.html (2010).