Title
A new look at prostate cancer treatment complications

Journal
Nature Reviews Clinical Oncology, 11(6)

ISSN
1759-4774

Author
Cooperberg, Matthew R

Publication Date
2014-06-01

DOI
10.1038/nrclinonc.2014.58

Peer reviewed

PROSTATE CANCER

A new look at prostate cancer treatment complications

Matthew R. Cooperberg

A recent population-based analysis from Nam and coauthors found high complication rates occurring within 5 years of prostatectomy or radiation therapy interventions for prostate cancer. These findings emphasize that treatments should be reserved for men at significant risk of disease progression, and perhaps further concentrated into higher-volume centres of excellence.

Cooperberg, M. R. *Nat. Rev. Clin. Oncol.* **11**, 304–305 (2014); published online 1 April 2014; doi:10.1038/nrclinonc.2014.58

The optimal approach for the management of localized prostate cancer remains the subject of much controversy that focuses primarily on questions of variations across treatments in terms of oncological efficacy and toxicity. A recent paper published by Nam *et al.*[1] presented an analysis of men undergoing open radical prostatectomy or radiotherapy in Ontario between 2002 and 2009.[1] This report was unique in its focus on longer-term—within 5 years—treatment-related complications aside from urinary incontinence and erectile dysfunction, domains that have been already exhaustively studied. The primary finding was the high rates of complications overall. Patients who underwent prostatectomy required more urinary interventions, whereas patients who received radiotherapy were hospitalized more frequently for complications, and required more anorectal procedures and open operations. Patients receiving radiotherapy also had more secondary malignancies.

An obvious major strength of this paper is its analysis of a population-based database. Canada's provincial single-payor system lends itself well to such analysis, and avoids some of the major limitations of US Medicare analyses (such as restriction to men >65 years of age and to those patients enrolled specifically in Medicare fee-for-service rather than managed care). Administrative claims data are better suited for the purposes of identifying short-term to intermediate-term complications than they are for determining quality-of-life outcomes, for which patient-reported outcomes are by far the more valid metrics.[2]

Key points

- Prostatectomy and radiation therapy are both associated with significant risks of complications requiring hospitalization and/or surgical intervention within the first 5 years after treatment
- Minimizing this burden of complications involves both avoiding overtreatment among men with low-risk disease, and concentrating treatment efforts in higher volume centres with demonstrable high-quality outcomes

The data source of the article by Nam *et al.*[1] is limited, however, in its external validity. The authors do not discuss the extent to which practices and outcomes in Ontario may differ from those in other provinces. Moreover, it is well-established that perioperative complications of prostatectomy vary inversely with hospital and surgeon case volume: higher volume surgeons cause fewer complications and their patients have less incontinence and require fewer procedures.[3] Information regarding these parameters of surgeon and/or hospital volume in the Ontario database would have been helpful. For a rough projection: the 15,870 cases of prostatectomy identified in the database over 8 years correspond to about 1,984 cases per year. Ontario's urological workforce has been estimated at 200 urologists;[4] the average volume of 9.9 prostatectomy procedures per urologist thus calculated compares well with the 7.1 procedures observed in a US population-based analysis.[5] Notably, the volume of radical prostatectomies is not distributed evenly, and it is quite likely that in Ontario (as in the USA), a relatively small number of urologists do a high volume of procedures while many do few procedures; in the US analysis, the median prostatectomy volume was only three.[5]

Similar analyses of men undergoing brachytherapy found that those patients treated by higher volume practitioners have better oncological outcomes, but not necessarily lower toxicity.[6] Few data exist regarding the volume–outcomes relationship related to external-beam radiotherapy (EBRT). In any case, the lack of distinction between EBRT and brachytherapy in the Nam *et al.*[1] study is an acknowledged limitation, as these treatments are associated with somewhat divergent patterns of complications.

> "An obvious major strength of this paper is its analysis of a population-based database"

The paper analysed only open radical prostatectomy, as laparoscopic prostatectomy, with or without robot assistance, was uncommon in Ontario during the study period (2002–2009).[1] By contrast, by the end of this period in the USA, these approaches accounted for nearly half of cases.[2] This rapid evolution in practice patterns may limit the applicability of the findings from Nam *et al.*[1] for US practice. Although oncological outcomes between open and robot-assisted radical prostatectomy seem to be essentially comparable,[7] the impact of the surgical approach on quality of life—specifically urinary and sexual function—is more controversial, and the results of analyses depend heavily on how assessments were performed, when, and among which patients. On the one hand, the preponderance of evidence on this question suggests that for these

outcomes the approach and technology are less important than the skill and experience of the surgeon.[8] On the other hand, there seems to be little question that robot-assisted prostatectomy is associated with fewer short-term complications than open radical prostatectomy, including at least a 50% relative reduction in perioperative mortality, and significant improvements in multiple other categories.[2,7]

> “...the simple truth is that high-volume providers achieve better outcomes”

The differences in rates of secondary malignancy are striking. However, the fact that the differences in rates are at least as great for out-of-field malignancies (such as lung cancer) as for in-field pelvic malignancies suggests that this observation may be confounded by greater age, comorbidity, and adverse environmental and/or lifestyle factors among the group treated with radiotherapy. On a more general note, Nam *et al.*[1] began with the premise that there are no survival differences following surgery or radiation. In point of fact, a growing body of literature indicates that radical prostatectomy is associated with improved risk-adjusted cancer-specific and overall-mortality compared with EBRT, and that the greatest benefits are observed in men with higher-risk tumours.[9]

Perhaps the most important message of the paper by Nam *et al.*[1] is that all prostate cancer treatments are associated with risks of complications, and that men should be exposed to these risks only if they are likely to obtain a survival benefit from treatment. In the setting of early detection efforts, nearly half of newly diagnosed prostate cancers are characterized as having a low risk of progression. For many of the men with these tumours, early intervention does not affect oncological outcomes, and a growing consensus supports active surveillance rather than immediate treatment for men with these low-risk tumours, as a strategy to defer or avoid the potential risks of radical prostatectomy, radiotherapy, and other treatments.[10]

Nam *et al.*[1] suggest that their population-based complication rates are ‘more accurate’ than the lower rates reported from centres of excellence. This is not really a fair statement; the simple truth is that high-volume providers achieve better outcomes. This concept is an important one, as summary statements regarding prostate cancer management and decision aids based on such statements routinely report only the population-based results, ignoring a large body of evidence indicating what is achievable in high-volume settings. In truth, both cohort reports and population-based analyses must be considered in making overall assessments of prostate cancer treatment outcomes.

Ultimately, however, the best way to track prostate cancer treatment outcomes is not through delayed retrospective analysis of administrative claims, but rather through prospective collection of clinical and patient-reported data through a disease registry, with near-real time feedback to providers on their own performance. The American Urological Association (AUA) has recently announced the launch of exactly such a registry for the US, the AUA Quality (AQUA) registry (www.auanet.org/aqua), which is expected to yield high-quality data on practice patterns and outcomes to drive the next generation of prostate cancer research.

Departments of Urology and Epidemiology and Biostatistics, University of California, 1600 Divisadero Street, San Francisco, CA 94143-1695, USA.
mcooperberg@urology.ucsf.edu

Competing interests
The author declares no competing interests.

1. Nam, R. K, *et al.* Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. *Lancet Oncol.* **15**, 223–231 (2014).
2. Sonn, G. *et al.* Differing perceptions of quality of life in patients with prostate cancer and their doctors. *J. Urol.* **182**, 2296–2302 (2009).
3. Begg, C. *et al.* Variations in morbidity after radical prostatectomy. *N. Engl. J. Med.* **346**, 1138–1144 (2002).
4. Pace, K. T., Provan, J. L. & Jewett, M. A. The urology work force in Ontario for the 21st century: feast or famine? *Can. J. Surg.* **42**, 181–189 (1999).
5. Savage, C. J. & Vickers, A. J. Low annual caseloads of United States surgeons conducting radical prostatectomy. *J. Urol.* **182**, 2677–2679 (2009).
6. Chen, A. B., D'Amico, A. V., Neville, B. A., Steyerberg, E. W. & Earle, C. C. Provider case volume and outcomes following prostate brachytherapy. *J. Urol.* **181**, 113–118 (2009).
7. 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.* **62**, 1–15 (2012).
8. 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).
9. Cooperberg, M. R., Vickers, A. J., Broering, J. M. & Carroll, P. R. Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. *Cancer* **116**, 5226–5234 (2010).
10. Ganz, P. A. *et al.* National Institutes of Health State-of-the-Science Conference: role of active surveillance in the management of men with localized prostate cancer. *Ann. Intern. Med.* **156**, 591–595 (2012).

PROSTATE CANCER

Muddying the waters by overlooking treatment modality

Ronald D. Ennis and S. Aidan Quinn

Although large, population-based studies are a powerful tool for elucidating real-world outcomes and uncommon events, confounding factors must be tightly controlled. A recent report from Nam and coauthors has neglected such a confounding factor and, therefore, stands in need of further study to clarify the findings.

Ennis, R. D. & Quinn, S. A. *Nat. Rev. Clin. Oncol.* **11**, 305–307 (2014); published online 1 April 2014; doi:10.1038/nrclinonc.2014.52

Patients with prostate cancer often choose between various forms of radiotherapy and radical prostatectomy in situations in which cancer control outcomes after these treatments are similar. As a result, complication risks often have a significant role in patients' decision making. To date, complication analyses have focused largely on incontinence, impotence and, to a lesser extent, second malignancies after radiotherapy. Although it has been known that some patients require invasive urological and anorectal procedures as well as hospitalizations after treatment as a result of complications, these problems have not been previously well quantified.