

Revisiting the role of radical surgery in early stage prostate cancer

Is it time to walk the line between overtreating indolent disease and undertreating aggressive disease?

Few other health care issues in Australia have been as contentious as the diagnosis and treatment of early prostate cancer. Debate centres on two hotly contested but important issues: do prostate cancers diagnosed by an elevated serum prostate-specific antigen (PSA) level pose a significant threat to health, and if they do, can intervention alter the natural history of the disease? In this editorial, we consider the contribution that two recently published studies make to this debate, with a focus on survival and the role of surgical management.

Study one: In the first study, Albertsen and colleagues presented an update of a retrospective cohort study first published in 1998.¹ They estimated 20-year survival after clinically localised prostate cancer was treated without curative intent in 767 men diagnosed with this condition between 1971 and 1984. After a median of 24 years, the men's current vital status was obtained and the contribution of prostate cancer to any subsequent mortality was determined by examining death certificates. Survival was assessed on a competing risk analysis, and stratified for age and tumour differentiation. The primary finding was that the risk of death from localised prostate cancer did not increase significantly with time from diagnosis — leading the authors to suggest that aggressive management of localised prostate cancer is perhaps unnecessary. The study also found that prostate cancer graded as Gleason sum 7 and above (moderately to poorly differentiated) is lethal.

These results can directly inform our current debate only if the population studied is comparable to contemporary patients, and as these men were diagnosed in the pre-PSA era, there are major differences in this regard. Of the men in the cohort, 71% were diagnosed on the basis of surgical intervention for benign prostatic hyperplasia, either by transurethral resection of the gland or open prostatectomy. Both of these procedures sample the transition zone exclusively, where less than 25% of all prostate cancers originate. A relatively high proportion of these T1 tumours are true “transitional zone tumours”, which are well recognised to be smaller in volume and better differentiated, and to run a more indolent biological course. This is reflected in the finding that 33% of the cohort had cancers with Gleason sums of between 2 and 5 — well differentiated tumours. In contrast, significant or lethal prostate cancer with high Gleason sums is found predominantly in the posterolateral part of the prostate, the peripheral zone. Prostate cancer diagnosed after a finding of an elevated PSA level with sampling of the peripheral zone shows cancer with a Gleason sum of less than 6 in less than 5% of cases, with most cancer detected by PSA testing scoring 6 or 7 (moderately differentiated). Thus, this study cohort contained a high number of clinically insignificant prostate tumours that would be less likely to be diagnosed by needle biopsy.

Any comparison with contemporary prostate cancer series detected by PSA testing is also confounded by the late age of diagnosis (median, 69 years) and the high rate of significant comorbidity in this cohort. Further, 42% of patients with clinically localised disease received some form of androgen deprivation

therapy within 6 months of diagnosis (which was presumably continued until death), despite there being no evidence of disease progression. It is now becoming increasingly appreciated that hormonal therapy creates a disease in itself, which can contribute significantly to mortality from other causes (particularly cardiovascular mortality from diethylstilboestrol).²

Despite its differences from more contemporary studies, the study by Albertsen and colleagues does offer striking insights into the biology of conservatively treated prostate cancer. Clearly, cancers graded Gleason 7 and above are lethal when managed conservatively, even in a population of sick elderly men. Conversely, at least up to 15 years of follow-up, cancers graded Gleason 2 to 5 run an indolent course, which suggests that in elderly and medically compromised men, a more conservative course can be followed. However, data from another series which is less contaminated with transition zone tumours suggested that low grade tumours can dedifferentiate and metastasise, which has particular relevance to men diagnosed at a younger age.³

Study two: In the second study under consideration, Bill-Axelsson and colleagues directly addressed the second point of contention — can intervention alter the natural history of prostate cancer?⁴ Again, this was an updated analysis of a previously reported study. It was an elegant study premised on a beguilingly simple hypothesis that:

- by removing prostate cancer that is confined to the gland via radical prostatectomy, metastases can be prevented;
- by preventing metastases, death from prostate cancer can be reduced; and
- by reducing death from prostate cancer, overall survival is improved.

Radical prostatectomy is the surgical removal of the prostate and seminal vesicles by dividing the prostate at the bladder neck and urethra, and suturing a vesicourethral anastomosis over the catheter. It has been performed by open abdominal surgery and, more recently, by a minimally invasive laparoscopic or robotic approach. In Bill-Axelsson and colleagues' randomised controlled trial, 695 men with clinically localised prostate cancer were allocated to either radical prostatectomy or “watchful waiting”. In both groups, hormonal therapy (medical or surgical castration) could be introduced at the discretion of the treating physician. Mean age at diagnosis was 64 years, and mean serum PSA level at diagnosis was 13 ng/mL. Median follow-up was 8.2 years.

Importantly, this study is more representative of the era in which PSA testing is used to detect prostate cancer. Diagnosis was by contemporary sextant, ultrasound-guided needle biopsy of the peripheral zone, and only 11% of diagnoses were at transurethral resection of prostate, although a higher proportion had palpable disease than a modern series might. In this study, 77% of cancers were T2 (organ-confined) prostate cancers. In contrast to the Albertsen study, 77% of tumours were graded Gleason 5 to 7, and only 13% were graded Gleason 2 to 4. Nearly half (48%) of Bill-Axelsson and colleagues' cohort had a PSA level greater than 10 ng/mL at

diagnosis. In all, this cohort of patients represents a somewhat more advanced disease group than would be representative in Australia in 2005 (where PSA testing is now more prevalent, and more cancer is being discovered in the 4–10 ng/mL PSA range).

Nonetheless, the results presented by Bill-Axelson and colleagues are instructive, underscoring the biological truth of the study hypothesis. In men treated with surgical intervention, the incidence of metastatic disease and risk of death from prostate cancer was significantly reduced compared with those who were managed by watchful waiting. This led to a significant reduction in all-cause mortality, providing evidence for the first time that radical intervention for localised prostate cancer can deliver a real health benefit.

This health benefit was highest in men younger than 65 years of age, with 19% of watchful-waiting patients compared with 8% of patients treated with surgery dying from prostate cancer at 10 years. Although the study authors remained cautious, suggesting further research needs to be done before introducing an immediate change in clinical practice, their results were impressive in terms of metastatic rate (14% in the surgery group versus 23% in the watchful-waiting group) and local progression of prostate cancer (64 in the surgery group versus 149 in the watchful-waiting group, showing a 25% risk reduction in local progression in the surgery group at 10 years). Further, 177 of the patients in the watchful-waiting arm versus 110 in the surgery arm received hormone therapy, with a median time to hormone therapy treatment of 4 years.

So, now that Bill-Axelson and colleagues have shown in a randomised controlled trial that surgery for prostate cancer saves lives, do we have all the answers? Would that this were so. These data are extremely important in guiding men about the relevance of PSA testing, the risk of death and risk of metastatic and local progression from untreated histologically significant prostate cancer. However, the injudicious application of prostate testing has opened a Pandora's box. We have seen an explosion in diagnosis of potentially insignificant non-life-threatening prostate cancer. There is now a strong push in the United States to have the PSA cutpoint for prostate cancer biopsy lowered from 4 ng/mL to 2.5 ng/mL or even lower.⁵ Some suggest all men have a prostate biopsy at the age of 50 years.

The PSA test is good, but not great. It doesn't help us differentiate between the indolent and dangerous prostate cancer. Gleason histology grading does help as a differentiator. But what is the cost-benefit balance of making a diagnosis of indolent microfocal Gleason 6 prostate cancer in a 78-year-old man with a PSA level of 6 ng/mL? We can take comfort in the proven knowledge that surgery is indicated for younger men with at least 15 years of life expectancy. However, a more judicious approach in managing older men with comorbidities will be needed. Countering this, newer technical developments in prostate cancer surgery, including laparoscopic and robotic radical prostatectomy, will further improve outcomes for men by reducing the morbidity of the operation and improving cancer control.⁶⁻⁸

Perhaps the next big question (and answer) in prostate cancer surgery has been articulated by Klotz.⁹ They are conducting a program of active surveillance with regular PSA testing and repeat biopsy, with surgical intervention with curative intent if there is cancer progression, in men with defined low-risk prostate cancer. This approach may help us to reduce unnecessary treatment in men at low-risk of disease progression. Eventually, an improved

molecular understanding of the biology of these cancers will help us to predict precisely long-term outcomes in patients with prostate cancer and, thus, to decide on the most appropriate management for each individual patient.

Anthony J Costello

Head, Department of Urology, The Royal Melbourne Hospital; and Professor, University of Melbourne Division of Surgery

Niall M Corcoran

Senior Research Fellow

Scott Van Appledorn

Senior Clinical Fellow
Department of Urology, The Royal Melbourne Hospital
Melbourne, VIC

- 1 Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localised prostate cancer. *JAMA* 2005; 293: 2095-2101.
- 2 Higano CS. Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. *Urology* 2003; 61 (2 Suppl 1): 32-38.
- 3 Johansson JE, Andren O, Andersson SO, et al. Natural history of early, localised prostate cancer. *JAMA* 2004; 291: 2713-2719.
- 4 Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2005; 352: 1977-1984.
- 5 Catalona WJ, Bartsch G, Rittenhouse HG, et al. Serum pro-prostate specific antigen preferentially detects aggressive prostate cancers in men with 2 to 4 ng/ml prostate specific antigen. *J Urol* 2004; 171: 2239-2244.
- 6 Guillonnet B, Cathelineau X, Doublet JD, et al. Laparoscopic radical prostatectomy: assessment after 550 procedures. *Crit Rev Oncol Hematol* 2002; 43: 123-133.
- 7 Tewari A, Srivasatava A, Menon M, et al. A comparison of radical retropubic and robot-assisted prostatectomy: experience in one institution. *BJU Int* 2003; 92: 205.
- 8 Herrell SD, Smith JA Jr. Laparoscopic and robotic radical prostatectomy: what are the real advantages? *BJU Int* 2005; 95: 3-4.
- 9 Klotz L. Active surveillance with selective delayed intervention: using natural history to guide treatment in good risk prostate cancer. *J Urol* 2004; 172: S48-S51. □

MJA
CHRISTMAS
COMPETITION

TIME IS RUNNING OUT!
Let our readers share the experience of your unusual and humorous medical stories. Send us your strange images, quirky quips and gory stories. Anything from prose to cartoons. You can win great prizes AND be published in the MJA, Australia's premier medical journal.

Entries close 10 October 2005.

For full submission details visit:
<http://www.mja.com.au/public/information/instruc.html>
or contact our Editorial Administrator:
Phone: 02 9562 6666 Email: medjaust@ampco.com.au
OR visit last year's entries at:
www.mja.com.au/public/issues/181_11_061204/contents_061204.html