

# Surgery Versus Radiation for High-risk Prostate Cancer: The Fight Continues. But Is It Time To Call a Draw and Reach Consensus?

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Management of high-risk prostate cancer (PC) is one of the most contentious issues that urologists face. Level 1 evidence shows that adding external beam radiotherapy (EBRT) to androgen deprivation therapy (ADT) improves survival outcomes in high-risk and locally advanced PC [1]. The only randomized trial examining surgery in this setting, SPCG-15 ([www.spcginfo.org](http://www.spcginfo.org)), will not report for another 10 yr, so urologists can either refer patients with high-risk PC for radiotherapy (RT) plus ADT or consider an unproven treatment like radical prostatectomy (RP). Lack of evidence for a benefit is not evidence of a lack of benefit, however, and a survey found that 60% of European urologists preferred RP as the initial treatment for high-risk PC, with only 29% preferring EBRT + ADT [2]. Furthermore, the UK National Prostate Cancer Audit showed that approximately 20% of all men with locally advanced PC underwent RP ([www.npca.org.uk](http://www.npca.org.uk)), and the British Association of Urological Surgeons RP national audit found that more than 1800 men per annum in the UK are having surgery for high-risk PC, making up roughly one-quarter of all RP cases (Aning et al., manuscript accepted for *BJU International*). The EMPaCT international study group of high-volume RP centers across Europe and the USA has also operated on more than 5000 men with high-risk PC with excellent survival outcomes, albeit not in a comparative study [3].

It is thus important for the urology community to understand the comparative effectiveness of standard-of-care RT approaches versus RP, specifically for men with high-risk PC. A study using a large, national, population-based database

from Sweden (PCBaSe) examined survival outcomes (PC and other-cause mortality) among 34 515 men with PC treated with RP or RT [4]. Among men with high-risk PC, RT was associated with significantly higher crude PC mortality than RP (propensity score hazard ratio [HR] 1.50, 95% confidence interval [CI] 1.19–1.88; adjusted HR 1.63, 95% CI 1.28–2.06). Although a later study demonstrated that these results were unlikely as a result of comorbidity differences between RP and RT patients [5], a remaining criticism was that the RT was suboptimal in relation to current standards.

In this issue of *European Urology*, Berg and colleagues [6] provide data from the National Cancer Data Base (NCDB), a tumor registry jointly managed by the American Cancer Society and American College of Surgeons. Among 13 985 men aged  $\leq 65$  yr with high-risk PC followed for a median of 92 mo, 88% ( $n = 12\ 283$ ) underwent RP while 12% ( $n = 1702$ ) received EBRT plus brachytherapy (BT). In this study, RP for young and healthy men was associated with an overall survival benefit ( $p < 0.008$ ) when compared with EBRT + BT. These data are thus highly welcome in contributing to the evidence base for the comparative effectiveness of RP versus RT in high-risk PC.

Nonetheless, we suggest caution in using these data to advocate RP for men with high-risk PC. The overall survival rates were very high in both groups, with small absolute differences (a few percentage points) between treatments. The RT doses used are not reported and may have been suboptimal in some centers, as the study included community practices. Lack of optimal care for the RT arm is also likely, as only 69% received ADT, meaning that nearly

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one-third of patients did not receive proven radiosensitizing systemic care. Interestingly, 15% of men in the surgical arm also received ADT, and we do not know what proportion also received adjuvant or salvage RT. Despite inverse probability of treatment weights to adjust for known confounders, unknown confounding can never be eliminated; thus, differences in the intrinsic fitness or frailty of RP versus RT candidates not captured by crude scores such as the Charlson comorbidity index could account for the small absolute survival differences. Confounding by indication is also likely because of differences in the size of the assigned cohorts, with nearly 90% of cases receiving RP. Furthermore, the NCDB does not record cause of death, and thus competing causes of mortality cannot be accounted for. We also do not know the rates of second malignancies in the groups, which is an important consideration in treating young men. In a population-based Canadian study, Nam and colleagues [7] showed that the risk of developing a second malignancy 5–9 yr post-treatment was 113 per 100 000 person-years in the RP group and 309 per 100 000 person-years in the radiation group. Here again, questions remain because patients receiving RP may not be an appropriate control group for comparison to those receiving RT, as they have a lower standardized mortality ratio for second malignancies than the general population [8]. Thus, prospective randomized cohorts must be used to address the question of excess risk of second malignancy from RT, and based on these, the excess risk appears low [9].

While the study by Berg et al. [6] has the aforementioned limitations, they have demonstrated that men with high-risk PC who undergo surgery fare well. It is likely that given the wealth of observational data now available, including this study, that if there are differences between the two treatment options they are likely to be small ( $\leq 3\%$  as suggested by this study). What is now required is quality-of-life studies so that men presenting with high-risk PC can be adequately counseled as to which approach is likely to cause least detriment to their functional status, assuming equivalent or near-equivalent cancer control. With advances in surgical and radiation techniques, such as Retzius-sparing robotic RP and stereotactic body radiation, these data become even more important to elicit.

The time has come for urologists and oncologists to reach a consensus. Clearly, patients who are young, fit, and

motivated to undergo RP should indeed be given that option. But these men should understand that they are selecting an invasive procedure with a side-effect profile and a risk of complications, and that they may require RT  $\pm$  ADT afterwards. For men who wish to have upfront RT + ADT, the urology community should support that as evidence-based practice and not “oversell” the surgery option. Finally, the urology and oncology communities should come together to perform quality-of-life studies to assess the real impacts of these treatments on the men we are aligned to help.

**Conflicts of interest:** The authors have nothing to disclose.

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