Radical Prostatectomy versus Radiation Therapy:
Can Pretreatment Nomograms Be Used to Select the Appropriate Prostate Cancer Treatment?

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At the time of prostate cancer diagnosis, men who require treatment are often faced with a dilemma: radical prostatectomy (RP) or radiation via external beam radiation therapy (EBRT) or brachytherapy. Each treatment represents an acceptable method for localized prostate cancer, so preoperative nomograms are often used to predict biochemical recurrence (BCR)-free survival for each treatment modality and to aid in treatment selection [1–3]. However, because these nomograms often predict unequivocal BCR-free survival between treatments, there is a temptation to select a given treatment according to the highest predicted rate of BCR-free survival. However, as the definitions of BCR differ across the various treatments, the ability of these nomograms to appropriately correlate BCR with the more important endpoint of prostate cancer–specific mortality (PCSM) among different treatments remains unclear.

In an observational study by Lee et al published in this issue of European Urology, the authors examined a large group of men who underwent RP (n = 8308), EBRT (n = 2839), or brachytherapy (n = 2656) to compare outcomes among the three treatments [4]. Men were treated at one of two large academic practices within the USA between 1995 and 2008. For each patient, the risk of BCR was calculated using a pretreatment nomogram [1–3]. Men were then stratified into four risk groups according to their nomogram-calculated 5-yr BCR progression-free probability (PFP; <25%, 26–50%, 51–75%, and >75%) [1–3]. Within each PFP category, outcomes were compared among the three treatment approaches. Multivariate competing-risk analysis was also used to compare PCSM risk by treatment after adjusting for nomogram-predicted 5-yr PFP.

There were two key findings from this study. (1) Even after adjusting for the higher risk of BCR, men treated with EBRT had a higher risk of PCSM. Specifically, after accounting for the fact that men treated with EBRT had worse disease at baseline, the risk of PCSM was 50% higher compared to men treated with RP (p = 0.006). (2) Brachytherapy was associated the same risk of PCSM as RP.

For men treated with brachytherapy, 95% had a calculated PFP >75%, which was similar to the RP arm, with PFP >75% for 85% of cases. Thus, the risk of PCSM was low in these men. These data indicate that for low-risk men with >75% PFP as predicted by the nomogram, both RP and brachytherapy are associated with comparable PCSM risk. These analyses were underpowered for assessing the true comparative effectiveness of brachytherapy in the other risk groups, and therefore the study does not address the utility of brachytherapy when PFP <75%.

For EBRT the data are consistent with multiple other reports showing that even after adjusting for disease severity, the risk of PCSM is higher in men treated with EBRT (± androgen deprivation therapy [ADT]) versus RP (± EBRT) [5]. Although one study found no difference in survival by treatment type [6], the majority of the literature, albeit from non-randomized studies, suggests that RP is a better cancer treatment than EBRT. However, simply because
most of the literature suggests that RP is better does not make it better.

First, it is reasonable to assume that some patients in the RP population would have received either adjuvant or salvage radiation therapy [7], which can lower PCSM risk, but these details are not provided. If such is the case, a better conclusion might be that RP plus EBRT is better than EBRT alone. Second, although RP techniques did not change dramatically over the reported time period, randomized evidence has shown improved biochemical control with higher radiation doses [8], and improved survival for neoadjuvant/concurrent ADT for intermediate-risk [9,10] and high-risk prostate cancer [11]. Therefore, the inclusion of patients who did not receive current standard treatments (18% of the high-risk EBRT patients and up to 56% of the intermediate-risk EBRT patients) may have driven the higher PCSM rates in the EBRT population. Finally, patients were matched based on PFP risk using nomograms to predict BCR. However, because definitions of BCR after surgery and radiation vary, it is not clear that they are comparable. Therefore, the clear differences in case mix between the two groups may not have been appropriately adjusted for.

Given all of these caveats, the results must be interpreted with caution. However, what if, just for a minute, we accept that RP is indeed superior to EBRT. Among treated men who had a 5-yr PFP >75% (85% of RP patients and 56% of EBRT), the 10-yr risk of PCSM for RP (the “better” treatment) was 0.9%. Thus, on an adjusted basis, it would be 1.35% (1.5 times the RP rate) for EBRT. Thus, PCSM is increased by an absolute 0.45%. In other words, for every 1000 men who receive EBRT, four or five will die because of inferior treatment at 10 yr. By contrast, 995–996 of 1000 will be spared the side effects of EBRT (although they will be exposed to EBRT side effect). In short, for the vast majority of men, the impact of a 50% relative increase in PCSM (if real) is likely dwarfed by the impact of the treatment on their quality of life, with some men more willing to accept the side effects of one treatment over another.

However, for higher-risk men, the impact of a 50% increase in PCSM (if real) could be quite large. It should be noted that for high-risk men who are surgical candidates, if the question is RP versus EBRT, the literature is increasingly clear in suggesting that RP (± EBRT) may be better than EBRT alone. However, this is not the right question. Rather, the question should be “What is the best combination of treatments?” Indeed, according to studies like the one by Lee et al, there is increasing interest in the role of more aggressive multimodal therapy for men with high-risk prostate cancer. For example, the data reported by Lee et al show that >20% of men in the highest-risk group died from prostate cancer at 10 yr despite the commonly used treatments of RP (± EBRT) or EBRT (± ADT). Thus, for these men, it is clear that the current combination therapies including either EBRT or RP alone are not good enough. These men stand the most to benefit from novel approaches. This could include RP as the first step in a multimodal therapy approach. Alternatively, it could include intensified radiation that includes brachytherapy and EBRT + ADT. Furthermore, improvements may be seen for novel hormonal therapies or cytotoxins to enhance EBRT or RP. In summary, the work by Lee et al joins a growing list of studies that suggest that we have a lot more work to do for high-risk patients.

Conflicts of interest: The authors have nothing to declare.

References