Editor’s Choice

Is there a role for pure clinical prediction models in prostate cancer in the contemporary era?

The identification of men with localised prostate cancer at higher risk of adverse pathological outcomes after radical prostatectomy (RP) would assist physicians in preoperative patient counselling and in tailoring the most appropriate treatment strategy. In this issue of the BJUI, Tosoian et al. [1] have updated the Partin Tables in contemporary patients with localised prostate cancer. The authors should be commended for undertaking a well-performed study evaluating a large cohort of patients treated at a high-volume centre. Notably, they were able to show that the Partin Tables still represent an accurate tool for identifying men at higher risk of adverse pathological features [1]. Having said this, the first question we should ask ourselves is whether preoperative models based on clinical variables only still play a role in contemporary patients. The Partin Tables were developed in 1993 and since then they have undergone a series of updates, all of which are based on virtually the same variables included in the original analyses [1]. However, recent implementations, including biomarkers and imaging, have been introduced to better stage prostate cancer. These novel approaches are usually added to clinical variables to improve patient risk stratification. Multi-parametric MRI (mp-MRI) represents the major game changer in this setting, being now recommended for prostate cancer staging in all men with high-risk disease and in those with less favourable intermediate-risk prostate cancer [2]. In the era of modern and sophisticated approaches, are models using clinical variables only still clinically valuable? To answer this question, we can consider two major settings, namely nodal and local staging.

When assessing the risk of lymph node invasion (LNI) at diagnosis, mp-MRI and positron emission tomography/CT scan are characterised by a low sensitivity and, therefore, are not recommended for the identification of patients who should receive a lymph node dissection (LND) [2,3]. Conversely, the updated Partin Tables depicted a remarkably high accuracy (>90%) in predicting LNI. This supports what is currently recommended by virtually all guidelines, which indicate that candidates for extended LND (eLND) should still be identified according to a combination of clinical variables only. However, although the Partin Tables might assist clinicians in identifying patients more likely to harbour LNI, the lack of the uniform adoption of an eLND template might have resulted in a substantial under-estimation of the real LNI risk [4]. Other tools specifically developed to predict LNI among men treated with eLND could better assist clinicians in identifying men who should receive an eLND [2,5].

Similarly, when considering local staging, mp-MRI is characterised by a high specificity but a relatively low sensitivity in detecting small, microscopic foci of extracapsular extension and seminal vesicle invasion (SVI) [6]. Conversely, the updated Partin Tables depicted a predictive accuracy of >80% in predicting SVI, despite the lack of individualised data on the extent and volume of extraprostatic extension. For all these reasons, clinical risk models still represent the cornerstone for the identification of men at higher risk of adverse pathological findings. Additional data coming from sophisticated imaging modalities may further improve individualised risk predictions [6] and better assist clinicians in tailoring the most appropriate treatment approach. However, imaging and biomarkers should complement, rather than substitute, currently available clinical risk models.

In conclusion, preoperative predictive tools based on clinical parameters still play an important role in the management of patients with clinically localised prostate cancer. Any staging model including additional approaches, such as imaging and/or biomarkers, is welcomed only when it is shown to improve prostate cancer staging in terms of both accuracy and cost-effectiveness.

Conflicts of Interest
None.

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References
Between 1960 and 1975, the Veterans Association Cooperative Urological Research Group (VACURG) conducted a series of large randomized trials to test several oestrogenic compounds in varying doses and combinations with regard to their efficacy and safety in the treatment of all stages of prostate cancer [1]. The major message conveyed by these trials was the significant cardiovascular morbidity and mortality associated with 5 mg of oral diethylstilbestrol and the adverse impact on overall survival. Much less attention was given to the cancer-specific survival in the oestrogen arms of the study, which prompted the trial statistician to attribute the favourable effect of oestrogen to testosterone-lowering as well as to a direct cytotoxic effect. One half-century later clinical trial investigators in the UK are reevaluating the therapeutic utility of oestrogen delivered via a transdermal rather than an oral route to address and rebalance the risk–benefit equation?

Oestrogen redux: will transdermal delivery rebalance the risk–benefit equation?

Between 1960 and 1975, the Veterans Association Cooperative Urological Research Group (VACURG) conducted a series of large randomized trials to test several oestrogenic compounds in varying doses and combinations with regard to their efficacy and safety in the treatment of all stages of prostate cancer [1]. The major message conveyed by these trials was the significant cardiovascular morbidity and mortality associated with 5 mg of oral diethylstilbestrol and the adverse impact on overall survival. Much less attention was given to the cancer-specific survival in the oestrogen arms of the study, which prompted the trial statistician to attribute the favourable effect of oestrogen to testosterone-lowering as well as to a direct cytotoxic effect. One half-century later clinical trial investigators in the UK are reevaluating the therapeutic utility of oestrogen delivered via a transdermal rather than an oral route to address and challenge some of the major conclusions of VACURG. The PATCH (Prostate Adenocarcinoma: TransCutaneous Hormone, MRC, PR 09) trial is an ongoing randomized trial comparing transdermal oestrogen with LHRHa analogues in men with advanced prostate cancer. Among the critical endpoints will be overall survival, cancer-specific survival, PSA progression and quality of life. Castrate levels of testosterone have been achieved more rapidly in the transdermal oestrogen arm, there is no testosterone flare, and dose escalation may further improve on the 92–93% of patients reaching castrate levels of testosterone. Trial data published thus far have shown that transdermal oestrogen has a significant advantage with regard to maintaining bone health [2].

In the present issue of BJU, Gilbert et al. [3] address quality-of-life outcomes for 700 patients, representing > 80% of the study cohort, who submitted pre-treatment and 6-month post-treatment questionnaires. For all ages, 6-month global quality of life declined in both arms, but to a statistically lesser extent in the transdermal oestrogen arm compared with the LHRHa arm. There was also a statistically lesser decline in physical function and fatigue and sexual interest with transdermal oestrogen. Sexual interest decline was more pronounced for men aged < 70 years. As expected, hot flashes were significantly lower with transdermal oestrogen and were responsible, along with associated sleep disturbances, for a significant component of the quality-of-life decline in the LHRHa arm. Also, as expected, gynecomastia was more frequent with transdermal oestrogen but was associated with a decline in quality of life only in a small minority (8%) of patients who reported ‘very much’ gynecomastia. Only two patients underwent surgery for gynecomastia. For the small percentage of men for whom gynecomastia/dynia is problematic, more frequent employment of subcutaneous mastectomy could be of benefit. The acceptance of gynecomastia is likely to be quite different between cultures and countries.

The finding that sexual interest was improved in the transdermal oestrogen arm compared with the LHRHa arm. It is beneficial to be only monohormone-deprived (testosterone) rather than dual-hormone-deprived (testosterone and oestrogen). Additional benefits associated with oestrogen in the male have been reviewed by Wibowo et al. [5].

The previously reported bone health advantage and the current quality-of-life data would appear quite convincing in favour of transdermal oestrogen as a preferred or at least an alternate option for androgen deprivation therapy; however, the association of oestrogen with cardiovascular toxicity has