Editorial

Affordable and underutilized: the paradox of surgical castration

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Comment on: Paul CJ, Garje R, Kreder KJ, *et al.* Significant financial differences of chemical and surgical androgen deprivation in a contemporary cohort. Transl Androl Urol 2022;11:1252-61.

Keywords: Prostate cancer; androgen deprivation therapy; surgical castration

Submitted Oct 20, 2022. Accepted for publication Dec 05, 2022.
doi: 10.21037/tau-22-696
View this article at: https://dx.doi.org/10.21037/tau-22-696

Surgical castration is an established effective and cost-efficient treatment modality for hormone sensitive metastatic prostate cancer (mPCa). The vast majority of these patients, however, are treated with medical androgen deprivation therapy. In this article, we revisit the main points skewing real world prescription patterns towards medical androgen deprivation therapy and discuss the pertinence of surgical castration in current practice.

With the rapid developments in treatment algorithms for mPCa, adequate androgen deprivation therapy (ADT) remains the primary modality of choice for disease control. This can be achieved either via medical treatments such as luteinizing hormone releasing hormone (LHRH) agonists and antagonists, or surgical castration with simple bilateral orchidectomy. The recent article by Paul *et al.* refreshed the enduring debate between these two treatment options for mPCa (1). The article highlighted the cost-effectiveness of surgical castration, yet ironically, there were drastically fewer patients recruited in the surgical arm compared to medical therapy, which reflects the real-world patterns favoring the latter. In this review, we revisit the roles of these two treatment modalities in the management of mPCa.

The comparison between medical deprivation therapy and surgical castration should be discussed in a hierarchical manner. As with other comparative drug analysis, clinical efficacy is the primary determinant before other considerations. Definitions of clinical efficacy varies across studies, with some using testosterone-related outcomes (2) (testosterone nadir), others using prostate specific antigen (PSA)-related outcomes (PSA nadir and time to PSA nadir) (3), and others adopting the more important survival outcomes (time to castrate-resistant disease, clinical progression, and overall survival) (4,5). Vogelzang *et al.* found that bilateral orchidectomy and medical androgen deprivation therapy had similar efficacy in terms of serum testosterone suppression (2). A more recent systematic review by Seidenfeld *et al.* reported similar overall survival between patients who received either treatment modality (6). Similarly, Tan *et al.* also described comparable time to castrate-resistance and overall survival for patients receiving either form of treatment (7). Suffice to say, there is a clear consensus on the clinical equivalence between these two treatment modalities.

The second important consideration is the difference in side effects profiles. ADT-induced hypogonadism can have detrimental effects on the patient's overall health status, with higher incidence of metabolic syndrome, cardiovascular events, anemia and osteoporosis (7-10). In our previous report, we found similar rates of reported side effects between surgical and medical treatment groups (7). Vogelzang *et al.* also found similar patterns of adverse events, although we note they did not report metabolic syndrome related events (2). On the other hand, Vargas *et al.* and Sun *et al.* both reported worse metabolic side effects with medical ADT (8,11). The available studies published on this topic report conflicting findings and make it difficult to derive consistent recommendations for clinical practice. Interestingly, recent studies comparing LHRH antagonist and agonist had suggested a lower rate of metabolic syndrome of cardiovascular events with the former, but this assertion needs further prospective studies

and is clearly outside the scope of this review. Surgical orchidectomy has not been associated with a poorer side effects profile.

Given that surgical castration and medical ADT have similar clinical efficacy and side effects profiles, the disproportionately skewed treatment patterns remained unfathomable. We herein propose a few explanations for this observation. First, medical therapy allows the practice of intermittent ADT, which may reduce the incidence of adverse effects without compromising oncological outcomes (12). However, Hussein had cautioned the interpretations of these results because of the inherent varied threshold for restarting ADT (13). The role of intermittent ADT is also reducing as standards of care now recommend intensification of ADT with either chemotherapy or novel hormonal agents, which makes continuous ADT almost mandatory. The practice of intermittent ADT should be reserved for a highly selected minority group of patients.

Second, there is a widespread assumption of greater psychosocial impact in patients undergoing surgical orchidectomy. The preference for medical therapy over surgical castration was vindicated by the avoidance of physical and psychological discomfort. To our knowledge, this assumption appears to be preconceived and lacks well supported evidence. In fact, a small study by Montgomery suggested that there was no difference in self-concept between patients who underwent bilateral orchidectomy and those receiving medical therapy (14).

Third, treatment of mPCa has predominantly been managed by medical oncologists; even more so now that treatment intensification with chemotherapy to prolong survival is the standard of care. Under these circumstances, surgical castration is less likely to be offered as an option for androgen suppression. However, with the rapid development of novel hormonal agents which offer greater ease of prescription and monitoring, complemented with the increasing role of uro-oncologists in the management of hormone sensitive prostate cancer, we may see more patients willing to consider upfront surgical castration in the future. The cost-effectiveness of surgical castration, as highlighted by Paul *et al.*, would be particularly relevant in offsetting the higher costs of treatment intensifications with novel hormonal agents.

Lastly, although difficult to prove, we believe the industrial support for medical therapy drives a bias against surgical castration and perpetuates the scarcity of literature describing effects of bilateral orchiectomy. This phenomenon has been discussed in other areas of medical practice and prostate cancer treatment is unfortunately not immune to it (15).

To conclude, we agree with Paul *et al.* that surgical castration still has a strong role to play in the management of advanced prostate cancer. It remains a pragmatic option with no compromise in clinically efficacy and side effects profile. We emphasized the specific circumstances when surgical castration maybe preferable in our previous paper (7): (I) the need to rapidly attain castrate level of testosterone, especially for symptomatic patients with acute complications such as cord compression, severe bone pain and brain metastases; (II) for patients undergoing concomitant palliative surgery such as spinal cord decompression and channel transurethral resection of prostate; (III) limited access to healthcare facilities which may affect compliance to the regular medical therapy; and (IV) patients with financial difficulties (7). To this end, we perceive cost-effectiveness with low regard in the prescription algorithm because most matured healthcare systems would have national medical reimbursement schemes or insurance to cushion the higher costs of medical therapy. Ultimately, the choice between surgical castration and medical therapy should be a fully-shared decision with the patients.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Andrology and Urology*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-22-696/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Gatsinga R, Chen W, Chen K, Tay KJ, Yuen JSP, Tan YG. Affordable and underutilized: the paradox of surgical castration. Transl Androl Urol 2022;11(12):1618-1620. doi: 10.21037/tau-22-696