



Financial toxicity differences between chemical versus surgical androgen deprivation therapy

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Androgen deprivation therapy (ADT) is the cornerstone of treatment for locally advanced and metastatic prostate cancer (1). ADT can be achieved either through medical or chemical castration via administration of gonadotropin hormone-releasing hormone (GnRH) agonists or antagonists, or through surgical castration with bilateral orchiectomy. Historically, early studies comparing equivalence of medical versus surgical castration was performed in the late 1950's when the Veterans Administrative Cooperative Urological Research Group (VACURG) established several trials with the goal of comparing chemical castration in the form of diethylstilbestrol (DES) which served as an estrogenic compound that could suppress GnRH production at the hypothalamic level and served to compare it with surgical orchiectomy with estrogen (2), showing no difference in outcomes between the 2 arms effectively establishing a new standard of care at the time with the use of chemical castration. However, use of DES later fell into disfavor after reports of cardiovascular side-effects and development of clear cell vaginal carcinoma in girls who were exposed in utero to DES (3). It wasn't until after discovery and purification of GnRH-agonists in 1970's by Schally *et al.* (4), that later led to the comparison of GnRH-agonists to DES (5) and subsequent commercialization and wide adoption of GnRH-agonists that are commonly used today. Further evolution in the treatment of advanced prostate cancer included the use of GnRH-antagonists that resulted

in immediate testosterone suppression (6), and even oral formulation with relugolix that demonstrated equivalence to GnRH-antagonists with lesser cardiovascular events in the subgroup analyses (7).

The trial by Paul *et al.* showed significant financial differences between chemical and surgical castration arising from a single institution (8). The methodical strategy was simple, to acquire billing data from 2014 to 2019 and compare men who underwent either bilateral orchiectomy as surgical castration versus chemical ADT in the form of GnRH-agonists and antagonists. Chemical castration or ADT included drug costs as well as charges of nursing administration and projected net value pricing. For orchiectomy, overall charges for surgery including the pre-operative visit and testing alongside the orchiectomy procedure. In addition, cumulative total charges which included charges for clinic visits, imaging and non-ADT drugs were obtained to provide a comprehensive view of cost analysis of metastatic prostate cancer treatment. A hypothetical analysis of each ADT agent was constructed to reflect a simulated charge equivalence as if patients received only one agent to account for the different ADT agents. A net present value (NPV) analysis was also done for each agent which is a hypothetical charge savings that is calculated as discounted dollars to today's value pricing using an interest rate. In essence, the NPV analysis determined the savings associated with surgery over chemical castration over a period of 183 weeks, which was

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used given the hypothetical median survival for metastatic prostate cancer. In addition, performance analysis of ADT was done using weekly 7-day time increments since dosing intervals are measured by number of weeks, for practical calculation of weekly charges as total drug charge divided by drug efficacy duration. A linear mixed effects regression model was used to estimate cumulative direct care charges in patients receiving chemical castration and time to cumulative charges exceeding \$13,000 in costs associated with surgical castration was calculated and compared using a Cox regression model.

The study included 137 patients who received chemical ADT while only 7 patients received surgical castration in a 5-year cumulative period. The analysis showed median and mean surgical charges of about \$13,000 and patients undergoing chemical castration already surpassed this surgical charge by only 38 weeks of treatment. Highest cost was \$167,000 for those who underwent leuprolide.

The results from this single institution were not at all surprising. While this analysis was limited to a single institution, the experience described herein is reflected in a national retrospective cohort registry in the United States that showed surgical castration rates declined from a low utilization of 8.5% in 2004 to 3.5% in 2016 (9), in part perhaps due to socioeconomic factors, where men in the lower socioeconomic group are offered more surgery compared to higher socioeconomic strata being offered more chemical ADT, as was seen in another large cancer registry in California (10). While there are several advantages associated with surgical castration in terms of lesser side-effects in terms of cardiovascular effects, peripheral arterial disease, or fractures (11), or general reduced need for longer-term follow-up (12), or better treatment adherence, which all potentially favors surgical castration, there are also physical and psychological effects of surgical castration and the idea of irreversibility also weighs heavily amongst men even while treatment for metastatic prostate cancer entails indefinite ADT which would negate the issue of reversibility for majority of men. There was also a significant period of time when treatment with ADT was related to financial incentives that was made more apparent during the Medicare Modernization act when frequency of use of ADT notably went down with lower reimbursements especially for those who clearly did not benefit from its use (13). Despite equivalence in oncologic outcomes with either surgical or chemical castration, as demonstrated in the large retrospective national registry showing a median survival [hazard ratio

(HR) =1.02, 95% confidence interval (CI): 0.95–1.09, P=0.6] between surgical versus medical castration (9), use of surgical castration has been dwindling over time.

While there are still known potential adverse effects that are inherent in every surgical procedure, bilateral surgical orchiectomy would not be expected to result in excessive morbidity nor mortality, as it can be performed as simple orchiectomy entailing scrotal incisions with removal of the seminiferous tubules that can be done with relative ease. In this small cohort of 7 patients, one patient did incur re-admission which was not accounted for in this dataset analysis. However, assuming the worse potential side-effects does not compare to the costs incurred with years of lifelong therapy, especially now with advances in metastatic prostate cancer treatment with prolonged survival with the promise of triplet therapy (14), cost containment and healthcare utilization are relevant issues to address as societal stewards of care. If there are no great detrimental harms posed by surgical castration and it is more economical, then further exploration of this modality in men with metastatic prostate cancer who require lifelong ADT, would be worthwhile. On the other hand, non-ADT factors may play a role in the choice of surgical versus chemical castration (15), since health insurance, race or ethnicity (10), and even provider bias may also be factors (16). Financial toxicity is a growing concern which influences quality of life, it would therefore be imperative to revitalize discussions not just for purposes of oncologic efficacy but also cost differences and equity. Perpetuating lifelong misconceptions regarding detrimental aesthetic and sexual effects of surgical over chemical castration may translate to a huge disservice to this population of men with metastatic prostate cancer who ultimately need indefinite ADT.

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Footnote

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