Re: Use of Phosphodiesterase Type 5 Inhibitors May Adversely Impact Biochemical Recurrence after Radical Prostatectomy


**To the Editor:** I read with interest the study by Michl et al, who found that the risk of biochemical relapse after prostatectomy was 1.38 times greater in patients using phosphodiesterase type 5 (PDE5) inhibitors compared to those not using these drugs. A study by Li et al similarly showed that the risk of malignant melanoma was 1.84 times greater in patients using sildenafil compared to nonusers.¹ Both series were observational cohort studies and were controlled for several covariates. Both groups cite previous animal and in vitro experiments demonstrating theoretical results in favor of and against the potential carcinogenicity of PDE5 inhibitors. While PDE5 inhibitors can be true carcinogens, there may also exist confounding mechanisms, such as better detection of cancer among users of PDE5 inhibitors.

A prostate cancer survivor using PDE5 inhibitors needs repeated drug prescriptions, and, therefore, visits a doctor more often than a nonuser. The patient may simultaneously present with other common complaints (eg musculoskeletal pain, raising the possibility of bone metastasis), giving the doctor an indication to rule out cancer relapse. This course of events leads to additional prostate specific antigen tests and, as a consequence, earlier and more frequent findings of increased prostate specific antigen values.

The melanoma case is similar. Before prescribing medication for erectile dysfunction the doctor is likely to study the cardiovascular system, asking the patient to reveal his upper body for auscultation. Li et al found sildenafil use to be associated with melanoma but not with nonmelanoma skin cancers.¹ More than 80% of basal and squamous cell skin cancers are located on sun exposed body areas (and only 3.8% on the back),² and they may thus be easily visible to the patients or their contact persons. Conversely 43% of melanomas among males are located on the trunk, especially on the back (35%).³ These sites are difficult for self-detection but are better accessible on medical examination. Of males only 33% self-detect a melanoma.⁴ Elderly long-term users of sildenafil at urology wards have active sexual behavior,⁵ thus giving their partners the opportunity to detect melanomas on their skin. The same may not apply to the non-users. Thus, differences in cancer location, behavior and medical scrutiny may (at least partly) explain dissimilarities in finding melanoma/nonmelanoma skin cancer among sildenafil users.

The current study and the series by Li et al¹ do not describe patient mortality. Due to the aforementioned reasons, it is possible that cancers among users of PDE5 inhibitors are more effectively and earlier detected, which may even exert a favorable effect on cancer specific mortality. These drugs seem to possess cardiovascular benefits,⁶ which should be weighed against the potential harms. Due to the great number of users of PDE5 inhibitors worldwide, further studies are extremely important. Ideally all cause mortality among users of PDE5 inhibitors should be compared to that in a feasible control group of nonusers before definitive recommendations on use of PDE5 inhibitors can be made.

Respectfully,

Tapio Vehmas
Institute of Clinical Medicine
Helsinki University
Helsinki, Finland

http://dx.doi.org/10.1016/j.juro.2015.01.116
Vol. 194, 595-601, August 2015
Printed in U.S.A.
Re: Combined Chemoradiation as Primary Treatment for Invasive Male Urethral Cancer

M. Kent, L. Zinman, L. Girshovich, J. Sands and A. Vanni


To the Editor: Kent et al attempt to define the role of combined chemoradiation as primary treatment for males with invasive urethral cancer. We commend them for addressing a controversial topic. However, some points need further explanation.

While assessing outcomes, the authors make no mention of tumor location (whether in the penile, bulbomembranous or prostatic urethra), although tumor location has an important bearing on disease course and prognosis. Furthermore, they do not stratify results according to disease stage and grade, which otherwise would have helped to better define the indications and criteria for combined chemoradiation as the primary treatment in males with invasive urethral cancer.

No mention is made regarding morbidity or adverse effects due to chemoradiation. Neither do the authors describe the differences between radiation dosage or field in node positive and node negative cases. In addition, almost all patients in the study had squamous cell carcinoma, while a significant proportion of patients with urethral carcinoma have other histological types. Therefore, generalization of results seems difficult. We request that the authors consider and explain these confounding factors and their effects.

Respectfully,

Amit Verma, Vikas Giri and Sher Singh Yadav
Department of Urology
Sawai Man Singh Medical College
Jaipur, Rajasthan, India

Reply by Authors: The main purpose of our study was to evaluate the efficacy and intermediate term outcomes of a combined chemoradiation protocol for the treatment of primary invasive carcinoma of the male urethra. Our treatment regimen is based on the Nigro protocol, which was developed and is still widely used to treat squamous cell carcinoma of the anal canal. For this reason tumor histology has a central role when it comes to deciding which patients are best suited to participate in the chemoradiation protocol. In our series all but 1 patient had squamous cell histology. We mentioned this fact in multiple sections of the article, and we explicitly stated in the discussion that we do not use this protocol to treat patients with transitional cell carcinoma. We recognize that this fact limits the generalization of our results to other histological tumor types but we believe that it strengthens the applicability of this treatment to patients with urethral squamous cell carcinoma.

Our protocol uses an identical radiation field in all patients regardless of node status, with the intention of treating micrometastatic disease in this aggressive tumor. All patients, regardless of node status, received a radiation dosage of 45 to 55 Gy during an interval of 5 weeks, with some delay in patients who experienced local toxicity. Additionally we did not directly evaluate retrospectively the morbidity and adverse effects associated with this protocol beyond the end point of death, partly due to the fact that chemoradiation is widely used to treat many different medical conditions, and the associated morbidity and adverse effects are well understood.