Statins and biochemical recurrence after radical prostatectomy – who benefits?

In the present issue of the BJUI Allott et al. [1] report results from a study where they used the Shared Equal Access Regional Cancer Hospital (SEARCH) database to explore the risk of biochemical recurrence (BCR) after radical prostatectomy (RP) among men who used statins after RP. They report improved BCR-free survival among statin users, especially among men with high-risk disease at baseline. The results provide some new insights into the current discussion on statins and prostate cancer outcomes.

Statins have recently shown promise as chemotherapeutic agents against prostate cancer. There is conflicting evidence on the effect on overall prostate cancer risk, but most studies able to evaluate the risk by tumour stage have reported lowered risk of advanced prostate cancer among statin users compared with the non-users [2], and lowered prostate cancer-specific mortality [3].

Taken together, these epidemiological findings suggest that statins may not strongly lower the risk of initiation of prostate cancer, but may be able to slow down the progression of the most dangerous form of the disease. In vitro studies support this by reporting growth inhibition and lower metastatic activity of prostate cancer cells after statin treatment [4].

Despite this, there has been recent controversy on statins’ effect on BCR of prostate cancer after radical treatment. A recent meta-analysis concluded that statin users may have a lower risk of BCR after external beam radiation therapy, but not after RP [5]. This could be due to statins acting as radiation sensitizers. Reports of improved BCR-free survival in statin users after brachytherapy would support this [6].

However, there are also differences in the characteristics of patients managed with RP or radiation therapy. Men undergoing RP have localised disease, which usually means low- to medium-grade tumours (Gleason ≤7), as high-grade disease (Gleason 8–10) progresses early and is more often locally advanced or already metastatic at diagnosis, leading to the choice of radiation therapy with neoadjuvant androgen deprivation instead of RP if curative treatment is still deemed possible.

This leads to the question whether the differing association between statins and BCR by treatment method is explained by patient selection, and whether statins are most effective against progression of high-grade disease. The study reported by Allott et al. [1] in this issue of the BJUI certainly suggests so. They report lowered risk of BCR among men who used statins after RP. They were able to study the effect of statin usage occurring after RP, not just usage at the time of RP. When the analysis was stratified by tumour characteristics, the improvement in relapse-free survival was strongest among men with high-risk disease (Gleason score ≥4 + 3; positive surgical margins).

The present study [1] supports the notion that statins could target a mechanism that is essential for progression of high-risk prostate cancer. This would be in concordance with the previously reported lowered risk of advanced prostate cancer and decreased prostate cancer mortality among statin users, as high-grade/high-risk cancer is the type progressing into advanced and fatal stages. On the other hand, if statins do not affect low-grade prostate cancer, this could explain why many RP series have not observed differences in biochemical relapses by statin use, as patients in these studies often have low-grade disease.

As always, statins’ benefits against prostate cancer are not really proven until verified in randomised clinical trials properly designed and powered to detect a difference in cancer endpoints. Designers of such trials should consider targeting the statin intervention to men with high-grade and/or high-risk prostate cancer for efficient study design.

Conflicts of Interest
Lecture fee from Jansse-Cilag. Participation in scientific congresses at the expense of Astellas, GSK, and Janssen-Cilag.

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This study from Kaag et al. [1] investigates predictors of renal functional decline after radical nephroureterectomy (RNU) in patients with upper tract urothelial carcinoma (UTUC). They evaluate early (2 months) and late (6 months) predictors of renal functional decline, finding that on a multivariable model only age at surgery and preoperative renal function were independently associated with early postoperative function. This is an intuitive finding whereby we expect older patients and those with lower renal function to have a more dramatic decrease in renal function after RNU.

Age, preoperative renal function, and Charlson score were associated with late functional recovery. The latter is a counterintuitive finding, as higher Charlson score was associated with less decrease in renal function. Charlson comorbidity was not significant on univariate analyses. Why it would become significant on multivariate is unclear. Whether it is an artifact related to study methodology or is a real phenomenon will require further study.

Unquestionably, this study [1] adds to the growing discontent of our current management of UTUC. The authors cogently discuss the issues related to better risk stratification as a natural consequence of instituting a neoadjuvant chemotherapy paradigm in those with high-risk disease. Multiple retrospective studies have failed to show a benefit of adjuvant chemotherapy, whereas now we have a matched-cohort study showing significant rates of downstaging and complete remission [2], and as well significantly improved 5-year survival, with institution of a neoadjuvant paradigm [3]. One cannot view the dismal outcomes of this disease without being discontent and wishing for progress. We need to continue getting out the message to not only urologists who reflexively institute RNU in patients with a risk-unstratified upper tract filling defect, but as well many medical oncologists who can only function based on guidance from level I data, which for this disease, will be a long time coming.

Conflict of Interest
No conflict of interest in relation to this writing.

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‘Discontent is the first necessity of progress’,
Thomas A. Edison