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Renal Masses: To Treat or Not to Treat – If that is the Question are Contemporary Biomarkers the Answer?

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In 2008, the limitations of most surgical datasets are well recognized. Even in contemporary series, tremendous treatment biases exist including lead time, length time, selection and researcher bias. Moreover, surrogate endpoints of success often lead to conclusions or inferences that may not be fully substantiated. The net result is that many surgical interventions may risk over or under treating the inherent biology of a pathological process. The inability to accurately match surgical treatment modalities to tumor biology is becoming more apparent in oncology. In urologic oncology, clinicians have long recognized this conundrum summarized by Willet Whitmore when he asked, “Is it possible to cure prostate cancer when it is necessary and is it necessary to cure prostate cancer when it is possible?”.

Hence the disciplines of evidence based medicine (EBM) and outcomes research have emerged. EBM is defined as the “conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients”.¹ Levels of evidence now range from properly designed randomized control trials (level I) to descriptive studies and reports of experts (level III). EBM has demoted individual retrospective studies to the least valid form of evidence. Unfortunately these data represent the majority of the existing literature regarding the surgical management of kidney cancer. Although the medical community has recognized the benefits of engaging in systematic EBM, significant scientific, statistical, social, financial, and industrial barriers remain. Additionally, data from evidence based studies are exceptionally difficult to accrue and analyze and even in the face of level 1 evidence, practice patterns may be slow to change.

It is increasingly being recognized that successful management of small localized renal cell carcinoma, particularly in the elderly or infirmed, may be more a function of the tumor's indolent biology than a triumph of technology. For example, recent meta-analysis evaluating excision, ablation or observation of localized small renal masses (n=6,471, mean tumor diameter = 3.26 cm) demonstrated that ablation (mean follow-up of 16-18 months) was not oncologically superior to active surveillance (mean follow-up of 33 months).² In this issue of the *Journal of Urology*, Abouassaly et al from Cleveland Clinic report their experience on 110 patients with localized SRMs > 75 years old with a median Charlson co-morbidity index of 2. Over a median follow-up of 24 months, the median growth rate was 0.08cm/year which included 43% of patients with a net zero growth. This figure is similar to a previous review of “zero growth” renal mass lesions under active surveillance by Kunkle et al.³ When Abouassaly removed the non-growing lesions, the median growth rate was only 0.31cm/yr, consistent with a previously published meta-analysis (Chawla et al reference #15). Importantly, 31% of the patients under active surveillance died of unrelated causes and no patient progressed. Recent data from Crispen et al demonstrate that active surveillance with judicious delayed intervention is safe and incurs minimal risk of progression.⁴ When taken together the data suggest that a period of active surveillance may decrease overtreatment bias in cases of appropriately selected patients with SRMs.

Conversely, in cases of metastatic RCC (mRCC), surgical under treatment is of greater concern. While level 1 data demonstrate that cytoreduction may improve survival, it rarely cures systemic disease.⁵ Therefore the ultimate goal of surgical oncology is to match the surgical intervention to the tumor's inherent biology. Unfortunately there are currently no reliable clinical or radiographic markers to predict progression in kidney cancer and so multiple biomarkers are being investigated.⁶

In this issue of the Journal, the evaluation of two biomarkers are presented to evaluate the risk of recurrence (Li et al) and prognosis (Tatokoro et al) for high risk kidney cancer. In the first report, Li et al report on serum levels of carbonic anhydrase IX (CA9) in 91 patients versus 32 controls. With a median follow-up of 38 months they demonstrate that patients with a higher CA 9 levels are more likely to have mRCC at diagnosis and/or to develop recurrent disease. The data suggest that serum CA9 elevation is associated with tumor progression and recurrence. Similarly Tatokoro evaluated serum levels of the c- reactive inflammatory protein CRP in 41 patients with mRCC who underwent cytoreduction. Over a median follow-up of 31 months, their data support CRP kinetics as a potential predictor of clinical course.

Currently neither of these biomarkers can be considered robust enough to be clinically relevant in the management of kidney cancer. Moreover, even if we had an outstanding candidate biomarker, there is always a trade off between sensitivity and specificity. Although at times biomarkers may muddy our understanding of a tumor's biology (ie PSA), they remain essential and sought after tools in the delivery of patient care. In this era where the causal genetics and molecular pathways of kidney cancer are becoming better understood and effective targeted therapies have been approved, the long anticipated kidney cancer biomarker may not be far off. Until then, to treat or not to treat remains the question that is best answered using evidence based approaches.

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