



Words of Wisdom

Re: Prognostic Relevance of Capsular Involvement and Collecting System Invasion in Stage I and II Renal Cell Carcinoma

Klatte T, Chung JS, Leppert JT, Lam JS, Pantuck AJ, Figlin RA, Belldegrun AS

BJU Int 2007;99:821–4

Expert's summary:

Klatte and coworkers examined the prognostic relevance of capsular involvement with no invasion of the perinephric fat and collecting system invasion in a series of 519 patients with intracapsular renal cell carcinoma (RCC) treated with partial or radical nephrectomy and followed for a median of 49 mo (range: 1–199 mo).

Capsular involvement and collecting system invasion were reported in 21.6% and 7.5% of patients, respectively. Capsular involvement was significantly associated with a higher nuclear grade and larger tumors, whereas collecting system invasion was significantly associated only with microvascular invasion. In addition, capsular involvement and collecting system invasion were not associated with each other, but had a significant impact on recurrence-free survival ($p = 0.007$ and $p < 0.001$, respectively). Interestingly, patients with capsular involvement had the same recurrence-free survival as patients diagnosed as having pT3a N0 M0 RCC. In multivariate analysis, both capsular involvement and collecting system invasion were independent predictors of recurrence-free survival with a reported risk ratio of 1.84 and 3.78, respectively.

Expert's comments:

RCC has an unpredictable natural history, with a range of biologic and clinical behavior from relatively favorable to extremely aggressive. Intracapsular RCC usually has a relatively favorable prognosis but metastatic progression occurs in some

cases. The available published evidence indicates that the 2002 TNM staging system is an independent predictor of cancer-specific survival [1]. However, the TNM classification, considering the tumor's greatest dimension as the only prognostic indicator for intracapsular RCC, will never succeed in obtaining prognostically homogeneous groups of patients, regardless of the size threshold and the number of thresholds chosen [2,3].

Fuhrman nuclear grade is also regarded as an independent predictor of cancer-specific survival [4,5] and an integrated staging system considering tumor size and nuclear grade is eagerly awaited. Indeed, within intracapsular pT2 tumors, nuclear grade is an important morphologic variable for predicting long-term survival and the identification of nuclear grade 3–4 is prognostically important to determine the metastatic potential of pT2 tumors [5].

Nevertheless, additional prognostic factors could be of great value to improve the prognostic prediction of intracapsular tumor aggressiveness and to define patient subgroups at high risk for metastases.

Klatte and coworkers confirmed in a large series of intracapsular RCC that capsular and collecting system invasions are independent prognostic factors; thus, a revised TNM excluding those patients with capsular involvement or collecting system invasion from the pT1–T2 category, might improve its prognostic validity [6,7]. In this respect, the pathologic characteristics and prognostic role of tumor pseudocapsule, which we are evaluating in an ongoing prospective study, should be investigated thoroughly; the presence of a pseudocapsule with signs of infiltration within its layers or completely penetrated (as in a third of patients undergoing nephron-sparing surgery), could represent the first pathologic evidence of the capacity achieved by tumor cells to infiltrate and invade surrounding tissue.

Cancer cell invasion into surrounding tissue is an early and crucial step of carcinogenesis and several recent studies emphasized the role of a biologic approach to identify the genes and expression of their corresponding products that might have a role in local and metastatic progression, including the von Hippel-Lindau/hypoxia-inducible factor (VHL/HIF-1 α) gene pathway, matrix metalloproteinases, and adhesion molecules of the integrin family, and therefore prognostic and therapeutic significance, especially for the clear cell RCC subtype [8–11].

In conclusion, this study from UCLA represents an important advance in the development of an accurate staging system for patients with intracapsular RCC and shows that the TNM classification might also be improved through the careful examination of the pathologic specimen. Nevertheless, the incorporation of molecular factors into current prognostic algorithms will surely result in better prognostic tools that might eventually guide the choice of different adjuvant treatments and appropriate follow-up schemes.

Conflicts of interest

The authors have nothing to disclose.

References

- [1] Ficarra V, et al. *Cancer* 2005;104:968–74.
- [2] Klatte T, et al. *J Urol* 2007;178:35–40.
- [3] Minervini A, et al. *J Urol* 2005;174:1203–7, discussion 1207.
- [4] Novara G, et al. *J Urol* 2007;177:430–6.
- [5] Minervini A, et al. *Cancer* 2002;94:2590–5.
- [6] Jeong IG, et al. *Urology* 2006;67:709–12.
- [7] Terrone C, et al. *Eur Urol* 2004;46:472–6.
- [8] Kim HL, et al. *Clin Cancer Res* 2004;10:5464–71.
- [9] Di Cristofano C, et al. *Am J Surg Pathol* 2007;31:1875–81.
- [10] Miyata Y, et al. *Clin Cancer Res* 2006;12:6998–7003.
- [11] Jones J, et al. *J Cell Mol Med* 2007;11:826–38.

Marco Carini, Andrea Minervini
Department of Urology, University of Florence,
Careggi Hospital,
Florence, Italy

E-mail address: carini@unifi.it

DOI: 10.1016/j.eururo.2008.01.036

(I) Re: Prostate Specific Antigen Velocity in Men with Total Prostate Specific Antigen Less than 4 ng/ml

Loeb S, Roehl KA, Nadler RB, Yu X, Catalona WJ

J Urol 2007;178:2348–53

Expert's summary:

This study analyses the prostate-specific antigen (PSA) determinations of 11,709 men with two or more PSA measurements within approximately 12 mo, an initial PSA of <4 ng/ml, and using biopsy indications of PSA ≥ 2.5 ng/ml or ≥ 4.0 ng/ml. The authors found that PSA velocity (PSAV) thresholds in the range of 0.4 ng/ml/yr should be used to help guide the need for biopsy in men with a total PSA level <4 ng/ml. Receiver operating characteristic (ROC) analysis showed that the area under the curve (AUC) was 0.68 for PSAV and 0.87 when total PSA was included in addition to PSAV.

Expert's comments:

This is the third time that a paper, which deals with the value of PSAV in the early detection of prostate cancer, is commented on and once more the conclusion is that inadequate methodology leads to incorrect results.

In both the earlier commented studies of Berger et al and Sun et al [1,2] the following statements were made: "Correctly assessing the discriminating value of a biomarker for having a particular disease, yes or no, requires a similar method of verification of the disease status in all men".

In the current study, the cohort consisted of 11,792 men with a total PSA <4.0 ng/ml and two or more PSA measurements within about 12 mo, which allowed determination of PSAV. In these men 501 cases of prostate cancer were diagnosed. Several multivariate analyses showed that a PSAV threshold of 0.4 ng/ml/yr is most useful in recommending biopsy in men with total PSA values <4.0 ng/ml.

The method of verification in this case would have been to biopsy all 11,792 men. This was not done because the indication for biopsy was a serum PSA value of ≥ 4.0 ng/ml or ≥ 2.5 ng/ml (after May 1995). Next to this the predictive ability of the different predictors entered into the multivariate model are valued suboptimally. It is regrettable that studies like the one dealt with here are published without a proper discussion on the effect of these issues on the outcome.

Two attempts are made here to clarify the effect of misinterpreting the value of the different predictors for biopsy outcome and verification bias with