Extraprostatic Extension into Periprostatic Fat is a More Important Determinant of Prostate Cancer Recurrence than an Invasive Phenotype

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Purpose: Although micrometastasis development correlates closely with the depth of invasion of many tumor types, it is unclear whether invasion into but not through the prostatic pseudocapsule has a negative impact on prognosis, similar to extraprostatic extension. We defined the impact of pseudocapsular invasion on the risk of post-prostatectomy biochemical recurrence.

Materials and Methods: Patients with pT2-3a prostate cancer were identified from a prospectively recorded database. Those with pT2 disease were categorized according to pseudocapsular invasion presence or absence. The impact of pseudocapsular invasion on biochemical recurrence was determined by univariable and multivariable Cox regression analysis.

Results: In a cohort of 1,338 patients we identified 595 with organ confined cancer positive for pseudocapsular invasion. Compared to tumors without evidence of invasion, pseudocapsular invasion was positively associated with higher Gleason grade and tumor volume (1.2 vs 1.9 cc, each $p < 0.001$). On univariable analysis there was no difference in biochemical recurrence-free survival between patients with vs without pseudocapsular invasion, although those with extraprostatic extension had significantly lower biochemical recurrence-free survival ($p < 0.001$). This was confirmed on multivariable analysis, which revealed that extraprostatic extension was a significant independent predictor of biochemical recurrence (HR 1.53, $p = 0.018$). The presence of pseudocapsular invasion had no effect (HR 0.81, $p = 0.33$).

Conclusions: Pseudocapsular invasion is not a pathological feature associated with an adverse outcome after prostatectomy. Thus, the depth of tumor invasion is not a continuum of risk and access to periprostatic adipose tissue is a more important determinant of disease behavior than an invasive phenotype.

Key Words: prostate; prostatic neoplasms; neoplasm invasiveness; neoplasm recurrence, local; prostate-specific antigen

Abbreviations and Acronyms

EPE = extraprostatic extension
OC = organ confined
PCI = pseudocapsular invasion
PSA = prostate specific antigen

Accepted for publication June 19, 2013.
Study received institutional review board approval.

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THE prostate gland lies deep in the pelvis, surrounded by retroperitoneal fat. The gland does not have a true capsule. Rather, tubulo-alveolar glands are separated from the enclosing adipose tissue by an incomplete condensation of fibromuscular tissue (the pseudocapsule) on its anterior and posterolateral surfaces.[1]

The ability of cancer cells to invade normal tissue boundaries is considered a hallmark of malignancy. In prostate cancer extension of the tumor outside the pseudocapsule is a

0022-5347/13/1906-2061/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.06.050
Vol. 190, 2061-2067, December 2013
Printed in U.S.A.

well established poor prognostic feature. Invasion is widely seen as the first step in metastatic spread with primary masses spawning pioneer cells, which move out, invade adjacent tissue and travel to distant sites.[2] Notably, in other tumor types such as colorectal cancer the depth of invasion closely correlates with the risk of metastasis.

Although it is well documented that the spread of prostate cancer beyond the confines of the gland into the seminal vesicles or visceral fat is associated with a higher rate of recurrence after prostatectomy,[3–6] it remains unclear whether an invasive phenotype itself defines higher metastatic risk or whether access to the extraprostatic environment is an important, independent contributing factor. This uncertainty surrounding the clinical significance of PCI invasion is reflected by the changes made to the TNM system by UICC in the 1990s, which down-staged tumors invading but not penetrating through the pseudocapsule to pT2, citing inadequate prognostic data to justify inclusion in the pT3 category.[7]

A few small series assessed the role of PCI (malignant epithelium in but not through the pseudocapsule) for stratifying the biochemical recurrence risk in patients with OC disease, although data remain sparse and conflicting.[8–12] We performed the current study to fill this gap in the literature, which may have an important impact on clinical decision making regarding adjuvant treatment. We examined the relationship between PCI and biochemical recurrence in a large cohort from the prostate cancer database at a single institution.

METHODS

Patient Selection

Consecutive patients who underwent radical prostatectomy, as performed by participating surgeons at Epworth Hospital between June 2004 and September 2012, were identified from a prospectively recorded prostate cancer database. Patients with pathological stages T2 (OC) and T3a (EPE) according to the American Joint Committee on Cancer (AJCC) 2010 classification system were included in analysis. From an initial cohort of 1,708 men 370 were excluded due to the lack of information on PCI status (275), the presence of seminal vesicle invasion (83) or microscopic involvement of the bladder neck in the absence of concomitant extension into periprostatic soft tissue (12), leaving a final study cohort of 1,338.

PCI was defined as the histological appearance of tumor abutting and/or infiltrating the delineation between prostatic and extraprostatic tissue or showing perineural invasion at this junction but importantly not extending through the capsule into extraprostatic tissue (fig. 1). Distortion of the pseudocapsule alone in the absence of tumor extension into extraprostatic tissue was classified as OC PCI positive for this study. In all cases PCI was routinely reported in the text description by 1 of 2 uropathologists.

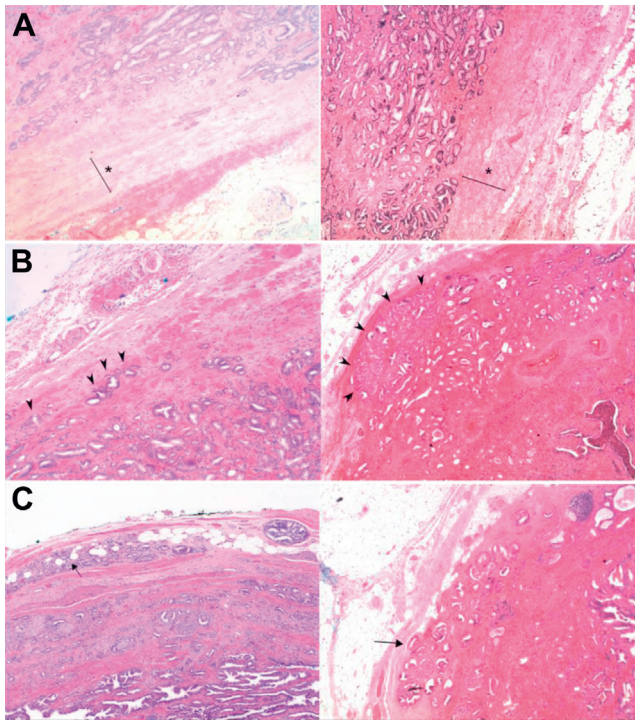

Figure 1. Photomicrographs show prostatectomy specimens. *A,* organ confined disease. Asterisk indicates prostate pseudocapsule. *B,* PCI (arrowheads). *C,* established extraprostatic extension (arrows). Reduced from ×40.

Pathological Processing

After formalin fixation the entire specimen was embedded. Standard blocks were cut at 3.5 mm intervals perpendicular to the urethra from apex to base. Apical and bladder neck shaves were cut radially. Sections (5 μm) of each block were submitted for hematoxylin and eosin staining.

Tumors were graded according to the International Society of Urological Pathology (ISUP) 2005 modified Gleason system and staged using the AJCC 2010 classification system, as described. Pathological margins were considered positive when cancer cells were visualized in the inked margin of the specimen. Tumor surface area was calculated after scanning each tumor marked slide with the image processing and analysis tool NIH Image (http://rsb.info.nih.gov/nih-image/). Tumor volume was then estimated by calculating tumor areas of each slice, multiplying them by section thickness (3.5 mm) and summing the results.[13]

Data

Collection. All standard clinical and pathological data, and PSA followup were recorded prospectively in a dedicated prostate cancer database. PCI data were not recorded routinely but rather manually collected retrospectively from the original pathology report for each patient.