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Current Conundrums with Cribriform Prostate Cancer

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In recent years, cribriform morphology has become a hotly debated histological pattern in prostate cancer pathology. In prostate cancer, cribriform morphology is defined as a confluent sheet of contiguous malignant epithelial cells containing multiple glandular lumens, with no intervening stroma or mucin, which are easily visible at low power [1,2]. Cribriform morphology in prostate cancer can be present as invasive cribriform cancer or as intraductal carcinoma of the prostate (IDCP). Cribriform morphology has been investigated as an independent negative prognostic indicator for prostatic adenocarcinoma. In 2014, it was decided that all cribriform tumors would be categorized within Gleason Grade 4 [3] and in 2019, consensus statements by the Genitourinary Pathology Society (GUPS) and the International Society of Urological Pathology recommended reporting cribriform morphology in prostate biopsies and radical prostatectomies [4,5]. However, much remains unknown in our understanding of the significance of cribriform prostate cancer, how it impacts patient outcomes, and how it should influence clinical management.

Once cribriform morphology is identified, a key challenge is differentiating between IDCP and invasive cribriform prostate cancer. Both entities can show a cribriform pattern of growth, and although they often co-exist, studies have shown there are concrete differences between the two [6,7]. Separating IDCP from invasive cribriform cancer often requires immunohistochemistry to determine the presence of basal cells, which would be seen in IDCP. Staining for the presence of basal cells in all areas of a tumor with cribriform morphology to distinguish IDCP from invasive cribriform cancer is both time consuming

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and has additional costs. Most studies to date that have investigated cribriform morphology have combined both IDCP and cribriform cancer in their statistical analyses. This may be problematic, as some studies have shown a difference in prognosis when separating the two [7,8,9]. A study by Spieker et al. showed that a combination of IDCP and invasive cribriform cancer was an independent prognostic indicator for biochemical recurrence [7]. However, when splitting the two entities, only invasive cribriform cancer remained statistically significant while IDCP did not [7]. Additionally, some studies also suggest that there may be genomic alterations associated with one, but not the other histologic feature. PTEN loss, for example, has been demonstrated to be more frequent in IDCP, while this change is not seen as commonly in invasive cribriform cancers [6,7,10].

The problematic inconsistencies in defining and reporting are additionally paralleled by variation in how clinicians use the presence or absence of cribriform features to impact clinical management. There are three substantial categories in this realm. The first is how cribriform morphology impacts active surveillance decisions for patients with intermediate risk prostate cancer (Grade Group 2). The second issue is whether tumors with cribriform morphology respond differently to radiation and hormonal therapies, which has been rarely studied and with small cohort numbers [9,11]. The third is determining how our molecular understanding of cribriform tumors effects germline testing. Early studies suggested an association between IDCP and *BRCA2* germline mutations [12], leading to the NCCN guidelines to recommend considering germline testing in patients with IDCP [13]. Further studies have refuted this proposed association [14], highlighting the need to re-evaluate these early scientific findings.

One largely unexplored area is the molecular changes specific to cribriform prostate cancer and its tumor microenvironment [10, 15]. Challenges for research in this area include the imprecise gathering of fresh prostate cancer from radical prostatectomy specimens. Prostate cancer can be very difficult to identify grossly and due to tumor heterogeneity, any tumor gathered fresh from a specimen may or may not have cribriform morphology. Often-times cribriform morphology is intermixed with other morphologic patterns, or present in some malignant areas of the prostate but not in others. Therefore, blind acquisition of fresh prostate cancer may not have sampled the cribriform component. If specifically seeking to study the cribriform elements of a cancer, we recommend using frozen section techniques for the rapid histologic evaluation of any fresh prostate tissue harvested to ensure cribriform tumor has been sampled.

Recurring issues in the peer reviewed literature includes small sample sizes and combining IDCP with invasive cribriform prostate cancer for analyses, especially for patients with intermediate risk Gleason Score 3+4=7 (Grade Group 2) prostatic adenocarcinoma. Additionally, creation of a valid control group is challenging. As recommendations for cribriform reporting were only recently a standard of care, studies should ensure independent pathology review of all specimens, rather than relying on historic pathology reports, given the potential for under-reporting of cribriform features. In addition, due to the well documented issues with sampling cribriform prostate cancer and the poor detection rate on biopsy [16,17], studies that choose to use prostate biopsies as a method of understanding the biologic potential and clinical significance of these tumors may be

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misleading. The low detection rate means that many prostate biopsies with no cribriform tumor may be false negatives and harbor this morphology upon final pathology on the radical prostatectomy. There is also an issue with long term follow up and the change in the method of sampling prostate cancer over time. Studies that have >greater than 10 years of clinical follow up will be utilizing biopsies that have fewer cores, as the standard of care shifted from 6 core sextant sampling to 12 core extended sextant sampling, and more recently, to targeted sampling using multiparametric MRI of the prostate. Given the potential for false negative designations when using prostate biopsies, studies examining cribriform morphology as an independent prognostic indicator should focus on radical prostatectomy specimens submitted for comprehensive pathologic review, rather than using data from patients in which only biopsies are available. In addition, when considering disease-specific survival and biochemical recurrence-free survival, cohorts should refrain from combining men who had different modes of primary therapy or adjuvant therapies. The issue remains that the perfect cohort, which would include large numbers of men with cribriform prostate cancer who underwent standard 12 core plus MRI-targeted biopsy followed by radical prostatectomy and then standardized postoperative adjuvant therapy with long term clinical follow-up, does not exist at this time.

Consistent reporting among pathologists, risk of under detecting cribriform morphology on biopsy, the significance of the size of the cribriform tumor, and the significance of the amount of cribriform tumor all remain problematic areas in need of further investigation. Studies have created different definitions for “large” versus “small” cribriform glands and have shown different findings when it comes to whether size matters [8,18, 19]. Additionally, there is a paucity of data investigating whether the extent of the cribriform pattern impacts prognosis and, therefore, clinical decisions. Should a patient with Gleason Score 3+4=7 (Grade Group 2, 5–10% pattern 4) and a single small cribriform gland be excluded from active surveillance? Does it matter whether that one gland is invasive or intraductal? Should pathologists be required to perform immunohistochemistry on every prostate biopsy case with cribriform cancer to distinguish between IDCP and invasive cribriform tumor? On radical prostatectomy, if a prostatic adenocarcinoma Gleason Score 3+4=7 (Grade Group 2, 5–10% pattern 4) has 1% cribriform morphology, does that have the same significance as a tumor with the same Grade Group and 10%, 25%, or 40% cribriform tumor? Does it matter what percentage of the component is invasive? The aforementioned studies demonstrate some thought-provoking findings, however these questions need to be properly investigated to provide more compelling evidence, before we can accurately use cribriform morphology to help direct patient management.

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