Ali Amin
Rhode Island Hospital,
Alpert Medical School-Brown University,
Providence, RI
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Behavior of prostate ductal adenocarcinoma: A review of 93 cases

ABSTRACT

Prostate ductal adenocarcinoma (PDA) is an uncommon variant of prostate cancer usually identified admixed with prostate acinar adenocarcinoma. This study evaluates the association of PDA and stage, considering the grade of the accompanying acinar carcinoma. In a cohort of 18,552 radical prostatectomy cases performed from 1995 to 2008, 93 cases with a ductal adenocarcinoma component were identified. After classification of cases based on their ductal/acinar ratio (< 10% vs. ≥ 10% and < 50% vs. ≥ 50%), different staging parameters such as extraprostatic extension (EPE), margin involvement, seminal vesicle invasion (SVI) and lymph node metastasis (LN) were compared. There was no age, race, and serum prostate specific antigen (PSA) difference between patients with and without PDA. Cases with PDA were less likely to be organ confined (36.6% vs. 65.6%) and more likely to show SVI (19.3% vs. 5.3%), P < 0.0001. There was no difference in LN or margin positivity with and without PDA. An increasing percentage of the ductal component correlated with an increased risk of EPE (P = 0.04) and SVI (P < 0.0001). In Gleason score 7 cases with ≥ 10% ductal differentiation, cases with ductal features were more likely to have nonfocal EPE (64%) compared to cases without ductal features (34.7%), P = 0.002. In this group, there was no statistically significant difference in SVI or LN between For Gleason score 7 cases with < 10% ductal features, there was no difference in pathologic stage vs. nonductal cases. There was no difference in pathologic stage between ductal and nonductal cases for Gleason score 8 to 10 cases, regardless of the percentage of the ductal component. In summary, Gleason score 7 cases with admixed low-grade acinar and PDA are associated with more aggressive behavior and higher stages than pure acinar Gleason score 7 carcinomas, as long as the ductal component occupies ≥ 10% of the tumor. When PDA occupies < 10% of the prostate carcinoma, the difference does not exist. In Gleason score 8 to 10 tumors with ductal features, it is the high grade acinar carcinoma that determines the behavior, regardless of presence of a ductal component.

INTRODUCTION

Prostate adenocarcinoma is the most common tumor in adult male, ranking second among the causes of cancer related death in men in 2008 [9]. Prostate ductal adenocarcinoma (PDA) is an uncommon variant of prostate cancer that was first described as endometrioid carcinoma of prostatic utricle in 1967 [10], but later studies supported a prostatic origin. Earlier studies reported that less than 5% of prostate adenocarcinomas have a ductal component [3]. The frequency is much less for pure PDA (< 1%). PDA is more frequently found in the area adjacent to the prostatic urethra and can cause urinary obstruction; therefore, it may clinically be mistaken for urothelial carcinoma. As PDA typically coexists with higher grade prostate carcinoma (Gleason score 7 and higher), the International Society of Urological Pathology (ISUP) 2005 Consensus Meeting recommended to report the ductal component as Gleason pattern 4. Correspondingly, a pure PDA is graded as Gleason score 4 + 4 = 8 with disclosure of ductal adenocarcinoma [6]. Studies have shown that PDA in radical prostatectomy specimens is associated with higher stage tumor and worse prognosis [4,5,13]. However, it is not clear whether or not PDA is more aggressive when matched for Gleason score (assigning the ductal component as Gleason pattern 4); or if a certain percentage of ductal component is needed to account for more aggressive behavior.

MATERIALS AND MTHODS

Morphologic Criteria for PDA Diagnosis

PDA can be seen in different morphologic patterns, most common of which are papillary, cribriform, solid and high-grade prostatic intraepithelial neoplasia (PIN)-like patterns. These patterns can be seen individually or in various combinations. The most frequent pattern is the papillary pattern, in which the tumor is comprised of simple or branching papillary structures lined by columnar epithelium (Figure 1A). The second common pattern is cribriform, in which there are tight back-to-back clusters of glands lined by columnar epithelium

forming intraglandular epithelial bridging and irregular slit-like glandular lumina (Figure 1B). In the aforementioned patterns, individual tumor cells have ample amount of amphophilic, eosinophilic or seldom clear cytoplasm (hypernephroma-like). Nuclei are commonly enlarged with prominent nucleoli, appearing pseudostratified. It is of note that nuclear morphology can sometimes be deceptively bland. In contrast, the cribriform pattern of acinar prostate adenocarcinoma is composed of cuboidal epithelium with punched out round lumina. The cribriform and the papillary patterns of PDA usually coexist (Figure 1C), and are uniformly considered Gleason pattern 4. Less common patterns of PDA include solid pattern, in which tumor forms solid sheets composed of tightly packed papillary structures. Papillary fronds can be commonly found in less crowded areas (Figure 1D). Individual tumor cells preserve their tall columnar morphology, and thin fibrovascular septa can be identified (Figure 1E). Tumor necrosis may be present in the tumor.

In the recently introduced PIN-like PDA, the tumor is composed of crowded aggregates of simple enlarged glands lined by flat or tufting tall columnar cells without any true papillary structure (Figure 1F). Nuclei of the tumor cells show uniform crowding with pseudostratification. High grade PIN (HGPIN) is an important differential diagnosis for this pattern. Identification of high concentration of glands, less nuclear atypia compared to HGPIN and absence of basal cell markers in the majority if not all of atypical glands support a PIN-like PDA. In contrast, HGPIN lacks the true papillary structures of PDA, and commonly shows higher nuclear grade and preservation of the basal layer. It is important to note that PIN-like ductal adenocarcinoma acts like Gleason score 6 acinar carcinomas [14]; therefore, it was excluded from analysis of PDA cohort in our study.

Intraductal carcinoma of the prostate can be mistaken for PDA [7,12]. This lesion usually reflects intraductal spread of invasive high-grade acinar carcinoma with cuboidal tumor cells arranging in micropapillary or cribriform patterns with rounded lumina. The differential is possible by observing marked nuclear atypia, absence of fibrovascular cores, and general preservation of the basal layer in intraductal carcinoma [14]. Most PDAs lack basal cells, yet 31.4% may show a patchy basal cell layer as the cancer spreads inside ducts and acini [8].

Case Selection

After reviewing a cohort of 18,552 radical prostatectomy specimens obtained from 1995 to 2008 at the Johns Hopkins Hospital (Baltimore, MD), we identified 93 PDA cases (0.5%). Follow-up was available in 90 patients. We assessed the percentage of ductal component on pathology slides, and classified the cases based on ductal/acinar ratio (< 10% vs. ≥ 10% and < 50% vs. ≥ 50%). Of the 93 cases with PDA component, 52.7% had < 10%, 38.7% had ≥ 10 and < 50%, and 8.6% had ≥ 50% ductal component. The analyzed staging variables included extraprostatic extension, positive margins, and involvement of seminal vesicle and lymph node.

RESULTS

No significant difference was found in age, race or serum PSA values between patients with and without the PDA component. Cases with PDA were less likely than acinar carcinoma to be organ-confined and more likely to have seminal vesicle invasion. Although PDA was associated with a higher risk of lymph node involvement and margin positivity compared to acinar carcinoma, the differences did not reach statistical significance. An increasing percentage of the ductal component correlated with an increased risk of extraprostatic extension and seminal vesicle invasion, yet not lymph node metastases or involvement of the margin.

To account for the overall different Gleason scores between ductal and nonductal cases and the effect of differing percentages of ductal features, tumor stage was assessed on the prostatic carcinoma cases with Gleason scores of 7 and ≥ 8 separately. For Gleason score 7 tumors, cases with ≥ 10% admixed ductal features were more likely to have nonfocal extraprostatic extension compared to purely acinar cancers. In these cases, there was no statistically significant difference in seminal vesicle invasion or lymph node involvement between ductal and nonductal tumors. For Gleason score 7 cases with < 10% ductal features, there was no difference in pathologic stage compared to nonductal cases. There was also no difference in pathologic stage between ductal and nonductal cases for Gleason score 8 to 10 cases, regardless of the quantity of PDA.

DISCUSSION

Owing to the difficulty of diagnosing PDA, it is difficult to determine its accurate incidence. Bock and Bostwick reported that ductal adenocarcinoma of the prostate was admixed with acinar prostatic carcinoma in approximately 5% of radical prostatectomy specimens [2]. However, some of their images of ductal adenocarcinoma would be considered to be intraductal acinar carcinoma in current practice. In a study by Samaratunga et al 12.7% of 268 radical prostatectomy specimens had a PDA component [13]. In their study, the patterns of ductal adenocarcinoma included papillary, cribriform, solid, and invasive glandular patterns. The

description of the so-called “invasive glandular” pattern is identical to the PIN-like PDA, which was excluded from our study. In the Surveillance, Epidemiology and End Results (SEER) data looking at 17 cancer registries from multiple cities and states, 371 out of 442,881 (0.08%) were recorded as PDA [11]. Using strict criteria, we found that the frequency of PDA in our series was 0.5%. Cases of mixed ductal/acinar cancers in which the ductal component is limited may be more difficult to identify. The present study showed that when the ductal component is < 10%, it has no effect on prognosis, such that the underdiagnosis of focal ductal features at radical prostatectomy has no adverse consequences for the patient. In the only other study addressing this issue, the results were at odds with this study. Samaratunga et al found that the proportion of PDA did not significantly modify the strength of the observed association with pathologic stage [13].

Among the contemporary studies on prognosis of PDA, Aydin et al reported a series of 13 cases treated by radical prostatectomy, of which 4 had Gleason score 7, and 8 had Gleason score ≥ 8 cancer [1]. Extraprostatic extension, seminal vesicle invasion, and lymph node metastases were present in 7, 6, and 2 cases, respectively. Samaratunga et al evaluated 34 cases of ductal adenocarcinoma and 234 acinar cancers treated by radical prostatectomy [13]. Ductal adenocarcinomas had a higher likelihood of having extraprostatic extension (73%) relative to acinar carcinoma (32.9%), even adjusting for tumor volume and Gleason score > 7. In an analysis of the SEER database, which represents pooled pathology reports from multiple institutions in different states, 371 PDAs were compared with 442,881 acinar cancers [11].[11] Although the number of cases in the latter study is large, it suffers from absence of case review by urological pathologists, lack of a Gleason score in 70.4% of cases, and assigning Gleason score 6 to 19% of PDA. Recognizing these deficiencies, ductal cases were more likely to present with distant metastasis (12% vs. 4%) and lower serum PSA levels.

The present study shows that ductal adenocarcinoma admixed with Gleason pattern 3 is more aggressive than Gleason score 7 acinar cancer without a ductal component, as long as the ductal component is ≥ 10%. In cases with a very minor ductal component (< 10%), the difference is lost. The more extensive ductal component was associated with a higher likelihood of extraprostatic extension and seminal vesicle invasion. In this cohort, the difference in prognosis after radical prostatectomy was not statistically significant; this may be due to the relatively small number of cases with extensive ductal component (N = 44). In contrast, Gleason score 8 to 10 tumors with ductal features do not seem to be significantly more aggressive than acinar Gleason score 8 to 10 cancers in which the high grade tumor, regardless of ductal features, determines the behavior.

It was not possible to avoid limitations such as potential selection bias (since more advanced PDA cases would not be considered as candidates for radical prostatectomy and were excluded from this study) and lack of review of Gleason pattern 4 acinar cancers without a ductal component. Consequently, it is not possible to determine whether our findings are applicable to all the Gleason 4 patterns. On the basis of the available data, it is important to include the presence and the estimated percentage of PDA in radical prostatectomy specimens, especially when the overall Gleason score is 7.

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