Gleason Score 7 Adenocarcinoma of the Prostate With Lymph Node Metastases
Analysis of 184 Radical Prostatectomy Specimens

Oleskandr N. Kryvenko, MD; Nilesh S. Gupta, MD; Nilam Virani, MD; Daniel Schultz, MD; Juan Gomez, MD; Ali Amin, MD; Zhaoli Lane, MD; Jonathan I. Epstein, MD

Context.—Prostate cancer (PC) with lymph node metastases (LN+) is relatively rare, whereas it is relatively common in disease with a Gleason score (GS) 8 to 10 and virtually never seen in PC with GS 6 or less. It is most variable in GS 7 PC.

Objective.—To determine clinicopathologic features associated with GS 7 PC with LN+ compared with a control group without lymph node metastases (LN-).

Design.—We analyzed 184 GS 7 radical prostatectomies with LN+ and the same number of LN- Gleason-matched controls. The LN+ cases were GS 3+4=7 (n=64; 34.8%), GS 4+3=7 (n=66; 35.9%), GS 3+4=7 with tertiary 5 (n=10; 5.4%), and GS 4+3=7 with tertiary 5 (n=44; 23.9%).

Results.—The LN+ cases demonstrated higher average values in preoperative prostate-specific antigen (12.2 versus 8.1 ng/mL), percentage of positive biopsy cores (59.1% versus 42.9%), prostate weight (54.4 versus 49.4 g), number of LNs submitted (12.7 versus 9.4), incidence of nonfocal extraprostatic extension (82.6% versus 63.6%), tumor volume (28.9% versus 14.8%), frequency of lymphovascular invasion (78.3% versus 38.6%), intraductal spread of carcinoma (42.4% versus 20.7%), incidence of satellite tumor foci (16.4% versus 4.3%), incidence of pT3b disease (49.5% versus 14.7%), and lymphovascular invasion in the seminal vesicles (52% versus 30%). There were differences in GS 4 patterns and cytology between LN+ and LN- cases, with the former having higher volumes of cribriform and poorly formed patterns, larger nuclei and nucleoli, and more-frequent macronucleoli. All P ≤ .05.

Conclusion.—Gleason score 7 PC with LN+ has features highlighting a more-aggressive phenotype. These features can be assessed as prognostic markers in GS 7 disease on biopsy (eg, GS 4 pattern, intraductal spread, cytology) or at radical prostatectomies (all variables), even in men without LN dissection or LN- disease.

Regional lymph node (LN) metastases in prostate cancer (PC) are a proven, independent risk factor for increased risk of biochemical recurrence and death from disease. The selection of candidates for LN dissection, as well as the extent of LN dissection, is based on preoperative risk. Numerous nomograms have been created to stratify patient's risk preoperatively, mainly based on routinely available variables, such as prostate-specific antigen (PSA) level, clinical stage, and biopsy Gleason score (GS). Given the prevalence of screening programs and lower PSA levels to trigger biopsy, more men are eventually found to have LN metastases (LN+) with early stage, nonpalpable PC. The incidence of LN+ is relatively low in contemporary practice, averaging approximately 1% to 2% for all prostatectomies, with noticeably higher rates for men with GS 8 or higher disease at radical prostatectomy. There are no reports describing LN metastases in patients with GS 6 or less prostatic carcinoma at radical prostatectomy after ubiquitous adoption of Gleason grading recommendations from the International Society of Urological Pathology 2005 consensus conference. Although older reports described cases of metastatic disease with GS 6 or less, because of differences in Gleason grading, applying current criteria to those cases might have identified areas of Gleason pattern 4 cancer.

Whereas a significant percentage of GS 8 to 10 cancers at radical prostatectomy is associated with LN metastases, it is uncommon for GS 7 disease to have regional LN involvement, and little is known about the morphology of these tumors. The current study describes the common morphologic features in GS 7 prostatic carcinoma associated with regional LN metastases compared with Gleason-matched tumors lacking spread to pelvic LNs.
**MATERIALS AND METHODS**

After obtaining approval from the institutional board review committees, we identified all cases of GS 7 radical prostatectomies with pelvic LN metastases from 2000 to 2010 at Henry Ford Hospital (Detroit, Michigan) and from 1993 to 2010 at The Johns Hopkins Hospital (Baltimore, Maryland). Preoperative clinical and biopsy data were retrieved from the electronic medical records of the corresponding institutions. Only patients without prior hormonal or radiation therapy of PC were included in the study. The control group was selected from the surgical pathology archive of Henry Ford Hospital and included the same number of GS-matched, continuous cases with LN dissection that was negative for metastases (LN−). The case-control pairs were also matched for the tumor extension, that is, cancers limited to the prostate (pT2) and those with extension beyond the prostate (pT3). For pT3 control cases, we used all continuous, GS-matched pT3 prostatectomies without matching to either extraprostatic extension (pT3a) or seminal vesicle invasion (pT3b). Because of a much greater incidence of seminal vesicle invasion in men with LN metastases, it was not possible to case control for seminal vesicle invasion, and we included pT3 subcategories as analyzed variables between the study and control groups. The prostatectomies at both institutions were weighed, measured, serially sectioned, and entirely submitted as whole-mount sections or conventional cassettes, correspondingly. Both institutions submitted bilateral seminal vesicles and dissected LNs in toto.

From electronic medical records, we collected patient age, number of biopsy cores, and number of positive cores (only invasive cancer was counted, cores with atypical glands were dismissed), preoperative PSA level, and prostate weight. Radical prostatectomy slides from all cases were simultaneously reviewed by 2 urologic pathologists (O.N.K. and J.I.E., the latter was blinded for LN status at review) in a multiheaded microscope for the following parameters: tumor grade and stage, tumor volume, extraprostatic extension, percentage of each Gleason 4 pattern (glomeruloid, cribriform, fused, and poorly formed; presence of mucinous and ductal components was recorded), intraductal spread of cancer, and lymphovascular invasion. We defined mucinous carcinoma only when at least 25% of the tumor contained extracellular mucin with floating malignant epithelium.14,15 Tumor grade was assigned according to the International Society of Urological Pathology 2005 consensus conference recommendations.20 Extraprostatic extension was categorized as focal or nonfocal, based on the criteria suggested by Epstein et al16 in 1993. Seminal vesicle involvement by tumor was classified as nonfocal extraprostatic extension. Tumor volume was visually assessed by mapping the tumor in each slide and then assigning a percentage of the tumor to the slide. The percentages of tumor in all slides were summed and divided by the total amount of prostate tissue slides, yielding the overall tumor volume in percent of involved gland volume.15 Intraductal spread was evaluated based on the criteria described by McNeal and Yemoto,14 and further delineated by Guo and Epstein.15 For assessment of lymphovascular invasion, strict criteria were used from the most recent International Society of Urological Pathology consensus recommendations.18 Cytologic features of invasive cancer were subjectively graded (nuclear enlargement, nuclear pleomorphism, size and distribution of macronucleoli) using a semiquantitative scale from 1 to 3. Nuclear size was compared with the size of nuclei in nonneoplastic cells: grade 1 was less than 2 times larger, grade 2 was 2 to 3 times larger, and grade 3 was more than 3 times larger. Cherry-red, large macronucleoli, easily visible at low-power magnification, were grade 3. While grade 1 and grade 2 are not easily seen on low-power magnification, and occupying minor portion of the nucleus were graded as 1 (micronucleoli). Nucleoli in the intermediate range were assigned grade 2. The extent of the macronucleoli (nuclear enlargement grades 2 and 3) was graded according to the percentage of the cells demonstrating them: grade 1 was less than 10%, grade 2 was 10% to 50%, and grade 3 was more than 50% of tumor cells. The assessment of cytologic features was performed at ×400 magnification (×40 objective and ×10 ocular; Olympus BX41, Olympus America Inc, Center Valley, Pennsylvania). Cytologic features were not graded in intraductal spread of carcinoma because high-grade cytology is one of the diagnostic criteria of that phenomenon.16,19

Remote tumor foci, with a distance from a dominant tumor nodule of more than a section thickness (≥4 mm) and having the same morphology as the dominant tumor, were classified as satellite tumor foci; otherwise, they were interpreted as multifocal disease. Cases with extensive involvement of the prostate by tumor or multiple foci throughout the gland were excluded from this analysis. Another rejection criterion for classifying a remote tumor focus as a satellite was its association with high-grade intraepithelial neoplasia.

Contingency-table analysis of categoric data was performed with either a χ² test or a Fisher exact test when appropriate with SAS software (version 9.2, SAS Institute, Cary, North Carolina). Differences in means of continuous variables (age, weight, volume, and percentage) were analyzed using the 2-tailed t test. Analytic results were considered significant at P < .05. Logistic regression analysis was used for multivariate analysis.

**RESULTS**

From 2000 to 2010, 124 of 5213 (2.4%) and 150 of 11526 (1.3%) radical prostatectomy specimens had pelvic LN+ at Henry Ford Hospital and The Johns Hopkins Hospital, respectively. Of the 184 cases of GS 7 with LN+; 51 (27.7%) and 133 (72.3%) were contributed by Henry Ford Hospital and The Johns Hopkins Hospital, respectively. From 2005 to 2010 at The Johns Hopkins Hospital, 7.4% (482 of 6476) of radical prostatectomy specimens had GS 8 to 10, compared with 10.2% (383 of 3760) at Henry Ford Hospital. Similarly, GS 7 at radical prostatectomy was also more prevalent at Henry Ford (60%; 2256 of 3760) than it was at The Johns Hopkins Hospital (37.8%; 2443 of 6476). None of the cases with LN+ at either institution had GS 6 or less. At Henry Ford Hospital, the Gleason-specific incidence of LN+ from 2005 to 2010 was 1.8% (40 of 2256, GS 7) and 16.4% (63 of 383, GS ≥ 8), whereas at The Johns Hopkins Hospital, it was 1.9% (46 of 2443, GS 7) and 10.0% (48 of 482, GS ≥ 8). There were only very rare cases at either The Johns Hopkins Hospital or Henry Ford Hospital that were aborted, and those were only cases with a grossly positive LN which had the prostatectomy canceled. Subsequent analyses combine the data from both institutions.

There was no difference (P = .08) seen in ages between metastatic (mean, 59.2 years; range, 40–78 years) and control group (mean, 60.5 years; range, 44–81 years). Mean preoperative PSA was significantly (P = .001) higher in LN+ cases (12.2 ng/mL; range, 2–113.3 ng/mL) than in LN− cases (8.1 ng/mL, range, 2–96.8 ng/mL). The fraction of positive biopsy cores (ie, the number of positive cores divided by the total number of biopsy cores) was higher for LN+ cases than it was for LN− cases (59.1% versus 42.9%, P < .001).

At radical prostatectomy, the distribution of GS in LN+ cases was as follows: GS 3 + 4 = 7 (n = 64; 34.8%), GS 4 + 5 = 7 (n = 66; 35.9%), GS 3 + 4 = 7 with tertiary 5 (n = 10; 5.4%), and GS 4 + 3 = 7 with tertiary 5 (n = 44; 23.9%). The same number of Gleason-matched cases was analyzed in the control group. The number of positive LNs per case varied from 1 to 11 (mean, 1.4). The average number of dissected LNs was 12.7 in LN+ cases (range; 1–35), and in LN− cases it was 9.4 (range, 1–32) (P < .001). Sixteen cases (8.7%) were organ confined (pT2). Ninety percent of pT3 LN+ cases (152 of 168) showed nonfocal extraprostatic extension, whereas in the pT3 control group, nonfocal...
extraprostatic extension was seen in 69.6% (117 of 168) of cases \( (P < .001) \). Analyzing pT3 subcategories, 54.2% (91 of 168) of LN\(^+\) cases had pT3b stage, whereas only 16.1% (27 of 168) of the LN\(^-\) cases were pT3b. The pT3b cases with LN\(^+\) showed more-frequent lymphovascular invasion in the seminal vesicles and/or surrounding soft tissue (52%; 47 of 91) compared with the pT3b cases with LN\(^-\) (30%; 8 of 27) \( (P = .05) \). Mucinous Gleason pattern 4 carcinoma was seen in 2 LN\(^+\) cases (1.1%) and 12 LN\(^-\) cases (6.5%) \( (P = .006) \). There was no statically significant difference in the incidence of prostatic duct carcinoma component in LN\(^+\) (5 of 184; 2.7%) and LN\(^-\) (2 of 184; 1.1%) cases. Other radical prostatectomy findings stratified by the presence of LN\(^+\) are depicted in Table 1. Statistically significant differences between the groups were seen in most analyzed features. Among them were prostate weight, tumor volume, size of nuclei and nucleoli (Figure 1, A and B), extent of macronucleoli, frequency of lymphovascular invasion (Figure 2, A and B), intraductal spread of carcinoma (Figure 3, A and B), presence of satellite tumor foci (Figure 4), and patterns of Gleason 4 carcinoma (Figure 5, A through D). After performing logistic regression analysis, including lymphovascular invasion, intraductal spread of carcinoma, tumor volume, fraction of positive biopsy cores, and PSA, only lymphovascular invasion and tumor volume proved to be independent predictive variables of LN\(^+\).

Regardless of LN status, average tumor volume in cases with lymphovascular invasion was 27.2% \( (n=215; \text{range}, 2-95\%) \), compared with 13.8% \( (n=153; \text{range}, 1-70\%) \) in cases negative for lymphovascular invasion \( (P < .001) \). Similarly, average tumor volume was 30.1% \( (n=116; \text{range}, 3-95\%) \) in cases with intraductal spread of carcinoma, compared with 17.7% \( (n=252; \text{range}, 1-90\%) \) without this finding \( (P < .001) \). Lymphovascular invasion and intraductal spread of carcinoma were more common in cases with a high proportion of cribriform and/or poorly formed architecture in Gleason 4 pattern. Both of these findings were less likely in cases where more of the Gleason 4 pattern was represented by glomeruloid and/or fused glands (Table 2). Ninety-three percent of cases with satellite tumor foci (28 of 30) demonstrated lymphovascular invasion, compared with 48.5% in cases (132 of 272) without this finding \( (P < .001) \).

### Table 1. Findings in Radical Prostatectomies in Cases With and Without Lymph Node Metastases

<table>
<thead>
<tr>
<th>Variable</th>
<th>LN(^+)</th>
<th>LN(^-)</th>
</tr>
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<tbody>
<tr>
<td>Prostate weight ((P = .007), g, mean (SD)/range)</td>
<td>54.5 (20.5)/22–136</td>
<td>49.4 (15.1)/24–113</td>
</tr>
<tr>
<td>Tumor volume ((P &lt; .001), % mean (SD)/range)</td>
<td>28.9 (24.6)/13–95</td>
<td>14.8 (11.6)/1–65</td>
</tr>
<tr>
<td>Lymphovascular invasion ((P &lt; .001), %)</td>
<td>78.3 (n=144)</td>
<td>38.6 (n=71)</td>
</tr>
<tr>
<td>Intraductal spread of carcinoma ((P &lt; .001), %)</td>
<td>42.4 (n=78)</td>
<td>20.7 (n=38)</td>
</tr>
<tr>
<td>Satellite tumor foci ((P &lt; .001), %)</td>
<td>16.4 (n=23)</td>
<td>4.3 (n=7)</td>
</tr>
<tr>
<td>Gleason 4 pattern, mean % in tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cribriform ((P = .04))</td>
<td>28.9</td>
<td>23.7</td>
</tr>
<tr>
<td>Glomeruloid ((P = .01))</td>
<td>5.5</td>
<td>10.5</td>
</tr>
<tr>
<td>Poorly formed ((P &lt; .001))</td>
<td>29.0</td>
<td>15.9</td>
</tr>
<tr>
<td>Fused ((P &lt; .001))</td>
<td>36.6</td>
<td>49.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Cytology, average of 1–3 scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear enlargement ((P &lt; .001))</td>
<td>2.03</td>
<td>1.63</td>
</tr>
<tr>
<td>Size of macronucleoli ((P = .002))</td>
<td>1.63</td>
<td>1.45</td>
</tr>
<tr>
<td>Nuclear pleomorphism ((P = .44))</td>
<td>1.89</td>
<td>1.93</td>
</tr>
<tr>
<td>Nuclear extent ((P = .005))</td>
<td>1.64</td>
<td>1.45</td>
</tr>
</tbody>
</table>

**Abbreviations:** LN\(^+\), positive for lymph node metastases; LN\(^-\), negative for lymph node metastases.

* Total of 140 patients included in LN\(^+\) group, and 162 in LN\(^-\) group (see inclusion criteria in text).

### COMMENT

To our knowledge, this is the first work focusing on comparing the morphologic findings at radical prostatectomy between GS 7 cases with and without pelvic LN\(^+\). We combined the specimens from 2 large, tertiary care, referral institutions to acquire more statistical power from the data. Our goal was to analyze features specifically in GS 7 disease to highlight which features are typical of metastatic cancers. GS 7 cancer with tertiary pattern 5 has significantly more-aggressive behavior than pure GS 7 PC.21–25 For this reason, we matched LN\(^+\) cases for an equivalent number of LN\(^-\) cases with tertiary pattern 5.

Higher-grade tumor was more prevalent at radical prostatectomy in Henry Ford Hospital compared with The Johns Hopkins Hospital. The potential explanation is that patients with higher-grade tumors might have been more often treated by radical prostatectomy at Henry Ford Hospital than they were at The John Hopkins Hospital, reflecting differences in surgical-selection criteria. Patients with obvious systemic metastases were not considered candidates for surgery in either institution. Other subtleties in preoperative workup are less likely to explain the observed difference in the incidence of aggressive disease. The same may explain the difference in LN\(^+\) frequency (124 of 5213, 2.4%; versus 150 of 11 526, 1.3%) because both institutions had similar dissection and pathologic processing of pelvic LNs. However, this study did not include cancers of GS greater than 7 for analysis, which were probably different between the 2 institutions and largely accounted for the overall difference in the incidence of LN\(^-\). Rather, we focused only on GS 7 disease, which had an equal incidence of LN\(^-\) at both institutions.

Prior works have demonstrated the role of tumor volume as a risk factor of progression in PC.26–29 The current study looking at only cases with radical prostatectomy GS 7 cancer found tumor volume was twice as high in patients with LN\(^+\) (28.9%) compared with nonmetastatic cases (14.8%). Logistic-regression analysis demonstrated tumor volume as an independent risk factor of LN\(^+\), whereas many other variables were interrelated. In cases with high tumor volume, lymphovascular invasion and intraductal spread of carcinoma were frequently seen as well. Tumor volume correlates well with serum PSA levels,30 which is consistent
Figure 1. Cytology. A, Grade 3 cytology with large and pleomorphic nuclei, prominent nucleoli, high nuclear-cytoplasmic ratio, and deeply amphophilic cytoplasm. B, Grade 1 cytology; features are the opposite of those in Figure 1, A, despite higher Gleason grade (hematoxylin-eosin, original magnifications ×400 [A and B]).

Figure 2. Lymphovascular invasion. A, Intravascular tumor attached to a vessel wall. Note the disproportional size of the tumor embolus and vessel size and the proteinaceous material occupying vascular lumen. B, Microvasculature invasion. Erythrocytes and more amphophilic staining of cytoplasm may facilitate recognition of vascular invasion (hematoxylin-eosin, original magnifications ×200 [A and B]).

Figure 3. Intraductal spread of carcinoma. A, Intraductal spread with comedo necrosis. B, Dense cribriform pattern of intraductal carcinoma with residual corpora amylacea (hematoxylin-eosin, original magnifications ×200 [A and B]).
with our finding demonstrating the 50% difference in mean preoperative PSA levels between the 2 groups (12.2 ng/mL versus 8.1 ng/mL). By itself, a high level of preoperative PSA is associated with higher risk of LN\textsuperscript{+}.\textsuperscript{31} There was a higher fraction of positive cores in biopsies from the metastatic cases, reflecting previously reported correlations between the number of positive cores on biopsy and tumor volume at radical prostatectomy.\textsuperscript{32}

The mean weight of the prostates in the metastatic cases was on average 5 g higher than it was in the control group. This result conflicts with prior studies, which concluded that there was an inverse correlation between prostate weight and more-advanced disease.\textsuperscript{33–35} However, none of the reviewed studies analyzed prostate weight in respect to LN status, and we find our observation novel.

As expected, the stage distribution was more in keeping with the aggressive behavior of metastatic carcinoma.\textsuperscript{3} Less than 9% of the cases (16 of 184) were organ confined. Nonfocal extraprostatic extension dominated in cases with LN\textsuperscript{+}. Seminal vesicle invasion (pT3b) was seen in nearly half of the cases with LN\textsuperscript{+} (91 of 184) as opposed to only 14.7% in the control group (27 of 184). On average, LN\textsuperscript{+} cases had 3 more LNs dissected than did LN\textsuperscript{−} cases. Other studies have also stressed the importance of higher numbers of dissected LNs in accurate nodal staging of prostate cancer.\textsuperscript{36,37}

Gleason pattern 4 has more variability in its patterns than any other grade has. It includes poorly formed, fused, cribriform, and glomeruloid architectures.\textsuperscript{6} Prostatic duct adenocarcinoma, mucinous (colloid), and hypernephromatoid adenocarcinoma are considered equivalent to Gleason pattern 4 conventional acinar adenocarcinoma.\textsuperscript{6} Poorly formed and cribriform patterns comprised a higher proportion of Gleason 4 cancer in cases with LN\textsuperscript{+}. Moreover, both of these patterns were associated with other features of aggressive phenotype, such as intraductal spread of carcinoma and lymphovascular invasion. In a recent work, Iczkowski et al\textsuperscript{38} reported that, among Gleason 4 pattern, cribriform had a particularly adverse implication for outcome in 153 men. In their series, 46 of 76 patients with PSA failure (61%) had cribriform pattern 4 component at radical prostatectomy compared with 12 of 77 patients without biochemical recurrence (16%), \(P < .001\). Our series demonstrates a similar significance of cribriform Gleason 4 pattern in GS 7 disease along with the adverse association of poorly formed glands. The opposite is true for fused and glomeruloid patterns seen to a larger extent in cases without LN\textsuperscript{+}. This observation is in keeping with our prior study describing glomeruloid glands as an early pattern of cribriform glands.\textsuperscript{7} Some experts regard mucinous PC as equivalent to Gleason pattern 4, whereas others grade based on the underlying architectural pattern.\textsuperscript{6} The current study found that mucinous GS 7 PC, defined based on the underlying architectural pattern, had a low incidence of metastasis. Similar conclusions were made by Lane et al\textsuperscript{14} and Osunkoya et al\textsuperscript{15} who collectively analyzed 61 cases of poor mucinous adenocarcinomas of the prostate and concluded that their behavior might be less aggressive than conventional acinar prostate adenocarcinoma. The later authors reported regional LN\textsuperscript{+} metastasis in only 1 of 47 cases (2%) with available information.

Prostate cancer grading differs from other epithelial malignancy grading systems (eg, the International Federation of Gynecology and Obstetrics [FIGO] and the Nottingham grading systems in gynecologic and breast pathology, respectively) by lack of incorporation of cytologic features. Higher-grade cytology is reported as a feature of prostatic duct adenocarcinoma and intraductal spread of carcinoma.\textsuperscript{18,19,39} In our series, most metastatic cases demonstrated higher-grade cytology, but occasional metastatic cases had higher-grade cytology.
bland cytology, scoring the lowest points in all 4 cytologic categories analyzed. The differences between the study and control groups in nuclear enlargement, nucleolar size and extent were highly significant, although there was no significant difference in nuclear pleomorphism. There have been numerous works during the past 20 years analyzing cytology in prostatic carcinoma to use it as an ancillary factor for Gleason grading. Hofer et al performed a study on 110 radical prostatectomies with N1 status and found nuclear grade as a significant risk factor for LN+. Several publications released during the past few years by the Johns Hopkins group indicate the predictive value of nuclear morphometry (eg, nuclear enlargement, nuclear pleomorphism, chromatin nature, among others) assessed by computer-assisted image

### Table 2. Relationship of Lymphovascular Invasion and Intraductal Spread of Carcinoma With Average Proportions of Different Patterns of Gleason Grade 4 Carcinoma in Prostatectomy Specimens

<table>
<thead>
<tr>
<th>Gleason 4 Pattern</th>
<th>LVI</th>
<th>IDS</th>
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<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Poorly formed, %</td>
<td>25.5</td>
<td>18.9</td>
</tr>
<tr>
<td>Fused, %</td>
<td>36.3</td>
<td>51.7</td>
</tr>
<tr>
<td>Cribriform, %</td>
<td>31.3</td>
<td>19.9</td>
</tr>
<tr>
<td>Glomeruloid, %</td>
<td>6.9</td>
<td>9.5</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Abbreviations: LVI, lymphovascular invasion; IDS, intraductal spread.

* Data are in mean proportions of individual Gleason 4 patterns in cases with (Yes) and without (No) analyzed feature. Data calculated from 368 specimens.
In one recent work by Wittschieber et al., the authors tried to apply the Fuhrman grading system to prostatic carcinoma, correlating it to GS. Although based on nuclear enlargement and size of nuclei, there was no association with pathologic T stage, the authors did not address the association between the nuclear grade and pathologic LN status. Based on our observations and reviewed literature, at the current stage, we do not recommend describing cytocentric features in routine clinical reports. However, as our study indicates, there is additional prognostic information that can be gleaned from cytology of prostate cancer that warrants further research.

Lymphovascular invasion is an established independent risk factor for adverse outcome in prostatic carcinoma. For assessment of lymphovascular invasion, we used strict criteria and interpreted equivocal cases as negative. We elected not to use immunohistochemical assessment of lymphovascular invasion because that is not a routine clinical practice. Characteristics we find valuable in distinguishing true vascular invasion from a retraction artifact are (1) vessel walls that are usually convoluted in contrast to the rigid smooth borders of clefts, (2) vessel shapes that do not repeat the contour of the tumor mass, (3) vessel size that is disproportionately larger than the tumor size is, (4) a visualized, continuous, endothelial cell layer, and (5) the presence of red blood cells or fibrin in the lumen. The tumor emboli may be attached to a vessel wall or, more commonly, free floating within the lumen. Our findings indicate that lymphovascular invasion is one of the features distinguishing aggressive disease in GS 7 cancers. With tumor volume, these were the only 2 independent variables in multivariate analysis that correlated with LN status in Gleason-matched cases. Lymphovascular invasion was 2 times more frequent in metastatic cases (78.3%; 144 of 184) than it was in the control group (38.6%; 71 of 184). The frequency of lymphovascular invasion in LN− cases was comparable to that reported recently by Tokuda et al. Our relatively high frequency of lymphovascular invasion in LN− cases is comparable to other reports. Herman et al. analyzed 157 GS 7, pT3N0, consecutive radical prostatectomies and found lymphovascular invasion in 36% of them (n = 56). The incidence of lymphovascular invasion in GS 8 cases almost doubled in their series (61%; 19 of 31). In our series, pT3b cases with LN+ had a higher incidence of lymphovascular invasion in seminal vesicles or the perivesical soft tissue. In some cases, lymphovascular spread may be a mechanism of progressing to pT3b stage in cases with LN−. Intraductal spread of prostatic carcinoma is a feature typically seen in GS 8 to GS 10 disease. Because of overlapping features with high-grade prostatic intraepithelial neoplasia, strict criteria need to be applied to diagnose intraductal carcinoma. The most critical scenario to distinguish intraductal spread from high-grade prostatic intraepithelial neoplasia and invasive Gleason grade 4 carcinoma is when interpreting a needle core biopsy. In our cohort, intraductal spread was seen associated with large tumor nodules. No intraductal spread of carcinoma was seen in low-volume tumors. Approximately 40% of cases (78 of 184) in the metastatic group demonstrated intraductal spread of carcinoma, whereas that feature was seen in only about 20% of cases (38 of 184) in the control group. The frequency of intraductal spread of carcinoma was directly related to the proportion of the cribriform Gleason 4 pattern, which is the closest mimicker of intraductal spread. The current study supports prior data that intraductal spread of carcinoma is a phenotype associated with aggressive prostate cancer.

The final feature analyzed was the presence of satellite tumor foci. A significantly higher proportion of cases in the metastatic group demonstrated this feature, which was also associated with lymphovascular invasion. We interpret this phenomenon as a possible intraprostatic spread of carcinoma by either lymphovascular routes or perineural spaces akin to intramammary spread seen in a subgroup of patients with multifocal breast cancer.

Analyzing loss of heterozygosity, size of microsatellites, and X-chromosome inactivation pattern, similar concept of intraorgan metastases has been advocated in other organs, such as lung, kidney, liver, and thyroid. Using the same methodology, other researchers have demonstrated a field cancerization effect giving rise to multiple primary independent foci of cancer in epithelial organs. Moreover, in hollow organs intraluminal seeding and intraepithelial migration of malignant epithelia have been documented resulting in multifocal cancer. Despite the scientific evidence of intraorgan metastasis in other organs, such phenomenon in the prostate may face a traditionally believed dogma of primary multifocal disease. Further molecular investigations and additional focused studies are needed to discover its nature and demonstrate its clinical implications.

In summary, within GS 7 prostatic carcinoma, there are significant differences between the cases with and without metastases in the LN. Some of the factors are well known in the literature as adverse features, including high preoperative PSA levels, high tumor volume, and lymphovascular invasion. Others are less well recognized, such as intraductal spread of the tumor, satellite tumor foci, and high nuclear grade, as determined by nuclear enlargement and size and frequency of macronucleoli. Future studies should include analysis of these variables as prognostic markers of GS 7 carcinoma in biopsy specimens as well as in radical prostatectomies with LN− or for men who have not had LN dissection.

The authors thank Mani Menon, MD, and Mireya Diaz, PhD, Vattikuti Urology Institute, Henry Ford Hospital (Detroit, Michigan) for providing statistical data on prostate cancer incidence at Henry Ford Hospital and their critical review of the manuscript.

References


