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## DO ADENOCARCINOMAS OF THE PROSTATE WITH GLEASON SCORE (GS) $\leq 6$ HAVE THE POTENTIAL TO METASTASIZE TO LYMPH NODES?

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### Abstract

Although rare, there are cases within reported series of men with GS  $\leq 6$  in radical prostatectomies that have pelvic lymph node (LN) metastases. However, there are no studies as to whether pelvic LN metastases occur in tumors GS  $\leq 6$  using the International Society of Urological Pathology (ISUP) updated Gleason scoring system. We performed a search of the radical prostatectomy databases at 4 large academic centers for cases of GS  $\leq 6$ . Only prostatectomies submitted and embedded in entirety with pelvic lymph node dissections were included. A combined total of 14,123 cases were identified out of which 22 cases had a positive LN. Histopathology review of 19 cases (3 cases unavailable for review) showed higher grade than originally reported by the pathologists in all cases. Of the 17 pre-ISUP reviewed cases, 2 were upgraded to 4+3=7 with both cribriform and poorly formed glands. One case was upgraded to 4+3=7 with tertiary pattern five displaying cribriform glands, poorly formed glands, and cords of single cells. Eleven cases were upgraded to 3+4=7 with glomeruloid structures and small to large cribriform glands (1 of these also had ductal adenocarcinoma features). Two cases had tertiary pattern 4 with small cribriform glands. One case had a prominent colloid component that would currently be graded as 4+5=9 due to large cribriform glands and solid sheets of cells within mucin. Of the two post-ISUP cases, one demonstrated tertiary pattern 4 and the other showed Gleason score 3+4=7 with irregular cribriform glands. Under-grading primarily accounts for LN positivity with GS  $\leq 6$ , which has decreased significantly since the adoption of the ISUP grading system in 2005. Out of over 14,000 totally embedded RPs from multiple institutions, there was not a single case of a GS  $\leq 6$  tumor with LN metastases. In contrast to prevailing assumptions, Gleason score  $\leq 6$  tumors do not appear to

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metastasize to lymph nodes. Rather, Gleason patterns 4 or 5, as better defined by the current ISUP updated grading system, is required for metastatic disease.

### Keywords

Gleason score; radical prostatectomy; lymph node metastases

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## INTRODUCTION

Men with Gleason score (GS)  $\leq 6$  on biopsy are considered to have a risk, albeit very low, of lymph node (LN) metastases at radical prostatectomy (RP). The updated Partin Tables predict a percent probability of LN metastases at RP of  $\sim 1\%$  for men with biopsy GS  $\leq 6$  if the PSA is also less than  $\sim 10$  ng/ml. The predicted rate increases up to 5% if the PSA is  $>10$  ng/ml and the clinical stage is T2b or T2c.<sup>(20)</sup> These cases could suffer from sampling artifact where higher grade cancer in the RP accounts for the source of the metastatic disease. However, large series of RP from both single and multi-institutional data sets confirm the low rate of LN metastases for men with GS  $\leq 6$  at RP. (2,6,7,26,33,34)

All of these series include cases that were graded prior to the publication of the 2005 International Society of Urology Pathology (ISUP) consensus conference on Gleason grading.<sup>(9)</sup> The consensus paper outlined several patterns of Gleason 4 that in the past were considered as Gleason pattern 3 if one strictly used the original 1967–1971 Gleason grading system. In the current study, we performed a multi-institutional review of RP specimens with reported GS  $\leq 6$  or less and LN metastases. We hypothesized that these cases would be undergraded according to the modern post ISUP grading scheme and that true Gleason pattern 3+3=6 does not have the potential to metastasize to lymph nodes.

## MATERIALS AND METHODS

A total of 14,123 RPs from 1975–2010 reported as GS  $\leq 6$  were identified from the combined RP databases of four large academic centers. Participating institutions were The Johns Hopkins Hospital, Henry Ford Hospital, University of California San Francisco (UCSF), and Baylor College of Medicine. Only RPs that were serially sectioned and entirely submitted were included in this study. Cases were additionally split into two groups with December 2004 as the breakpoint, reflecting when information of the updated ISUP Gleason grading scheme was available for the authors of the current study.

The extent of pelvic lymph node dissection was variable between surgeons. At all the institutions, given that the vast majority of the patients in the current study were low risk preoperatively, most urologists performed a standard node dissection consisting of the obturator and external iliac lymph nodes, with a minority performing extended dissections also removing the internal iliac nodes. For all participating institutions, the mean number of lymph nodes removed including both the left and right sides was 8.7.

Of the 10,935 men identified in the RP database at The Johns Hopkins Hospital (JHH), 25 cases were coded by urologists in the database as GS  $\leq 6$  with a positive LN. Three cases were excluded due to an error in database entry or coding: pathologic reports confirmed either a higher grade or lack of positive LN. Another two cases were excluded due to presence of a tertiary pattern 4 described in the initial pathology report but not accounted for in the database. Of the remaining 20 cases, 18 had blocks and/or slides available for review. Of the 3,188 men identified in the RP databases at the remaining three academic centers (Henry Ford Hospital, UCSF, Baylor College of Medicine) combined, 6 cases were coded

by in the database as GS 6 with a positive LN. Similar to the JHH database, four cases were excluded to an error in database entry or coding: pathology reports confirmed higher grade in two cases or lack of a positive LN in another two cases. Of the remaining two cases, one case was available for review, yielding a total of 19 cases for review from all institutions.

Significance testing was performed for continuous variables using a t-test for the comparison of means. For dichotomous variables we performed the Pearson's chi-square test. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using STATA release 12 (StataCorp LP, College Station, Texas, USA).

## RESULTS

Considering the RP database at JHH separately, 10,935 men were identified with GS 6 at RP: 7,332 pre-ISUP and 3,603 post-ISUP. The pre-ISUP group appeared to have worse disease than the post-ISUP group with a higher mean pre-surgery PSA levels (6.3 versus 5.2,  $p < 0.0001$ ). Similarly, pre-ISUP, there were 19 cases with positive LNs compared to only 1 case post-ISUP (0.26% vs 0.03%,  $p = 0.008$ ). Eighteen of 19 pre-ISUP cases with LN metastases had non-focal extraprostatic extension (EPE) with 4 invading seminal vesicles. The 1 post-ISUP case with a LN metastasis had focal EPE.

Out of the combined total of 14,123 cases from all 4 academic centers, including JHH, 22 cases were identified with GS 6 and a positive LN. Histopathologic re-review showed higher grade than originally reported by the pathologists in all 19 reviewed cases (three unavailable for slide review) (Table 1). Of the 17 pre-ISUP cases, two were upgraded to 4+3=7 displaying both cribriform and poorly formed glands. One case was upgraded to 4+3=7 with tertiary pattern five displaying cribriform glands, poorly formed glands, and cords of single cells (Fig. 1). Eleven cases were upgraded to 3+4=7 showing several patterns considered Gleason 4 including glomeruloid structures, small to large cribriform glands, and ductal adenocarcinoma features (Fig. 2A–C). Two cases had a tertiary pattern 4 with small cribriform glands (Fig. 2D). One case had a prominent colloid carcinoma component that had not been factored into the grade in the original pathologic report. This case would be currently graded as 4+5=9 with large irregular cribriform glands and solid sheets of cells within pools of mucin (Fig. 2E). Of the two post-ISUP cases, one demonstrated a cribriform gland of tertiary pattern 4 present on deeper section as the original slides were not available. The second post-ISUP case was reported as 3+4=7 on biopsy. Although the RP Gleason score was initially reported as 3+3=6, re-review showed Gleason score 3+4=7 with irregular cribriform glands (Fig. 2F).

## DISCUSSION

Reported large series of RP from both single and multi-institutional data sets report, albeit at a low rate, that GS 6 cancer has the ability to metastasize to pelvic lymph nodes. Von Bodman et al. evaluated biochemical recurrence in patients with positive LN at RP and reported 3 patients with GS 6 and positive LN out of a total cohort of 4,648.(33) Similarly, Allaf et al. reported 2 patients with GS 6 and a positive LN out of 4000 radical prostatectomies performed between 1992–2003.(2) A multi-institutional series evaluating pre-operative LN metastases prediction tools, used data from the Surveillance, Epidemiology, and End Results (SEER). Out of 7,765 men identified with GS 6 on RP, LN metastases were reported in 17 (0.2%).(1) Other large outcome series have shown higher LN metastasis rate of up to 3% in men with reported GS 6 at RP.(6,7,26,34)

In order to determine the true rate of GS 6 with positive LN at RP, we retrospectively identified and histologically reviewed these cases using the updated Gleason grading

schema. Prior to histological review of the cases in the current study, a hypothesis to explain the higher incidence of GS 6 with LN metastases pre vs. post 2005 might have been that the earlier era encompassed cases prior to PSA detected prostate cancer; pre PSA larger GS 6 tumors might have had an increased risk of LN metastasis. This explanation would have been consistent with the higher pre-operative mean PSA in the pre-2005 cases when compared to the cohort post-2005.

However, histological review confirmed that under-grading primarily accounted for the larger number of cases with LN positive GS 6 in the pre-ISUP era. Combining all 4 academic centers, 14 pre-ISUP cases were upgraded to Gleason score 7 (3+4 in 11 cases, 4+3 in 2 cases, 4+3 with tertiary 5 in 1 case). Cribriform glands were present in all 14 cases and represented the dominant source of upgrading on review of the slides. A major point of divergence of the updated from the original Gleason system is grading cribriform glands. Within Gleason's original illustrations of his cribriform pattern 3, he depicted large, cribriform glands.<sup>(10)</sup> At the time of the 2005 ISUP grading consensus meeting, expert uropathologists uniformly had been diagnosing these lesions as cribriform pattern 4. The consensus conference proposed extremely stringent criteria for cribriform Gleason pattern 3.<sup>(9)</sup> However, when various images were shown to the participants of the consensus meeting, almost none of them met the criteria for cribriform pattern 3 based on subtle features, such as slight irregularities of the outer border of the cribriform glands. It was the consensus that the vast majority of cribriform patterns be diagnosed as Gleason pattern 4 with only rare cribriform lesions satisfying diagnostic criteria for cribriform pattern 3. Subsequent to the 2005 meeting, a study reviewed 3590 consecutive prostate cancers where 30 needle biopsy cases were selected that possibly represented cribriform Gleason pattern 3 cancer.<sup>(18)</sup> Even in a highly selected set of images thought to be the best candidates for cribriform pattern 3, most experts interpreted the cribriform patterns as pattern 4. There was poor reproducibility amongst experts as to cribriform pattern 3 vs. pattern 4 due to: 1) Disagreement as to what were the key diagnostic features in a given case (i.e. irregular distribution of lumina & variable slit-like lumina, favor pattern 4 vs. small glands & regular contour, favor pattern 3; and 2) Disagreement as to assessment of given criteria: regular vs. irregular distribution of lumina & regular vs. irregular contour. In a subsequent study specifically addressing the prognosis of cribriform prostate cancer glands, both small and large cribriform glands were equally linked to progression after radical prostatectomy.<sup>(16)</sup> These findings fit conceptually, as one would expect the change in grade from pattern 3 to pattern 4 to be reflected in a distinct architectural paradigm shift where cribriform as opposed to individual glands are formed, rather than merely a subjective continuum of differences in size, shape and contour of cribriform glands. The only reason why cribriform pattern 3 even exists is because of the original Gleason schematic diagram. Gleason never specifically published the prognostic difference between what he called cribriform Gleason pattern 3 compared to Gleason pattern 4. Many of Gleason's cribriform Gleason pattern 3 cancers may not even have been infiltrating carcinomas due to the lack of availability of immunohistochemistry for basal cell markers. Today we might have diagnosed them either as cribriform high grade PIN or intraductal carcinoma of the prostate (concepts not present in Gleason's era).<sup>(3,25)</sup> Based on all the above data, all cribriform cancer should be interpreted as Gleason pattern 4 and not pattern 3.

In the current series, three of our initially undergraded cancers also contained glomeruloid glands which we now regard as Gleason pattern 4. Glomeruloid structures are characterized by dilated glands containing an intraluminal cribriform structure with a single point of attachment. There was no consensus in the 2005 ISUP conference on grading glomeruloid glands. A study from our institution subsequent to the consensus conference indicated that glomerulations were overwhelmingly associated with concurrent Gleason pattern 4 or higher grade carcinoma.<sup>(19)</sup> One can also see a transition between small glomerulations, large

glomeruloid structures, and cribriform pattern 4 cancer. These data suggest that glomerulations represent an early stage of cribriform pattern 4 cancer and are best graded as Gleason pattern 4.

Other minor patterns responsible for upgrading in our series included 3 cases with poorly formed glands and one with ductal adenocarcinoma features. These patterns were also only added to the Gleason grading schema as Gleason pattern 4 after the ISUP consensus panel in 2005.(9)

The presence of tertiary pattern 4 in the RP represented a source of undergrading in several of our cases. In radical prostatectomy specimens, tertiary Gleason patterns are associated with higher pathological stage and biochemical recurrence as compared to the same Gleason score cancers without tertiary patterns. (12,13,22,24,27,28,30,32,35) Gleason score 3+3=6 with tertiary pattern 4 has a prognosis that is in between Gleason score 3+3=6 without tertiary pattern 4 and Gleason score 3+4=7. A problem with tertiary grade patterns in RP is that they are not incorporated in the Gleason score but just noted separately in the pathology report. When institutions report GS in their databases and subsequent articles relating to their databases, tertiary patterns are typically not included, which occurred in two cases within the current series. Another three cases had tertiary grade patterns that were identified on review that were not noted in the original pathology report; tertiary grade patterns in RP were only first emphasized in 2000. (22,24)

One case in our series was upgraded to Gleason 4+5=9. Upon review, there was a large colloid carcinoma dominant nodule that had irregular cribriform structures and sheets of cells floating in mucin. Gleason pattern 3+3=6 was seen in a separate nodule. The original pathology report had only assigned a grade to the non-colloid adenocarcinoma. The ISUP consensus panel was split on whether to grade all colloid carcinomas as 4+4=8 or ignore the extracellular mucin and grade the tumor on the underlying architecture. Either method used would still upgrade the tumor in our case.

In addition to upgrading due to utilization of the updated Gleason grading system, 7 cases initially identified as GS 6 with LN metastasis in our databases represented an error in database entry. One study analyzing error in research oncology databases at a single institution detected error rates up to 13.5% per database.(11) Errors were commonly seen with both incorrect and missing information.

One potential criticism of our study is that we did not review the cohort of GS 6 RP without LN metastases. Presumably, some of those cases would also be upgraded upon review. Although it may have reduced the denominator of total number of GS 6, the numerator of cases with GS 6 and LN metastasis would have been unchanged. Our conclusion would similarly be the same that reports of LN metastases of GS 6 at RP are most likely due to pathologic undergrading. Another limitation of the current study is that most patients did not undergo extended lymph node dissection, such that metastases may have been missed. However, the more limited node dissection is currently standard of care in the United States for low risk patients.

This study was particularly difficult to perform since many institutions do not submit and embed the prostate in its entirety. Otherwise, one could not be sure that a small focus of Gleason pattern 4 was left unsampled. Even for the institutions in the current series, some potential cases were limited by an only recently adopted policy of total submission of the prostate in RP specimens. Additionally, many surgeons do not perform LN dissections at the time of surgery with a GS 6 on biopsy unless the patient appears to be clinically high stage and/or a high PSA. This restricted the number of participating institutions to 4 despite an initial attempt to include additional centers with large RP databases. However, out of over



14,000 totally embedded RPs from multiple institutions with concurrent LN dissections, there was not a single case of a GS  $\leq 6$  tumor with LN metastases. In contrast to prevailing assumptions, Gleason score  $\leq 6$  tumors do not appear to metastasize to LNs. Rather, Gleason patterns 4 or 5, as better defined by the current ISUP updated grading system, is required for metastatic disease.

The current study also indirectly supports that the updated Gleason system is more accurate. The majority of studies have found that the updated needle biopsy grade correlates better with radical prostatectomy grade than does the original Gleason grade system.(14,23,31) Several studies have also demonstrated better correlation between the updated radical prostatectomy grade and outcome, compared to the original Gleason system grade. (4,5,29,31) A consequence of the updated Gleason system is overall higher Gleason scores when compared to the original Gleason system, reflecting that some of the histological features of Gleason pattern 3 in the original Gleason system are now classified as Gleason pattern 4 in the updated Gleason system. (5,8,14,17,23,29) In the updated Gleason system, GS  $\leq 6$  is histologically more uniform with a more predictable excellent prognosis. In a previous study from one of the authors evaluating biochemical recurrence in men with pathologically organ-confined GS  $\leq 6$  at RP, histological review assigned a higher grade to 24 of 38 cases with recurrence. Excluding these regraded cases, biochemical and local recurrence in this population was extremely rare.(21) Even including patients with non-organ confined disease, patients with Gleason score  $\leq 6$  in the post-ISUP era have an excellent prognosis with a 5 year biochemical cure rate of 94.6% following RP (Hopkins unpublished data). In an associated study, post-operative follow-up of over 2500 patients with GS  $\leq 6$  at RP (median 5 years) showed no development of systemic disease or death due to prostatic adenocarcinoma.(15) Based on the current study, it can now be added that GS  $\leq 6$  using the updated system lacks the potential to metastasize to pelvic lymph nodes.

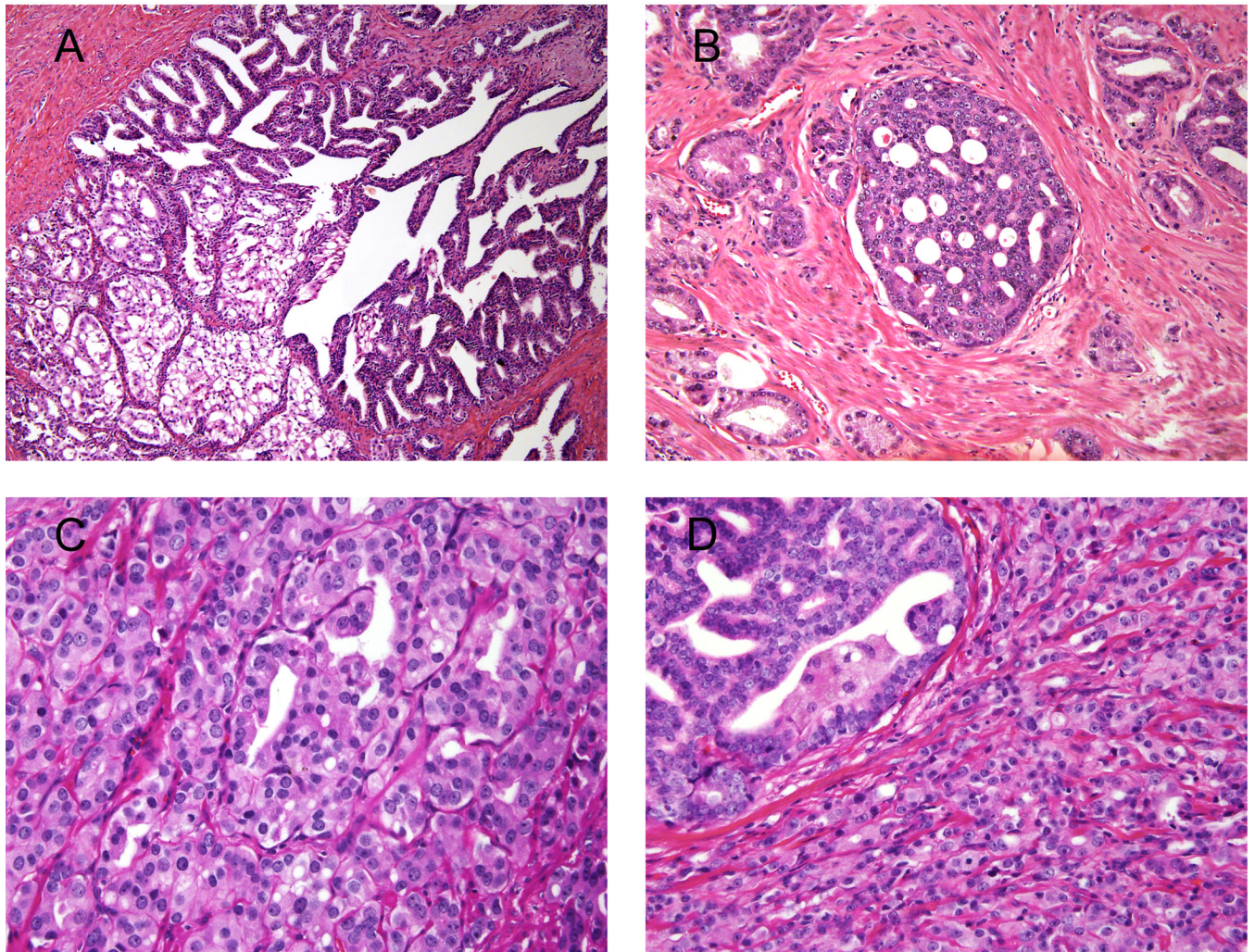
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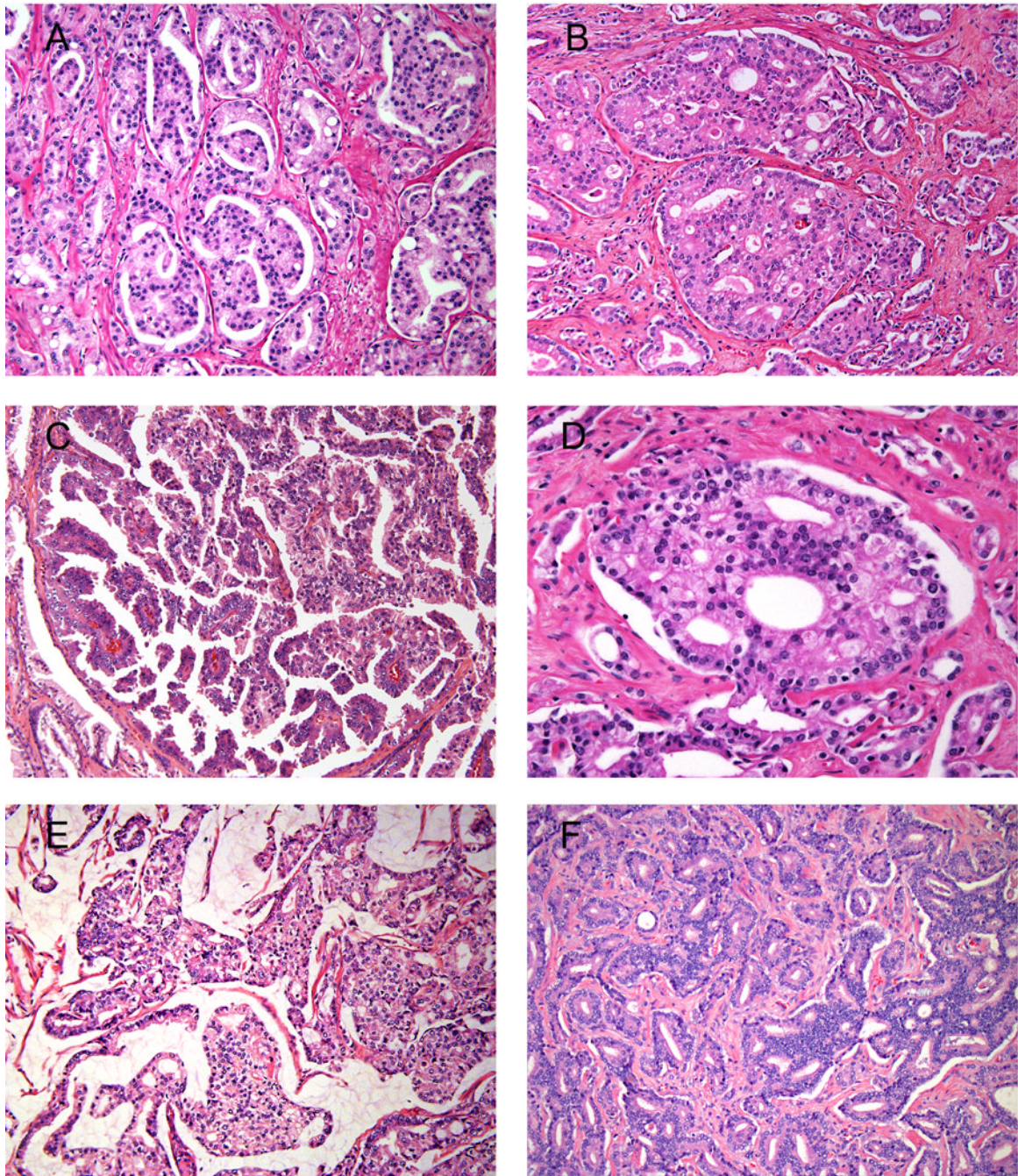




**Figure 1.**

Cases of Gleason score  $4+3=7$  and  $4+3=7$  with tertiary pattern 5 from our series. (A) Gleason pattern 4 cribriform glands invading seminal vesicles. (B) Gleason pattern 4 with medium-sized rounded cribriform gland that may have been considered pattern 3 prior to 2005. Associated small glands of pattern 3. (C) Gleason pattern 4 with poorly formed glands. (D) Gleason pattern 4 with a cribriform gland with adjacent tertiary component of Gleason pattern 5 consisting of cording of individual malignant cells comprising less than 5% of the tumor.





**Figure 2.**

(A) Gleason score 3+4=7 with Gleason pattern 4 glomeruloid glands transitioning to small cribriform glands. (B) Gleason scores 3+4=7 with Gleason pattern 4 medium to large irregular cribriform glands. (C) Case of Gleason score 3+4=7 demonstrating ductal adenocarcinoma features (Gleason pattern 3 not shown). (D) A tertiary component of Gleason pattern 4 consisting of small cribriform glands comprising less than 5% of the tumor. (E) Gleason score 4+5=9 with cribriform glands and sheets of malignant cells floating within mucin. (F) Gleason score 3+4=7 demonstrating medium-sized irregular cribriform glands in a post-ISUP case.

**Table 1**

Reclassification of “Gleason score 6” cancer with positive lymph nodes from 4 academic centers.

<b>Pathology at re-review</b>	<b>No. of cases</b>	<b>Patterns underdiagnosed</b>
<b>RP prior to 2005 (pre-ISUP group)</b>		
Gleason Score 3+3=6 with tertiary pattern 4	2	Cribriform glands
Gleason Score 3+4=7	11	Glomeruloid structures Cribriform glands Ductal adenocarcinoma (1 case)
Gleason Score 4+3=7	2	Cribriform glands Poorly formed glands
Gleason Score 4+3=7 with tertiary pattern 5	1	Cribriform glands Poorly formed glands Cords of single cells
Gleason Score 4+5=9	1	Colloid carcinoma with cribriform glands and solid sheets of cells
<b>RP after 2005 (post-ISUP Group)</b>		
Gleason Score 3+3=6 with tertiary pattern 4	1	Small cribriform glands
Gleason Score 3+4=7	1	Cribriform glands