ORIGINAL ARTICLE

The Clinical Significance of Either Extraprostatic Extension or Microscopic Bladder Neck Invasion Alone Versus Both in Men With pT3a Prostate Cancer Undergoing Radical Prostatectomy

A Proposal for a New pT3a Subclassification

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Abstract: The prognosis of prostate cancers exhibiting extraprostatic extension [other than bladder or seminal vesicle invasion (EPE)] and/or microscopic bladder neck invasion (mBNI) is variable, and further risk stratification is required. We herein assessed radical prostatectomy findings and long-term oncologic outcomes in consecutive 957 patients with pT3a disease. The patient cohort was divided into 4 groups, focal EPE (F-EPE) only (n=177; 18.5%), nonfocal/established (E-EPE) only (n = 634; 66.2%), mBNI only (n = 51; 5.3%). The rate of positive surgical margin and estimated volume of tumor were significantly higher in patients with both EPE and mBNI than in those with either. In addition, compared with F-EPE or mBNI only, E-EPE only was significantly associated with higher Grade Group, lymph node metastasis, and larger tumor volume. Kaplan-Meier analysis revealed a comparable prognosis after prostatectomy between those showing F-EPE only versus mBNI only ($P = 0.986$), and these 2 cohorts were combined for further analysis. Then, patients showing E-EPE only had a significantly higher or lower risk of progression compared with those showing F-EPE or mBNI only ($P < 0.001$) or both EPE and mBNI ($P < 0.001$), respectively. These significant differences in progression-free survival were also seen in subgroups, including those with or without undergoing adjuvant therapy before recurrence and those showing no lymph node metastasis. In multivariate analysis, F-EPE or mBNI only (hazard ratio = 0.524, $P = 0.003$) or both EPE and mBNI (hazard ratio = 1.465, $P = 0.039$) (vs. E-EPE only) showed significance for progression. Based on these findings, we propose a novel pT3a subclassification, pT3a1 (F-EPE or mBNI alone), pT3a2 (E-EPE alone), and pT3a3 (both EPE and mBNI).

Key Words: prostate cancer, extraprostatic extension, bladder neck invasion, prognosis, staging

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Prostate cancer remains one of the most commonly diagnosed malignancies among men.[1,2] Moreover, cancer-related deaths throughout the world have risen from 307,500 estimated in 2012[1] to 375,304 reported in 2020.[2] Although radical prostatectomy offers excellent oncologic outcomes in most patients with localized disease, a considerable number of these patients develop recurrent disease following surgery.[3,4] Accordingly, accurate risk stratification is critical for adequate patient management.

The spread of cancer beyond the boundary of the prostate (ie, "extraprostatic extension"), including invasion into the bladder and the seminal vesicle, is well known to be a key prognostic factor. Of these, the presence of extraprostatic extension (other than bladder or seminal vesicle invasion EPE) or microscopic bladder neck invasion (mBNI) is classified as pT3a in the current American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system for prostate cancer.[5] In various studies, EPE, compared with organ-confined pT2 disease, has been associated with a considerably higher risk of biochemical recurrence after radical prostatectomy.[6–10] Similarly, the prognostic impact of mBNI in radical prostatectomy cases has been explored.[6,7,11,12] Meanwhile, we recently demonstrated that the presence or absence of EPE and/or mBNI could prognostically stratify patients with pT3b prostate cancer exhibiting seminal vesicle invasion.[13]

Remarkably, pT3a prostate cancer does not uniformly indicate a poor prognosis. Indeed, attempts have been made to substage pT3a based on the extent of EPE.

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Although no specific method for its quantification is not yet established,[7] "extensive" EPE has been implicated as an independent risk factor.[9,10,14] In the present study, to further subclassify pT3a disease, we compared radical prostatectomy findings and long-term oncologic outcomes in men with pT3a prostate cancer exhibiting either EPE or mBNI versus both.

MATERIALS AND METHODS

Upon approval by the institutional review board including the request to waive the documentation of patient consent, we assessed consecutive patients who had undergone robot-assisted radical prostatectomy for prostate cancer at our institution between 2009 and 2018. Within our surgical pathology database, we identified a total of 957 men who met the inclusion criteria for pT3a disease after excluding those undergoing neoadjuvant therapy before prostatectomy.

Gleason score/Grade Group (GG) (primarily in "dominant" nodule(s) in each case) was reevaluated by a senior author (H.M.) based on the most recent recommendations by the International Society of Urological Pathology[15] as well as the Genitourinary Pathology Society.[16] We retrieved clinicopathologic findings, such as age at surgery, preoperative prostate-specific antigen (PSA) value, pN and surgical margin status, and estimated cancer volume. We then histologically reevaluated the presence or absence of EPE/mBNI. EPE was defined as a tumor extending out of the prostate into periprostatic soft tissue, and its extent was subdivided, based on the Epstein criteria,[17] into focal (only a few cancer glands, up to 3 in the present study; F-EPE) and nonfocal/established (more extensive; E-EPE). mBNI was defined as the microscopic involvement of the thick smooth muscle bundles characteristic of the bladder neck region by prostate cancer in the absence of benign prostatic glandular tissue, primarily in perpendicularly sectioned specimens.

Follow-up data for disease recurrence/progression and mortality were also collected. Biochemical recurrence in patients with no adjuvant therapy immediately after prostatectomy (n = 803) was defined as a single PSA level of ≥ 0.2 ng/mL or the introduction of adjuvant therapy. PSA failure in those undergoing adjuvant treatments, such as hormonal therapy (n = 38), radiotherapy (n = 67), or their combination (n = 49), before disease progression was defined as an increase in PSA value of ≥ 2 ng/mL or $\geq 50\%$ over nadir or the introduction of salvage therapy.[18,19] The PSA recurrence in those both with and without adjuvant therapy was considered a disease progression.

Data were analyzed using the Student *t* test for continuous variables and the χ^2 test or Fisher exact test for noncontinuous variables. The survival rate was calculated by the Kaplan-Meier method, and a comparison was made by the log-rank test. In addition, the Cox proportional hazards model was used to determine the statistical significance of prognostic factors in a multivariate setting. All statistical analyses were performed using EZR software,[20] a graphical user interface for R, version 4.0.2 (The R Foundation for Statistical Computing), or GraphPad Prism, version 5 (GraphPad Software). A *P*-value <0.05 was considered to be statistically significant.

TABLE 1. Clinicopathologic Features of 957 Patients

	n
Age (median/mean ± SD) (y)	63.9/63.7 ± 6.8
Preoperative PSA (median/mean ± SD) (ng/mL)	6.40/8.78 ± 7.99
GG	
1	3 (0.3%)
2	438 (45.8%)
2 with minor tertiary 5	41 (4.3%)
3	235 (24.6%)
3 with minor tertiary 5	69 (7.2%)
4	55 (5.7%)
5	116 (12.1%)
pT3a lesion	
F-EPE only	177 (18.5%)
E-EPE only	634 (66.2%)
mBNI only	51 (5.3%)
Both F-EPE and mBNI	9 (0.9%)
Both E-EPE and mBNI	86 (9.0%)
pN	
0	793 (82.9%)
1	89 (9.3%)
X	75 (7.8%)
Surgical margin	
Negative	711 (74.3%)
Positive	246 (25.7%)
Tumor volume (median/mean ± SD) (mL)	7.1/9.1 ± 7.1
Adjuvant therapy before recurrence	
Not performed	803 (83.9%)
Performed	154 (16.1%)

RESULTS

In a retrospective, blinded manner, we examined a total of 957 radical prostatectomy cases with pT3a disease. Table 1 summarizes the clinicopathologic features of these patients. Overall, F-EPE only, E-EPE only, mBNI only, and both EPE and mBNI were found in 177 (18.5%), 634 (66.2%), 51 (5.3%), and 95 (9.9%; F-EPE: n = 9; E-EPE: n = 86) of the cases, respectively.

We first compared clinicopathologic findings among the 4 groups (Table 2). The presence of both EPE and mBNI was significantly associated with a higher level of preoperative PSA, higher rate of positive surgical margin, larger estimated volume of tumor, and more likelihood of adjuvant therapy before recurrence, compared with E-EPE only, EPE (ie, either F-EPE or E-EPE) only, mBNI only, or either EPE or mBNI only. In addition, tumor grade was significantly higher in those showing both EPE and mBNI than in those showing mBNI only, but not in other groups. There were also significant differences in PSA, GG, pN, tumor volume, and adjuvant therapy between the combined F-EPE only and mBNI only versus E-EPE only groups.

Kaplan-Meier analysis coupled with a log-rank test was next performed to assess the impact of EPE and/or mBNI on the prognosis following radical prostatectomy.

TABLE 2. Clinicopathologic Findings in Cases Showing EPE or mBNI Only or Both

	n								
	Category 1 (C1): F-EPE Only	Category 2 (C2): E-EPE Only	Category 3 (C3): mBNI Only	Category 4 (C4): EPE and mBNI	*P* (C1/C3 vs. C2)	*P* (C2 vs. C4)	*P* (C1/C2 vs. C4)	*P* (C3 vs. C4)	*P* (C1-C3 vs. C4)
N	177	634	51	95					
Age (mean) (y)	63.8	63.9	62.2	63.0	0.397	0.246	0.249	0.517	0.308
PSA (mean) (ng/mL)	6.88	8.43	7.28	15.43	<0.001	<0.001	<0.001	<0.001	<0.001
GG					<0.001	0.277	0.110	<0.001	0.054
1	3 (1.7%)	0 (0%)	0 (0%)	0 (0%)					
2	104 (58.8%)	267 (42.1%)	38 (74.5%)	29 (30.5%)					
2 with minor tertiary 5	14 (7.9%)	21 (3.3%)	2 (3.9%)	4 (4.2%)					
3	37 (20.9%)	162 (25.6%)	6 (11.8%)	30 (31.6%)					
3 with minor tertiary 5	9 (5.1%)	47 (7.4%)	3 (5.9%)	10 (10.5%)					
4	7 (4.0%)	42 (6.6%)	1 (2.0%)	5 (5.3%)					
5	3 (1.7%)	95 (15.0%)	1 (2.0%)	17 (17.9%)					
pN					0.014	1.000	0.855	0.101	0.854
0	149 (84.2%)	521 (82.2%)	43 (84.3%)	80 (84.2%)					
1	10 (5.6%)	68 (10.7%)	1 (2.0%)	10 (10.5%)					
X	18 (10.2%)	45 (7.1%)	7 (13.7%)	5 (5.3%)					
Surgical margin					0.708	<0.001	<0.001	0.023	<0.001
Negative	151 (85.3%)	494 (77.9%)	30 (58.8%)	36 (37.9%)					
Positive	26 (14.7%)	140 (22.1%)	21 (41.2%)	59 (62.1%)					
Tumor volume (mean) (mL)	6.4	9.2	6.5	14.2	<0.001	<0.001	<0.001	<0.001	<0.001
Adjuvant therapy					0.004	<0.001	<0.001	0.001	<0.001
Not performed	163 (92.1%)	532 (83.9%)	46 (90.2%)	62 (65.3%)					
Performed	14 (7.9%)	102 (16.1%)	5 (9.8%)	33 (34.7%)					

We first compared progression-free survival among the 4 groups (Fig. 1A). As expected, E-EPE only was associated with a significantly higher risk of disease progression compared with F-EPE only ($P<0.001$). The risk of progression was also significantly higher in patients with E-EPE only than in those with mBNI only ($P=0.030$). Interestingly, the prognosis was comparable between the F-EPE only and mBNI only groups ($P=0.986$). In addition, patients with both EPE and mBNI had significantly higher risks of progression compared with those with E-EPE only ($P<0.001$), mBNI only ($P<0.001$), or EPE (ie, either F-EPE or E-EPE) only ($P<0.001$). Meanwhile, in the cohort with both EPE and mBNI, there was no significant difference in progression-free survival between those showing F-EPE versus E-EPE (Fig. 1B).

We then combined the F-EPE only and mBNI only groups showing comparable outcomes, as shown above, and thus compared the 3 groups. The prognosis was worse in the following order: F-EPE or mBNI only (category 1), E-EPE only (category 2), and both EPE and mBNI (category 3), and the differences in any 2 groups were statistically significant (eg, F-EPE or mBNI only vs. E-EPE only: $P<0.001$; E-EPE only vs. both EPE and mBNI: $P<0.001$) (Fig. 2A). In addition, when dichotomized groups (ie, EPE or mBNI only vs. both EPE and mBNI) were compared, the difference in progression-free survival was still significant (Supplemental Fig. 1A, Supplemental Digital Content 1, http://links.lww.com/PAS/B386). There were also statistically significant differences in the comparisons of cancer-specific survival in the 3 groups (ie, F-EPE or mBNI only vs. E-EPE only vs. both EPE and mBNI) (Fig. 2B) and the 2 groups (ie, EPE or mBNI only vs. both EPE and mBNI) (Supplemental Fig. 1B, Supplemental Digital Content 1, http://links.lww.com/PAS/B386). Furthermore, the differences in progression-free survival among the 3 cohorts (ie, F-EPE or mBNI only vs. E-EPE only vs. both EPE and mBNI) remained significant in subgroups of patients, such as those without (Supplemental Fig. 2A, Supplemental Digital Content 2, http://links.lww.com/PAS/B387) or with (Supplemental Fig. 2B, Supplemental Digital Content 2, http://links.lww.com/PAS/B387) adjuvant therapy before disease recurrence and those with no lymph node metastasis (Supplemental Fig. 2C, Supplemental Digital Content 2, http://links.lww.com/PAS/B387), but not in those with pN1 disease (Supplemental Fig. 2D, Supplemental Digital Content 2, http://links.lww.com/PAS/B387).

To further determine if EPE and mBNI were independent predictors of disease progression following radical prostatectomy, multivariate analysis was performed using the Cox model. When E-EPE only was considered as a reference, the presence of F-EPE or mBNI only (hazard ratio [HR] = 0.524, 95% confidence interval [CI] = 0.341-0.805, $P=0.003$) or both EPE and mBNI (HR = 1.465, 95% CI = 1.020-2.103, $P=0.039$) was associated with a significantly lower or higher risk of progression, respectively (Table 3). In addition, when the cohort was dichotomized for pT3a lesions, the presence of both EPE and mBNI (vs. either EPE or mBNI) showed

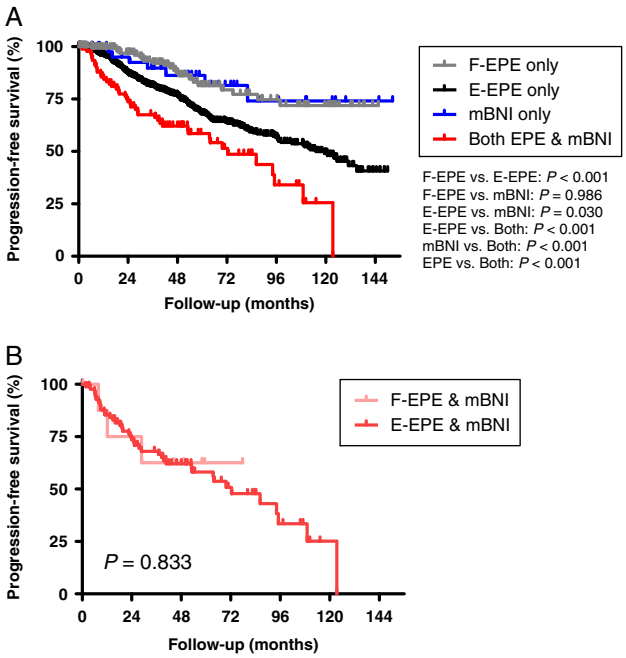


FIGURE 1. Kaplan-Meier curves for progression-free survival in patients with F-EPE only (n = 177) versus E-EPE only (n = 634) versus mBNI only (n = 51) versus both EPE and mBNI (n = 95) (A) or F-EPE and mBNI (n = 9) versus E-EPE and mBNI (n = 86) (B). Comparisons between 2 groups were made by the log-rank test.

significance for progression (HR = 1.600, 95% CI = 1.116-2.293, $P = 0.011$) (Table 4).

DISCUSSION

The presence of EPE or mBNI in prostate cancer has been considered to be an adverse prognostic factor. However, clinical outcomes in patients with pT3a disease are variable. Although the prognostic value of EPE only versus mBNI only versus both was explored when mBNI was included in the pT4 category (ie, 2002 AJCC TNM staging),[6] the clinical significance of either EPE or mBNI versus both of them in the current pT3a prostate cancer remains uncertain. The present study thus aimed to prognostically stratify patients with pT3a disease by comparing radical prostatectomy findings and long-term oncologic outcomes in a total of 957 men with prostate cancer exhibiting EPE and/or mBNI.

As aforementioned, the extent of EPE has been implicated in patient outcomes after radical prostatectomy.[9,10,14] Specifically, the subclassification of EPE as focal and nonfocal, while there are several methods to distinguish these,[7,14,17,21] has led to the improvement in the prediction of biochemical recurrence in those with pT3a disease. F-EPE could thus be defined as the extension of only a few neoplastic glands, cancer extension of <1 HPF in up to 2 separate sections, and that on only one focus. In other studies, pT3a has been substaged based on maximum radial distance or total circumferential length of EPE.[14,22–24] Using one of the criteria commonly used (ie, a few cancer glands),[17] we confirmed the prognostic impact of F-EPE only versus E-EPE only. In addition, compared with F-EPE only, E-EPE only was significantly associated with higher preoperative PSA ($P < 0.001$), higher tumor grade (eg, GG5: 15.0% vs. 1.7%, $P < 0.001$), higher incidence of positive surgical margin ($P = 0.035$) or adjuvant therapy before

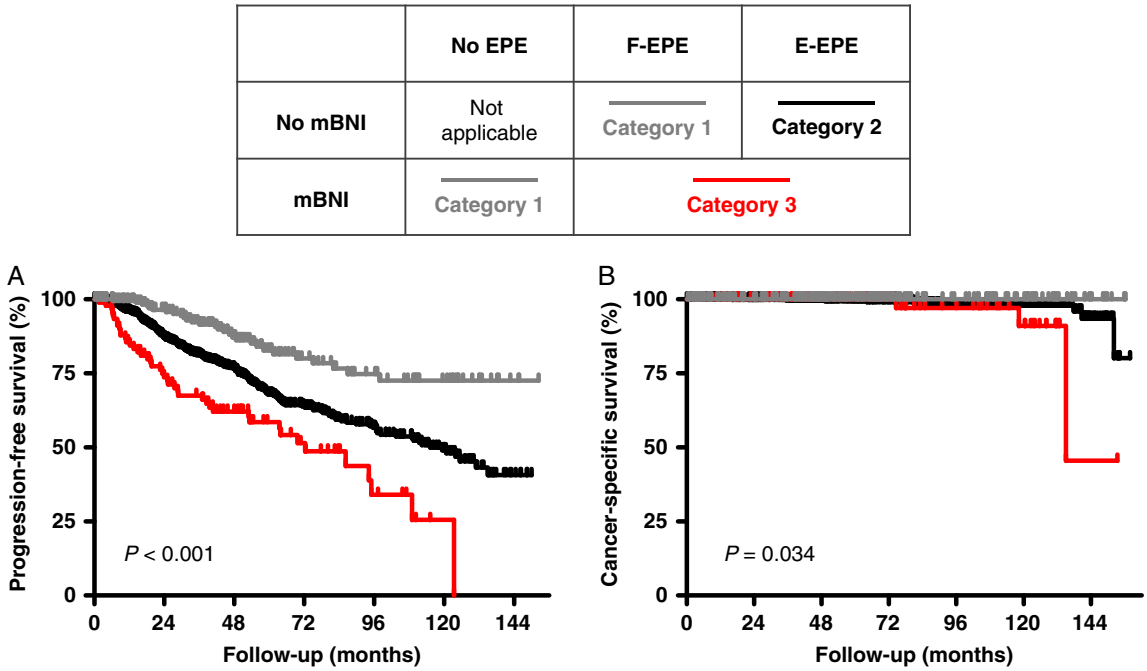


FIGURE 2. Kaplan-Meier curves for progression-free survival (A) and cancer-specific survival (B) in category 1 (n = 228) versus category 2 (n = 634) versus category 3 (n = 95) patients. Comparisons were made by the log-rank test.

TABLE 3. Multivariate Analysis of Prognostic Factors, Including F-EPE or mBNI Only Versus E-EPE Only Versus Both EPE and mBNI, for Disease Progression

	HR	95% CI	P
GG			
1 or 2		Reference	
2 with minor tertiary 5	1.644	0.844-3.205	0.144
3	1.575	1.105-2.244	0.012
3 with minor tertiary 5	2.732	1.761-4.238	<0.001
4	2.835	1.760-4.564	<0.001
5	2.057	1.345-3.146	<0.001
Lymph node metastasis	1.211	0.779-1.883	0.395
Surgical margin	1.387	1.035-1.859	0.029
Tumor volume	1.004	0.987-1.022	0.625
Adjuvant therapy before recurrence	1.047	0.735-1.491	0.800
pT3a lesion			
F-EPE or mBNI only	0.524	0.341-0.805	0.003
E-EPE only		Reference	
Both EPE and mBNI	1.465	1.020-2.103	0.039

recurrence ($P=0.007$), and larger tumor volume ($P<0.001$). Importantly, when mBNI was concurrently present, the difference in progression-free survival between F-EPE and E-EPE was found to be marginal ($P=0.833$).

We then found that the prognosis of patients showing F-EPE only versus mBNI only was comparable. We, therefore, combined these 2 cohorts and further assessed the prognostic impact of the new subgrouping of pT3a disease. Patients with F-EPE only or mBNI only had a significantly lower risk of progression than those with E-EPE only. Between the F-EPE or mBNI only versus E-EPE only groups, there were also significant differences in clinicopathologic features, such as preoperative PSA, GG, lymph node metastasis, tumor volume, and adjuvant therapy immediately after prostatectomy. Similarly, E-EPE only was associated with a significantly lower risk of progression compared with both EPE and mBNI. Those with both EPE and mBNI also showed significantly higher PSA, significantly higher incidence of positive surgical margin or adjuvant therapy, and significantly larger tumor volume compared with E-EPE only. More importantly, in multivariate analysis with E-EPE only as a reference, both F-EPE/mBNI only and EPE+mBNI were found to be independent prognosticators. There were also significant differences in progression-free survival in subgroups of patients including those with or without undergoing adjuvant therapy before recurrence and those showing no lymph node metastasis, as well as in cancer-specific mortality in the entire cohort. Based on these significant findings, we believe it is logical to propose a novel subclassification of the current pT3a prostate cancer for better predicting the prognosis in this context: pT3a1 (F-EPE or mBNI alone); pT3a2 (E-EPE alone); and pT3a3 (both EPE and mBNI). Although the 3-tiered subclassification provides the optimal prognostication, a 2-tier subclassification without the need for evaluating the extent of EPE which can be problematic due to no universal method to quantify it, pT3a1 (either EPE or mBNI) and pT3a2 (both EPE and mBNI), also precisely stratifies the postoperative risk of disease progression in pT3a patients. Notably, our present study is unique in that it incorporates mBNI into substaging without the tedious task of, for example, measuring the distance of EPE.

TABLE 4. Multivariate Analysis of Prognostic Factors, Including EPE or mBNI Only Versus Both EPE and mBNI, for Disease Progression

	HR	95% CI	P
GG			
1 or 2		Reference	
2 with minor tertiary 5	1.606	0.824-3.132	0.164
3	1.667	1.171-2.375	0.005
3 with minor tertiary 5	2.844	1.834-4.409	<0.001
4	3.047	1.895-4.899	<0.001
5	2.282	1.494-3.486	<0.001
Lymph node metastasis	1.186	0.762-1.846	0.449
Surgical margin	1.379	1.029-1.849	0.032
Tumor volume	1.007	0.990-1.024	0.419
Adjuvant therapy before recurrence	1.045	0.732-1.492	0.807
pT3a lesion			
Either EPE or mBNI		Reference	
Both EPE and mBNI	1.600	1.116-2.293	0.011

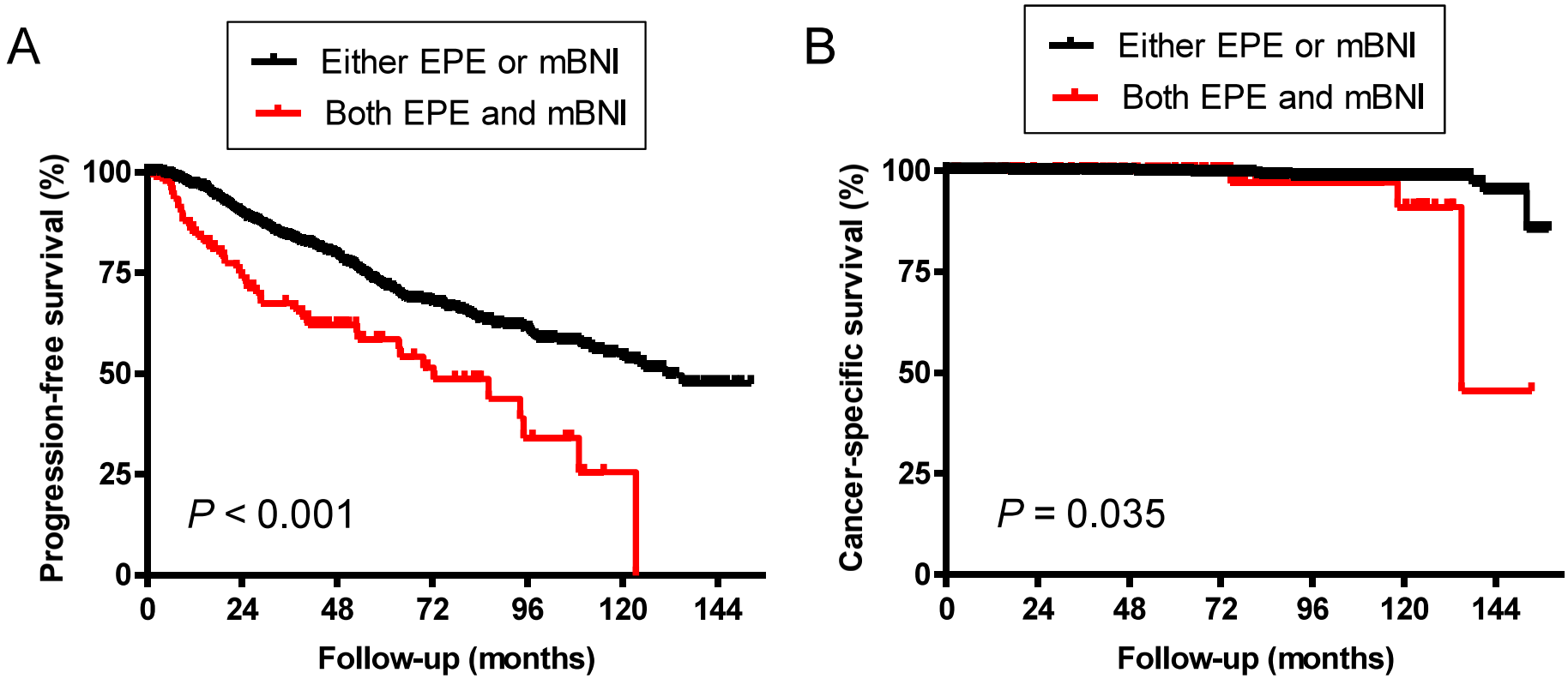
It is worthy to mention that there is interobserver variability among pathologists in the detection of pT3a lesions, especially EPE, in radical prostatectomy specimens.[25–27] Indeed, the concordance rate for EPE among general pathologists has been reported to be not very high (eg, 58% to 76%), which is substantially inferior than those for seminal vesicle invasion (eg, 94% to 95%) and surgical margin status (eg, 69% to 92%).[25,26] It may be particularly problematic to make a histopathologic diagnosis of EPE when cancer is possibly beyond the condensed smooth muscle of the edge of the prostate without adipose tissue involvement.[7,28] Meanwhile, the lack of a definitive method for sampling the bladder neck (eg, radial/cone vs. parallel/parasagittal sections) possibly makes the diagnosis of mBNI (as well as margin status) challenging. Moreover, it is sometimes difficult to distinguish bladder neck muscle fibers from other fibromuscular tissues in relatively small specimens submitted for histologic assessment. These issues may have resulted in controversial data on the prognostic values of pT3a lesions, especially mBNI, in previous studies.[7,11]

There are several limitations in our investigation. First, the present study is subject to potential selection bias due to the retrospective design, although we have analyzed consecutive patients who met the inclusion criteria. Second, we compared only radical prostatectomy cases, and the clinical impact of EPE and/or mBNI in patients undergoing other treatment options, such as radiation therapy and hormonal therapy, was not evaluated. Third, the clinical significance of PSA progression in those who had versus had not received adjuvant therapy before disease recurrence might be different, although we additionally performed outcome analysis in each subgroup. Finally, relatively small sample size in some cohorts, such as patients showing both F-EPE and mBNI, and pN1 cases showing F-EPE or mBNI only, might complicate their accurate risk stratification.

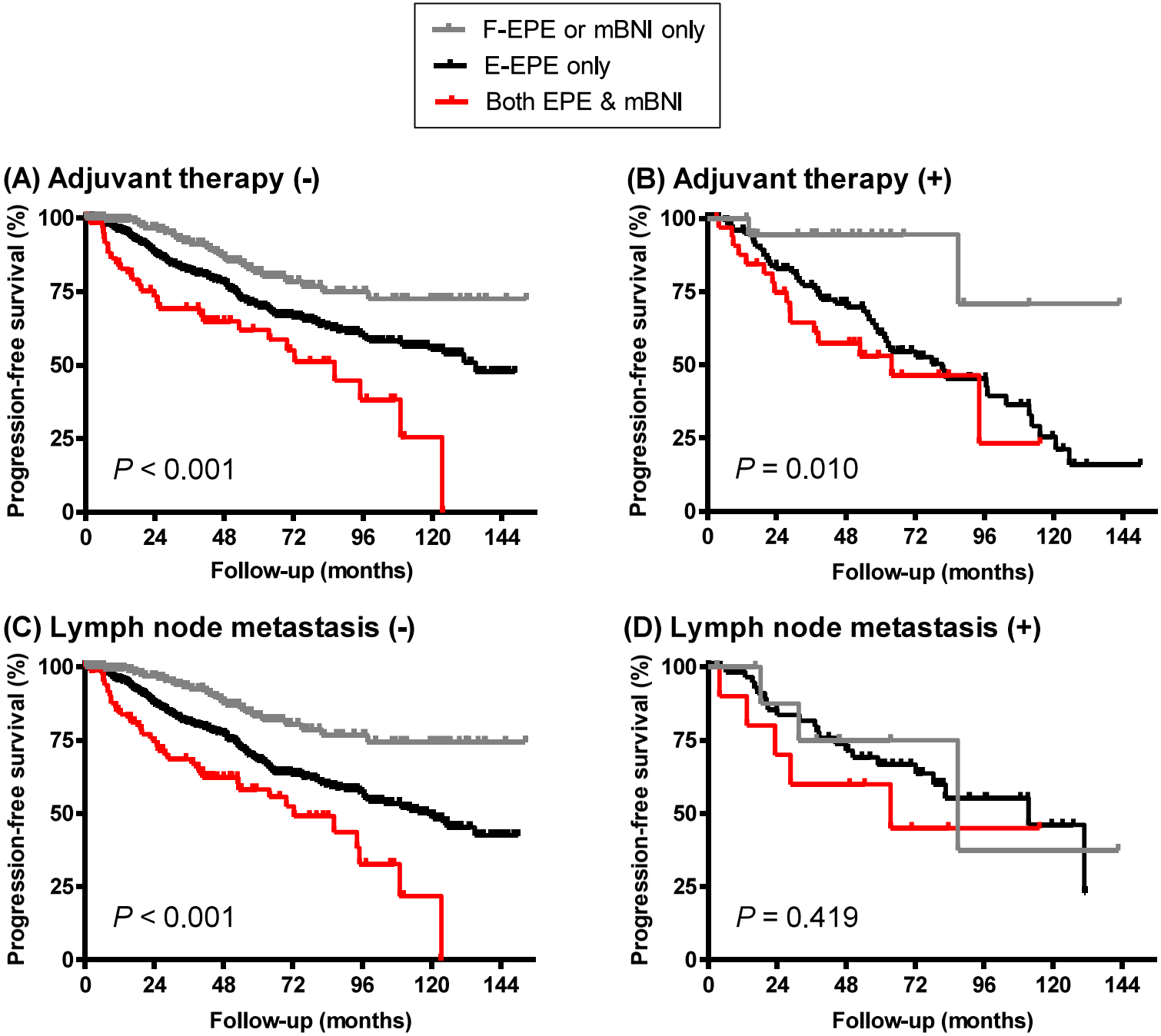
In conclusion, the presence of both EPE and mBNI in pT3a prostate cancer, as an independent predictor, was found to be associated with poorer survival outcomes, while the prognosis of pT3a diseases showing F-EPE only versus mBNI only was comparable. These findings support the importance of specifying the presence or absence of F-EPE/E-EPE, as well as mBNI, in radical prostatectomy specimens. We also believe our present data provide a logical rationale for a new subclassification which more accurately stratifies the prognosis of the current pT3a prostate cancer. Future prospective studies in larger patient cohorts with pT3a disease are warranted to validate our results.

REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistic, 2012. *CA Cancer J Clin*. 2015;65:65–108.
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistic 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249.
3. Lancee M, Tikkinen KAO, de Reijke TM, et al. Guideline of guidelines: primary monotherapies for localised or locally advanced prostate cancer. *BJU Int*. 2018;122:535–548.
4. Van den Broeck T, van den Bergh RCN, Briers E, et al. Biochemical recurrence in prostate cancer: the European Association of Urology prostate cancer guidelines panel recommendations. *Eur Urol Focus*. 2020;6:231–234.
5. Amin MB, Edge S, Green F, et al. *AJCC Cancer Staging Manual*, 8th Edition. New York, NY: Springer; 2017.
6. Rodríguez-Covarrubias F, Larré S, Dahan M, et al. Prognostic significance of microscopic bladder neck invasion in prostate cancer. *BJU Int*. 2008;103:758–761.
7. Magi-Galluzzi C, Evans AJ, Delahunt B, et al. International Society of Urological Pathology (ISUP) Consensus Conference on handling and staging of radical prostatectomy specimens. Working Group 3: extraprostatic extension, lymphovascular invasion and locally advanced disease. *Mod Pathol*. 2011;24:26–38.
8. Kapoor J, Namdarian B, Pedersen J, et al. Extraprostatic extension into periprostatic fat is a more important determinant of prostate cancer recurrence than an invasive phenotype. *J Urol*. 2013;190:2061–2067.
9. Ball MW, Partin AW, Epstein JI. Extent of extraprostatic extension independently influences biochemical recurrence-free survival: Evidence for further pT3 subclassification. *Urology*. 2015;85:161–164.
10. Jeong BC, Chalfin HJ, Lee SB, et al. The relationship between the extent of extraprostatic extension and survival following radical prostatectomy. *Eur Urol*. 2015;67:342–346.
11. Ploussard G, Rotondo S, Salomon L. The prognostic significance of bladder neck invasion in prostate cancer: is microscopic involvement truly a T4 disease? *BJU Int*. 2009;105:776–781.
12. Zhou M, Reuther AM, Levin HS, et al. Microscopic bladder neck involvement by prostate carcinoma in radical prostatectomy specimens is not a significant independent prognostic factor. *Mod Pathol*. 2009;22:385–392.
13. Numbere N, Teramoto Y, Gurung PMS, et al. The clinical impact of pT3a lesions in patients with pT3b prostate cancer undergoing radical prostatectomy: A proposal for a new pT3b subclassification. *Arch Pathol Lab Med*. 2022;146:619–625.
14. Danneman D, Wiklund F, Wiklund NP, et al. Prognostic significance of histopathological features of extraprostatic extension of prostate cancer. *Histopathology*. 2013;63:580–589.
15. van Leenders GJLH, van der Kwast TH, Grignon DJ, et al. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on grading of prostatic carcinoma. *Am J Surg Pathol*. 2020;44:e87–e99.
16. Epstein JI, Amin MB, Fine SW, et al. The 2019 Genitourinary Pathology Society (GUPS) white paper on contemporary grading of prostate cancer. *Arch Pathol Lab Med*. 2021;145:461–493.
17. Epstein JI, Carmichael MJ, Pizov G, et al. Influence of capsular penetration on progression following radical prostatectomy: a study of 196 cases with long-term followup. *J Urol*. 1993;150:135–141.
18. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376:1147–1154.
19. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol*. 2015;33:272–277.
20. Kanada Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*. 2013;48:452–458.
21. Wheeler TM, Dillioglugil Ö, Kattan MW, et al. Clinical and pathological significance of the level and extent of capsular invasion in clinical stage T1-2 prostate cancer. *Hum Pathol*. 1998;29:856–862.
22. Sung MT, Lin H, Koch MO, et al. Radial distance of extraprostatic extension measured by ocular micrometer is an independent predictor of prostate-specific antigen recurrence: a new proposal for the substaging of pT3a prostate cancer. *Am J Surg Pathol*. 2007;31:311–318.
23. van Veggel BA, van Oort IM, Witjes JA, et al. Quantification of extraprostatic extension in prostate cancer: different parameters correlated to biochemical recurrence after radical prostatectomy. *Histopathology*. 2011;59:692–702.
24. Park CK, Chung YS, Choi YD, et al. Revisiting extraprostatic extension based on invasion depth and number for new algorithm for substaging of pT3a prostate cancer. *Sci Rep*. 2021;11:13952.
25. Ekici S, Ayhan A, Erkan I, et al. The role of the pathologist in the evaluation of radical prostatectomy specimens. *Scand J Urol Nephrol*. 2003;37:387–391.
26. van der Kwast TH, Collette L, Van Poppel H, et al. Impact of pathology review of stage and margin status of radical prostatectomy specimens (EORTC trial 22911). *Virchows Arch*. 2006;449:428–434.
27. Evans AJ, Henry PC, Van der Kwast TH, et al. Interobserver variability betwee urologic pathologists for extraprostatic extension and surgical margin status in radical prostatectomy specimens. *Am J Surg Pathol*. 2008;32:1503–1512.
28. Miyamoto H, Hernandez DJ, Epstein JI. A pathological reassessment of organ-confined, Gleason score 6 prostatic adenocarcinomas that progress after radical prostatectomy. *Hum Pathol*. 2009;40:1693–1698.



Supplemental Figure 1. Kaplan-Meier curves for progression-free survival (A) and cancer-specific survival (B) in patients with either EPE or mBNI (n=862) vs. both EPE and mBNI (n=95). Comparisons were made by the log-rank test.



Supplemental Figure 2. Kaplan-Meier curves for progression-free survival in patients with F-EPE only or mBNI only vs. E-EPE only vs. both EPE and mBNI who did not (A) or did (B) undergo adjuvant therapy immediately after radical prostatectomy or who did not (C) or did (D) have lymph node metastasis. Comparisons were made by the log-rank test.