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The Relationship of Morphological Tumor Heterogeneity with Lymph Node Metastasis in Prostatic Adenocarcinomas

Prostat Adenokarsinomlarında Morfolojik Tümör Heterojenitesinin Lenf Nodu Metastazı ile İlişkisi

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ABSTRACT

Aim: The aim of our study isto investigate effect of prostatic carcinoma histopathological subtypes to the lymph node metastasis (LNM).

Materials and methods: A total of 102 patients who underwent radical prostatectomy and pelvic lymph node disection were included in the study. Tumor grades, accompanying intraductal carcinoma (IDC-P)/ductal adenocarcinoma (PDA), LNM, extraprostatic extension (EPE) and seminal vesicle invasion (SVI) were recorded.

Results: While 76 (74.5%) of the tumors had pure acinar adenocarcinoma (AC) histology, IDC-P accompanied AC in 17 (16.7%) and PDA in 9 (8.8%) cases. The tumors accompanying IDC-P and PDA were all stage 3 and stage 4. In pure AC cases, there was a statistically significant difference between the increased tumor grade and advanced stage (p<0.001). There was a statistically significant difference between groups; high GG with LNM, SVI and EPE in pure AC cases (p=0.001, p<0.001. p<0.001, respectively). LNM was observed in 11 of 17 cases (64.7%) accompanied by IDC-P, SVI in 10 (58.8%), and EPE in 16 (94.1%) cases. All 9 cases with PDA accompanying the tumor had EPE, 8 (88.9%) of the cases had LNM and SVI. There was a statistically significant difference between presence of LNM, SVI, EPE and accompanying IDC-P/PDA. When high graded tumors were examined, similar to results mentioned above, it was observed that IDC-P/PDA has accompanied AC thus, the risk of having LNM increased.

Conclusion: In our study, it was noted that the presence of IDC-P/PDA accompanying the tumor significantly increased the risk of LNM, and it was thought that considering both these data in LNM risk analysis may provide a more accurate approach in treatment planning.

Keywords: Prostate adenocarcinoma; lymph node; metastasis;

ÖZET

Amaç: Çalışmamızın amacı prostat karsinomu histopatolojik alt tiplerinin lenf nodu metastazına (LNM) etkisini araştırmaktır.

Gereç ve yöntem: Çalışmaya radikal prostatektomi ve pelvik lenf nodu diseksiyonu uygulanan toplam 102 hasta dahil edildi. Tümör dereceleri, eşlik eden intraduktal karsinom (IDC-P)/duktal adenokarsinom (PDA), LNM, ekstraprostatik yayılım (EPE) ve seminal vezikül invazyonu (SVI) kaydedildi.

Bulgular: Tümörlerin 76'sında (%74,5) saf asiner adenokarsinom (AK) histolojisi bulunurken, 17'sinde (%16,7) IDC-P, 9'unda (%8,8) PDA'ya AK eşlik etti. IDC-P ve PDA'ya eşlik eden tümörlerin tümü evre 3 ve evre 4 idi. Saf AK vakalarında, artmış tümör derecesi ile ileri evre arasında istatistiksel olarak anlamlı bir ilişki gözlendi (p<0,001). Saf AK olgularında yüksek GG ile LNM, SVI ve EPE arasında pozitif ilişki saptandı (p=0,001, p<0,001, p<0,001).17 olgunun 11'inde (%64,7) LNM, 10'unda (%58,8) IDC-P, SVI ve 16'sında (%94,1) EPE izlendi. Tümöre eşlik eden PDA'lı 9 olgunun hepsinde EPE, 8'inde (%88,9) LNM ve SVI vardı. LNM, SVI, EPE varlığı ile eşlik eden IDC-P/PDA arasında istatistiksel olarak anlamlı bir ilişki gözlendi. Yüksek dereceli tümörler incelendiğinde, yukarıda belirtilen sonuçlara benzer şekilde, IDC-P/PDA'nın AC'ye eşlik ettiği ve bu nedenle LNM olma riskinin arttığı görülmüştür.

Sonuç: Çalışmamızda tümöre eşlik eden IDC-P/PDA varlığının LNM riskini anlamlı olarak arttırdığı belirtilmiş ve LNM risk analizinde bu iki verinin de dikkate alınmasının tedavi planlamasında daha doğru bir yaklaşım sağlayabileceği düşünülmüştür.

Anahtar Kelimeler: Prostat adenokarsinom; lenf nodu; metastaz; prostatektomi

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Prostatic adenocarcinoma (PCa) is the most common solid organ malignancy in men and the second most common cause of cancer-related death (1). Treatment is planned according to the tumor grade and tumor stage at the time of diagnosis. Radical prostatectomy (RP) is one of the treatment options, and the position of the pelvic lymph node dissection (PLND) is still controversial (2). Although the presence of lymph node metastasis (LNM) has been reported to be an important prognostic factor, current data have shown that PLND is associated with increased intraoperative / perioperative complications and has no clear effect on survival (2).

In order to make the staging accurately and to determine the treatment approach after RP, it is accepted that performing PLND on selected patients according to risk groups would be a more correct approach (2).

Intraductal carcinoma of the prostate (IDC-P) is defined as the replacement of normal epithelial cells by neoplastic cells, which show structural and cytological atypia, and demonstrating intraacinar and / or intraductal proliferation. The basal layer is preserved in this tumor (3). IDC-P typically coexists with high grade tumor and advanced stage PCa. Studies have reported that IDC-P is an independent prognostic factor for progression-free survival (PFS) and cancer-specific survival (CSS) (4).

Prostatic ductal adenocarcinoma (PDA) is the most common histological tumor subtype among non-acinarprostatic carcinomas, and may appear in the pure or mixed type. Pure PDA is very rare and mostly accompany acinar adenocarcinoma (AC). It is reported that PDAs, which are morphologically defined as large ducts lined with pseudostrative neoplastic epithelium, have an increased risk of biochemical recurrence compared to AC and are associated with advanced stage and increased mortality rate (3).

Herein, we aimed to evaluate the tumor grade group (GG), coexistence with IDC-P / PDA, LNM, seminal vesicle invasion (SVI) and extraprostatic extension (EPE) in patients who underwent RP and PLND treatment.

Materials and Methods

A total of 102 cases who underwent RP and PLND with the indication of PCa in our hospital between 2010-2020 were included in the this retrospective study. In the cases included in the study, lymph node dissection was extended in all cases, and the decision was made according to preoperative nomograms. SBU İzmir Tepecik Education and Research Hospital SUAM Non-Invasive Clinical Investigations Local Ethics Committee granted approval for this study (date: 08.07.2020, number:2020/8-13). Seventy-seven cases were reported by two pathologists (UK, SE) and hematoxylin-eosin stained slides of the remaining 25 cases were also reevaluated by the same two pathologists. Age, stage and survival information of the cases were obtained from the urology department. Histopathologically, AC's Gleason scores (GS) were evaluated according to the modified Gleason grading system (GG) (3). Data related to tumor grade, accompanying IDC-P / PDA, and LNM, EPE and SVI were recorded. Patients who underwent RP and PLND in our hospital due to PCa and whose hematoxylin&eosin sections could be accessed were included in the study. RP cases without PLND were excluded from the study.

Statistical Methods

Statistical analysis was done using Statistical Package of Social Sciences version 24 (IBM Corp.; Armonk, NY, USA). The data were evaluated by chi-square and Fisher Exact test. P values less than 0.05 were interpreted as statistically significant.

Results

While 76 (74.5%) of 102 cases had pure AC, 17 (16.7%) had IDC-P accompanying AC, and 9 (8.8%) had PDA acompanying AC. Mean ages of the cases, distributions of tumor GG scores and stages were summarized in Table 1.

There was a statistically significant difference between groups; AC accompaying IDC-P/PDA with increasing tumor grade and advanced stage ($p<0.001$, $p<0.001$). GG scores with the stages of the tumors in the groups were the summarized in Table 2.

In pure AC cases, there was a statistically significant difference between the increased tumor grade and advanced stage ($p<0.001$). Presence of LNM, SVI and EPE were evaluated with data. There was a statistically significant difference between groups; high GG with LNM, SVI and EPE in pure AC cases ($p=0.001$, $p<0.001$, $p<0.001$, respectively) (Table 3).

Lymph node metastasis, EPE and SVI were compared between groups (Table 4). There was a statistically significant difference between presence of LNM, SVI, EPE and accompanying IDC-P / PDA. Lymph node metastasis, EPE and SVI were evaluated only high grade tumors (GG4, GG5) (Table 4).

There was a statistically significant difference between presence of LNM and accompanying IDC-P ($p=0.046$). There was not a statistically significant difference between groups; SVI and EPE ($p=0.280$, $p=0.458$). There was a statistically significant difference between AC accompaying PDA with LNM and SVI. There was not a statistically significant difference EPE ($p=0.002$, $p=0.013$, $p=0.299$).

Table 1: Avarege ages, tumor grade and stages in pure AC, AC with IDC-P and with PDA groups.

	Pure AC n (%)	AC+IDC-P n (%)	AC+PDA n (%)	p
Mean age ± SD (min-max)	64,8 ± 6,56 (48-79)	64,1±6,61 (53-73)	65,1±7,89 (52-74)	
Tumor GG				
GG1	17 (22,4)	0	0	
GG2	27 (35,5)	2 (11,8)	1 (11,1)	<0,001
GG3	13 (17,1)	2 (11,8)	2 (22,2)	
GG4	8 (10,5)	4 (23,5)	0	
GG5	11 (14,5)	9 (52,9)	6 (66,7)	
Tumor stage				
Stage 2	32 (42,1)	0	0	
Stage 3	35 (46,1)	6 (35,3)	1 (11,1)	<0,001
Stage 4	9 (11,8)	11 (64,7)	8 (88,9)	

(AC: Acinar adenocarcinoma, grade group (GG), PDA: Prostatic ductal adenocarcinoma, IDC-P: Intraductal carcinoma of the prostate) (Ki-square analysis, Fisher exact test)

Table 2: Tumor grade and stage distribution in pure AC, AC with IDC-P and with PDA groups.

	GG1	GG2	GG3	GG4	GG5
Stage 2	13 (40,6%)	14 (43,8%)	2 (6,3%)	3 (9,4%)	0
Stage 3	4 (11,4%)	12 (34,3%)	8 (22,9%)	5 (14,3%)	6 (17,1%)
Stage 4	0	1 (11,1%)	3 (33,3%)	0	5 (55,6%)
AC with IDC-P	**GG1**	**GG2**	**GG3**	**GG4**	**GG5**
Stage 3	0	1 (16,7%)	0	2 (33,3%)	3 (50%)
Stage 4	0	1 (9,1%)	2 (18,2%)	2 (18,2%)	6 (54,5%)
AC with PDA	**GG1**	**GG2**	**GG3**	**GG4**	**GG5**
Stage 3	0	1 (100%)	0	0	0
Stage 4	0	0	2 (25%)	0	6 (75%)

(AC: Acinar adenocarcinoma, grade group (GG), PDA: Prostatic ductal adenocarcinoma, IDC-P: Intraductal carcinoma of the prostate) (Ki-square analysis, Fisher exact test)

Table 3: Tumor GG, LNM, EPE and SVI distribution in pure AC.

Pure AC	LNM (+)	SVI (+)	EPE (+)
Tumor GG			
GG1	0	0	1 (2,4%)
GG2	1 (11,1%)	2 (13,3%)	14 (33,3%)
GG3	3 (33,3%)	5 (33,3%)	11 (26,2%)
GG4	0	1 (6,7%)	5 (11,9%)
GG5	5 (55,6%)	7 (46,7%)	11 (26,2%)
p	**0,001**	**<0,001**	**<0,001**

(AC: Acinar adenocarcinoma, GG: grade group, LNM: lymph node metastasis, SVI: seminal vesicle invasion, EPE: extraprostatic extension) (Ki-square analysis, Fisher exact test)

Table 4: LNM, EPE and SVI distribution in all tumors and only high grade tumors.

	LNM (-/+)	SVI (-/+)	EPE (-/+)
Pure AC (76)	67 (91,8%) / 9 (45%)	61 (89,7%) / 15 (60%)	34 (97,1%) / 42 (72,4%)
AC+IDC-P	6 (8,2%) / 11 (55%)	7 (10,3%) / 10 (40%)	1 (2,9%) / 16 (27,6%)
p	**<0,001**	**0,001**	**0,003**
Pure AC (76)	67 (98,5%) / 9 (52,9%)	61 (98,4%) / 15 (65,2%)	34 / 42 (82,%)
AC+PDA	1 (1,5%) / 8 (47,1%)	1 (1,6%) / 8 (34,8%)	0 / 9 (17,6%)
p	**<0,001**	**<0,001**	**0,010**
	LNM (-/+)	**SVI (-/+)**	**EPE (-/+)**
High grade pure AC (n:19)	14 (73,7%) / 5 (26,3%)	11 (57,9%) / 8 (42,1%)	3 (15,8%) / 16 (84,2%)
AC+IDC-P (n.13)	5 (38,5%) / 8 (61,5%)	5 (38,5%) / 8 (61,5%)	1 (7,7%) / 12 (92,3%)
p	**0,046**	0,280	0,458
High grade pure AC (n:19)	14 (73,7%) / 5 (26,3%)	11 (57,9%) /8 (42,1%)	3 (15,8%) / 16 (84,2%)
AC+PDA (n:6)	0 / 6 (100%)	0 / 6 (100%)	0 / 6 (100%)
p	**0,002**	**0,013**	0,299

(LNM: lymph node metastasis, SVI: seminal vesicle invasion, EPE: extraprostatic extension) (Ki-square analysis, Fisher exact test)

Discussion

Epithelial tumors of the prostate in the published World Health Organization classification were divided into subgroups of acinar, ductal, intraductal, squamous, urothelial and basal cell carcinoma of the prostate (3). Approximately 90% of newly diagnosed PCa cases are AC (5). The Gleason grading system still maintains its position as the most important prognostic factor in prostatic adenocarcinomas, and directly determines the clinical approach (6). Gleason Score (GS) was considered to be an important prognostic factor for predicting PFS, and CSS (4). Today, it is recommended to use International Society of Urological Pathology grading system to predict outcome in cases with PCa (3, 4). In parallel with the literature, it was observed that the tumor grade increased in our pure AC series in line with advanced tumor stage.

Among histological subtypes of non-acinar carcinoma of the prostate the most common variant is PDA. Ductal adenocarcinoma of prostate is characterized by pseudostrafied tall columnar cells that can show cribriform, papillary or solid growth patterns (7-11). Pure PDA is very rare and accounts for less than 1% of PCa while the incidence of mixed PDA is reported as 3-12.7% (9). In the case series of Amin et al, consisting of 17,966 cases series with PCA and PDA accompanied only 0.5% (n=93) of the cases (12). In a series consisting of 1051 RP cases, Seipel et al, reported that in only 86 (8.2%) cases with PCa characteristic features of PDA were observed, and only 2 of these cases had pure PDA (13). However, Meeks et al. analyzed the 1970-2007 Surveillance, Epidemiology and End Results (SEER) program data of the National Cancer Institute, and identified 442,169 cases with AC, 435 cases with pure PDA and only 3 cases with mixed type PDA (1). No pure PDA was seen in our series. Acinar adenocarcinoma accompaying PDA (mixed type) was detected in nine cases. Mixed type PDA rate was 8.8%, similar to study of Seipel et al (13), in our series.

In various studies it has been reported that PDA has a worse prognosis than AC, and biochemical recurrence occurs at a relatively early period after RP. Besides the mortality rate is higher and surgical margin positivity, EPE, SVI and LNM are frequently seen in cases with PDA (11). In their review article, Meeks et al. analyzed SEER program data, and stated that pure PDA cases were inmore advanced stage and had higher mortality rates than AC. In the same study, pure PDA and GS 8 ACs was reported to have similar cancer-specific mortality rates (10).

Amin et al. reported that in case the incidence of PDA accompanying GS 7 PCa, is less than 10%, then the tumor has a pathological stage similar to AC of the same grade. In the same study, it was reported that SVI was observed at a higher rate compared to AC in cases accompanied with PDA, and that the presence of PDA occupying more than 10% of the tumor size was associated with EPE and SVI (12). Seipel et al, reported that the tumor grade was ≥ GG3 in all of the cases accompanied by PDA, and in these cases, EPE and SVI had an increased risk compared to AC (13). Lakymenko et al. reported that PDA alone is not an increased risk factor for EPE, SVI, and LNM. It has been reported that the number of tumor nodules and tumor volume, especially those containing mixed type tumors, high GG AC and PDA, are poor prognostic factors (14). Similarly, Kryvenko et al. were reported that PDA causes an increased risk of biochemical recurrence after RP, but the presence of negative pathological findings such as high tumor grade and advanced PCa is more important (15). For this reason, it is said that PDA alone may not be a poor prognostic factor and that the cases should be evaluated together with all clinical-pathological findings (15). In our case series, it was seen that PDA frequently accompanied high grade tumors. While GG1 tumors were not associated with PDA, most of the cases accompanied GG5 tumors. However, it was noteworthy that PDA was not associated with eight GG4 tumors in the series. It was thought that this was due to the insufficient number of cases with GG4 tumors. In addition, AC accompanying the PDA was associated with advanced stage disease in parallel with the literature. Besides, cases where PDA accompanied tumor had stage 3 and stage 4 disease. In addition, in our study, EPE and SVI were observed more frequently in AC cases accompanied by PDA rather than pure AC. Since there have been low grade cases in the pure AC series, the possibility of the results being affected has risen. Because of that reason only tumors GG4 and GG5 have been taken into comparison. In those cases it has been seen that AC accompanied by PDA has continued it's relation to SVI but the relationship between EPE has not continued.

Intraductal carcinoma of prostate; is a unique type of prostatic glandular neoplasia that involves and expands benign prostate ducts and acini (3). Studies have shown that IDC-P harbours genetic changes frequently observed in Gleason pattern4/5 tumors (16). The presence of IDC-P has been considered to be associated with aggressive, high grade (Gleason pattern 4/5), high volume PCa (4,16,17). In a high-risk PCa case series of 206 patients, Kimura et al. reported that the risk of EPE, and SVI increased significantly in patients with IDC-P, and the presence of IDC-P was reported to be an independent prognostic factor on PFS and CSS, regardless of whether or not antineoplastic treatment was given (4).

In a meta-analysis investigating the effect of IDC-P on prognosis, it was reported that IDC-P is more common in advanced PCa and is a poor prognostic factor for both

localized and advanced PCa (18).

In our cases, it was detected that IDC-P accompanied high grade tumors and associated with advanced stage, and presence of EPE and SVI. However, when the high graded tumors examined; it has been detected that there was no relation between EPE and SVI anymore. This result was different from the current literature.

Regional LNM is considered as an independent risk factor for mortality due to increased biochemical nomograms used to predict the risk of LNM do not take into account tumor heterogeneity. In our study, recurrence and disease rates (19,20). Lymph node metastasis detection rates in PLND ranged from 1,1% to 26% (21). Although it has been shown that PLND has no effect on survival in the treatment of PCa is recommended for, accurate staging of the disease, so as to be able to determine the treatment modality after RP. It is reported that application of PLND will be a more correct approach for selected patients in the risk groups identified due to increased intraoperative / perioperative complications in PLND (2).

In the clinical guideline of European Association of Urology, localized and locally advanced PCa cases are defined as low, intermediate and high risk groups according to the risk of biochemical recurrence. These risk groups are determined by considering serum PSA level (≥10ng), tumor GS (≥7), and tumor T stage and presence of LNM (22).

In the proposed Briganti nomogram to determine the risk of LNM; serum PSA level, clinical stage, GS and positive core percentage data are used (21). Pelvic lymph node dissection is recommended for cases with LNM risk >5% in European Association of Urology guidelines. Accordingly, since probability of LN metastasis is <5% in low-risk cases, PLND is not recommended in these cases. Whereas in the high-risk group, and also in the medium-risk group, if the probability of LNM is >5%, then application of extended PLND is recommended (22). Although this risk analysis is considered to have a fairly good performance, it was noted that heterogeneous histology of PCa has not been taken into account in the evaluation.

Amin et al. reported that LNM and surgical margin positivity were higher in patients with PDA accompanying the tumor, but this difference was not statistically significant (12). In contrast, in the SEER program analysis of Meeks et al, PDA was said to have no significant effect on risk of development LNM (10). Amin et al. reported that IDC-P accompanied to 40% of cases with LNM in the GS7 PCa series and in 20% of the cases in the nonmetastatic group (12). In the 184 case series of Kryvenko et al. with similar study design IDC-P was obsserved in 42.4% of the group with LNM whereas in the group without LNM, this rate was reported as 20.6% (23). In our series, LNM was observed in 8 of 9 cases (88.9%) accompanied by PDA and in 11 of 17 cases (64.7%) accompanied by IDC-P. It was also seen that coexistence of IDC-P / PDA is an increased risk factor for LNM. When high graded tumors have been examined, similar to results mentioned above, it has been seen that IDC-P/PDA has accompanied AC thus, the risk of having LNM increased.

In conclusion; today, the treatment of PCa is mainly managed by considering serum PSA level, tumor stage and GS. However, it is an accepted fact that PCa has heterogeneous histology, genetics and clinics. Today, it was noted that the presence of IDC-P/PDA accompanying the tumor significantly increased the risk of LNM, and it was thought that considering both these data in LNM risk analysis may provide a more accurate approach in treatment planning.

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Authors' contribution:

SE: design, interpretation of data and writing, ÜK: design, interpretation of data, istatistic, writing and study supervision, CKT: interpretation of data, study supervision, EK: interpretation of data and writing. All authors took part in the study design and approved the final version of the manuscript.

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