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Effect of Variant Histopathology on Survival in Prostate Adenocarcinoma

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Abstract **Original Research Article**

Purpose*:** It was aimed to determine the possible effects of variant pathology associated with prostate adenocarcinoma on survival. ***Material and Methods: Data of patients who underwent radical prostatectomy for localized prostate cancer between January 2014 and 2020 were retrospectively analyzed. The survival rates according to the presence of variant histology associated with prostate adenocarcinoma were analyzed and compared in relation to the clinical and demographic data of the cases. ***Results***: A total of 244 patients were operated for localized prostate cancer. Preoperative The ISUP grades and percentages of the patients were respectively as ISUP 1 (42%), ISUP 2 (38%), ISUP 3 (10%) and ISUP > 3 (10%). Variant histopathology was present in 26% of the patients [intraductal (81%), foamy cell (11%), ductal (6%) and neuroendocrine (2%)]. When prostate cancer and prostate cancer associated with variant histopathology groups were compared, the mean age and postoperative 1st month PSA values were 62.29± 6.36 vs 64.33± 5.77 years p=(0.025) and 0.32± 1.53 and 1.01± 2.98 ng/dl (p=0.022) respectively. Mean follow-up time for prostate cancer and prostate cancer associated with variant pathology was statistically similar (60.33±21.66 vs. 60.42±16.88 months). The mortality rates of the patients with and without variant histopathology were respectively as 11% and 14% (p=0.416). ***Conclusions***: Associated variant pathology does not show a statistically significant decrease in survival rates of patients with localized prostate cancer receiving standard therapy. Rather, advanced age may have a role in the non-significant 3% difference in survival rate.

Keywords Prostate adenocarcinoma, radical prostatectomy, variant pathology, survival.

INTRODUCTION

"According to WHO, prostate cancer is the second most frequently diagnosed cancer in men, with an estimated 1.4 million diagnoses worldwide in 2020, after lung cancer. The incidence of prostate cancer varies greatly by geographic region. While the incidence of prostate cancer is highest in Australia/New Zealand and North America, largely due to the use of prostate-specific antigen (PSA) testing and an aging population; the incidence is low in East and South-Central Asia [1]. Family history of prostate cancer, age, and ethnicity; they are proven risk factors, but there are also environmental factors that play a role in the development of prostate cancer [2].

Although mostly typical acinar adenocarcinoma morphology (%90), there is a spectrum of morphological variants and prostate cancer subtypes. Because of their rarity, it is important for pathologists to correctly diagnose and grade these tumors. These variant subtypes include ductal carcinoma, neuroendocrine (NE) differentiated prostate cancer, squamous cell carcinoma, sarcomatoid carcinoma, basaloid carcinoma, mucinous carcinoma, signet ring cell carcinoma, and atrophic, foamy gland, and pseudo hyperplastic carcinomas [3]. In this study, our aim is to investigate the effect of variant histopathology on prostate cancer survival and to compare it with adenocarcinoma in terms of survival.

MATERIAL AND METHODS

The data of patients who underwent radical prostatectomy for localized prostate cancer between January 2014 and 2020 were analyzed retrospectively. Patients with variant histopathology results were identified. Additional treatment requirements such as radiotherapy, hormone therapy and chemotherapy were also examined in the follow-up of the patients. Patients

whose follow-up process was interrupted due to the pandemic were not included in the study. The patients with unclear pathology reports or missing clinical data were excluded. We compared the survival according to the presence of variant histology in relation to the clinical and demographic data of the cases. This study was approved by the institutional local Ethics Committee.

RESULTS

A total of 244 patients were operated for localized prostate cancer. Age avg. 62.29 ±6.36, mean body mass index was 26.7±3.8. Preoperative mean PSA values were 13.84±18.83 (25-75 percentile 5.75-13.80) ng/dL. The mean prostate volume was 42.63±18.13 cc. In 62% of the patients, one or more HT (41%) and DM (20%) more comorbidities were present. In 7% of patients, secondary malignancy was present.

The ISUP grade and percentages of the patients were 1 (42%), 2 (38%), 3 (10%) and >3 (10%), respectively. LVI (17%), PNI (29%) and surgical margin positivity (34%) were present. 31% of patients received adjuvant therapy (only RT 11%, RT + hormone therapy 18% and only hormone therapy 2%). Chemotherapy was applied in 4% of patients with progression.

Variant histopathology was present in 26% of the patients [intraductal (81%), foamy cell (11%), ductal (6%) and neuroendocrine (2%)]. When prostate cancer and prostate cancer associated with variant histopathology groups were compared, the mean age and postoperative 1st month PSA values were different; 62.29± 6.36 vs 64.33± 5.77 years p= (0.025) and 0.32± 1.53 and 1.01± 2.98 ng/dl (p=0.022), respectively. Table related to the relevant data are shown in table 1.

Mean follow-up time for prostate cancer and prostate cancer associated with variant pathology was statistically similar (60.33±21.66 vs. 60.42±16.88 months). 11% of patients in the only prostate cancer group resulted in mortality during follow-up. In the variant group, 14% resulted in mortality and it was not statistically significant (p=0.416). Demographics and distribution of histopathologic results are shown in table 1. The Kaplan-Meier survival analysis is shown in Figure 1.

Legends of the Figures

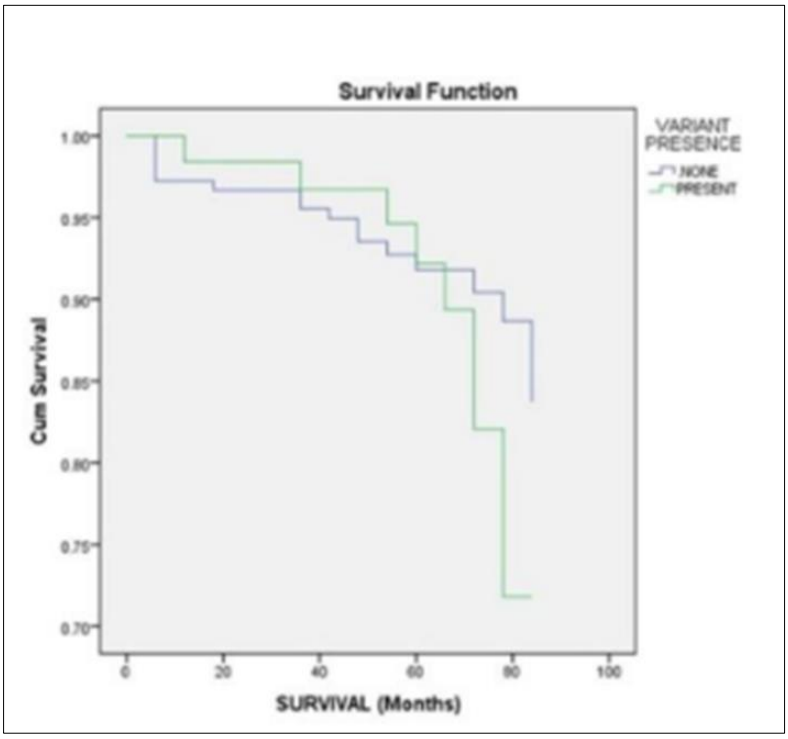

Figure 1: Kaplan-Meier survival analysis

Table 1: Datasets of all cases

DEMOGRAPHICS			
n=244	**Acinar adenocarcinoma**	**Variant pathology**	**p value**
Mean age	62.29 6.36	64.33 5.77	0,025
Mean 1st month PSA (ng/dl)	0.32+ 1.53	1.01+ 2.98	0,022
Mortality (%)	11	14	0,416
Mean follow-up time (month)	60.33+21.66	60.42+16.88	0,322
Number of patients(n)	244		

DEMOGRAPHICS			
n=244	**Acinar adenocarcinoma**	**Variant pathology**	**p value**
Mean age	62.29 +6.36		
Mean BMI	26.7+3.8		
Mean preop. PSA	13.84+18.83		
Mean prostate vol.	42.63+18.13		
DISTRIBUTION OF HISTOPATHOLOGY			
Acinar adenocarcinom	74%		
Variant pathology	26%		
Intraductal	81%		
Foamy cell	11%		
Ductal	6%		
Neuroendocrine	2%		
ISUP 1	42%		
ISUP 2	38%		
ISUP 3	10%		
ISUP >3	10%		

DISCUSSION

There is a lot of current information describing the morphological changes of prostate carcinoma variants. Because they are seen rarely, it is important not to overlook them during diagnosis. Although intraductal type comes to the forefront in terms of frequency; there are many prostate cancer variants that differ in terms of Gleason scoring, histopathology, and prognosis. Studies on the effect of variant pathology on survival in prostate cancer are very, very limited.

These variants have been expressed by WHO as foamy, pseudohyperplastic, atrophic, microcystic, mucinous, pleomorphic giant cell variant, and sarcomatoid [4].The importance of variant pathologies, these variants; It may differ in disease progression, survival, treatment, and follow-up compared to acinar prostate adenocarcinomas [5, 6]. Moreover, some variants may have different Gleason scores and show different clinical courses than acinar adenocarcinoma [7].

As we mentioned before; variants of prostate cancer are rare and account for 5-10% of carcinomas of prostate origin. Some variants may develop after treatment for acinar adenocarcinoma. These species are often aggressive and have poor oncological outcomes [6].

Adenoid cystic carcinoma / basal cell carcinoma; it is a prostate cancer variant with very few cases reported in the literature. In this subtype, incidental detection by pathology, especially after TUR-P, is a common feature. It generally shows a slow course with local infiltrative behavior [8]. While PSA expression is usually not observed; specific monoclonal antibodies anti-cytokeratin 34βE12, p63 and BCL-2 were strongly positive [9]. It has been shown that ACC/BCC, which was first described in 1974 and thought to have a slow and good prognosis in the ongoing process, generally does not show an indolent character, but instead tends to spread to loco-regional areas with the potential for metastasis [10].

Pleomorphic giant cell carcinoma (PGCC) of the prostate is a rare entity among prostate cancers. PGCC differs from classical acinar prostate adenocarcinoma by having markedly enlarged and pleomorphic cells. Another important feature is that it can be confused with urothelial carcinoma. Poor prognosis, occurrence in elderly patients, and frequent association with previous therapy are some of the characteristic features of PGCC [11]. In a case in the literature; it has been reported that an 81-year-old patient with pleomorphic giant cell adenocarcinoma rapidly developed bone metastases after diagnosis and died 1 year later. This variant has an extremely poor prognosis and is rare. The main differential diagnosis among other pathologies is with urothelial carcinoma. Loss of expression of markers such as PSA is likely. In this study; HOXB13 showed as a sensitive and specific marker in prostate cancer and in this case; HOXB13 expression has been observed in PGCC [12]. In another case series of 30 patients, all cases had an ISUP grade of 5. 37% of all patients died an average of 8 months after diagnosis [13]. No PGCC was detected in our series.

Mucinous adenocarcinoma of the prostate one of the rare variants of prostate cancer. It was defined as a tumor variant containing mucin in <25% of the resected RRP material [7]. Although it is included in variant pathologies; some publications have shown that the mucinous variant may have a less aggressive course than classical acinar adenocarcinoma [14].

Foamy gland variant carcinoma is a variant of prostatic acinar adenocarcinoma characterized by rich foamy cytoplasm and frequently pyknotic nuclei. In the radical prostatectomy series of 477 patients presented by Hudson J. *et al*., foamy variant prostate cancer was observed in 69 (14.5%) patients. When the foamy variant group and the remaining 408 patients without foamy

variant were compared as two groups; no significant difference was found in terms of Gleason score and recurrence (23% vs. 22%) [15]. In our series of 244 patients, foamy variant prostate cancer was observed in 7 patients. Although not all variants were specifically compared separately, there was no significant difference in mortality and recurrence in the variant pathology group compared to classical prostate adenocarcinoma.

Intraductal carcinoma of the prostate; defined by the WHO as "typically high-grade or high-grade prostate carcinoma that has some of the features of high-grade prostatic intraepithelial neoplasia (HGPIN) but exhibits a much greater structural and/or histopathological atypia." [16]. Presence of intraductal carcinoma in pathology specimens; it is associated with aggressive pathological features such as high Gleason score, high tumor stage, and poor clinical course such as early biochemical recurrence and distant metastasis. This variant type has higher TMPRSS2-ERG fusions and loss of PTEN; it may have different genomic profiles, with a higher prevalence of BRCA2 mutations [17]. In our study, the predominant type (81%) among variant groups is intraductal carcinoma. Although we did not compare it specifically, no statistically significant increase in mortality was observed in the variant group.

One of the rare prostate cancer variants is ductal adenocarcinoma. Ductal adenocarcinoma contains large glands lined with long columnar and pseudostratified epithelium. Compared to classical acinar carcinomas, it is associated with higher-stage disease, higher PSA recurrence and mortality risk and shows an aggressive course [18]. Chow *et al*., in the study comparing 202 ductal variant prostate carcinoma and 2037 acinar adenocarcinoma; in the survival analysis, patients with acinar histology had longer salvage-free survival (22.0 vs. 8.1 months, $p = 0.03$) and metastasis-free survival (78.6 vs. 6.7 months, $p < 0.0001$); and it was concluded that it was statistically significant [19].

In the review by Soundararajan *et al*., attention was drawn to the importance of a signaling pathway in the pathogenesis of neuroendocrine/aggressive variant prostate cancer. It has been shown that cellular plasticity induced by epithelial-to-mesenchymal (EMT) signaling may contribute to the development of this variant pathology [20].

The molecular networks that drive the genesis and maintenance of variant pathology are still unclear; however, many factors have been associated with the initiation and progression of neuroendocrine differentiation in typical adenocarcinomas, such as loss of androgen-receptor expression, conventional therapy, and impaired cytokine system [20]. Some of the limitations of our study are that it is single-centered and retrospective, that variant types cannot be compared in terms of survival separately, and that there is no possibility to perform any genetic analysis.

CONCLUSIONS

Prostate cancer survival with associated variant pathology does not show a statistically significant reduction in survival rates for patients with localized prostate cancer receiving standard therapy. The insignificant 3% difference in the survival rate may be due to older age. Especially in the future, molecular and genetic studies may contribute to the development of variant histopathology.

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Author Contribution

Research conception and design: all authors. Data acquisition: all authors. Data analysis and interpretation: Hikmet Köseoğlu. Drafting of the manuscript: all authors. Critical revision of the manuscript: all authors. Supervision: Hikmet Köseoğlu. Approval of the final manuscript: all authors.

Conflict of Interest: None declared

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