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Investigating PMS2 and MSH6 Repair Proteins in Radical Prostatectomies: A Study of 635 Samples

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Abstract

Introduction: Prostate cancer is the second most frequent neoplasm in men. Recent studies suggest that the rate of microsatellite instabil) andimary prostate tumors is <4% and that the loss rate of the repair gene in these tumors is <3%. The objective was to characterize primary prostate tumors in terms of immunohistochemical staining of PMS2 and MSH6.

Methods: There were 635 samples from patients with prostatic adenocarcinoma who underwent radical prostatectomy in a referral hospital. For this purpose, a retrospective cohort was constituted and immunohistochemical reactions were studied in tissue microarrays from samples taken from non-neoplastic and neoplastic tissues.

Results: The rate of simultaneous positive labeling was 90.5% and no case had concomitant negative labeling. The Gleason score of patients with no marking of PMS2 or MSH6 after the review ranged from 2 to 4 and the pathological staging of the cases ranged from pT2 to pT3b.The group without MSH6 and/or PMS2 scores had higher Gleason scores, and those only without MSH6 score had worse staging conditions. There was a higher frequency of metastasis among patients without MSH6 labeling.

Discussion/Conclusion: Age older than 60 years was not statistically significant in relation to the absence of PMS2 and MSH6.Negative labeling of MSH6 was related to biochemical recurrence. PMS2 and MSH6 gene expression was not associated with PSA levels above 10 ng/ml. The values of Gleason scores were higher in the unmarked group. There was a higher frequency of metastasis in patients without MSH6 labeling. The loss rate of the MSH6 repair gene in the sample was 0.15% and of PMS2 was 0.30%, Similar to literature data. More studies should be carried out to corroborate these findings.

Keywords: Prostate cancer; PMS2; MSH6; Immunohistochemistry; Prostatectomy

Introduction

Prostate cancer is the second most frequent neoplasm in men, following non-melanoma skin cancer, **[1,2]** and hormone deprivation therapy is one of the oldest forms of targeted cancer therapy [3].

Approximately 10% of advanced/metastatic prostate tumors have a very high rate of single nucleotide mutation [4,5], almost always due to underlying somatic and/or germline inactivation of genes of the mismatch repair family (MMR), frequently accompanied by microsatellite instability (MSI) [4], Similar to the situation observed in colorectal carcinoma **6**.

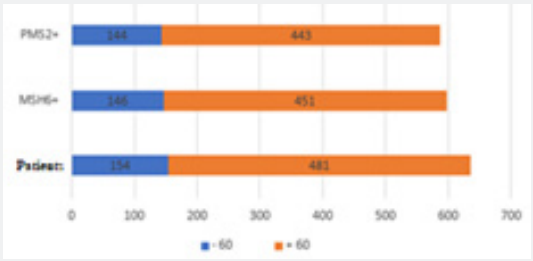
Previous studies have suggested that the MSI rate in primary prostate tumors is <4% [7] and that the loss rate of the MMR gene in these tumors is even smaller, <3% [8]. Advanced prostate tumors with loss of the MMR gene and hypermutation can respond favorably to PD-1-targeted immunotherapies [9,10]. MLH1, MSH2, PMS2 and MSH6 are varieties of MMR proteins. The MSH2 protein is stabilized via interaction with the MSH6 protein, enabling it to act in varied substrates and through diverse pathways [11]. Pritchard CC et al. reported that MSH2 and MSH6 mutations predominate in patients with prostate cancer, unlike the literature reports on colon and endometrial cancer, where MSI is more often due to epigenetic silencing of MLH1, thus supporting the presence

of an alternative mechanism by which MSI is acquired in prostate cancer [4]. Guedes LB et al. concluded that the loss of the protein MSH2 is correlated with its inactivation and appears to be most common among very high-grade primary tumors [12]. Therefore, more research is necessary regarding markers, among them PMS2 and MSH6, to obtain more data on their predictive potential, through an easily accessible technique such as IHC. The objective of this article is to characterize primary prostate tumors in terms of immunohistochemical staining of PMS2 and MSH6.

Materials and Methods

This is a retrospective cohort study of patients who underwent radical prostatectomy to treat prostate cancer at Hospital Haroldo Juaçaba/Cancer Institute of Ceará in the period from January 2009 to December 2016.

We excluded patients with diagnoses of another malignant neoplasm before or concomitantly with the diagnosis of prostatic adenocarcinoma, patients submitted to neoadjuvant therapy (HT and/or RxT) or with metastases diagnosed prior to surgery by means of computed tomography, scintigraphy and/or nuclear magnetic resonance, patients without postoperative PSA measurement, patients without records of clinical follow-up of at least two months, and patients without archival material in paraffin blocks and histological slides for review and preparation of tissue microarrays (TMAs). Finally, no biopsy results were included. The final study universe was composed of 680 samples of TMAs from patients with single prostate adenocarcinoma who underwent radical prostatectomies performed at Hospital Haroldo Juaçaba/ Cancer Institute of Ceará (associated with Federal University of Ceará -UFC). Initially we analyzed the histopathological reports and reviewed the physical/electronic hospital records. In parallel, we examined the IHC slides with marking for construction of the TMAs (Figure 1).



Graph 1: Correlation between age and IHC staining of MSH6 and PMS2

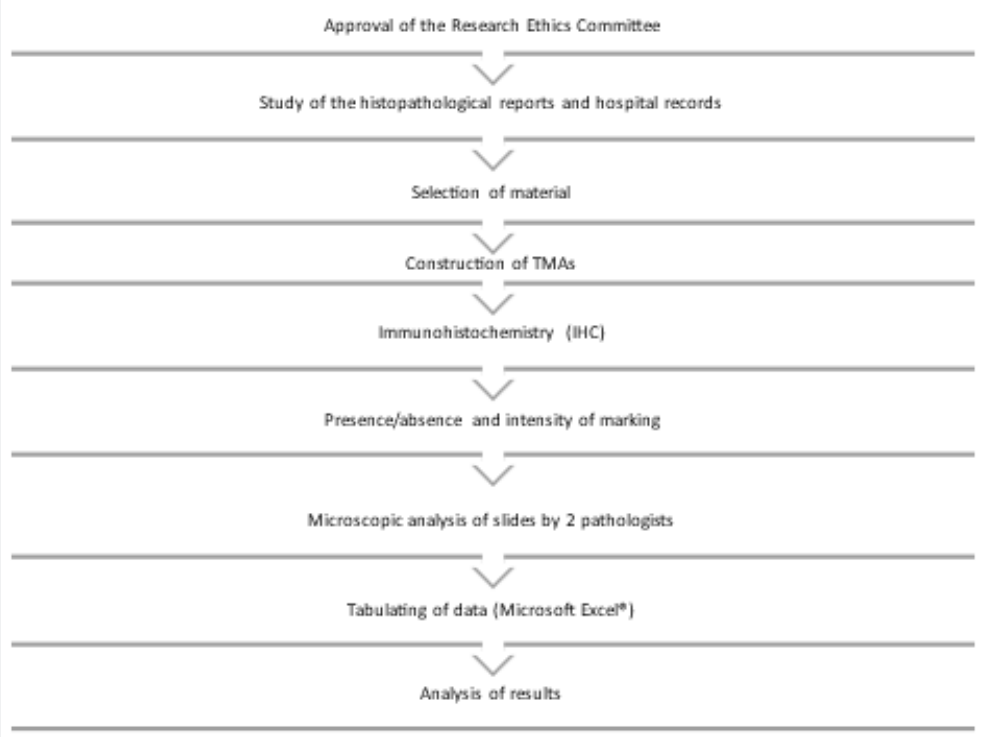


Figure 1: Flowchart of casuistry and methods

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The TMAs were constructed based on neoplastic glandular tissue samples from paraffin-embedded blocks obtained with a 2.0 mm punch. Analysis of tissue microarrays (TMAs) is a technique described in 1998 by Kononen et al., with wide global acceptance among researchers and clinicians. Based on a very simple concept, it involves grouping of a large number of tissue samples in a single paraffin block, allowing study of the expression of molecular markers in large scale with only small amounts of archival material, quickly and at low cost [13]. Next, we prepared the IHC slides with the PMS2 and MSH6 markers. For the MSH6 slides, we used a mouse monoclonal antibody (clone 44). and in the PMS2 case we used a rabbit monoclonal antibody (clone EPR3947) (Figure 1.1). The slides were examined by two pathologists who were blinded regarding the patients' evolutive situation. The data were tabulated in spreadsheets and graphs were plotted using Microsoft Excel®.

The analysis of the PMS2 (Figures 2 and 3) and MSH6 markers (Figures 4 and 5) involved scoring each point of the histological section microarray containing tumor cells, to indicate the presence or absence of a nucleus MMR protein signal. The results were expressed as positive when there was at least one marked cell; negative if any tumor cell at any point showed loss of MMR protein expression, with intact coloration in the mixed benign prostate glands and/or surrounding stromal cells, endothelial cells or lymphocytes; and as inconclusive in the absence of tumor lesion and/or points without internal control staining [12].

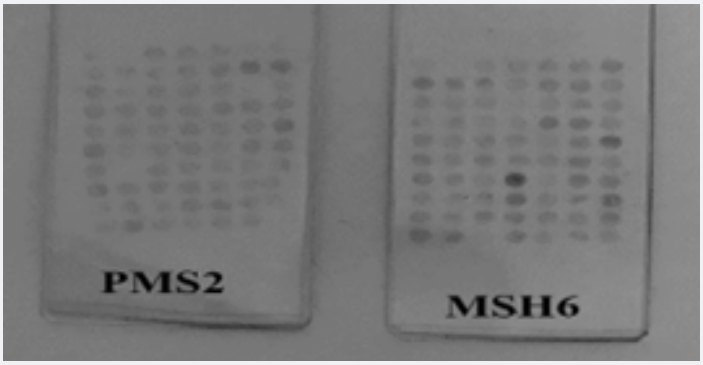

Figure 1.1: TMA slide of markers PMS2 and MSH6

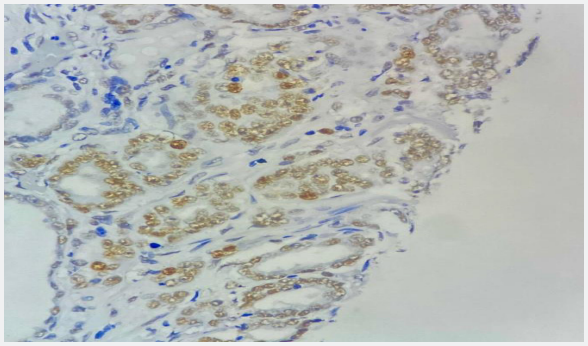

Figure 2: Photomicrograph of immunostaining of PMS2 in a neoplasm. Immunohistochemistry, 400x magnification, marking in magenta of the nuclei of the adenocarcinoma cells

The cases in which the marking was considered doubtful or without internal control, or when there were no tumor cells in sections for immunohistochemical staining, were not considered for statistical effects. This happened in 37 samples for evaluation of MSH6 and in 46 samples for evaluation of PMS2.

The analyses were performed with a Nikon Eclipse E200® microscope.

Besides detecting the presence or absence of IHC staining for PMS2 and MSH6, we also correlated the marking of the clinical and pathological characteristics, such as age, PSA level, pathological staging, detection of metastasis, biochemical persistence, and Gleason grade after revision. We selected the Gleason grade and PSA level because they are two criteria utilized by clinicians to define prognostic risk groups and to guide treatment [14].

Age was obtained during review of the hospital records and was considered as a factor on the day of the prostatectomy and categorized as ≤60 or >60 years [15].

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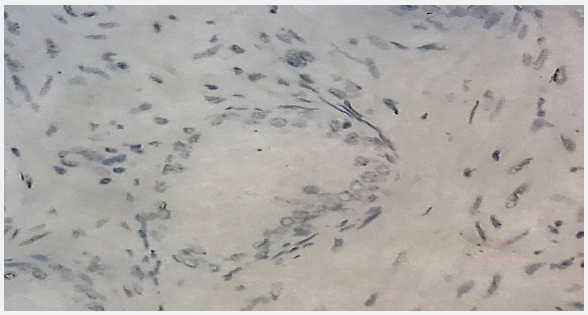

Figure 3: Photomicrograph or PMS2 protein loss in neoplasm, with intact coloration in the surrounding stromal cells, endothelial cells or lymphocytes. Immunohistochemistry, 400x magnification

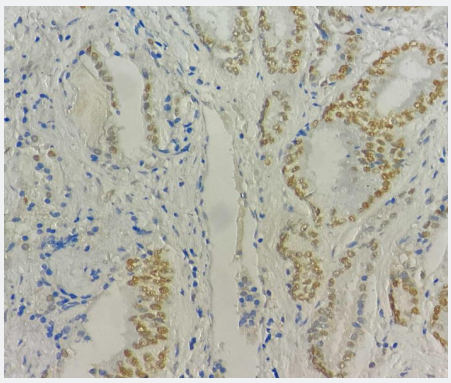

Figure 4: Photomicrograph of immunostaining of MSH6 in neoplasm. Immunohistochemistry, 400x magnification, marking in magenta of the nuclei of the adenocarcinoma cells

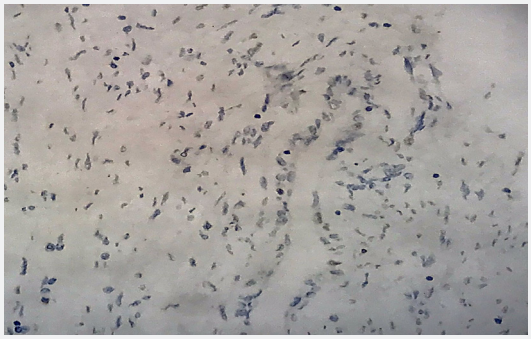

Figure 5: Photomicrograph of the loss of MSH6 protein in neoplasm, with intact coloration in the surrounding stromal cells, endothelial cells or lymphocytes. Immunohistochemistry, 400x magnification.

The serum level of PSA before surgery was also obtained by review of the hospital records, considering the highest level of PSA before the prostatectomy, categorized as ≤10 or >10 ng/ml [16]. In turn, the Gleason pattern, plotted as 3, 4 or 5, was defined by examination of slides of prostatectomy tissues and TMA samples, evaluated according to the recommendation of the World Health Organization (WHO) [17]. The global Gleason scores of the surgical specimens were obtained from the examination of the histological slides and evaluated according to the recommendations of the WHO (2016) [17].

The pathological T staging was obtained by examining the histological slides of the prostatectomy tissue, according to the recommendations of the American Joint Committee on Cancer (AJCC) (2017) [18], plotted as pT2, pT3a and pT3b. The analysis of the extra prostatic extension and infiltration of seminal vesicles, for realization of the T staging, was carried out according to the

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guidance from the International Society of Urological Pathology (ISUP) [19,20]. The existence of metastasis was defined according to detection of distant metastases (bones and lungs) during follow-up by imaging tests (scintigraphy, computed tomography and/or nuclear magnetic resonance). The results were divided into present or absent.

The biochemical persistence (BP) [19] was determined by the reduction or not of the serum PSA level to less than or equal to 0.2 ng/ml between 60 and 90 days after prostatectomy, based on two consecutive measurements. The results were divided into present or absent and the BP time was that elapsed between the date of surgery and the date of the postoperative PSA measurement above the nadir value, expressed in months.

Biochemical Recurrence (RB) 19.1 was defined as a decrease in postoperative serum PSA below 0.2 ng/ml in 60 to 90 days after surgery and with subsequent elevation above this nadir, in at least two consecutive measurements19.2. The results were divided into present or absent and the RB time was the time between the date of surgery and the date with PSA above the nadir, considered in months. Patients with BP who underwent adjuvant therapy were excluded from the RB analysis.

The statistical analysis and plotting of graphs were performed with the SPSS 26® software. Cases of missing data were absent. Differences between groups were evaluated by the Mann-Whitney test and odds ratio significance test through logistic and multinomial logistic regression with the stats model's package of Python.

Results

The study included 680 samples from patients with prostate adenocarcinoma submitted to radical prostatectomy. Of these 680 samples, 45 were excluded according to exclusion criteria, leaving a total of 635 samples (Table 1).

Table 1: Demographic, laboratory, and morphological parameters of 635 patients submitted to radical prostatectomy at Hospital Haroldo Juaçaba between 2009 and 2016. Continuous data related to the median with minimum and maximum values.

Factor	Serial data
age (years)	65.0 (40.0-80.0)
≤60 years	154 (24.3%)
>60 years	481 (75.7%)
PSA before surgery (ng/ml)	9.7 (001.2 – 133.4)
≤10 ng/ml	325 (51.2%)
>10 ng/ml	291 (45.8%)
Absent data	019 (03.0%)
ISUP prognostic group	
Group 1	170 (26.7%)
Group 2	237 (37.4%)
Group 3	108 (17.0%)
Groups 4 and 5	120 (18.9%)
Surgical margins	
Free	431 (67.9%)
Compromised	204 (32.1%)
Tumor staging	
pT2	410 (64.6%)
pT3a	149 (23.5%)
pT3b	076 (11.9%)
PSA before radiotherapy	0.324 (0.3-88.00)
PSA before hormonal therapy	1.290 (0.3-42.690)

Regarding the microsatellite instability markers MSH6 and PMS2, we detected that the average age was 65 years, and 90.5% (575/635) had simultaneous positive staining and none had simultaneous negative staining. Besides this, we noted that the loss rate of the MSH6 repair gene in the sample was 0.15% (1/635) while in PMS2 it was 0.30% (2/635), with an average of 0.23% and mean age of 58 years (minimum of 55 years and maximum of 61 years).

The patients older than 60 years presented respective odds ratios of absence of PMS2 and MSH6 staining of 4.31 and 1.58. These values were not statistically significant at 5% (respective p-values of 0.10 and 0.12), but there was strong clinical evidence that old age was associated with absence of PMS2 and MSH6 staining. In relation to the MSH6 marker, only one patient (1/635) presented negative staining; 22/635 did not have any tumor tissue in the sample; 15/635 samples did not have internal controls and the remainder had positive staining (597/635).

With regard to PMS2, two patients (2/635) presented negative staining of PMS2; 17/635 did not have any tumor tissue in the sample; and 29/635 samples did not have internal controls (587/635).

Hence, there was only one case of loss of the repair protein MSH6 (1/635) and two cases of loss of the PMS2 protein (2/635). Correlation of age and positive staining indicated that of the patients aged 60 years or younger, 94% (146) had positive MSH6 staining and 93.5% (144) had positive PMS2 staining. The corresponding data for the patients older than 60 years were 93.8% (451) with positive MSH6 and 92% (443) with positive PMS2 staining (Graph 1). Correlation of IHC staining of the markers PMS2 and MSH6 with the staging of cancer patients submitted to radical prostatectomy revealed there were no pT4 cases. Of the positive MSH6 cases, 380 were pT2, 143 were pT3a and 74 were pT3b, while for the positive PMS2 cases, 373 were pT2, 142 were pT3a and 72 were pT3b. Thus the majority were pT2.

Since more advanced staging is correlated with worse prognosis, and patients with indication of radical prostatectomy generally have tumors located in advance, it was not surprising that the majority of the patients had tumors confined to the organ (pT2). Considering only the patients who had total loss of staining, we noted one case had loss of the repair protein MSH6 and two

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had loss of PMS2. The patient with loss of MSH6 was younger than 60 years, presented weak and focal PMS2 and had staging of pT3a. In turn, the two patients with loss of PMS2 were 55 and 61 years old, and one of them had strong staining for MSH6 while for the other it was not possible to evaluate this aspect since there was no neoplastic tissue in the sample. These two patients had respective staging of pT2 and pT3a. Therefore, the only samples without staining came from patients between the ages of 55 and 61 years and none of the cases had a simultaneous negative marking, that is, none of the cases marked neither PMS2 nor MSH6. With regard to the Gleason grade, of the patients with loss of PMS2 or MSH6 after revision there was one case with grade 2, one case with grade 3 and one case with grade 4.

For every increase in the intensity level of the MSH6 staining, there was a reduction of 5% in the chances of observing PSA > 10 ng/ml, with p-value of 0.07. Patients without positive MSH6 staining presented odds ratio of 6.40 for biochemical recurrence (p-value < 0.01). According to the Mann-Whitney test, the group without MSH6 staining had higher Gleason scores (p-value < 0.05). In the comparison of the presence of metastasis between the groups with and without MSH6 staining, the Mann-Whitney test suggested greater frequency of metastasis among patients without MSH6 staining (p-value < 0.05). The same observation applies to the staging. The group of patients without MSH6 staining had had worse staging (p-value < 0.05 of the Mann-Whitney test).

There was no significant difference regarding the PMS2 staining and levels of PSA above 10 ng/ml. The p-value of the significance test obtained from the logistic regression model was 0.36. The same was observed for the biochemicals recurrence, with p-value near 1. According to the Mann-Whitney test, there was no statistically significant difference between the groups with and without PMS2 staining in relation to the biochemical recurrence (p-value = 0.96) and presence of metastasis (p-value = 0.99). For staging, the Mann-Whitney test had p-value of 0.06, not considered to be significant at the 10% level, for example. In relation to Gleason scores, the patients without PMS2 staining had higher scores (p-value < 0.05). Of the total sample, biochemical persistence was observed in 13.2% (84/635) of the sample. And no case showed loss of PMS2 and MSH6.

Metastasis was detected in 4.3% (27/635) of the patients. The time for development of metastases varied from 1 to 107 months, with an average of 39 months. Of the cases with detection of metastases, there were no negative readings of microsatellite instability of MSH6 and PMS2.

Discussion and Conclusions

It is known that because prostate cancer is a heterogeneous disease, with indolent and aggressive forms, it is not possible to accurately predict the clinical behavior of patients, principally those now classified as having low risk [21,22]. In this scenario, biomarkers are used as elements that make it possible to better understand the biological mechanisms, acting in a diagnostic, predictive and/or prognostic way [23]. The study of these markers can alert clinicians about patients who are at greatest risk of the aggressive form of the disease, and thus formulate treatment strategies that can be adapted based on individual needs. We detected a loss rate of the repair gene MSH6 in the sample of 0.15% (1/635), and of PMS2 of 0.30% (2/635), with average of 0.23% and mean age of 58 years (minimum of 55 years and maximum of 61 years). Our results (p-value < 0.01) agree with the findings of previous articles, in which the authors suggested that the MSI rate in primary prostate tumors is <4% [7] and that the loss rate of the MMR gene in these cases are smaller still (<3%) [8].

Patients with age older than 60 years presented odds ratios in relation to absence of PMS2 and MSH6 staining of respectively 4.31 and 1.58, meaning, for example that a patient older than 60 years is 4.31 times less likely to present PMS2 staining. These values were not statistically significant in the present study, however there is strong clinical evidence that older age is associated with the absence of PMS2 and MSH6 marking.

The Gleason grade of the patients with loss of PMS2 or MSH6 after revision varied from 2 to 4; and the pathological staging of the cases ranged from pT2 to pT3b. These findings differed from those presented by Guedes et al., who suggested that patients with PMS2 loss more commonly have primary tumors with very high grades [12]. This difference may have been due to the fact our sample was composed mainly of low-risk patients. There were no cases of stage pT4 in our sample.

Regarding the PSA value before surgery, we found that 45.8% (291) of the patients had PSA greater than 10 ng/ml, 51.2% (325) had level lower than 10 ng/ml and 3% (19) cases were not evaluated. According to Tosoian et al., serum PSA lower than 10 ng/ml is considered to be one of the criteria for delaying any modality of intervention, with the objective of reducing the negative effects of overdiagnosis and overtreatment [24-26]. Our results corroborate those findings, since in our sample, of the patients with PSA lower than 10 ng/ml (51.2%, 325/635), only 4.6% (15) had biochemical persistence.

Like new information gained we can quote the dimension of the effect of the microsatellite instability genes PMS2 and MSH6, which may have practical clinical utility, although no studies were found in the literature that corroborate or correlate the results of the present study regarding clinical evolution and despite the fact that the MSH6 and PMS2 markers were not significantly associated with many of the assessed outcomes, a fact that we can explain due to the fact that our patients belong to a low-risk group.

As limitations of this study, we can mention the retrospective model with analysis based on reactions of archived samples, with probable interference in the antigen retreivel for immunohistochemical reactions, loss of information about patient follow-up, loss of fragments in reactions based on TMAs, using

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data from a single treatment center, and operations performed by multiple surgeons. In the future, the prognosis of prostate cancer can depend on small panels of markers that can predict the presence of the disease, its staging, Gleason grade, phase and metastasis. More research is necessary to corroborate the findings reported in previous works, and future studies can use our data for associations with other clinical outcomes.

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