

Comparative Histological Quantification of Prostate Cancer on Surgical Specimens

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ABSTRACT: Prostatic acinar adenocarcinomas (PAA) are frequently diagnosed by biopsy, but sometimes they can be identified incidentally on transurethral resection (TURP) tumor fragments. The classical histological information provided by resection and prostate biopsy specimens is the basis for the therapeutic approach and the establishment of the prognosis of the tumors. In this study, we analyzed 135 PAA that were diagnosed incidentally or for which curative therapy was practiced, for which we established the diagnostic differences for tumor type, tumor grade, presence of perineural (IPN) and lymphovascular invasion (LVI) on radical prostatectomy (RP) and TURP specimens. The tumor type, especially foamy PAA (FPAA) and colloid PAA (CoPAA) were identified mainly on PR, while atrophic PAA (APAA), and pseudohyperplastic PAA (PPAA) mainly on TURP. High ISUP 3-5 grading groups were associated mainly with RP, while ISUP 1-2 were more frequently present on TURP. IPN was present in both types of specimens, while the presence of LVI was more frequent on RP. For the most accurate evaluation of the histological parameters associated with PAA, the information provided by TURP seems insufficient and can be complemented by targeted biopsies for the accuracy of the therapeutic decision and prognosis.

KEYWORDS: Prostatectomy, transurethral resection, histology.

Introduction

Prostate cancers are common tumors in elderly men, with a good prognosis in localized disease, but with unpredictable evolution in case of loco-regional and distant extension [1,2].

Prostatic acinar adenocarcinomas (PAA) constitute the most frequent malignant form of prostatic tumors and the prognosis is based on histopathological parameters represented by the type, grade, tumor stage, vascular or perineural invasion, along with hormonal dependence and neuroendocrine differentiations [3-5].

The accuracy of HP parameters is closely related to clinical-imaging data and therapeutic attitude, which may consist of clinical follow-up, neoadjuvant treatment, radical prostatectomy (RP) and specific oncological therapy [6].

Thus, different surgical specimens can be obtained from a PAA patient, most commonly biopsies followed by RP, but also fragments of transurethral tumor resection (TURP), when tumors are discovered incidentally.

The diagnosis rates of PAA have increased due to screening programs and diagnostic techniques, but nevertheless there are cases discovered incidentally [7].

Incidental PAA on fragments is around 10%, and most of the time these cases belong

to the ISUP1-2 grading group, with an affected of less than 5% of the prostate tissue [8].

In these cases, TURP is obtained following interventions related to urinary obstructive symptoms [9].

However, in general biochemical and clinical suspicion is followed by transperineal or transrectal biopsies to establish the diagnosis [8].

The type of specimen obtained can influence the HP parameters associated with PAA, with an impact on prognosis and therapy [10], and in this context it is of interest whether TURP fragments provide sufficient data for the histological characterization of tumors.

At the same time, one of the problems generally related to studies investigating carcinomas with different locations including the prostate is related to the surgical specimen analyzed, especially in cases where the group is not homogeneous.

However, there are rare studies in which the usefulness of TURP in the management of PAA or in the composition of the study groups is addressed, and some parameters are not mandatory to be reported, even if they are useful for assessing aggressiveness and prognosis [10-13].

In this context, it is important to establish the diagnostic chances of the parameters, which can provide a confidence interval in the initial diagnosis on targeted extracted fragments such as biopsies or randomly in the

case of incidental diagnosis in the case of TURP, an aspect that can improve the diagnostic criteria, reporting and establishing the prognosis of patients with PAA.

Objective

In this study, we investigated the differences in the quantification of histological parameters of PAA depending on the surgical specimen, which can have an impact on clinical practice and research.

Methods

The study included 135 cases of prostatic acinar adenocarcinomas (PAA) that came from patients hospitalized and operated on in the Urology Department of Emergency Clinical County Hospital Craiova, during 2020-2023.

The biological material was represented by prostatectomy and transurethral resection of the prostate (TURP) specimens, which were fixed in 10% neutral formaldehyde for 24-48 hours and subsequently processed automatically, embedded in paraffin, sectioned at 4-5 μ m and stained with Hematoxylin-Eosin.

The diagnosis was made in the Pathology Department, based on the criteria formulated by the World Health Organization (WHO) for PAA in 2022 [14].

The study analyzed the distribution of cases in relation to the surgical specimen obtained and the histopathological parameters of PAA aggressiveness.

In order to obtain a more homogeneous group, which would serve the histopathological investigation and subsequent molecular analysis, only primitive PAA were included in this study, without other oncological or immunomodulatory treatments in the antecedents and without other transurethral prostatic resection interventions that would modify the histological structure of the organ.

Also, only cases without major electrocoagulation artifacts in the case of TURP and without primary processing artifacts were included, for each case the most representative section was selected for the histological classification of the lesions.

No biopsy fragments were used in this study, in order to preserve the tissue that is already in limited quantity, for potential future investigations for the patient.

In the case of incidental diagnosis on TURP fragments of PAA, followed by prostatectomy,

tumor resection fragments were chosen only in cases where preoperative oncological treatment was performed, or a surveillance attitude was adopted.

Prostatectomies following positive biopsies were selected only in the absence of preoperative neoadjuvant treatment.

Statistical analysis used the χ^2 (chi square)/Fisher comparison tests within the Statistical Package for the Social Sciences (SPSS12), and p values were considered significant for values <0.05.

Results

Prostatic acinar adenocarcinomas (PAA) belonged to a group of patients with a mean age of 69.7 \pm 10.3 years, for whom radical prostatectomy (PR) was performed in 70 cases (51.8%) or transurethral tumor resection (TURP) in 65 cases (48.2%) for therapeutic purposes for the diagnosed tumor, respectively for urinary symptoms.

Most PAA were of the conventional type (CPAA, 81.4%), in the 2nd grading group (ISUP 2), with perineural invasion (PNI) in 60 cases (44.4%) and lymphovascular invasion (LVI) in 19 cases (14%) (Table 1).

Depending on the tumor type, the 110 cases of CPAA were diagnosed equally on RP and TURP specimens, they belonged mainly to the ISUP 2 (43 cases) and ISUP 4 (23 cases) groups, with IPN in 50% (55 cases) and LVI in 15.4% (17 cases).

Foamy cell PAA (FPAA) was identified in 13 cases, most on RP (11 cases), located in the ISUP 1 group (9 cases), with rare PNI and LVI (1 case each) (Figure 1A).

Atrophic PAA (APAA) was present in 6 cases, most diagnosed on TURP (5 cases), all in the ISUP 1 group, which rarely presented PNI (1 case) and without LVI (Figure 1B).

Pseudohyperplastic PAA (PPAA) was identified in 3 cases, only on TURP fragments, all in ISUP 1, and without PNI or LVI (Figure 1C).

Colloid PAA (CoPAA) was present in 3 cases, all diagnosed on RP, being in groups ISUP 5 (2 cases) and ISUP 3 (1 case), all with IPN, and sometimes with LVI (1 case).

The analysis of the percentage differences of the diagnosis of the type on RP and TURP was 69.3% for FPAA, 66.7% for APAA, 100% for PPAA and CoPAA and 0% for CPAA.

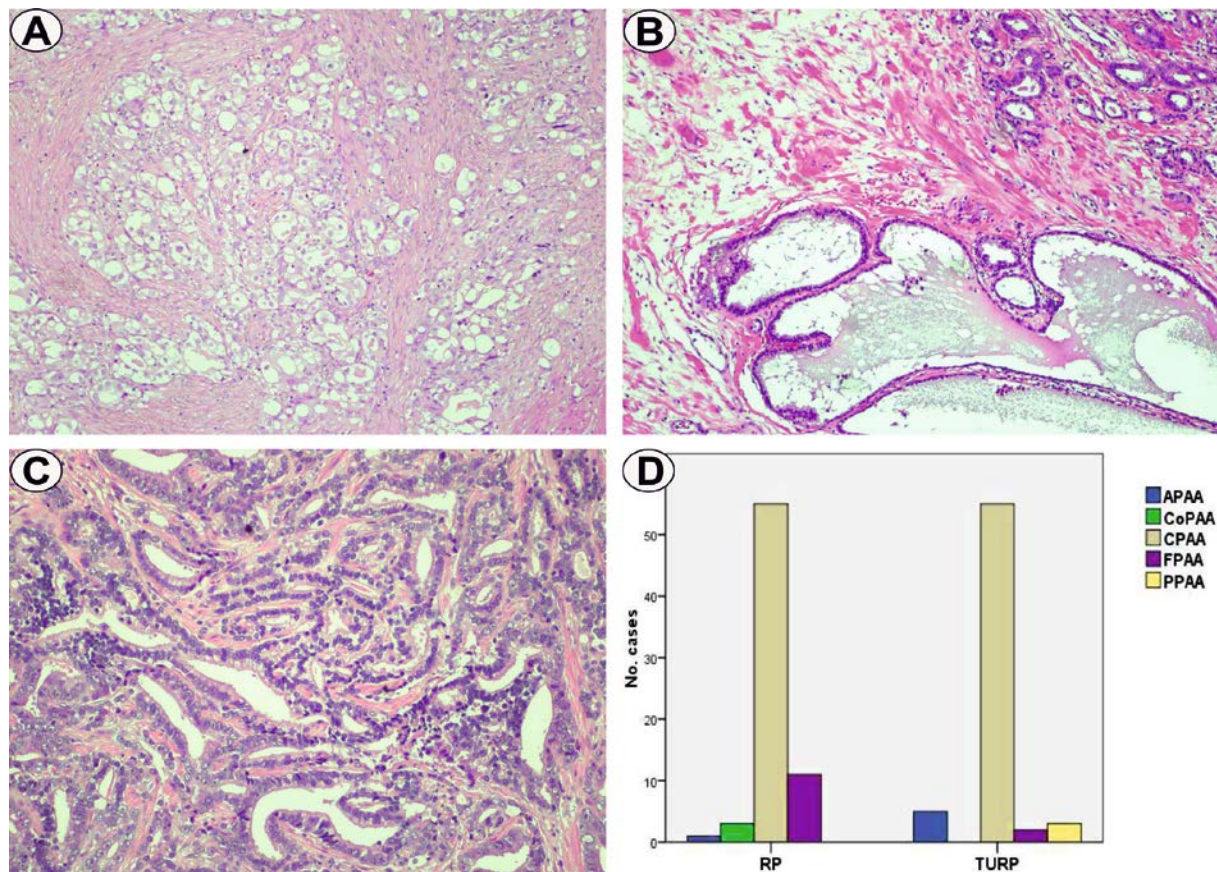


Figure 1. A. Foamy PAA (FPAA), RP, HE staining, x100; B. Atrophic PAA (APAA), RP, HE staining, x100; C. Pseudohyperplastic PAA (PPAA), RP, HE staining, x200; D. Cases distribution depending on specimen type and histopathological type.

Statistical analysis indicated significant differences in the distribution of cases diagnosed on RP and TURP, in the sense that FPAA and CoPAA were diagnosed mainly on

RP while APAA and PPAA were identified mainly on TURP ($p=0.005$, χ^2 test) (Figure 1D).

Table 1. Distribution of cases in relation to histopathological parameters of PAA and surgical specimens.

HP parameters		RP (no. cases)	TURP (no. cases)	p value (χ^2 / Fisher tests)
Histological type	CPAA	55	55	0.005
	FPAA	11	2	
	APAA	1	5	
	PPAA	0	3	
	CoPAA	3	0	
Grade groups (ISUP)	ISUP 1	10	21	<0.001
	ISUP 2	2	42	
	ISUP 3	19	0	
	ISUP 4	22	1	
	ISUP 5	17	1	
PNI	Present	30	30	0.731
	Absent	40	35	
LVI	Present	18	1	<0.001
	Absent	52	64	

HP: histopathological parameters; RP: radical prostatectomy; TURP: transurethral resection of the prostate; CPAA: conventional prostate acinar adenocarcinoma; FPAA: foamy prostate acinar adenocarcinoma; APAA: atrophic prostate acinar adenocarcinoma; PPAA: pseudohyperplastic prostate acinar adenocarcinoma; CoPAA: colloid prostate acinar adenocarcinoma; ISUP: International Society of Urological Pathology; PNI: perineural invasion; LVI: lymphovascular invasion

Regarding the grading groups, ISUP 1 was present in 31 cases, most of which were diagnosed on TURP fragments (21 cases); some of these presented IPN (13 cases), but without LVI (Figure 2A).

ISUP group 2 was present in 44 cases, almost all of which were diagnosed on TURP fragments (42 cases), with relatively frequent IPN (15 cases) and without LVI (Figure 2B).

ISUP group 3 was observed in 19 cases, all diagnosed on RP, with relatively rare IPN and LVI (3 cases and 1 case) (Figure 2C).

ISUP 4 was observed in 23 cases, most of which were on RP (22 cases), almost half presenting IPN (11 cases), some with LVI (3 cases) (Figure 2D).

ISUP 5 was diagnosed in 18 cases, most on RP (17 cases), all with IPN and most with LVI (15 cases) (Figure 2E).

The analysis of the percentage differences in the diagnosis of grade on RP and TURP was 35.5% for ISUP 1, 90% for ISUP 2, 100% for ISUP 3, 91.3% for ISUP 4 and 88.9% for ISUP 5.

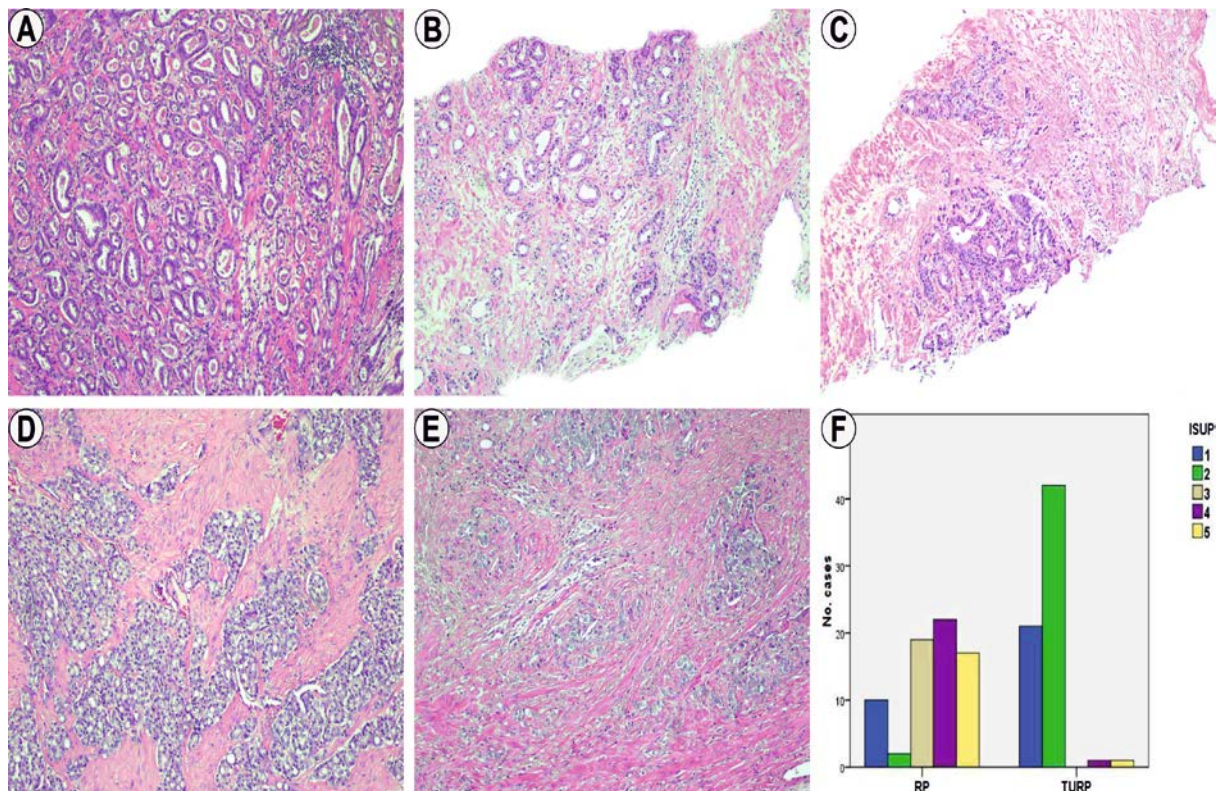


Figure 2. Prostate acinar adenocarcinoma (PAA), HE staining, x100. A. ISUP 1, RP; B. ISUP 2, TURP; C. ISUP 3, TURP; D. ISUP 4, RP; E. ISUP 5, RP; F. Cases distribution depending on specimen type and grading groups.

Statistical analysis indicated significant differences in the distribution of ISUP groups in relation to surgical specimens, groups 1-2 being associated with TURP fragments while groups 3-5 were associated with R ($p < 0.001$, χ^2 test) (Figure 2F).

IPN was diagnosed equally on RP and TURP (30 cases each), the statistical differences being non-significant ($p > 0.05$,

Fisher test), which may suggest that this parameter has a higher chance of being accurately established on any type of biological material (Table 1).

The analysis of the percentage differences in the diagnosis of IPN on RP and TURP was 6.7% in the case of absence and 0% in the case of presence.

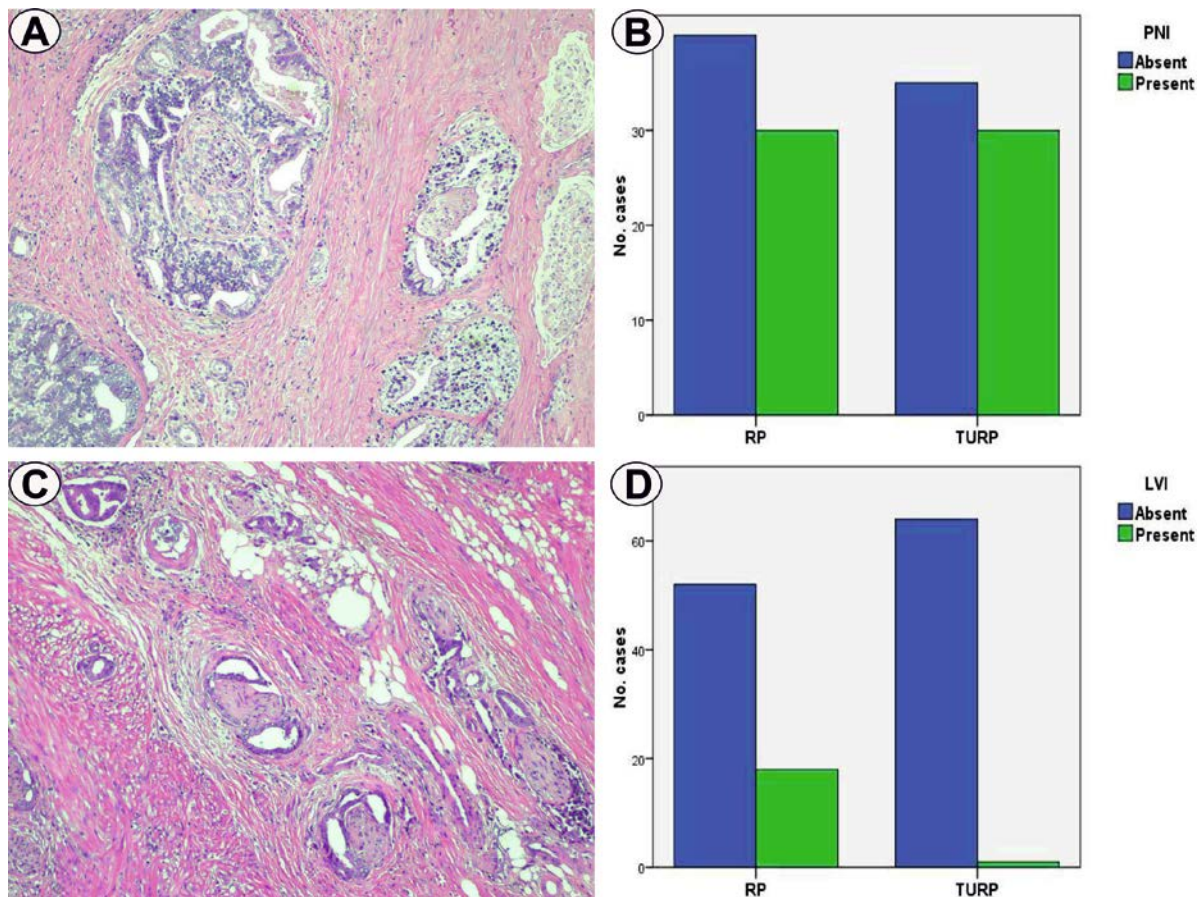


Figure 3. A. Prostate acinar adenocarcinoma (PAA), perineural invasion, RP, HE staining, x100; B. Cases distribution depending on specimen type and perineural invasion; C. Prostate acinar adenocarcinoma (PAA), perineural and lymphovascular invasion, RP, HE staining, x100. D. Cases distribution depending on specimen type and lymphovascular invasion.

LVI was diagnosed in the vast majority on RP, the differences reported in the identification on TURV fragments being statistically significant ($p < 0.001$, Fisher test).

The analysis of the percentage differences in the diagnosis of LVI on RP and TURP was 10.3% in the case of absence and 89.5% in the case of presence.

This aspect means that LVI has relatively low chances of being diagnosed on TURV fragments, especially in the case of incidental PAA, with a mild histological type (atrophic, pseudohyperplastic) and/or in ISUP groups 1-2.

Even in the case of high grading groups (ISUP 3-5), although the chances of identification on reduced tissue fragments are higher, LVI is still more frequently diagnosed on complete resection specimens.

Discussion

Incidental diagnosis of PAA on TURP fragments is limited to 1/10 cases, 20% of which belong to a tumor group that does not have major symptoms [8].

In this study, we investigated a relatively balanced group of PAA diagnosed incidentally on TURP (48.2%) or on RP (51.8%), performed after positive biopsies.

Among the causes that lead to the heterogeneity of results in cancer studies in general are the method of grouping, namely the inclusion criteria, the method of their application, the primary or molecular processing, the standardization of methods (automatic vs. manual), the method of quantification and interpretation [2,15].

Among these, the type of biological specimen used can have a major impact on the results, which is also true in the case of acinar prostate adenocarcinomas (PAA).

Ideally, studies in which HP parameters of PAA are evaluated or reported on these

parameters should aim for group homogeneity for several reasons: the Gleason score and grading group increase in the case of prostatectomy compared to biopsies and TURP, also lymphovascular invasion and extraprostatic extension are more likely to be correctly assessed in prostatectomies [10,16,17].

It is clear from the beginning that the accurate determination of HP parameters associated with PAA can be achieved especially on RP, if we compare it with other types of specimens that are quantitatively and qualitatively limited.

On the other hand, especially in molecular studies biopsies can be used in a limited way and are not recommended, especially since the biological material is reduced and subsequent requests of patients for biological material for additional determinations are possible; in addition, there may be the option of active surveillance, to reduce the adverse effects of radio and chemotherapy on patients, especially in the case of incidental, limited and/or slow-growing tumors [10,18].

As such, the most indicated ones seem to be prostatectomies-but here too, one must take into account the impact that androgen deprivation, frequently used in these cases, can induce the so-called regressive changes in both the parenchyma and the tumor stroma, with difficulties in interpreting both the histological aspects (atrophic changes, nuclear deformations and hyperchromasia, cytoplasmic vacuolization, fibrosis and stromal inflammation, the presence of hyperplasia or metaplasia of various forms) and the molecular reactions [19,20].

In this context, an ideal group without previous treatments (oncological, immunomodulatory, etc.) is necessary, preferably with prostatectomies, or as balanced as possible so that neither the patients nor the objectivity of the real statistical trends are affected.

In our study, the analysis of the PAA type in relation to the surgical specimen indicated the association of FPAA and CoPAA with RP and APAA and PPAA with TURP, while CPAA was evenly distributed on the two types of biological material.

These results indicate a diagnostic difficulty especially of the non-conventional types on limited biological material such as TURP, which is also in agreement with other studies [21].

In this study, for the forms diagnosed predominantly on TURP with evolution and a better prognosis compared to the other forms [14,21], it is expected, especially if they are limited in extension, not to associate relevant clinical-imaging data and to be identified incidentally; likewise, FPAA and CoPAA, require higher quantitative tissue material to be relevant as a percentage of 25% for CoPAA and 10% for FPAA [14,22].

Thus, the tendency is that even if there are foci of CoPAA and FPAA associated with a CPAA on TURP or biopsies, they should be classified as CPAA with differentiations, the actual type established in percentage being possible especially on RP, in which the diagnostic percentage is usually over 10% [21,23,24].

Regarding the grading groups, ISUP 1-2 were associated with TURV while groups 3-5 with RP.

As in the case of tumor type, PAA with good differentiation are more likely to be diagnosed incidentally on TURP fragments, compared to the moderate/poorly differentiated groups which, in addition to advanced extension and therapeutic association with RP, also require investigation of the entire organ.

Data from the literature indicate that the PAA grade increases on RP in 20-30% of cases, and discordant findings occur mainly due to high grades appearing on PR and not on biopsies [16,17].

A particular aspect in these cases refers to the intermediate risk groups, which if they meet certain criteria can be subject to active surveillance, as in those with low risk [10,18].

In this study, there were no differences in diagnosis between RP and TURP regarding IPN.

Even though it is a predictor of advanced tumor stage, positive margins and poor survival, IPN is not mandatory to report on biopsies, and its incidence is 20% and is not an independent factor, and patients can remain under active clinical surveillance in certain conditions [10,18,25].

In our study, LVI was associated with RP specimens.

The identification rate of LVI on RP is 2.8-21.5% in large studies, and it is an independent factor of prognosis and biochemical recurrence [10,26,27].

LVI is generally considered rare even on RP, with problems related to the diagnosis of HP, some studies indicating that there is no

difference between the definite or uncertain presence of LVI on RP and that it is not mandatory to report [10-13].

Overall, RP is clearly superior to TURP for the diagnosis of non-conventional types, high tumor grade and LVI. In addition, TURP fragments frequently have electrocoagulation and sectioning artifacts, as well as telescoping [9].

In the context of the percentage differences in the diagnosis of HP parameters on RP and TURP specimens, it seems necessary to at least conduct imaging investigations and perform targeted saturation biopsies in the case of incidental diagnosis on TURP.

If we take into account that TURP mainly includes fragments from the periurethral area and PAA frequently develops in areas in the periphery of the prostate, these targeted biopsies are all the more necessary.

Knowing the potential/chance of establishing a HP parameter for PAA, can improve the criteria for recommendation for a certain therapeutic attitude or for assessing the prognosis.

It can also have an impact on the way in which study groups are constituted in which PAA are analyzed HP and/or molecularly.

Conclusions

The study indicated significant differences in the reporting of histopathological parameters associated with PAA on RP and TURP specimens, especially related to non-conventional tumor types, high grade and lymphovascular invasion.

Performing additional investigations or repeating targeted tumor harvests may have a positive impact on the efficacy of treatment and prognosis.

Author Contributions

Conceptualization, A.E.S. and A.M.S.; Methodology, A.M.S., B.C.A. and O.I.C.; Investigation, A.M.S. and O.I.C.; Data analysis, A.E.S., A.M.S. and B.C.A.; Manuscript writing and initial draft preparation, A.M.S.; Manuscript review and editing, A.M.S., B.C.A. and O.I.C.; Supervision, A.E.S.. All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare no competing interests.

Institutional Review Board

The study was conducted according to the guidelines of the Declaration of Helsinki; the study and the protocols utilized therein were approved by the Ethics Committee of University of Medicine and Pharmacy of Craiova (223/28.09.2023).

Consent Statement

Not applicable for a retrospective descriptive study.

Data availability

All data presented in the manuscript are available from the authors upon request.

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