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# Contribution of Anti-p63 Antibodies in the Interpretation of Benign Label Prostatic Biopsies

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## Abstract

**Introduction:** Prostate cancer is the second most common cancer in men. The diagnosis is most often based on the prostate biopsies' analysis and on histological criteria recognizable on standard coloring. In some cases, the use of immunohistochemistry is important. **Objectives:** This paper aims to specify the p63 phenotypic profile of lesions diagnosed benign, with minimal suspect foci, difficult to interpret, HGPIN (high grade intraepithelial neoplasia) and LGPIN (low-grade prostatic intraepithelial neoplasia) and evaluate the manual technique of p63 immunohistochemistry. **Patients and Method:** This was a retrospective, descriptive study of prostate biopsies recorded in the PAC service of the HALD from January 1st, 2018 to December 31st, 2018. It was completed by a manual immunohistochemical study of the blocks enrolled from November 19th to December 4th, 2020 in the PAC department of the HPD. The studied parameters were: registry number, age, clinical stage, prostate volume, PSA level, microscopic appearance and p63 immunohistochemical profile. **Results:** Our study included 60 prostate biopsies. The ages of our patients varied from 45 to 77 years, with an average of 64.2 years and a standard deviation of 6.2. The majority of patients were at clinical stage cT2b (33%) with a prostate volume varying between 33.15 and 169.4 cc. The minimum value of PSA in our series is 5 ng/ml, the maximum being 100 ng/ml with an average level of 24.1 ng/ml and a standard deviation of 21.2. Our series included 50 adenomyomatous hyperplasias, 7 adenomyomatous hyperplasias associated with chronic prostatitis, 2 HGPIN and 1 LGPIN. After re-reading we found 5 discordant cases, which corresponded to minimal suspect foci (kappa = 0.5098). The p63 marking was informative in 53 cases, *i.e.* 88%, and non-informative in 7 cases, *i.e.* 12%. Among the uninformative markings, 2 were due to lack of tissue adhesion to the slides. Among the in-

formative markings, 11 were negative. p63 immunohistochemistry was useful in all suspected foci and detected 6 other minimal foci of adenocarcinoma. **Conclusion:** The immunostaining with the anti-p63 antibody in the prostate cancer diagnosis is of considerable benefit. It made it possible to correct 11.3% of benign diagnosis in minimal malignant focus in our context. Despite the difficulties associated with the manual technique, it is possible to have an informative rate, similar to the automatic technique.

## Keywords

Prostate, Cancer, Diagnosis, Anti-p6 Antibody

## 1. Introduction

According to Globocan, prostate cancer is the second most common cancer and the fifth leading cause of cancer death in men in 2020 worldwide. It is the most frequent and deadliest cancer in men in Africa, especially in Sub-Saharan Africa [1] [2]. In Senegal, it ranks first among cancers in the elderly [3] and has a high probability of diagnosis at an advanced stage (T3/T4) [4] [5]. In view of these data, it is important to optimize the definitive diagnosis of this condition, based on the analysis of prostate biopsies and on histological criteria recognizable on standard coloring. In some cases, the histological lesions may mimic cancer, such as atrophy, atypical adenomyomatous hyperplasia, or foci of prostatic intraepithelial neoplasia (PIN). These require the pathologist to resort to more advanced techniques, such as immunohistochemistry, to confirm or deny the diagnosis [6], thus avoiding repeated biopsies. In our context, a country with limited resources, the majority of prostate biopsy results are reported on the basis of a standard histological examination. We were interested in determining the value of the use of the anti-p63 antibody in benign lesions diagnosed from prostate biopsies treated at the Aristide Le Dantec hospital in Senegal.

The objectives of the study were:

- To determine the p63 phenotypic profile of lesions diagnosed benign, in order to determine whether there were false negatives;
- To determine the p63 phenotypic profile of lesions with minimal suspect foci, difficult to interpret;
- To evaluate the manual technique of p63 immunohistochemistry.

## 2. Material and Method

Our study was carried out in the PACL (Pathological Anatomy and Cytology Laboratories) of the Aristide Le Dantec University Hospital Center (HALD). It was a retrospective, descriptive study, over a period of one year, from January 1st to December 31st, 2018, relating to the archives of anatomopathological reports and blocks of 60 prostate biopsies, completed by a manual immunohistochemical study. During our counting, we collected 308 prostate biopsies during

the study period, *i.e.* 199 adenomyomatous hyperplasias (64.6%), 4 HGPIN (1.3%), 1 LGPIN (0.3%) and 104 adenocarcinomas (33.8%).

We included all archived prostate biopsy slides and blocks from the study period with a "benign" result and documented PSA level. A total of 204 cases were included. We excluded cases of prostate biopsies with exhausted or insufficient blocks. This represents 85 cases.

This left 119 cases included. Secondly, due to a lack of resources, 60 biopsy cases meeting the inclusion criteria were randomly selected, and all were immunostained for anti-p63 antibody.

We used a mouse anti-p63 monoclonal antibody (clone 4A4 diluted 1:200 in blocking solution, Ventana Inc., Tucson, AZ, USA). Data collection and analysis were carried out identically in all patients. The studied parameters were: age, clinical stage of the disease, prostate volume, PSA level, histological characteristics, anti-p63 antibody marking.

## 3. Procedure

Sixty reports of anatomopathological results with their blocks were selected meeting the above-mentioned criteria.

The blocks of all the selected protocols were disintegrated by melting the old paraffin in a mold. These samples were then counted, recovered and then reintegrated in new paraffin. They were then cooled on a freezer plate, and thus new blocks of paraffin were obtained. These new blocks of paraffin were roughed out, then microtome cut into ribbons 3 micrometers thick. These were then spread, stained with hematoxylin eosin (HE), mounted between slide and coverslip and then reread under an optical microscope by an experienced pathologist. All preparations were fully explored to find the targeted area(s) of interest at the IHC. We started with the low magnification (for an architectural view) and then moved on to a stronger lens (for the cell-scale study). This was followed by a manual immunohistochemical study on super frost loaded slides which took place from November 19th to December 4th, 2020.

## 4. The Immunohistochemical Technique (The Steps Are Similar to Those of the Standard Technique until the Making of the Blocks)

- The microtome cut

Cutting is done using a rotating microtome fitted with a razor blade holder. First, you have to roughen the block to 20 µ. As soon as the sample appears, the microtome is set for 5 µ or 4 µ sections. The obtained ribbons are immersed in a water bath without albuminous water. The temperature of the water bath is 40˚C. These slides are then placed on a hot plate (between 45˚C and 53˚C) for at least 2 hours, then left on the plate turned off until the next day. The slides are then kept cool between 2 and 8 degrees for at least 24 hours.

- Deparaffinization

It consists in removing the paraffin contained in the fragments by placing

them in three successive baths, of 5 minutes, of Xylene. This step lasts a total of 15 minutes.

- Hydration (Figure 1)

It consists in hydrating the fragments by putting them in two alcohol baths at 100 degrees for 5 minutes each and a final alcohol bath of 95 degrees for 5 minutes. This step lasts a total of 15 minutes.

- Rinse with running water for 30 to 60 seconds.
- Then immerse the slides in distilled water for 5 minutes.
- Restoration of antigenic sites (Figure 2)

Turn on the water bath containing tap water from the start of the manipulations, then set it to 98 degrees. Place the slides in a preheated CCS (Cell Conditioning Solution) bath and immerse them in the water bath for 30 to 40 min.

- Cooling: let it cool for about 25 min in the open air.
- Then immerse the slides in distilled water for 1 minute.
- Framing: delimit the fragments with a marker, such as Dakopen, in order to visualize the area properly and to prevent the leakage of reagents towards the entire slide.

Figure 1. Objects slides in an alcohol container.


Figure 2. Water bath (A); Water bath containing two CCS containers with slides for objects (B).

- Create a wetland (Figure 3). In our case we put two long racks in a tray with tap water. The slides were placed on the racks for the remainder of the manipulation.
- Oxygenated water (Figure 4): put a drop on each slide then cover the tray with a mold for 10 minutes. The $H_2O_2$ acts as an endogenous peroxidase.
- Rinse with Buffer tampon for 5 min; the tampon is first collected in a squeeze bottle.
- Inhibitor: neutralizes non-specific proteins. Pour a drop on each slide, create a dark room (Figure 5) cover it and wait 5 min.
- Rinse 5 min with the Buffer.
- Put a drop of antibody (anti-p63) on the samples, then cover until the next day.
- Rinse with buffer for 5 minutes three times.

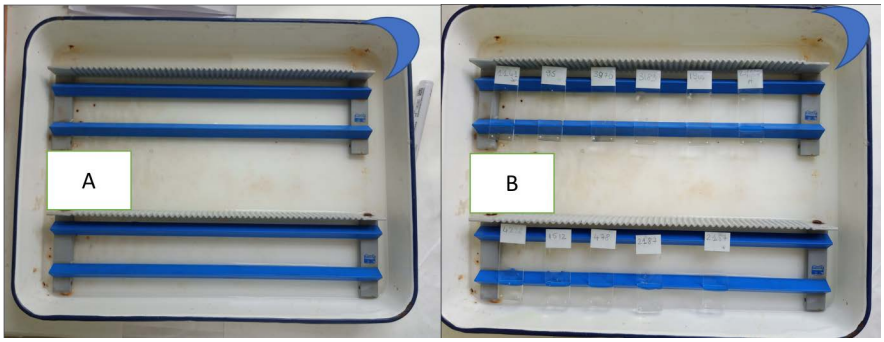


Figure 3. Wetland (A); wet area with blades (B).


Figure 4. Kit-box (A); application of the $H_2O_2$ to the slides (B).

Figure 5. Covered wetland (darkroom).

- Put bio line (secondary antibody) and cover for 30 minutes.
- Rinse with buffer for 5 minutes three times.
- HRP (horseradish peroxidase): one drop on each sample and cover for 30 minutes.
- Rinse with buffer for 5 minutes three times.
- Preparation of $H_2O_2$ and Chromogen: put as many drops as $H_2O_2$ and chromogen in a dry tube. The quantity depends on the number of blades. Cover the slides for 10 minutes.
- Put the slides in distilled water for one minute.
- Hematoxylin: one drop on the samples for 2 minutes.
- Put the slides in distilled water for 5 minutes.
- Then 95 degrees alcohol for 5 minutes and two 100 degrees alcohol baths for 5 minutes.
- Put in three successive xylene baths for 5 minutes each.
- Fit the blades. The assembly of the colored slides consists of placing a coverslip on the face of the slide with the cutting tape using the Eukitt.
- Reading of prostate biopsy slides with IHC p63 staining.

## 5. All Blocks Benefited from a Manual p63 Immunohistochemical Study

❖ The coloring is said to be informative:

- Positive: When only the nuclei of basal tumor cells and normal cells are stained (Figure 6).

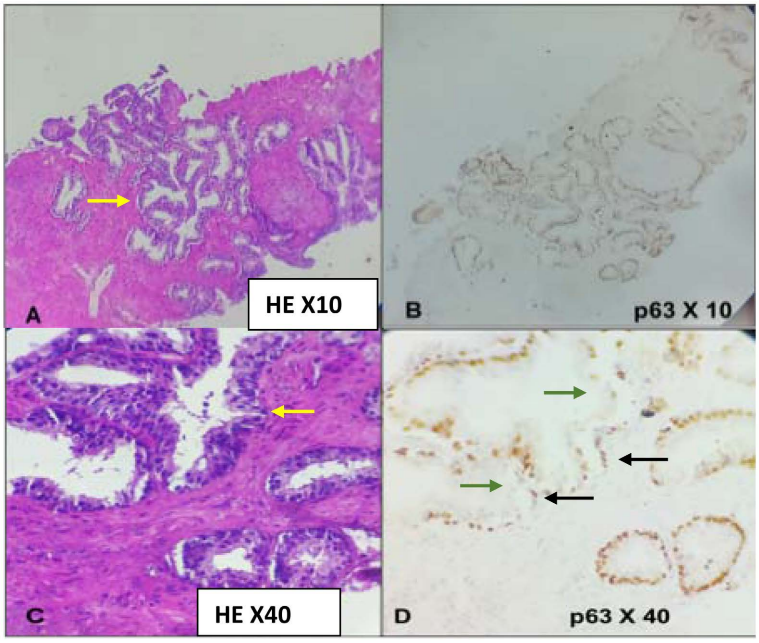


Figure 6. Two prostate biopsies with positive immunostaining for p63. (A) and (C): Histological image of adenomyomatous hyperplasia (←), at HES (Haematoxylin-Eosin-Saffron); (B) and (D): IHC p63+ marking; there is a marking of the basal cells (←), the luminal cells are not marked (→).

- Negative: when the basal cell tumor nucleus is not marked with a labeled positive control (marked in normal cells) (Figure 7).

❖ The coloring is called non-informative when any marking other than that of the nucleus of the basal cells is observed, or when no labeling is observed even in the positive control, as well as when there is a detachment of the sections of sampling (Figure 8).

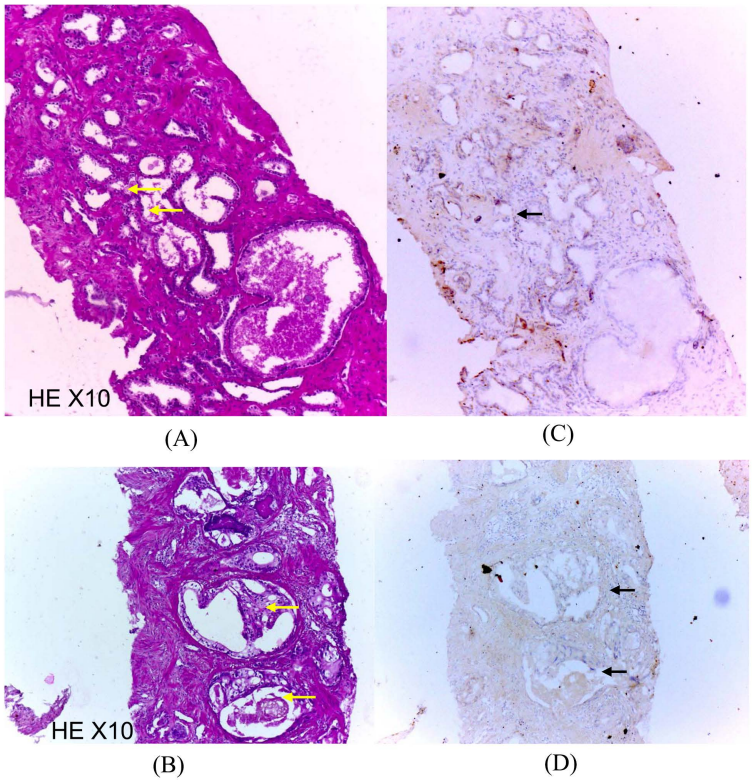


Figure 7. Two prostate biopsies with negative p63 immunostaining. We see in (A) and (B) a suspect zone (⟵). In (C) and (D), we see an absence of the basal cells' marking (←) of certain glands with the presence of internal positive control.

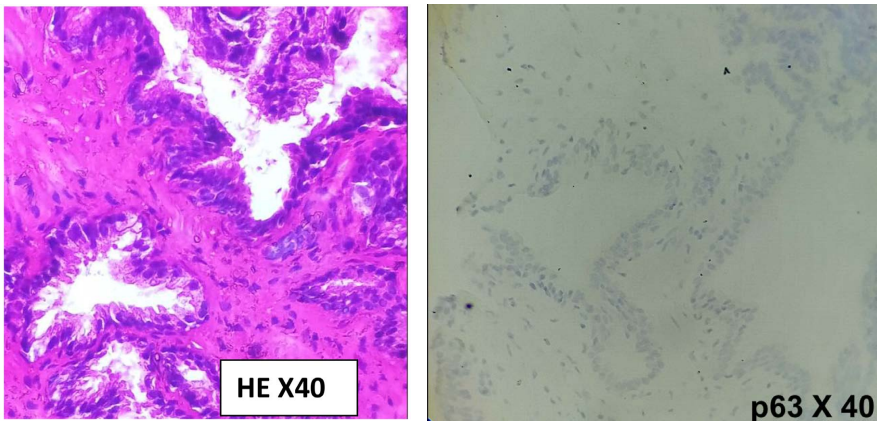


Figure 8. Histological image of adenomyomatous hyperplasia (A); Prostate biopsy showing uninformative p63 immunostaining: total absence of marking even in normal glands (B).

➢ **Data processing**

The data collected were entered using Epi data software and analyzed using Epi info 3.5.4 software. Tables and figures were produced using Microsoft Excel 2016 and Word 2016 software. In the descriptive analysis, qualitative variables were described by frequency tables and bar charts. Quantitative variables were described by their position (mean, median) and dispersion (standard deviation, extremes) parameters. Cohen's Kappa statistical test [7] was calculated to assess agreement between the two readings.

Interpretation of the result:

- <0: Disagree;
- 0 - 0.20: Very weak agreement;
- 0.21 - 0.40: Weak agreement;
- 0.41 - 0.60: Moderate agreement;
- 0.61 - 0.80: Strong agreement;
- 0.81 - 1.00: Almost perfect agreement.

## 6. Results

➢ **Descriptive study**

During the study period we identified 308 prostate biopsies. Among them, 60 prostate biopsies were randomly included. The ages of our patients varied from 45 to 77 years, with an average of 64.2 years and a standard deviation of 6.2. The most represented age group was that between 61 - 70 years (or 45%) (**Figure 9**).

The clinical stage was given in 12 cases, *i.e.* 20%, dominated by the cT2b stage and represented 33.3% of cases (**Table 1**).

Prostate volume was noted in 17 patients (28.33%). It varied between 33.15 and 169.4 cc (**Table 2**).

The PSA level was reported in all our patients and varied between 5 and 100 ng/ml with an average level of 24.1 ng/ml and a standard deviation of 21.2 (**Figure 10**).

Histological result:

- Initial diagnosis

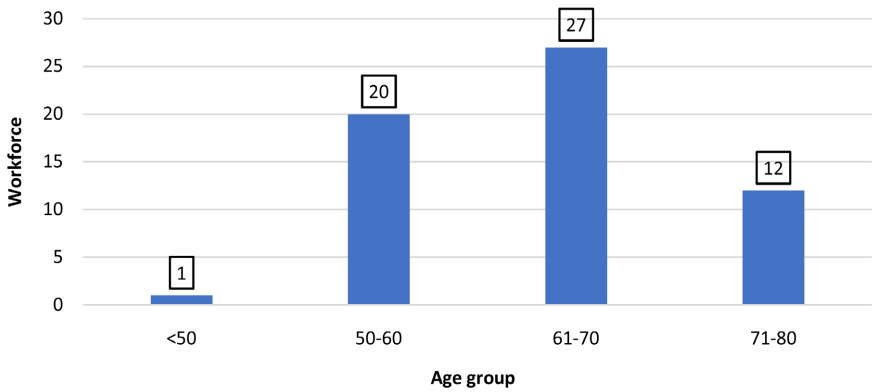


**Figure 9.** Distribution of patients by age group.

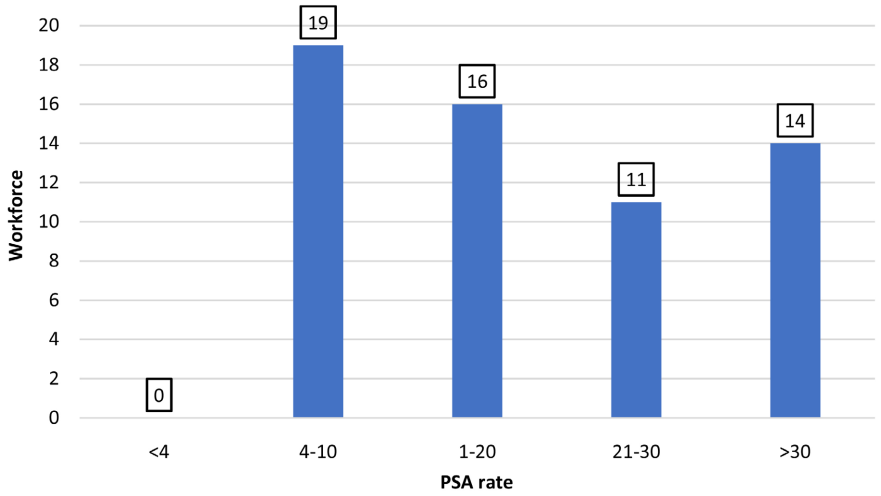


**Figure 10.** Distribution of patients according to the PSA level.

**Table 1.** Distribution by clinical stage.

| Clinical stage | workforce | Percentage |
|---|---|---|
| cT0 | 3 | 25 |
| cT2a | 2 | 16.7 |
| cT2b | 4 | 33.3 |
| cT2c | 3 | 25 |
| Total | 12 | 100 |

**Table 2.** Distribution according to prostate volume.

| Prostate volume | Workforce | Percentage |
|---|---|---|
| 30 - 59 | 6 | 35.3 |
| 60 - 79 | 4 | 23.5 |
| 80 - 99 | 2 | 11.8 |
| ≥à 100 | 5 | 29.4 |
| Total | 17 | 100 |

Initially our series included 83.3% of adenomyomatous hyperplasia (*i.e.* 50 cases), followed by 11.7% of adenomyomatous hyperplasia associated with chronic prostatitis lesions (*i.e.* 7 cases), 3.3% of HGPIN lesions (*i.e.* 2 cases) and 1.7% of LGPIN lesion (*i.e.* 1 case).

- Diagnosis after proofreading

All the blocks were cut and marked with HES (Haematoxylin-Eosin-Saffron). After reading, we found 4 sit slides of suspected malignancies in the 50 adenomyomatous hyperplasias (Table 3). The kappa test in our study was 0.509.

Immunohistochemical coloring was informative in 53 cases, *i.e.* 88%, and

non-informative in 7 cases, or 12%. Regarding the non-informative markings, 2 were due to the lack of adhesion of the tissue on the slides. Among the informative markings 11 were negative (Table 4). Immunostaining was informative in all suspect foci (Table 4). All 5 suspicious lesions found on HE (Hematein-Eosin) on the second reading were confirmed as indeed malignant on IHC. Five other minimal foci of adenocarcinoma were found at IHC among the 46 BPHs (Table 4) and the lesion of HGPIN was shown to be a malignant lesion. These lesions corresponded to a Gleason 6 (3 + 3), ISUP 1.

In total, the use of immunohistochemistry made it possible to correct 6 diagnoses, 5 minimal suspect foci and a HGPIN with a purely malignant lesion (Figure 11).

Table 3. Comparison between the initial reading and the second reading.

| Diagnosis | First lecture | | Second reading | |
|---|---|---|---|---|
| | Workforce (N) | Percentage (%) | Workforce (N) | Percentage (%) |
| BPH (benign prostatic hyperplasia) | 50 | 83.3 | 46 | 76.6 |
| BPH and chronic prostatitis | 7 | 11.7 | 7 | 11.7 |
| LGPIN | 1 | 1.7 | 1 | 1.7 |
| HGPIN | 2 | 3.3 | 1 | 1.7 |
| Total | 60 | 100.0 | 60 | 100.0 |

Table 4. Distribution of the quality of the immunostaining according to the final diagnosis and details of the informative and non-informative immunostaining.

| Final diagnosis | p63 marking | | | | Total |
|---|---|---|---|---|---|
| | Informative | | Not informative | | |
| | Negative | positive | Lack of membership | Marking of Internal witnesses | |
| BPH | 5 | 35 | 2 | 4 | 46 |
| BPH and chronic prostatitis | - | 6 | - | 1 | 7 |
| Minimal foci suspected of malignancy | 5 | - | 0 | - | 5 |
| LGPIN | - | 1 | 0 | - | 1 |
| HGPIN | 1 | - | 0 | - | 1 |
| Total N (%) | 11 (18.3%) | 42 (70%) | 2 (3.3%) | 5 (8.3%) | 60 (100%) |

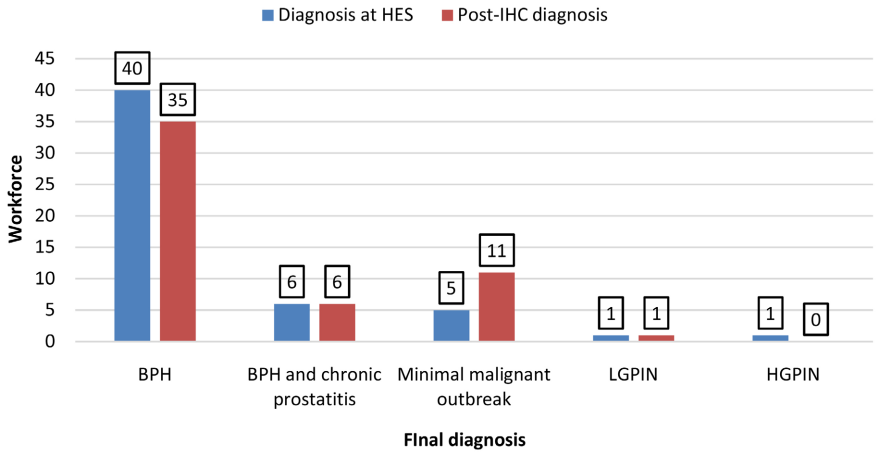


**Figure 11.** Comparison of diagnosis between HES and IHC.

## 7. Discussion

➢ **Age**

The average age of our patients was 64.2 years and the most represented age group was between 61 - 70 years or 45%. These results were similar to those of the study in Mali by Traoré *et al.* [8] which found an average age of 71.5 years, and age groups between 60 - 69 years and 70 - 79 years, respectively 33.7% and 41.5%. These data show that benign prostatic tumor pathology is the apanage of the elderly. Our study found an avarage age lower than the data in the literature, partly explained by the selection criteria, including the PIN lesions and the foci of suspected malignancy, and the small size of the sample.

➢ **PSA level**

The average PSA level in our study was high at 24.13 ng/ml with extremes of 5 and 100 ng/ml, therefore 8 times higher than normal (3 ng/ml). On the same vein, the study in Mali by Traoré *et al.* [8] showed an average level of PSA, 5 times higher than normal (16 ng/ml). PSA which is a serine protease produced by the prostate epithelium is not specific for prostate cancer, but rather for the prostate organ. In fact, an increase in the PSA level can be found in patients developing prostate cancer as well as in patients with benign prostatic pathologies (such as benign adenomyomatous hyperplasia of the prostate, prostate inflammation etc…) [9].

➢ **Discrepancy between first and second reading**

In our study, 8.3% of cases (5/60) presented a discrepancy between the first and second reading. All the discordant cases were micro-foci less than 2 mm. These results are in agreement with a study carried out by the AFU, which found 7.1% of discordant cases (10/141) [10] with an agreement between readers considered to be excellent (kappa = 0.865). All of these discordant cases were also micro-foci less than 2 mm (**Table 5**). The concordance between readers in our context was judged to be moderate, possibly explaining by the fact that these certain blocks were not well debited, preventing with ease the localization of the microfocuses.

**Table 5.** Concordance between the first and second reading.

| IHC | Similar cases | | Discordant cases | | Total |
|---|---|---|---|---|---|
| | Workforce (n) | Percent (%) | Workforce (n) | Percent (%) | |
| French Urology Association | 131 | 92.9 | 10 | 7.1 | 141 |
| Our study | 55 | 91.7 | 5 | 8.3 | 60 |

➢ **Quality of immunostaining**

The marking in our case, done using a manual technique, was informative in 88.4% and non-informative in 11.6%. A study carried out in Boston-United States, by Weinstein *et al.* [11] shows that with an automatic technique, the coloring was generally informative in 78.6% of cases, more precisely it was informative respectively in 93% of cases and 75% of cases, when it was performed on loaded and unloaded slides, respectively. In our study 3.3% of cases were uninformative to immunostaining related to a lack of tissue adhesion. This percentage is lower than that of several studies in particular that of Rajal *et al.* [12] which showed 6% of non-interpretable slides due to a lack of adhesion of the tissue and the study of Weinstein *et al.* [11] which presented 20% of cases. In our study, 8.3% of cases showed no marking in all benign glands. This rate is lower than that of the study by WU *et al.* which was 17% [13]. These data show that despite the difficulties associated with the manual technique, it is possible to have an excellent informative rate, similar to the automatic technique.

➢ **Usefulness of the p63 antibody**

The p63 marking made it possible to confirm the malignancy of all our suspected cases, to discover 5 other small foci of malignancy less than 2 mm among samples initially labeled benign and finally to reclassify a PINHG lesion as a malignant lesion. These data are compatible with the data from the European Randomized Screening for Prostate Cancer (ERSPC) study on the centralized re-reading of prostate biopsies which confirmed all cancers diagnosed by initial pathologists and found 10 discordant cases (out of a total of 141), all of which were micro-foci of less than 2 mm [10]. The diagnostic utility of the p63 antibody for prostatic pathology has been demonstrated by several studies, as has ours. p63 is one of the most sensitive and specific markers of the basal cells of the benign prostate glands [11]. Its presence in the basal cells of a glandular focus argues against a diagnosis of invasive prostate carcinoma (PC), although there are a few examples in the literature of prostate carcinoma that stain focal, with some of the basal cell markers, such as p63. These cases are usually easily diagnosed on the basis of standard histologic examination at the HE and are unlikely to be confused with their benign imitators [12] [13]. The negative p63 coloring is considered informative when it has failed to mark cells from a glandular focus diagnosed as malignant and a good positive internal control coloring is present. Special attention to morphology is necessary when interpreting atypical glands marked with p63 in a discontinuous manner [12]. Benign lesions that can mimic

prostate adenocarcinoma are relatively rare, multiple and are classified according to the four major architectural categories of the Gleason diagram. A trained pathologist can diagnose them with standard morphology. The most frequent immitators belong to architectural category I (small glands) such as, atrophy, post-atrophic hyperplasia, atypical adenomyomatous hyperplasia and seminal vesicle [14]. However, data from the literature, in particular the International Society of Urological Pathology (ISUP) [15] and the study by Molinié V. *et al.* [6] recommend immunohistochemistry, either with the use of high molecular weight cytokeratins (34$\beta$E12 or CK5/6 or others), or with p63 or preferably a combination of the two with AMACR (P504s) in double or triple cocktail (PCa), in the evaluation of small foci of atypical glands suspicious of prostate adenocarcinoma [15].

## 8. Conclusion

The immunostaining of the anti-p63 antibody in the diagnosis of prostate cancer is of considerable benefit in our context. It made it possible to correct 11.3% of benign diagnosis in minimal malignant focus. Despite the difficulties associated with the manual technique, it is possible to have an excellent information rate, similar to the automatic technique. Good knowledge of diagnostic pitfalls and regular use of immunohistochemical tools increase diagnostic reliability in prostate cancer.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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