(RESEARCH ARTICLE)

Immunohistochemical analysis of Progesterone receptors in all Prostatic lesions, Case series study of 40 cases and review of Literature

Babita Sodhi [1, *] and Jyotsna Punj [2]

[1] Senior Consultant, Department of Pathology, Max Super Specialty Hospital, New Delhi, India.
[2] Professor, Department of Anesthesia, AIIMS, New Delhi, India.

Abstract

Background: In scenario of scant data literature, this study was conducted for progesterone receptor as future hormone therapy in prostate lesions especially prostate cancer.

Introduction: Prostate cancer as leading cause of mortality, progesterone receptor to be envisaged as future adjunct hormone therapy to reduce morbidity and mortality of prostate. Carcinoma prostate being heterogenous disease, not much is known about biological behaviour of Progesterone receptors.

Material and methods: 40 cases of prostate, BHP, BHP with prostatitis, HGPIN and Adenocarcinoma were included where expressions of Progesterone receptors was carried out immunohistochemically.

Conclusion: PR analysed as Good prognostic marker, can be authenticated as future adjunct hormone therapy, More Studies required to authenticate it, Our study has been adjunct to that

Keywords: PR (progesterone receptors); ER (Estrogen receptors); IHC (immunohistochemistry); BHP (benign hyperplasia prostate); ADC (Adenocarcinoma); HGPIN (High grade prostatic intraepithelial neoplasia)

1. Introduction

Prostate being largest vital accessory organ of male reproductive system, anatomically divided onto anterior, middle, posterior and lateral lobes and Peripheral Zone (where most carcinomas arise, hence asymptomatic), central and transistion zones (periurethral) , where benign hyperplasia prostate occurs and symptomatic) [1]. Histologically is a tubuloalveolar organ, branching duct-acinar glandular system embedded in anteriorly placed fibromuscular stroma. Microscopically epithelium is central luminal secretory and outer basal cell layer. Prostate is prone to many pathological condtions like carcinoma , BHP, including inflammatory entities, prostatitis and Granulomatous prostatitis. More than 1 lesion can be in combination with each other, BHP (Benign hyperplasia Prostate) with Prostatitis. Prostate located in front of rectum, below and behind base of bladder with seminal vesicles situated superior and posterior to prostate. Role of Progesterone receptors in pathophysiology and biology of the prostate is in progress with ongoing added literarature from future studies.

---

* Corresponding author: Babita Sodhi

PR, Progesterone receptors one of steroid hormone receptor family including androgen receptors (AR) and estrogen receptors (ER), are intranuclear in their localization, are increasingly recognized for its role in prostatic pathological and biological processes.

Protein occurs as 3 isoforms, PRA, PRB, PRC and 11 splice variants. PRB being full length receptor, whereas PRA is truncated one lacking in 164 amino acids at N terminus, which are unique to PRB. These isoforms perform different physiological functions. PRA may even inhibit PRB production.

PR can function by both genomic and non genomic modes of signalling and may determine relevance and validity of PR in progression, prognosis and management of prostate cancers.

PR get expressed in prostate stroma and epithelium and their expression can indicate its role in prostate diseases. PR localization in healthy prostate and its various lesions is well carried through widely accepted staining technique of IHC.

IHC, a scientific laboratory technique, includes highly specific binding between antibody and its target antigen, providing visual inspection of protein expression within tissue sections.

IHC is crucial for assessment of multiple predictive and prognostic biomarkers and its role in PR expression is vital as PR in prostate physiology and carcinogenesis still to be understood fully.

Current literature with some contradictory studies regarding its presence in tumor cells, make IHC essential to offer deeper insights into disease progression and to identify PR as novel therapeutic agent.

Prostate cancer is second most common cancer in Men in Asia and 5th leading cause of mortality worldwide, disease of elderly, average age being >65yrs. Globally North America has highest incidence (73.1%) [African Americans at highest risk], followed by Europe (62.1%), Africa (36.6%), Asia (11.5%). Difference attributable to different sociological, environmental and genetic factors.In Asia [2]. Japanese are more prone to prostate cancer due to genetic polymorphism of PR Gene, but through consumption of Soy products, paneer (Tofu) and soy milk, they have brought down incidence to lowest, ISOFLAVONES IN SOY DIET HAS HELPED them [3].

Aim of Study of Immunohistochemical analysis of PR in all prostatic lesions is to document PR as future targeted therapy in Prostatic Carcinoma.

Aims and Objectives

To study immunohistochemical Expression of Progesterone receptors,

- Their role and Prognostic impact in different lesions of prostate, especially BHP and Adenocarcinoma Prostate, differentiate benign from malignant and in situ lesions(HGPIN).
- Differentiate primary Adenocarcinomas from metastatic deposits in prostate.
- Correlate expressions of various grades of different types of prostatic carcinoma.
- Correlate expressivity with metastatic disease and thus evaluate prognostic significance.

2. Material and methods

Study was Conducted in 40 cases of prostate biopsy (TURP) in tertiary care hospital, out of which 33 cases of BHP(24 of pure BHP, 8 of BHP with prostatitis and 1 case of BHP with extensive squamous metaplasia), 4 Cases of HGPIN, 3 cases of Adenocarcinoma in which 2 cases being frankly malignant and 1 case focally malignant. 10 positive controls of proliferative phase Endometrium (uterus) with no evidence of any uterine lesion were also put.

3. Results

Most common presentation in BHP was frequency of urination in 80% and nocturia, dysuria, retention urine with dribbling in rest of cases.

1 case of adenocarcinoma presented with bony pains, while other 2 cases and 4 cases of HGPIN were asymptomatic except that with anaemia, general unwell being and emaciation. No case presented with blood in urine.

BHP, disease of prostate in 5th to 8th decade with no case less than 40, 2 cases each in 5th to 6th decade, 17 cases in 7th decade and 1 case in 8th decade.
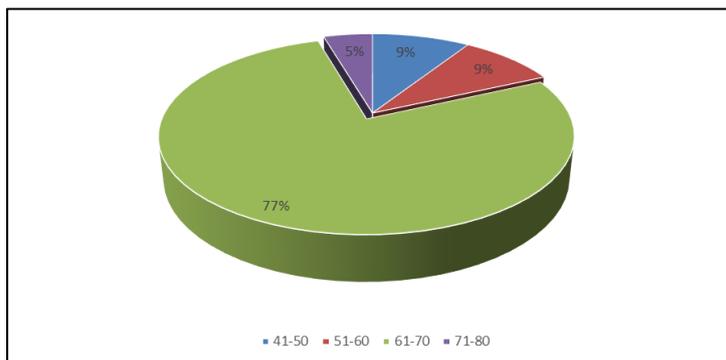

Figure 1 Age wise Distribution of BHP (percentage)

HGPIN, disease of prostate in 6th – 8th decade, 1 case each in 6th and 7th decade and 2 cases in 8th decade and no case in 9th decade.
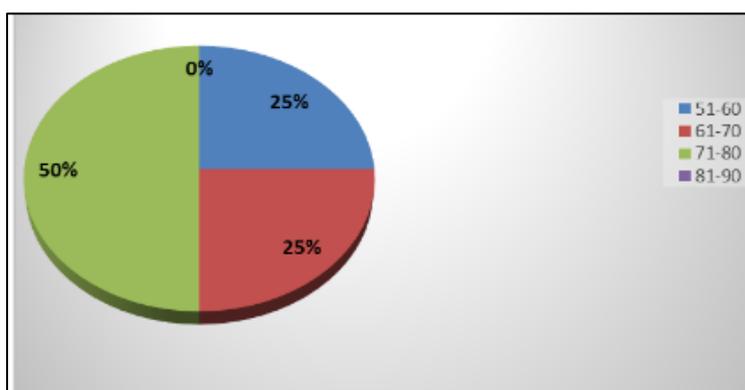

Figure 2 Age wise Distribution of HGPIN (percentage)

Results:- Adenocarcinoma of prostate in 7th – 9th decade, 1 case each in 7th, 8th and 9th decade
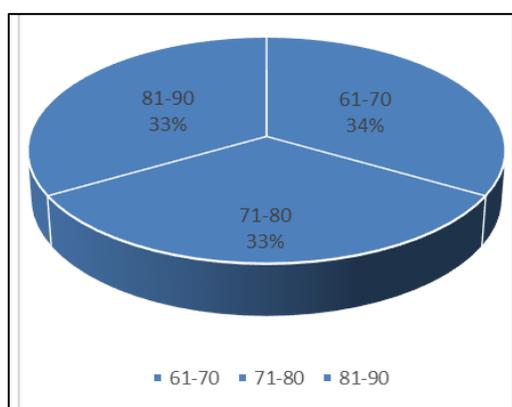

Figure 3 Age wise Distribution of Adenocarcinoma (Percentage)

3.1. Immunoscoring

Quick score method of assessment was used to assess range of immunostaining.

1 of 33 BHP Cases, was strongly positive (brown colour) 4+, both glandular epithelium and stroma (100%), 11 BHP cases with %age positivity of 14- 21%, total score(intensity + proportion score) of 3+, while rest of 21 BHP cases with %age positivity of 13-20% with total score of 2+.

Only 1 of 4 HGPIN cases was mildly positive (18%),total score of 1+, while rest 3 cases of PIN were ssion of totally negative.

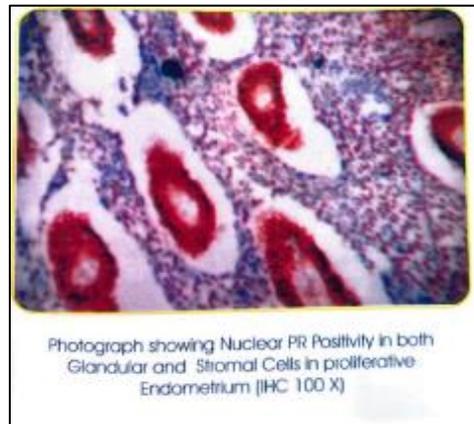All 3 Adenocarcinoma cases were negative for expression (Zero score)

Photograph showing Nuclear PR Positivity in both Glandular and Stromal Cells in proliferative Endometrium (IHC 100 X)

Figure 4 Control (Endometrium)

Photograph showing PR Immunostaining (positive) in a case of BHP (x 400)

Figure 5 BHP, PR Immunostaining

Photograph showing negative PR immunostaining in a case of HGPIN (x 400)

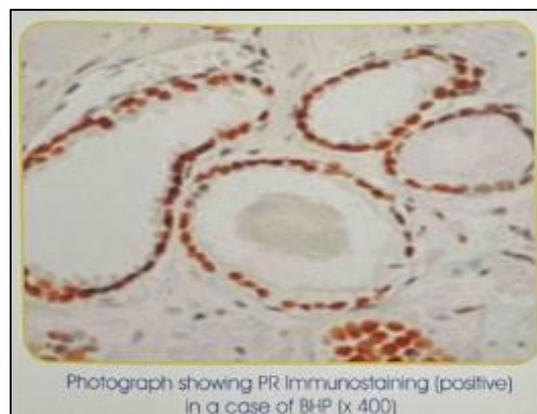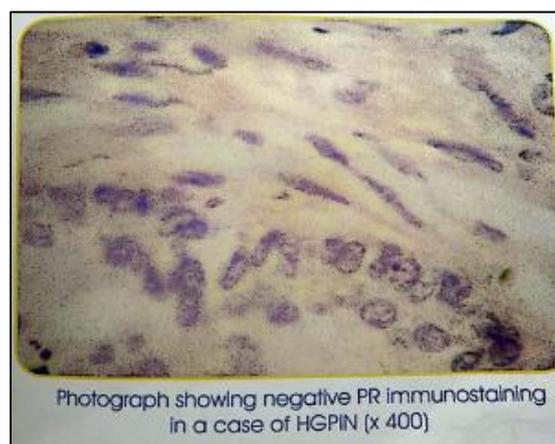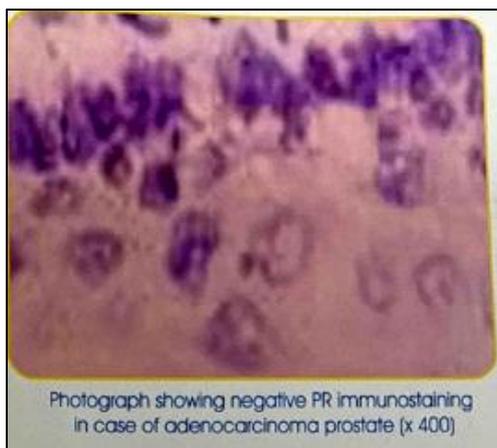**Figure 6** HGPIN, PR Immunostaining

Figure 7 Adenocarcinoma, PR Immunostaining

4. Discussion

Prostate cancer accounts for 25% of all male cancers, testicular 1%, penile cancers even rarer(4). Remarkable sharp Increase in incidence of prostate cancer with age is hallmark of this cancer. Incidence in Iraqi population is rising at par with global increase in incidence. [5], Quasi vegan diet in Japan having protective function in prostate cancer has played significant role in lowering its incidence in japanese population [6].

In our study of analysis of 40 cases, PR expression is reduced in Carcinoma indicating that it prevents tumorigenesis, hence proving itself as a Good Prognostic marker.

Progesterone reported to inhibit BHP and Prostate cancer possibly due to its effect on SRD5A2 (gene that encodes for enzyme, steriod 5 alpha reductase 2 and LH (Leutinizing hormone) release.
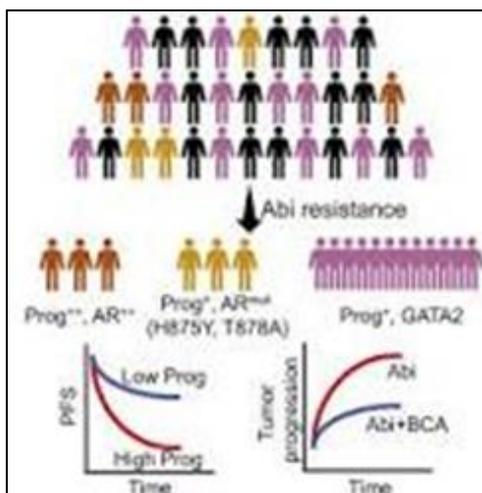
Figure 8 Progesterone effect on steroid 5 alpha reductase 2 (SRD5A2)

Pagi S et al documented expression of PR in BHP and Adenocarcinoma cases in similar way as our study [7].

Focus is more on malignant and premalignant lesions (Hgpin) [8].

 PR are nuclear family of receptors, of 2 types, PRA and PRB expressed in human tissues including prostate and in some cancers [9,10].

Bera KN and Yadav et al analysed immunoexpression of ER Beta, PR in Prostatic Adenocarcinoma and results matched with our study [11].

Other organs expressing them include breast, brain, kidney, Nasal extranodal NK/T cell lymphoma and ovarian carcinomas [12-16].

PR shows its expressivity not only in sex correlated cancers (reproductive), but also in other tissues (Non reproductive), like human leukemia [17], hepatocellular carcinoma [18], pancreatic neoplasms19], central nervous system tumors (Meningioma and fibroma) [20], uterine Leiomyoma [21], Leiomyosarcoma [22] and Cervical intraepithelial neoplasia (CIN III) [23] (Non reproductive functions).

Role of progesterone and Progesterone receptors was further elaborated in human reproduction and cancer [24]. Terranut et al further documented systemic distribution of progesterone receptors in human tissues [25].

Progesterone in BHP can suppress stromal cell proliferation thus inhibiting hyperplasia and also differential expression of AR, ER and PR was studied in benign hyperplasia prostate [26, 27,28].

Grindstad et al documented increased levels of PRB isoform associated with disease progression which is contrary to our study, and that can be possibly due to different types of isomers, different Antigen retrieval as well [29].

Table 1 Comparative Immunohistochemical Expression of Progesterone Receptors in Benign Prostatic Hyperplasia and Prostatic Adenocarcinoma

Characteristic	Benign Prostatic Hyperplasia (BPH)	Prostatic Adenocarcinoma (PCa)	Key Findings/Role	Relevant Snippet IDs
Cellular Localization	Primarily stromal cells (fibroblasts, smooth muscle cells).[10] Negative in lining epithelial cells.[7]	Detected in primary tumor cells (epithelial) [30] and tumor stromal cells.[29] Conflicting reports on epithelial presence.[29]	PR is present in stromal compartments of both, but its presence in epithelial cells is more characteristic of PCa, especially advanced disease.[30]	[29]
PR Expression Level/Pattern	Generally negative in epithelial cells (density score 0).[7] Increased expression in stroma compared to normal prostate.[28]	Higher density and intensity scores compared to BPH.[7] PR density scores 1-3 (45% with score 3).[7] PR intensity: weak (17.5%), moderate (40%), strong (42.5%).[7]	Malignant cases tend to exhibit higher PR density and intensity, though some studies show similar positivity rates in both.[31]	[7]
Correlation with Disease Features	Positive correlation with prostate size.[38] No statistically significant difference in PR expression when considering age, PSA, testosterone, Gleason score (compared to PCa).[37]	Higher PR density/intensity correlated with higher Gleason Grade Groups (GG3, GG4, GG5).[7] High PR density in tumor cells is an independent negative prognostic factor for clinical failure, especially in GG≥7.[29]	PR expression patterns may be linked to disease severity and progression, but correlations with traditional clinical markers are not always straightforward.	[29]
Proposed Role	Promoting role in BPH pathogenesis, associated with increased stromal cell proliferation.[10] However, PRA/PRB inhibit stromal cell proliferation.[32]	Oncosuppressor, reducing malignization and inhibiting progression (especially stromal PR).[7] Decreased stromal PR contributes to progression.[32] High tumor cell PR is a negative prognostic factor.[29]	Contradictory roles depending on cellular compartment and isoform.	[29]

Wagenfeld A et al documented PR as Selective modulators (SPRM's) in endometrium as future gynaecological therapies [30], similar to our study.

Naskar et al studied correlation of histopathology, biochemical marker and immunohistochemical expression of androgen, estrogen and progesterone receptors in prostatic growth [31].

SK Grover et al analyzed expression of ER beta and ki67 in benign and malignant human prostate tissue [32].

Li Yet al documented that loss of progesterone receptor through epigenetic regulation is associated with poor prognosis in solid tumors [33].

Liao Wenqiang et al documented Trends in estrogen and progesterone receptors in prostate cancer through bibliometric analysis [34].

Spirina LV et al analyzed Progesterone Receptor Expression in the Benign Prostatic Hyperplasia and Prostate Cancer Tissues, its relation with Transcription, Growth Factors, Hormone Reception and Components of the AKT/mTOR Signaling Pathway which is a novel in itself [35].

Bonkhoff et al elucidated PR expression in prostate cancer and its relation with tumor progression [36].

Y YU et al documented expression and function of PR in human prostate stroma [37].

Wang H et al analysed prostatic specific antigen, AR, ER and PR in BHP [38].

4.1. Our study is unique in itself,

- Being 1st elaborated study from Indian subcontinent (North India) of IHC Expression of PR in prostatic lesions, other studies have included other receptors like Androgen, estrogen receptors and some even KI67 as well in different combinations.
- Also being only study in literature where we have included various inflammatory conditions as well, like acute, chronic Prostatitis and granulomatous prostatitis, elucidating that inflammation increases the risk of BHP.
- It will add to helping in documentation of PR as one of the future targeted therapies

Limitations of current studies

Limitations of current studies being that - Due to paucity of Standard IHC protocols in the form of methodological variability, different antigen retrieval methods, different antibody clones, different scoring criteria are hurdles in future project devolpment of PR as future hormone therapy. Small study samples may not be effective for reproducing of results.Carcinoma prostate being heterogenous disease, different studies don't contribute much to different molecular subtypes or evolutionary history of disease Many studies are not able to differentiate between different PR isoforms, as PRA, PRB and membrane PRs, having different functions. IHC, revealing protein expression may not be effective in translating well into functioning of PR, So further future functional studies are required to know precisely about effect of PR on prostate carcinog

Future research agenda

Need to have gold standard IHC protocols and to formulate precise, global, universal scoring system and large sample size, so as to have comparability and reproducibility of findings in different studies.

5. Conclusion

PR Immunohistochemically, analysed as good prognostic markers inhibiting hyperplasia(BHP) as well as carcinoma thus being suppressor of tumorigenesis.

Take home message is that In view of scant literature, this study can be helpful in designing progesterone as future targeted hormone therapy for better survival and prognostic outcomes of pts.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1]   Bhavsar, Anil, Verma, Sadhna, Anatomic Imaging of the Prostate, BioMed Research International, 2014, 728539, 9 pages.

[2]   Rawla P. Epidemiology of Prostate Cancer. World J Oncol. 2019 Apr;10(2):63-89.

[3]   Takahiro kimura, Shin Egawa. Epidimeology of Prostate cancer in Asian (Japan) countries. Int j uro 2018;25(6):524-531.

[4]   Tumors of the male genital tract, Marie O'Donnell MB.BCh.BAO (NUI) FRCPath Version of Record 11 October 2022.

[5]   The Possible Role of Progesterone Receptors in Prostate Cancer Incidences in the Iraqi Population Jaleel Ibrahim Asaad1 , Khalid S. A. Alazzawi2 , Sara S. Rasheed2 , Rebah N. Algafari2,* , Rehab S. Ramadhan3 , Marwah Amer Qamandar4 , Sura S. Talib2 , Rawnaq Z. Fadhil2. 24 September 2024.

[6]   Mark F. McCarty, The Japanese experience suggests that lethal prostate cancer is almost wholly preventable with a quasi-vegan diet, soy products, and greentea,MedicalHypotheses, 2022;164:110839.

[7]   Pagi S, Nerune SM. Study of Expression of Progesterone Receptor in Prostatic Adenocarcinoma And Benign Prostatic Hyperplasia. AJBR. 2024;27(3S):3960-3968.

[8]   Zhou M. High-grade prostatic intraepithelial neoplasia, PIN-like carcinoma, ductal carcinoma, and intraductal carcinoma of the prostate. Mod Pathol. 2018 Jan;31(S1):S71-79.

[9]   Da Silva MHA, De Souza DB. Current evidence for the involvement of sex steroid receptors and sex hormones in benign prostatic hyperplasia. Res Rep Urol. 2019 Jan 7;11:1-8.

[10]   Yu, Y. (2014). The progesterone receptors in human prostate (T). University of British Columbia. Retrieved from https://open.library.ubc.ca/collections/ubctheses/24/items/1.0167408.

[11]   Bera KN, Yadav SK, Prakash O, Singh S, Sarin N. Immunoexpression of estrogen receptor-β and progesterone receptor in prostate adenocarcinoma, does it inhibit neoplastic proliferation and invasion? Indian J Pathol Microbiol. 2020 Feb;63(Supplement):S30-S33.

[12]   Inwald E, Klinkhammer-Schalke M, Hofstädter F, Zeman F, Koller M, Gerstenhauer M, et al. Ki-67 is a prognostic parameter in breast cancer patients: Results of a large population-based cohort of a cancer registry.Breast Cancer Res Treat 2013;139:539-52.

[13]   Johannessen AL, Torp SH. The clinical value of Ki-67/MIB-1 labeling index in human astrocytomas. Pathol Oncol Res 2006;12:143-7.

[14]   Kankuri M, Söderström KO, Pelliniemi TT, Vahlberg T, Pyrhönen S, Salminen E. The association of immunoreactive p53 and Ki-67 with T-stage, grade, occurrence of metastases and survival in renal cell carcinoma. Anticancer Res 2006;26:3825-33.

[15]   Li S, Feng X, Li T, Zhang S, Zuo Z, Lin P, et al. Extranodal NK/T-cell lymphoma, nasal type: A report of 73 cases at MD Anderson Cancer Center. Am J Surg Pathol 2013;37:14-23.

[16]   14 Münstedt K, von Georgi R, Franke FE. Correlation between MIB1-determined tumor growth fraction and incidence of tumor recurrence in early ovarian carcinomas. Cancer Invest 2004;22:185-94.

[17]   Narges Fallahi, Mitra Rafiee, Ehsaneh Azaryan, David Wilkinson, Vahid Bagheri, Inhibitory effects of progesterone on the human acute lymphoblastic leukemia cell line, Gene Reports,2024;36:101991,ISSN.

[18]   Shchelkunova, T.A., Levina, I.S., Morozov, I.A. et al. Effects of Progesterone and Selective Ligands of Membrane Progesterone Receptors in HepG2 Cells of Human Hepatocellular Carcinoma. Biochemistry Moscow 88, 1920–1932 (2023).

[19]   Alexey I. Goncharov, Aitsana A. Maslakova, Anna V. Polikarpova, Elena A. Bulanova, Alexandra A. Guseva, Ivan A. Morozov, Petr M. Rubtsov, Olga V. Smirnova, Tatiana A. Shchelkunova,Progesterone inhibits proliferation and modulates expression of proliferation—Related genes in classical progesterone receptor-negative human BxPC3 pancreatic adenocarcinoma cells,Journal of Steroid Biochemistry and Molecular Biology.PartB,2017;165:293-304.

[20] Agopiantz M, Carnot M, Denis C, Martin E, Gauchotte G. Hormone Receptor Expression in Meningiomas: A Systematic Review. Cancers (Basel). 2023 Feb 3;15(3):980.

[21] Ali M, Ciebiera M, Vafaei S, Alkhrait S, Chen H-Y, Chiang Y-F, Huang K-C, Feduniw S, Hsia S-M, Al-Hendy A. Progesterone Signaling and Uterine Fibroid Pathogenesis; Molecular Mechanisms and Potential Therapeutics. Cells. 2023; 12(8):1117.

[22] Ben Davidson, Marna Lill Kjæreng, Mette Førsund, Håvard Emil Danielsen, Gunnar Balle Kristensen, Vera Maria Abeler, Progesterone Receptor Expression Is an Independent Prognosticator in FIGO Stage I Uterine Leiomyosarcoma, American Journal of Clinical Pathology. April 2016;145(4): 449–458.

[23] Garrido F, Wild CM, Jeschke U, Dannecker C, Mayr D, Cavailles V, Mahner S, Kost B, Heidegger HH, Vattai A. Expression of Progesterone Receptor A as an Independent Negative Prognosticator for Cervical Cancer. International Journal of Molecular Sciences. 2023; 24(3):2815.

[24] Check, J. H., and Cohen, R. The role of progesterone and the progesterone receptor in human reproduction and cancer. Expert Review of Endocrinology and Metabolism.2013;8(5):469–484.

[25] Teeranut Asavasupreechar a, Ryoko Saito a, Yasuhiro Miki a, Dean P. Edwards b, Viroj Boonyaratanakornkit c d, Hironobu Sasano. A Systemic distribution of progesterone receptor subtypes in human tissues. jr of Steroid Biochemistry and Molecular Biology. May 2020;199:105599.

[26] Ng M, Leslie SW, Baradhi KM. Benign Prostatic Hyperplasia. [Updated 2024 Oct 20]. In: StatPearls [Internet]. Treasure Island (FL):

[27] Song L, Shen W, Zhang H, Wang Q, Wang Y, Zhou Z. Differential expression of androgen, estrogen, and progesterone receptors in benign prostatic hyperplasia. Bosn J Basic Med Sci. 2016 Jul 2;16(3):201-8.

[28] Gajanan Sherbet, PGR (progesterone receptor)Atlas Genet Cytogenet Oncol Haematol.2017-02-01.

[29] Grindstad, Thea and Richardsen, Elin and Andersen, Sigve and Skjefstad, Kaja and Donnem, Tom and Ness, Nora and Nordby, Yngve and Bremnes, Roy and Al-Saad, Samer and Busund, Lill-Tove. Progesterone Receptors in Prostate Cancer: Progesterone receptor B is the isoform associated with disease progression. Scientific Reports.2018; 8. 10.1038/s41598-018-29520-5.

[30] Wagenfeld A, Saunders PT, Whitaker L, Critchley HO. Selective progesterone receptor modulators (SPRMs): progesterone receptor action, mode of action on the endometrium and treatment options in gynecological therapies. Expert Opin Ther Targets. 2016; Sep20(9):1045-54.

[31] Naskar S, Kundu SK, Bhattacharyya NK, Bhattacharyya PK, Kundu AK. A study to correlate histopathology, biochemical marker and immunohistochemical expression of sex-steroid receptors in prostatic growth. Indian J Med Paediatr Oncol. 2014 Jan;35(1):40-3.

[32] Grover SK, Agarwal S, Gupta S, Wadhwa N, Sharma N. Expression of estrogen Receptor Beta and ki67 in benign and malignant human prostate lesions by immunohistochemistry.12253-014-9870-y. Epub 2014 Dec 20. Jan;35(1):40-3.

[33] Li Y, Huang C, Kavlashvili T, Fronk A, Zhangi Y, Dai D, Devor EJ, Meng X, Thiel KW, Leslie KK, Yang S. Loss of progesterone receptor through epigenetic regulation is associated with poor prognosis in solid tumors. Am J Cancer Res. 2020 Jun 1;10(6):1827-1843.

[34] Liao Wenqiang , Sui Xuxia , Hou Gaoming , Yang Mei , Lin Yuxue , Lu Junjie , Yang Qingtao.Trends in estrogen and progesterone receptors in prostate cancer: a bibliometric analysis Frontiers in Oncology.2023;13.

[35] Spirina LV, Kovaleva IV, Usynin EA, Goorbunov AK, Kondakova IV. Progesterone Receptor Expression in the Benign Prostatic Hyperplasia and Prostate Cancer Tissues, Relation with Transcription, Growth Factors, Hormone Reception and Components of the AKT/mTOR Signaling Pathway. Asian Pac J Cancer Prev. 2020 Feb 1;21(2):423-429.

[36] Bonkhoff H, Fixemer T, Hunsicker I, Remberger K. Progesterone receptor expression in human prostate cancer: correlation with tumor progression. Prostate. 2001 Sep 15;48(4):285-91.

[37] Yu Y, Liu L, Xie N, Xue H, Fazli L, Buttyan R, Wang Y, Gleave M, Dong X. Expression and function of the progesterone receptor in human prostate stroma provide novel insights to cell proliferation control. J Clin Endocrinol Metab. 2013 Jul;98(7):2887-96.

[38] Wang H, Liu C, Dong Z, Chen X, Zhang P. Prostate-specific antigen, androgen, progesterone and oestrogen receptors in Benign prostatic hyperplasia: human tissues and animal model study. Aging Male. 2024 Dec;27(1):2391380.