Articulos Originales

Incidence of adenocarcinoma in the transitional zone of the prostate in a public institution. Cochabamba, Bolivia

Incidencia de adenocarcinoma en zona transicional de próstata en institución pública. Cochabamba, Bolivia

Ferrufino Iriarte, Javier; López Ovando, Nicol; Luizaga Salazar, Alejandra; López Vargas, Daniel

Javier Ferrufino Iriarte *
ferrujavi@gmail.com
Hospital Clínico Viedma, Bolivia
Nicol López Ovando
Universidad Mayor de San Simón, Bolivia
Alejandra Luizaga Salazar
Universidad Mayor de San Simón, Bolivia
Daniel López Vargas
Universidad Mayor de San Simón, Bolivia

Gaceta Médica Boliviana
Universidad Mayor de San Simón, Bolivia
ISSN: 1012-2966
ISSN-e: 2227-3662
Periodicity: Semestral
vol. 43, no. 1, 2020
gacetamedicaboliviana@gmail.com

Received: 09 October 2019
Accepted: 14 June 2020

URL: http://portal.amelica.org/ameli/journal/414/4141742026/

DOI: https://doi.org/10.47993/gmb.v43i1.12

Abstract: Transitional zone cancer represents 20-25% of the cases (in radical prostatectomy specimens), its diagnosis is frequently incidental, being clinically identified as presumed adenomas.
Objetive: to determine the incidence of adenocarcinoma in the transitional zone of the prostate and identify precancerous stages in patients with clinical BPH.
Methods: retrospective longitudinal study from 2013-2018 in the city of Cochabamba-Bolivia; study population: patients submitted to simple, retropubic and/or transvesical prostatectomy. Data collection: based on medical records, patients with clinical symptoms of benign prostatic hyperplasia and total PSA < 4ng/ml.
Results: 76 patients were identified, of which 5 were found to have Adenocarcinoma and 9 with: High Grade Prostatic Intraepithelial Neoplasia 2.6%, Atypical small acinar proliferation 7.9%, thus representing 10.5%. As for invasion, 5.3% represented perineal invasion, 2.6% lymphovascular invasion and none with extravascular invasion.
Discussion: patients with transitional zone prostate cancer, present a high prostate specific antigen suspicious to adenocarcinoma. However, this study found high-risk prostate adenocarcinoma with total prostate specific antigen less than 4 ng/ml. In spite of the clinical instruments and indications for surgical therapy of a presumed benign prostatic hyperplasia, the incidence of Adenocarcinoma in the Transitional Zone was 6.5%, with a 10.5% incidence of precancerous forms, and 17.1% of the patients were at risk of lethality from the disease.

Keywords: prostate cancer, adenocarcinoma, hyperplasia.

Resumen: El cáncer en la zona de transición representa el 20-25% de los casos (en piezas de prostatectomías radicales), su diagnóstico con frecuencia es de manera incidental, siendo identificados clínicamente como supuestos adenomas.
Objetivo: determinar la incidencia de Adenocarcinoma en la Zona transicional de Próstata e identificar etapas precancerosas en pacientes con clínica de HPB.
Métodos: estudio longitudinal de tipo retrospectivo desde el 2013-2018 en la ciudad de Cochabamba-Bolivia; población de estudio: pacientes sometidos a prostatectomía simple, retropúbica y/o transvesical. Recolección de datos: a partir de

historias clínicas, en pacientes con clínica de hiperplasia benigna de próstata y PSA total < 4 ng/ml.
Resultados: se identificó 76 pacientes, de los cuales; 5 pacientes resultaron con Adenocarcinoma y 9 pacientes con: Neoplasia Intraepitelial Prostática de Alto Grado 2,6 %, Proliferación acinar pequeña atípica 7,9%, representando así un 10,5%. En cuanto a la invasión representaron un 5,3% con invasión perineal, 2,6% invasión linfovascular y ninguno con invasión extravascular.
Discusión: pacientes con cáncer de próstata zona transicional, presentan un Antígeno prostático específico alto susceptibles a Adenocarcinoma. Sin embargo, en esta investigación se encontró Adenocarcinoma de próstata de alto riesgo con Antígeno prostático específico total menor a 4 ng/ml. A pesar de los instrumentos clínicos e indicaciones para la decisión de terapia quirúrgica de una supuesta hiperplasia prostática benigna, existe en el estudio una incidencia del 6,5% de Adenocarcinoma en Zona Transicional, con un 10,5 % de incidencia de presentación de formas precancerosas y el 17,1% de los pacientes del estudio se encuentran en riesgo de letalidad de la enfermedad.

Palabras clave: cáncer de próstata, adenocarcinoma, hiperplasia.

Introduccion

McNeal's contribution of a zonal model allowed the division of the glandular prostate into four zones: the peripheral zone (70%), central zone (25%), transition zone and periurethral glandular region[1].

The Peripheral Zone (PZ) has been considered the predominant location for the origin of prostate cancer 80%[2,3]and the proximity of this zone to the rectal surface facilitates the diagnosis of PZ cancers by digital rectal examination (DRE) and transrectal needle biopsy[2]. On the other hand, malignant prostate neoplasms arising from the Transitional Zone (TZ)[1]; account for 20-25% of cases[4].

Most TZ cancers are located in the mid and apical prostate and due to their location, they are not palpable and are less frequently detected by standard biopsy schemes; consequently, they are larger when diagnosed compared to PZ cancers[5], their diagnosis is often incidental in transurethrally resected specimens.

PSA_2 detection has improved prostate cancer (CA) detection[6], however, there is no specific normal or abnormal PSA concentration in the blood, and concentrations may vary over time, depending on the laboratory method, 4.0 ng/ml or less is considered the standard PSA value. The Gleason score is the most important predictor of prostate CA follow-up, metastasis and specific mortality. It is associated with an increased risk of biochemical recurrence and disease progression[4] (Table 1).

Author notes

* **Correspondence to:** Dr. Javier Ferrufino Iriarte
E-mail: ferrujavi@gmail.com

Conflict of interest declaration

the authors declare that there is no conflict of interest.

PSA level (ng/mL)	PCa risk (%)	Gleason risk = 7 PCa (%)
0,0-0,5	6,6	0,8
0,6-1,0	10,1	1,0
1,1-2,0	17,0	2,0
2,1-3,0	23,9	4,6
3,1-4,0	26,9	6,7

TABLE 1
Risk of PCA in relation to low PSA values.
Dong F, Kattan MW, Steyerberg EW, Jones JS, Stephenson AJ, Schröder FH, et al. (2008)[6]

Grignon and Sakr reported that TZ cancer has a distinctive histological appearance, consisting of well-differentiated glands covered by cells with clear cytoplasm and minimal nuclear atypia, including abnormal DNA content, which was much less frequent in TZ than in PZ cancers[3] .

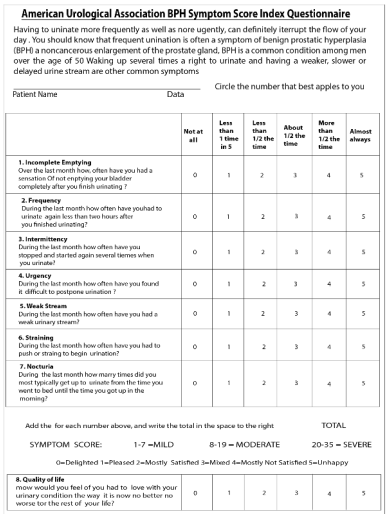
TZ prostate cancers are associated with better clinical outcomes[4], because they show more favourable biological behaviour compared to those arising from PZ[5].

Therefore, the aim of this research is: to determine the incidence of Adenocarcinoma in the Transitional Zone of the Prostate and to identify the grade of Adenocarcinoma and precancerous stages of the same in patients with clinical BPH and PSA< 4ng/ml.

Material and methods

The universe consisted of patients treated for BPH in the Urology Service of the Hospital Clínico Viedma, a tertiary care centre in the city of Cochabamba, Bolivia.

The type of study was longitudinal and retrospective from January 2013 to December 2018. The study population included patients with IPSS -International Prostate Symptoms Score clinical picture based on answers concerning urinary symptoms and one question concerning quality of life[7,8] (Figure 1)[8] , rectal examination, vesico-prostatic abdominal ultrasound with measurement of residual urine). Inclusion criteria were simple prostatectomy, retropubic and/or transvesical prostatectomy or also called prostate adenectomy, PSA< 4ng/ml. Exclusion criteria: patients with PSA ≥4ng/ml, operated radical prostatectomy and transurethral resection of the prostate (due to risk of loss of chips during examination in the pathology cassettes).



American Urological Association BPH Symptom Score Index Questionnaire

Having to urinate more frequently as well as nore ugently, can definitely iterrupt the flow of your day . You should know that frequent urination is often a symptom of benign prostatic hyperplasia (BPH) a noncancerous enlargement of the prostate gland, BPH is a common condition among men over the age of 50 Waking up several times a right to urinate and having a weaker, slower or delayed urine stream are other common symptoms

Patient Name _____ Data _____ Circle the number that best apples to you

	Not at all	Less than 1 time in 5	Less than 1/2 the time	About 1/2 the time	More than 1/2 the time	Almost always
1. Incomplete Emptying Over the last month how often have you had a sensation Of not enptying your bladder completely after you finish urinating ?	0	1	2	3	4	5
2. Frequency During the last month how often have youhad to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3. Intermittency During the last month how often have you stopped and started again several tiemes when you urinate?	0	1	2	3	4	5
4. Urgency During the last month how often have you found it difficult to postpone urination ?	0	1	2	3	4	5
5. Weak Stream During the last month how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Straining During the last month how often have you had to push or straing to begin urination?	0	1	2	3	4	5
7. Nocturia During the last month how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5

Add the for each number above, and write the total in the space to the right TOTAL

SYMPTOM SCORE: 1-7 =MILD 8-19 = MODERATE 20-35 = SEVERE

0=Delighted 1=Pleased 2=Mostly Satisfied 3=Mixed 4=Mostly Not Satisfied 5=Unhappy

8. Quality of life How would you feel of you had to love with your urinary condition the way it is now no better no worse tor the rest of your life?	0	1	2	3	4	5

FIGURE 1 .
IPSS (International Prostate Sympthoms Score) which is based on responses about urinary symptoms and asks about the quality of life.

The information was obtained from medical records filled out by urology specialists, for each patient taking into account benign prostatic hyperplasia, based on the Pathology Review System of the International Society of Urological Pathology (ISUP)[9] with or without atypia and neoplasms.The following criteria were used: prostate adenocarcinoma; prostate adenocarcinoma, ISUP 2016 modified Gleason System, within the Gleason range 6 to 10; with quantified total PSA of 0 to 4 ng/ml; high-grade PIN (intraepithelial neoplasia G2-G3) with prominent nucleolus; positive atypical small acini proliferation (ASAP); and extracapsular, lymphovascular and perineural invasion were also taken into account.

Data were collected and analysed using the Statistical Package for the Social Sciences (SPSS), descriptive statistics and absolute incidence formula.

Results

The study identified 76 patients from the Viedma clinical hospital, who underwent prostate adenectomy during 2013 to 2018, which showed the following results (Figure 2), 5 patients resulted with CA (adenocarcinoma 6.5%). In terms of invasion, they accounted for 80% with perineal invasion (5.3% of the 76 patients), 40% with lymphovascular invasion (2.6% of the 76 patients) and none with extravascular invasion (Table 3).

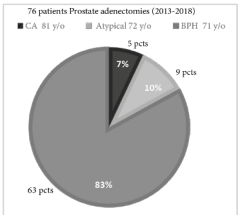


FIGURE 2
Percentage of patients with benign prostatic hyperplasia (BPH), cancer (CA), atypia during 2013-2018)

Adenocarcinoma (Gleason)	Extracapsular Invasion	Lymphovascular Invasion	Perineural Invasion
1. (3+4)= 7	Negative	Negative	**Positive**
2. (5+4)= 9	Negative	**Positive**	**Positive**
3. (4+5)= 9	Negative	Negative	**Positive**
4. (3+4)= 7	Negative	**Positive**	Negativo
5. (4+5)= 9	Negative	Negative	**Positive**
Total	**0**	**2**	**4**

TABLE 3.
Patients with adenocarcinoma according to invasiveness

The 5 patients with adenocarcinoma represent a median age of 82 years, who are at risk of lethality during the next few years due to ISUP grade 3-5 and considering the invasion characteristics.

Regarding precancerous or atypical stages, there were 9 patients representing 10.5% (Table 2), with high-grade PIN (Intraepithelial Neoplasia G2-G3) 2.6%, ASAP, 7.9%. Of these, 8 patients are older than 75 years who are at risk for cancer development during the next 10 years.

Patients (Age)	High grade PIN (Intraepithelial Neoplasia G2 - G3	ASAP (Proliferation of Atypical Small Acinus)	Adenocarcinoma (Gleason)
79	1.**Positive**	Negative	1. (3+4)=7
82	Negative	Negative	2. (5+4)=9
79	Negative	Negative	3. (4+5)= 9
79	Negative	Negative	4. (3+4)=7
85	Negative	Negative	5. (4+5)= 9
79	2. Positive	Negative	Negative
73	Negative	1. Positive	Negative
65	Negative	2. Positive	Negative
63	Negative	3. Positive	Negative
70	Negative	4. Positive	Negative
70	Negative	5. Positive	Negative
77	3. Positive	Negative	Negative
78	Negative	6. Positive	Negative
Total	9		5

TABLA 2
Results of high-grade PIN patients, ASAP, adenocarcinomas in Gleason scale, according to age.

INDICATIONS FOR SURGICAL TREATMENT OF BENIGN PROSTATIC HYPERPLASIA
Severe BPH (severe symptoms)
Repeated episodes of urinary retention due to BPH
Recurrent prostate and urinary tract infections due to BPH
Bladder stones
Renal failure due to infravesical obstruction of urinary tract (ureterohydronephrosis)
Recurrent macroscopic hematuria
Other indications:
I-PSS score/quality of life not improving sufficiently with medical treatment
Increasing postvoid residual values
Low flow rate (flowmetry)
Source: Gimeno F, Piñango I, Ortin M, Gomiz JJ, Patología prostática. Madrid: Martgraf ed., 1994.

TABLE 4.
Indications for the surgical treatment of benign prostatic hyperplasia

Discussion

Some controversy has arisen between TZ and PZ prostate cancer and about differences in biological behaviour compared to those arising in PZ. In many respects, patients with TZ and PZ cancer appear to be similar. However, we identified several important differences between TZ and PZ cancer that suggest differences in their biology. Despite many similarities in the clinicopathological features of these cancers, TZ cancers showed better clinical outcomes with respect to biochemical recurrence, local and distant metastasis, TZ cancers are diagnosed at larger cancer volumes and higher serum PSA levels[5]. However, total PSA does not have normal values for prostate CA negativity[10], but values from 0 to 4 ng/ml were available, and the further away from zero, the higher the risk of prostate CA and intermediate-high risk prostate CA[11]. However, the significance of this investigation was to find high-risk prostate CA (3 patients with ISUP 5), presenting with total PSA less than[4].

Despite the clinical instruments and surgical indications (Table 3)12 for the decision of surgery for presumed benign prostatic hyperplasia (BPH)[12], there is a 6.5% incidence of adenocarcinoma in the Transitional Zone in the study conducted.

The role of immunohistochemistry is important and with it that of Ki67 protein as a prognostic marker, androgen receptor overexpression plays an important role in disease progression and correlates with high Ki67 expression and has been shown to be an independent prognostic factor in the biochemical recurrence-free period[13] and Matrix Metalloproteinases (MMPs) as markers of invasion[14].

In the study, there is a 10.5% incidence of presentation of atypical ASAP and PIN forms, which are more important precursors of prostatic carcinoma. High Grade PIN (HGPIN): tufts, micropapillary, cribriform and flat identifies patients at risk of malignancy[15], which according to the literature has a 40-50% risk of progression to prostate cancer (CAP), with progression to indeterminate Gleason grades and indeterminate time[16]. As mentioned by Bostwick, most patients with PIN will develop carcinoma within 10 years[17]. In the study 17.1% of patients are at risk of disease lethality. It can be assumed that patients older than 75 years at risk of cancer mortality were in optimal condition and probably had a life expectancy of more than 10 years when they underwent adenectomy and were at low to intermediate surgical risk and ASA II, so that

they are at risk of cancer mortality in the next 10 years. Predicting the aggressiveness of PDA is critical for appropriate surveillance and early selection of adjuvant therapies. There are new advances that help in this type of prediction such as the advances of Rojas et al. who presented the genetic score as a novel tool for predicting indicators of aggressive CAP[18].

Although the difference in the consequences of PDA remains controversial, due to its cause by location and/or particular biology, tumour location was strongly associated with the risk of extracapsular extension, seminal vesicle invasion, lymphovascular invasion and lymph node metastasis after adjusting for Gleason score, high-grade disease volume and serum PSA[5]. An advance in the understanding of PDA by location will mean improved diagnosis and follow-up of the disease and the creation of specific clinical guidelines for each of these identities. In conclusion, the 6.5% incidence of adenocarcinoma in the Transitional Zone of the prostate is not negligible, even more so given that 60% of patients are high risk, despite the fact that the patients presented with a presumed clinical picture of BPH and that most have a life expectancy of more than 10 years. It is therefore suggested that the patient be fully and thoroughly informed about: 1) The management of prostate tissue performed in the different modalities of surgical therapies. Close monitoring of PSA, especially when atypical forms are present. Even in patients operated on for presumed BPH, a follow-up plan should be established for the only instrument available: PSA, individualisation of adjuvant therapies, and immunohistochemistry for TZ with Ki-67, MMP-2 and MMP-9 antibodies should always be taken into account.

Bibliographic references

1. Cirella E José L. Un poco de anatomía sobre la glándula prostática. UCLA. Citado el 21 de abril de 2019. Available from: http://bibmed.ucla.edu.ve/edocs_bmucla/VisionMorfologica/No.2Ano4/VM02_PAG3-4.pdf
2. Sakai I, Harada K, Kurahashi T, Yamanaka K, Hara I, Miyake H. Analysis of differences in clinicopathological features between prostate cancers located in the transition and peripheral zone; Int J Urol. (internet) abril 2006 (Citado el 21 de abril de 2019); 13(4):368-372 Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1442-2042.2006.01307.x
3. Sakai I, Harada K, Hara I, Eto H, Miyake H. A comparison of the biological features between prostate cancers arising in the transition and peripheral zones. BJU Int. (internet) septiembre 2005 (Citado el 21 de abril de 2019);96(4):528-532. Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1464-410X.2005.05678.x
4. Lee JJ, Thomas IC, Nolley R, Ferrari M, Brooks JD, Leppert JT.Biologic Differences Between Peripheral and Transition Zone Prostate Cancer. Prostate.(internet) febrero 2015 (Citado el 21 de abril de 2019); 75(2):183-190. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25327466
5. King CR, Ferrari M, Brooks JD. Prognostic significance of prostate cancer originating from the transition zone. Urol Oncol. (internet) noviembre-diciembre 2009 (Citado el 21 de abril de 2019);27(6):592-597. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1078143908001233?via%3Dihub
6. Dong F, Kattan MW, Steyerberg EW, Jones JS, Stephenson AJ, Schröder FH, Klein EA. Validation of pretreatment nomograms for predicting indolent prostate cancer: efficacy in contemporary urological practice. J Urol. (internet) julio 2008 (Citado el 24 de abril de 2019); 180(1):150-154.Available from: https://www.ncbi.nlm.nih.gov/pubmed/18485398
7. Staff H. American Urological Association Symptom Index. CS Mott Children`s Hospital Michigan Medicine. Septiembre 26, 2018 (Citado el 12 de julio de 2019); Available from: https://www.mottchildren.org/health-library/ug1952
8. Roy A, Singh A, Singh SD , Jindal RP, Malhotra M, Kaur H. New Visual Prostate Symptom Score versus International Prostate Symptom Score in Men with Lower Urinary Tract Symptoms: A Prospective Comparision in Indian Rural Population. Niger J Surg. (Internet) Jul-Dec 2016; (Citado el 12 de julio de 2019); 22(2): 111–117; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013737/

9. Epstein J, Zelefsky M, Sjoberg D, Nelson JB , Egevad L d, Magi-Galluzzi C , Vickers AJ. et al A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score EURURO-6287; 2015 (Citado el 10 de julio de 2019); Nº 8

10. NIH . Análisis del antígeno prostático específico (PSA). Instituto nacional de cancer. (internet) 4 de octubre de 2017 (Citado el 24 de abril de 2019); Available from: https://www.cancer.gov/espanol/tipos/prostata/hoja-informativa-psa

11. Fernández M, Toirán GR, Varela ÁA, Segura RO. Cáncer prostático: correlación entre el valor del antígeno prostático específico y el resultado anatomoclínico AMC vol.19 no.1 (Internet) Camagüey, 2015 (Citado el 20 de abril de 2019); Available from: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1025-02552015000100008

12. BLASCO VM, TIMÓN GA, LÁZARO MV. Abordaje de la hiperplasia benigna de próstata. Actuación Atención Primaria-Especializada. MEDIFAM (internet) 3– Marzo 2003; (Citado el 24 de abril de 2019); Vol. 13 – Núm.; 13: 133-142; Available from: http://scielo.isciii.es/pdf/medif/v13n3/colabora.pdf

13. Cedeño DO. Influencia pronóstica de la expresión inmunohistoquímica de las moléculas implicadas en las vías de señalización en cáncer de prostata. TESIS (internet) Madrid, 2018 (Citado el 21 de abril de 2019); Available from http://eprints.ucm.es/47136/1/T39815.pdf

14. Clemente LM. Estudio histológico e inmunohistoquímico diferencial de inmunofenotipo, angiogénesis y patrón de metástasis en el cáncer inflamatorio mamario canino con respecto a otros tumores mamarios malignos. TESIS. (internet) Madrid, 2010 (Citado el 21 de abril de 2019) ; Available from https://eprints.ucm.es/10508/1/T31122.pdf

15. Brawer KM. Prostatic Intraepithelial Neoplasia: An Overview . Rev Urol(Internet) 2005 (Citado el 21 de abril de 2019); 7(Suppl 3): S11–S18. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1477603/

16. Epstein JI, Herawi M. Prostate Needle Biopsies Containing Prostatic Intraepithelial Neoplasia or Atypical Foci Suspicious for Carcinoma: Implications for Patient Care. J Urol. (Internet) marzo 2006 (Citado el 21 de abril de 2019); 175(3 Pt 1):820-834. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16469560

17. Bostwick DG, Qian J. High-grade prostatic intraepithelial neoplasia. Modern Pathology. (Internet) 2004 (Citado el 28 de abril de 2019); 17(): 360–379 Available from: https://www.nature.com/articles/3800053

18. Rojas P, Viviani P, MontecinosV, Ting ZY, Morales C, Godoy A, San Francisco I. Score Genetico predice agresividad del cancer de próstata. ARS medica revistas de ciencias médicas. (internet) 2018 (Citado el 30 de abril de 2019); vol 43;2;17-24 Available from: https://arsmedica.cl/index.php/MED/article/view/1116/1232

Alternative link

http://www.scielo.org.bo/scielo.php?
script=sci_arttext&pid=S1012-29662020000100003&lng=es&nrm=iso&tlng=es (html)