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DIAGNOSTIC ACCURACY OF PREOPERATIVE URINARY SMEAR TEST IN PATIENTS WITH BLADDER UROTHELIAL CARCINOMA IN A HIGH-VOLUME CENTER.

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Summary.- OBJECTIVES: To determine diagnostic accuracy of urinary cytology (smear test) in patients with preoperative diagnosis of urothelial bladder carcinoma.

METHODS: Clinical records of the patients with urotelial bladder carcinoma at the Instituto Nacional de Cancerología (Bogotá D.C., Colombia) from January 2006 to November 2010 were reviewed. Demographic data, pathological reports of preoperative cytology and definitive surgery, tumor classification and time between sample taking for cytology and final pathology were extracted. Descriptive statistics and graphs for continuous and categorical variables were performed.

RESULTS: We included 52 patients, 20 underwent cystectomy and 32 transurethral resection of the bladder tumor (TURB). 41 were male. Mean age was 66.6 ± 10.7 years. 151 smears were obtained before surgery, with a median of 3 smears performed per patient at 2.5 ± 1.8 months before definitive surgery. 107 were negative, 14 low grade positive and 30 high grade positive. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were 30.7%, 90.9%, 97.7%, 9.34%, 3.37 and 0.76 respectively. When the high-grade cytology was compared with the high-grade definitive report some characteristics increased (Sensitivity 47.4%, Specificity: 97.8%, Positive Likelihood Ratio: 21.8) and also when compared with muscle invasion (Sensitivity: 73.9, Positive Likelihood Ratio: 7.27).

CONCLUSION: Preoperative cytology has sensitivity and specificity similar to those described in other clinical settings. Also noteworthy is that one high-grade preoperative cytology has a high positive likelihood ratio for high-grade tumor and invasive tumor (≥T2).

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Resumen.- OBJETIVO: Determinar la validez diagnóstica de la citología urinaria preoperatoria en los pacientes con diagnóstico de carcinoma urotelial de vejiga.

MÉTODOS: Se revisaron los registros de los pacientes con diagnóstico de carcinoma urotelial de vejiga en la base de datos del Instituto Nacional de Cancerología (Bogotá D.C., Colombia) desde enero de 2006 hasta noviembre de 2010. Se extrajeron datos demográficos, reportes histopatológicos de las citologías preoperatorias y de la pieza quirúrgica definitiva, clasificación del tumor y tiempo transcurrido entre la toma de la muestra para la citología y la patología definitiva. Se utilizó estadística descriptiva y gráficos acordes para las variables continuas y categóricas.

RESULTADOS: Se incluyeron 52 pacientes, 20 llevados a cistectomía y 32 a resección transuretral (RTU). 41 fueron masculinos. El promedio de edad fue 66,6 ± 10,7 años. Se obtuvieron 151 citologías preoperatorias, con una mediana de 3 citologías por paciente realizadas 2,5 ± 1,8 meses antes de la cirugía definitiva. 107 fueron negativas, 14 positivas de bajo grado y 30 positivas de alto grado.
La sensibilidad, especificidad, valor predictivo positivo y negativo, razón de probabilidad positiva y negativa (LR + y LR -, de su descripción en inglés) generales fueron respectivamente: 30,7%, 90,9%, 97,7%, 9,34%, 3,37 y 0,76. Cuando se comparó la citología de alto grado con el reporte definitivo de alto grado algunas características aumentaron (sensibilidad: 47,4%; especificidad: 97,8%; LR+: 21,8) así como cuando se comparó la citología de alto grado con el reporte definitivo con invasión muscular (sensibilidad: 73,9; LR+: 7,27).

CONCLUSIÓN: La citología urinaria preoperatoria presenta sensibilidad y especificidad similares a las descritas en otros contextos clínicos. Además se destaca que una citología urinaria preoperatoria positiva de alto grado tiene una razón de probabilidad muy elevada para diagnóstico de tumor invasivo (>=T2) o de alto grado.

Palabras clave: *Orina. Citología. Neoplasias de la vejiga urinaria. Técnicas de diagnóstico urológico.*

INTRODUCTION

Bladder urothelial cell carcinoma is the seventh most common cancer in the world. In the United States this explains 70,980 new cases and 14,330 deaths each year (according to statistics from 2009) (1), with crude rates of incidence for 2005 in Cali (Colombia) of 5.8 and 2.3 per 100,000 habitants / year (men and women respectively) and mortality rates for 2008 of 1.7 and 1 per 100000 habitants / year (men and women) (2). 75-85% of these tumors are papilar non-muscle invasive (3) and they can be treated with transurethral resections with or without intravesical adjuvant therapy. Despite the

initial success of the management, tumor recurrence rate is 30 to 50% and progression to invasive tumor is 10 to 30% (4-6). This is the reason why every patient should have strict monitoring during the next few years and it should be based on cystoscopy and urine cytology as management protocols of each institution.

Since the discovery of cytology by Papanicolaou over 60 years ago, we have monitored patients with non-invasive urothelial cancer of the bladder with urine cytology and several studies have shown that the higher sensitivity is associated with invasive tumors, high-grade tumors or carcinoma in situ (Cis) (7).

Multiple studies have demonstrated the usefulness of urinary cytology in following up patients with a history of bladder urothelial carcinoma with a wide range of sensitivity and specificity however there are very few studies that assess preoperative usefulness of cytology. According to this the aim of this study was to determine the diagnostic accuracy (sensitivity, specificity, predictive values and likelihood ratios) of preoperative urinary cytology in patients with bladder urothelial carcinoma.

METHODS

A retrospective pilot cross-sectional study was performed (diagnostic test). Medical records of patients diagnosed with urothelial bladder cancer in the database of the Instituto Nacional de Cancerología (Bogotá D.C. - Colombia) from January 2006 to November 2010 were reviewed. Gender, age, the results of presurgical cytology (positive or negative), the time between the sampling and the "final" pathology (see definition below) and the histopathologic features of the definitive surgical specimen as histological grade, tumor stage and the presence of carcinoma in situ were extracted as important variables.

Inclusion criteria

• Patients older than 18 years old.
• Histopathological diagnosis of urothelial bladder cancer.
• At least one preoperative cytology.

Exclusion criteria

• Other types of bladder cancer (adenocarcinoma, squamous cell carcinoma).
• Patients with muscle-invasive bladder cancer on TURB, which did not go for cystectomy.

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•Patients with pT1 bladder cancer who were not brought to reclassification TUR.

•Reports of urinary cytology or final pathology performed in health institutions different from the Instituto Nacional de Cancerología.

Sample size was not calculated as we had the complete data to review (52 patients).

Definitions

Preoperative cytology was taken from the time of diagnosed bladder tumor (by cystoscopy or images) to before the surgical procedure (TURB or radical cystectomy). They were classified as negative, low grade and high grade. The research group classified suspicious smears arbitrarily as negative.

None extra institutional cytology was included except in cases in which a new lesion was found on cystoscopy or images and the patient was taken to a new surgical procedure at the Instituto Nacional de Cancerología.

The pathology report that correlated with the results of urine cytology was obtained from radical cystectomy or transurethral resection of a noninvasive tumor in which reclassification transurethral resection (when indicated) showed no tumor. This report was defined as "final".

Both the final pathology and cytology were assessed by a group of experienced pathologists and cytologists in oncological urology. Tumor stage was assigned according to the 2002 Tumor-Node-Metastasis (TNM) classification and tumor grade according to the 2004 guidelines of the World Health Organization.

All cytologies and final pathologies variables were analyzed, but we emphasized on the high-grade cytologies and invasive and high-grade pathologies, since as the literature has shown that It is in these cases in which cytology acquires greater sensitivity and specificity.

We used descriptive statistics and related graphics for continuous and categorical variables. With the data obtained from the results of urine cytology and histopathology reports of definitive surgery were performed and the analysis of diagnostic accuracy (sensitivity, specificity, predictive values and likelihood ratios), Receiver Operator Curves was not performed because these variables were categorical not continuous. All analysis was performed in Microsoft Excel 2008 for Mac v 12.0.

We followed national and international standards in human ethics research (Helsinki and 8430 law in Colombia). Classified as Research with minimal risk.

RESULTS

During the period stated at the Instituto Nacional de Cancerología 68 patients were taken to radical cystectomy and 111 TUR of bladder tumor, of these, 20 radical cystectomies and 32 TUR met the inclusion criteria.

Of the 52 patients included, 41 were male (78.8%). The average age was 66.6 years with a standard deviation of 10.7 years. The median number of preoperative cytology was 3 (Range 1 - 6). They were performed on average at 2.5 ± 1.8 months before definitive surgery.

Of the 151 samples of preoperative cytology, 107 were negative (70.9%), 14 low-grade (9.3%) and 30 high-grade (19.8%).

There were 52 final reports: 4 were negative (7.7%), 26 low-grade (50%) and 22 high grades (42.3%). As for its stage, 4 were classified as pT0 (7.7%), 28 as pTa (53.8%), 11 as pT1 (21.1%), 3 as pT2 (5.8%), 4 as pT3 (7.7%) and 2 as pT4 (3.9%). 7 reports reported the presence of carcinoma in situ (13.5%). None patient or data was missed.

With these results an analysis of diagnostic accuracy (sensitivity, specificity, predictive values and likelihood ratios) was created of the preoperative urine cytology versus the final pathology. Analysis was performed for a total number of cytologies as well as for the results when we had 2 or at least 3 samples, looking for any important changes in the accuracy in cases where those who had a greater amount of presurgical cytologies (Table I).

Despite differential cytology, with one or more samples, the diagnostic accuracy showed no statistical differences between these groups.

DISCUSSION

Thanks to the discoveries of Papanicolaou and Marshall, for 65 years we have used urine cytology in monitoring patients with bladder urothelial carcinoma (8) and multiple studies have shown that cytology has low sensitivity (which may increase in invasive tumors, poorly differentiated or carcinoma in situ) and high specificity. We found 15 to 73%

Table 1. Diagnostic accuracy of preoperative urinary smear test in patients with bladder urothelial carcinoma between 2006 and 2010 at the National Cancer Institute (n = 151).

Smear test	Pathology	SEN	SPC	PPV	NPV	LR+	LR-
All smear tests							
Positive	Positive	30,71	90,9	97,72	9,34	3,37	0,76
Low grade	Low grade	15	97,18	85,71	50,36	5,32	0,87
High grade	Cis	20	80,14	10	90,08	1	0,99
High grade	High grade	47,45	97,82	93,33	74,38	21,83	0,53
High grade	Invasive (≥ T2)	73,91	89,84	56,67	95,04	7,27	0,29
At least two smear tests							
High grade	High grade	48,21	98,33	96,42	67,04	28,92	0,52
High grade	Cis	15,38	80	7,14	90,43	0,76	1,05
High grade	Invasive (≥ T2)	76,19	90,16	57,14	95,65	7,74	0,26
At least three smear tests							
High grade	High grade	47,91	98,38	95,83	70,93	29,7	0,53
High grade	Cis	0	80,64	0	91,74	0	1,24
High grade	Invasive (≥ T2)	75	89,74	50	96,33	7,31	0,27

SEN: sensibility; SPC: specificity; PPV: Positive predictive value; NPV: Negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio.

of Sensitivity for all positive smear tests, according to literature, which is found to be 15 to 44% during patient's follow-up (1, 9-12)

Currently it is considered that the role of urine cytology is focused on the detection of lesions not visualized by cystoscopy in patients with a history of bladder urothelial carcinoma that had been treated (Follow up) (9). In the world literature abounds with studies evaluating the utility of urine cytology (and tumor markers) in monitoring patients (9-12), but few focus on its utility before treatment. This study focuses on urinary cytology taken after the diagnosis of bladder mass (by direct vision or image) and before any surgical procedure; this is probably the most important characteristic of this study.

For invasive tumor, high-grade pathology or in-situ carcinoma, we found that sensitivity varies from 20 to 73%, specificity from 80 – 89% and the positive likelihood ratio from 1 to 21. These results were found in the ranges described according to literature and increased in the same way when the Tumor is found high grade or invasive (9-12).

Table II compares the diagnostic accuracy obtained in this study with those published. It identifies the number of patients and urine smear tests, their indication (following patients with a history of bladder cancer, hematuria, and patients with risk factors for urothelial carcinoma or preoperative cytology) and the values reported (10-12).

The most important operative characteristic of this study is the positive likelihood ratio (LR+: 7.72), which could suggest a change in clinical decision making in our practice, for example, a patient who undertook a cystoscopy and an experienced observer

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Table II. Comparison of the diagnostic accuracy of urine cytology with some reports in the literature.

Publication	n (NOP)	n (CIT)	Indication	SEN	SPC	PPV	NPV
Restrepo et al.	52	151	Pre	30,7	90,9	97,7	9,34
Talwar et al. (10)	196	588	Seg/Hem	21,1	98,6		
Grossman et al. (11)	1331	1331	FR	15,8	99,2	54,6	94,9
Garbar et al. (12)	139	592	Seg/Hem	37-44	95-99		
Lotan et al. (9)	882	8574	Pre	47,1			
Yafi et al. (13)	1114	2979	Seg/Hem	32	88,1	90,4	27

n (NOP): Number of patients; n (Cit): Number of smear tests; Pre: presurgical;
fol: follow up of bladder cancer; Hem: hematuria; RF: Risk factors

considers this to be a 60% pretest probability of being an invasive tumor, if someone adds a high grade cytology to this pretest probability, it would have a posttest probability of 92.1% about having an invasive tumor, so an opportunity to perform a radical surgery rather than TURB could be taken.

It is noteworthy that the accuracy found when invasive or high-grade tumor did not vary significantly (Sensitivity from 15- 75%) when it took at least two or three preoperative smear tests that differ with published recommendations of taking 3 consecutive samples in the first morning urine before the surgical procedure or during the follow up (13).

It should be noted that this study does not differentiate the samples taken by spontaneous voiding or bladder lavage. This is an important information as It is already shown that smears obtained from bladder lavage will have a higher sensitivity. (1)

Possible limitations of this study are: First, a sample size was not calculated as we had the full data to perform our analysis. Second, a possible selection bias could be found, since the Instituto Nacional de Cancerología receives highly complex patients and the results may not apply to the general population. Third, arbitrarily We classified Pap smear tests defined suspicious as negative, unlike the study of Garbar et al (12) in which it was classified into 5 categories and then the analysis was made classifying suspicious as truly positive also arbitrarily.

It is necessary to conduct studies with more patients and smears taken in the general population

to give more statistical weight to the results and to determine if the preoperative urine cytology may change the surgical planning of patients with bladder masses indeed.

CONCLUSIONS

This study shows that preoperative high grade urine cytology has a high positive likelihood ratio for invasive or high grade bladder tumor.

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