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THE CLINICAL AND FORENSIC ROLE OF CITOLOGY IN PTA AND PT1 BLADDER CANCER MONITORING. CASE STUDY REVISION FOR THE PERIOD 2008 - 2017

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ABSTRACT

Introduction*: The Authors describe the results of a retrospective study that analyzes importance of a proper bladder cancer monitoring, comparing the use of the different methods available, both in terms of diagnostic delay and in terms of legal medical repercussions.*

Materials and methods*: Using the database of the Pathological Anatomy Department of the Modena Polyclinic, we have isolated a series of 238 patients with histological diagnosis of bladder urothelial carcinoma in pTa and pT1 stages with an observational minimum time interval after first diagnosis of at least 5 years. The observational statistical analysis of the data stored was made through a statistical software (SPSS report 11.00 USA).*

Results*: The results of the present study show how cytological screening, performed constantly with urine tests during early-stage monitoring of bladder tumors, can be a valid tool for the timely diagnosis of tumor stage evolution. Indeed positivity of the cytological examination can direct to a rapid diagnostic and therapeutic re-planning.*

Conclusion*: It would be desirable to standardize the best screening strategies about bladder cancer. With a correct standardization, a valid reference could be obtained both from a clinical point of view, and for a correct legal medical evaluation in term of diagnostic delay and, consequently, reduction in the chance of survival.*

Keywords: *bladder cancer, diagnosis, diagnostic delay, malpractice.*

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Introduction

Bladder carcinoma is the fourth most common cancer among neoplasms of the genitourinary system in men, and the seventh in women. The proportion of cases increases with age and the maximum peak is in the seventh decade. The bladder carcinoma, currently, shows a rather varied distribution. The standardized incidence rate in the world is 10.1 per 100,000 men, and 2.5 per 100,000 women. Particularly affected in Europe are the populations of the Mediterranean basin countries (France, Italy and Spain) where the mortality rate puts this neoplasm in fourth place, in particular the male sex, that is 4 - 5 times more affected than the female sex[(1-2)]. Epithelial neoplasms of the bladder are structured on three differentiating lines[(3)]. Most frequent is the Transitional type, that represent the 90% of all; after there are the Squamous and Glandular types, with respectively the 3-5% and 2% of incidence.

In addition, the bladder may be affected by sarcomatous, lymphomatous and anaplastic lesions but also metastases and melanomas. However, the neoplastic bladder event is characterized by a histological monotony (> 90% of neoplasms are transitional exophitic forms and vegetating protrusions in the lumen and more than 80% are initial forms pTa and pT1)[(4)].

Urinary cytology is extremely important in diagnostic and surveillance management. This involves the microscopic identification of exfoliated tumor cells based on purely cytological criteria[5]. This represents a non-invasive, simple and repetitive method of detection.

The sediments containing the tumor cells are processed by centrifugation following the Papanicolaou procedure.

The method has a high specificity but a relative low sensitivity, especially in well-differentiated bladder tumors[6].

Urinary cytology[7] can always be performed concurrently with cystoscopic control but should be considered a complementary method to cystoscopy that remains the gold standard.

The diagnostic delay of the stage evolution during the monitoring of early-stage tumors is, on clinical level, an extremely serious event, as it may have repercussions on therapeutic planning and may imply a worse prognosis, highlighting significant medical implications in the field of medical professional responsibility. Catching the first signs of disease progression is of paramount importance, especially when this goal can be achieved by simple, rapid and non-invasive investigations.

If we consider that cytological examination of urine is easily performed without any invasive method, with minimal resources and short time, we can understand how valid prevention campaigns can be, raising awareness among health workers and the population at risk.

Following this path, analyzing the monitoring of 238 patients with histological diagnosis of bladder urothelial carcinoma in pTa and pT1, for at least 5 years (since 2008), and using the traditional cytological examination of urine, we would like to provide an effective value in terms of behavioral predictability of this method and, to highlight if its execution is useful in monitoring this neoplasm.

Materials and methods

Through the consultation of the report database of the Pathological Anatomy Department of the Modena Polyclinic, we have isolated a series of 238 patients with histological diagnosis of bladder urothelial carcinoma in pTa and pT1 stages with an observational minimum time interval after first diagnosis of at least 5 years (minimum 5 years, maximum 10 years)[8]. Subsequently, the historiography of diagnostic tests pertinent to our service was obtained and evaluated, carried out essentially through urinary screening cytology. All results were digitally archived through the creation of a database. Then, an observational statistical analysis of the frequencies of the data stored was made through a statistical software (SPSS report 11.00 USA).

Results

238 patients undergoing bladder cancer removal surgery, who resulted in the pTa and pT19 stages, were included in the present work. There were 193 males (81.1%) and 45 females (18.9%) (Table 1).

		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	Male	193	81,1	81,1	81,1
	Female	45	18,9	18,9	100,0
	Total	238	100,0	100,0	

Table 1: Examined patients divided by gender.

Patients' age at diagnosis showed a global average of 72.01 ± 9.97 years with a difference in sex, reaching higher levels in women (74.1 vs 71.4 years) (Table 2 and 3).

	N	Min	Max	Mean	Std. Deviation
Age	238	43,23	92,00	72,0120	9,97726
Valid N (listwise)	238				

Table 2: Mean, minimal and maximal age of examined patients.

	N	Mean	Std. Deviation	Std. Error	Minimum	Maximum
Male	193	71,6696	9,82982	0,70757	44,08	92,00
Female	45	73,4807	10,57505	1,57643	43,23	90,00
Total	238	72,0120	9,97726	0,64673	43,23	92,00

Table 3: Mean age based on gender.

In the examined period, no significant changes in the age of onset of the neoplasia were observed, and the age when the diagnosis was first made varied between 70 and 74 years, with a stabilization over 72 years in the last years observed, as shown in the table 4.

	N	Mean	Std. Deviation	Std. Error	Minimum	Maximum
2008	42	70,1798	10,26302	1,58362	44,08	86,00
2009	27	74,3526	8,80432	1,69439	53,24	89,00
2010	25	72,8292	7,85070	1,57014	57,19	89,00
2011	40	71,1515	12,26384	1,93908	43,23	90,00
2012	66	72,4394	9,69874	1,19383	46,00	92,00
2013	38	72,0000	9,65905	1,56691	45,00	92,00
Total	238	72,0120	9,97726	0,64673	43,23	92,00

Table 4: Cancer onset mean age in the years taken in consideration.

As far as the observational period is concerned, the diagnoses related to the cases documented in the 2008-2013 interval were included, in order to guar-

antee a follow-up of at least 5 years (2013 year cases) and a maximum of 10 years (2008 year cases) of the subjects taken in examination (Table. 5) (Fig. 1).

		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	2008	42	17,6	17,6	17,6
	2009	27	11,3	11,3	29,0
	2010	25	10,5	10,5	39,5
	2011	40	16,8	16,8	56,3
	2012	66	27,7	27,7	84,0
	2013	38	16,0	16,0	100,0
	Total	238	100,0	100,0	

Table 5: Patients divided by diagnosis year.

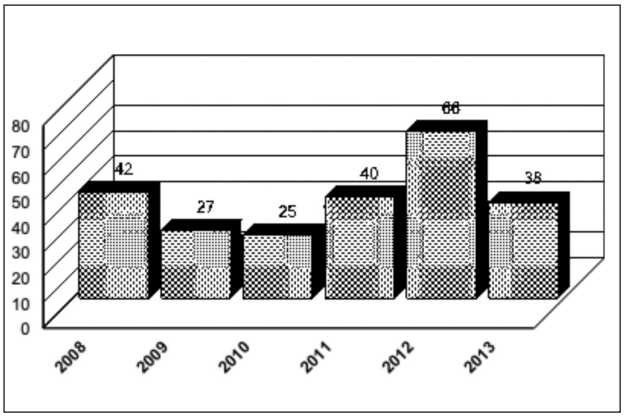


Fig. 1: Patients divided by diagnosis year.

Most cases were found (74.8%) in pTa stage, while regarding the degree of differentiation most were moderately differentiated (41.2%) (Table 6 - 7).

		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	pTa	178	74,8	74,8	74,8
	pT1	60	25,2	25,2	100,0
	Total	238	100,0	100,0	

Table 6: Patients divided by cancer stage.

		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	Well	51	21,4	21,4	21,4
	Mod	98	41,2	41,2	62,6
	Poorly	89	37,4	37,4	100,0
	Total	238	100,0	100,0	

Table 7:Patients divided by cancer grade.

For all cases the digital archive was consulted to check the follow-up urine citologic exam. For 69 cases (equal to 28.99%) no further follow-up examinations were detected at our Institute; most likely, subsequent investigations were carried out at private facilities or other public institutions.

Therefore, of the 169 traceable cases, subsequent analyzes of urinary sediment were documented with a frequency ranging from a minimum of 1 to a maximum of 43. The sampling average number after the first diagnosis was 9.50 ± 9.47 (minimum 1, maximum 43) (Table 8).

	N	Minimum	Maximum	Mean	Std. Deviation
N. of citologies carried out after the first diagnosis	169	1,00	43,00	9,5089	9,47247

Table 8: Mean number of citologies carried out after first diagnosis.

Specifically, the analisys of urinary tests frequency has documented an enormous variability ranging from one citologic exam performed in 15 cases to 43 cytologies in one case (Table 9). However, for most of cases the cytological examinations were about 3 (performed in 44 patients equal to 18.5%) and 6 (performed in 27 patients equal to 11.3%) (Table 9).

Cytology Number	Frequency	Percentage
1,00	15	6,3
2,00	5	2,1
3,00	44	18,5
4,00	10	4,2
5,00	4	1,7
6,00	27	11,3
7,00	2	0,8
8,00	2	0,8
9,00	7	2,9
10,00	1	0,4
11,00	1	0,4
12,00	6	2,5
13,00	2	0,8
15,00	6	2,5
16,00	2	0,8
17,00	2	0,8
18,00	5	2,1
19,00	1	0,4
20,00	2	0,8
21,00	5	2,1
22,00	1	0,4
23,00	2	0,8
24,00	1	0,4
25,00	1	0,4
26,00	1	0,4
27,00	2	0,8
30,00	4	1,7
32,00	2	0,8
33,00	2	0,8
36,00	1	0,4
39,00	1	0,4
41,00	1	0,4
43,00	1	0,4
99 Lost	69	29,0
Total	238	100

Fig. 9: Frequency of patients by the number of citologies carried out.

If we consider these results based on the initial stage (pTa and pT1) there is a loss of 35 cases (out of the total 69 cases lost) for pTa and 34 cases for pT1 (similar percentages). In 143 pTa cases, the incidence of urinary sediment analysis was a minimum of 1 and a maximum of 43 with an average of 11.35 ± 7.26, while for pT1 an incidence of minimum 1 was found in 7 cases and a maximum incidence of 22 in one case with an average of 9.33 ± 6.24 (not significant) (Table 10).

pTa		pT		Total
		pT1		
N. of citologies performed after the diagnosis	1,00	8	7	15
	2,00	3	2	5
	3,00	39	5	44
	4,00	5	5	10
	5,00	4	0	4
	6,00	25	2	27
	7,00	2	0	2
	8,00	2	0	2
	9,00	6	1	7
	10,00	1	0	1
	11,00	1	0	1
	12,00	6	0	6
	13,00	2	0	2
	15,00	6	0	6
	16,00	0	2	2
	17,00	2	0	2
	18,00	5	0	5
	19,00	1	0	1
	20,00	2	0	2
	21,00	4	1	5
	22,00	0	1	1
	23,00	2	0	2
	24,00	1	0	1
	25,00	1	0	1
	26,00	1	0	1
	27,00	2	0	2
	30,00	4	0	4
	32,00	2	0	2
	33,00	2	0	2
	36,00	1	0	1
	39,00	1	0	1
	41,00	1	0	1
	43,00	1	0	1
Total	143	26	169	

Table 10: Frequency of the patients by citology number divided by presentation stage.

Thus, it would appear that neoplasms in the early stage pTa undergo a greater number of con-trols than in the pT1 stage. The analysis of the available data, after the diagnosis of carcinoma in pTa or pT1 stage, has basically highlighted that there is a long time period range in which patients undergo a preven-tive check after a new onset carcinoma through urinalysis. In fact, it goes from a minimum of 1 year to a maximum of 6 years (Table 11).

Surveillance time period (in years)		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	1,00	3	1,3	1,8	1,8
	2,00	37	15,5	21,9	23,7
	3,00	62	26,1	36,7	60,4
	4,00	42	17,6	24,9	85,2
	5,00	20	8,4	11,8	97,0
	6,00	5	2,1	3,0	100,0
	Total	169	71,0	100,0	
Missing	System	69	29,0		
Total		238	100,0		

Table 11: Frequency of surveillance time period (in period).

However, on average, affected individuals undergo a control after a time interval longer than 3 years (3.31 ± 1.098) (Table 12).

	N.	Minimum	Maximum	Mean	Std. Deviation
Surveillance period in years	169	1,00	6,00	3,3195	1,08766
Valid N (listwise)	169				

Table 12: Global average of the surveillance period.

The subsequent study of control cytologies showed, in the 169 cases available for comparison, that the most repetitive pathology was dysplasia10 with 83 cases equal to 49.1% (Table 13), followed by hyperplasia with 39 cases (23.1%). In the examination of the subsequent control urine tests, the last finding was taken into consideration and in the case of association of several pathological pictures (hyperplasia / dysplasia or phlogosis / hyperplasia or dystrophy / hyperplasia), the most serious one. In 10 cases a frank relapse of neoplastic disease was documented (5.9% of cases).

Lesions		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	1 Displasia	83	34,9	49,1	49,1
	5 Iperplasia	39	16,4	23,1	72,2
	6 Flogosi	4	1,7	2,4	74,6
	9 Carcinoma	10	4,2	5,9	80,5
	10 Negativo	33	13,9	19,5	100,0
	Total	169	71,0	100,0	
Missing	System	69	29,0		
Total		238	100,0		

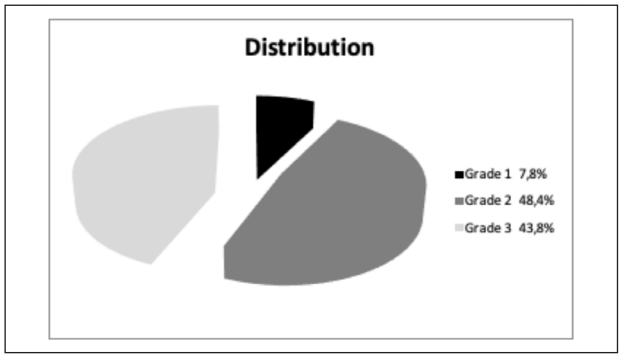
Table 13: Frequency of lesions detected with cytology in subsequent control urinary samples.

However, considering also the ultrasound examinations and cystoscopy, performed for the suspect cases11, the actual number of recurrent neoplasias was greater. Specifically, the search for neoplasia through the consultation of the histological reports of the same patients subjected to the control cytology has documented a higher number of relapse of the disease in the years of control (minimum 5), equal to 86 cases (50.88%), while in 83 cases (49.12%) the controls were negative over time (Table 14).

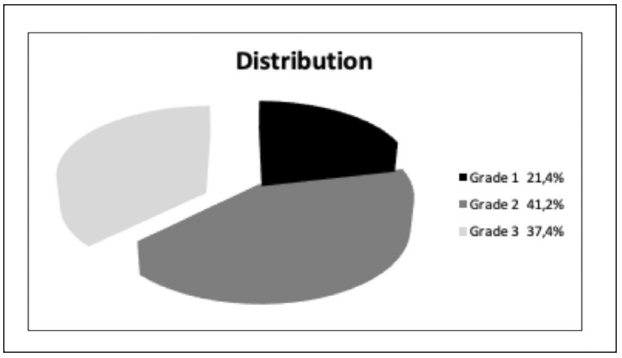
Number of neoplasms found		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	0,00	83	34,87	49,11	49,11
	1,00	46	19,32	27,21	76,32
	2,00	28	11,76	16,56	92,88
	3,00	5	2,10	2,95	95,83
	4,00	4	1,68	2,36	98,19
	5,00	3	1,26	1,77	100,0
	Total	169	71.00		
Missing	System	69	29.00	100	
Total		238	100,0		

Table 14: Frequency of cancer lesions documented in the successive years through the hystological exams.

The examination of these new cancers has documented a net prevalence of 2nd and 3rd grade in comparison to grade 1 stage (graphs 1 and 2).



Graphic 1: Distribution of histological grade in recidivant tumors.



Graphic 2: Distribution of histological grade in primitive tumors.

The evaluation of the number of relapses based on the initial stage (pTa and pT1) showed that most cases had at least one recurrence (Tab. 15 and 16) but the incidence of recurrences was greater in the pT1 forms (24 % vs 34.5%).

The analysis of the differentiation grade instead, documents a clear difference in evolution, finding a grade 2 in the pTa forms compared to a grade 3 in the pT1 forms (Tables 17 and 18).

The temporal comparison of the recurrence rate of neoplasms from the initial stage shows a greater incidence of negativity and/or absence for the pTa stage compared to the pT1 stage (64.7% vs 35.3%) and a substantial parity for first and second onset (Table. 19).

Finally, it should be emphasized that three cases (2.22%) during the follow-up period had an evolution in carcinoma in situ, a trasformation of greater agressivity. All cases started from a less favorable diagnosis: pT1 and grade 3 (specifically two males and 1 female; average age 71.33 years).

Carcinoma in pTa		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	0,00	22	29,3	40,0	40,0
	1,00	18	24,0	32,7	72,7
	2,00	19	12,0	16,4	89,1
	3,00	1	1,3	1,8	90,9
	4,00	2	2,7	3,6	94,5
	5,00	3	4,0	5,5	100,0
	Total	55	73,3	100,0	
Missing	System	20	26,7		
Total		75	100,0		

Table 15: Number of recidivant cancers in pTa patients.

Carcinoma in pT1		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	0,00	12	20,7	27,9	27,9
	1,00	20	34,5	46,5	74,4
	2,00	9	15,5	20,9	95,3
	3,00	2	3,4	4,7	100,0
	Total	43	74,1	100,0	
Missing	System	15	25,9		
Total		58	100,0		

Table 16: Number of relapses in pT1 cases.

Grading in pTa		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	0,00	22	29,3	40,0	40,0
	1,00	3	4,0	5,5	45,5
	2,00	22	29,3	40,0	85,5
	3,00	8	10,7	14,5	100,0
	Total	55	73,3	100,0	
Missing	System	20	26,7		
Total		75	100,0		

Table 17: Grade of recidivant cancers in pTa cases.

Grading in pT1		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	0,00	12	20,7	27,9	27,9
	1,00	2	3,4	4,7	32,6
	2,00	9	15,5	20,9	53,5
	3,00	20	34,5	46,5	100,0
	Total	43	74,1	100,0	
Missing	System	15	25,9		
Total		58	100,0		

Table 18: Grade of recidivant cancers in pT1 cases.

		K						
		,00	1,00	2,00	3,00	4,00	5,00	Total
1 pTa	Count	22	18	9	1	2	3	55
		64,7%	47,4%	50,0%	33,3%	100,0%	100,0%	56,1%
2 pT1	Count	12	20	9	2	0	0	43
		35,3%	52,6%	50,0%	66,7%	,0%	,0%	43,9%
Total	Count	34	38	18	3	2	3	98
		100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

Table 19: Relapse frequency of neoplasms for each initial stage.

Discussion

The pTa and pT1 stage urothelial carcinomas are considered neoplasms with a favorable clinical course[12]. However, it is known that approximately 30% of pTa or pT1 cases mature over time an aggressive biological behavior[13], which appears in the form of recurrence and/or a progression in

terms of differentiation (evolution to a higher degree) and/or appearance of stromal and muscular infiltration.

Some peculiar aspects of the tumor have been identified as risk factors of progression, including dimensions beyond one centimeter, high-grade differentiation, multifocality and history of previous carcinoma in situ[14]. Exactly for this reason, they have recently been classified as of low and high recurrence risk. All this justifies a follow up[10].

Bladder cancer is the most common malignant neoplasm of the urinary tract and cystoscopy in conjunction with cytology is currently considered the gold standard for the detection and surveillance of primitive tumors and for the follow-up of patients undergoing TURV[11-15]. Although cytology has a low sensitivity for intermediate bladder carcinoma, the high specificity, non-invasiveness and low cost justify the use of this exam. The diagnostic objective in non-muscle invasive low-grade bladder cancer is the ongoing detection of those lesions that could progress to a high-grade urothelial carcinoma[16-18].

The modern urinary cytology, first introduced in 1947 by Papanicolau and Marshall, is still used for its many advantages[19]:

• Simple, non-invasive method thanks to the easy collection of exfoliated cells;

• Specificity of the urothelium;

• High specificity (28-100%) in the diagnosis of in situ carcinoma;

• High sensitivity for high grade tumors.

The disadvantages, on the other hand, are:

• Low sensitivity for low grade tumors;

• Operator-dependent method;

The evaluation could be distorted by the instruments, by the few exfoliated cells, by inflammation, infections, and stones.

One of the advantages of cytology, which still makes it indispensable today, is the early recognition of the tendentially more infiltrating forms such as carcinoma in situ, thanks to its ability to recognize highly malignant cells, even before cystoscopy, which is strongly operator-dependent[19-20].

The importance of an early diagnosis lies in the fact that in 54% of patients with carcinoma in situ there is a progression of the lesion towards a muscle-invasive form. The great limitation of urinary cytology consists in its low sensitivity.

For this reason the research over the years has moved towards identifying urinary markers that could increase the sensitivity of the cytology and the diagnostic capacity for these low-grade tumors, as well as decrease the number of invasive instrumental tests such as cystoscopy.

Such a a urinary marker, must have the following characteristics:

• Low cost;

• Non-invasiveness;

• Quick results;

• Simplicity of interpretation;

• High specificity and sensitivity.

Based on these considerations, various methods have been developed.

The BTA (Bladder tumor antigen), NMP-22 (Nuclear matrix protein-22), Immunocyt test, Urovysion test were the most effective markers developed, but nevertheless, none of these has the same specificity of urinary cytology in high grade bladder carcinomas[21].

For this reason the role of urinary cytology is still of primary importance in the diagnosis and follow-up of high-grade carcinomas. As far as grade I and II lesions are concerned, tumor markers can be an excellent complementary tool to cytology but currently, we are still far from being able to consider them an alternative.

The knowledge currently acquired on the neoplastic dynamics of the bladder is further supported in our study and the need for a greater surveillance of the forms that present ab initio a greater expression of potentially dangerous parameters such as the grade and stage is re-proposed. Nevertheless, in view of the enormous multi-factoriality and facet of this neoplasm, even the less aggressive forms must not be neglected[22].

Cytological screening, performed constantly with urine tests during early-stage monitoring of bladder tumors, can be a valid tool for the timely diagnosis of tumor stage evolution. The positivity of the cytological examination can direct towards an intensification of investigation and, consequently, to a rapid diagnostic and therapeutic re-planning.

It must be emphasized that in recent years the number of disputes concerning medical professional responsibility has increased in Italy[23-27]. The present study shows, regarding the legal medical problems related to the diagnostic delay, the risk that this could determine an unfavorable prognosis and, consequently, a reduction in the chance of survival.

In this perspective, in the light of the results of specific studies, it would be desirable to standardize the best screening strategies. In fact, from

standardization, a valid reference could be obtained in the evaluation and in the forensic medical judgment.

In terms of potential biases of the data examined, we must consider the great heterogeneity of this type of neoplasm. However, the absence of a subdivision of the cases observed according to the presence of more or less factors of malignancy, makes the distribution of the cases homogeneous, and the respective role of cytology is standardized.

The only aspect to consider is that urinary tests frequency has documented an enormous variability, so we don't have a homogeneous time control of each case. From an operational point of view, however, this aspect impacts on the sensitivity of the method and not on the specificity, which is the true point that we wanted to highlight. Without prejudice to this single objection, the results obtained confirm the importance of cytology as the best method to reach an early diagnosis of neoplasia, combined and not replaced by other methods like BTA (Bladder tumor antigen), NMP-22 (Nuclear matrix protein-22), Immunocyt test and Urovysion test.

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