The value of cytological examination of the urine in the staging of invasive carcinoma of the cervix

A prospective study

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Summary

During the period July 1976 - December 1978 midstream urine specimens were collected from all new patients with invasive cervical carcinoma admitted to Tygerberg Hospital, Parowvallei, CP. All specimens were cytologically screened to try and establish any correlation between the cytological result and the clinical staging. A very high proportion (24,2%) of specimens unsuitable for screening and unacceptable false-negative and false-positive rates forced us to abandon this prospective study. From January 1979 to July 1980 the study was repeated on catheter specimens of urine. The final analysis of the second series revealed that a catheter specimen had definite advantages, but a detection rate of only 37,5% and a false-negative rate of 62,5% forced us to conclude that urinary cytological examination is at present too inaccurate to be of any value in the staging of invasive cervical carcinoma.

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The need for better and safer methods of staging cervical carcinoma still exists. On re-evaluation of existing methods, various authors have proved that none of the routine investigations can be omitted with safety.[1-3] Although there is a 2,5-20% chance of bladder infection after cystoscopy in these patients,[4-6] this investigation cannot be omitted.[1]

With these facts in mind a prospective study of the value of urinary cytological examination in the staging of invasive cervical carcinoma was undertaken at Tygerberg Hospital, Parowvallei, CP, in the hope that this less invasive test may replace cystoscopy. In the first phase of the study a midstream urine specimen was examined cytologically, and during the second phase use was made of a catheter specimen.

Patients and methods

During the period July 1976 - December 1978 a total of 369 new patients with invasive cervical carcinoma underwent clinical staging in the Department of Gynaecological Oncology, Tygerberg Hospital, and the existing methods of staging were re-evaluated.[1] Concurrently, midstream urine specimens for cytological screening were collected from the patients by the nursing staff. From January 1979 to July 1980 a second series of 162 new patients with invasive cervical carcinoma underwent staging at the same hospital. In these cases the midstream urine specimen was replaced by a catheter specimen.

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Midstream urine specimens

Midstream urine specimens were collected by the nursing staff in the early morning. The vulva and urethral opening were cleaned with a 1:1 000 solution of chlorhexidine in water, and the specimen was collected directly in a sterile bottle containing heparin and 20 ml normal saline. The specimen was processed in the cytology laboratory within 30 minutes of collection by means of microfiltration,[7] and two slides were prepared for cytological screening.

Catheter urine specimens

Catheter urine specimens were collected by the registrar under strict aseptic and antiseptic conditions before commencing with the bimanual examination required for clinical staging of the carcinoma. The object was to minimize the chances of secondary infection of the bladder and to avoid possible contamination of the specimen with vulval and vaginal cells. The urine was collected directly into a sterile bottle containing heparin and delivered to the cytology laboratory within 30 minutes. At the laboratory it was microfiltered[7] and two slides were prepared for cytological screening.

A total of 426 midstream specimens were collected from the 369 patients in the first series. Because cystoscopic examination could only be performed on 356 patients, the remaining 13 had to be excluded from the final analysis. In the second series 162 catheter specimens from 162 patients were examined, but in the final analysis 1 patient had to be excluded because she died of renal failure before cystoscopy could be performed. Cytological examination of the urine in this case happened to be negative.

Criteria for cytological screening

Cytological evaluation was performed on the basis of four major subgroupings: (*i*) unsatisfactory specimen; (*ii*) normal urothelial and squamous cells; (*iii*) inflammatory changes of urothelium, which may have shown a spectrum from minor to major abnormality; and (*iv*) the presence of malignant squamous cells.

A specimen was not considered suitable for cytological examination when amorphous debris together with polymorphonuclear leucocytes and severe degeneration of squamous cells and/or urothelial cells was present (Fig. 1).

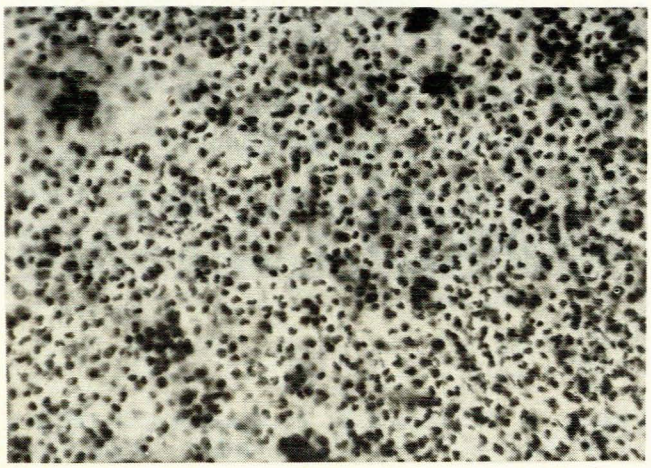

Fig. 1. Cytological specimen unsuitable for evaluation as cellular and nuclear detail not discernible (X 500).

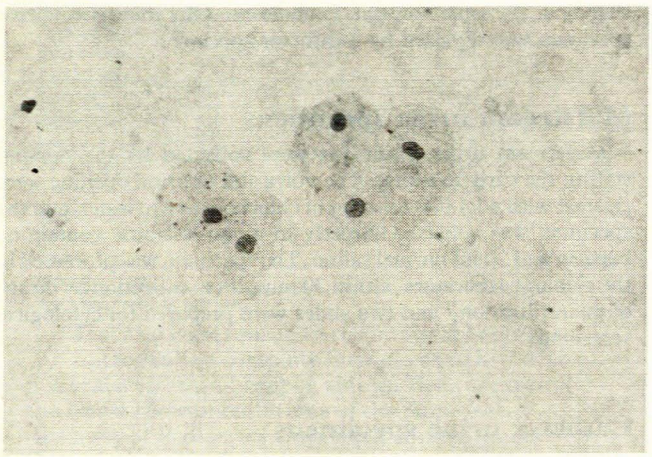

Fig. 2. Normal urothelial cells demonstrating polygonal configuration of the cells. Nuclei show a finely granular chromatin pattern with single regular nucleolus (X 500).

Normal urothelial cells are usually isolated, few in number and vary from large, flat and polygonal cells measuring 50-60 μm in diameter to those which are small, round and 20 μm in diameter. The cells have thin, transparent cytoplasm with a vesicular nucleus and finely granular chromatin. Superficial cells with pyknotic nuclei and intermediate cells with vesicular nuclei are similar to those found in the vagina (Fig. 2).

Inflammatory changes were classified as ranging from mild inflammatory changes in the urothelial cells to atypia. When inflammatory change was present occasional polymorphonuclear leucocytes, lymphocytes and red blood cells were observed. Karyorrhexis of urothelial cells was present. Atypia was considered to be present when the urothelial cells occurred in greater numbers, being shed in small isolated clusters of papillary fragments. This could be due to severe inflammatory processes, papillomas, calculi or catheterization. Smooth cellular borders were considered to be representative of papillary fronds, while rounded borders were probably caused by the forcible removal of fragments which occurs during catheterization (Fig. 3). In general the cells show cellular and nuclear enlargement, hyperchromasia of the nucleus may be observed, and there is vacuolation in the cytoplasm.

The malignant squamous cells are generally similar to those found in cervical preparations. The cells are mostly spindle-shaped and vary in size. There is extreme pleomorphism of the nuclei and the cytoplasm may show keratinization varying in relation to the degree of differentation of the neoplastic process (Fig. 4).

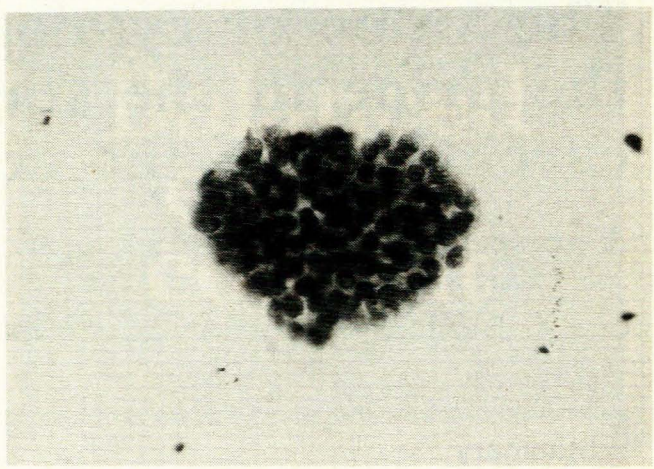

Fig. 3. Urothelial cell cluster demonstrating variability of nuclear sizes together with hyperchromasia. These changes may be due to catheterization (X 500).

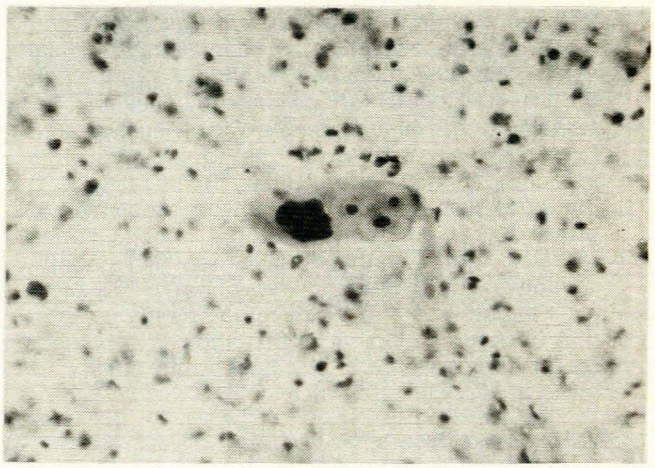

Fig. 4. Well-differentiated squamous carcinoma cell demonstrating keratinization of the cytoplasm. Note the presence of a hyperchromatic pleomorphic malignant nucleus (X 500).

Results

The diagnosis arrived at after cytological examination of the 426 specimens from the 369 patients screened in the first series are compared with those for the 162 catheter specimens from the 162 patients in the second series (Table I). The proportion of specimens showing inflammatory changes was equal in the two series (16,2% *v.* 16,7%). In the catheter specimens there was a marked drop in the proportion of those unsuitable for screening (7,4% *v.* 24,2%), while there was a sharp rise in the proportion of specimens demonstrating atypia (55,6% *v.* 12%). It is interesting to note that there were almost twice as many negative results in the midstream specimens and that in this series the proportion of positive results indicating squamous carcinoma was much higher (16,9% *v.* 4,3%).

The various reasons for considering a specimen unsuitable for screening are analysed in Table II. In the catheter specimen series only two reasons were given, namely overwhelming infection and too few transitional cells. These reasons were of minimal importance in the midstream series. Here the main reason was that only squamous cells were present in the specimen, with the result that no opinion could be given.

TABLE I. CYTOLOGICAL EXAMINATION OF 426 MIDSTREAM AND 162 CATHETER SPECIMENS OF URINE

	Midstream		Catheter	
Result	No.	%	No.	%
Negative	131	30,7	26	16,0
Negative with acute infection	69	16,2	27	16,7
Not suitable	103	24,2	12	7,4
Atypia	51	12,0	90	55,6
Positive	72	16,9	7	4,3
Total	426	100	162	100

TABLE II. ANALYSIS OF URINE SPECIMENS NOT SUITABLE FOR CYTOLOGICAL EXAMINATION

	Midstream		Catheter	
Result	No.	%	No.	%
Squamous cells only	78	75,7	—	—
Too few transitional cells	11	10,7	5	41,7
Overwhelming infection	14	13,6	7	58,3
Total	103	100	12	100

The correlation between the cystoscopic findings and the cytological diagnoses in the two series is summarized in Tables III and IV. In the first series there were 39 proven cases of squamous carcinomatous infiltration of the bladder mucosa. Urinary cytological examination was positive in 26 (66,6%) of these cases and negative in 13 (33%) (Table III). Of the 16 patients in the second series in whom cystoscopy revealed invasion of the bladder mucosa 6 (37,5%) had a positive cytological result and 10 (62,5%) a negative one (Table IV).

The cytological reports for the patients in whom cytological examination was negative but cystoscopy was positive are analysed in more detail in Table V. The commonest cause for the negative reports was few or absent transitional cells in the urinary specimens, while inflammatory changes and atypia were additional factors.

TABLE III. CORRELATION BETWEEN CYTOLOGICAL EXAMINATION OF MIDSTREAM URINE AND CYSTOSCOPIC DIAGNOSIS IN 356 PATIENTS

		Midstream urine			
		Positive		Negative	
Result	Cystoscopy	No.	%	No.	%
Invasion mucous membrane	39	26	66,6	13	33,3
Bullous oedema	33	12	36,4	21	63,6
Mucous membrane unaffected	284	34	12,0	250	88,0

TABLE IV. CORRELATION BETWEEN CYTOLOGICAL EXAMINATION OF CATHETER URINE AND CYSTOSCOPIC DIAGNOSIS IN 161 PATIENTS

		Catheter specimen			
		Positive		Negative	
Result	Cystoscopy	No.	%	No.	%
Invasion mucous membrane	16	6	37,5	10	62,5
Bullous oedema	27	1	3,7	26	96,3
Mucous membrane unaffected	118	0	0,0	118	100,0

TABLE V. ANALYSIS OF CYTOLOGICAL DIAGNOSIS IN PATIENTS WITH POSITIVE CYSTOSCOPIC AND NEGATIVE CYTOLOGICAL RESULTS

	Midstream		Catheter	
Diagnosis	No.	%	No.	%
Squamous cells only	4	30,8	0	0,0
Too few transitional cells	7	53,8	5	50,0
Overwhelming infection	2	15,4	3	30,0
Atypia	0	0,0	2	20,0
Total	13	100,0	10	100,0

The final diagnoses on cytological examination of the urine in patients found to have bullous oedema of the mucous membrane and a normal mucous membrane on cystoscopy are compared in Tables III and IV. It is obvious that the correlation between urinary cytological examination and cystoscopy is much better in the catheter specimen series. In 46 (63,9%) patients in the midstream specimen series in whom cytological examination of the urine was positive, cystoscopy was negative (Table VI). In 12 (26,1%) of these cases bullous oedema was noted and in 34 (73,9%) cystoscopy revealed no abnormality of the bladder mucosa. In the 1 patient (14,3%) in the catheter specimen series in whom cytological examination of the urine was positive and cystoscopy negative, bullous oedema of the mucous membrane was visible on cystoscopy. Table VI also reveals that the diagnosis of infiltration was confirmed on cystoscopy in only 26 (36,1%) of 72 patients with cytologically positive midstream specimens, compared with 6 out of 7 (85,7%) of those with positive catheter specimens.

Discussion

Once the results of the midstream series were analysed it was obvious that cytological examination of urine specimens collected in this manner was not accurate enough to be of value in

TABLE VI. CORRELATION BETWEEN CYTOLOGICAL AND HISTOLOGICAL EXAMINATION IN PATIENTS WITH A POSITIVE CYTOLOGICAL RESULT

Specimen	Positive cytology	Cytology positive, histology positive	Cytology positive, histology negative	Histology proven invasion
Midstream	72	26	46	39
Catheter	7	6	1	16

the staging of invasive cervical carcinoma. We were forced to come to this conclusion because of the very high percentage (24,2%) of specimens unsuitable for screening (Table I). In addition there was a false-negative rate of 33,3% in those midstream specimens suitable for cytological screening (Table III), in comparison with a false-positive rate of 63,9% (Table VI). The very high false-positive rate was due to contamination by squamous carcinoma cells from the vulva and vagina.

Realizing that the first study had failed we decided to carry out a second study using catheter specimens of urine. To ensure that the risk of secondary infection of the bladder be kept to the absolute minimum only senior personnel were allowed to obtain the specimens. When comparing the results of the second series with those of the first it was clear that the number of specimens not suitable for cytological screening was markedly reduced, and there was also a definite decrease in the number of specimens found to contain squamous carcinoma cells (Table I). The marked rise in the number of specimens diagnosed as atypical but not showing malignant change could be due to the effects of catheterization.

The proportion of false-negative cytological reports rose markedly in the second series (62,5% *v.* 33,3%). This is not surprising, since use of the catheter had decreased vaginal and vulval contamination. This also accounts for the higher false-positive rate in the midstream series. The false-positive rate dropped to 14,3% in the catheter series. The correlation between positive cytological features and positive histological features was lower, but these examinations were more accurate in the catheter series because contamination was kept to a minimum.

In the final analysis it is obvious that there are definite advantages in examining catheter specimens of urine. However, a detection rate of only 37,5% and a false-negative rate of 62,5% are conclusive evidence that cytological examination of the urine is at present too inaccurate to be of any value in the staging of invasive carcinoma of the cervix. Until better methods of collecting and preserving the specimens are developed, there appears to be no need for routine urinary cytological examination in patients with invasive cervical carcinoma.

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News and Comment/Nuus en Kommentaar

Pregnancy after oöcyte and sperm transfer to the uterus

In vitro fertilization of ova for the relief of infertility has obvious drawbacks. It is costly and tedious and presents moral and ethical problems. There may be a more acceptable alternative if the preliminary results of a technique used by Craft *et al.* (*Lancet* 1982; **i:** 1031) stand the test of time. What Craft *et al.* have done is to induce ovulation in 31 infertile women with clomiphene citrate and then capture oöcytes by laparoscopy 36 hours after giving an injection of chorionic gonadotrophin. They then incubated the oöcyte in a tissue culture medium for 6 hours, added sperm, continued culture for a further hour and then transferred the oöcyte and sperm directly into the uterus. Measurements of chorionic gonadotrophin levels in the urine indicated that there was some trophoblastic activity in 14 of the patients; 2 of the patients at the time of reporting have a continuing intra-uterine pregnancy. Further information will be eagerly awaited, since there are no moral or ethical problems associated with this technique and it might well be used in an ordinary infertility clinic attached to a general hospital.

Orale voorbehoedmiddels en serviks-karsinoom

Baie navorsers wil 'n verband sien tussen die gebruik van orale voorbehoedmiddels en die ontstaan van displasie van die cervix uteri. Ander is weer oortuig dat dieselfde verband tussen seksuele aktiwiteit en die ontstaan van maligne en premaligne serviksaandoeninge bestaan.

Swan *et al.* (*Am J Obstet Gynaecol* 1981; **139:** 52) het hierdie faktore by 69 vrouens met karsinoom *in situ* van die serviks ondersoek en die resultate vergelyk met dié van 216 gesonde vrouens van dieselfde ouderdom, huwelikstaat, geloof, sosiale status en pariteit. Hulle het 'n seksuele aanduiding gebruik wat bereken word uit die gegewens van die ouderdom ten tyde van die eerste huwelik, eerste koïtus, aantal huwelike, koïtusfrekwensie en die aantal veneriese infeksies.

Van die vrouens met 'n karsinoom *in situ* blyk 86% nooit orale voorbehoedmiddels te gebruik het nie teenoor 58% uit die kontrolegroep. Hier moet onthou word dat nie net die pilgebruiksters minder sitologies ondersoek is nie, maar ook dat vrouens uit die kontrolegroep selde 'n ginekologiese ondersoek ondergaan het. Sover dit die seksuele aanduiding betref, blyk dit dat die vrouens met karsinoom *in situ* gemiddeld twee maal soveel seksgeselle gehad het as die kontroles. Die gemiddelde aanvangsouderdom van gereelde geslagsverkeer was laer en die trou-ouderdom sowel as die eerste koïtus het op 'n vroeër stadium plaasgevind. Die aantal veneriese infeksies en terapeutiese aborsies het min verskil tussen die groepe. Die risiko van karsinoom *in situ* het toegeneem namate orale voorbehoed-middels gebruik is vir langer as 4 - 6 jaar. Daarna het die frekwensie weer afgeneem.

Wanneer die genoemde seksuele faktore in ag geneem word, is die verhoogde risiko as gevolg van pilgebruik egter nie langer statisties beduidend nie.