The use of microscopic haematuria can reduce the need for staging cystoscopy to exclude invasion of the urinary bladder by cervical carcinoma

L Vlok*, S Wessels, K Du Toit and A Van der Merwe

Department of Urology, Tygerberg Hospital and University of Stellenbosch, Cape Town, South Africa
*Correspondence: lwvlok@gmail.com

Introduction

Worldwide, cervical cancer is second only to breast cancer as the most common female malignancy—in both incidence and mortality—resulting in 570 000 cases and 311 000 deaths in 2018.1 The disease is the most commonly diagnosed cancer in 28 countries and the leading cause of death by cancer in 42 countries. The vast majority of these cases were reported in sub-Saharan Africa and Southeast Asia.1

South Africa has a burden of disease similar to that in the rest of developing world, with cervical carcinoma being the most common gynaecological malignancy.2 Unfortunately, in an under-resourced developing world setting, screening services are lacking. Many patients are therefore only diagnosed with advanced disease.3

Current FIGO (International Federation of Gynaecology and Obstetrics) staging of cervical cancer is based on clinical examination, imaging studies and further investigations—such as cystoscopy—to identify the spread of disease.4 Should cystoscopy and biopsy confirm bladder infiltration, it is seen as FIGO stage IV-A disease and this influences treatment options and prognosis.5

A major concern for gynaecologists and urologists is that apart from patients with possible invasion of the urinary bladder on imaging, the FIGO classification system does not clearly stipulate which patients should have a cystoscopy. A cystoscopy forms part of the local staging of cervical cancer and is used, especially in resource-limited settings, where more advanced imaging techniques like magnetic resonance imaging (which can be used to identify patients in true need of a cystoscopy) are not readily available or absent. A cystoscopy is an invasive procedure, requiring specialised equipment (rigid cystoscopes, light sources and biopsy forceps), skills and theatre time, which in a resource-limited setting may cause substantial delays in the investigation and treatment of patients with cervical cancer. Thus, numerous attempts have been made to identify less invasive tests to decide which patients will or will not require a staging cystoscopy. These tests include ultrasound,6 computer tomography,7 magnetic resonance imaging,8 the presence of positive urine cytology9 and the presence of microscopic haematuria on microscopy10

A small previous study assessing microscopic haematuria on microscopy as means of screening for bladder involvement by cervical cancer had a 100% sensitivity and a specificity of 60.3%. However, only four patients in the study had confirmed bladder invasion by cervical cancer.10 In urology clinics, the presence of microscopic haematuria has long been used as a screening test to identify patients with possible urological malignancy, with current guidelines recommending further investigation with imaging and cystoscopy if it is found.11,12

The primary aim of our study was to evaluate whether the absence of microscopic haematuria can be used as a screening test to exclude invasion of the urinary bladder by cervical cancer and therefore reduce the need for a staging cystoscopy.
Methods
The study was designed as a prospective observational study and was approved by the local ethics institutional review board. All patients with a histological diagnosis of cervical cancer, diagnosed between January 2015 and December 2016, who underwent a staging cystoscopy at our tertiary hospital to rule out invasion of the urinary bladder, were included. It is the protocol of our local institution that all patients with newly diagnosed stage 2 or higher cervical cancer undergo a staging cystoscopy.

Informed consent was obtained prior to cystoscopy to be enrolled in the study. None of the participants declined enrolment. A mid-stream urine specimen was then collected, whereafter a dipstick test (Bayer Multix 10SG dipstick; Bayer AG, Leverkusen, Germany) was performed to evaluate for the presence of microscopic haematuria. The specimen was then discarded. The same individual interpreted each participant’s dipstick test.

After 60 minutes the patient was placed in the lithotomy position, cleaned, draped and a Foley’s F 14 latex urinary catheter was placed into the urinary bladder. Urine specimens were then collected from the catheter. A dipstick test was performed on the catheter specimens and these specimens were sent to a laboratory for urine microscopy, culture and cytology. All the dipstick tests were once more interpreted by the same individual. The catheter was removed after urine collection and a cystoscopy was performed noting all relevant findings. All cystoscopies were performed by the same doctor who was unaware of the results of the urinary dipstick. If any suspicious lesions were identified with cystoscopy, a biopsy was performed and the specimen was sent for histopathological studies.

Data was entered on an Excel® database (Microsoft Corp, Redmond, WA, USA), using GraphPad InStat® (https://www.graphpad.com/scientific-software/instat/) software and Stata 12 (StataCorp, 2011, Stata Statistical Software: Release 12; StataCorp LP, College Station, TX, USA) for statistical analysis. Sensitivity, specificity, negative and positive predictive values as well as overall accuracy for haematuria as indicator of histologically proven invasion of the bladder by cervical cancer were calculated.

Results
A total of 144 patients participated in the study, with a mean age of 51 (SD 12.6) years. Of the 144 patients, 19 patients (13.2%) had invasion of the urinary bladder by cervical cancer, as confirmed by biopsy (Table 1).

The diagnostic accuracy of five different scenarios was tested. In scenario one, a midstream urinary dipstick test was evaluated. All 144 patients had the dipstick test on an initial midstream urine specimen. The dipstick test was positive in 88 (61%) patients and negative in 56 (39%). All patients who had cervical cancer with histologically confirmed bladder invasion had a positive urinary dipstick for haematuria. The specificity of the test was 1, the specificity 0.45, negative predictive value 1 and positive predictive value 0.22.

In scenario two, a dipstick test was performed on the urine obtained from the patient after catheterisation. One patient’s urine sample was not recorded so 143 patients’ data were included. The dipstick test was positive in 38 (27%) patients and negative in 105 (73%) patients. All patients who had cervical cancer with histologically confirmed bladder invasion had a positive urinary dipstick for haematuria. The sensitivity of the test was 1 and the specificity increased to 0.85. The negative predictive value was 1 and the positive predictive value also increased to 0.5.

Scenarios three, four and five were based on the presence of different levels of microscopic haematuria in the urinary catheter specimen sent for microscopy. Urine from all patients was sent for urine microscopy.

Scenario three assessed the diagnostic accuracy of more than 1 000 erythrocytes/ml urine to predict the invasion of the bladder by cervical cancer. The sensitivity of this test was 1, the specificity 0.77, the positive predictive value 0.4 and the negative predictive value 1.

### Table 1: Data collected from patients with cervical cancer (n = 144)

| Factor                  | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 | Scenario 5 |
|-------------------------|------------|------------|------------|------------|------------|
| Number of participants  | 144        | 143*       | 144        | 144        | 144        |
| Test positive           | 88         | 38         | 48         | 44         | 19         |
| Test negative           | 56         | 105        | 96         | 100        | 125        |
| Disease positive        | 19         | 19         | 19         | 19         | 19         |
| Disease negative        | 125        | 124        | 125        | 125        | 125        |
| Sensitivity             | 1          | 1          | 1          | 1          | 0.58       |
| Specificity             | 0.45       | 0.85       | 0.77       | 0.8        | 0.94       |
| Positive predictive value | 0.22       | 0.5        | 0.4        | 0.43       | 0.58       |
| Negative predictive value | 1          | 1          | 1          | 1          | 0.94       |

Total no. of patients with histologically confirmed bladder invasion = 19

*In scenario 2, one patient’s data on dipstick were not recorded.

Scenario 1 = urine dipstick—midstream urine sample.
Scenario 2 = urine dipstick—catheter sample.
Scenario 3 = urine for microscopy, > 1 000 erythrocytes = microhaematuria.
Scenario 4 = urine for microscopy, > 10 000 erythrocytes = microhaematuria.
Scenario 5 = urine for microscopy, > 100 000 erythrocytes = microhaematuria.
Scenario four assessed the diagnostic accuracy of more than 10,000 erythrocytes/ml urine. The sensitivity was 1, the specificity 0.8, the positive predictive value 0.43 and the negative predictive value 1.

Scenario five assessed the diagnostic accuracy of the presence of more than 100,000 erythrocytes/ml urine. The sensitivity was 0.58, the specificity 0.94, the positive predictive value 0.58 and the negative predictive value 0.94.

Discussion
Correct staging of cervical cancer remains the cornerstone for selecting the appropriate management for the patient. Bladder and rectal mucosal involvement are seen as locally advanced disease and are classified as FIGO stage 4 cervical cancer. The identification of Stage 4A disease is important as it determines the treatment and prognosis of the patient. Stage 4A cervical cancer is deemed irresectable and patients will either receive chemoradiation or palliative radiotherapy depending on the performance status of the patient. When surgery is performed in these patients it is in the palliative setting, with urinary diversion via ileal conduit in cases of vesico-vaginal fistula or faecal diversion via colostomy due to rectal infiltration.

In the revised 2019 FIGO staging of cervical cancer guidelines, it is stated that even from stage 1 disease cross-sectional imaging such as MRI or CT can be considered staging investigations. The routine use of cystoscopy, which is an invasive method for staging, is not recommend unless the patient has symptoms or imaging suggestive of bladder invasion. However, the guidelines do state that, in resource-limited settings, clinical staging can be performed without clearly stating what investigations the clinical staging includes.

With regard to imaging, MRI, CT and ultrasound are currently the most frequently used modalities for staging of advanced cervical cancer to assess bladder involvement. For staging, MRI imaging accurately depicts bladder involvement (sensitivity 75%) with a negative predictive value of nearly 100%. MRI is readily available in developed world countries, but in resource-limited settings, such as many African countries, MRI is a scarce modality. If it is available it is associated with significant cost, requiring skill to interpret, and is often associated with a significant waiting period, which results in treatment delays.

Studies by Chung et al. and Sharma et al. investigated the use of CT for identifying bladder invasion by cervical cancer. Both studies had a sensitivity and negative predictive value of 100%. CT, like MRI, is characterised by the same limitations, namely availability, cost and delays in treatment.

A study by Xue-Song Han and colleagues looked at the use of three-dimensional transvaginal ultrasound for local staging, with 80 patients included in the study. The overall accuracy for staging by transvaginal ultrasound was 92.5%, but no patients with bladder invasion were included in the study. The pitfall of ultrasound for staging is that it is operator dependent and offers a limited field of view.

In our institution, all patients with stage 2 and higher advanced stages of cervical cancer undergo a staging cystoscopy, due to resource limitations. This practice is still widely used in settings where there is limited or no access to CT and MRI as part of local staging. With theatre time also being a scarce resource, our aim was to assess whether we can use the absence of microscopic haematuria to identify patients not needing cystoscopy.

Our study indicated that in patients with cervical cancer, a mid-stream urine dipstick for haematuria, although sensitive, has a low specificity of 0.45 due to the contamination of urine by vaginal bleeding. Despite the low specificity of the dipstick test, the number of cystoscopies needed to be performed could have been reduced by 39% or by 56/144 in our study. This is already a significant reduction in the amount of theatre time required, without missing any patient with invasion.

In cases where more than 10,000 erythrocytes were used as cut-off for microhaematuria, there were no statistical difference between the detection of microhaematuria through urine dipstick testing performed on a catheter urine sample, or the urine microscopy in a laboratory. Both showed excellent sensitivity and specificity for predicting patients with possible bladder invasion.

By performing a urinary dipstick test on a catheter specimen, not a single patient with invasion would have been missed and only 38 cystoscopies had to be performed, as opposed to 144. When urine microscopy is used, it is best to use the presence of more than 10,000 erythrocytes to define microhaematuria. With urine microscopy, only 44 cystoscopies had to be performed and no patient with invasion was missed. If more than 100,000 erythrocytes were used to predict invasion, 8 of the 19 patients with invasion were not identified, resulting in a poor screening test. Urine dipstick testing still has an element of subjectivity as the colour change on the dipstick must be validated by an observer.

Our study, with a larger population group and more patients with bladder invasion by cervical cancer, had similar findings to the study by Chuttiantum and colleagues, which investigated haematuria for the screening of bladder invasion.

The findings presented indicate that the use of microscopic haematuria can reduce the number of cystoscopies that must be performed for local staging in cases of advanced cervical cancer.

Advantages of the study were that it was prospective, it had a relatively large percentage of patients with bladder invasion (13.2%) and the investigator was blinded to the dipstick results when performing the cystoscopy.

Limitations of the study include that it was conducted at a single institution and that it had a relatively small group of subjects.

Conclusion
The presence of microscopic haematuria on a catheter urine specimen confirmed either by urine dipstick testing or on laboratory microscopy (>10,000 erythrocytes), can be used as a screening test to identify patients with possible bladder invasion by cervical cancer, and who will need cystoscopy. The absence of microscopic haematuria readily excludes invasion of the urinary bladder by cervical cancer and identifies those patients who do not need cystoscopy. These findings will be of particular benefit in resource-limited clinical settings.
References
1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. http://doi.org/10.3322/caac.21492.
2. NHLS. Summary statistics of cancer diagnosed histologically in 2016 in females in South Africa.
3. Olorunfemi G, Ndlovu N, Masukume G, et al. Temporal trends in the epidemiology of cervical cancer in South Africa (1994–2012). Int J Cancer. 2018;143(9):2238–49. http://doi.org/10.1002/ijc.31610.
4. Bhatla N, Berek JS, Cuello Fredes M, et al. Revised FIGO staging for carcinoma of the cervix uteri. Int J Gynecol Obstet. 2019;145(1):129–35. http://doi.org/10.1002/ijgo.12749.
5. Committee F. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet. 2014;125(2):97–98. http://doi.org/10.1016/j.ijgo.2014.02.003.
6. Han XS, Ning CP, Sun LT, et al. Three-dimensional transvaginal tomo-graphic ultrasound imaging for cervical cancer staging. Ultrasound Med Biol. 2015;41(9):2303–9. http://doi.org/10.1016/j.ultrasmedbio.2014.10.005.
7. Sharma DN, Thulkar S, Goyal S, et al. Revisiting the role of computerized tomographic scan and cystoscopy for detecting bladder invasion in the revised FIGO staging system for carcinoma of the uterine cervix. Int J Gynecol Cancer. 2010;20(3):368–72. http://doi.org/10.1111/j.1525-1438.2010.00630.x.
8. Chung H, Ahn HS, Kim YS, et al. The value of cystoscopy and intravenous urography after magnetic resonance imaging or computed tomography in the staging of cervical carcinoma. Yonsei Med J. 2001;42:527Y531.
9. Otero-Garcia MM, Mesa-Álvarez A, Nikolic O, et al. Role of MRI in staging and follow-up of endometrial and cervical cancer: pitfalls and mimickers. Insights Imaging. 2019;10(1):6–7. http://doi.org/10.1186/s13244-019-0696-8.
10. Snyman LC, Zondagh BA, Dreyer G, et al. Urine cytology as a screening test for bladder infiltration in cervical cancer. Int J Gynecol Cancer. 2006;16(4):1587–90. http://doi.org/10.1111/j.1525-1438.2006.00630.x.
11. Chuttiangtum A, Udomthavornsuk B, Chumworathayi B. Hematuria screening test for urinary bladder mucosal infiltration in cervical cancer. Asian Pacific J Cancer Prev. 2012;13(10):4931–3. http://doi.org/10.7314/APJCP.2012.13.10.4931.
12. Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. J Urol. 2012;188(6 SUPPL.):2473–81. http://doi.org/10.1111/j.1960-1819.2012.09.078.
13. Linder BJ, Bass EJ, Mostafid H, et al. Guideline of guidelines: asymptomatic microscopic haematuria. BJU Int. 2018;121(2):176–83. http://doi.org/10.1111/bju.14016.
14. Marth C, Landoni F, Mahner S, et al. Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology. August 2017; 28(Supplement 4).
15. Ogbole GI, Adeyomoye AO, Badu-Peprah A, et al. Survey of magnetic resonance imaging availability in West Africa. Pan African Med J. 2018;30:240.

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