Diagnosis of Hydronephrosis or Ureteral Obstruction using Renal Sonography among Patients with Cervical Cancer

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ABSTRACT

Background. Cervical cancer is the second most common malignancy among Filipino women. The recent 2018 FIGO guidelines recommend imaging in cases of grossly invasive disease to determine the presence of hydronephrosis, which would immediately classify the disease as at least stage IIIB. CT and MRI are state-of-the-art modalities that can provide such information; however, these are costly and may not be accessible in areas with limited resources. Sonography is a safe and inexpensive alternative in this regard.

Objective. This study aimed to evaluate the diagnostic performance of renal sonography in identifying the presence of ureteral obstruction or hydronephrosis among patients with grossly invasive cervical cancer, with non-enhanced CT as the reference standard.

Methods. A blinded, prospective study was conducted among patients diagnosed with grossly invasive cervical cancer from the Philippine General Hospital. Participants underwent same-day evaluation with both renal sonography and non-enhanced CT. The presence of either ureteral obstruction or hydronephrosis secondary to cervical cancer was independently determined. The sensitivity, specificity, positive predictive value, and negative predictive value of renal sonography were calculated, with non-enhanced CT as the reference standard.

Results. A total of 127 participants were enrolled. The mean age was 46 years, with a range of 24 to 65 years. The majority had stage IIB (41.7%) and stage IIIB (52.0%) disease. On non-enhanced CT, 46 (36.2%) showed evidence of ureteral obstruction or hydronephrosis, while 81 (63.8%) had negative results. On renal sonography, 46 (36.2%) had positive results, and 81 (63.8%) had negative findings. The sensitivity, specificity, and positive and negative predictive values of sonography were 91.3%, 95.1%, 91.3%, and 95.1%, respectively. Among patients with stage IIIB disease, sonography was shown to have higher sensitivity and specificity of 92.1% and 96.4%, respectively. Meanwhile, among patients with stage IB to IIB disease, its sensitivity and specificity were 87.5% and 94.3%, respectively.

Conclusion. Renal sonography has high sensitivity and specificity in the diagnosis of ureteral obstruction or hydronephrosis in patients with grossly invasive cervical cancer. Its sensitivity is higher when used in patients with stage IIIB disease, compared with those having lower-stage tumors.

Key Words: Cervical cancer, hydronephrosis, ureteral obstruction, ultrasonography

INTRODUCTION

Cervical cancer is the fourth most common malignancy among females worldwide, following breast, colorectal, and lung cancers.[1] In low- and middle-income countries, including the Philippines, it is the second most commonly diagnosed malignancy and the third most common cause of cancer-related mortality among women.[1,2] In 2018, 7,190 new cases of cervical cancer, with an incidence rate of 9.1 per 100,000 women, were reported in the Philippines. There

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were 4,088 reported deaths, with a mortality rate of 9.8 per 100,000.[3]

The burden of cervical cancer in low-resource countries, such as the Philippines, is moderately high, where costs of both screening programs and treatment procedures impose significant limitations in the prevention and management of the disease. Approximately 85% of newly diagnosed cases and 90% of mortalities were reported to come from the economically disadvantaged bracket of the society.[1] The importance of developing cost-effective screening and treatment protocols cannot be undermined in these settings, as the success of cancer control depends on making these measures available and accessible to the public. In the Philippines, a high mortality rate from cervical cancer has been attributed to late diagnosis of the disease in 75% of patients, coupled with the observation that treatment is frequently unavailable, inaccessible or non-affordable.[2]

Disease staging is an important prognostic factor and is used to guide treatment planning. The International Federation of Gynecology and Obstetrics (FIGO) staging system has been widely used for this purpose and is chiefly based on clinical examination to describe the extent of local or regional pelvic disease. However, in its recent 2018 update, the importance of radiologic imaging in accurate disease staging has been recognized. In cases of grossly invasive tumor, it is recommended that radiologic imaging should be done, when resources permit, to determine the presence of hydronephrosis.[1] The presence of hydronephrosis or ureteral obstruction due to tumor immediately assigns a case as stage IIIB. This has been recognized as a significant prognostic factor that relates to poorer performance status and survival outcome, mainly due to the impairment of renal function resulting from ureteral obstruction.[4,5] In such circumstances, therapeutic management must include prompt measures to alleviate the uropathy and prevent its complications.

Ureteroscopy or open surgery is considered the gold standard for diagnosing ureteral obstruction; however, these are invasive methods and may not be appropriate in the pre-therapeutic stage. Non-invasive diagnostic modalities include intravenous pyelography (IVP), renal ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI). CT and MRI are state-of-the-art modalities that can give accurate information not only on ureteral involvement but also on tumor volume, pelvic extent, and lymph node status.[6,7,8] However, in areas where resources are limited, these modalities may not be practical and readily accessible. Sonography is an increasingly important modality in this aspect and has been widely used as the initial modality of choice in our institution.

Renal sonography is relatively inexpensive and does not require the use of contrast material or extensive patient preparation. It was reported to have a sensitivity of 76.5%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 85% when compared with IVP or CT as reference standards.[9] However, this previous study was conducted with small sample size, and the reference standard used was not uniform for all patients. This study thus aimed to evaluate the performance of renal ultrasound in diagnosing ureteral obstruction or hydronephrosis among patients with grossly invasive cervical cancer, with non-enhanced CT as the reference standard, using more robust sample size and study design.

MATERIALS AND METHODS

A blinded, prospective study was conducted among patients with newly diagnosed cervical cancer from the Cancer Institute of the Philippine General Hospital (PGH). Patients must be biopsy-proven to have cervical cancer and must have grossly invasive disease, defined as FIGO stage IB to IVA, as clinically assessed by a gynecologic oncologist. They must be 18 to 65 years of age and must participate in this study voluntarily. Patients who have undergone any form of cancer-related therapy or who are pregnant were excluded.

Using the sample size formula for testing sensitivity of a single diagnostic test,[10] a minimum target size of 126 participants was computed. This sample size would be able to detect a difference of 10% from the presumed sensitivity of 76.5% for renal US,[9] with α of 0.05 and β of 0.20. All eligible patients referred to the Department of Radiology of PGH were enrolled until the target sample size was reached. Patients underwent same-day evaluation with both sonography and non-enhanced CT, performed by trained and qualified radiologists, working independently from each other.

The renal US was performed using an Aplio 500 ultrasound system (Toshiba Medical Systems), equipped with a 3.5-MHz curvilinear transducer. The examination was a comprehensive evaluation of the kidneys, ureters, urinary bladder and cervical region, with the employment of various maneuvers to visualize these structures. Non-enhanced CT was done using a Somatom Emotion CT scanner (Siemens Healthcare). Contiguous 2-mm slices of the abdominopelvic region, from the upper renal poles to the bladder floor, were obtained. The examination was performed at 130 kV under automatic exposure control, with a table pitch of 1.5 and a rotation time of 0.6 seconds. Images were viewed using Philips Intellispace Portal 4.0.

Assessment using US and CT was done independently of each other. The sonologist and CT assessor were blinded to the clinical stage of the patients. For each patient on both US and CT, the presence of either ureteral obstruction or hydronephrosis, whether unilateral or bilateral, was scored as a positive result. Their absence was regarded as a negative result. Evidence of ureteral obstruction on either modality included encasement or extrinsic compression of the ureter by a tumor and dilatation of the ureter and pelvocalyceal system.

Statistical Analysis

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of US in diagnosing ureteral obstruction or hydronephrosis were calculated, with CT as the reference standard. The obtained values were compared with published rates using the test of two proportions.

Ethical Considerations

The protocol of this study was reviewed and approved by the University of the Philippines Manila Research Ethics Board (UPMREB) and was conducted in compliance with the Data Privacy Act of 2012. All participants were informed regarding the nature of the study, its benefits and risks, and were required to sign an informed consent form before the conduct of study procedures. Their identities and the right to privacy were respected. Each patient was given an alphanumeric identity code, which was used during data recording. Data were only used in the analysis of this study and were accessible only to the study investigators.

The conduct of US and CT on the study participants was done free-of-charge. There were no monetary incentives from the study. The use of CT involved exposure of each patient to a small dose of radiation (~10 mGy); however, this remained well within the acceptable limits for diagnostic radiologic examinations. No other additional risks were incurred by the participants.

RESULTS

Patient Demographics

A total of 127 participants was recruited for this study from January 2017 to June 2018 (Table 1). Their ages ranged from 24 to 65 years, with a mean of 46 (± 9.6) years. Based on the clinical assessment of the referring gynecologic oncologist, 3 (2.4%) had stage IB disease, 5 (3.9%) had stage IIA, 53 (41.7%) had stage IIB, and 66 (52.0%) had stage IIIB disease. Based on the histologic subtype, 90 (70.9%) had squamous cell carcinoma, 25 (19.7%) had adenocarcinoma, 5 (3.9%) had poorly differentiated carcinoma, 4 (3.1%) had adenosquamous carcinoma, and 3 (2.4%) had other rarer types.

Data and Outcomes

Table 2 shows the outcomes of renal US and non-enhanced CT of the sample population. Among the 127 patients, 46 (36.2%) showed evidence of ureteral obstruction or hydronephrosis on non-enhanced CT, while 81 (63.8%) had negative results. On renal US, 46 (36.2%) had positive results, and 81 (63.8%) had negative results. Of the 46 patients with positive results on renal US, 42 were true positives, and 4 were false positives. Of the 81 patients with negative results on renal US, 77 were true negatives, and 4 were false negatives.

Table 1. Demographic data of the sample population

Parameter	Frequency (n)	Percentage (%)
Age (years)		
24-29	2	1.6
30-39	37	29.1
40-49	45	35.4
50-59	29	22.8
60-65	14	11.0
Clinical stage		
IB	3	2.4
IIA	5	3.9
IIB	53	41.7
IIIB	66	52.0
Histologic subtype		
Squamous cell carcinoma	90	70.9
Adenocarcinoma	25	19.7
Poorly differentiated carcinoma	5	3.9
Adenosquamous carcinoma	4	3.1
Others	3	2.4
Total	127	

Table 2. Data outcomes of renal sonography and non-enhanced CT in the detection of ureteral obstruction or hydronephrosis in the study patients

Sonography	Computed Tomography		Total
	Positive	Negative	
Positive	42	4	46 (36.2%)
Negative	4	77	81 (63.8%)
Total	46 (36.2%)	81 (63.8%)	127

Table 3. Number and percentage of patients with positive findings for ureteral obstruction or hydronephrosis according to clinical stage

Clinical Stage	Number and percentage (%) of patients with positive result	
	Sonography	Computed Tomography
IB	0	0
IIA	1 (20.0)	0
IIB	9 (17.0)	8 (15.1)
IIIB	36 (54.5)	38 (57.6)
Total	46 (36.2)	46 (36.2)

The sensitivity, specificity, and positive and negative predictive values of renal US in the diagnosis of ureteral obstruction or hydronephrosis were calculated to be 91.3% (95% CI: 79.2%, 97.6%), 95.1% (95% CI: 87.8%, 98.6%), 91.3% (95% CI: 79.2%, 97.6%), and 95.1% (95% CI: 87.8%, 98.6%), respectively. Additionally, its positive and negative likelihood ratios were 18.5 (95% CI: 7.1, 48.3) and 0.09 (95% CI: 0.04, 0.23), respectively.

Table 3 shows the distribution of positive US and CT examinations according to clinical stage. One patient with stage IIA disease had a false-positive result in renal US. Among the 53 patients with stage IIB disease, nine (17.0%) had positive results in renal US, and eight (15.1%) had positive results in CT. Of these, two patients turned out to

Table 4. Prevalence of ureteral obstruction or hydronephrosis, and sensitivity and specificity of renal sonography, according to patients' clinical stage

Clinical Stage	Number of Patients	Prevalence (%)	Sensitivity (%)	Specificity (%)
IB to IIB	61	13.1 (5.8, 24.2)	87.5 (47.3, 99.7)	94.3 (84.3, 98.8)
IIIB	66	57.6 (44.8, 69.7)	92.1 (78.6, 98.3)	96.4 (81.7, 99.9)

Table 5. Data outcomes of renal sonography and non-enhanced CT in the detection of ureteral obstruction or hydronephrosis when expressed per number of individual kidneys assessed

Sonography	Computed Tomography		Total
	Positive	Negative	
Positive	64	10	74 (29.1%)
Negative	5	175	180 (70.9%)
Total	69 (27.2%)	185 (72.8%)	254

Table 6. Sensitivity, specificity, and positive and negative predictive values of renal sonography in the detection of ureteral obstruction or hydronephrosis, in terms of per individual patients and per individual kidneys assessed

Parameter (%)	Per individual patients (n = 127)	Per individual kidneys (n = 254)
Sensitivity	91.3 (79.2, 97.6)	92.8 (83.9, 97.6)
Specificity	95.1 (87.8, 98.6)	94.6 (90.3, 97.4)
Positive predictive value	91.3 (79.2, 97.6)	86.5 (76.5, 93.3)
Negative predictive value	95.1 (87.8, 98.6)	97.2 (93.6, 99.1)

be false positives in renal US. On the other hand, one stage IIB patient with negative US findings had a positive result in CT. Among the 66 patients with stage IIIB disease, 36 (54.5%) had positive US findings, and 38 (57.6%) had positive CT findings. Of these, only one registered to be a false positive in US. However, three patients with stage IIIB disease and negative US findings turned out to be false negatives.

Table 4 shows a subgroup analysis of the sensitivity and specificity of renal US in diagnosing ureteral obstruction or hydronephrosis according to the clinical stage.

In two of the four patients with false-positive US findings, the discrepancy between US and CT occurred only for their right kidneys. Their left kidneys were negative for hydronephrosis in both US and CT. Likewise, in three of the four patients with false-negative US findings, the discrepancy between US and CT occurred in their right kidneys, while their left kidneys were negative for hydronephrosis in both US and CT. In four patients with positive results in both US and CT, a unilateral discrepancy was noted wherein US showed a positive result for one kidney but CT gave a negative result.

Accounting for scenarios in which patients showed unilateral hydronephrosis or unilateral discrepancy between US and CT, the results of the study were also expressed in terms of the number of individual kidneys assessed (Table 5). Among the 254 kidneys visualized in the study, 69 (27.2%) exhibited hydronephrosis in CT, and 185 (72.8%) had negative results. On renal US, 74 (29.1%) were positive for ureteral obstruction or hydronephrosis, and 180 (70.9%) were negative. Of the 74 kidneys with positive results on US, 64 were true positives, and 10 were false positives. Of the 180 kidneys with negative US findings, 175 were true negatives, and 5 were false negatives.

When results were expressed per number of kidneys assessed, the sensitivity, specificity, and positive and negative predictive values of renal US were calculated to be 92.8% (95% CI: 83.9%, 97.6%), 94.6% (95% CI: 90.3%, 97.4%), 86.5% (95% CI: 76.5%, 93.3%), and 97.2% (95% CI: 93.6%, 99.1%), respectively. Its positive and negative likelihood ratios were 17.2 (95% CI: 9.4, 31.5) and 0.08 (95% CI: 0.03, 0.18), respectively.

Table 6 shows a comparison of the sensitivity, specificity, and positive and negative predictive values of renal US when data were analyzed based on the number of individual patients and the number of individual kidneys assessed.

DISCUSSION

Renal US is an inexpensive, readily accessible imaging tool in the evaluation of hydronephrosis among patients with cervical cancer. In this study, it was shown to have a high sensitivity of 91.3%, with non-enhanced CT as the reference standard. This supports its use as an acceptable imaging modality to screen patients for hydronephrosis, as false-negative results are few. When assessed in terms of per kidney visualized, sensitivity remained high at 92.8%, lending to the robustness of our findings. The high negative predictive value in this study indicates the reliability of renal US to exclude hydronephrosis when patients present with negative findings.

Similarly, the specificity of renal US in diagnosing hydronephrosis was high at 95.1% when assessed per patient examined, and 94.6% when assessed in terms of per kidney visualized. This suggests that it is also accurate in confirming patients with hydronephrosis, as false positives are few. A high positive predictive value also supports its reliability in diagnosing hydronephrosis when patients present with positive results.

In a study on 40 patients with cervical cancer by Vanderpuye, the sensitivity and specificity of renal US in diagnosing ureteral obstruction were reported to be 76.5% and 100%, respectively, when compared with either

intravenous urography or contrast-enhanced CT as the reference standard.[9] This sensitivity was significantly lower than that in our study ($Z = -2.5$, $p < 0.05$), but there was no significant difference between the specificities in her study and our study ($Z = 1.4$, $p > 0.05$). In another study involving an assessment of 420 individual kidneys by Frohlich *et al.*, renal US was reported to have a sensitivity of 96.30% and specificity of 96.75%, with intravenous pyelography as the reference standard.[11] This sensitivity was statistically higher than that in our study ($Z = 2.0$, $p < 0.05$), but there was again no significant difference between the specificities in their study and our study ($Z = 1.4$, $p > 0.05$).

In all false-positive cases in our study, mild pelvocalyceal dilatation was reported in renal US, but the pelvocalyces were found to be intact in CT. In one of these cases, an extrarenal pelvis was instead noted. Similarly, in the study by Frohlich *et al.*, all false-positive results were reported as minimal dilatation or grade I hydronephrosis, and no false-positive results indicated moderate or severe hydronephrosis.[11] Commonly cited causes of false-positive tests in renal US include non-obstructive pelvocalyceal dilatation, anatomical variants such as the extrarenal pelvis or large major calyx, and misinterpretation of intrarenal vessels for the pelvocalyces.[12]

In all false-negative cases on renal US in our study, CT showed mild dilatation of the ureters and pelvocalyces. Similarly, in the study by Vanderpuye, patients with false-negative US results showed only slight dilatation of the ureters on intravenous urography.[9] Other causes of false-negative US results cited by Webb include dehydrated state, presence of renal parenchymal disease that causes low urine output, and blood- or pus-filled pelvocalyces.[12]

In the most recent FIGO guidelines, radiologic imaging is encouraged, whenever resources permit, for accurate diagnosis of hydronephrosis or ureteral obstruction, the presence of which would immediately assign the tumor as at least stage IIIB. In the present study, 10 of 61 (16.4%) patients with clinical stage less than IIIB were diagnosed with hydronephrosis on renal US. Of these, two were determined to be false positives with CT as the reference standard. The prevalence of ureteral obstruction or hydronephrosis in patients with clinical stage less than IIIB was thus calculated to be 13.1%, indicating the need to upstage the tumor in this proportion of patients following radiologic evaluation. The sensitivity of renal US in this patient group was 87.5%, which is slightly lower than its sensitivity among patients with stage IIIB disease (92.1%). When assessed in terms of per individual kidney visualized, the sensitivity of renal US further decreased to 83.3% in patients with clinical stage less than IIIB, while its sensitivity among patients with stage disease IIIB remained robust at 94.7%. This suggests that renal US performs better as a diagnostic tool in patients with higher clinical stage.

An important limitation of US is its inability to identify the exact site of obstruction in many cases of hydronephrosis. The presence of overlying bowel gas usually precludes adequate visualization of the entire course of the ureters on US.[12] Additionally, US is less accurate than CT or MRI in the assessment of lymph node status and parametrial invasion, which are other important prognostic factors that may influence treatment planning and outcome.

An important limitation of this study is the lack of objective measurement used to define a dilated ureter or pelvocalyces. Assessments were made through the radiologists' interpretation, based on their professional experience and practice. Additionally, this study utilized non-enhanced CT as the reference standard to avoid certain confounding factors. Although contrast-enhanced CT is a better tool to visualize the ureters and if present, their points of obstruction, it is relatively contraindicated in patients with impaired renal function. The choice of using non-enhanced CT in this study served to avoid the risk of nephrotoxicity among the study participants and to eliminate potential bias if patients would not receive nephrology clearance to undergo contrast-enhanced study.

This study was limited to the evaluation of the role of renal sonography in diagnosing the presence or absence of hydronephrosis. In actual clinical settings, the presence of hydronephrosis, especially when mild, may not necessarily translate to significant impairment of renal function, which is better assessed using serum creatinine or other markers of glomerular filtration rate. Further studies to document and analyze the cost-effectiveness of US over other imaging modalities in actual clinical settings, taking into account their impact on patient management, may be done.

CONCLUSION

This study shows that renal US has high sensitivity and specificity in the diagnosis of ureteral obstruction or hydronephrosis among patients with grossly invasive cervical cancer when compared with non-enhanced CT as the reference standard. Subgroup analysis according to patients' clinical stage showed that its sensitivity is higher when used in patients with stage IIIB disease, compared with those having lower-stage tumors.

Statement of Authorship

All authors participated in the conceptualization and design of the study, data interpretation and analysis, and approved the final version submitted. Data collection was performed by Dr. Ong and Dr. Pauig.

Author Disclosure

All authors declared no conflicts of interest.

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