Pyuria in Cervical Cancer Patients Undergoing Concurrent Chemotherapy and Radiotherapy*

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ABSTRACT

Background. Cervical cancer is the second most common malignancy in women, with gold standard treatment of external beam radiation concurrent with chemoradiotherapy (CCRT) which has acute toxic effects on the genitourinary tract. Such changes are challenging, clinical interpretation of urinalysis and one of which is pyuria. Recent evidence is scarce when it comes to differentiating between radiation and infection induced cystitis. *Objectives.* This study aims to determine the prevalence of pyuria in cervical cancer patients receiving chemotherapy radiation treatment in a tertiary training government hospital from 2018- 2020. Furthermore, it sought to determine the incidence of pyuria with positive urine culture among patients receiving CCRT. *Materials and Method.* The study utilized quantitative descriptive retrospective review of 102 cervical cancer patients in terms of their urinalysis and culture results during CCRT treatment.

Results and Discussion. The prevalence of pyuria is at 56.86% (58/102) with positive urine culture at 18.97 %. 58 patients had pyuria, where 44 of them had no growth, 3 had growth with no important pathogen, and 11 were culture positive. Antibiotics therapy was prescribed in 50 of 58 patients who had pyuria. Moreover, pyuria and urine culture have a significant relationship at 0.01 level of significance. *Conclusion.* Patients aged 41-50 years old, with stage 3B cervical cancer, in their initial treatment would most likely have sterile pyuria without culture growth and still be prescribed with antibiotic therapy.

Keywords: *Pyuria, Cervical Cancer, CCRT, Culture Growth and Antibiotics Therapy*

INTRODUCTION

Cervical cancer ranks second as the most prevalent type among women ages 15 to 44 in other developing nations and in the local setting[1], with 85% of recorded mortality[2]. Presently, the standard treatment of locally advanced cervical cancer (LACC) include external beam radiotherapy with concurrent cisplatin-based chemotherapy (CCRT) with brachytherapy[3,4]. CCRT indisputably improves LACC outcomes rather than radiotherapy alone[5] but it also causes urinary toxicity[6] like genitourinary tract inflammation, most common is urinary tract infection[7]. UTI (Urinary Tract Infection) has an estimated incidence of 25%- 83%[8,9], and although common, there are challenges in terms of clinical interpretation on pyuria. Sterile pyuria is broadly defined as the presence of leucocytes (generally >10 WBC/hpf) in the urine in the absence of demonstrable urinary tract infection. There are various reasons why pyuria has become challenging. There is an overlap between pyuria and other condition like urinary tract infection, radiation cystitis and asymptomatic non-visible hematuria, plus the absence of symptoms makes it difficult to justify treatment[10]. In the institution where the study took place, patients undergo weekly urinalysis before CCRT. Any patient suspected of having urinary tract infection is subjected to antibiotic treatment and CCRT is interrupted. Antibiotic therapy is initiated in both cases where urinalysis shows pyuria, elevated leukocyte esterase, and nitrite levels. Same is true in asymptomatic pyuria, as empirical antibiotic therapy can be initiated while waiting for confirmation by urinary culture [11]. The decision for management rest on the clinician's judgement. In the institution, majority of cases go for the later rather than the former as sterile pyuria, in many cases, is caused by an infection[10]. But most often than not, urine cultures of urinalysis showing UTI have no culture growth, which may mean that the delay in treatment and antibiotic therapy may be deemed unnecessary and harmful. It can lead to antibiotic resistance, adverse drug effects, C. difficile infection, and contribute unnecessarily to medical care[12]. Aside from possible over treatment, delays in CCRT happen and when treatment duration exceeds >56 days, research shows that treatment time impacts pelvic failure

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

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3rd Place Philippine Obstetrical and Gynecological Society midyear convention research contest 2023
1st Place Philippine Obstetrical and Gynecological Society Region 1 research contest 2023
Poster Presentation XXVIII Asia Oceania Federation of Obstetrics and Gynecology, Busan South Korea 2024

(PF) and is associated with brachytherapy delay and a higher incidence of acute toxicities[13].

There are numerous gaps identified when dealing with pyuria among cervical cancer patients. First is the scarcity of evidences to clinically differentiate infectious and radiation cystitis, as the diagnosis of UTI in the general population is not applicable to the population subjected to pelvic radiation therapy[14]. Second, research and guidelines on the management of pyuria are inadequate due to diagnostic challenges, absence of management guidelines, and specimen collection issues. Differentiating pyuria from UTI can be quite problematic which results to inconsistent management like ignoring finding, over investigation and possibly unnecessary secondary care referral[10]. The lack of guidelines and the presentation of symptoms results in excessive use of resources that increase treatment cost, loss of resources, and compromises patient safety by excessive, unjustified use of antibiotics[14]. These beg the question on the incidence of misdiagnosis, over treatment, and unnecessary delay of treatment. Third is the diagnostic capacity of urinalysis in diagnosing pyuria. Studies show that it has not been formally studied in women receiving pelvic radiotherapy for gynecologic malignancies [15]. Urinalysis specimen are most of the time contaminated even if using ideal collection technique[16] due to vaginal leukocytes and inappropriate sample collection [17]. Aside from that, a recent study concluded that urinalysis, both dipstick, and microscopic evaluation, has slightly less diagnostic accuracy for predicting UTI in women undergoing pelvic radiotherapy[15]. Combined with the status quo regarding pyuria, these reality cast doubt and difficulty for physicians on the appropriate management i.e. antibiotic treatment, and delay of therapy.

Hence, this study's main objective is to determine the percentage of pyuria with positive urine cultures in cervical cancer patients undergoing CCRT. Specifically to determine the clinical profile of patients undergoing CCRT, urine culture growth, prevalent microorganisms present on urine culture, percentage of antimicrobial treatment on those with sterile pyuria and correlation between pyuria and positive urine culture.

MATERIALS AND METHODS

This is a quantitative study that utilized chart review. Previous records of cervical cancer patients who had undergone concurrent chemo and radiotherapy was retrieved from the medical records, electronic medical records of the tertiary training government hospital. The data gathered comprised of the identified independent variables and demographics. The data was collected by the primary investigator.

The charts and medical records were selected randomly by Microsoft excel. Patients with urinalysis and urine culture results were sorted. Urinalysis with results of pyuria were compared with urine culture if there will be bacterial growth. Bacterial growth on culture were noted. Urinalysis results of patients were compared based on their cycle of treatment to know if treatment it had contributed to the urinalysis results. All data were recorded in the data abstraction form (appendix C).

Exclusion criteria include sufficient lack of variables recorded in the chart, presence of excessive or confounding co-morbidities, and/or the presence of confounding factors that sufficiently degrade the validity of data from the chart.

Charts with incomplete or missing data were managed appropriately. This research followed 2 out of 3 recommendations of Altman and Bland (2007) where the main ways of handling missing data in a retrospective analysis includes: (a) omitting variables which have many missing values; (b) omitting individuals who do not have complete data.

RESULTS

Pyuria

Out of the 102 sample population, during their 25 days of treatment with external pelvic radiotherapy simultaneous with weekly Cisplatin regimen. 44 did not have pyuria hence prevalence is at 56.86% (n=58). (Figure 1)

Urine culture was done on those who had pyuria, where three specific outcomes were identified, more than 75% of them had no growth (n= 44), while positive culture yield is at 18.96% (n=11) and only 3 had no important pathogens. More importantly, it should be noted that 50 of the 58 pyuria positives received antibiotic therapy amidst having only 11 positive culture result.

Age

The mean age of the study population is 48.94. Majority of Cervical Cancer patients belong to age group of 41-50 years old at more than 33% of the study population, which also shows that they have the most incidence of sterile pyuria at 32.76%. Meanwhile, the youngest age group (<30 years old) has the least number of cervical cancer patients at 1.96%.

Stage of Cancer

Stage 3B has the highest number of patients at 68 (66.67%) followed by stage 3A at 24 (23.53%). The least

number is stage 4B with just 1 patient. Same trend is also seen when it comes to the presence of pyuria in terms of cancer staging where 43 (74.14%) stage 3B has pyuria with 7 of them as culture positive and 33 without growth. Although, it should also be considered that there is no equal distribution of sample population among the stages.

Type of Patient

All the 102 patients included in this study are newly diagnosed cervical cancer.

Stage of Treatment

The peak incidence of pyuria is at the start of treatment at 24.14% which is followed by a decline, only to increase again on the 5th week of treatment at 22.41%. The week with the least incidence of pyuria is the last week of treatment which is close to the end of receiving pelvic radiotherapy and chemotherapy. Only those who had an incidence of pyuria were included in this demographic hence the total of 58. (Table 1)

Table 1 shows the demographic characteristics of cervical cancer patients undergoing CCRT. 58 patients out of the total 102 had pyuria while 11 out of the 58 had culture growth. The mean age of the study population was 48.94. Most of them at stage 3B, least at 4B. Peak incidence of pyuria was noted at the initiation of treatment and at the 5th week.

Prevalent organisms and Antibiotic therapy

The total number of patients with pyuria and positive urine culture was 18.97%. The highest isolates were gram negative bacteria, with K. pneumoniae (27.27%) followed by ESBL organisms (18.18%) as shown in table 2. Out of the 50 patients who received antibiotics, the most prescribed is Ciprofloxacin at 38% of the cases (n=19) followed by Fosfomycin at 14% (n=7) and then Ceftriaxone and Cefuroxime with each at 12% (n=6). The least prescribed is Meropenem and Ampicillin Sulbactam at 6% each (n=3).

Pyuria and urine culture

Chi square test was done to determine the relationship between pyuria and positive urine culture. Since 102 is more than the critical value 11.34, we reject the null hypothesis hence, there is a statistically significant relationship between pyuria and urine culture. However, it should be noted that chi-square test cannot establish a causal relationship or the odds of having a positive culture with pyuria symptoms. The study cannot also do odds ratio as this is a retrospective study and urine culture is not usually done on patients with no pyuria (Table 4).

Discussion

18.97% of patients with pyuria are culture positive that is similar to another study at 18.8% on the management of pyuria among hospital admitted patients with non-urinary infections[18]. Meanwhile, other studies analyzed the effectiveness of urinalysis parameters in predicting positive urine culture in gynecologic cancer patients receiving pelvic radiotherapy [15], where 34.9% (n=84) urine cultures were positive for growth. Another study evaluated the appropriateness of empiric treatment based on microbial urine culture data and susceptibility testing of 6950 urine where 34.5% (n = 2400) revealed positive results where 26.8% (n=214) were prescribed empiric antibiotics that failed to have appropriate coverage of the identified pathogens[19]. Worst, 14.6% of the cases (n = 117) identified microorganisms to be resistant to the antibiotics prescribed. This can be a possible scenario as antibiotic prescription precedes awaiting culture results. Currently, prescribing antibiotics is seen as outweighing the benefits over the risk for cervical cancer patients who might develop further morbidity due to pyuria.

In terms of age, the findings are similar to an Indian study on cervical cancer patients [20] where majority were in the age group of 45–54 (31.76%), followed by 55–64 (29.15%) and only one-fifth (19.87%) were below the age of 45. The idea that older women are the most affected group with cervical cancer can be due to poor awareness on cervical cancer among the older population and/or differences in healthcare-seeking behavior[21].Health education across age groups focused on screening, signs and symptoms and when to seek consult should be highlighted to ensure that these age groups receive timely and life saving intervention. Moreover, younger women should be receiving mandatory shots for cervical cancer in order to prevent it on a later age.

For the stage of cancer, a similar study of 216 patients with gynecologic malignancies undergoing external pelvic radiotherapy(EBRT) were studied periodically every week for any evidence of urinary tract infection (UTI) and they found out that patients with stage III cervical cancer (33.3%) has the most infections with 50% having repeated UTI episodes amidst antibiotic treatment[22].With a high prevalence, the Philippine setting has a high burden of cervical cancer and this can be due to low screening further compounded by the lack of basic knowledge on prevention. Prophylactic HPV vaccination has already been approved yet national or government

vaccination policy has ever been implemented as of yet [23].

All the patients included in the study were 102 newly diagnosed cervical cancer patients. It can be due to the high mortality rate associated with advance cancer. In fact, the Philippines has a mortality-to-incidence ratio of 0.51[2] and 75% of Filipino cervical cancer patients are diagnosed at advanced stages [23]. However, some studies have reported that the recurrence rate for those with stage III to IVB Cervical cancer is as high as 70% [24,25]. With all the new cases being diagnosed everyday, it is not surprising that a huge percentage of women at 81.9% have poor knowledge about cervical cancer and it's screening (85.5%)hence a meager 7.22 % had undergone screening[26]. This means that poor knowledge leads to late diagnosis hence advance stages in new cases are being detected. Hence, it is the duty of physicians to help mass education, offer screening suggestions especially to high risk women and conduct community based education.

As for the stage of treatment, the result of the study implies that pyuria should be expected on the first week of treatment hence patients should be monitored closely at the initial phase of treatment and on week 5 of their treatment in order to enhance timely interventions and prevent morbidity associated with pyuria. Moreover, the result of the study also begs to question whether the administration of antibiotics is judicious enough especially at the initial phase of treatment. The study on pyuria among cervical cancer patients are scarce to rare, hence, related published literature specifically studying the weekly treatment and its correlates have no yield in any online search engine.

In terms of bacterial growth among the 11 culture positives, it should be noted that in the institution where this study took place, it is common practice to prescribe antibiotics to cervical cancer patients with sterile pyuria once they undergo CCRT. This means that while waiting for urine culture results, antibiotic management has been initiated regardless of the results. This is to prevent possible morbidities associated with the infection especially if urinalysis shows any of the following: positive leucocyte esterase, positive nitrite, and elevated bacterial counts. Moreover, patient may not return for follow up at the oncology clinic and since physicians deal with a huge number of patients, individually checking culture results is challenging. Pyuria was most strongly associated with infection caused by gram-negative bacilli[27]. In a similar Ethiopian study[28] on cancer patients with urinary tract infections during treatment, where majority are cervical cancer patients (36.6%), (6.3%) were culture positive cases with Escherichia coli (44.4%) as the most isolated followed by Klebsiella pneumoniae (22.2%) and some ESBL organisms were also identified and tagged as main sources of drug resistance. This is similar to the other findings [15] when Escherichia coli was also the most common isolate in the culture of 19/134 (22.6%) women undergoing pelvic radiotherapy.

For the antibiotics prescribed to the 50 patients, Ciprofloxacin was the most prescribed antibiotics amidst current guideline on sterile pyuria by the Philippine Society for Microbiology and Infectious Diseases (2013) says that quinolones like Ciprofloxacin should never be used as first line of treatment due to Quinolones having high efficacy and high propensity for collateral damage.In terms of antibiotic management[28], there is a high resistance rates to Ampicillin 12 (66.7%), Augmentin 11(61.1%), and Ceftriaxone 10 (55.6%) while a low resistance rate was detected for Meropenem 2(11.1%), and Ciprofloxacin 3 (16.7%). Such result is opposite to the findings of another study[15] where 23.8% of pathogens were resistant to trimethoprim/sulfamethoxazole, 16.7% were resistant to ciprofloxacin, and 11.1% were resistant to nitrofurantoin. In the current study, only ciprofloxacin, ceftriaxone an meropenem were prescribed. Recently, resistance to fluoroquinolones and trimethoprim-sulfamethoxazole (TMP-SMX) has been on the increasing among common UTI pathogens[29] with an increasing prevalence of extended-spectrum β-lactamase and other multi-drug resistant organisms[30,31,32]. Several strategies have been suggested on how to minimize the misuse and overuse of antibiotics in order to avoid increasing antibiotic resistance [33,34,35]; like identifying factors beyond the infection itself that may affect antibiotic treatment. Hence, it is still important to consider that not all pyuria in cervical cancer patients undergoing CCRT should be treated with antibiotics. Culture results and timing of pyuria should be considered. This results show that physicians must always rely on guidelines by waiting on culture studies to check which antibiotic is the identified bacteria susceptible.

Lastly, there is a statistically significant relationship between pyuria and urine culture, however a causal relationship cannot be established. Meanwhile,a recent study[36] defined the relationship of pyuria and positive bacterial growth in urine culture in 46,127 patients in acute care. Their study concluded that pyuria alone did not provide adequate diagnostic accuracy to predict bacteriuria hence antibiotic treatment based on urine analysis alone is insufficient. Moreover, a study[27] stated that pyuria is less strongly correlated with CAUTI and it should not be used as the sole criterion to initiate antibiotics.

CONCLUSION

This study concludes that more than half of the patients undergoing CCRT will have pyuria is seen mostly in patients aged 41-50 years old, with stage 3B cervical cancer and who are starting their treatment. Most patients will have no growth in their urine culture however. Direct correlation of pyuria and urine culture is not established hence urine culture result is needed prior to initiation of antibiotics.

RECOMMENDATIONS

The researchers recommend future studies on the following: a) Correlating antibiotic sensitivity analysis to the prescribed antibiotics, b) explore outcomes of those treated with antibiotics and those who were not prescribed antibiotics regardless of culture status c) correlate specific urinalysis parameters to culture outcomes, d) Prospective studies could be done to establish a causal relationship by odds ratio between pyuria and positive urine culture through adding urine culture on patients without pyuria and e) Recurrent pyuria on patients with recurrent cervical cancer. This study also recommends each hospitals treating cervical cancer patients to have a registry which is a specialized online hospital data base that contains all labs, diagnostics, biopsy, treatment and outcomes for easy access of accurate and available data for the continuous treatment of patients.

The results of this present study can be used by clinicians to decide on their judicious use of antibiotics on cervical cancer patients undergoing CCRT. Comparing to other studies, the present study considered the week of treatment and focused on the higher stages of the disease, which is not found in other studies.

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FIGURES

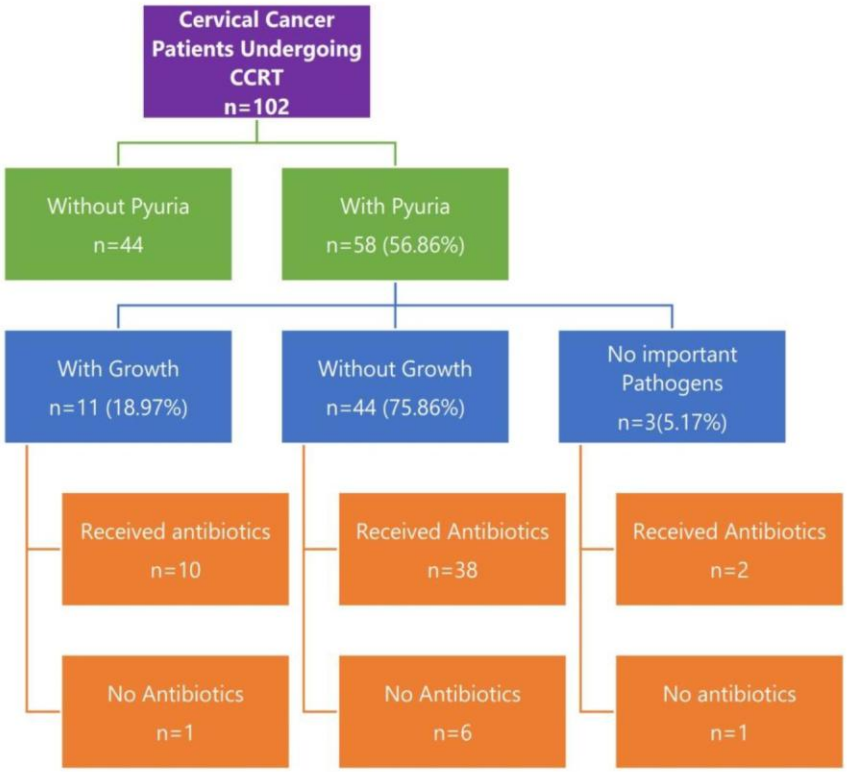

Figure 1. Pyuria among Cervical Cancer Patients undergoing Concurrent Chemoradiotherapy at a tertiary government hospital from 2018 to 2020.

Table 1. Demographic characteristics of Cervical Cancer patients while undergoing Concurrent Chemotherapy and Radiotherapy from 2018-2022 at a government tertiary hospital.

Demographic Characteristics	Total, n (%)	Sterile Pyuria	Culture Status			Antibiotics
	f(%)	f(%)	With Growth	No Growth	No Important Pathogens	Prescribed with antibiotics
Age	Mean ± SD	48.94 ± 11.84				
<30 years old	2 (1.96)	1 (1.72)	0	1	0	1
31-40 years old	22	16 (27.59)	2	13	1	12
41-50 years old	34	19 (32.76)	5	14	0	17
51-60 years old	25	11(18.97)	3	6	1	10
>60 years old	19	11(18.97)	1	10	1	10
Total	102	58	11	44	3	50
Stage of Cancer						
Stage 3A	24(23.53	10 (17.24)	3	7	0	9
Stage 3B	68(66.67	43 (74.14)	7	33	3	37
Stage 4A	9(8.82)	4 (6.90)	1	3	0	3
Stage 4B	1 (0.98)	1(1.72)	0	1	0	1
Total	102	58	11	44	3	50
3. Type of Patient						
New	102	58(100)	11	44	3	50
Recurrent	0	0	0	0	0	0
Total	102	58	11	44	3	50
4. Stage of Treatment						
Week 1	14 (24.1)	14 (24.1)	3	10	1	11
Week 2	10 (17.2)	10 (17.2)	2	8	0	8
Week 3	6(10.3)	6(10.3)	1	4	1	5
Week 4	7(12.1)	7(12.1)	1	6	0	6
Week 5	13(22.4)	13(22.4)	3	9	1	13
Week 6	6(10.3)	6(10.3)	1	5	0	5
Week 7	2(3.4)	2(3.4)	0	2	0	2
Total	58	58	11	44	3	50

Table 2. The prevalent microorganisms found in the urine culture of cervical cancer patients with pyuria.

Microorganisms	Type	f	%
Pseudomonas paucimobilis (-)	Gram Negative	1	9.09
Klebsiella pneumoniae (-)	Gram Negative	3	27.27
Proteus mirabilis(-)	Gram Negative	1	9.09
Enterobacter cloacae (-)	Gram Negative	1	9.09
Streptococcus agalacticus(+)	Gram Positive	1	9.09
Serratia marcescens(-)	Gram Negative	1	9.09
Escherichia coli (-)	Gram Negative	1	9.09
ESBL (E.COLI and Klebsiella Oxytoca)	Gram Negative	2	18.18
		11	**100**

Table 3. Antibiotics Prescribed to Cervical Cancer Patients with Pyuria

Antibiotics	Frequency	Percentage
Ciprofloxacin	19	38
Fosfomycin	7	14
Ceftriaxone	6	12
Cefuroxime	6	12
Ofloxacin	6	12
Ampicillin Sulbactam	3	6
Meropenem	3	6
Total	50	100

Table 4. Chi Square test of Independence between pyuria and urine culture among cervical cancer patients undergoing CCRT.

Chi-Sq	p-value	x-crit	significance	Decision
102	5.77E-22	11.34487	yes	REJECT NULL

*Significant at 0.01 level of significance