

IIIB-Plus: A New Classification Recommended for Stage IIIB Cervical Cancer Patients with Renal Impairment

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Abstract

Objective: This study was designed to define the differences between Stage IIIB cervical cancer patients with and without renal impairment (RI), particularly with regard to the pathology results, laboratory values, therapies, and prognoses, in order to justify the need for separate classifications for these two different patient types. **Materials and Methods:** A retrospective cohort technique was used to evaluate consecutive Stage IIIB cervical cancer patients from July 2010 to July 2015. The data collected included the age, parity, cancer cell type, pelvic wall involvement, hydronephrosis degree and bilateral involvement, laboratory values (urea, potassium, and creatinine), treatment modalities, 3-month postradiation treatment response, hospital stay duration, and 1-year survival rate. **Results:** The study patients included 102 Stage IIIB cervical cancer patients with RI and 204 individuals without RI. The results showed significant differences between individuals with and without bilateral pelvic wall involvement (100% vs. 68.1%, respectively), hydronephrosis degree (severe hydronephrosis incidences: 69% vs. 3.9%, respectively), bilateral hydronephrosis (96.5% vs. 6.9%, respectively), median urea level (148 vs. 22 mg/dl, respectively), median creatinine level (8.0 vs. 0.8 mg/dl, respectively), and median potassium level (5.8 vs. 3.9 mEq/L, respectively). The hazard ratio was 3.07 for the survival analysis. **Conclusion:** Cervical cancer patients with RI are faced with worst prognosis, and their treatment modalities are limited due to their renal comorbidities, resulting in lesser type of therapy modalities (such as chemotherapy procedure prohibition), longer hospital stays, and a lower survival rate. Therefore, a new classification for cervical cancer patients with kidney impairment, named Stage IIIB-plus, should be considered.

Keywords: Cervical cancer, IIIB, laboratory, pathology, renal impairment, therapy

INTRODUCTION

Cervical cancer is a major threat to women's health. In 2012, the World Health Organization reported more than 528,000 new cases of cervical cancer, with 90% of them occurring in developing countries. In addition, more than 1 million women are currently living with this disease, but most of these cases remain undiagnosed or undertreated. Moreover, in 2012, as many as 266,000 women died from cervical cancer, and 87% of these women were from developing countries. It is projected that the cervical cancer mortality rate will increase significantly (17%) in the next 6 years.^[1-4] In Indonesia, cervical cancer is the second-most frequently diagnosed cancer, with a prevalence of 34.4%.^[5] The 5-year rate of survival from cervical cancer at Stages I, II, III, and IV was 50%, 40%, 20%, and 0%, respectively.^[6] The 10-year (2008–2018) database from Dr. Cipto Mangunkusumo General Hospital, Indonesia, which is the national referral hospital, indicated that 37.7% of

these patients seek medical care during the beginning stages of cervical cancer, whereas the rest are already in advanced stages (III and above) before seeking medical attention.^[7] According to the International Federation of Gynecology and Obstetrics (FIGO), the cervical cancer stage classifications are based on the local and regional spreading of the mass. Stage IIIB is defined as cervical cancer spreading into the pelvic wall or cervical cancer associated with hydronephrosis or renal impairment (RI).^[1,8-10] This stage (IIIB) is accompanied by urological complications, and a higher stage signifies a higher degree of complications. Possible urological complications include urinary tract infections, vesicovaginal fistulas, ureter

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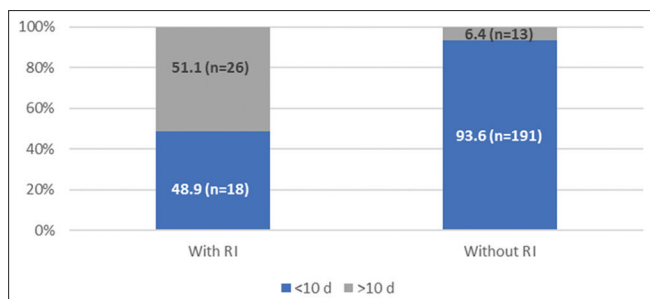


Figure 1: Comparison of the hospital stay durations (%) of the study population (RI: Renal impairment)

obstructions, hydronephrosis, and renal failure, and any of these can increase the morbidity and mortality of advanced stage cervical cancer patients.^[8,9,11,12] The aim of this study was to determine the demographic and clinical profiles of two Stage IIIB cervical cancer patient groups: those with and without RI. These data, including the pathology results, laboratory values, therapies, and prognoses, were compared between these two groups of patients, both in IIIB stage, in order to justify a new classification for cervical cancer with RI, i.e., IIIB-plus.

MATERIALS AND METHODS

From July 2010 to July 2015, a consecutive retrospective cohort technique was used to gather data from Stage IIIB cervical cancer patients with and without RI who were diagnosed and treated at the Division of Gynecology Oncology of Dr. Cipto Mangunkusumo General Hospital in Indonesia. The study inclusion criteria were completed medical records in database, the cause of RI was mass suppression at the pelvic wall or lymph node metastasis, and patients undergoing radiotherapy treatments during the 5-year study period. The study exclusion criteria were patients with a previous history of pelvic surgery, congenital urinary tract malformation, retroperitoneal fibrosis, and/or kidney stones in the urethra.

The Stage IIIB cervical cancer patients were divided into two groups as follows: those with and those without RI. For the purposes of this study, RI was defined as the presence of renal abnormalities, whether structural or functional, which later caused renal dysfunction. The renal function status was recorded when the patient was admitted to the hospital. Detailed patient data were obtained from the medical records, including the demographic information, age, parity, cancer cell type, mass association with the pelvic wall, hydronephrosis degree and bilateral involvement status, laboratory values (urea, potassium, and creatinine), urine diversion therapy modality, chemotherapy, radiotherapy, treatment response after 3 months of radiotherapy, hospital stay duration, and 1-year survival status. The collected data were analyzed using the Statistical Package for the Social Sciences version 10.0 (SPSS Inc., Chicago, IL, USA) to determine the *P* value, which was compared with the α value (0.05) with a 95% confidence interval (95% CI). If

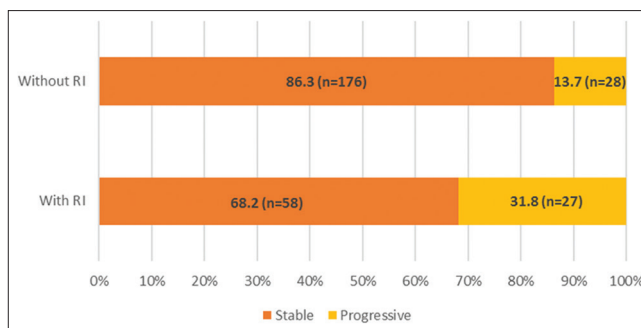


Figure 2: Comparison of the 3-month posttherapy responses of the study population (RI: Renal impairment)

Table 1: Demographic characteristics of the study population

Characteristics	With RI (%)	Without RI (%)
Age (years)	51.9±8.7	52.6±8.9
Marital status		
Married	85 (100)	203 (99.5)
Not married	-	1 (0.5)
Socioeconomic status		
Low	69 (81.2)	127 (62.3)
Middle	11 (12.9)	64 (31.4)
High	5 (5.9)	13 (6.3)
Parity		
Nulligravida	-	1 (0.5)
Primigravida	10 (11.8)	13 (6.4)
Multigravida	55 (64.7)	137 (67.2)
Grand multipara	20 (23.5)	53 (25.9)

RI: Renal impairment

Table 2: Clinical characteristics of the study population

Characteristics	With RI (%)	Without RI (%)	<i>P</i>
Cancer cell type			
SCC	71 (83.5)	167 (81.9)	0.343
ASC	4 (4.7)	17 (8.3)	
AC	5 (5.9)	15 (7.4)	
Others	5 (5.9)	5 (2.5)	
Pelvic wall involvement			
None	-	-	<0.001
Unilateral	-	65 (31.8)	
Bilateral	85 (100.0)	139 (68.1)	
Lymph node involvement			
No	67 (78.8)	189 (92.6)	<0.001
Yes	18 (21.2)	15 (7.35)	

RI: Renal involvement, SCC: Squamous cell carcinoma, ASC: Adenosquamous carcinoma, AC: Adenocarcinoma

P < 0.05, the cross-sectional data exhibited a statistically significant relationship. Ethical approval for this study was obtained from Dr. Cipto Mangunkusumo General Hospital Ethical Committee (number 1076/UN2.F1/ETIK/2015). Informed consent was not needed for this study because the research was not invasive, i.e., only the patients' conditions were observed.

Table 3: Laboratory results of the study population

Laboratory test	n	Median (minimum-maximum)	P
Urea (mg/dl)			
With RI	85	148.0 (20.0-597.0)	<0.001
Without RI	204	22.0 (5.0-74.0)	
Creatinine (mg/dl)			
With RI	85	8.0 (0.8-33.7)	<0.001
Without RI	204	0.8 (0.2-3.8)	
Potassium (mEq/l)			
With RI	85	5.8 (2.3-8.9)	<0.001
Without RI	204	3.9 (2.8-5.5)	

RI: Renal impairment

Table 4: Hydronephrosis symmetry status of the study population

Patients	None, n (%)	Unilateral, n (%)	Bilateral, n (%)	P
With RI	1 (1.2)	2 (2.4)	82 (96.5)	<0.001
Without RI	179 (86.8)	13 (6.4)	12 (6.9)	
Total	180 (61.6)	15 (5.2)	94 (33.2)	

RI: Renal impairment

Table 5: Hydronephrosis degrees of the study population

Patients	None, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	P
With RI	1 (1.2)	2 (2.4)	23 (27.4)	58 (69.0)	<0.001
Without RI	179 (87.7)	13 (6.4)	4 (2.0)	8 (3.9)	
Total	180 (62.5)	15 (5.2)	27 (9.4)	66 (22.9)	

RI: Renal impairment

Table 6: Therapy modalities of the study population

Therapy	Yes, n (%)	No, n (%)	P
Urine diversion			<0.001
With RI	67 (78.8)	18 (21.2)	
Without RI	1 (0.5)	203 (99.5)	
Total	68 (23.5)	221 (76.5)	
Chemotherapy			<0.001
With RI	0 (0)	85 (100)	
Without RI	106 (78.8)	70 (39.8)	
Total	112 (44.5)	138 (55.3)	
Radiotherapy			0.022
With RI	83 (97.6)	2 (2.3)	
Without RI	200 (98.5)	3 (1.5)	
Total	279 (96.9)	9 (3.1)	
Dialysis			<0.001
With RI	49 (61.2)	31 (38.8)	
Without RI	0 (0)	189 (100)	
Total	49 (18.3)	220 (81.7)	

RI: Renal impairment

RESULTS

From July 2010 to July 2015, there were 1272 Stage IIIB cervical cancer patients, but only 961 patients were eligible for this study.

From the latter group, 102 patients had RI, and they were all included in the RI group. However, only 85 patients completed this study and had complete data. In addition, 204 of the other eligible patients were chosen for the comparison group (no RI).

Comparison of the patient demographics showed that the ages of the two groups were not significantly different, with mean ages of 51.9 years old for the patients with RI and 52.6 years old for those without [Table 1]. Almost all the patients were married (99.7%). Most of the patients in both groups were of low socioeconomic status and multigravida. The clinical data collected included the cancer cell type, pelvic wall involvement, and lymph node involvement. The most frequently diagnosed cancer cell type was squamous cell carcinoma (SCC) in both groups (83.5% of the patients with RI and 81.9% of the patients without). The bilateral pelvic wall involvement rate was 100% for the RI patients and 68.1% for those without RI. Clinical characteristics of the study population are presented in Table 2.

The laboratory data collected from each group included the urea, creatinine, and potassium levels. The means of all of these results (urea, creatinine, and potassium) were higher in the patients with RI ($P < 0.001$ for all). In both groups, the hydronephrosis status was measured by the bilateral involvement and degree. Of the patients with RI, 96.5% had bilateral hydronephrosis, whereas 86.8% of the patients without RI had no hydronephrosis. Laboratory results and hydronephrosis symmetry status of the study population are shown in Table 3 and Table 4, respectively.

A few of the RI patients had none to a moderate degree of hydronephrosis, while 69.0% of them had a severe degree of hydronephrosis. The percentage of patients without RI with no hydronephrosis was 87.7%. The therapy modalities used to treat the study patients included urine diversion, chemotherapy, radiotherapy, and dialysis. The patients with RI tended toward undergoing urine diversion surgery, radiotherapy, and dialysis (78.8%, 97.6%, and 61.2%, respectively); however, none of them underwent chemotherapy. None of the patients without RI underwent dialysis. Hydronephrosis degrees and therapy modalities of the study population are presented in Table 5 and Table 6, respectively.

The hospital stay duration of the patients with RI tended to be longer. Only 6.4% of the patients with hospital stays longer than 10 days were patients without RI. The P values of the hospital stay duration calculations were all < 0.001 [Figure 1]. After 3 months of radiotherapy, the patients were followed up in order to monitor their therapy responses (stable or progressive). In both groups, most of the patients had stable responses, but the progressive response proportion in the RI patients was higher (31.8%). At the end of the 1-year follow-up, 37 patients had died, including 24.7% (21 out of 85) of the patients with RI and 7.8% (16 out of 204) of the patients without RI [Figure 2]. The hazard ratio was 3.07 (95% CI = 1.60–5.89).

DISCUSSION

The demographic data, including the age, marital status, socioeconomic status, and parity, were not significantly different between the two groups. The mean ages of the patients with and without RI were 51.9 years and 52.6 years, respectively. These results correspond with those of a previous study, suggesting that most cervical cancer patients are diagnosed between 46 and 55 years of age.^[8] The low socioeconomic status percentage rates of the patients with and without RI were 82.9% and 63.4%, respectively, which corresponds with the results of another study showing a strong relationship between cervical cancer and low socioeconomic status factors, such as low educational level, financial conditions, and a lack of health-care access.^[13]

The majority of the cervical cancer types in both groups constituted SCC, which corresponds with the reported prevalence of SCC cases.^[8,14] Moreover, all the RI patients had bilateral pelvic wall involvement. This finding suggests that those patients with RI must have had ureter malfunctions caused by suppression via mass enlargement or lymph node invasion.

The urea, creatinine, and potassium laboratory results were significantly different between the two groups, with the RI patients exhibiting higher values. These substances are normally removed from the body by the kidneys; therefore, malfunctions in these organs will result in increases in these values.^[15] Almost all the patients with RI (96.5%) exhibited bilateral hydronephrosis, whereas almost all the patients without RI (86.8%) exhibited no hydronephrosis. RI is often found in cervical cancer patients with hydronephrosis, in which a urine outflow obstruction can result in the distention of the renal calyces.^[8] This obstruction has a strong relationship with the patient prognosis, with hydronephrosis being an independent predictor of a cervical cancer patient's survival.^[15] Moreover, the results indicated that the patients with bilateral hydronephrosis had worse prognoses than the patients with unilateral hydronephrosis. Therefore, the FIGO cervical cancer classification regarding the symmetry of hydronephrosis may be reconsidered.^[15] Some of the therapies available for treating cervical cancer patients include surgical urinary diversion, chemotherapy, radiotherapy, and dialysis. Renal malfunctions should first be addressed using urinary diversion or dialysis because chemotherapy and radiotherapy can make the malfunction worse.^[16] In this study, the majority of the RI patients underwent surgical urinary diversions (78.8%), whereas only 1% of the patients without RI underwent urine diversion surgeries due to hydronephrosis. None of the RI patients (100%) underwent chemotherapy, but 78.8% of the patients without RI did.

The hospital stay durations of the majority of the RI patients (51.1%) were longer than 10 days; however, 93.6% of the patients without RI had hospital stays shorter than 10 days. This is likely due to the fact that the RI patients underwent more complex treatments, beginning with common

recovery times and moving toward special therapies, such as surgical urinary diversions and dialysis treatments.^[17] The 3-month postradiotherapy responses were different between the two study groups. In the patients with RI, 31.8% had progressive responses, whereas 86.3% of the patients without RI had stable responses. The lower progression-free survival rates in the cervical cancer patients with hydronephrosis^[8] were likely due to the presence of a renal comorbidity or obstructive uropathy^[18] that required more difficult therapy for its confined modality. The 1-year survival rate of the Stage IIIB cervical cancer patients with RI was 24.7%, with a hazard ratio of 3.07. The higher the degree of a cancer, the lower the survival time, with Stage III cervical cancer having a correspondingly low survival rate.^[19] Based on the results of this study, there is a clinical obligation to require the more complex involvement of specialists (internists, urologists, renal hypertension experts, clinical nutritionists, and palliative experts) for the management of cervical cancer patients with kidney disease. Moreover, a new classification for cervical cancer patients with RI, IIIB-plus, may be considered. Comparison of the hospital stay durations and the 3 month post-therapy responses are presented in Figures 1 and 2, respectively.

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Conflicts of interest

There are no conflicts of interest.

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