Original Research Article

IMPACT OF HYDROURETERONEPHOSIS ON PROGNOSIS OF STAGE IIIB CERVICAL CANCER

ABSTRACT

Aims: To compare differences in response to Chemo-radiation in patients with and without hydroureteronephrosis in patients with Stage IIIB cervical cancer.

Study design: Hospital-based, retrospective cohort study.

Place and Duration of Study: Samples were collected from the Department of Gynecological Oncology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India, between 1st January 2015 and 31st December 2015.

Methodology: A retrospective analysis of all patients presenting to the outpatient department of Dr. Bhubaneshwar Borooah Cancer Institute (BBCI), Guwahati with cervical cancer Stage IIIB (The International Federation of Gynecology and Obstetrics 2014 staging) between 1st January 2015 to 31st January 2015 was done. Eligible patients were divided into two groups, the study group was patients with hydronephrosis, and the control group patients were without hydronephrosis. Both the groups were compared based on demographic profile, cancer cell type, treatment duration, radiotherapy dose, chemotherapy, residual disease after 6weeks, 5-year overall survival.

Results: Total number of patients with Cervical Cancer Stage IIIB included in the study was 87, out of which 20 patients had Hydronephrosis (study group) and 67 patients without hydronephrosis (control group). The Mean age of patients in the study group was 53 years(44- 62) and in the control group was 51years(41-61). Among patients with hydronephrosis, 55% underwent urinary diversion procedures. The mean 5-year overall survival is 28.4 months (Median – 19.3months) in patients with hydronephrosis and 55.4 (Median-66.5 months) in patients without hydronephrosis (P= 0.001).

Conclusion: The presence of hydronephrosis in patients with Cervical cancer is a predictor of poor outcome. Thus, special mention in staging should be considered about the presence of hydronephrosis. The management should be done by a multi-disciplinary team and patient counseling should be done thoroughly.

Keywords: Hydroureteronephrosis, Hydronephrosis, Cervical Cancer, Stage IIIB, Overall survival.

1. INTRODUCTION

Cervical cancer is the fourth most common and fourth leading cause of cancer death among women in the world [1] India contributes to 1/5th worldwide cases of cervical cancer. Cervical cancer is second leading site among women of North-East India with Age-adjusted incidence rates (AAR) of 10.7 per 100,000 population. Only one-fourth of the cases are diagnosed at localized stage. 63.5% of women are diagnosed with distant metastasis.[2] Cervical Cancer Stage IIIB (The International Federation of Gynecology and Obstetrics 2014 staging) is defined as extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause) and the recommended management option is Concurrent Chemo-radiation (CCRT). [3] The survival of such patients is poor due to advanced stage, interruption of chemotherapy due to deranged kidney functions, poor performance status. However, whether the correction of kidney parameters result in improved outcome is yet to be known. This is the first study done in North-East India to study the impact of hydroureteronephrosis/ hydronephrosis (HDN) on prognosis of Stage IIIB Cervical Cancer.

2. MATERIAL AND METHODS

A retrospective analysis of patients diagnosed with Stage IIIB Cervical Cancer (FIGO 2014) from 1st January, 2015 to 31st December, 2015 was done. Patients with congenital anomalies of renal system, renal/ureteric calculus, pelvic surgery, recurrence or relapse of carcinoma cervix were excluded from the study. The eligible patients were divided in two groups based on absence or presence of HDN. After initial workup, treatment modality was decided in multi-disciplinary tumor board. Urinary diversion procedure, namely Double J (DJ) stenting, per-cutaneous nephrostomy was done in patients with HDN prior to commencement of treatment. Curative treatment was given with External-Beam Radiotherapy of 2.5Gy/day, 5 days a week in 25 fraction with concurrent weekly chemotherapy (Cisplatin/Carboplatin) followed by vaginal brachytherapy 6.5-7Gy/week in 3-4 fractions. Palliative radiotherapy was given as 3Gy/day in 10 fractions and palliative chemotherapy consisted 3-weekly Carboplatin and Paclitaxel for 6 cycles. Patients were followed up after 6weeks, 1-year, 5-year of completion of treatment. Both the groups were compared based on demographic profile, cancer cell type, treatment duration, radiotherapy dose, chemotherapy, residual disease after 6weeks, 5-year overall survival. Overall Survival was calculated from the day of presentation till last follow -up or death. Overall survival rates were calculated using Kaplan Meier plots of time. Cox regression model was used to estimate hazard ratio (HR), along with a 95% profile-likelihood confidence interval (CI).*P* value < 0.05 was considered statistically significant.

3. RESULTS

Total number of patients with Stage IIIB Cervical Cancer in the study period 199. Number of patients eligible for analysis were 87, out of which 20 patients had Hydronephrosis (study group) and 67 patients without hydronephrosis (control group).

3.1 PATIENT CHARACTERISTICS

The Mean age of patients in study group was 53 years (44- 62) and in control group was 51years (41-61). More than 2/3rd of the patients belonged to ECOG (Eastern Cooperative Oncology Group Performance Status) 1 on presentation.

Table 1 represents the presenting complaints of women in both the groups. Majority of the women presented with post-menopausal bleeding as the chief complaint 90% in study group and 74.6% in control group.

Table 1: Showing chief complaints of patients at presentation

Presenting symptoms	Study group (with HDN) Number (%)	Control group (without HDN) Number (%)
Bleeding Post-menopausal bleeding Heavy menstrual bleeding Post-coital bleeding	 18(90) 2 (10) 0 (0)	 50(74.6) 9 (23.4) 1 (1.5)
White discharge per-vagina	0(0)	7(10.4)
Chronic pelvic pain	4(20%)	0(0%)
Swelling of lower limbs	1(5%)	0(0%)

Study group patients presented with chronic pelvic pain in 4 (20%) patients and swelling of lower limbs in 1(5%) patient. The most common histological type was Squamous cell carcinoma (Non-keratinizing Large Cell) in both the groups (85% in study group, 67.2% in control group). The patients with hydronephrosis had significantly more anemia, higher levels of pre-treatment urea and creatinine as compared to those without hydronephrosis.

Among 20 women with hydronephrosis, 12 (60%) had mild, 7 (35%) had moderate and 1(5%) had severe degree of hydronephrosis. 14 (70%) women had unilateral and 6 (30%) had bilateral hydronephrosis. Urinary diversion procedure was done prior to commencement of treatment in 55% cases of study group, either Double J (DJ) stenting (45%) or per-cutaneous nephrostomy (PCN) (10%). However, 45% of women with hydronephrosis did not undergo any intervention.

3.2 TREATMENT CHARACTERISTICS

The treatment characteristics of both the groups is tabulated in Table 2. All patients in the control group received radical treatment whereas in study group 75% patients were given radical treatment. Mean treatment duration from start of external radiation to completion of brachytherapy was 8.2±4.2 weeks (range 1.8-17weeks) in study group and 9.9±2.9 weeks (range 6.8-19.5 weeks) in control group (P =0.04). Mean radiotherapy dose to the pelvis was 57.6±19.74 Gy and 72.35±2.52 Gy in study group and control group respectively (P <0.05)

Table 2: Showing treatment characteristics of patients

Treatment characteristics	Study group (with HDN) Number (%)	Control Group (without HDN) Number (%)	*P* value
Treatment intent (Radical)	15 (75)	67 (100)	-
Treatment intent (Palliative)	5 (25)	0 (0)	-
Concurrent Chemotherapy - Nil - Cisplatin - Carboplatin	 6 (30) 5(25) 9 (45)	 0 (0) 27 (40) 40 (60)	-
Mean total radiotherapy dose to pelvis (Gy)	57.6±19.74	72.35±2.52	<0.05
Mean treatment duration (weeks)	8.2±4.2 (Range 1.8-17)	9.9±2.9 (Range:6.8-19.5)	0.04

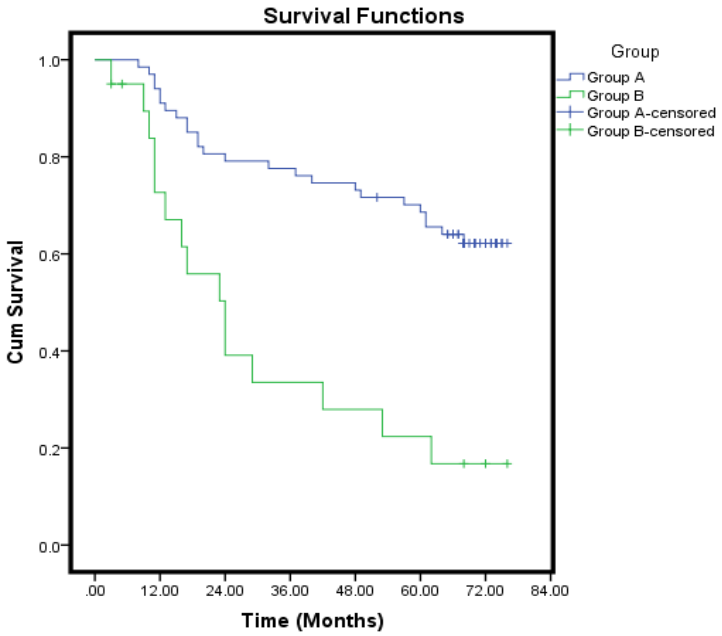
3.3 OUTCOME

The response to treatment at 6weeks in both group of patients is tabulated in Table 3. The risk of death is 6.5 times more if there is presence of residual disease after 6weeks of completion of definitive therapy (HR- 6.527, 95% CI 3.348-12.727, *P* =0.001). The mean 5-year overall survival is 28.4 months (Median – 19.3months)in patients with hydronephrosis and 55.4 (Median-66.5 months) in patients without hydronephrosis. The 5-year OS is significantly worse in patients with hydronephrosis (*P* <0.05). Graph 1 shows Kaplan Meier survival curve of study and control group.

Table 3: Showing response to treatment after 6weeks

Response to treatment (after 6 weeks)	Study group (with HDN) Number (%)	Control Group (without HDN) Number (%)	*P* value
Complete	5 (25)	51 (76.1)	<0.0001
Residual disease present	15 (75)	16 (23.9)	

Graph 1: Showing Overall Survival (5years)



The survival of patients at 1 years, 3year, 5years, as shown in Table 4 is significantly decreased in women with hydronephrosis (72.6%, 33.5%, 25% respectively) as compared to those without hydronephrosis (94%, 77.6%, 62.7% respectively) (p value <0.001). There is dramatic rise in death among patients with hydronephrosis at the end of 3years of treatment (33.5 %).

Table 4: Showing survival percentage of both groups.

Survival percentage	1 year	3 years	5 years	*P* value
Study Group (%)	72.6	33.5	25	<0.001
Control Group (%)	94	77.6	62.7	

3.4 PREDICTORS OF OUTCOME IN STUDY GROUP

On multivariate analysis, the predictors of poor outcome in patients with hydronephrosis, as shown in Table 5, were bilateral hydronephrosis, para-aortic nodal involvement, residual disease after treatment. Treatment of hydronephrosis does not improve the outcome of patients.

Table 5: Predictors of outcome in patients with Hydronephrosis.

Variable	Hazard Ratio	95% Confidence Interval		*P* value
		Lower limit	Upper limit	
Age (<50years/>50years)	0.5	0.1	1.4	0.21
Pelvic lymph nodes	1.5	0.7	3.1	0.23
Para-aortic lymph nodes	**3.1**	1.1	9.0	**0.03**
Urinary diversion procedure	1.0	0.3	2.9	0.92
Residual disease after treatment (6weeks)	**6.5**	3.3	12.7	**<0.001**
Hydronephrosis	**3.7**	1.9	7.2	**<0.0001**
Unilateral	**3.0**	1.4	6.3	**0.003**
Bilateral	**8.1**	2.9	22.3	**<0.001**

4. DISCUSSION

The survival of patients with Stage IIIB cervical cancer as demonstrated by various studies is dismal. Our study further consolidates this observation. The effect of age on survival of patients with hydronephrosis was documented by *N. B. Elizabeth et al* [4]. The 5-year overall survival was significantly poor in patients > 50years of age as compared to those ≤50years. In our study no association was found between age and overall survival of women with hydronephrosis.

The morbidity associated with hydronephrosis among 20 patients in our study was reported in the form of chronic pelvic pain in 4 (20%) patients and swelling of lower limbs in 1(5%) patient. *K Patel et al* reported hydronephrosis-related morbidity such as pain, urinary tract infections, nausea and vomiting, renal failure, and urinary tract bleeding.[5]

The prognosis of patients with bilateral hydronephrosis was worse as compared to those with unilateral hydronephrosis in our study. The difference in survival was not seen studies by *Goklu et al* [6] and *Rose et al* [7]. However, analysis by *T S Pradhan et al* showed significant difference in survival of patients with bilateral and unilateral hydronephrosis.[8] Thus, authors recommended to mention symmetry of hydronephrosis in staging.

The management of patients with hydronephrosis is challenging because of several factors such as lack of guidelines, no consensus among experts that relief of obstruction improves the prognosis, no recommended procedure of choice for urinary diversion, dilemma among treating physicians regarding offering radical treatment to all patients after diversion procedure or focusing on palliative treatment for all. In our study, at the end of 5 years, 20.2% of patients with intervention and 25% patients without intervention were alive. Thus, the overall survival is not statistically different with or without urinary diversion procedure. *Lapitan MC et al* reported that urinary diversion procedure improved short-term survival markedly (at 6 months) without compromising the quality of life however, there was no difference in survival at 12 months. [9] Contradictory findings were documented *by Rose et al,* median PFS for patients without hydronephrosis was 46.6months, with hydronephrosis (diversion procedure done) was 17 months, with hydronephrosis (diversion procedure not done) was 10 months. [7]

There is vast literature to support the fact that hydronephrosis is a harbinger of death. In our study, the mean 5-year survival of patients with hydronephrosis was 28.4 months whereas that of patients without hydronephrosis was 55.4 months. The loss of 27 months of life is solely due to the presence of hydronephrosis.

Thus, the decision regarding which group of Stage IIIB patients with hydronephrosis requires diversion procedure, the choice of diversion procedure, and which group should be receive radical treatment should be taken by a multi-disciplinary team. The patients should be informed in details

about the prognosis of their disease. Special emphasis should be given on the complications associated with the each of the diversion procedures and its unproven impact on the outcome of the disease.

5. CONCLUSION

One of the most important predictors of survival among patients with cervical cancer is stage. Among Stage IIIB patients, presence of hydroureteronephrosis should be considered as important prognostic factor and should be mentioned distinctly. Management of patients hydroureteronephrosis should be streamlined based on evidence-based guidelines. The poor predictors of outcomes among this subset of patients such as performance status, severity of hydroureteronephrosis should be highlighted. Identification of cohort of patients who will be relieved by diversion technique followed by radical treatment is crucial. Individualised approach is ideal after thorough discussion in multidisciplinary tumour board. Patient and attendants should be counselled regarding poor prognosis and informed consent should be taken prior to commencement of therapy.

CONSENT AND ETHICAL APPORVAL

Patient consent and ethical approval has been taken as per Institution's ethical committee and is preserved by the author.

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APPENDIX

HDN= Hydronephrosis/Hydroureteronephrosis

ECOG= Eastern Cooperative Oncology Group

FIGO= The International Fegeration of Gynecology and Obstetrics

HR= Hazard Ratio