Original Article

Para-Aortic Nodal Involvement: A Significant Determinant of Treatment-Related Toxicity in Cervical Cancer Patients

Abstract

Cervical cancer treatment is associated with significant early and late treatment-related toxicity. Understanding the treatment-related factors that contribute to higher toxicity is key to improving patient outcomes and long-term quality of life. Data from 435 patients with carcinoma of the cervix who received radical treatment were retrieved from the hospital records of a tertiary care cancer center. The required information was extracted and recorded in predesigned study proformas. The data were analyzed using Stata IC Software version 15. Pearson's Chi-square and Fisher's Exact tests were used for univariate association analysis. Multivariate logistic regression was employed to adjust for confounders and identify the associations between various risk factors and toxicities.

Sixty-three patients (14.4%) experienced any grade of acute treatment-related toxicity. Hematological toxicity was the most common, affecting 36 patients (57.1%), followed by dermal toxicities in 15 patients (23.8%) and gastrointestinal toxicities in 11 patients (17.5%). One patient (1.6%) experienced mucosal toxicity. Univariate and multivariate analyses revealed that only para-aortic nodal involvement was significantly associated with an increase in both acute and late treatment-related toxicities (P = 0.006). Other factors, such as age, hemoglobin levels, stage, previous surgery, parametrial bulk, extension to the pelvic side-wall, and dose to point A, did not significantly affect the overall incidence of toxicity. The number of chemotherapy cycles <4 was also associated with higher acute toxicity (P = 0.031). Para-aortic nodal involvement was significant for both acute and late treatment-related toxicities. The use of modern conformal radiotherapy techniques in these patients may help reduce treatment-related toxicities.

Keywords: *Risk factors, Toxicity, Cancer cervix, Treatment-related*

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Introduction

Cervical cancer is the second most common gynecological malignancy among Indian women, as per Globocan 2020.[1] Worldwide, it has a 5-year prevalence of 26,68,819 cases and an incidence of 6,04,127 new cases per year. As per ICMR data, carcinoma cervix has an incidence of 79,103 cases per year in India and a cumulative risk of 11.1 between ages 0-74 years, and the burden is projected to increase to 85,241 cases by 2025.[2] Cancer of the cervix has cure rates reaching up to 90% with the use of multimodality treatment.[3-6] However, the cancer-directed treatment used in carcinoma cervix is associated with severe acute and late side effects. These are of special importance in today's era, when survival is prolonged, and a significant percentage of patients are expected to have a long enough survival to experience these late treatment-related adverse events.

In this study, we undertook to determine treatment and disease-related factors that could be responsible for higher acute and late treatment-related toxicities in carcinoma cervix patients.

Materials and Methods

This study was conducted at a Tertiary care cancer center. Data was collected retrospectively from hospital records. The required information was entered into a pre-designed proforma. As this was a retrospective observational study, ethical committee clearance was not required.

Inclusion and exclusion criteria

All Radically treated stage I-IVA, histopathologically proven carcinoma cervix patients were included in this study. Those with a history of prior pelvic radiation or second malignancy were excluded.

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Data collection

Data was collected on a predesigned digital proforma. International Federation of Gynecology and Obstetrics (FIGO) 9 staging system was used for staging purposes.[7] Acute and Late toxicities graded as per RTOG[8] Criteria were also recorded in the proforma. Acute toxicities were regarded as those toxicities that occurred within the first 90 days of treatment initiation. Among acute toxicities, Mucosal, Gastrointestinal, skin, haematological toxicities, and nephrotoxicity were recorded. Among late toxicities, that is those occurring more than 90 days after treatment, bladder and bowel toxicity, lymphedema, and second malignancy were documented.

Statistical analysis

Data was entered in a Microsoft Excel spreadsheet, cleaned for errors, and analyzed using Stata IC Software version 15. Descriptive statistics were used to summarize the toxicity profile. Frequencies and their percentages were used to describe categorical variables. Given fewer toxicity events, the total acute and late toxicities had to be combined to get meaningful results Pearson Chi-square and Fischer Exact test were used for univariate association analysis. We used multivariate logistic regression for adjustment of confounders to find an association between various risk factors and toxicities. Adjusted Odds Ratios with their 95% confidence interval were calculated to predict risk factors for toxicity. A two-sided p-value of < 0.05 was considered statistically significant.

Results and Discussion

A total of 435 patients were enrolled in this study. The median age of the presentation was 52 years. All patients were treated with a radical intent. Radiotherapy was delivered using a 2-dimensional radiotherapy technique using a Cobalt-60 machine. This was followed by a brachytherapy boost in the majority of patients and a supplemental External beam radiotherapy boost in those not suitable for brachytherapy. Concurrent weekly cisplatin was administered in the majority (85.7%) of the patients. Patient and treatment-related characteristics are summarised in **Table 1**.

Table 1. Summary of Patient and Treatment-Related Parameters

Patient Characteristic		Number (N)	Percentage (%)
Age	< 52 years	206	47.4
	>/= 52 years	229	52.6
	Total	435	
Hemoglobin	</= 12 mg/dl	340	78.2
	> 12mg/dl	95	21.8
	Total	435	
Histology	Squamous Cell Carcinoma	406	93.3
	Others	29	6.7
	Total	435	
Stage	I	7	1.6
	IIA	12	2.8
	IIB	278	63.9
	IIIA	9	2.1
	IIIB	126	28.96
	IVA	3	0.7
	Total	435	
Parametrial involvement	Unilateral	125	28.7
	Bilateral	286	65.7
	Not known	24	5.5
	Total	435	
Parametrial Bulk	Minimal	49	11.3
	Less than half	72	16.6
	More than half	291	66.89
	Not known	23	5.3
	Total 435		
Pelvic side wall	Unilateral	100	22.98
	Bilateral	36	8.3
	Not known	299	68.7
	Total	435	

Lymph nodes	No involved lymph nodes	275	63.2
	Pelvic lymph nodes	112	25.7
	Para-aortic Lymph nodes	48	11
	Total	435	
Treatment Characteristics		**Number (N)**	**Percentage (%)**
Overall Treatment Time	< 8 weeks	155	35.6
	> 8 weeks	276	63.4
	Not available	4	0.91
	Total	435	
Treatment Interruption	Yes	6	1.4
	No	427	98.1
	Not available	2	0.46
	Total	435	
Pelvic Boost	Brachytherapy	315	72.4
	Supplement RT	115	26.4
	No Boost	5	1.14
	Total	435	
Dose to Point A	>/= 80 Gy	236	54.3
	<80 Gy	199	45.7
Concurrent chemotherapy	No chemotherapy	62	14.2
	> 4 cycles	361	82.9
	< 4 cycles	12	2.8
	Total	435	

Treatment-related toxicity

Sixty-three patients (14.4%) experienced any grade acute treatment-related toxicity. Of these, haematological toxicity was most common i.e. 36 patients (57.1%) followed by dermal toxicities in 15 patients (23.8%) and gastrointestinal in 11 patients (17.5%). One patient was documented to experience mucosal toxicity (1.6%). Treatment-related toxicities have been summarised in **Tables 2 and 3**.

Table 2. Percentage of Treatment Related Acute and Late Toxicities

Acute Toxicity	Number	Percentage of Total Number of Patients
Hematological	36	8.3
Dermal	15	3.4
Gastrointestinal	11	2.5
Mucosal	1	0.23
	Late Toxicities	
Rectal Toxicity	35	8.04
Bladder Toxicity	16	3.7

Table 3. Grade Wise Distribution of Acute and Late Treatment Related toxicities

Acute Toxicity	Grade	Number (N)	Percentage (%)
Hematological	1	0	0.0
	2	33	91.7
	3	3	8.3
	4	0	0
	Total	36	100
Dermal toxicity	1	1	6.7
	2	12	80
	3	2	13.3

	4	0	0
	Total	15	100
Gastrointestinal	1	0	0
	2	7	63.6
	3	4	36.3
	4	0	0
	Total	11	100
Mucosal Toxicity	4	1	100
	Total	1	100
Late Toxicities			
Rectal toxicity	1	1	2.8
	2	17	48.6
	3	7	20
	4	10	28.6
	Total	35	
Bladder toxicity	1	1	6.25
	2	11	68.75
	3	2	12.5
	4	2	12.5
	Total	16	100

Chemotherapy-induced nephrotoxicity was seen in two patients (0.46%), one patient experienced grade 2 and one grade 4 toxicity. Among late toxicities, Rectal toxicity was experienced by 35 patients (8.1%), and bladder toxicity was experienced by 16 (3.6%) patients. No other late toxicities were documented in patients' charts.

On analysis, it was found that only para-aortic nodal involvement was associated with a significant increase in both acute and late treatment-related toxicities. Other factors such as age, haemoglobin, stage, previous surgery, parametrial bulk, extension up to pelvic side-wall, and Dose to point A, did not have a significant impact on the overall incidence of toxicity.

Number of chemotherapy cycles <4 was also associated with higher acute toxicity. This was contrary to expectation and was probably due to the stoppage of chemotherapy early consequent to higher grade 3 and 4 toxicity in these patients.

The majority (98.1%) of patients were able to complete treatment without interruption within the stipulated time (i.e. <8 weeks). The results have been summarized in **Table 4**.

Table 4. Summary of Factors Impacting Acute and Late Treatment-Related Toxicities in Carcinoma Cervix Patients

Variable		Toxicity (Acute +Late)		Relative Risk (CI)	Adjusted Odds Ratio (CI)	P-Value
		Absent N (%)	Present N (%)			
Age	< 52 years	158(76.7)	48(23.3)	0.98(0.89-1.08)	0.94(0.59 - 1.5)	0.798
	> 52 years	179(78.17)	50(21.83)			
Chemotherapy cycles	< 4 cycles	49(66.22)	25(33.78)	0.83(0.69-0.98)	0.53 (0.30-0.94)	0.031*
	> 4 cycles	288(79.78)	73(20.22)			
Hemoglobin	< 12gm%	262(77.06)	78(22.94)	0.98(0.87-1.1)	1.0 (0.55- 1.81)	0.996
	> 12gm%	75(78.95)	20(21.05)			
Para-aortic Nodal involvement	Absent	309(79.84)	78(20.16)	1.34(1.05-1.70)	2.54(1.31-4.90)	0.006*
	Present	28(59.57)	19(40.43)			
Parametrial involvement	Unilateral	112(77.78)	32(22.22)	1.01(0.91-1.13)	0.92(0.50- 1.67)	0.780
	Bilateral	220(76.92)	66(23.08)			
Parametrial Bulk	< /=1/2	105(78.36)	29(21.64)	1.02(0.92-1.14)	1.10 (0.59-2.04)	0.758

	> 1/2	223(76.4)	69(23.63)			
Pelvic Sidewall extension	Unilateral	306(77.27)	90(22.73)	0.99(0.83-1.2)	0.81(0.33-2.0)	0.652
	Bilateral	28(77.78)	8(22.22)			
Stage Classification	I and II	235(79.12)	62(20.88)	1.07(0.96-1.2)	1.32 (0.77-2.28)	0.31
	III and above	101(73.7)	36(26.28)			
Surgery	Not Done	325(77.01)	97(22.99)	0.83(0.71-0.98)	0.32(0.04- 2.57)	0.286
	Done	12(92.31)	1(7.69)			
Dose to Point A	< 80 Gy	189(80.43)	46(19.57)	1.08(0.97-1.2)	1.35 (0.84 -2.16)	0.212
	> 80 Gy	148(74.37)	51(25.63)			

This study was undertaken to assess the impact of several diseases and treatment-related factors on the incidence of acute and late toxicities in radically treated cervical cancer patients. Para-aortic nodal involvement was the only significant factor associated with an increase in toxicities. Extended field radiotherapy technique used in these patients to cover para-aortic nodes, irradiates a larger volume of normal tissues predisposing to higher toxicity. Number of concurrent chemotherapy cycles less than four was also associated with an increased incidence of toxicity, however, this is contrary to expectation as chemotherapy has a radiosensitizing effect and fewer chemotherapy cycles should be associated with lower toxicity. We found that the average total radiation dose to point A in patients receiving less than 4 cycles of chemotherapy was 79.36 Gy which was slightly higher than in patients receiving more than 4 cycles i.e. 77.2 Gy. However, a more plausible explanation could be that chemotherapy was stopped after a few cycles in these patients due to greater treatment-related toxicity. This is also supported by the fact that fewer (13.8%) patients in chemotherapy cycles> 4 arms experienced acute toxicity compared with those receiving less than 4 cycles (18.9%).

Comparison with different types of toxicity and grades could not be done due to fewer number of events documented in each group and only the total toxicity (any grade and any site) was used for analysis. Among acute toxicities, grade II hematological toxicity was the most documented (7.6%) followed by Grade 2 dermal toxicity. Acute grade 3 and 4 toxicity was documented in only 2.3% of the patients. Late toxicities were documented for the bladder and rectum and were more common in the rectum (8.1% versus 3.6%), which is supported by previous studies and is due to lower radiation tolerance of the rectum as compared to the bladder.

The incidence of early toxicities reported in previous studies was much higher and up to the tune of 50-80%,[9-11] with grade I and II toxicities and gastrointestinal toxicities being more common. The toxicities documented were much less in this study and can be attributed to lower average dose to point A, poor documentation, and lesser use of brachytherapy due to non-availability, in some patients.

Factors predisposing to the development of acute and late toxicities are not well understood to date and are considered to be an interplay of genetic, treatment, and environment-related factors. Different individuals may respond differently to the same treatment. Limited research available regarding the study of these factors is deterred by poor documentation of toxicities. Kuku *et al*.[9] in a retrospective study reported younger age, type of malignancy, smoking, previous surgery, and initial presentation with symptom clusters of bloating, per-rectal bleeding, abdominal pain, and mucus, to be significantly associated with late bowel toxicity. Fecal urgency was the most commonly reported symptom. Hernandez *et al*.[10], found chemotherapy to be independently associated with significant late bowel toxicity.

Age more than 52 years was found a significant predictor of higher acute toxicity in a study by Holmqvist *et al*.[11] Older age was associated with a higher frequency of nausea/vomiting and increased grade ≥ 3 toxicity during CRT compared to younger patients. Toxicity grade ≥ 3 of nausea/vomiting was associated with increased frequency of weight loss, reduced activities of daily living (ADL), and dose modifications of both radiotherapy (RT) and chemotherapy (CT) compared to toxicity grade 2. The frequency of diarrhea and weight loss was also higher in older patients compared to younger ones.

In another study,[12] body mass index (BMI), and radiation dose received by the bladder and rectum were reported of important for the occurrence of acute radiation toxicity (ART), and the use of angiotensin-converting enzyme (ACE) inhibitors was associated with the decreased chances of the ART. None of the above factors were found to be significant in our study.

Due to the retrospective nature of this study, there was unstructured documentation of toxicities. Mild toxicities were underreported as these may be missed on routine outpatient visits. Due to a limited number of events in different subsets, the effect of different variables on the type and grade of toxicities could not be analyzed separately. The gastrointestinal symptoms of patients before treatment initiation were not documented to rule out pre-existing bowel disease. In patients with the persisting disease after treatment it was difficult to distinguish treatment-related toxicities from disease-related symptoms, these patients were also less likely to report treatment-related symptoms.

In order to understand the factors affecting treatment-related toxicities in cervical cancer patients, well-structured prospective studies are needed with thorough documentation. An understanding of these factors will pave the way for timely intervention and prevention of acute and late side effects, which will not only improve patient treatment outcomes but also improve the quality of life in survivors.

Conclusion

Para-aotic nodal involvement was found to be a significant predictor of incidence of toxicity in cervical cancer patients. Techniques to reduce bowel irradiation such as using modern radiotherapy techniques in patients who are candidates for extended field radiotherapy may help reduce side-effects. To understand the impact of different variables on the occurrence of treatment-related toxicities, larger prospective trials are needed.

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None

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None

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