



**“AN OBSERVATIONAL STUDY TO EVALUATE THE TOXICITIES TO RECTUM AND BLADDER WHILE USING A SPECIALLY DESIGNED RECTUM BLADDER SPACER BALLOON IN HIGH DOSE RATE BRACHYTHERAPY IN PATIENTS OF CARCINOMA CERVIX.”**

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**ABSTRACT** **BACKGROUND:** Worldwide, Cervical carcinoma is the fourth most common cancer in women and seventh most Common overall (GLOBOCAN 2018). Carcinoma cervix accounts for about 569,847 patients around the world out of which 311,365 accounts for death worldwide. Total 14,389 patients were registered in Dr. BRAM Hospital (2012-2015). Out of these 2738 patients were carcinoma cervix. Carcinoma cervix consists of 18% of total cancer registered. Brachytherapy has got a pivotal role in the treatment of carcinoma cervix. Modern day image based brachytherapy has further improvised the treatment results. To allow for maximal tumor radiation dose while limiting exposure to the immediate adjacent organs at risk (OARs) during ICRT in carcinoma cervix, the method available is to manually displace these OARs so that they are located at some distance from the tumor. This is conventionally accomplished by using vaginal gauge packs around central tandem to allow required space between source and rectum. **OBJECTIVE:** To evaluate the toxicities to rectum and bladder while using a specially designed rectum bladder spacer balloon in high dose rate brachytherapy in patients of carcinoma cervix. **METHOD:** This prospective clinical study involved 50 histopathological proven patients, conducted during October 2017 to December 2018 in the department of Radiotherapy, Pt. JNM medical college and Regional cancer centre (RCC) of Dr. BRAM Hospital Raipur. Informed written consent, detail history and complete Physical examination were performed in every patient. The vaginal applicators were applied aseptically with spacer balloon and proper simulation with CT, treatment was executed i.e. 7 Gy in 3 # with usage of balloon applicator every time. Patients were assessed every month for toxicities till one year post treatment. USG and physical examination was done post treatment for assessing clinical response. Frequency tables were used to describe impact of treatment on different stages using chi-square test. **RESULT:** In this study the majority of patients (34%) had per vaginal bleeding and per vaginal white discharge as symptoms, 92% of patients had histology squamous cell carcinoma rest were had different histopathology In this study maximum number of patients 46% belonged to 50-60 years age group followed by 22% in 30-40 year group. 37 out of 50 (82%) patients were of low socioeconomic status. 50% patients in this study belonged to stage IIB, and 34% were having stage IIIB disease. 16% patients did not show any rectal toxicity in any of follow-up, 9% patients had grade 1 toxicity in all follow-ups while 11% showed grade 2 toxicity on 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> follow-up. 18% patients did not show any bladder toxicity in any of follow-up, 8% patient had grade 1 toxicity in all follow-ups while 9% showed grade 2 toxicity on 3<sup>rd</sup> follow-up. Overall grade 3 bladder and rectal toxicities were seen in fewer patients it was due to use of spacer balloon. **CONCLUSION:** We observed in our study that the majority of patients were in old age groups and were presented in locally advanced stages; the most common histopathology found was squamous cell carcinoma. Toxicities to rectum was shown reduced in among 16% of cases. Overall grade 3 bladder and rectal toxicities were seen in fewer patients it was due to use of spacer balloon.

**KEYWORDS :** Carcinoma cervix, Brachytherapy, ICRT, Spacer Balloon, Rectum.

#### INTRODUCTION

Cervical cancer is 2<sup>nd</sup> most common cancer in Indian women. In India, cervical cancer had increased from 0.11 million in 2000 to 0.16 million in 2010. [1] The proportion ranged from 15% to 55% of female cancers from different parts of the country. Over 80% of the cervical cancer present at a fairly advanced stage and annually around 80,000 deaths are reported in India. [2] According to global cancer statistics, cervical cancer is now the third most commonly diagnosed cancer and the fourth leading cause of cancer death in female's worldwide, accounting for 9% (529,800) of the total new cancer cases and 8% (275,100) of the total cancer deaths among females in 2008. More than 85% of these cases occur in developing countries. India, the second most populous country in the world, accounts for 27% (77,100) of the total cervical cancer deaths. Human papilloma virus (HPV) infection causes cervical cancer and is prevalent in almost 100% of cases. [3] HPV16 and HPV18 are the most common carcinogenic types, associated with 55% and

15% of cervical cancer cases respectively. Risk factors for HPV persistence include immunocompromised state (human immunodeficiency virus (HIV), post organ transplantation), potential genetic host susceptibility and smoking. [4]

The majority of cases are locally advanced at diagnosis and most commonly present with abnormal bleeding, usually inter-menstrual, post-coital or post-menopausal. The most common early presentation of early disease is post-coital bleeding. Women may also complain of vaginal discharge or dyspareunia. [5] Diagnosis must be confirmed histologically, usually by biopsy at colposcopy or EUA. Approximately 80-90% is squamous cell carcinomas. Other pathologies include adenocarcinoma (10-15%), adeno-squamous carcinoma (3-5%), clear cell carcinoma (rare), and neuroendocrine carcinomas (rare). [6] In general, squamous cell carcinoma represents a chemotherapy and radiotherapy (RT) sensitive group whereas

adenocarcinomas are less chemotherapy and RT sensitive.

For women who develop locally advanced cervical cancer, the standard of care has evolved from external beam radiation therapy (EBRT) alone, to EBRT plus brachytherapy, to combined EBRT plus brachytherapy with concurrent chemotherapy. The external beam portion of treatment encompasses treatment to the pelvic lymph nodes, parametria, and primary tumor, to a dose adequate to control microscopic disease. The addition of brachytherapy serves to boost the gross tumour, and improves disease control and survival.<sup>[7]</sup> The addition of chemotherapy serves predominantly as a radio sensitizer, resulting in improvements of about 5% in overall survival. Brachytherapy involves the application of a radioactive source in close proximity to the tumour. It takes advantage of the inverse-square law, whereby radiation dose is inversely proportional to the square of the distance from the source.<sup>[8]</sup> In practical terms, this allows for a very high dose to the tumour with relative sparing of the surrounding normal structures. Brachytherapy is the only demonstrated method of providing the high dose required to control cervical cancer (>80 Gray [Gy]), without causing undue side effects. The aim of this review is to explore current best practice and state-of-the-art developments in cervical cancer brachytherapy, including patient selection, applicator selection, operative technique, and radiation treatment planning. It is intended for those with a general interest in the treatment of cervical cancer.<sup>[9]</sup> Brachytherapy (BT) delivers short distance radiation near to or inside tumour. It is given after EBRT to boost primary tumour dose and involves surgical insertion of an intra-uterine tube and ovoids or ring at the vaginal fornixes. A radiation source e.g. Iridium 192 (for 31 high dose rate (HDR)) is inserted into these tubes to deliver radiation internally with a steep dose drop off allowing high tumour dose and low OAR dose. Many different regimens and delivery methods are used, including low dose rate (LDR), medium dose rate (MDR), HDR, and pulsed BT. For HDR BT, most commonly used due to short treatment delivery time, 21Gy-28Gy in 3-4 fractions is an established prescription.<sup>[10]</sup>

**Objective:** Evaluation the doses to rectum while using a specially designed Rectum Bladder Spacer Balloon in high dose rate brachytherapy in patients of carcinoma cervix.

## MATERIAL AND METHOD

**Method:** This prospective clinical study involved 50 histopathological proven patients, conducted during October 2017 to December 2018 in the department of Radiotherapy, Pt. JNM medical college and Regional cancer center (RCC) of Dr. BRAM Hospital Raipur.

### Patient Inclusion Criteria

- 1) Histopathological proven cases of carcinoma cervix.
- 2) ECOG performance score of 0 or 1.
- 3) Patient with normal liver function test, renal function test and hematological parameters.
- 4) Patient with normal electrocardiogram.

### Patient Exclusion Criteria

- 1) ECOG performance score of 4 or 5.
- 2) Patient with any other malignancy.

### Major Variables

- 1) Age
- 2) Sex
- 3) Histopathology
- 4) Socioeconomic status
- 5) Stage of disease

### Outcome Variables

- 1) Acute Toxicities to bladder and rectum.
- 2) To assess late toxicities to bladder and rectum.

## METHODOLOGY

- This study was performed in the Department of Radiotherapy, Regional Cancer Centre, Pt. J.N.M. Memorial Medical College & Dr BRAM Hospital Raipur, C.G.
- 50 Histopathological proven cases of carcinoma cervix were taken for this study.
- Informed written consent was taken from every patient.
- Detail history was recorded from each patient pertaining to the onset and duration of present complaint.

- Physical examination was done on all patients including general, local and systemic examination.
- All the routine investigations including CBC, RFT, LFT, X-ray chest, ECG, CT scan of pelvis was done on all the cases.
- Patients were simulated with appropriate technique in minor OT. Evaluation of the plan for dose to primary site and dose to organ at risk was done and best better plan was executed.
- Treatment planning was performed using ONCENTRA TPS and treatment was delivered.
- Fractionation schedule used for this study was 7Gy per #/ once a week for three weeks.
- Patients were assessed every month for toxicities to bladder and rectum.
- After completion of treatment patients were on follow up for 12 months. Patients were assessed by CT scan pelvis every three months.

### Calculation of result:

In this study, clinical characteristics between the two treatments were compared using chi-square test. A p-value of <0.05 was taken as significant. Data were analysed using the chi-square test.

### Follow up:

After completion of treatment patients were on follow up for 12 months. Patients were assessed by CT scan pelvis every three months. They were assessed for acute and late toxicities and loco-regional recurrence / distant metastasis by clinical examination and/or by necessary investigations.

## RESULTS

This prospective clinical study involved 50 histopathological proven patients, conducted during October 2017 to December 2018 in the department of Radiotherapy, Pt. JNM medical college and Regional cancer center (RCC) of Dr. BRAM Hospital Raipur. All patients were evaluated with a detailed history, clinical examination, hematological and radiological investigations. The patients were assessed every three months for 12 months. The results were as follows:

### Age

23 out of 50 patients (46%) were belonged to 50-60 years age group followed by 22% in 30-40 year group and 20% in 40-50 years age group shows that cervical cancer is common among old women. The median age of the patients was 55 years.

**Table 1** Age wise distribution of patients

Age Range	Number	%
31-40	11	22.0
41-50	10	20.0
51-60	23	46.0
61-70	6	12.0
Total	50	100

### Socio-economic status

37 out of 50 patients (82.2%) were belonged to lower socioeconomic strata on the other hand 18% patients were of middle class economy status. This states that carcinoma cervix is more common in poor people and in rural areas due to the reason that hygiene and cleanliness play a pivotal role in deciding the risk factors causing carcinoma cervix.

**Table 2** Socio-economic status wise distribution of patients

SES	Number	Percentage
Middle Class	8	17.8
Lower Class	37	82.2
Total	50	100

### Symptoms

17 out of 50(34%) patients were presented with the complaints of per vaginal bleeding and white discharge per vaginal together. 28% patients had symptoms PV bleed + White Discharge + Pain Abdomen together.

**Table 3** Symptoms wise distribution of patients

Symptoms	Number of subjects
No Symptoms	4 (8%)
1 Symptom	10 (20%)
Continuous PV Bleed	6

White PV Discharge	2
Abdominal Pain	1
Back Pain	1
<b>2 Symptoms</b>	<b>17 (34%)</b>
PV bleed + White Discharge	16
Abdominal + Back Pain	1
<b>3 Symptoms</b>	<b>14 (28%)</b>
PV bleed + White Discharge + Appetite loss	5
PV bleed + White Discharge + Pain Abdomen	5
PV bleed + White Discharge + Back Pain	4
<b>4 Symptoms</b>	<b>3 (6%)</b>
PV bleed + White Discharge + Abdominal + Back Pain	3
<b>5 Symptoms</b>	<b>4 (8%)</b>
PV bleed + White Discharge + Abdominal + Back Pain + Irregular Bowel Movements	4

**Histology**

46 out of 50 (92%) patients had squamous cell carcinoma variant of histology, out of which 26% were well differentiated and 60% were moderately differentiated type. 6% patients had adenocarcinoma histology in which 60% were well differentiated and 26% were moderately differentiated type. This finding showed that in most of the cases the tumor occupied the external part (exocervix) than endocervix.

**Table 4** Histology wise distribution of patients

Type of Carcinoma	Number	Percent
<b>1. Squamous Cell Carcinoma</b>	<b>46</b>	<b>92</b>
Well Differentiated Carcinoma	13	26
Moderately Differentiated Carcinoma	30	60
<b>Poorly Differentiated Carcinoma</b>	<b>3</b>	<b>6</b>
2. Adenocarcinoma	3	6.0
Well Differentiated Adenocarcinoma	2	60.0
Moderately Differentiated Adenocarcinoma	1	26.0
<b>3. Clear Cell Carcinoma</b>	<b>1</b>	<b>2.0</b>
Total	50	100.0

**Stage**

25 out of 50(50%) patients had disease in stage IIB, 17 out of 50(34%) patients were in stage IIIB, and 8% was shared among stage IB and stage IIA patients. This observation stated that most of the patients were in locally advanced stage in the study group

**Table 5** Staging wise distribution of patients

Stage	Number	Percentage
IB	4	8
IIA	4	8
IIB	25	50
IIIB	17	34

**Rectal and Bladder toxicities post procedure**

16% patients did not show any rectal toxicity in any of follow-up, 9% patients had grade 1 toxicity in all follow-ups while 11% showed grade 2 toxicity on 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> follow-up. 18% patients did not show any bladder toxicity in any of follow-up, 8% patient had grade 1 toxicity in all follow-ups while 9% showed grade 2 toxicity on 3<sup>rd</sup> follow-up. Overall grade 3 bladder and rectal toxicities were seen in fewer patients it was due to use of spacer balloon.

**Table 7:** Rectal and Bladder toxicities profile during the follow up period

Site	Grade	Follow up - Number (%)					
		1	2	3	4	5	6
Bladder toxicity	0	18	18	18	18	18	18
	1	8	8	8	8	8	8
	2	8	9	9	8	10	8
	3	6	4	4	4	2	4
Rectal	0	16	16	16	16	16	16
	1	9	9	9	8	9	9
	2	8	11	11	11	10	11
	3	7	3	3	3	4	3

**Correlation among different parameters**

**Table 8:** Correlation tables for Follow-up 6 month, toxicity, and dose at Rectum during ICRT

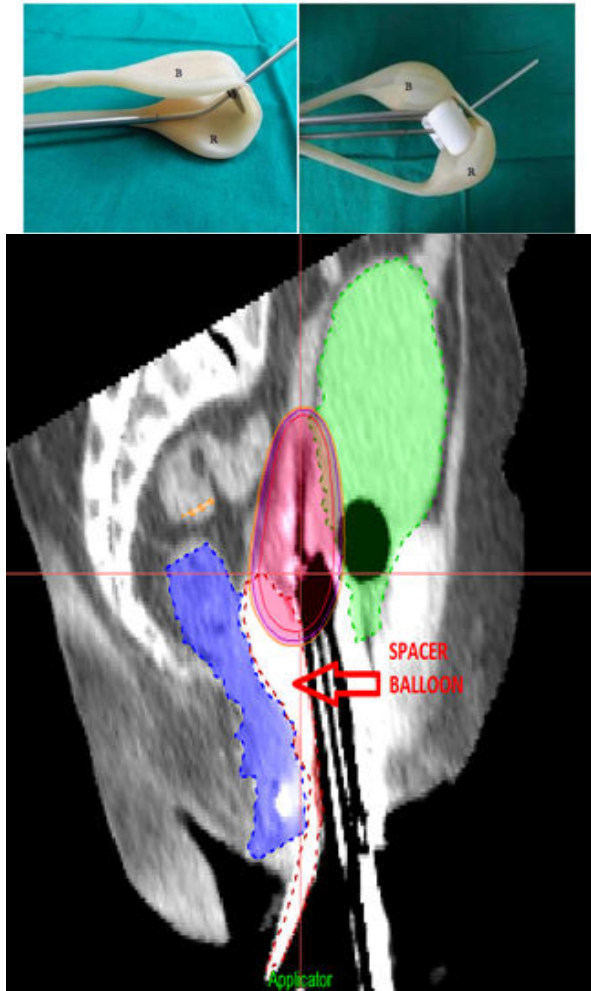
Volume	Toxicity Grade 0	Toxicity Grade 1	Toxicity Grade 2	Toxicity Grade 3	Spearman's Correlation Coefficient (pValue)
<b>0.01cc</b>	708.25	709.05	712.81	708.54	0.097
Median	(692.45 -	(700.31 -	(690.79 -	(694.25 -	0.563
(IQR)	710.45)	714.25)	720.96)	708.58)	
<b>0.02cc</b>	586.32	596.45	613.77	615.25	0.577
Median	(576.58 -	(587.38 -	(606.86 -	(602.75 -	0.000
(IQR)	589.85)	602.28)	619.47)	622.01)	
<b>2cc</b>	478.25	486.38	488.65	498.32	0.599
Median	(462.85 -	(478.47 -	(486.48 -	(490.25 -	0.000
(IQR)	485.21)	499.30)	498.64)	498.69)	
<b>5cc</b>	391.54	392.99	398.57	395.25	0.217
Median	(380.45 -	(388.81 -	(395.50 -	(389.73 -	0.191
(IQR)	399.39)	398.89)	404.62)	400.02)	

**DISCUSSION**

Cervical cancer remains a significant cause of morbidity and mortality among women globally, even though it is the cancer with the greatest potential for secondary prevention. In some regions of the world the incidence is alarmingly high, which includes India. [12] However in some regions in India there is decline in AARs over past few years. [11] This disease is highly preventable and curable. Brachytherapy has got a pivotal role in the treatment of carcinoma cervix. Modern day image based brachytherapy has further improvised the treatment results. To allow for maximal tumor radiation dose while limiting exposure to the immediate adjacent organs at risk (OARs) during ICRT in carcinoma cervix, the method available is to manually displace these OARs so that they are located at some distance from the tumor. This is conventionally accomplished by using vaginal gauge packs around central tandem to allow required space between source and rectum and bladder. Our study was performed using a specially designed Bladder Rectum spacer Balloon during ICRT to separate the rectum and bladder from source and dose to various volumes of rectum during all three fractions of ICRT were analyzed. [15] In our study, 23 out of 50 patients (46%) were belonged to 50-60 years age group followed by 22% in 30-40 year group and 20% in 40-50 years age group shows that cervical cancer is common among old women. The median age of the patients was 55 years. The incidence was rising with up till age 50 years at peak then fallen rapidly. In study by *Aswathy Sreedevi et al.*, the peak age of occurrence of cervical cancer in India is between 55 and 59 years. [11] Our study also correlates with the above studies.

We observed in our study that 37 (82.2%) patients belonged to lower socioeconomic group; lower middle group contained 8 (17.8%) patients and no patients from upper middle SEC group. In a study by *B. Benard et al.*, in developing countries, like India lack of awareness, low socioeconomic status, illiteracy, poverty are the main risk factors for carcinoma cervix. [12] In our study we found that most patient were presented with bleeding per vagina and white discharge per vagina. More symptoms correlates with the advanced stage of the disease. The lack of education, illiteracy and lack of awareness are mainly responsible of the advanced stage of the disease. The most common presenting symptom of cervical cancer is per vaginal bleeding (e.g. post-coital, intermenstrual or post-menopausal). *Christopher M. Tarney et al* suggested Post Coital bleeding is the earliest presentation of carcinoma cervix. [13] Our study showed that 4(8%) patients were presented with stage IB, 4(8%) patients were presented with stage IIA, 25(50%) patients had stage IIB, 0(0%) patients had stage IIIA and 17(34%) patients had presented with stage IIIB. Complete response was seen 16 patients of stage IIB , 9 patient with stage IIIB, 4 patients of stage IIA and 3 patient with stage IB. Partial response was seen among 2 patients of stage IIB , 3 patients with stage IIIB, no patients of stage IIA, no patient with stage IB . One patient had progressive disease which was seen in stage IIB. There were two patient of stage IIIB who died till reaching last follow up. In a study by *Benedetti-Panici P et al.*, Earlier the stage of the disease better is the response to the treatment and prognosis. 5 years disease free survival rate is 96% for stage IA. In Stage IB, 5 years disease free survival rate is 86-92% and in Stage IIA is 75%. In stage IIB- IIIB, 5 years disease free survival rate is 60%. [14] Affected population mostly belongs to low socioeconomic status and not aware of the potential risks hence they come in advanced stage. In our study, 46(92%) were diagnosed as having squamous cell carcinoma, 3(6%) were adenocarcinoma, and 1(2%) was clear cell carcinoma but the grade of differentiation was 12(24%) had well differentiated tumor cells, 33(66%) had moderately differentiated tumor cells and 4(8%) had poorly differentiated tumor cell. 1 patient with moderate differentiated adenocarcinoma and 1 patient with clear cell carcinoma. In a study by *Eriko Yokoi et al* ,

Locally advanced cervical cancer patients with Adenocarcinoma / adenosquamous carcinoma histology experience significantly worse survival outcomes than those with SCC.



Treatment of carcinoma cervix includes surgery and /or chemo radiotherapy. Most patient are treated with concurrent chemo radiotherapy *Beck T et al*. Definitive chemoradiotherapy consists of external beam RT with chemotherapy followed by brachytherapy. Brachytherapy is mainstay treatment of cervical cancer. It provides opportunity to deliver very high dose to tumor with minimal dose to OARs. In cervical cancer patients cumulative overall and  $\geq 2$  grade rectal toxicity has been recorded in 12%–19% by a study of *Chen SW et al*. A new technique was thought to be an interesting option for patients with cervical carcinoma undergoing EBRT and BT. A separation of at least 10–15 mm would be sufficient to achieve 80% rectal dose reduction *Susil et al*. It takes advantage of the inverse-square law, whereby radiation dose is inversely proportional to the square of the distance from the source. In practical terms, this allows for a very high dose to the tumor with relative sparing of the surrounding normal structures. On 1<sup>st</sup> follow up 9 patient (22.5%) had grade 1 toxicity, 11 patient (27.5%) had grade 2 toxicity and 8 patient (20%) had grade 3 toxicity. 12 patient had no toxicity on 1<sup>st</sup> follow up. On 6<sup>th</sup> follow up 10 patient (26.3%) had grade 1 toxicity, 10 patient (26.3%) had grade 2 toxicity and 6 patient (15.78%) had grade 3 toxicity. 12 patient reported no toxicity on 1<sup>st</sup> follow up. 2 patient died while reaching up to 6<sup>th</sup> follow up. A Non parametric SPEARMAN'S CORRELATION TEST was used to assess the level of correlation between dose of radiation and grades of toxicity. The dose is described as median and inters quartile range. At 0.1 cc of volume of rectum there was no correlation with toxicity (p value -0.629) while a statistical significant positive moderate correlation at volumes .2cc, & 2cc and toxicity grades were observed. Which means that as the dose increased the grades of toxicity increased.

## CONCLUSION

This prospective clinical study involved 50 histopathological proven patients, conducted during October 2017 to December 2018 in the department of Radiotherapy, Pt. JNM medical college and Regional

cancer center (RCC) of Dr. BRAM Hospital Raipur Fractionation schedule used for this study was 7Gy per #/ once a week for three weeks. Patients were assessed every month for response and toxicities. After completion of treatment patients were on follow up for 12 months. Patients were assessed by CT scan pelvis every three months for clinical response. We found in our study that 23 out of 50 patients (46%) were belonged to 50–60 years age group followed by 22% in 30–40 year group and 20% in 40–50 years age group shows that cervical cancer is common among old women. We observed in our study that 37 (82.2%) patients belonged to lower socioeconomic group which depicts that in developing countries, like India lack of awareness, low socioeconomic status, illiteracy, poverty are the main risk factors for carcinoma cervix. Our study showed that 4(8%) patients were presented with stage IB, 4(8%) patients were presented with stage IIA, 25(50%) patients had stage IIB, 0(0%) patients had stage IIIA and 17(34%) patients had presented with stage IIIB. Complete response was seen 16 patients of stage IIB, 9 patients with stage IIIB, 4 patients of stage IIA and 3 patients with stage IB. Rectal toxicity was observed in majority of patients. On 1<sup>st</sup> follow up 9 patient (22.5%) had grade 1 toxicity, 11 patient (27.5%) had grade 2 toxicity and 8 patient (20%) had grade 3 toxicity. 12 patient had no toxicity on 1<sup>st</sup> follow up. On 6<sup>th</sup> follow up 10 patient (26.3%) had grade 1 toxicity, 10 patient (26.3%) had grade 2 toxicity and 6 patient (15.78%) had grade 3 toxicity. a statistical significant positive moderate correlation at volumes .2cc, & 2cc and toxicity grades were observed. This means that as the dose increases the grades of toxicity were increased.

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