Analysis of Radiation Cystitis and Radiation Proctitis Cases in Patients with Carcinoma Cervix: A Retrospective Study

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Carcinoma cervix is commonly seen in India and is mostly diagnosed at an advanced stage where radiation therapy forms the basis of its treatment. Radiation cystitis and proctitis are commonly seen in these patients and contribute to increased morbidity and mortality. The aim of our study was to analyze the factors associated with radiation cystitis and proctitis in treated patients of carcinoma cervix. A retrospective observational study. All treated patients of carcinoma cervix from 2012 to 2017 with radiation induced cystitis and proctitis attending GOPD were analyzed. Descriptive statistics applied using SPSS software (Version 16). Chi square test and Fischer t test applied for calculating significance values. 100 cases were analyzed in toto. 89% belonged to radiation proctitis group and 11% to radiation cystitis group. All patients received external beam radiotherapy either in the form of conventional (90%) or IMRT technique (10%). Prevalence of radiation proctitis and cystitis in conventional radiotherapy group was 10.4% and 1.31% respectively and in IMRT group was 6.29% and 0.69% respectively. The patients were followed up after treatment for a minimum of 6 months. 100% cystitis cases were cured. But, 15.7% of proctitis cases did not get relieved of their symptoms. Radiation proctitis was seen more in patients receiving conventional radiotherapy via LINAC accelerators as compared to IMRT technique. More patient load, lack of adequate packing methods may contribute to increased incidence of RT related complications. Further evaluation of these patients is required to suggest management protocols and also to avoid them.

Key words: radiation cystitis, radiation proctitis, carcinoma cervix, IMRT technique.

INTRODUCTION

GLOBOCAN 2018 ranks cervical cancer as the fourth commonest cancer worldwide. The incidence of the same is 6.6% and mortality 7.5%. In India, cervical cancer is the third most common cancer but is the second most common cancer in women after breast cancer (GLOBOCAN 2018). Radiation cystitis and proctitis are defined as the inflammation of bladder and bowel mucosa respectively. These complications are major and occur commonly during and after radiotherapy. The overall incidence of radiation cystitis and proctitis is variable due to various radiotherapy doses.

Cervical cancer is commonly being diagnosed in the north eastern population of India as well. According to National Cancer Registry program of 2012-2014; the AAR (age adjusted rate) of cervical cancer in Kamrup urban district of Guwahati, Assam in the year 2010-14 was 14.89 (Barmon D et al, 2017). The detection of Ca cervix is mostly done at a latter stage where radiation therapy forms the basis of its treatment other than radical surgery and chemotherapy. Radiation cystitis and radiation proctitis is commonly seen in these patients and contribute to their increased morbidity.

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Acute radiation proctitis develops within a time frame of 3 months from start of radiotherapy whereas chronic proctitis usually develops after 6 months of cessation of radiotherapy (Ramakrishnaiah et al. 2016). The tolerance dose for whole bladder has been estimated to be 65 Gy and for the 2/3rd bladder to be 80 Gy. Doses of radiation less than 45 Gy are seldom associated with long-term side effects to the rectum, while doses above 70 Gy have been noted to cause significant injury (M.V. Pilepich et al., 1987). Our study attempts to analyze the factors associated with these major complications and also aims to calculate the prevalence of the same.

**METHODOLOGY**

**Source of data**

- **Study subjects**

Inclusion criteria:

All patients of carcinoma cervix treated from 2012 to 2017 who presented with radiation induced cystitis and proctitis after completion of radiotherapy treatment attending GOPD (Gynecology outpatient department) at our Institute were studied.

All patients received 50 Gy radiation dose as EBRT (external beam radiotherapy) in 25 fractions with concurrent chemotherapy followed by 3 fractions of ICRT (intracavitary radiotherapy) with a dose of 7 to 7.5 Gy to point A. EBRT was given either via cobalt machine or linear accelerators or IMRT (intensity modulated radiotherapy) machine.

For analysis of toxicities; RTOG (Radiation therapy oncology group) scale for late toxicities was used. No acute toxicities were studied.

Once toxicities were diagnosed; patients were given appropriate treatment and were followed up for a minimum period of 6 months.

**Exclusion criteria:**

1. Patients other than carcinoma cervix with radiation cystitis and radiation proctitis.
2. Patients with history of piles.
3. Patients with any bleeding diathesis.
4. Patients with inflammatory bowel disease.
5. Patients with recurrence or relapse of carcinoma cervix.

**Methods of collection of data:**

- **Study design:** Hospital based, observational and retrospective study.

**Sample size:** All treated patients of carcinoma cervix from 2012 to 2017 with radiation induced cystitis and proctitis attending GOPD.

**Study analysis:** The diagnosis of radiation cystitis and radiation proctitis was confirmed by cystoscopy and colonoscopy respectively. Appropriate statistical measurements like mean, percentage, proportion, odd’s ratio and comparison within the groups using chi-square test was used. p value <0.05 will be taken as statistically significant. SPSS software version 16 was used.

**RESULTS**

In this present study, we retrospectively analyzed 100 women who developed radiation induced cystitis and proctitis following radiotherapy for the treatment of cervical carcinoma at Dr. B Borooah Cancer Institute, Guwahati, Assam from January 2012 to December 2017. The prevalence of radiation proctitis and radiation cystitis after receiving radiotherapy was investigated and the underlying risk factors were determined. Also, if their symptoms were relieved or not was analysed after giving them appropriate treatment with a minimum follow up period of 6 months.

**Age Distribution of 100 cases** (Table 1): It was seen that 40% cases belonged to the age group 50 to 59 years followed by 37% cases in the age group of 40 to 49 years. 15% cases belonged to the age group of 60-69 years, 5% cases belonged to age group 30-39 years and 2% cases belonged to 70-79 years age group. Least number of patients were seen in the age group of 20 to 29 years that is 1%.

**Table 1: Age Distribution of 100 cases**

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30-39</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>40-49</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>50-59</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>60-69</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>70-79</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

**Carcinoma Cervix stage Distribution of 100 cases:** 70% cases belonged to stage II B and 30% cases belonged to stage III B.

**Type of Complication encountered in 100 cases** (Figure 1): 89% patients had radiation proctitis and 11% patients had radiation cystitis.

**Distribution of 100 cases on the basis of type of Radiotherapy technique used** (Table 2): 90% cases received conventional radiotherapy and 10% cases received intensity modulated radiotherapy. In the conventional arm; conventional LINAC included 83% cases and conventional cobalt included 7% cases.
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Figure 1: Type of Radiation induced complication

Figure 2: Grades of Cystitis versus type of RT technique

Table 2: Distribution of 100 cases on the basis of type of Radiotherapy technique used

<table>
<thead>
<tr>
<th>Type of Technique</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>IMRT</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Grades of radiation cystitis compared with type of RT technique (Figure 2): It was seen that 10 cases belonged to the conventional arm whereas only one case belonged to the IMRT arm.

Grades of Radiation Proctitis compared with type of RT technique (Figure 3): It was seen that a total of 80 cases belonged to the conventional arm and 9 cases belonged to the IMRT arm. The toxicities were graded according to RTOG scale for late toxicities.

Time duration of development of radiation cystitis: The median time in months for development of radiation cystitis after completion of radiotherapy was calculated as 36 months. The minimum amount of time was 12 months and maximum 72 months. The standard deviation was calculated as 18.56.

Time duration of development of radiation proctitis: The median time in months for development of radiation proctitis after completion of radiotherapy was 13 months. The minimum amount of time was 6 months and maximum 48 months with a standard deviation of 7.43.

Follow up of 100 cases (Figure 4): The patients were given appropriate treatment and followed up. It was seen that all 11 cases of radiation cystitis were relieved of their symptoms and were doing well. But, in 89 cases of radiation proctitis; 75 cases were relieved of their complication that is 84.3% and 14 cases were still suffering from radiation proctitis that is 15.7% cases.

Figure 3: Grades of Proctitis versus RT technique

Figure 4: Follow-up of 100 cases

Prevalence of radiation proctitis and cystitis: For calculation of prevalence of radiation cystitis and proctitis; the data was collected with the help of pattern of care and survival study going on in our hospital.

It was seen that the total number of cases of carcinoma cervix from 2012 to 2017 were 2536. Out of these 2536 patients; radical radiotherapy that is 25 fractions of 45 to 50 Gy of EBRT followed by 3 fractions of ICRT was received by 1052 patients. Out of these 1052 patients; 908 were in our follow up. Amongst the 908 patients; 143 patients received IMRT and 765 patients received conventional technique of radiotherapy. Thus, the overall prevalence post radical radiotherapy of radiation proctitis was 9.8% and that of radiation cystitis was 1.21%.
The prevalence of radiation proctitis in the IMRT group was 6.29% and in the conventional group was 10.4%. Chi square test was applied to calculate the p value for patients with radiation proctitis; that was 0.124 and hence not significant. The prevalence of radiation cystitis in the IMRT group was 0.69% and in the conventional group was 1.31%. Fischer t test was applied to calculate the p value as the number of cases with radiation cystitis was small; that was 0.54 and was also not significant.

DISCUSSION

100 cases of radiation induced proctitis and cystitis were studied and the results compared with relevant literature.

Age Distribution of 100 cases: Paul F. Anseline et al. (1981) conducted a study on 104 patients with radiation induced rectal injury. They found that in their study maximum number of patients belonged to the age group of 50 to 60 years. Similar results were seen in our study. 40% of the study population belonged to 50 to 59 years age group. Also, Yang et al. (2012) found that in their study of radiation proctitis and cystitis; maximum study population belonged to the age group of 40 to 60 years that is 44.53%.

Carcinoma Cervix stage distribution of 100 cases: In our study, all patients belonged to the stage IIB or IIIB of cancer cervix. 70% cases belonged to stage IIB. In data analysed by Yang et al. [6] and Perez et al. (1999); maximum study population also belonged to stage II and III of carcinoma cervix. In another study by Kim et al. (2008), stage IIA was seen to have maximum number of patients. Helena Barbar Zobec Logar et al. (2013) in their study also had maximum study population belonging to stage IIB and IIIB cervical cancer.

Grades of Radiation proctitis: In our study the number of patients with radiation proctitis was 89. Out of these 89 patients; 48.3% of the cases presented with grade II radiation proctitis. Montana et al. (1989) reported a frequency of 11% for radiation proctitis with grade I presentation being the commonest. Yang et al.[6] reported a prevalence of grade III radiation proctitis to be more as compared to grades I and II. Kim et al. (2008) reported similar results when compared to our study. Maximum patients presented with grade II radiation proctitis that was 20.4% in their study.

Grades of Radiation cystitis: The number of patients with radiation cystitis in the present study was 11 with grades II and III as the commonest presentation. Kim et al on the other hand reported grade I cystitis as their commonest presentation. Yang et al (2012) had comparative results with our study showing grade III radiation cystitis as their most common presentation. But, Montana et al. (1989) showed grade I cystitis to be a more common presentation with the frequency of radiation induced cystitis as 33.

Median time of development of complications: The median time of development of radiation proctitis was calculated as 13 months and that of radiation cystitis was calculated as 36 months. Kim et al. (2008) on the other hand reported a median time for development of radiation proctitis as 26 months and that of radiation cystitis as 43 months. Zobec Logar HB et al. (2013) found that in their study the mean interval of development of late gastrointestinal complications post radiotherapy was 27.6 months and for genitourinary complications was 28.7 months.

Technique of RT used and prevalence of complications: In our study, it was seen that with the use of conventional technique; the development of radiation proctitis and cystitis was more as compared to the IMRT techniques. Mundt AJ et al. (2001) also showed that there was lower grade 2 gastro-intestinal toxicity rate with the IMRT technique. Roeske JC et al. (2000) also reported that with the use of IMRT technique the rate of small bowel complications were less due to reduced dose to the surrounding structures. The results of their study were significant with p value <0.05. Heron DE et al. (2003) found out that with the IMRT technique there was a 66% reduction in the rectal dose and a 36% reduction in the bladder dose and thus decreasing the rate of acute and potentially late radiation related toxicities. Portelance L et al (2001), Georg D et al (2008) and Yang B et al. (2012) all showed lesser radiation induced toxicities with the use of IMRT technique as compared to conventional technique. The results by Gerg D et al. (2008) were significant; p<0.05. The overall prevalence of radiation proctitis in our study was 9.8% and that of radiation cystitis was 1.21%. Montana et al. (1989) reported an overall frequency of radiation proctitis as 11% and radiation cystitis as 6%. Yang et al. (2012) reported the overall incidence of radiation proctitis as 10.6% and radiation cystitis as 6.19%. Kim et al. (2008) reported that 42.6% of their study population had late rectal complications and 18.5% to have late bladder complications. But, grade III bowel and bladder complications developed in 7.4% and 1.9% patients respectively. Present study also revealed the frequency of radiation proctitis as 89% and radiation cystitis as 11%.

In our study; a slight lower prevalence rate of radiation induced complications was seen which may be attributed to the fact that a lot of cases are under-reported due to lack of knowledge about these symptoms and lack of follow-up post radiation treatment.

The efficacy of IMRT in cervical cancer patients was also evaluated by Hasselle MD et al (2011). In their study they evaluated 111 patients of cancer cervix who were treated with IMRT. The disease free survival rate in their study was 69% and 3 year overall survival rate was 78%. 7% patients in their study had late grade 3 toxicities.
ILLUSTRATIONS

CONCLUSION

Radiation cystitis and proctitis represents a relevant problem for those who have undergone pelvic radiotherapy. It increases the morbidity of the patients in a significant amount. Rates of gastrointestinal toxicities have been decreasing with improved radiation therapy techniques that allow for the targeted delivery of higher doses of radiation. Similar results were seen in our study. Radiation proctitis and cystitis was seen more frequently in patients receiving conventional radiotherapy as compared to the IMRT technique but our results were not significant. Further evaluation of these patients is required to suggest management protocols and also to avoid these complications. Also, prospective studies on radiation related toxicities can help us prevent them and improve treatment related outcomes in gynecological malignancies and achieve significant results.
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