

Prospective study of radiation related adverse events and its management in cancer patient at tertiary care teaching hospital

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ABSTRACT

Background: Radiation therapy is associated with certain adverse events which may cause significant discomfort to patient and may affect patient's life. The objective of the study was to assess radiation related adverse events in the patients who are on radiation therapy and to prevent and manage these adverse events.

Methods: A prospective observational study was conducted on 193 patients receiving radiotherapy in Oncology Department at Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab. One fraction (2 Gray) dose had been given to patients daily for five days in a week and monitor. The collected data was analyzed by applying IBM SPSS v21.

Results: The clinical results observed in 193 consecutive patients with follow-up of 7 weeks and graded according to RTOG Acute Radiation Morbidity Scoring Criteria. Majority of events were reported in age group of 41-60 years followed by 61-80 years, 20-40 years. Epidermal, mucosal, Genitourinary and Lower G.I. reactions are graded. The reactions managed by providing symptomatic treatment.

Conclusions: Radiation related adverse events have been found frequently in patients with radiotherapy and chemo-radiotherapy both. As the number of doses increase with time the grade of reactions also increases. Appropriate follow-up and management of these events reduces patient burden of treatment.

Keywords: Adverse events, Chemo-radiation effects, Management, RTOG, Radiotherapy

INTRODUCTION

Radiotherapy along with chemotherapy is an important approach to cancer treatment, however radiation therapy is associated with certain adverse event which may cause significant discomfort to patient and may impact on their day to day effect. The purpose of the study was to assess

radiation related adverse event in patient who are on radiation therapy and its management to provide maximum benefit to the patient with minimal side effects and to monitor the impact of adverse event in cancer patients. In all the cancers, the cells start dividing into multiple immature cells in uncontrollable way and spread into nearby tissues. In the case of cancer, the process of

formation of newer cells and apoptosis become imbalance and the body form non-stop new immature cells.¹ WHO report of 2012 worldwide shows that 14.1 million new cases of cancer in 5 years, out of which 8.2 million died and 32.6 million cases living with cancer. 57% new cases of cancer, 65% cases died, and 48% cases occurred in less developed regions. Overall the incidence rate of men is 25% higher than women.² Radiotherapy makes use of high energy waves or particles like protons, x-rays, electron beams or gamma rays for killing and destroying the cancerous cells. It is also called as radiation therapy, x-ray therapy or irradiation.³ Main purpose of radiotherapy is to destroy or kill the cancer cells and to decrease the growth of tumor cells, without harming the nearby healthy cells and tissue.^{4,5} Radiotherapy is given for the cancer therapy and for adjuvant therapy i.e. treatment after the main therapy to target or kill the remaining cancer cells.^{6,7} For some patients radiation therapy is sufficient to cure disease and for some patients it require in combination with immunotherapy, chemotherapy, hormone therapy or surgery.⁷

Adverse event is defined according to Common Terminology Criteria for Adverse Events, as it is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.⁸ According to National cancer institute an adverse event is unexpected medical problem that happens during treatment with a drug or other therapy.⁹

For skin toxicity grade 0 means no change over baseline, grade I means Follicular, faint or dull erythema/ epilation/ decreased sweating/ dry desquamation, grade II means Tender or bright erythema, moderate edema / patchy moist desquamation, grade III means Confluent, pitting edema, moist desquamation other than skin folds and grade IV means Ulceration, necrosis, hemorrhage. For mucosal toxicity grade 0 means no change over baseline, grade I means injection/ may experience mild pain not requiring analgesic, grade II means patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia, grade III means confluent fibrinous mucositis/ may include severe pain requiring narcotic and grade IV means Ulceration, hemorrhage or necrosis. For genitourinary toxicity grade 0 means No change, grade I means frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication, grade II means frequency of urination or nocturia which is less frequent than every hour, dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium), grade III means frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/ without clot passage and grade IV means hematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration or necrosis. For lower gastrointestinal including

pelvis toxicity grade 0 means no change, grade I means Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics, grade II means diarrhea requiring Para sympatholytic drugs (e.g., Lomotil)/ mucous discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics, grade III means Diarrhea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pags/abdominal distention (flat plate radiograph demonstrates distended bowel loops) and grade IV means Acute or sub-acute obstruction, fistula or perforation; gastrointestinal bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion. Any toxicity which caused death is graded V. All toxicities Grade III, IV or V must be verified by the Principal Investigator.¹⁰

METHODS

The study was conducted at Department of Oncology, Guru Gobind Singh Medical College and Hospital (GGSMCH), Faridkot. This was a prospective observational study. The study was carried out for a period of six months i.e. November 2015 to April 2016. Patients receiving radiation therapy and chemotherapy with radiotherapy for treatment of cancer both were included. Patients taking radiation treatment from Cobalt 60 and Linear accelerator (LINAC) machine were included. Daily one fraction (2 Gray) of dose has given to patients, five days in a week.

Patient receiving only chemotherapy, pregnant, lactating and nursing mother, children less than 18 years old, patient more than 85 years old, psychiatric patient and palliative patients were excluded. All the relevant data was collected from patient treatment chart, patient radiation chart, patient case sheet, interviewing the patients and communicating with senior radiation oncologist. Institutional Human Ethical Committee of ISF College of Pharmacy, Moga, Punjab approved the study ref. no: ISFCP/IEC/2015-16/P-07 on dated: 15-Sep-2015. A specially designed data collection form was developed. It includes demographic details like name, age, gender, medical history, height, weight, clinical data such as diagnosis, therapeutic details such as radiotherapy or chemo-radiotherapy, radiotherapy details such as dose, fraction, duration, machine used, adverse events observed, grade, type of treatment given, outcome, and management. The same details were documented electronically in specially design data base using SPSS v21. All the patients who were on radiation therapy or chemo-radiotherapy were monitored as per Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria for occurrence of radiation related epidermal, mucosal, genitourinary and lower G.I. reactions if any, and were assessed for different grades. Management of the reactions taken on the basis of grade of reaction and follow-up. The collected data was analyzed by applying IBM SPSS v21 statistics software for windows.

RESULTS

A total 193 patients satisfied inclusion criteria, were included in the study and shown adverse event induced by the radiation therapy.

Table 1: Patient’s demographic and related information.

Demographic data		Number of patients	Percentage of patients
Age (years)	<20	00	0.0%
	20-40	26	13.5%
	41-60	114	59.1%
	61-80	49	25.4%
	>80	04	2.1%
Gender	Female	147	76.2%
	Male	46	23.8%
Payment scheme	Government insured	174	90.2%
	Self-payment	19	9.8%
Social history	No Addiction	144	74.6%
	Tobacco	11	5.7%
	Alcoholic	33	17.1%
	Smoker	05	2.6%

Breast cancer was most commonly reported (n=82,42.5%), followed by head and neck cancer (n=53, 27.5%) and cervix cancer (n=47, 24.4%). 70% of the patients (n=136) were on radiotherapy alone and 30% patients (n=57) were on radiotherapy with chemotherapy. Linear accelerator (n=129,66.8%) is the most common used instrument for radiotherapy followed by cobalt 60 (n=64, 33.2%).

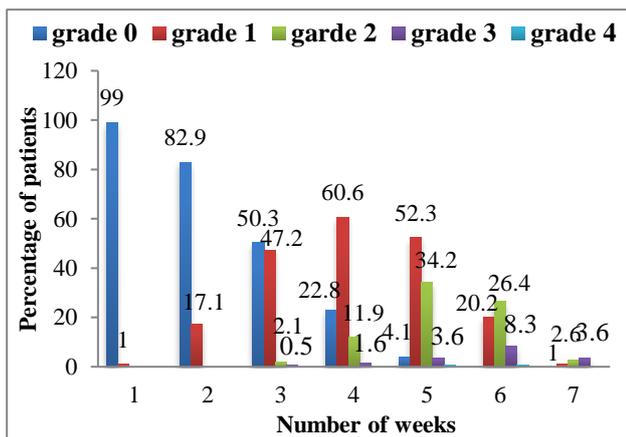


Figure 1: Epidermal reactions in cancer patients.

As shown in Figure 1, according to RTOG criteria out of 193 patients on week 1, 99% patients were showing grade 0 and 1% patients were showing grade 1 epidermal reactions. On week 2, 82.9% patients were showing grade 0 and 17.1% patients were showing grade 1 epidermal reactions. On week 3, 50.3% patients were showing grade

0, 47.2% patients were showing grade 1, 2.1% patients were showing grade 2 and 0.5% patients were showing grade 3 epidermal reactions. On week 4, 22.8% patients were showing grade 0, 60.6% patients were showing grade 1, 11.9% patients were showing grade 2 and 1.6% patients were showing grade 3 epidermal reactions. On week 5, 4.1% patients were showing grade 0, 52.3% patients were showing grade 1, 34.2% patients were showing grade 2, 3.6% patients were showing grade 3 and 0.5% patients were showing grade 4 epidermal reactions. On week 6, 20.2% patients were showing grade 1, 26.4% patients were showing grade 2, 8.3% patients were showing grade 3 and 0.5% patients were showing grade 4 epidermal reactions. On week 7, 1% patients were showing grade 1, 2.6% patients were showing grade 2 and 3.6% patients were showing grade 3 epidermal reactions.

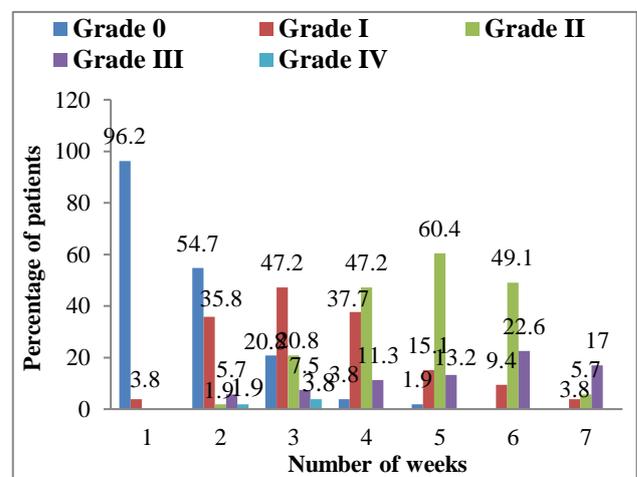


Figure 2: Mucosal reactions in head and neck cancer patients.

As shown in Figure 2, according to RTOG criteria out of 53 patients with Head and Neck cancer at week 1, 96.2% patients shown grade 0 and 3.8% patients shown grade 1 mucosal reaction. On week 2, 54.7% patients have shown grade 0, 35.8% patients shown grade 1, 1.9% patients shown grade 2, 5.7% patients shown grade 3 and 1.9% patients shown grade 4 mucosal reactions. On week 3, 20.8% patients have shown grade 0, 47.2% patients shown grade 1, 20.8% patients shown grade 2 and 7.5% patients shown grade 3 and 3.8% patients shown grade 4 mucosal reactions. On week 4, 3.8% patients have shown grade 0, 37.7% patients shown grade 1, 47.2% patients shown grade 2 and 11.3% patients shown grade 3 mucosal reactions. On week 5, 1.9% patients have shown grade 0, 15.1% patients shown grade 1, 60.4% patients shown grade 2 and 13.2% patients shown grade 3 mucosal reactions. On week 6, 9.4% patients have shown grade 1, 50.9% patients shown grade 2 and 22.6% patients shown grade 3 mucosal reactions. On week 7, 3.8% patients have shown grade 1, 5.7% patients shown grade 2 and 17.0% patients shown grade 3 mucosal reactions.

As shown in Figure 3, according to RTOG criteria out of 58 patients with pelvic cancer at week 1, 100% shown

grade 0 genitourinary reactions. On week 2, 96.6% patients shown grade 0 and 3.4% patients shown grade 1 genitourinary reactions. On week 3, 89.7% patients have shown grade 0, 8.6% patients shown grade 1 and 1.7% patients shown grade 2 genitourinary reactions. On week 4, 72.4% patients have shown grade 0, 24.1% patients shown grade 1 and 3.4% patients shown grade 2 genitourinary reactions. On week 5, 58.6% patients have shown grade 0, 36.2% patients shown grade 1 and 5.2% patients shown grade 2 genitourinary reactions. On week 6, 32.8% patients have shown grade 0, 58.6% patients shown grade 1 and 8.6% patients shown grade 2 genitourinary reactions.

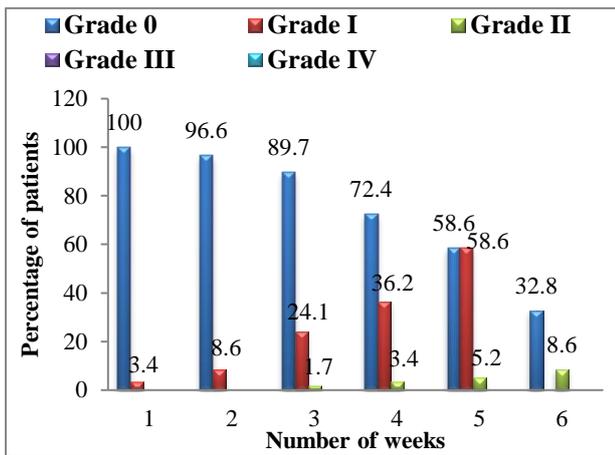


Figure 3: Genitourinary reactions in pelvic cancer patients.

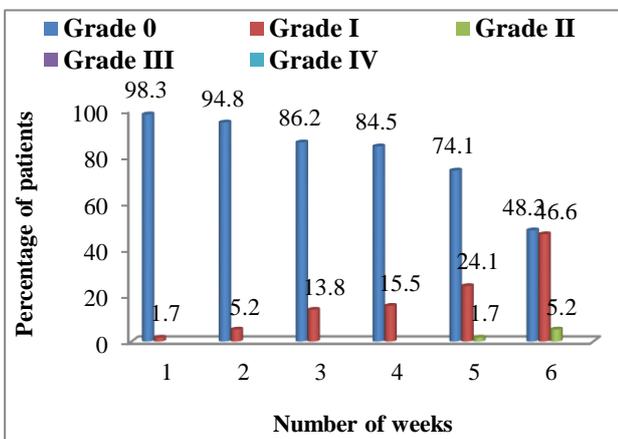


Figure 4: Lower G.I. reactions in pelvic cancer patients.

As shown in Figure 4, according to RTOG criteria out of 58 patients with pelvic cancer at week 1, 98.3% shown grade 0 and 1.7% patients showed grade 1 lower G.I. reactions. On week 2, 94.8% patients shown grade 0 and 5.2% patients shown grade 1 lower G.I. reactions. On week 3, 86.2% patients have shown grade 0 and 13.8% patients shown grade 1 lower G.I. reactions. On week 4, 84.5% patients have shown grade 0 and 15.5% patients shown grade 1 lower G.I. reactions. On week 5, 74.1% patients

have shown grade 0, 24.1% patients shown grade 1 and 1.7% patients shown grade 2 lower G.I. reactions. On week 6, 48.3% patients have shown grade 0, 46.6% patients shown grade 1 and 5.2% patients shown grade 2 lower G.I. reactions.

Management of adverse event

Table 2: Treatment of radiation induced epidermal reactions.

Grade	Number of patients	Management
1	117	No medicine
2	66	Gentian violet application on affected part
3	16	Stop the radiation 3-4days and gentian violet paint application on affected part
4	01	Stop the radiation 3-4days and gentian violet paint + metronidazole application on affected part

Table 3: Treatment of radiation induced mucosal reactions.

Grade	Number of patients	Management
0	53	Suggested steam inhalation and gargles of lukewarm water + 2 pinch table salt with beginning of radiotherapy
1	25	Vitamin B complex
2	32	Vitamin B complex + Benzylalkonium chloride
3	12	Stop the radiation for 3-4 days and cyclohexidine gargles or betadine gargles
4	02	Stop the radiation for 3-4 days and Cotromazole + Dexamithasone + Ranitidine (candid mouth paint + Dexona + Rantac).
	01	Lignocain + Vitamin B complex + pantoprazole

The epidermal reactions of the breast cancer, head and neck cancer and pelvic cancer patients had managed by providing symptomatic treatment. Patients had advised that do not apply any cream, lotion or oil to the radiation treated area, because it causes increase in the intensity of the radiation on epidermal surface. This may damage epidermal surface to high grade. The patients who developed grade 3 or 4 reactions, the radiation dose stopped for 3-4 days, this help in the stabilization of reactions which was further not increased on continuing the radiation treatment. Table 2 showing the number of

patients treated for different grades of reaction management.

The patients of head and neck cancer had advised to take steam inhalation and gargles of lukewarm water with 2 pinch table salt with beginning of radiotherapy for the prevention of mucosal reactions. The patients who developed grade 3 or 4 reactions, the radiation dose stopped for 3-4 days, this help in the stabilization of reactions which was further not increased on continuing the radiation treatment. The management treatment given for the different grades of mucosal reactions has shown in Table 3.

Table 4: Treatment of radiation induced genitourinary reactions.

Grade	Number of patients	Management
0	58	Suggested to drink plenty of water
1	34	Amikacin
2	05	Stop the radiation and amikacin

Table 5: Treatment of radiation induced lower G.I. reactions.

Grade	Number of patients	Management
0	58	suggested to drink plenty of water
1	27	Loperamide (Eldoper)
2	03	Stop the radiation and Ranitidine + Loperamide (Rantac + Eldoper)

The patients of pelvic cancer had developed genitourinary and lower G.I. reactions. Patients advised to drink plenty of water for the prevention of radiation reactions. The patients who developed grade 3 or 4 reactions, the radiation dose stopped for 3-4 days, this help in the stabilization of reactions which was further not increased on continuing the radiation treatment. The management treatment given for the different grades of reactions for genitourinary and lower G.I. has shown in Table 4 and 5 respectively.

Table 6: Outcome of the events.

Outcomes	Number of patients	Percentage of patients
Recovered	57	29.53%
Recovering	87	45.07%
Continuing	28	14.50%
Unknown	17	8.80%
N/A	04	2.07%

Outcome of the adverse events after its management and symptomatic treatment majority of the patients were recovering (n=87,45.07%) followed by recovered (n=57, 29.53%) then continuing (n=28, 14.50%), unknown (n=17, 8.80%) and N/A (n=4, 2.07%).

DISCUSSION

The result of our study suggests that patient undergoing radiation therapy is at increased risk of several acute adverse effects. Majority of events were reported in age group of 41-60 years (59.1%) followed by 61-80 years (25.4%), 20-40 years (13.5%). This could be explained by number hospital admission or the chance of getting disease in individuals or these age groups. The result is in concordance with recent cancer statistics obtained from government of U.K. in which about 53% of the cancer occurred in people age group of 51-70 years and 10% in patients belonging to age group 30-69 years.¹¹

Study was conducted by Singla S, et al to evaluate the severity of oral mucositis and xerostomia at different doses of radiation therapy among patients of head and neck cancer. Evaluation for oral mucositis was done at 10 gray, 20 gray, 40 gray and 60 gray. The mean value of oral mucositis was 0.00, 0.00, 1.84, 3.84 at 10, 20 40 and 60 gray respectively. They found that there was no oral mucositis at 10 and 20 gray. Out of 25 patients at 40 gray, 21 patients were having grade-2 mucositis and 4 patients were having grade-1 mucositis. Similarly, out of 25 patient at 60 gray 21 were having grade-4 mucositis and 4 were having grade-3 mucositis.¹² In our study, evaluation for oral mucositis was done on weekly basis at dose 2 gray per day. Out of 53 patients, at week 1, 2 patients have shown grade 1 mucositis. On second week, 19 patients shown grade 1, 1 patient has shown grade 2, 3 patients shown grade 3 and 1 patient shown grade 4 mucositis. On 3rd week, 25 patients have shown grade 1, 11 patients shown grade 2 and 4 patients shown grade 3 and 2 patients shown grade 4 mucositis. On 4th week, 20 patients have shown grade 1, 25 patients shown grade 2 and 6 patients shown grade 3 mucositis. On 5th week, 8 patients have shown grade 1, 32 patients shown grade 2 and 60 patients shown grade 3 mucositis. On 6th week, 5 patients have shown grade 1, 26 patients shown grade 2 and 12 patients shown grade 3 mucositis. On 7th week, 2 patients have shown grade 1, 3 patients shown grade 2 and 9 patients shown grade 3 mucositis. A study conducted on 53 head and neck cancer patients and Grade 3-4 mucositis was observed in 21 patients (39.6%). 51 of the patients (96.2%) received the full dose of RT (70 Gy) over a median period of 50 days (range 46-62 days).¹³

In a study shows total 157 patients (56%) experienced Radiation Therapy Oncology Group Grade 0 or I acute skin toxicity; 102 patients (43%) developed Grade II acute skin toxicity and only 3 (1%) experienced Grade III toxicity. The cosmetic results at 12 months (95 patients analyzable) were rated as excellent/good in 94 patients (99%). No skin telangiectasias, significant fibrosis, or

persistent breast pain was noted.¹⁴ In our study on grade I reactions no medicine prescribed, on grade II reactions gentian violet paint was prescribed, on grade III reactions radiation was stopped for 3-4 days and gentian violet paint was prescribed and on grade IV reactions radiation was stopped for 3-4 days and gentian violet paint + metronidazole was prescribed. The outcome result at 7th week of treatment (76 patients who develop skin toxicity were analyzable) was good 43 patients recovered and 33 patients recovering.

Duration of study was confined only for 6 months.

Limitation of the study was due to short duration of study we could not identify delayed adverse event and adverse events occurred after discharging patients were not reported.

CONCLUSION

The patients observed with follow-up of 7 weeks. Radiation related adverse events were found frequently in patients with radiotherapy and chemo-radiotherapy both. The patients which are on radiation therapy were definitely develop the adverse reactions therefore patients on the radiation and chemo-radiation therapy required proper monitoring and careful follow-up to identify radiation induced toxicity. Appropriate follow-up and management of these events reduces patient burden of treatment.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Human Ethical Committee of ISF College of Pharmacy, Moga, Punjab (ISFCP/IEC/2015-16/P-07)

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