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Original Article

Sociodemographic, clinical profile, and treatment characteristics of oncology patients developing radiation recall phenomenon: Two tertiary care center's experience of an eternal unpredictable phenomenon of cancer treatment

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Abstract

Objectives: To determine the socio-demographic and clinical profile of cancer patients developing radiation recall phenomenon or radiation recall dermatitis following chemotherapy administration, previously treated with external irradiation. We assessed its incidence, severity, frequency, differentiation from radio-sensitization and radiation-dermatitis, its correlation with radiation dose and chemotherapeutic agent, and various parameters affecting its occurrence. **Materials and Methods:** This observational prospective study was designed for 1092/2676 (50.2%) patients of histologically proven carcinoma breast, carcinoma lung, lymphomas, chest wall sarcomas, thymomas, thymic carcinomas, nasopharyngeal cancer, bladder carcinoma, rectal cancer, and metastatic cases who received radiation therapy followed by chemotherapy. Intake, treatment, observation, and follow-up were done from July 2014 to July 2021 for 7 years in two tertiary care cancer institutes of government setup. **Results:** In our study, majority of recall phenomena were reported in breast carcinoma 43/71 (60.5%) followed by carcinoma esophagus with 07/71 (9.8%) cases. Females developed 54.9% grade-I/II and 90% grade-III/IV recall cases compared to males with 45.1% and 10% cases, respectively ($P = 0.005$). Median radiation dose used was 45 Gy (dose range 8–70 Gy) ($P = 0.656$). Docetaxel resulted in 55% recall cases followed by paclitaxel with 12.7% of cases. Combination therapy reported 71.8% of cases compared to monotherapy with 28.2% of cases. Recall-cases recorded in the time period of 3–4 weeks between radiation and chemotherapy were 59/71 (83%) and those reported in >4 weeks were 12/71 (17%). Time-gap between 3 and 4 weeks reported 49% grade-I/II and 100% grade-III/IV recall-cases while time-gap >4 weeks resulted in 26% and 0% cases respectively ($P = 0.000$). **Conclusion:** In this study, taxanes and platinum-agents were the most common chemotherapeutic drugs involved in the occurrence of the recall phenomenon. Multi-drug regimens resulted in higher recall cases compared to monotherapy. Radiation dosage did not cause any significant impact. The risk and severity of recall reactions increased with female gender and shorter time-interval between radiation and systemic therapy, while early-onset recall cases displayed greater severity. This precedented but unpredictable phenomenon ceases to be a topic to be discarded in this modern era of highly conformal radiation therapy techniques and targeted cancer therapy.

Keywords: *Chemotherapy, Radiation recall dermatitis, Radiation recall phenomenon, Radiation therapy*

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Introduction

Radiation recall phenomenon (RRP) or radiation recall dermatitis (RRD) has been described by authors both as the "moderately common" and "moderately rare"[1] nemesis of radiation-therapy (RT) following its first report way back

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in 1959 by D'Angio[2] describing recall associated with actinomycin-D [2,3]. In this rather interesting phenomenon, the skin/mucosa recalls the earlier irradiation effect after chemotherapeutic, cytotoxic agents, or other drug classes are administered, in the form of inflammatory reactions ranging from mild to severe [4,5], resulting in significant morbidity and even mortality. Majority of published literature have described RRD as a synonym of RRP, others have reported reactions affecting the internal tissues[6] such as oral mucosa, lung parenchyma, gastrointestinal tract (GIT), especially esophagus, genitourinary tract [7,8], central nervous system [9], and even muscular layer [10], RRD has been mainly reported in breast carcinoma patients receiving thoracic irradiation, while its occurrence in malignancies such as melanoma [11], lung [7,8,12], oropharynx [13], nasopharynx [8], and non-Hodgkin lymphomas[8] have also been published.

RRP is generally diagnosed based on presenting history, symptoms, signs, and clinical examination without any substantial need of pathological [7,14,15] or radiological confirmation [15]. However, biopsy may be done in case of suspicion of skin infection or recurrence [15]. The severity of RRD ranges from mild to moderate to severe [12], graded as per various versions of the United States National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) published over the years. Radiation-dermatitis (RD) is the most common acute manifestation of radiation which may mimic RRD making it imperative to differentiate between RD and RRD. RD generally appears within the second week of the RT schedule and majority of patients who develop RRD have no RD during or at the conclusion of RT. RRD must occur after completion of RT and resolution of acute RD. Another clinical entity resembling RRD is radio-sensitization (RS) which is any physical, chemical, or pharmacological intervention that increases the lethal effects of radiation when administered in conjunction with it within a week [4]. A week less and a week more between RT and systemic therapy has been described as the discriminating point between RS and RRD respectively [4-8]. RRD being rarer than RS, have a time-frame of days to months to years for its initial occurrence [13-15]. Cellulitis, fungal infection, contact dermatitis, eczema, lichen planus, pemphigus, erythema multiforme, toxic epidermal necrolysis, and Stevens–Johnson syndrome are few dermatological pathologies which need to be ruled out.

The pathophysiology of RRP/RRD still remains under the magnifying glass without a clear-cut etiology. Several hypotheses have been postulated over years like drug hypersensitivity reactions[4] causing nonautoimmune inflammatory response with prior exposure to radiation therapy resulting in cytokine release [4,7,16,17], long-term changes in cellular morphology by RT [4], upregulation of cytokines by chemotherapy (CMT) [15-20], DNA damage due to oxidative stress culminating in keratinocyte necrosis [4,7,15-20], "remembered" reaction of stem-cells surviving the initial radiation exposure, after successive CMT [4,16,17], endothelial cell damage leading to vascular insufficiency, upregulation of thymidine phosphorylase [18,19], p53 mutation [20], mitochondrial dysregulation [19-22] and activation of thymidine-phosphorylase causing angiogenesis in the irradiated area due to pro-drug activation [23]. Diverse drugs have caused RRP without any pattern or characteristic and it has been difficult to predict which therapeutic agent will cause recall-reaction. Cytotoxic-drugs causing RRP/RRD include anthracycline (adriamycin/doxorubicin), taxanes (docetaxel and paclitaxel), antimetabolites (gemcitabine and capecitabine), bevacizumab [24], pemetrexed [12], gefitinib [25], Herceptin [5], ixabepilone[7] and BRAF-inhibitors such as dabrafenib and trametinib [11]. Regarding RT, no particular dose threshold has been associated with RRP since most reports are single case studies, although higher doses have been implicated [26]. Symptomatic care with anti-histamines, corticosteroids, and nonsteroidal anti-inflammatory drugs have been used to tide over the acute symptoms. Using low-dose RT and prolonging the time interval between RT and CMT has been postulated as the main measures to prevent RRP [5,7,26,27].

Materials and methods

Study design, sample size, inclusion, and exclusion criteria

A prospective observational study was designed to determine the clinical profile of cancer patients developing RRP/RRD undergoing treatment in the department of malignant disease treatment center of two tertiary care cancer institutes with academic and research potential of government setup. Cases who were actively undergoing RT and CMT were periodically observed and evaluated for the occurrence of RRP. All patients were treated as per standard of care and international guidelines. The only intervention done was to manage the recall reactions. The intake planned treatment, and follow-up were conducted from July 2014 to July 2021 over 7 years. The study population consisted of patients belonging to any gender, race, or ethnicity from both rural and urban backgrounds. Out of the total of 2676 cases registered during the study period, 1092 histologically confirmed locally advanced cases of carcinoma breast, lung, lymphomas, soft-tissue sarcoma (STS), thymomas, thymic carcinomas, nasopharyngeal cancers, bladder, and rectal cancer cases were enrolled. Metastatic cases were also included as per inclusion criteria: (1) age18–75 years, (2) cases receiving CMT after previous RT, (3) Karnofsky Performance Status (KPS) of ≥60%, (4) no allergic/anaphylaxis history, and (5) no active skin infection. Exclusion criteria: (1) cases receiving RT or CMT from other institutes, (2) patients who discontinued RT before completion, (3) time-interval between RT and CMT <07 days, (4) nonhealing RD, (5) RS, and (6) patients with KPS <60%. All procedures were in accordance with the institutional scientific advisory, ethical and regulatory committee, National research committee, and 1964 declaration of Helsinki. The IRB (Institutional review board) reference number of the manuscript is IRB/CHSC/64/2019. Consent of the patients and their relatives were taken.

Disease evaluation

To maintain the uniformity of study, severity grades of recall phenomenon were evaluated according to CTCAE versions 4.0: Grade-I: Combined area of ulcer <1 cm;

nonblanchable erythema of intact skin with associated warmth or edema; Grade-II: Combined area of ulcer 1–2 cm, partial thickness skin loss involving skin or subcutaneous fat; Grade-III: Combined area of ulcer >2 cm, full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia; Grade-IV: Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone or supporting structures with or without full-thickness skin loss; Grade-V: Death. When the patients presented with lesions characteristic of RRP/RRD, they were jointly and exhaustively evaluated by the principal workers of two institutes in concurrence with the medical oncologists in multi-disciplinary tumor boards and oncology clinics. Further, these patients were regularly monitored in the weekly radiation clinics to confirm the morphology of RRP/RRD.

Treatment and follow-up

As this study was undertaken in a government set-up, all patients were treated with the 2-dimensional-RT (2-DRT) technique in both institutes. RT doses were imparted according to the stage of malignancies, ranging from 8 Gy in metastatic cases to 70 Gy in primary cases. CMT regimen was chosen according to the neoplastic pathology and stage. Three monthly follow-ups included physical examination, laboratory analysis, chest radiography, and pan-endoscopy. Computed tomography, magnetic resonance imaging, and 18-fluoro-deoxy glucose whole-body positron-emission tomography scan were performed at 6 months and 12 months, thereafter on case-to-case basis. Telephonic follow-up was done for patients who were unable to come physically. Patients developing RRP/RRD were managed symptomatically and ongoing treatments were resumed after their resolution.

Statistical analysis

Data were entered from predesigned forms into an electronic spreadsheet (Microsoft-excel) and analyzed using Statistical Product and Service Solutions version-20 (SPSS-20, IBM, Armonk, NY, USA). Pearson Chi-square test for Fisher's Exact was used to compare proportions. Univariate analysis was used to assess the severity of RRP/RRD as per specific sociodemographic and clinical factors. Two-tailed $P < 0.05$ was taken as statistically significant. To assess the precision of the estimate 95% confidence intervals for all probabilities were calculated.

Results

Overall, 2676 cases of various malignancies were registered over 7 years duration and 1092/2676 (50.2%) cases of malignancies fulfilled the eligibility criteria. Patient characteristics and distribution of malignancies as per inclusion criteria registered from July 2014 to July 2021 are shown in Table 1. RRP was recorded in 71/1092 (6.5%) patients. Males constituted 25/71 (35.2%) and females 46/71 (64.8%) cases. The median age for males was 65 years (age range 40–78 years) and for females 61 years (age range 45–71 years). Maximum RRP was reported in breast carcinoma patients accounting for 43/71 (60.5%) cases [Figures 1-3] followed by carcinoma esophagus with 07/71 (9.8%) cases, carcinoma prostate 06/71 (8.5%),

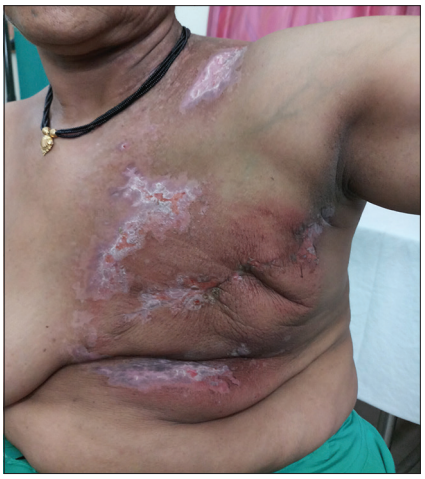

Figure 1: Post-modified radical mastectomy case in a left sided breast carcinoma with grade-III radiation recall dermatitis developing over left chest wall and left supra-clavicular area within 1 week after docetaxel monotherapy

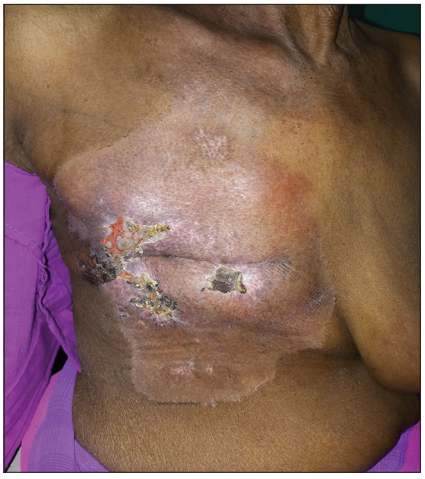

Figure 2: Grade-III radiation recall dermatitis seen over right chest wall in post-modified radical mastectomy breast carcinoma patient in less than a week after combination therapy with docetaxel and Herceptin

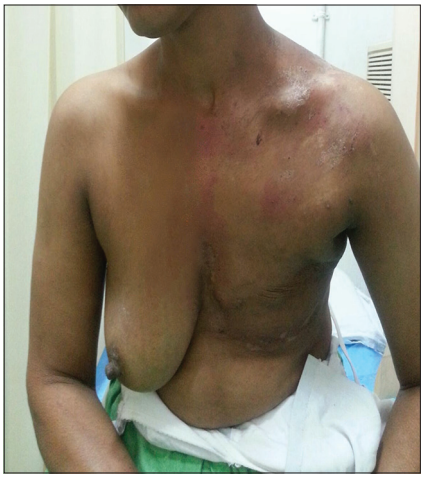

Figure 3: Grade-II radiation recall dermatitis developing over left chest-wall and left supra-clavicular area in less than a week after adjuvant therapy with single-agent docetaxel in a post-modified radical mastectomy breast carcinoma case

Table 1: Patient characteristics, sociodemographic factors and distribution of malignancies as per inclusion criteria enrolled from July 2014-July 2021

Type of malignancy and number of cases enrolled, *n*/*N* (%)	Number of cases developing RRP, *n*/*N* (%)	Median age of patients developing RRP years (range)	Gender, *n*/*N* (%)	Co-morbidity, *n*/*N* (%)	Geographical distribution, *n*/*N* (%)	Median KPS % (range)	Stage, *n*/*N* (%)
Carcinoma breast: 389/1092 (35.6)	43/389 (11.1)	61 (45-71)	Female=43/43 (100) Male=0 (0)	HTN=10/43 (23.3) DM=03/43 (6.9) CAD=01/43 (2.3)	North=19/43 (44.2) South=15/43 (34.9) East=3/43 (6.9) West=6/43 (14.0)	70 (60-80)	II=05/43 (11.6) III=36/43 (83.7) IV=02/43 (4.7)
Carcinoma lung: 87/1092 (7.9)	4/87 (4.5)	69 (65-71)	Female=1/4 (25) Male=3/4 (75)	HTN=3/4 (75) CAD=1/4 (25)	North=4/4 (100)	70 (60-70)	III=1/4 (25) IV=3/4 (75)
Carcinoma rectum: 179/1092 (16.4)	3/179 (1.6)	50 (45-53)	Female=0 Male=3/3 (100)	Nil	North=1/3 (33.3) South=1/3 (33.3) East=1/3 (33.3)	70 (60-80)	III=2/3 (66.7) IV=1/3 (33.3)
Carcinoma Nasopharynx: 51/1092 (4.6)	2/51 (3.9)	46 (40-52)	Female=0 Male=2/2 (100)	Nil	South=1/2 (50) West=1/2 (50)	80 (80-80)	II=1/2 (50) III=1/2 (50)
Thymoma: 14/1092 (1.2)	1/14 (7.1)	54	Female=1/1 (100) Male=0	Nil	North=1/1 (100)	80	III=1/1 (100)
Carcinoma esophagus: 149 (13.6)	7/149 (4.6)	64 (56-70)	Female=1/7 (14.3) Male=6/7 (85.7)	DM=1/7 (14.3)	North=4/7 (57.1) South=2/7 (28.6) West=1/7 (14.3)	80 (70-80)	II=2/7 (28.6) III=5/7 (71.4)
Lymphoma: 37 (3.3)	3/37 (8.1)	43 (40-51)	Female=0 Male=3/3 (100)	Nil	North=1/3 (33.3) South=1/3 (33.3) West=1/3 (33.3)	70 (60-70)	II=1/3 (33.3) III=2/3 (66.7)
Soft tissue sarcoma: 43 (3.9)	2/43 (4.6)	62 (59-65)	Female=0 Male=2/2 (100)	Nil	North=2/2 (100)	80 (80-80)	III=2/2 (100)
Carcinoma prostate: 110 (10.0)	6/110 (5.4)	71.5 (65-78)	Female=0 Male=6/6 (100)	HTN=4/6 (66.7) DM=2/6 (33.3)	North=1/6 (16.7) South=3/6 (50) West=2/6 (33.3)	60 (60-80)	III=2/6 (33.3) IV=4/6 (66.7)

KPS: Karnofsky performance status, HTN: Hypertension, DM: Diabetes Mellitus, CAD: Coronary artery disease, RRP: Radiation recall phenomenon

carcinoma lung 04/71 (5.6%), [Figures 4 and 5] carcinoma rectum 03/71 (4.2%), [Figure 6] lymphoma 03/71 (4.2%), nasopharyngeal carcinoma 02/71 (2.8%), STS 02/71 (2.8%) [Figure 7], and thymoma with 01/71 (1.4%) cases [Figure 8]. No RRP was reported in thymic carcinoma and carcinoma bladder cases. Overall, grade-I RRP was reported in 32/71 (45%) cases, grade-II in 19/71 (26.7%), grade-III in14/71 (19.7%), and grade-IV in 06/71 (8.4%) cases. No grade-V reaction was recorded [Table 2].

A detailed description of RT dose and CMT regimens, time-interval between RT and CMT, time of onset of RRP postCMT, manifestations, and grades of RRP have been presented in Table 3. RRD constituted 66/71 (93%) cases while recall esophagitis was seen in 02/71 (2.8%), recall proctitis in 01/71 (1.4%) [Figure 6], recall mucositis in 01/71 (1.4%) and recall pneumonitis in 01/71 (1.4%) cases [Figure 7]. The median RT dose at which RRP/RRD appeared was 45 Gy (RT dose range 8–70 Gy). Different CMT regimens were used for various malignancies as per their clinicopathological stage. In breast cases, combined docetaxel/Herceptin resulted in 16/43 (37.2%) RRD cases and 4/5 (80%) grade-IV severity while docetaxel as monotherapy resulted in 14/43 (32.6%) cases with 1/5 (20%) grade-IV reaction. Docetaxel was involved in 31/43 (72.1%) RRD cases, paclitaxel in 9/43 (20.9%), doxorubicin in 1/43 (2.3%), herceptin in 1/43 (2.3%), and tamoxifen in 1/43 (2.3%) cases [Table 3]. Maximum RRD was seen in patients undergoing modified radical mastectomy with 29/41 (70.7%) cases compared to breast conservative surgery with 12/41 (29.3%) reports [Table 3].

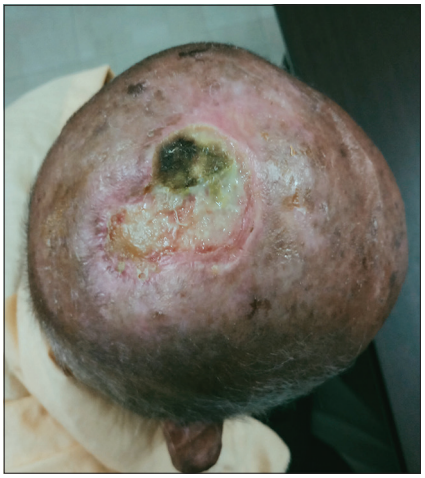

Figure 4: In a case of metastatic carcinoma lung with brain metastasis Grade-IV radiation recall dermatitis developing over the scalp of the patient after combination-therapy with carboplatin, pemetrexed and pembrolizumab

Figure 5: Grade-I radiation recall dermatitis appearing over left upper-limb in metastatic carcinoma lung with bone metastasis after subsequent systemic-therapy with carboplatin, paclitaxel and bevacizumab

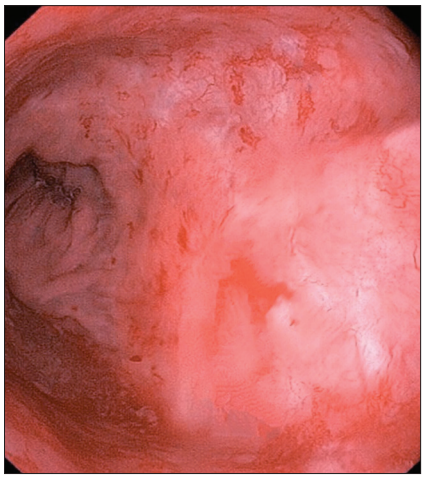

Figure 6: Grade-II recall-proctitis detected on procto-colonoscopy within a month of completing 4 cycles of CAPEOX regimen in carcinoma rectum

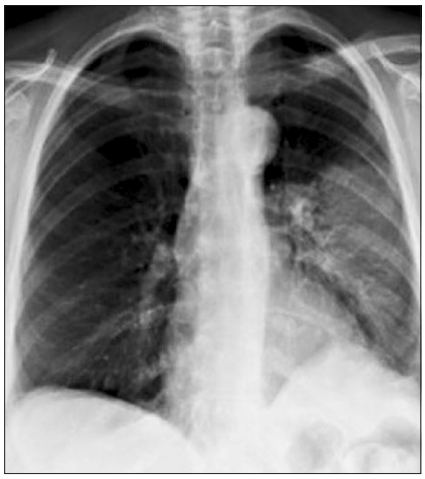

Figure 7: Grade-I recall-pneumonitis detected on chest-radiograph in chest wall sarcoma case 1 month after completion of 5 cycles of MAID regimen

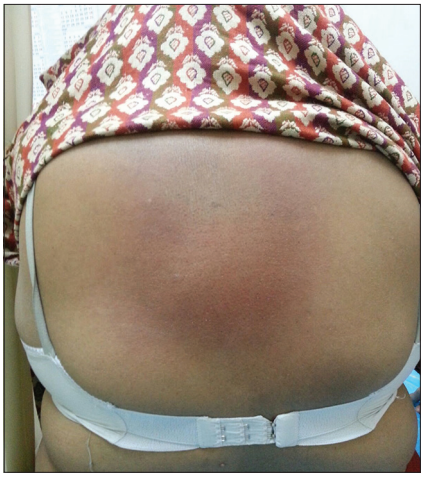

Figure 8: Grade-I radiation recall dermatitis developing over the back in postsurgery (R1-resection) recurrent thymoma patient within a month of starting chemotherapy

In carcinoma lung cases, carboplatin/pemetrexed resulted in grade-IV RRD of the scalp while cisplatin/pemetrexed caused grade-II reaction; however, due to only very few cases this result could not be compared directly [21]. In rectum patients, 5-fluorouracil (5-FU) resulted in recall dermatitis while capecitabine resulted in recall proctitis. In esophageal adenocarcinoma cases, docetaxel/5-FU/cisplatin resulted in grade-I recall dermatitis while in squamous cell carcinoma capecitabine resulted in grade-II recall-esophagitis. In relapsed diffuse large B-cell lymphoma carboplatin/cisplatin/rituximab/etoposide/ifosfamide caused RRD, while in classical Hodgkin's lymphoma cisplatin/cytarabine resulted in recall-esophagitis. Doxorubicin along with ifosfamide resulted in grade-I RRD in extremity sarcoma while it resulted in grade-I recall pneumonitis [Figure 7] when combined with dacarbazine in chest-wall sarcoma. Combination therapy of doxorubicin/cyclophosphamide/cisplatin resulted in grade-I recall dermatitis [Figure 8] in recurrent thymoma [Table 3]. Overall, either as monotherapy or as combination-therapy, docetaxel was involved in 39/71 (55%) recall cases, followed by paclitaxel with 09/71 (12.7%), 5-FU with 09/71 (12.7%), oxaliplatin with 08/71 (11.3%), cisplatin with 07/71 (9.8%), carboplatin with 04/71 (5.6%), doxorubicin with 04/71 (5.6%), and capecitabine with 02/71 (2.8%) cases. Single-agent CMT recorded 20/71 (28.2%) cases while combination therapy resulted in 51/71 (71.8%) recall phenomenon [Table 3].

The time interval between RT and CMT was recorded at 3–4 weeks and >4 weeks. The number of RRP/RRD cases observed in 3–4 weeks period were 59/71 (83%) and those reported in >4 weeks were 12/71 (17%). The severity of RRP/RRD observed in 3–4 weeks were grade-I 21/32 (65.6%), grade-II 18/19 (94.7%), grade-III 14/14 (100%), and grade-IV 06/06 (100%). Gap of >4 weeks resulted in 11/32 (34.4%) grade-I, 01/19 (5.3%) grade-II, but no grade-III or grade-IV cases [Table 2]. Similarly, the time of onset of RRP/RRD after administration of CMT was recorded at <1 week, 1–3 weeks, 3–5 weeks, and >5 weeks. The number of RRP/RRD cases which occurred in <1 week were 35/71 (49.3%), 1–3 weeks 04/71 (5.6%), 3–5 weeks

Table 2: Sequence of treatment regimens used in the study and grades of radiation recall phenomenon observed in each malignancy

Sequence of treatment regimens used in malignancy (*n*)	Grades of RRP/RRD, *n/N* (%)				
***n*=Number of cases developing RRP**	**I**	**II**	**III**	**IV**	**V**
Carcinoma breast (43)	14/43 (32.5)	11/43 (25.5)	13/43 (30.2)	5/43 (11.6)	0/43 (0.0)
Upfront MRM → adj CMT → RT → CMT/HT (17)	6/17 (35.2)	4/17 (23.5)	5/17 (29.4)	2/17 (11.7)	0/17 (0.0)
Upfront BCS → adj CMT → RT → CMT/HT (5)	2/5 (40.0)	2/5 (40.0)	1/5 (20.0)	0/5 (0.0)	0/5 (0.0)
NACMT → surgery → RT → CMT/HT (19)	4/19 (21.0)	5/19 (26.3)	7/19 (36.8)	3/19 (15.7)	0/19 (0.0)
Upfront metastatic					
(Bone) palliative RT → palliative CMT (2)	2/2 (100)	0/2 (0.0)	0/2 (0.0)	0/2 (0.0)	0/2 (0.0)
Carcinoma lung (4)	2/4 (50)	1/4 (25)	0/4 (0.0)	1/4 (25)	0/4 (0.0)
NSCLC (1)	1/1 (100)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
RT/CCRT → CMT/TT					
Upfront metastatic					
(Brain) palliative RT → palliative CMT (2)	0/2 (0.0)	1/2 (50)	0/2 (0.0)	1/2 (50)	0/2 (0.0)
(Bone) palliative RT → palliative CMT (1)	1/1 (100)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
Carcinoma rectum (3)	2/3 (66.6)	1/3 (33.3)	0/3 (0.0)	0/3 (0.0)	0/3 (0.0)
Primary (2)	1/2 (50)	1/2 (50)	0/2 (0.0)	0/2 (0.0)	0/2 (0.0)
NACCRT → surgery → adj CMT					
Upfront metastatic					
(Bone) palliative RT → palliative CMT (1)	1/1 (100)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
Carcinoma nasopharynx (2)	1/2 (50)	0/2 (0.0)	1/2 (50)	0/2 (0.0)	0/2 (0.0)
Primary (2)	1/2 (50)	0/2 (0.0)	1/2 (50)	0/2 (0.0)	0/2 (0.0)
CCRT → adj CMT					
Thymoma (1)	1/1 (100)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
Recurrent (1)	1/1 (100)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
Carcinoma esophagus (7)	5/7 (71.4)	2/7 (28.5)	0/7 (0.0)	0/7 (0.0)	0/7 (0.0)
Primary ADC (5)	3/5 (60)	2/5 (40)	0/5 (0.0)	0/5 (0.0)	0/5 (0.0)
NACCRT → surgery → CMT					
Primary SCC (2)	2/2 (100)	0/2 (0.0)	0/2 (0.0)	0/2 (0.0)	0/2 (0.0)
NACCRT → surgery → CMT/TT					
Lymphoma (3)	1/3 (33.3)	2/3 (66.6)	0/3 (0.0)	0/3 (0.0)	0/3 (0.0)
Relapsed DLBCL (2)	1/2 (50)	1/2 (50)	0/2 (0.0)	0/2 (0.0)	0/2 (0.0)
CMT → RT → CMT					
Refractory CHL (1)	0/1 (0.0)	1/1 (100)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
CMT → RT → CMT					
Soft tissue sarcoma (2)	1/2 (50)	1/2 (50)	0/2 (0.0)	0/2 (0.0)	0/2 (0.0)
Extremity sarcoma (1)	0/1 (0.0)	1/1 (100)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
NART → surgery → CMT					
Chest wall sarcoma (1)	1/1 (100)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
NART → surgery → CMT					
Carcinoma prostate (6)	5/6 (83.3)	1/6 (16.6)	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)
Recurrent primary (2)	2/2 (100)	0/2 (0.0)	0/2 (0.0)	0/2 (0.0)	0/2 (0.0)
RT + ADT → CMT + ADT					
Upfront metastatic					
ADC (bone) (3)	2/3 (66.6)	1/3 (33.3)	0/3 (0.0)	0/3 (0.0)	0/3 (0.0)
Palliative RT → palliative CMT					
Others (bone) (1)	1/1 (100)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
Palliative RT → palliative CMT					

RT: Radiation therapy, CMT: Chemotherapy, HT: Hormonal therapy, TT: Targeted therapy, ADT: Androgen deprivation therapy, ADC: Adenocarcinoma, SCC: Squamous cell carcinoma, MRM: Modified radical mastectomy, BCS: Breast conservative surgery, NACMT: Neo-adjuvant chemotherapy, NACCRT: Neo-adjuvant concurrent chemo-radiotherapy, NART: Neo-adjuvant radiotherapy, CCRT: Concurrent chemo-radiotherapy, NSCLC: Nonsmall cell lung carcinoma, STS: Soft tissue sarcoma, DLBCL: Diffuse large B-cell lymphoma, CHL: Classical Hodgkin's lymphoma, RRP: Radiation recall phenomenon, RRD: Radiation recall dermatitis

19/71 (26.8%) and >5 weeks 13/71 (1.9%). As for the grades of RRP, onset <1 week demonstrated 06/32 (18.8%) grade-I, 12/19 (63.2%) grade-II, 12/14 (85.7%) grade-III, and 5/6 (83.3%) grade-IV cases. Onset between 1 and 3 weeks showed 03/32 (9.4%) grade-I, 01/19 (5.3%) grade-II, and no grade-III, and grade-IV cases. Onset between 3 and 5 weeks resulted in 13/32 (40.6%) grade-I, 04/19 (21%) grade-II, 02/14 (14.3%) grade-III, and no grade-IV recall-reactions. For onset >5 weeks, 10/32 (31.3%) grade-I, 2/19 (10.5%) grade-II, no grade-III and 1/6 (16.7%) grade-IV cases were recorded [Table 3]. For the purpose of determining the statistical significance of different socio-demographic and clinical factors which may influence the incidence and severity of RRP, we divided the recall cases into two groups. Group-1

Table 3: Detailed summary of radiation recall cases associated with radiation-therapy and chemotherapeutic regimens used in the study

Malignancy (*n*)	RT dose (Gy)	CMT/HT/TT regimen	Manifestation of RRP (*n*)	Grades of RRP/ RRD I/II/III/ IV/V (*n*)	Time-interval between RT and CMT (weeks)	Time to onset of RRD/RRP after CMT (weeks)
Carcinoma breast (43)						
Upfront MRM (17)	45-50	Docetaxel 100 mg/m^2 (3 weekly)	Dermatitis (5)	I (1), II (1), III (2) [Figure 1], IV (1)	3-4	<1
	45-50	Docetaxel 100 mg/m^2 + herceptin 4/2 mg/kg (3 weekly)	Dermatitis (7)	I (1), II (2), III (3) [Figure 2], IV (1)	3-4	<1
	50	Paclitaxel 80 mg/m^2 (weekly)	Dermatitis (2)	I (2)	3-4	3-5
	45	Paclitaxel 80 mg/m^2 + herceptin 4/2 mg/kg (weekly)	Dermatitis (3)	I (2), II (1)	3-4	3-5
Upfront BCS (5)	40	Docetaxel 100 mg/m^2 (3 weekly)	Dermatitis (1)	I (1)	3-4	1-3
	40	Docetaxel 100 mg/m^2 + herceptin 4/2 mg/kg (3 weekly)	Dermatitis (3)	II (2), III (1)	3-4	<1
	42.5	Paclitaxel 175 mg/m^2 (2 weekly)	Dermatitis (1)	I (1)	>4	>5
NACMT → surgery (MRM/BCS) (19)	40-50	Docetaxel 75 mg/m^2 (2 weekly)	Dermatitis (6)	I (1), II (2) [Figure 3], III (3)	3-4	<1
	40-50	Docetaxel 100 mg/m^2 + herceptin 4/2 mg/kg (3 weekly)	Dermatitis (8)	II (2), III (3), IV (3)	3-4	<1
	45	Paclitaxel 80 mg/m^2 (weekly)	Dermatitis (1)	I (1)	>4	3-5
	40/45	Paclitaxel 80 mg/m^2 + herceptin 4/2 mg/kg (weekly)	Dermatitis (2)	II (1), III (1)	3-4	3-5
	45	Herceptin 4 mg/kg IV loading dose and 2 mg/kg IV (weekly)	Dermatitis (1)	I (1)	>4	>5
	50	Tamoxifen 20 mg	Dermatitis (1)	I (1)	>4	>5
Bone metastasis (2)	20	Doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m2 (3 weekly)	Dermatitis (1)	I (1)	>4	>5
	8	Docetaxel 75 mg/m^2 + pertuzumab 840/420 mg + herceptin 8/6 mg/kg (3 weekly)	Dermatitis (1)	I (1)	>4	>5
Carcinoma lung (4)						
NSCLC (1)	60	Cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2	Dermatitis (1)	I (1)	3-4	3-5
Brain metastasis (2)	30	Carboplatin AUC 5 + pemetrexed 500 mg/m^2 + pembrolizumab 200 mg (3 weekly)	Dermatitis (1)	IV (1) [Figure 4]	3-4	>5
	30	Cisplatin 75 mg/m2 + pemetrexed 500 mg/m^2 + pembrolizumab 200 mg	Dermatitis (1)	II (1)	>4	>5
Bone metastasis (1)	20	Carboplatin AUC 6 + paclitaxel 200 mg/m^2 + bevacizumab 15 mg/kg	Dermatitis (1)	I (1) [Figure 5]	>4	>5
Carcinoma rectum (3)						
Primary (2)	45	5-FU 2400 mg/m^2 + leucovorin 400 mg/m^2 + oxaliplatin 85 mg/m^2 (3 cycles)	Dermatitis (1)	I (1)	>4	3-5
	50.4	Capecitabine 1000 mg/m^2 + oxaliplatin 130 mg/m^2 (CAPEOX for 4 cycles)	Proctitis (1)	II (1) [Figure 6]	3-4	3-5
Bone metastasis (1)	8	5-FU 2400 mg/m^2 + leucovorin 400 mg/m^2 + oxaliplatin 85 mg/m^2 + bevacizumab 10 mg/kg	Dermatitis (1)	I (1)	>4	>5
Carcinoma nasopharynx (2)						
Primary (2)	70	Cisplatin 75 mg/m^2 + 5-FU 800 mg/m2 (3 cycles)	Mucositis (1), dermatitis (1)	I (1), II (1)	3-4	3-5
STS (2)						
Extremity sarcoma (1) (Stage III/IV with acceptable functional outcome)	50	Doxorubicin 20 mg/m^2/day + ifosfamide 1500 mg/m^2/day + mesna 225 mg/m^2 (AIM for 3 cycles)	Dermatitis (1)	II (1)	3-4	1-3
Chest wall sarcoma (1)	50	Doxorubicin 20 mg/m^2 + ifosfamide 2500 mg/m^2 + dacarbazine 300 mg/m^2 + mesna 2500 mg/m^2 (MAID for 5 cycles)	Pneumonitis (1)	I (1) [Figure 7]	3-4	3-5

Contd...

Table 3: Contd...

Malignancy (*n*)	RT dose (Gy)	CMT/HT/TT regimen	Manifestation of RRP (*n*)	Grades of RRP/ RRD I/II/III/ IV/V (*n*)	Time-interval between RT and CMT (weeks)	Time to onset of RRD/RRP after CMT (weeks)
Carcinoma esophagus (7)						
Primary ADC (5)	41.4-50.4	5-FU 2600 mg/m^2 + leucovorin 200 mg/m^2 + oxaliplatin 85 mg/m^2 + docetaxel 50 mg/m^2 (FLOT 3 cycles)	Dermatitis (4)	I (2), II (2)	3-4	<1
	45	5-FU 2000 mg/m^2 + cisplatin 50 mg/m^2 (4 cycles)	Dermatitis (1)	I (1)	3-4	3-5
Primary SCC (2)	45	Capecitabine 1000 mg/m^2 + oxaliplatin 130 mg/m^2 (4 cycles)	Esophagitis (1)	I (1)	3-4	3-5
	50.4	Nivolumab 240 mg 2 twice weekly (5 cycles)	Dermatitis (1)	I (1)	3-4	>5
Lymphoma (3)						
Relapsed DLBCL (2)	36 (PR)	Dexamethasone 40 mg + cytarabine 2000 mg/m^2 + cisplatin 100 mg/m^2 + rituximab 375 mg/m^2 (3 cycles)	Dermatitis (1)	I (1)	3-4	3-5
	30 (CR)	Ifosfamide 5000 mg/m^2 + carboplatin AUC 5 + etoposide 100 mg/m^2 (2 cycles)	Dermatitis (1)	II (1)	3-4	>5
Refractory CHL (1)	36	Dexamethasone 40 mg + cytarabine 2000 mg/m^2 + cisplatin 100 mg/m^2 (2 cycles)	Esophagitis (1)	II (1)	3-4	>5
Thymoma (1)						
Recurrent (1)	54	Cisplatin 50 mg/m^2 + doxorubicin 50 mg/m^2 + cyclophosphamide 500 mg/m^2 (2 cycles)	Dermatitis (1)	I (1) [Figure 8]	3-4	3-5
Carcinoma prostate (6)						
Recurrent (2)	70	ADT + docetaxel 60 mg/m^2 (4 cycles)	Dermatitis (2)	I (2)	3-4	1-3
Bone metastasis (ADC) (3)	20	Abiraterone 1000 mg PO + prednisone 5 mg PO (5 cycles)	Dermatitis (2)	I (1), II (1)	3-4	<1
	8	Docetaxel 75 mg/m^2 (4 cycles)	Dermatitis (1)	I (1)	>4	>5
Bone metastasis (others) (1)	20	Docetaxel 60 mg/m^2 + carboplatin AUC 5 (3 weekly)	Dermatitis (1)	I (1)	>4	>5

Gy: Gray (unit of radiation therapy), AUC: Area under curve, PO: Oral administration, 5-FU: 5-Fluoro Uracil, CR: Complete response, PR: Partial response, RRP: Radiation recall phenomenon, RRD: Radiation recall dermatitis, RT: Radiation therapy, CMT: Chemotherapy, HT: Hormonal therapy, TT: Targeted therapy, ADC: Adenocarcinoma, ADT: Androgen deprivation therapy, MRM: Modified radical mastectomy, CHL: Classical Hodgkin's lymphoma, DLBCL: Diffuse large B-cell lymphoma, SCC: Squamous cell carcinoma, STS: Soft tissue sarcoma, NSCLC: Nonsmall cell lung carcinoma, MRM: Modified radical mastectomy, BCS: Breast conservative surgery, NACMT: Neoadjuvant chemotherapy

included the number of grade-I and grade-II cases, while group-2 comprised grade-III and grade-IV cases [Table 4]. Statistical significance was seen only with gender and time-gap between RT and CMT. Females developed 54.9% grade-I/II and 90% grade-III/IV recall cases compared to males with 45.1% and 10% of cases, respectively (P = 0.005). Time-gap between 3 and 4 weeks reported 49% grade-I/II and 100% grade-III/IV recall cases, while time-gap >4 weeks resulted in 26% and 0% cases, respectively (P = 0.000) [Table 4].

Discussion

In this prospective observational study, we investigated the clinical profile of cancer patients developing RRP/RRD covering all parameters that may affect its occurrence. This study recorded an overall incidence of 6.5% [Table 1] compared to the reported incidence of 8.8% by Kodym *et al*. [28], 9.7% by Harsh *et al*. [29], and 1%–10% as per previous studies [1,2,7]. Maximum recall cases were of breast carcinoma, so the overall number of females was more compared to males (F:M = 46:25). Univariate analysis showed statistically significant higher severity grades in females compared to males (P = 0.005) [Table 4]. However, no gender predilection has been reported by previous studies [5,7,26-29]. The median age of males was 65 years (40–78) and of females was 61 years (45–71). No statistical correlation was found between occurrence and severity of RRP with the age of the patient (P = 0.173), maybe because of the heterogeneity of this phenomenon. Patients who had no RD initially developed grade-IV RRD later, as was seen in patients of carcinoma lung with brain metastasis [Figure 4]. Those with grade-I RD developed grade-III RRD in breast cases, while those with initial grade-III proctitis developed grade-II recall-proctitis [Figure 6]. The area of RRD was comparable to the earlier RD area, however, some spread or generalization was observed.

In our study, the median RT dose was 45 Gy (dose range 8–70 Gy), while Harsh *et al*. [29], used median RT dose of 36.4 Gy (30–50 Gy) in breast carcinoma cases. We observed that 30 Gy resulted in grade-IV, while 70 Gy caused grade-I recall reactions [Table 3] consistent with previous studies [7,27,30]. This study could not attribute any threshold RT dose for the severity of RRP (P = 0.656) [Table 4], similar to world literature [7,27,30]. However, few studies have postulated that photon energy ≤6 MV [7,30] and higher

Table 4: Statistical analysis based on parameters which may influence the incidence and severity of radiation recall cases

Variable	RRP Grade 1 and 2, *n* (%)	RRP Grade 3 and 4, *n* (%)	*P*
Age (years)			
<60	19 (37.3)	11 (55)	0.173
>60	32 (62.7)	9 (45)	
Gender			
Male	28 (54.9)	18 (90)	0.005
Female	23 (45.1)	2 (10)	
Co-morbidity			
Absent	36 (70.6)	14 (70)	0.961
Present	15 (29.4)	6 (30.0)	
KPS (%)			
≤70	30 (58.8)	10 (50)	0.500
>70	21 (41.2)	10 (50)	
RT dose (Gy)			
≤45	31 (60.8)	11 (55)	0.656
>45	20 (39.2)	9 (45)	
Use of CMT (docetaxel)			
No	26 (51)	6 (30)	0.110
Yes	25 (49)	14 (70)	
CMT regimen used			
Monotherapy	18 (35.3)	8 (40)	0.711
Combination therapy	33 (64.7)	12 (60)	
Time-interval between RT and CMT (weeks)			
3–4	25 (49)	20 (100)	0.000
>4	26 (51)	0 (0)	

RRP: Radiation recall phenomenon, RT: Radiation therapy, CMT: Chemotherapy, KPS: Karnofsky performance status

Table 5: Therapeutic protocols used in the study for management of radiation recall cases

Grade of RRP/RRD (*n*)	Management	Resolution period (weeks)=*n/N* (%)
Dermatitis Grade-I (29)	Discontinuation of CMT + normal saline compresses + aqueous based cream + topical steroid 0.1% mometasone furoate cream/0.1% betamethasone cream + antihistamines	<1=3/29 (10.3) 1-2=11/29 (37.9) >2=15/29 (51.7)
Dermatitis Grade-II (17)	Discontinuation of CMT + normal saline compresses + aqueous based cream + 10% glycerine + topical steroid 0.1% mometasone furoate cream/1% hydrocortisone cream + gentian violet dressing + oral NSAIDs	1-2=8/17 (47.1) 2-3=6/17 (35.3) >3=3/17 (17.6)
Dermatitis Grade-III (14)	Discontinuation of CMT + normal saline compresses up to 4 times daily + 0.1% betamethasone cream/1% hydrocortisone cream + topical antibacterial 1% SSD + sterile wound gel hydrogel + oral NSAIDs + oral antibiotics + oral chymoral forte	1-2=1/14 (7.1) 2-3=4/14 (28.6) 3-4=7/14 (50) >4=2/14 (14.3)
Dermatitis Grade-IV (6)	Discontinuation of CMT + hospitalization + normal saline compresses + normal saline and soap wash + 1% SSD + 0.1% betamethasone cream + hydrocolloid dressings/silver nylon dressing + surgical debridement + intra-venous fluids + parenteral antibiotics like linezolid + parenteral NSAIDs + oral chymoral forte + oral morphine in few cases	3-4=2/6 (33.3) >4=4/6 (66.7)
Proctitis Grade-II (1)	Discontinuation of CMT + hospitalization + hydration + antidiarrheals + rectal sucralfate 2 mg + steroid hydrocortisone enema/5-aminosalicylate enema + APC	1-2=01/01 (100)
Mucositis Grade-I (1)	Discontinuation of CMT + soda-saline gargles + 2% oral viscous lidocaine + analgesic benzydamine hydrochloride	1-2=01/01 (100)
Esophagitis Grade-I (1)	Discontinuation of CMT + avoiding potentially irritant foods + syrup sucralfate + 2% oral viscous lidocaine + oral PPI	<1=1/1 (100)
Esophagitis Grade-II (1)	Discontinuation of CMT + syrup sucralfate + syrup sucralfate + 2% oral viscous lidocaine + aluminum hydroxide-magnesium carbonate + oral PPI/H2-receptor blocker + prophylactic antifungal agents	1-2=1/1 (100)
Pneumonitis Grade-I (1)	Discontinuation of CMT + oral prednisone 60-100 mg/day for 2 weeks followed by a slow taper over 3-12 weeks + antitussive syrups + supplemental oxygen + oral antibiotic	12-14=1/1 (100)

SSD: Silver sulfadiazine cream, APC: Argon plasma coagulation, PPI: Proton-pump inhibitor, NSAIDs: Nonsteroidal anti-inflammatory drugs, CMT: Chemotherapy, RRP: Radiation recall phenomenon, RRD: Radiation recall dermatitis

RT dose may cause greater recall reactions [26]. Being a government set-up with no conformal RT techniques available, we used the 2-DRT technique to treat all patients. Since it was an observational study with no comparative-arm-like intensity-modulated RT (IMRT)/image-guided RT (IGRT)/volumetric-modulated arc therapy (VMAT), we were not able to correlate the occurrence of RRP with the RT technique. However, highly conformal RT techniques like IMRT, IGRT, VMAT, and precise target-dosimetry may reduce the incidence of RRP/RRD as it has benefitted in the reduction of RD [29-31]. No CMT was started within 7 days of completion of RT to differentiate with RS. For all malignancies included in this study, docetaxel was the most common drug involved and was taken as the prototype while determining its effect on the severity of RRP, however, no statistical significance was derived (P = 0.110) [Table 4]. Herceptin, tamoxifen, pemetrexed, nivolumab, and pembrolizumab were also involved, apart from variety of cytotoxic drugs with diverse doses and diverse regimens, making it extremely difficult to pinpoint which drug reacted in which patient. Although most reports have described single drug involvement [4,7,29], our study observed combination therapy resulting in 71.8% recall-cases compared to monotherapy with 28.2% recall reactions, although no statistical significance was seen (P = 0.711) [Table 4]. We also observed that capecitabine was associated with esophagitis and proctitis which may be attributed to enhanced mucosal involvement due to pro-drug activation [6,7,23].

This study highlighted the importance of time-gap between completion of RT and initiation of CMT. RRP/RRD cases observed in 3–4 weeks period were 83% and those reported in >4 weeks were 17%. Earlier studies have reported recall incidence of 5.1% in >4 weeks [29], 19.4% in ≤4 weeks, 7.4% in >3 weeks, 18% cases in ≤3 weeks, and 28.6% in <1 week[32] [Table 2]. Our study reaffirmed the postulated theory that the shorter the interval between RT and CMT, higher the risk of developing RRP/RRD [4,7,25,27]. The time gap also affected the grades of recall reactions. Time-gap between 3 and 4 weeks reported 49% grade-1 and 2 and 100% grade-3 and 4 recall-cases compared to time-gap >4 weeks which resulted in 26% and 0% cases, respectively (P = 0.000) [Table 4]. The above result verified the observation that the severity of RRD tends to be greater when the time period between RT and CMT is shorter [28]. The number and severity of cases were more when the time of onset of RRP/RRD after CMT was shorter. Onset of symptoms in <1 week showed total 49.3% cases compared to onset >5 weeks with 1.9% recall-cases [Table 3]. Management of RRP/RRD depends on its severity and the organ system involved [33]. Mild reactions resolved spontaneously or with symptomatic therapy but severe cases were managed with hospitalization, medical and surgical interventions [Table 5].

Conclusion

RRP/RRD is a puzzling phenomenon which has kept researchers and clinicians at bay regarding its occurrence and pathophysiology for over more than 60 years. In our experience, it is impossible to predict which drug, either single or in combination will cause RRP in which patient and which patient will react to which drug. No CMT regimen or RT dosage can be designed to prevent RRP. Females may be at increased risk of developing severe RRP compared to males. Taxanes, platinum agents, pyrimidines, and anthracyclines were identified as the serial culprits in the study. The treating clinician/oncologist should have a high degree of suspicion to differentiate between RS, RD, and RRD and report such cases whenever possible. However, prolonging the intervening period between the termination of RT and the start of CMT can reduce both the incidence and severity of RRP. The treatment approach for RRP remains organ-specific symptomatic management, with steroids and analgesics forming the cornerstone of therapy. Presently there is a dearth of published data which elaborates the correlation of different RT techniques with the occurrence of RRP and therefore, we recommend that more such comparative studies be undertaken in near future.

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Conflicts of interest

There are no conflicts of interest.

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