Prospective evaluation of acute radiation – induced skin reactions in patients after head and neck radiotherapy

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ABSTRACT

Acute Radiation- induced Skin reaction (ARISR) is a common side effect in the majority of patients receiving radiotherapy. ARISR is often characterized by swelling, redness, pigmentation, dry and moist desquamation, edema, ulceration, bleeding and necrosis of the Skin. This study was carried out to evaluate prevalence and severity of ARISR in patients with head and neck cancer undergoing radiotherapy and determining skin dose–response relationship. From December 2014 to September 2015, we evaluated 88 patients with head and neck cancer. The acute skin toxicity was scored based on RTOG toxicity criteria. Analysis of data using statistical software SPSS (version20) and ANOVA or chi- square test was done, with $P \leq 0.05$ considered as significant. 98.86% of patients experienced dermatitis, but were mild in most cases.There was no significant differences in age, sex, stage, and field size between patients with dermatitis.

Keywords: Radiotherapy; Head and Neck Cancer; Acute Radiation- induced Skin Reaction

INTRODUCTION

The incidence of cancer in different communities is increasing as cancer is the second leading cause of death in developed countries [1]. Head and neck cancers constitute two to five percent of these malignancies that represent a rather heterogeneous group of neoplasm originating from the oral cavity, oropharynx, hypo pharynx, larynx and other areas [2]. Radiotherapy is one of the main modality in the management of cancer treatment, along with chemotherapy and surgery. The goal of Radiotherapy is to provide maximum damage to tumor with the minimal side effect [3], and yet, it associated with a number of short-term and long-term side-effects [4].One of the most common side effects of radiation is acute skin reaction, affecting up to 95% of people receiving radiation treatment for their cancer [5], and sice skin is usually the first site of entry in radiation treatment, variable degrees of skin reaction can occur. The reactions are the result of radiation treatment disrupting the normal process of cell division and regeneration in the basal cell layer of the skin, resulting in cell damage or cell death [6]. The damage can be a result of several processes, including a reduction of endothelial cell changes, inflammation, and epidermal cell death [7]. Acute radiation- induced skin reactions are often characterized by swelling, redness, pigmentation, dry and moist desquamation, fibrosis, and ulceration of the skin; signs and symptoms are expressed as pain, warmth, burning and itching of the skin [8].Erythema is defined as the redness caused by flushing of the skin due to dilatation of the blood capillaries in the dermis [9]; dry desquamation is the shedding of the outer layers of the skin thins because the new cells reproduce faster than the old cells are shed so the skin begins to weep as a result of loss of integrity of the epithelial barrier and decrease in pressure exerted by plasma proteins on the capillary wall [9]. The cumulative effect of further doses of radiotherapy can then cause the skin to break down edematous with exudates leading to moist desquamation. Skin necrosis is rarely seen

primarily due to the advanced techniques used in the delivery of radiotherapy .Skin reactions related to radiation therapy usually manifest 1-4 weeks after radiotherapy onset, persist for the duration of radiation therapy, and may require 4-6 weeks to heal after completion of therapy [10], with the exception that the area may still look hyper pigmented (darker) [11].

Radiation- induced skin reaction have an impact on the level of pain/ discomfort experienced and the quality of life of those who undergo radiation treatment [12], and may even require changes to person's radiation schedule (if severe) [9]. In some cases, complex surgical reconstruction of damage skin may be required [13].

MATERIALS AND METHODS

This study was done at the radiation oncology department of Tohid hospital at Sanandaj, Iran. The department is equipped with a linear (Waxttan baxer Elekta synergy plat, Elekta) and 3D-conformal planning systems (Isogray from Dosisoft Company). We analyzed 88 patients with head and neck cancer that had been referred to our department from 1st of December 2014 to 30th of September 2015. All patients provided their written informed consent. There were no restrictions on age and gender of the patients. A pre-coded questionnaire was developed for this study, which included simple demographic details viz. age, gender, information regarding the malignancy i.e. tumor morphology and staging, information regarding the treatment i.e. radiotherapy alone or combined with chemotherapy, total tumor dose delivered to the patients, dose per fraction, treatment time, field size, skin dose at 2mm depth and complication. Complications were categorized into radiation therapy (RT) symptoms with skin (dermatitis). The cancers were staged using the UICC/AYCC TNM system [14]. Radiotherapy for all patients was planned using the Isogray three dimensional treatment planning system (Dosisoft medical system version 4.1) to facilitate treatment planning. CT of the head and neck was obtained for each patient with thermoplastic immobilization shell. The clinical target volume (CTV) was defined as the entire tumor invasion subsides. The planning target volume (PTV) was obtained by adding a 10 mm margin to the CTV and an additional 15 mm margin from the skin. Prophylactic neck lymph node area irradiation was performed. Radiation fields were customized as appropriate by a Multileaf collimator. All sites irradiated with 6-10 MV photon beams. The daily dose was 1.8 or 2Gy per fraction up to total dose, 5 days per week. As a standard practice, all cases were treated with acceptable tolerance doses to the organs at risk, namely spinal cord, brainstem and optic chiasma. Skin dose at a depth of 2 mm was calculated using the three dimensional treatment planning system and collapsed cone algorithm from point kernel section. For each patient contour with 7 cm^3 volume size in the treatment field was drawn. In computing software, voxels size was 2 mm^3. Chemotherapy was done with an intravenous loading dose of cetuximab (400-600 mg/m^2) or Cisplatin (50 mg/ m^2) during radiotherapy. The median cycle of chemotherapy was six cycle.

Acute dermatitis were assessed weekly during treatment up to 13 weeks from beginning of radiotherapy and graded according to the radiation therapy oncology group/ European organization for research and treatment of cancer criteria (RTOG/EORTC) [15].

Table 1. RTOG acute radiation scoring criteria-skin

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
No change Over baseline	Follicular, faint or dull erythema; epilation; dry desquamation; decreased sweating	Tender or bright Erythema, patchy moist desquamation; moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis

RTOG (Radiation Therapy Oncology Group) and EORTC (European Organization for Research and Treatment of Cancer). All analyses were performed using SPSS software (version 20) to investigate the relationship between skin reaction in different grades of RTOG/ EORTC with variables, ANOVA and Chi-square test was used as the main tool. Turkey's post hoc test was used to study the difference in the incidence of skin reactions in various grades. P value of 0.05 or less was considered statistically significant.

RESULTS

Between December 2014 and September 2015, 88 patients with head and neck cancer received RT in Tohid hospital at Sanandaj, Iran. Table 2 shows patient characteristics.

Table2. Patient and tumor characteristics (n=88)

Variable	Number	(%)
Age (years- median)	18-85 (58)	
Gender		
Male	60	(68.2)
Female	28	(31.8)
Primary tumor site		
Larynx	26	(21.3)
Thyroid	9	(10.4)
Parotid	7	(7.9)
Neck	12	(13.7)
Oral cavity	7	(7.9)
Nasopharynx	4	(4.6)
maxilla	4	(4.6)
Hypo pharynx	2	(2.3)
Mandible	7	(7.9)
Cervical esophagus	5	(5.7)
Unknown origin of region	5	(5.7)
Stage		
I	14	(15.9)
II	25	(28.4)
III	47	(53.4)
IV	2	(2.3)
Pathology		
Squamous cell carcinoma	64	(72.7)
Sarcoma	10	(11.4)
Lymphoma	14	(15.9)
Concurrent chemotherapy		
Yes	40	(45.5)
No	48	(54.5)
Surgery		
Yes	35	(39.8)
No	53	(60.2)

The median age was 58 years old (range 18-85). 60 (68%) patients were male and 28 (31%) were females. Radiation doses ranging were from 13 to 75 GY (median = 58 GY), skin dose at 2 mm depth ranging were from 11 to 66 GY (median= 44 GY).The dose per fraction was 1.8 GY in 46 (52%) patients, 2 GY in 32 (36%) patient, and 10 (11%) were treated with both fraction sizes, and treatment time ranged from 21 to 64 days, with a median of 42 days. Concurrent chemotherapy with radiotherapy was done for 40 (45%) patients, surgery was performed in 35 (39%) patients. the medium field size was 77 cm^2 (rage, 16-297 cm^2), primary tumor site were the larynx in 26, thyroid in 9, parotid in 7, oral cavity in 7, nasopharynx in 4, maxilla in 4, hypopharynx in 7, mandible in 7, neck esophagus in 5, neck in 12 and unknown origin of region in 5 patients. 64 (73%) patients had squamous cell carcinoma (SCC), 10(11 %) had sarcoma and 14 (15%) had lymphoma. 14 (15%) of the patients were stage I, 25(28%) were stage II, 47(53%) were stag III and 2 (2%) were stage IV.

Considering the fact that the average length of treatment time is six week (42 day), we analyzed prevalence and severity of acute radiation- induced skin reactions in 6 and 13 weeks as acute complications during and after treatment with confounding factors like age, gender, tumor stage, treatment method, field size, total dose, skin dose at 2 mm depth, dose per fraction and treatment time. Radiotherapy was completed in all patients. 98.86% of patients experienced dermatitis (RTOG grades 1-4) (tables 3, 4).

Table 3. Acute adverse effects during treatment

Grade	0	1	2	3	4
Dermatitis	1	44	38	4	1

RTOG/ EORTC

Table 4. Acute adverse effects after treatment

Grade	0	1	2	3	4
Dermatitis	24	61	3	0	0

RTOG/ EORTC

Dermatitis grade 1 and 2 were the most common acute toxicity while one patient had grade 4 toxicity. We observed that the severity of ARISR is higher with increasing total dose, skin dose at 2mm depth, and dose per fraction and treatment time. Furthermore, we analyzed the severity of ARISR with tumor stage and treatment method. We observed that the severity of ARISR is higher in larger T-stage. In patient that radiotherapy was done with chemotherapy, complications were more severe. Regarding sex, we observed that the incidence of complications is higher in men than in women and is less severe. However, there were no significant difference in age, gender, tumor stage, field size, total dose and skin dose at 2mm depth between patient with complication ($p>0.05$), but dose per fraction (during treatment) and treatment time (after treatment) had significant effect on complication ($p<0.05$) (tables 5-8).

Table 5. Association of clinical factors and the risk of acute skin reaction during treatment

Variable		**Grade0**	**Grade1**	**Grade2**	**Grde3**	**Grade4**	**X^2**	**P-value**
Age	>50	0(0)	11(47.8)	12(52.2)	0(0)	0(0)	8.98	0.342
	50-70	0(0)	24(51.1)	18(38.3)	4(8.5)	1(2.1)		
	>70	1(5.6)	9(50)	8(44.4)	0(0)	0(0)		
Gender	Male	0(0)	32(53.3)	27(45)	1(1.7)	0(0)	8.28	0.082
	Female	1(3.6)	12(42.9)	11(39.3)	3(10.7)	1(3.6)		
Stage	I	1(7.1)	8(57.1)	5(35.7)	0(0)	0(0)	11.42	0.0494
	II	0(0)	14(56)	9(36)	2(8)	0(0)		
	III	0(0)	20(42.6)	24(51.1)	2(4.3)	1(2.1)		
	IV	0(0)	2(100)	0(0)	0(0)	0(0)		
Concurrent chemotherapy	Yes	0(0)	20(50)	19(47.5)	0(0)	0(0)	5.683	0.224
	No	1(2.1)	24(50)	19(39.6)	4(8.3)	0(0)		
Dose per fraction	1.8 GY	1(2.2)	24(52.2)	21(45.7)	0(0)	0(0)	9.152	0.01
	2 GY	0(0)	16(50)	12(37.5)	4(12.5)	0(0)		
	Both	0(0)	4(40)	5(50)	0(0)	1(10)		

Abbreviations: RTOG = Radiation Therapy oncology Group; EORTC=European organization for Research and Treatment of Cancer; GY= Gray; OTT=Overall Treatment time

Table 6. Association of clinical factors and the risk of acute skin reaction during treatment

Variable	**Skin Reaction (RTOG-Grade)**	**Number**	**Median**	**Std. deviation**	**95% Confidence Interval**	**p-value**
Field size(cm^2)	Grade0	1	60.13	0	0	0.599
	Grade1	44	86.81	68.73	65.91-107.7	
	Grade2	38	68.7	37.15	56.49-80.91	
	Grade3	4	67.27	20.63	34.49-100.11	
	Grade4	1	45.1	0	0	
Total dose	Grade0	1	45	0	0	0.734
	Grade1	44	57.48	10.78	54.2-60.76	
	Grade2	38	58.83	11.9	54.92-62.75	
	Grade3	4	59	6.63	48.44-69.55	
	Grade4	1	64	0	0	
Skin dose at 2mm depth	Grade0	1	25.83	0	0	0.413
	Grade1	44	45.04	12.99	41.08-48.99	
	Grade2	38	44.61	11.7	40.71-48.51	
	Grade3	4	47.68	7.82	35.23-60.13	

	Grade4	1	59.18	0	0	
OTT(day)	Grade0	1	31	0	0	0.694
	Grade1	44	42	10.07	38.93-45.06	
	Grade2	38	43.63	9.35	40.55-46.7	
	Grade3	4	44.5	8.22	31.41-57.58	
	Grade4	1	45	0	0	

Abbreviations: RTOG = Radiation Therapy oncology Group; EORTC=European organization for Research and Treatment of Cancer; GY= Gray; OTT=Overall Treatment time

Table 7. Association of clinical factors and the risk of acute skin reactions after treatment

Variable		**Grade0**	**Grade1**	**Grade2**	**X^2**	**P-value**
Age	<50	6(26.1)	17(73.9)	0(0)	2.8	0.592
	50-70	13(27.7)	3(66)	3(6.4)		
	>70	5(27.8)	13(72.2)	0(0)		
Gender	Male	16(26/7)	43(71.7)	1(1.7)	1.85	0.396
	Female	8(28.6)	18(64.3)	2(7.1)		
Stage	I	5(35.7)	9(64.3)	0(0)	7.85	0.249
	II	10(40)	13(52)	2(8)		
	III	9(19.1)	37(78.7)	1(2.1)		
	IV	0(0)	2(100)	0(0)		
Concurrent chemotherapy	Yes	6(15)	34(85)	0(0)	9.152	0.01
	No	18(37.5)	27(56.2)	3(6.2)		
Dose per fraction	1.8 GY	14(30.4)	32(69.6)	0(0)	7.35	0.118
	2 GY	9(28.1)	20(62.5)	3(9.4)		
	Both	1(10)	9(90)	0(0)		

Abbreviations: RTOG = Radiation Therapy oncology Group; EORTC=European organization for Research and Treatment of Cancer; GY= Gray; OTT=Overall Treatment time

Table8. Association of clinical factors and the risk of acute skin reactions after treatment

Variable	**Skin reaction (RTOG-Grade)**	**Number**	**Median**	**Std. deviation**	**95%Confidence Interval**	**P-value**
Field size(cm^2)	Grade0	24	85.82	63.91	58.83-112.80	0.658
	Grade1	61	74.54	52.63	61.06-88.02	
	Grade2	3	66.03	25.09	3.69-128.37	
Total dose	Grade0	24	54.4	10.76	46.85-58.94	0.149
	Grade1	61	59.32	11.16	56.46-62.18	
	Grade2	3	62	3.46	53.39-70.6	
Skin dose at 2mm depth	Grade0	24	43.25	9.61	39.19-47.31	0.611
	Grade1	61	45.34	13.38	41.88-48.80	
	Grade2	3	49.87	7.93	30.15-69.59	
OTT(day)	Grade0	24	37.62	6.68	33.53-41.71	0.007
	Grade1	61	44.4	9/02	42.18-46.8	
	Grade2	3	47.66	6.42	31.69-13.63	

Abbreviations: RTOG = Radiation Therapy oncology Group; EORTC=European organization for Research and Treatment of Cancer; GY = Gray; OTT=Overall Treatment time

DISCUSSION

Radiation skin reactions are an inevitable consequence of radiotherapy. Although the widespread use of linear accelerators has reduced the severity of skin reactions through more sophisticated skin-sparing techniques, the increased use of concomitant chemotherapy and high-dose radiotherapy means that skin reactions can still be a significant problem for patients. A survey carried out in the early 1990s by Barkham A reported that more than 80% of

UK radiotherapy departments frequently face skin reactions, although these were not usually severe [16]. The results of the present study show that Grade 3 and 4 acute radiation dermatitis occurred in 5% of patients. The adverse event profile in our study was mostly in line with those originally reported by Bonner et al [17]. In general areas of body that contain skin fold are more likely to be affected by radiation such as under the breast, axilla and H&N, because of a phenomenon called the "bolus effect". These areas are more likely to receive a higher dose of radiation and more prone to bacterial contamination [18].This study was performed to analyze the influence of confounding factors on the development of acute radiation-induced skin toxicity, and also to determine skin dose at 2mm depth -response that can be used as a dosimeter in clinic. We observed that in patients with 50-70 years of age, skin toxicity was higher than patients in>70 years old group. Canhua X, et al. found that increased age resulted in an impaired ability to heal [19], and alternative explanation for our finding is that the older patients (>70 years old) were less likely to have received chemotherapy and that might have affected the degree of skin reactions they experienced. Chan et al. [20] reported that they observed a 61% rate of grade III to IV radiation dermatitis among HNSCC patients treated with concurrent radiotherapy and cetuximab.O'Rourke ME et al, A etal, and Suga T et al found that chemo radiation regime increases the severity of skin reactions. The main principle of chemotherapy is that two treatments work synergistically so as to improve overall response, but radiation side effects tend to be exacerbated by the addition of chemotherapy; our data support that finding. In fact the adverse effect complications were in line with those expected with the concomitant administration of cetuximab and radiotherapy [21-22-23]. In terms of total dose and skin dose, Archambeau et al found that basal cell loss began once the radiation dose reached 20-25 Gy, and maximum depletion occurred at a dose of 50Gy, and by the time higher doses of up to 60 Gy had been absorbed, repopulation of basal cells had occurred, so that levels were similar to those existing prior to radiotherapy [24]. Giro et al observed that a higher total dose and skin dose were significantly correlated with the development of high grade dermatitis [25]. Corresponding to those studies, we found that higher total dose and skin dose at 2mm depth had a positive trend to development of toxicity. In fact in our study ARISR were potentiated at the end of treatment, Grade 1 and 2 complications occurred at a median skin dose at 2mm depth of 44-45 Gy and Grade 3and 4 complications occurred at a median dose of 47-60 Gy. Mendenhall et al reported that higher daily fraction doses resulted in higher local control rates without a significant increase in acute adverse effect [26]. Chan et al found that a smaller daily radiation dose decreases the risk of radio dermatitis [20]. We observed that the occurrence of ARISR was lower among patients treated with smaller daily fraction dose. Overall treatment time was thought to be one of the keys for tumor control. Our study showed an association between longer treatment time and higher rate of ARISR, because longer treatment time results in higher total dose, hence, more complications [26]. Lee IJ et al reported that patients with larger tumors had more complications, probably experienced more trauma to surrounding tissue during surgery, and thus had a reduced potential for wound healing. Our finding support the forementioned theory, as larger T-stages showed a positive trend to development of higher acute toxicity [27]. Corresponding to Alvarengea LM et al. studies [28], superiority of males was evident as 68/2% of patients were male, and they also experienced more complications. In contrast to our data, Marie k et al found no correlation between sex and acute radio dermatitis [29]. As the policies in radiation departments head and neck tumor treatment with different radiation field such as anterior, posterior, lateral and tangential, and target volume (PTV) shrinkage related to the clinical target volume (PTV) in the proximity of the skin, we determine the severity of skin toxicity and smallest field size which had a longer exposure time,. Contrary to Alvarengea LM et al, we found higher rates of radiation dermatitis in smaller field size [28].

CONCLUSION

A number of treatment and patient related factors are identified that can modify the risk for the development of acute radiation- induced skin reactions. In this study, we analyzed the

effect of some of them. Our results indicated that the incidence rate of ARISR in head and neck cancer patients undergoing radiotherapy or chemo radiation were high. They should be kept in mind in order to increase the safety of the treatment. Moreover, we proposed that a mean dose under 25 GY delivered to the 2mm depth of skin are safe, through doses of 45-47 GY should be given with caution and extra monitoring; doses greater than 50 GY are dangerous and likely to produce grade 4 acute radiation dermatitis .

"The authors declare no conflict of interest"

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