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Correlation of degree of acute radiation dermatitis (RD) with skin dose distribution in head and neck squamous cell carcinoma patients treated with definitive concurrent chemoradiation

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ABSTRACT

Background: Radiation dermatitis (RD) or skin toxicity is one of the most common acute side effects of radiation in head and neck cancer patients. This study aims to correlate the pattern of volumetric-modulated arc therapy (VMAT) dose distribution to the skin with the grades of RD.

Materials and methods: 80 plans of histopathologically proven squamous cell carcinoma head and neck patients already treated with definitive concurrent chemoradiation [66–70 Gy in 33–35# or 66 Gy in 30# in simultaneous integrated boost (SIB), with concurrent Cisplatin 100 mg/m^2 3 weekly] at our institution between November 2022 and November 2023 were retrieved from our digital archives. For each plan, 1 ring structure was created 3mm below the external skin surface, and the parameters V_{40}, V_{50}, V_{60} and D_{max} were collected from the same. These parameters were correlated with grades of RD as per Common Terminology Criteria for Adverse Events (CTCAE) v5.0. The statistical analysis was done using MedCalc software version 22.021.

Results: The incidence of G2/G3 RD was 52.5%, and its incidence was significantly correlated with all of the four parameters. Statistically significant ($p < 0.001$) dosimetric predictive accuracy was provided by 71.66 cc, 29.98 cc and 7.624 cc of the 3mm skin ring V_{40}, V_{50} and V_{60}, respectively.

Conclusion: The dose distribution pattern to a skin layer stationed 3mm below the surface may help predict the development of severe RD in head and neck cancer patients receiving concurrent chemoradiation.

Key words: head and neck cancer; predictive accuracy; radiation dermatitis; squamous cell carcinoma

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Introduction

Radiation dermatitis (RD) or skin toxicity is one of the most common acute side effects of radiation in head and neck cancer patients. If higher grade, it can cause unwanted delay or untimely stoppage of treatment, and considerable physical as well as psychological suffering of the patients. Radiobiologically, the development of RD has long been known to be dependent on dose-volume and overall-treatment-time [1]. Concurrent chemotherapy [2] increases the risk of RD sig-

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nificantly, as well as other acute side effects such as oral mucositis and dysphagia. Modern conformal techniques, like intensity-modulated radiotherapy (IMRT) [3] and volumetric-modulated arc therapy (VMAT), are now standards of care in head and neck squamous cell carcinoma. Though highly conformal as per target volume coverage and Organs-at-risk sparing [4, 5], these modern techniques have been observed to result in a relative overdosage of patient's skin surface [6]. Apart from only a handful of previous studies, neither recommendations nor any guidelines are available [7] to use skin dose constraints to prevent the development of RD. Our study aims to correlate the pattern of VMAT dose distribution to the skin with the different grades of RD, and to assess whether specific skin dose-volume threshold values may be used as possible predictive factors for higher grades of toxicity in future studies. We hope that our study will help researchers in future to prospectively validate our data, and create a specific skin dose-constraint guideline so that treatment can be planned abiding those constraints to prevent acute skin toxicity of higher grade.

Materials and methods

Sample and treatment features

80 treatment plans of histopathologically proven inoperable non-metastatic head and neck squamous cell carcinoma patients of different subsites already treated with cisplatin-based definitive concurrent chemoradiation in VMAT technique at our institution between November 2022 and November 2023 were randomly selected, excluding the bolus-using plans (superficial gross tumour or skin infiltration). During treatment, concurrent cisplatin [8] was administered at a dose of 100 mg/m^2 3 weekly for patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–1 with dose modification, if needed, according to a kidney function test and general condition. For the different subsites, radiation dose was 66–70 Gy at conventional 2 Gy per fraction (33–35 fractions) in a phasic plan or 30 fractions in the simultaneous integrated boost (SIB) technique as per physician's choice. Initial pre-treatment nutritional status was assessed using Simplified Nutritional Appetite Questionnaire (SNAQ) and noted down [9]. Standard supportive care measures, such as pain management, maintenance of oral hygiene and nutritional counselling, were implemented on a routine basis.

For each of the patients, a personalized thermoplastic head-neck-shoulder mask was created. An institutional Philips Brilliance 16-slice CT Scan machine was used to acquire simulation scans of 3mm slice width. Target volume contouring was done according to international consensus guidelines [10] at Varian Somavision workstation. 7mm margin was given for planning target volume (PTV) around the clinical target volume (CTV) as per institutional protocol. For PTV, a negative 3mm margin was delineated from patient's body surface contour to avoid excessive accumulation of skin dose. Double arc-VMAT Treatment plannings were done using Eclipse v15.5 (VARIAN medical systems) software (RapidArc) and Anisotropic Analytical Algorithm (AAA) for dose calculation and optimization. The patients were treated in VARIAN TrueBeam linear accelerator (serial number- 3279). Informed consent was obtained before starting treatment from all individual patients included in this study.

Analysis of skin dose distribution

The selected 80 VMAT plans were retrieved from our digital archive. For each plan, 1 new ring structure of 3 mm thickness was created below the external skin surface up to 3mm depth as all the PTV margins were cropped 3mm from the skin surface as per institution protocol, further supported by published data [11, 12], and thus this 3mm-thick ring structure was a perfect model to study the skin dose parameters. These volumes of interest extended between the upper and lower limits of PTV plus a fixed 1cm margin in both cranial and caudal directions. For this '3mm ring' structure of each patient, the following parameters were collected — V_{40}, V_{50}, V_{60} and D_{max}, where V_{40}, V_{50} and V_{60} equal to the volume of the ring structure receiving a minimum of 40Gy, 50Gy and 60Gy dose respectively, and D_{max} represents the maximum absolute point dose anywhere within the structure. These parameters were correlated with different grades of RD as per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [13], as assessed by at least two of the authors at a time, once weekly during treatment and documented in the individual patient's treatment record files.

Outcome measures and statistical analysis

Descriptive statistics were used to report patient ECOG Performance Status, age, sex, smoking history, disease [primary site, American Joint Committee on Cancer (AJCC) 8th edition tumor–node–metastasis (TNM) staging], treatment (RT compliance, RT schedule) and skin dose distribution (explorative dosimetric parameters) — related characteristics as median and range for continuous variables. These continuous variables were tested with Mann-Whitney test as it is a common nonparametric test for comparing two groups of independent samples [14], while categorical variables were tested by Fisher's exact test due to its validity in analysing small sample of categorical variables and providing an exact p-value [15]. A p-value of < 0.05 was considered significant.

By plotting the receiver operating characteristic (ROC) curves, the optimal cutoff value was determined using Youden's approach. The Youden Index is a commonly used summary measure of the ROC curve, and it measures the effectiveness of a diagnostic marker or a test, and enables the selection of an optimal threshold value (cutoff point) for the marker or test [16]. Sensitivity, specificity, and area under the curve (AUC) at the cutoff value were calculated in order to study the ability of the variables predicting the risk of developing higher grades of RD. Risk ratio (RR) for the association between each variable and the risk of developing higher grades of RD were obtained by univariate analysis.

All the statistical analysis was done using MedCalc software version 22.021.

Table 1. Patients' characteristics

Characteristics	No. of patients (%) (n = 80)
Median age	
Years [range]	65 (16–78)
Sex	
Male	68 (85%)
Female	12 (15%)
ECOG performance status	
0	59 (73.75%)
1	17 (21.25%)
2	4 (5%)
Initial nutritional status	
Well nourished (BMI > 18.5, < 5% weight loss in last 6 months)	18 (22.5%)
Moderately malnourished (BMI > 18.5, 5–10% weight loss in last 6 months)	62 (77.5%)
Severely malnourished (BMI < 18.5, > 10% weight loss in last 6 months or > 5% in the last month)	0
Smoking history (pack–years)	
0	7 (8.75%)
0–10	11 (13.75%)
10–20	8 (10%)
> 20	54 (67.5%)
Primary tumour subsite	
Nasopharynx	12 (15%)
Oropharynx	23 (28.75%)
Hypopharynx	20 (25%)
Larynx	22 (27.5%)
Others	3 (3.75%)
AJCC Stage (8th edition)	
III	24 (30%)
IVA	51 (63.75%)
IVB	5 (6.25%)

ECOG — Eastern Cooperative Oncology Group; BMI — body mass index; AJCC — American Joint Committee on Cancer

Results

The selected 80 patients' characteristic features are summarized in Table 1. In brief, median age was 65 years; 85% of the patients were male, and 67.5% of the sample population were heavy smokers (> 20 pack–years). 77.5% of the patients initially had moderate malnutrition as per SNAQ criteria, whereas 22.5% were well-nourished. The proportion of patients in subsets of oropharynx, hypopharynx and larynx were almost similar (28.75%, 25% and 27.5%, respectively) whereas 15% patients had disease of nasopharyngeal origin. Human papilloma virus (HPV) testing was not done in the oropharyngeal primary patients due to unavailability of the facility in our institution. A large proportion (63.75%) of the patients had stage IVA disease according to TNM staging 8th edition. TPF (docetaxel, carboplatin and fluorouracil)-based Induction chemotherapy was prescribed for only 5 of these 80 patients (6.25%). Overall, treatment compliance was good as per the patients' attendance documented in the treatment room register, with only 6.25% having prolonged (> 4 days) RT treatment discontinuation due to toxicities.

Table 2. Treatment characteristics and radiation dermatitis

Characteristics	No. of patients
VMAT schedule	
Sequential	26 (32.5%)
SIB	54 (67.5%)
RT compliance	
No interruptions	62 (77.5%)
Temporary interruptions	18 (22.5%)
Median of interruptions (days, range)	4 (1–16)
< 3 days	13 (16.25%)
≥ 4 days	5 (6.25%)
Radiation dermatitis (RD)	
Grade 1	38 (47.5%)
Grade 2	34 (42.5%)
Grade 3	8 (10%)
Grade 4	0

VMAT — volumetric-modulated arc therapy; SIB — simultaneous integrated boost; RT — radiation therapy

Treatment features and toxicity rates are shown in Table 2. 47.5% patients had grade 1 RD, 42.5% suffered from grade 2, and only 10% had grade 3 RD as per CTCAE criteria. No patients in our study suffered from grade 4 acute skin toxicity.

Patient, disease, treatment-related features and skin dose-volume parameters are summarized in Table 3 as per development of grade 1 and grade 2/3 RD. Statistically significant association of higher grade of RD was found with higher skin volumes receiving 40 Gy, 50 Gy or 60 Gy dose, and with the higher maximum point dose in the skin ring structure. From plotting ROC curves, statistically significant optimal cutoff values were found using Youden's approach — 71.6632 cc for V_{40} (AUC = 0.972, p-value < 0.001), 29.98 cc for V_{50} (AUC = 0.982, p-value < 0.001), 7.624 cc for

Table 3. Distribution of variables according to the degrees of radiation dermatitis (RD)

Characteristics	Grade 1 RD (n = 38)	Grade 2/3 RD (n = 42)	p-value
Age			
< 65 years	20 (51.28%)	19 (48.71%)	0.508822
> 65 years	18 (43.90%)	23 (56.09%)	
Sex			
Male	33 (48.52%)	35 (51.47%)	0.66073
Female	5 (41.67%)	7 (58.33%)	
ECOG PS			
0	28 (47.45%)	31 (52.54%)	0.994319
1	8 (47.06%)	9 (52.94%)	
2	2 (50%)	2 (50%)	
Initial nutritional status			
Well nourished	11 (61.11%)	7 (38.89%)	0.188992
Moderately malnourished	27 (43.54%)	35 (56.45%)	
Severely malnourished	0		
Smoking history (pack–years)			
0	5 (71.43%)	2 (28.57%)	0.49967
0–10	6 (54.54%)	5 (45.45%)	
10–20	4 (50%)	4 (50%)	
> 20	23 (42.59%)	31 (57.41%)	
Primary subsite			
Nasopharynx	5 (41.67%)	7 (58.33%)	0.9254
Oropharynx	11 (47.83%)	12 (52.17%)	
Hypopharynx	9 (45%)	11 (55%)	
Larynx	12 (54.54%)	10 (45.45%)	
Others	1 (33.33%)	2 (66.67%)	
Stage (AJCC 8th edition TNM)			
III	10 (41.67%)	14 (58.33%)	0.7089
IVA	26 (50.98%)	25 (49.02%)	
IVB	2 (40%)	3 (60%)	

Table 3. Distribution of variables according to the degrees of radiation dermatitis (RD)

Characteristics	Grade 1 RD (n = 38)	Grade 2/3 RD (n = 42)	p-value
VMAT schedule Sequential SIB	 13 (50%) 25 (46.296%)	 13 (50%) 29 (53.7%)	0.7560
PTV (size, cc; median, range)	161.4 (96.8----247)	202.6 (128.9----274.6)	0.1247
Skin ring 3 mm V_{40} (size, cc; median, range)	51.4182 (18.05---80.095)	83.4892 (70.645----119.542)	< 0.00001
Skin ring 3 mm V_{50} (size, cc; median, range)	21.868 (4.37----37.812)	47.93 (30.1146----85.06)	< 0.00001
Skin ring 3 mm V_{60} (size, cc; median, range)	2.647 (0.0012----7.264)	10.4082 (0.000333----40.6)	< 0.00001
Skin ring 3 mm D_{max} (point value, Gy; median, range)	66.56 (56.412----74.243)	67.964 (60.697----74.26)	0.030084

ECOG — Eastern Cooperative Oncology Group; AJCC — American Joint Committee on Cancer; PTV — planning target volume; VMAT — volumetric-modulated arc therapy; SIB — simultaneous integrated boost; PS — performance status

Table 4. Univariate analyses

Variable	Grade 1 RD (n = 38)	Grade 2/3 RD (n = 42)	Relative risk (95% confidence interval)	p-value
V_{40} ≥ 71.66 cc < 71.66 cc	 6 32	 40 2	 14.7826 (3.8353–56.9772)	0.0001
V_{50} ≥ 29.98 cc < 29.98 cc	 6 32	 42 0	 57.2449 (3.6487–898.1137)	0.004
V_{60} ≥ 7.624 cc < 7.624 cc	 2 36	 18 24	 2.2500 (1.5973–3.1694)	< 0.0001
D_{max} ≥ 66.56 Gy < 66.56 Gy	 18 20	 38 4	 4.0714 (1.6346–10.1410)	0.0026

Note: only statistically significant variables are shown; RD — radiation dermatitis; RR — relative risk; CI — confidence interval

V_{60} (AUC = 0.859, p-value < 0.001), and 66.56Gy for D_{max} (AUC = 0.680, p-value = 0.04). RR with 95% confidence interval (CI) were calculated by univariate analysis, and all of the 4 variables (V_{40}, V_{50}, V_{60} and D_{max}) were significantly correlated with grade 2/3 skin toxicity as depicted in Table 4. V_{50} was found to have the best predictive accuracy among the four parameters (AUC 0.982) as the higher AUC values in ROC curve analysis indicate better test performance. Figures 1–4 show the ROC curves plotted in MedCalc software. Figure 5 shows the dose-volume histogram (DVH) of the 3mm ring structure in a sample VMAT treatment plan.

Discussion

IMRT is a highly precise conformal radiotherapy technique in which multiple small beamlets, each with a non-uniform intensity profile, create dose distributions that can accurately conform to convex and concave structures alike [17]. The introduction of IMRT into the treatment of head and neck cancer patients made the reduction of treatment-related morbidity possible along with exquisite dose distribution [18], although with a substantial risk of marginal geographic miss of target and increased integral dose. Lee et al. [6] in 2002 first considered the skin of the neck as a separate structure for

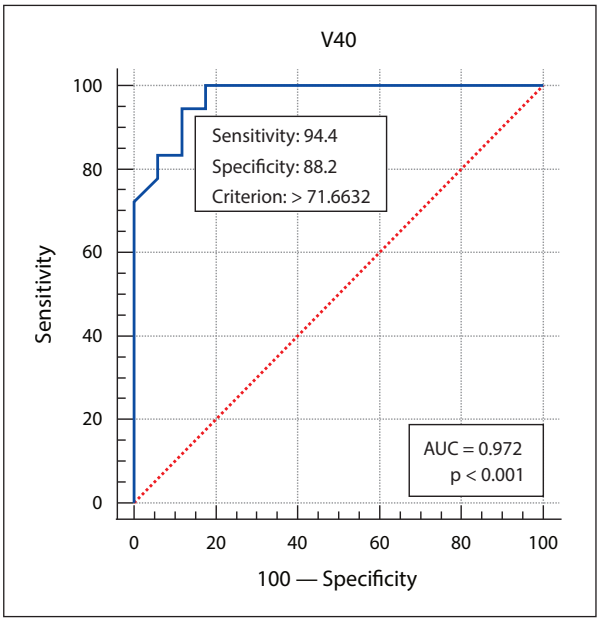

Figure 1. The receiver operating characteristic (ROC) curve analysis of skin ring 3 mm V_{40}. AUC — area under the curve

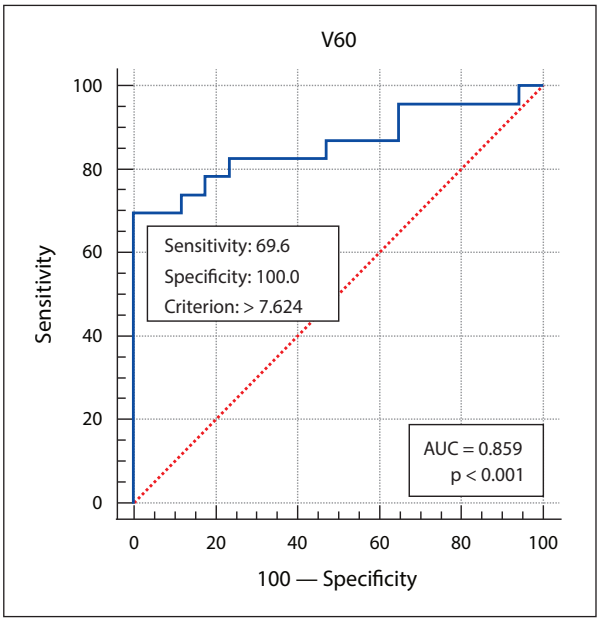

Figure 3. The receiver operating characteristic (ROC) curve analysis of skin ring 3 mm V_{60}. AUC — area under the curve

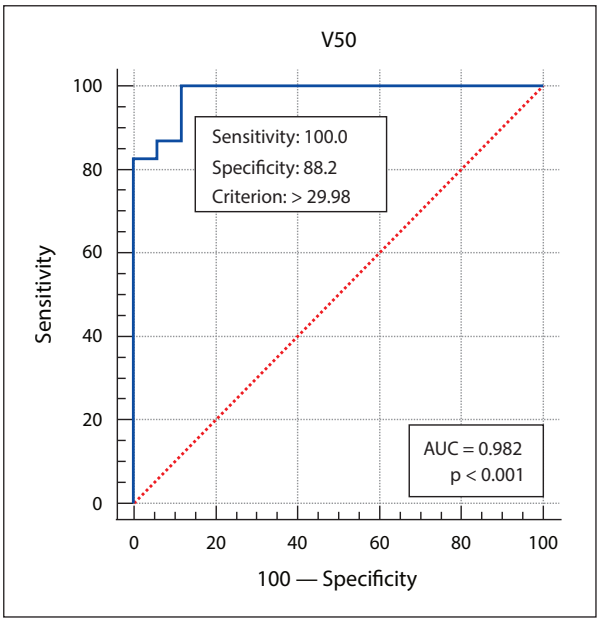

Figure 2. The receiver operating characteristic (ROC) curve analysis of skin ring 3 mm V_{50}. AUC — area under the curve

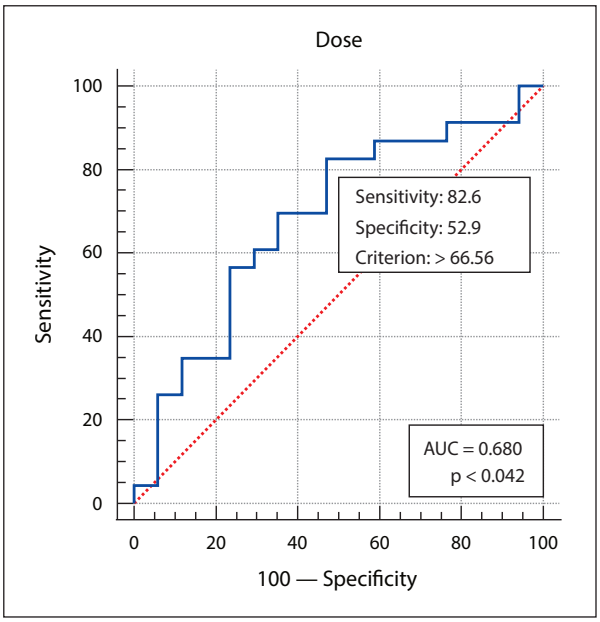

Figure 4. The receiver operating characteristic (ROC) curve analysis of skin ring 3 mm D_{max}. AUC — area under the curve

IMRT optimization, and showed that the volume of the skin exposed to > 45 Gy could be brought down by 20% compared with regular IMRT planning, as well as decreasing its mean dose by 6%. Price et al. [19] applied a 4-mm negative margin to the PTV from the body surface contour, and found the occurrence of superficial hotspots above 110% to be minimal, along with better rotational IMRT plan conformity with this increase of PTV to skin distance. In another study by Penoncello et al. [20] published in 2016, VMAT, a special form of IMRT delivering single or double arcs of precise radiation beams while continuously rotating around the patient's body [21] showed 5.6% reduction of mean

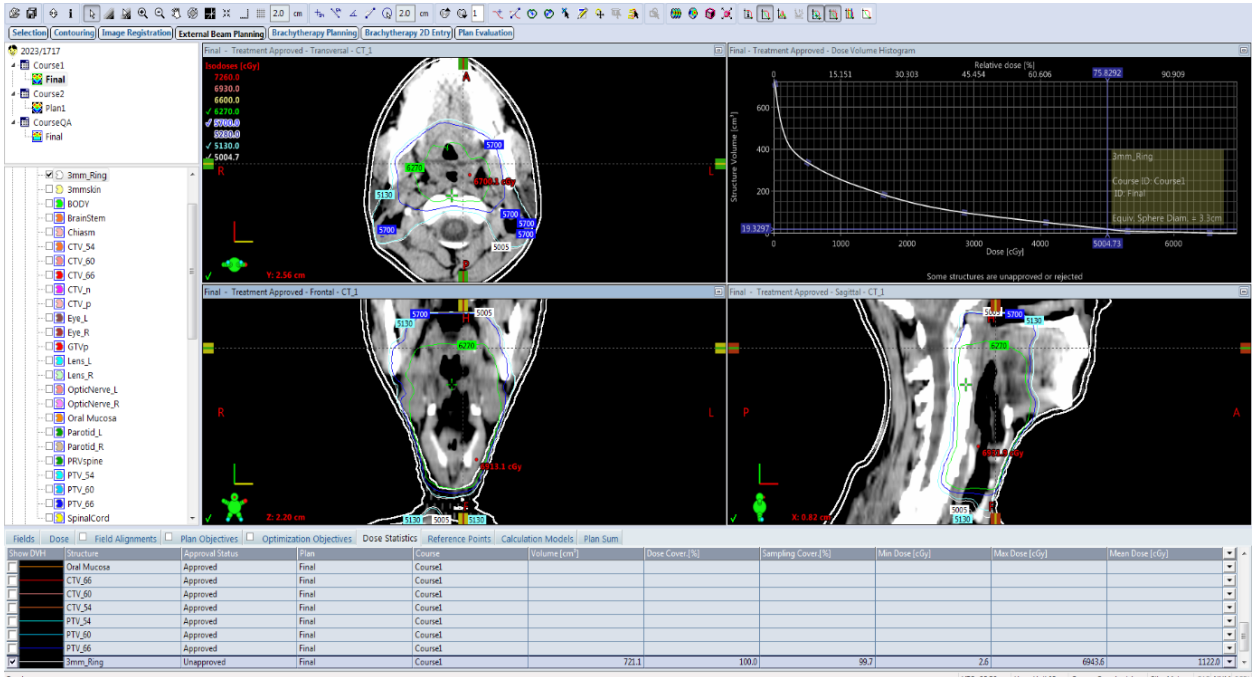

Figure 5. The dose-volume histogram (DVH) of the 3 mm ring structure in a sample volumetric-modulated arc therapy (VMAT) treatment plan

dose to the skin compared with static IMRT. However, the more modern refinements of IMRT techniques introduced neither any specific constraints to use for the skin nor any indications how to contour it in the irradiated area. Different OAR guidelines [22] recommend 3–6 mm skin thickness to be contoured, the variation depending on different skin thicknesses in different regions of interest. Studer et al. [11] in 2011 found a positive association between the incidence of Grade 3/4 RD and the radiation dose delivered to the larger skin volume in patients receiving cetuximab as concurrent chemotherapy. It was assessed by measuring skin doses > 50 Gy and > 60 Gy in the subdermal area 3mm below the skin. Severe RD was found in V_{50} 91cc and V_{60} 50 cc where grade 0–2 reactions were seen in V_{50} 61cc and V_{60} 27cc. In 2019, Mori et al. [23] found that a 2-mm thick superficial body layer DVH was associated with the risk of developing acute RD in patients treated with tomotherapy. They found V_{56}/V_{64} to be the most predictive parameters for grade 2/grade 3 RD. Optimal cutoff values were found to be 7.7 cc and 2.7 cc for V_{56} and V_{64}, respectively. V_{64} < 3 cc constraints should keep the risk of Grade III toxicity lower than 10%. Also in 2019, Bonomo et al. [12] created 3 ring structures, 2 mm, 3 mm and 5 mm below the skin to assess the correlation between skin dose-volume and Grade III/IV RD in 90 head and neck cancer patients treated with tomotherapy. They compared a concurrent cisplatin cohort with a cetuximab cohort. In multivariate analysis, they found statistically significant correlation of > 10 kg weight loss and performance status > 1 with the development of severe RD. The best predictive accuracy they found was at 2mm: an AUC 0.61 with V_{50} of 19.9cc and V_{60} of 5.8 cc. Our retrospective work adds to the available literature providing hypothesis-generating results, though the limitations must be acknowledged. Firstly, the relatively smaller sample size reduces the generalizability of our results. Secondly, the data collected retrospectively from our institutional datasheets may have interobserver differences. Thirdly, all the patients underwent the VMAT treatment according to the original plan. No weight loss was noted down, and no adaptive RT was considered due to heavy workload and logistical reasons. For that reason, we could not correlate the occurrence of moderate to severe RD with significant anatomic change (weight loss). But we think that proper prospective validation with a larger sample size and multivariate analysis are warranted based on our results, and specific skin dose-constraints can be recommended in future in-

ternational RT guidelines to decrease moderate to severe acute skin toxicity.

Conclusions

The dose distribution pattern to a 3 mm thick skin layer below the surface may help predict the development of moderate to severe radiation dermatitis in head and neck cancer patients receiving definitive concurrent chemoradiation. An optimum cut-off value of 29.98 cc for the volume of skin receiving at least 50 Gy radiation dose was found to be the strongest predictor of grade 2 and 3 radiation dermatitis in our study. This data may help future researchers to design large prospective studies incorporating these constraints. This will further validate the applicability of the present study in clinical setting to prevent radiation-induced skin toxicity.

Conflict of interest

The authors declare no potential conflict of interest.

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