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ORIGINAL ARTICLE

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Acute radiation dermatitis among patients with nasopharyngeal carcinoma treated with proton beam therapy: Prognostic factors and treatment outcomes

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Abstract

A high incidence of severe acute radiation dermatitis (ARD) has been reported for cancer patients treated by proton beam therapy (PBT). This observational study investigated the prognostic factors and treatment outcomes of ARD among patients with nasopharyngeal carcinoma (NPC) treated with PBT. Fifty-seven patients with newly diagnosed NPC and treated with PBT were enrolled. ARD was recorded weekly based on the criteria of Common Terminology Criteria for Adverse Events version 4.0 at treatment visits (1st to 7th weeks) and 1 week (8th week) and 1 month (11th week) after the completion of PBT. The maximum ARD grade was 1, 2, and 3 in 26 (45.6%), 24 (42.1%), and 7 (12.3%) of the patients, respectively. The peak incidence of grade 2 and 3 ARD was observed during the period of the 6th to 8th weeks. Treatment of ARD included topical corticosteroid alone in 24 (42.1%) patients, topical corticosteroid plus silver sulfadiazine in 33 (57.9%) patients, and non-adhering silicone dressing to cover severe skin wound area in 25 (43.8%) patients. In the 11th week, most grade 2 and 3 ARD had disappeared and 93.0% of the patients had ARD of grade 1 or lower. In the binary logistic regression model, we identified habitual smoking (odds ratio [OR]: 5.2, 95% confidence interval [CI]: 1.3-18.8, $P = .012$) and N2 to N3 nodal status (OR: 4.9, 95% CI: 1.6-15.4, $P = .006$) as independent predictors of grade 2 and 3 ARD. The results show ARD is a major concern for patients with NPC treated with PBT, especially those with habitual smoking or advanced nodal status. Topical corticosteroid, silver sulfadiazine, and non-adhering silicone dressing are effective for treating ARD induced by PBT.

KEYWORDS

acute radiation dermatitis, nasopharyngeal carcinoma, proton beam therapy, silver sulfadiazine, topical corticosteroid

Ko-Chun Fang and Chih-Hung Lee contributed equally to this study.

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Key Messages

- to investigate the prognostic factors and treatment outcomes of acute radiation dermatitis among patients with nasopharyngeal carcinoma treated with proton beam therapy
- habitual smoking and N2 to N3 nodal status were observed to be independent predictors of grade 2 and 3 acute radiation dermatitis
- topical corticosteroids, silver sulfadiazine, and non-adhering silicone dressing are effective for treating acute radiation dermatitis induced by proton beam therapy

1 | INTRODUCTION

Nasopharyngeal cancer (NPC) is a squamous epithelial carcinoma occurring in the mucosal wall of the nasopharynx. NPC is a geographically unique cancer, with an annual incidence of 1.5 per million people in the world and more than 70% of new cases occurring in East and Southeast Asia.[1] Radiotherapy (RT) with or without the combination of chemotherapy is the major treatment for NPC. Different from X-rays, proton beams are a kind of particle radiation. The use of proton beam therapy (PBT) to treat cancer patients is rapidly increasing nationwide, as evidenced by the rapid growth in the number of operational proton centres.[2]

A growing number of cancer centres in the world equipped with proton machine facilities have chosen PBT to radically treat patients with NPC.[3-6] Promising treatment outcomes of PBT with a reduction of swallowing-related functional outcomes and potential increase of patient survival have been reported compared with X-rays-based RT (XRT).[4,5,7-9] In radiation physics, PBT with its inherent properties of a Bragg peak, creating a sharp exit dose, has the benefit of dose distribution for cancer treatment. Protons have relatively low entrance (skin) doses when monoenergetic beams are used. However, tumour treatment volumes are complex targets with variable thicknesses and depths, requiring modulation of the beam energy to produce a spread-out Bragg peak that covers the target area. This process can result in a significant, and potentially full entrance dose with loss of the skin-sparing effect characteristic of high-energy X-rays (Figure 1), which represents a disadvantage for the surface area of the skin and might cause a heightened probability of acute radiation dermatitis (ARD).[10]

ARD can progress from erythema to dry desquamation to moist desquamation and even to necrosis.

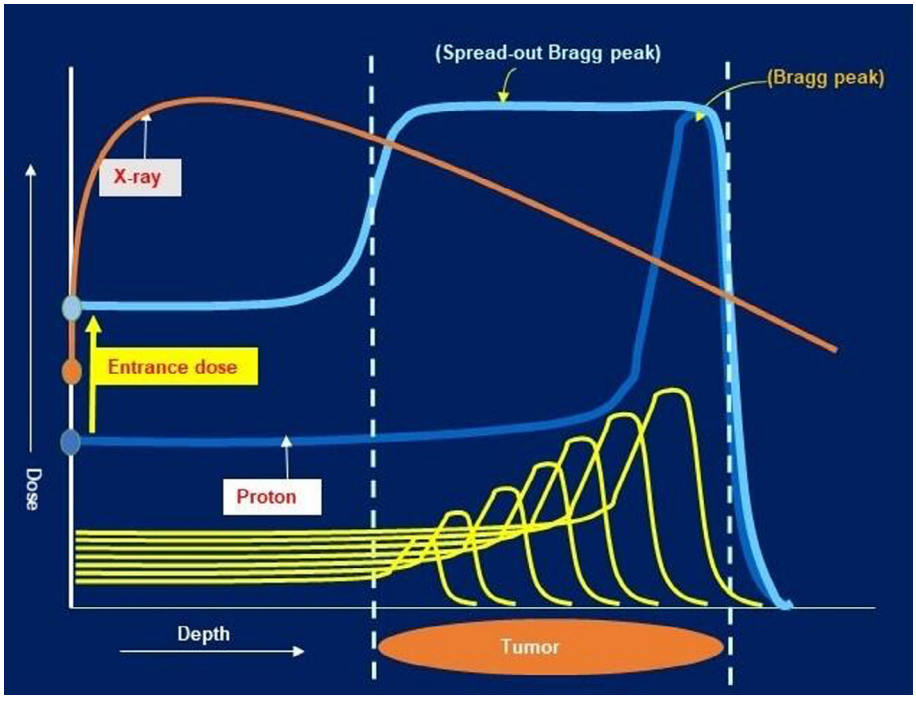

FIGURE 1 Depth-dose curves for proton beams and X-rays. The proton Bragg peak (dark blue line) allows for the elimination of an exit dose. Modulation of the proton beams (multiple yellow curve lines) results in a spread-out Bragg peak (light blue line) with the loss of skin-sparing effect (yellow arrow, increase of entrance dose), which is the characteristic of high-energy X-rays (orange line).

Severe ARD can lead to interruption of RT course, cause permanent skin changes, diminish aesthetic appeal, reduce the quality of life, and potentially negatively influence cancer control.[11-13] Some studies have reported a high incidence of severe ARD for cancer patients treated with PBT.[6,14-17] In this observational study, we investigated the treatment outcomes and prognostic factors of ARD for NPC patients treated with PBT at a single institute.

2 | MATERIALS AND METHODS

2.1 | Patient population

The proton centre of Kaohsiung Chang Gung Memorial Hospital in Taiwan started to treat NPC patients using PBT in January 2019. Those with newly diagnosed NPC and curatively treated with PBT for the whole treatment course were recruited. Patients who had not completed the proposed treatment course, or with a protracted treatment course due to interruption were excluded. With the approval of the institutional review board, 57 patients were enrolled for data analysis in the study. The patient characteristics are outlined in Table 1. The median age at the time of diagnosis was 48 (range 31-71) years old. Forty-two (73.7%) patients were male and 19 (33.3%) had a smoking habit. Those regarded with smoking habitual were current smokers as recorded for the first time when they visited the institute for the disease. The distribution of clinical stages based on the American Joint Committee on Cancer (AJCC) 8th edition was 7.0% in stage I, 28.1% in stage II, 38.6% in stage III, and 26.3% in stage IV, respectively. Fifty-two (91.2%) patients were treated in combination with chemotherapy.

TABLE 1 Patient characteristics (N = 57)

Variables	N (%)
Age, years	
Median	48
Range	31-71
Gender	
Male	42 (73.7)
Female	15 (26.3)
Smoking habit	
Yes	19 (33.3)
No	38 (66.7)
Body mass index (kg/m^2)	
<24.0	23 (40.3)
≥24.0	34 (59.7)
Comorbidity	
Diabetes mellitus	5 (8.8)
Hypertension	7 (12.3)
AJCC stage	
I	4 (7.0)
II	16 (28.1)
III	22 (38.6)
IV	15 (26.3)
T status	
T1	31 (54.4)
T2	9 (15.8)
T3	9 (15.8)
T4	8 (14.0)
N status	
N0	9 (15.8)
N1	21 (36.8)
N2	18 (31.6)
N3	9 (15.8)
Combination with chemotherapy	
No	5 (8.8)
Yes	52 (91.2)

Abbreviation: AJCC, American Joint Committee on Cancer staging system 8th edition.

2.2 | Assessment of ARD

ARD was graded using Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v. 4.0) reported weekly by physicians at treatment visits (1st to 7th weeks) and 1 week (8th week) and 1 month (11th week) after the completion of PBT. The grading is grade 1: faint erythema or dry desquamation; grade 2: moderate to brisk erythema, patchy moist desquamation, mostly confined to skin folds and creases, moderate edema; grade 3: moist desquamation in areas other than skin folds and creases, bleeding induced by minor trauma or abrasion; and grade 4: life-threatening consequences, skin necrosis or ulceration of full thickness dermis, spontaneous bleeding from involved site, skin graft indicated.

2.3 | PBT technique

The detailed technique of PBT for patients with NPC in the institute was published previously.[18] The scanning beam technique was used and delivered by a Sumitomo Proton Machine and the treatment planning was carried out by the RayStation treatment planning system (version 7, Raysearch Medical Laboratories, Stockholm,

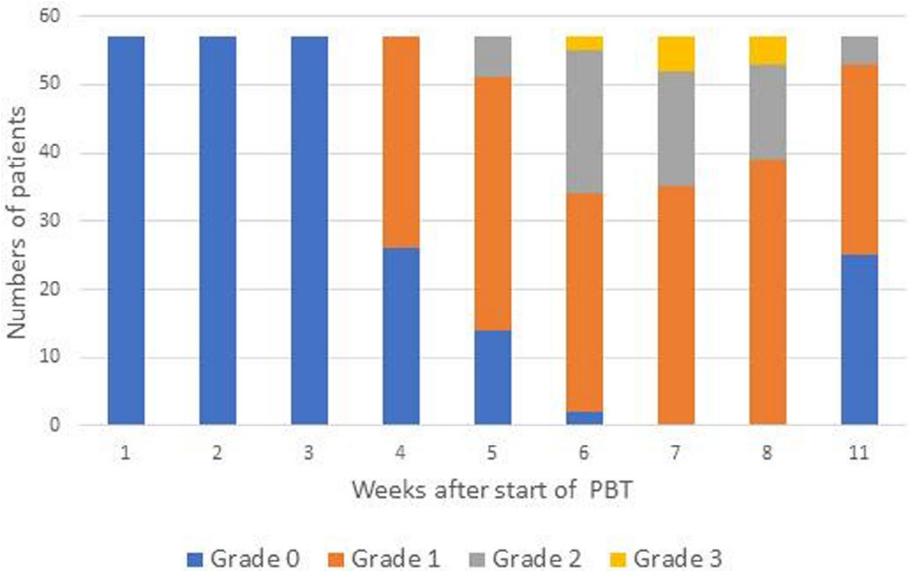

FIGURE 2 Incidence and severity of acute radiation dermatitis (ARD). The ARD of 57 nasopharyngeal carcinoma patients treated with proton beam therapy (PBT) was graded using Common Terminology Criteria for Adverse Events version 4.0 reported weekly by physicians at treatment visits (1st to 7th weeks) and 1 week (8th week) and 1 month (11th week) after the completion of PBT

Sweden). Computed tomography (CT) imaging with 1.25 mm per slice for treatment planning purposes was performed for all patients while supine with a customised thermoplastic mask for immobilisation. Three different dose levels of clinical target volume (CTV) were created. The high dose level of CTV (CTV-H) was defined as the gross tumour and nodes with an isotropic extension of 3 mm for the gross tumour volume (GTV) and gross nodes revealed in the image studies. The middle dose level of CTV (CTV-M) covered the neighbouring risky anatomic structures (eg, skull base, parapharyngeal space, upper neck lymphatics) of GTV, encompassing micro-metastasis routes of the disease. The low dose level of CTV (CTV-L) included the uninvolved subclinical lymphatics in the lower neck area. The prescribed dose and fractionation for CTV-H, CTV-M, and CTV-L was 69.96 Cobalt Grey Equivalent (CGE), 59.4 CGE, and 52.8-54.0 CGE in 33 fractions, respectively. The organs at risk (OARs) with specified dose constraints were contoured for treatment planning, including the brain, brainstem, spinal cord, optic nerve, chiasm, lens, cochleas, parotid glands, submandibular glands, constrictor muscle, mandible, oral cavity, larynx, upper oesophagus, thyroid gland. The constrains of these OARs generally followed the guideline recommended.[19] As regards the neck skin, the OAR of skin 5 mm (a layer structure of 5 mm inward from the head and neck contour) was optionally outlined and arbitrarily chosen as a constraint with the request of "as small as possible for V50CGE without compromising the coverage of CTV." Typically, three beam directions of posterior, left anterior oblique and right anterior oblique fields with multi-field optimization were used for the planning, with the objective of covering 99.5% of the CTVs and minimising dose to the OARs. Generally, robust optimization was used to take into consideration of the range (plus 3.5%) and positional uncertainties (plus 3 mm). Robust evaluation, which creates 21 plans from the worst to best-case scenarios, was conducted for the assessment of the planning result. Daily CT based image guide was conducted for set-up accuracy. Adaptive plan was performed in case of remarkable changes of GTV or patients' body shape to confirm at least 95% coverage of CTV.

2.4 | Chemotherapy

Neoadjuvant chemotherapy with the combination regimens of cisplatin (80 mg/m^2, day1) and gemcitabine (1 g/m^2, days 1 and 8) administered every 3 weeks was given for 3 cycles to those patients with clinical stages III-IV.[20] Concurrent chemotherapy with intravenous cisplatin 40 mg/m^2 weekly as a radiation sensitizer was given for 6-7 weeks during the course of PBT for those with clinical stages II-IV.

2.5 | Statistical analysis

Pearson's chi-squared test was used on the categorical variables between groups. Binary logistic regression method was performed in multivariate analysis. In the binary logistic regression analysis, the dependent variable is ARD (grade 2 and 3 vs grade 1) and the independent variables include age (≥48 vs <48 years), gender (male vs female), smoking habit (yes vs no), body mass index

(≥24.0 vs <24.0 kg/m^2), diabetes mellitus (yes vs no), T status (T3 to T4 vs T1 to T2), N status (N2 to N3 vs N0 to N1), and weekly cisplatin (yes vs no). A value of $P < 0.05$ was considered statistically significant. All statistical analysis was processed with IBM SPSS version 22 software (Chicago, Illinois, USA).

3 | RESULTS

3.1 | Incidence and severity of ARD

Figure 2 presents the incidence and severity of ARD assessed at the nine-time points. During the first 3 weeks, no patients presented with notable ARD. The maximum ARD grade was 1, 2, and 3 in 26 (45.6%), 24 (42.1%), and 7 (12.3%) of the patients, respectively. No grade 4 ARD was observed. The peak incidence of grade 2 and 3 ARD occurred from the 6th to 8th weeks. In the 11th week, most grade 2 and 3 ARD had disappeared and 93.0% of the patients had ARD of grade 1 or lower. However, some degree of chronic scar formation was observed in 3 of the 7 cases with grade 3 ARD after longer follow-up. All of the three cases had a smoking habit and one had comorbidity of diabetes. Figure 3A-C presents the typical pictures of ARD in a case of NPC patient, staged T1N3M0, who was treated with PBT in combination with weekly cisplatin. The grade 1 ARD appeared in the 4th week of PBT, progressing to grade 3 in the 7th week. In the 11th week, the severe ARD at the right lower neck skin fold area gradually healed but some scarring remained.

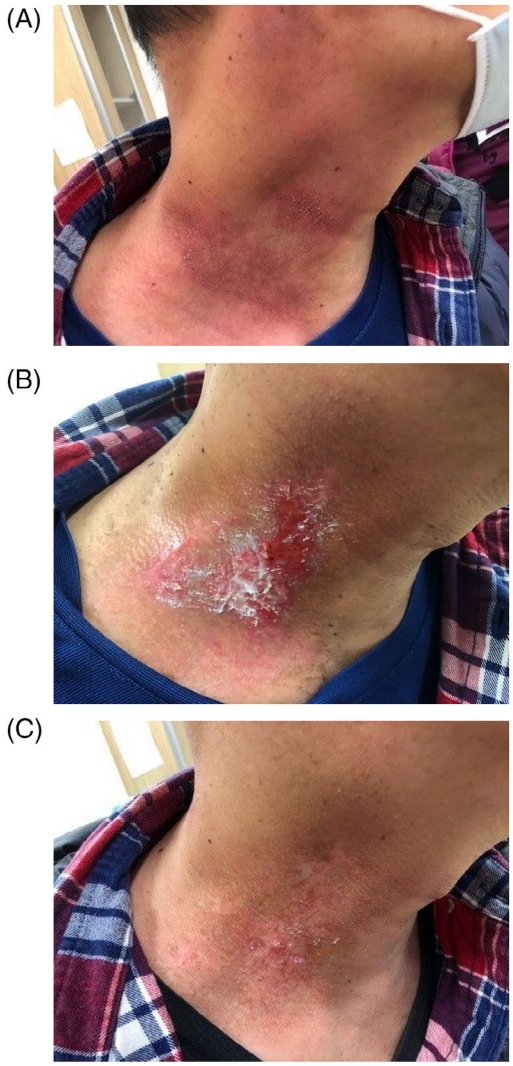

FIGURE 3 The clinical pictures of acute radiation dermatitis (ARD) for one nasopharyngeal carcinoma patient, staged T1N3M0, treated with proton beam therapy (PBT) in combination with weekly cisplatin. A, Grade 1 ARD appeared in the 4th week of PBT; B, progressing to grade 3 in the 7th week; and C, the severe ARD at the right lower neck skin fold area gradually healed but some scarring remained till the 11th week

3.2 | Treatment of ARD

Generally, topical corticosteroid was used when grade 1 ARD appeared, and silver sulfadiazine was added if ARD progressed to grade 2 or more. During the treatment course, 24 (42.1%) patients were treated with topical corticosteroid alone, and 33 (57.9%) patients received the combination of topical corticosteroid and silver sulfadiazine. An additional non-adhering silicone dressing (ADAPTIC TOUCH Non-Adhering Silicone Dressing; Systagenix, an Acelity Company, Gatwick, UK) was used to cover severe skin wound areas in 25 (43.8%) patients with grade 2 or 3 ARD. The topical corticosteroid was applied to the affected area of ARD, normally twice daily, but three times daily for the area with severe ARD. When the ARD have been alleviated, the topical corticosteroid could be continued while reducing the frequency of administration. The silver sulfadiazine was usually applied one to two times daily. The layer of medication could be about 1-2 mm thick. The area with severe ARD had better be covered with the cream all the time. Non-adhering silicone dressing may be applied over the cream, but only in the area with severe ARD. The dressing may be left in place for several days until the severe ARD is completely healed.

3.3 | Predictors of ARD

Table 2 presents the relationship between clinical variables and a maximum ARD of grades 2 and 3 in univariate and multivariate analysis. In the binary logistic regression model, we identified habitual smoking (odds

TABLE 2 Univariate and multivariate analysis of predictors of grade 2 and 3 acute radiation dermatitis

	Grade 2 and 3[a]				
	Univariate[b]		Multivariate[c]		
Variables	%	*P* value	OR	95% CI	*P* value
Age: ≥48 vs <48 years	55.6:53.3	1.000	0.9	0.2-4.1	.863
Gender: Male vs female	59.5:40.0	.236	3.7	0.7-20.4	.218
Smoking habit: Yes vs no	**78.9:42.1**	**.011**	**5.2**	**1.3-18.8**	**.012**
Body mass index: ≥24.0 vs <24.0 kg/m^2	61.8:43.5	.190	2.7	0.6-12.7	.218
Diabetes mellitus: Yes vs No	60.0:53.8	.999	0.8	0.1-12.7	.869
T status: T3 to T4 vs T1 to T2	58.8:52.5	.774	2.3	0.4-11.7	.325
N status: N2 to N3 vs N0 to N1	**74.1:36.7**	**.007**	**4.9**	**1.6-15.4**	**.006**
Weekly cisplatin: Yes vs no	56.9:33.3	.396	2.2	0.2-25.1	.537

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Grading was based on the criteria of Common Terminology Criteria for Adverse Events version 4.0.

[b]Chi-square test was used for the comparison of the clinical variables among patients presenting with a maximum ARD grade of 2 and 3, $P < 0.05$ was considered statistical significance.

[c]Binary logistic regression method was used for multivariate analysis, $P < 0.05$ was considered statistical significance.

ratio [OR]: 5.2, 95% confidence interval [CI]: 1.3-18.8, $P = .012$) and N2 to N3 nodal status (OR: 4.9, 95% CI: 1.6-15.4, $P = .006$) as independent predictors of grade 2 and 3 ARD. Age, gender, T status, body mass index, diabetes, and concurrent chemotherapy were not observed to impose a significant risk factor for ARD.

4 | DISCUSSION

ARD is often defined to occur within the first 90 days of RT, typically starting to occur after a moderately high dose (eg, 35-40 Gy in 2 Gy per fraction) has been delivered to the skin. Different patient characteristics and treatment techniques may lead to different degrees of ARD. A variety of ARD severity exists in the literature and our cohort for NPC patients treated with PBT. The proportion of patients with grade 1, 2 and 3 ARD after treatment with PBT ranged from 0%-64.3%, 25%-67.4%, and 3.6%-42.0%, respectively.[4-6,21]

General management of ARD begins with basic preventive measures, including self-care and the use of prophylactic topical corticosteroids and/or antibiotics. It is difficult to establish strong evidence-based clinical practice guidelines in the approach to self-care for ARD. The medication for ARD induced by PBT generally follows the clinical practice used for patients treated with XRT. Several clinical trials have demonstrated a favourable effect for the use of prophylactic topical corticosteroids[22-24] or silver sulfadiazine[25] to reduce ARD. In our cohort, topical corticosteroid was prescribed for patients with grade 1 ARD and silver sulfadiazine was added if the ARD progressed to grade 2 or more. Dressing adherence to the wound or peri-wound area is a common complication and can cause pain and trauma on removal and nonadherent wound contact layer dressings have been reported to reduce wound bed trauma during dressing changes.[26] An additional non-adhering silicone dressing was applied to cover sever skin wound in our patients. These regimens were observed to be effective in the treatment of ARD induced by PBT.

The severity of ARD is related to numerous risk factors that have been classified as being patient-related or treatment-related. Patient-related risk factors may include age, gender, smoking, nutritional status, body mass index, comorbidity, or genetic factors. Treatment-related factors include the total radiation dose, the dose fractionation schedule, RT technique, combination with chemotherapy, and the volume and surface area of irradiated tissue.[11,27,28] For NPC patients, in a large cohort study treated with XRT (including intensity-modulated RT or three-dimensional conformal RT), treatment with intensity-modulated RT, lower performance status and multicycle chemotherapy were observed to be predictors of severe ARD.[29] In our patients uniformly treated with PBT with standardised protocols including total dose and dose per fraction, chemotherapy regimens, and skin care, the variables of smoking habit and advanced nodal status were observed to be significant predictors for grade 2 and 3 ARD.

The correlation between habitual smoking with ARD remains inconsistent in the literature for patients treated with XRT.[27,30,31] For PBT, very limited data are available. The association between habitual smoking and the

severity of ARD after PBT has been previously reported in patients with breast cancer[14] but was reported for the first time in patients with NPC in the present study. The mechanism of the effect of smoking on ARD is unknown. However, strong evidence has demonstrated that smoking adversely impacts the wound healing process.[32] Tissue hypoxia is viewed as a fundamental mechanism through which cigarette smoking disrupts acute wound healing.[33] Cigarette smoking impairs the function of several cell types such as neutrophils and macrophages important to inflammatory and bactericidal activity and also compromises oxygen delivery to tissues.[34]

Patients with advanced nodal status often receive a higher radiation dose to the neck skin, putting them at a higher risk of severe ARD. The identification of neck skin as a sensitive structure for dose optimization during the process of treatment planning of RT could significantly reduce the skin dose to a tolerable level.[35] The volume of skin at 2 mm receiving a dose above 56 Gy was observed to be predictive of grade 2 and 3 ARD for head and neck cancer patients treated with XRT.[36] The dosimetric parameters related to the severity of ARD were not explored in the current study. As far as we know, a validated dosimetric constraint for neck skin used to mitigate the severity of ARD for patients treated with PBT in the head and neck area is still lacking, though, some dosimetric parameters related to severe ARD in chest skin or scalp have been reported in patients treated with PBT.[14,16]

The biological effects on normal tissue induced by PBT are not well established.[37,38] The pathogenesis of ARD involves a combination of direct radiation injury and subsequent inflammatory response, affecting cellular elements in the epidermis, dermis, and vasculature. Direct radiation injury causes changes in skin pigmentation through the migration of melanosomes, interrupted hair growth, and damage to the deeper dermis, which disrupts the normal process of skin cell repopulation, resulting in erythema due to dermal vessel dilation and release of a histamine-like substance.[39] The mechanism of radiation-induced inflammation is not yet completely understood, but keratinocytes, fibroblasts, and endothelial cells stimulate immune cells in the epidermal and dermal layers, as well as those in circulation.[40]

Some degree of chronic radiodermatitis was observed in our cases with grade 3 ARD after a longer follow-up. Grade 3 ARD at the end of XRT has been observed to be associated with neck fibrosis at 6 months in head and neck cancer patients.[41] Chronic radiodermatitis often presents several months to years after RT has been completed. Post-inflammatory hypo- and hyperpigmentation are common chronic changes seen in patients as a result of the dermo-epithelial junction being disrupted, which depends on patient- and treatment-related factors and may persist or normalise with time.[11] Telangiectasia and fibrosis are also common in chronic radiodermatitis in NPC patients. The incidence of symptomatic neck fibrosis varies from 2.3% to 38% in NPC patients treated with XRT.[42,43] The consequential effect of ARD induced by PBT on chronic skin injury warrants further investigation.

Admittedly, there are several limitations to the study. First, the grading of ARD relied on subjective assessments by treating physicians and the cases were limited to a single institute; it is therefore vulnerable to selection bias. Second, a dosimetric evaluation of the effects of PBT on the skin surface was not conducted due to the limited sample size. However, according to this observational study, we observe ARD is a major concern for patients with NPC treated with PBT, especially those with a smoking habit or advanced nodal status. Topical corticosteroids, silver sulfadiazine, and non-adhering silicone dressing are effective for treating ARD induced by PBT.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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