Utilizing a Second Flap to Address the Effect of Postradiotherapy Soft Tissue Fibrosis in Head and Neck Malignancy

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Abstract

Background Late effects of adjuvant radiation therapy (RT) on soft tissues can lead to hair loss, pigmentary changes, loss of tissue volume, and fibrosis, which appear months to years after the treatment. These changes are often progressive and are because of tissue hypoxia due to radiation-induced capillary endothelial damage. Tissue hypoxia may be compounded by subclinical infection following minor trauma, exposed hardware, or associated osteoradionecrosis. The combined effect of these factors causes significant deformities in soft tissue, affecting both function and appearance. Such changes are also seen in primarily transferred flaps, which have been radiated, resulting in severe, progressive soft tissue fibrosis, compromising function and aesthetics. In selected cases, a second flap may be needed to restore function and volume.

Methods Data of patients who underwent secondary soft tissue transfers for postradiotherapy-related soft tissue changes were collected from the hospital electronic medical records, from January 2019 to 2023. Details regarding the primary surgery, dose, duration of adjuvant RT, time interval between adjuvant RT and secondary soft tissue transfer, indications, and the choice of the second flap were analyzed.

Results Twenty-one patients had undergone secondary soft tissue transfer for extensive soft tissue fibrosis. In addition, associated compounding features like exposed implant and volume loss were observed. Two patients with osteoradionecrosis also had associated extensive soft tissue fibrosis necessitating replacement. Out of these 21 patients, 13 had undergone free tissue transfers, while 7 locoregional tissue transfers.

Conclusion Late sequelae of adjuvant RT changes usually present from 6 months onwards. The radiated hypoxic tissue, due to capillary damage, leads to a chronic progressive fibrotic stage, causing loss of soft tissue volume and fibrosis. Replacing this tissue with a vascularized flap helps to restore volume and correct these secondary changes, improving overall quality of life.

Keywords

- RT-induced soft tissue fibrosis
- secondary soft tissue transfer
- adjuvant RT

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Introduction

The late effects of adjuvant radiation therapy (RT) encompass a spectrum of manifestations, including hair loss, pigmentary changes, loss of flap volume, and fibrosis, which appear from 6 months and continue till several years postradiotherapy.[1] These persistent changes occur due to radiation-induced tissue hypoxia, attributed to capillary endothelial damage by ionizing radiation.[2] This problem is especially relevant in the context of head and neck reconstruction, as transferred tissue flaps frequently experience significant soft tissue fibrosis after RT which negatively affects both their functionality and appearance.[3–5] Tissue hypoxia, which is a major factor in causing these long-term issues, can worsen due to subclinical infections caused by minor injuries, exposed implants, or the presence of underlying osteoradionecrosis.[2] The cumulative impact of these factors can lead to significant soft tissue deformities resulting in functional and aesthetic compromise. In certain cases, replacement of affected tissue by another soft tissue flap mitigates the late complication of adjuvant RT.

A series of 21 patients who required replacement of previously transferred flaps with a second composite tissue transfer for secondary soft tissue changes following adjuvant RT is presented.

Materials and Methods

Retrospective data from January 2019 to 2023, retrieved from electronic medical records, were analyzed. Of 756 patients who had undergone primary excision and reconstruction, 21 individuals underwent a secondary soft tissue transfer to address severe soft tissue changes related to adjuvant RT. The age group of the patients ranged from 29 to 70 years, of these 17 were males and 5 were females.

Patients with tumor recurrence, plate removal alone, without soft tissue transfer, or those who underwent minor local tissue readjustments without soft tissue transfers were excluded. Those who underwent supplementary secondary procedures like fat grafting and scar revisions were likewise omitted from the analysis.

The parameters recorded included the clinical presentation and soft tissue fibrosis along with its underlying pathology requiring surgery. Volume loss (►**Fig. 1**), scarring (►**Fig. 2**), exposed hardware or fistulas leading to functional impairment (►**Figs. 3** and **4**), the duration elapsed since completion of radiotherapy, and

Fig. 1 (**A**) Primary marking showing extent of full-thickness excision. (**B**) Primary reconstruction with Fibula osseocutaneous free flap (FOCFF) and Anterolateral thigh (ALT) free flap. (**C**) Postsurgery prior to radiotherapy. (**D**) Severe soft tissue fibrosis with leathery, pigmented, and contracted skin along with discharging sinus and significant volume loss. (**E**) Topographic markings to show the extent of volumetric replacement planned using a differentially thinned flap (ALT). (**F**) Prior identification of superficial temporal vessels. (**G**) Volume and contour restored after secondary soft tissue transfer (ALT).

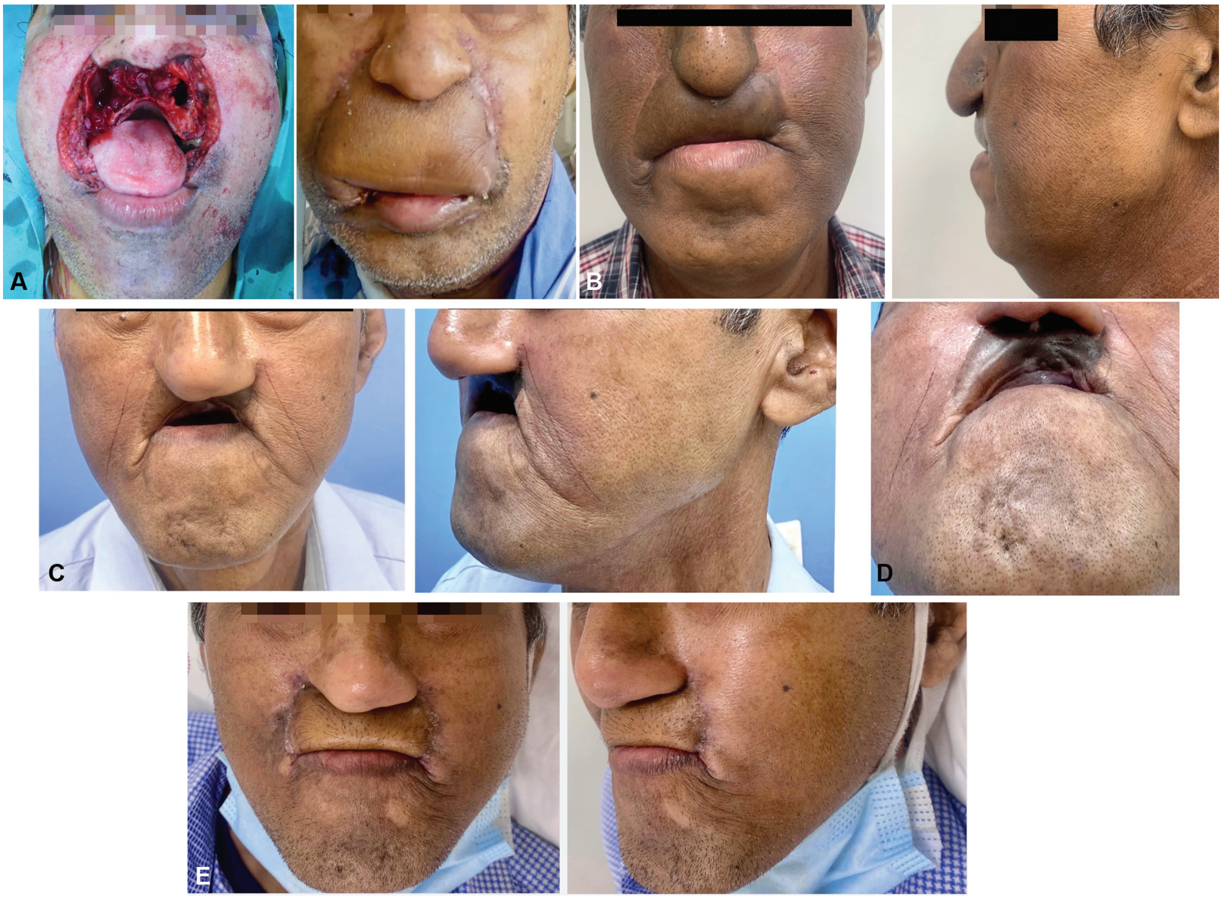


Fig. 2 (**A**) Postresection of carcinoma upper alveolus and nasal floor. (**B**) Primary reconstruction with Deep circumflex iliac artery (DCIA) and Radial artery forearm flap (RAFF) (note extent of overcorrection of lip). (**C**) Seven months postradiotherapy. (**D**) Two and half year postadjuvant radiotherapy showing complete loss of volume, causing deformity and incompetence of the upper lip. (**E**) Secondary soft tissue transfer with RAFF, to restore the lip along with placement of dental implants.

surgical method employed (free tissue transfer or pedicled flap cover) were recorded. Recipient vessels chosen and the ultimate outcome (focused on whether the intervention successfully achieved its intended goal) were also documented (►**Table 1**).

Results

The age demography of the cohort ranged from 29 to 70 years of which 17 were males and 5 were females.

Fig. 3 (**A**) Carcinoma lower lip showing extent of excision. (**B**) Primary reconstruction with Radial artery forearm flap (RAFF). (**C**) Six months postadjuvant radiation therapy —volume loss, exposed gingiva, loss of lip competence, and drooling. (**D**) One year postadjuvant RT—showing progress of soft tissue fibrosis. (**E**) Secondary soft tissue transfer (RAFF) with restoration of volume and lip competence.

Fig. 4 (**A**) Defect postexcision for carcinoma buccal mucosa. (**B**) Primary reconstruction with chimeric fibula osseocutaneous free flap (FOCFF) and proximal peroneal artery flap restoring adequate volume. (**C**) Immediately post-radiation therapy showing acute changes. (**D**) Osteoradionecrosis (ORN) with orocutaneous fistula along with severe soft tissue fibrosis. (**E**) Postreconstruction with double island Radial artery forearm flap (RAFF).

Primarily 10 patients had complex through-and-through defects, of these 4 were reconstructed using double free flaps (►**Table 1**) (►**Figs. 1** and **4**). Chimeric, fibula osseocutaneous flap, combined with proximal peroneal artery perforator flap were used in five of those patients and a radial artery forearm flap was used for lining and cover in one patient. The other 11 patients were addressed using single flaps (►**Table 1**).

All patients had received external beam radiation, using intensity-modulated RT (IMRT) with photon beams, delivering a total of 60 Gy over 30 fractions to the tumor (flap) bed. The period, from the conclusion of adjuvant radiotherapy and surgical intervention ranged from 5 to 108 months, with a mean of 20 months.

Nine patients presented with a discharging sinus with or without exposed plate, while 8 patients presented with exposed implant. Two patients had orocutaneous fistula (►**Fig. 4**), two patients complained of drooling and exposed gingiva with loss of lip competence (►**Fig. 3**), and two patients presented with deformity (►**Fig. 2**). Clinically associated with this underlying cause, the previously transferred flap was found to be pigmented, leathery, oedematous, and densely scarred (►**Fig. 1**).

Out of these 21 patients, 14 underwent a second free tissue transfer and 7 locoregional tissue cover. Of the 14 microvascular tissue transplants, radial artery flap was employed for 10, while the anterolateral thigh flap was used for 4 patients. Among the 7 regional flaps that were transferred, the deltopectoral flap (DP) was the most frequent, for 3 patients, followed by the pectoralis major myocutaneous flap for 2, while the latissimus dorsi myocutaneous flap and paramedian forehead flap were utilized for one patient each (►**Table 1**).

In 10 patients, the superficial temporal vessels were chosen as recipient vessels, while the unoperated contralateral neck vessels were chosen for 3 patients. Only in one patient the previously operated and radiated ipsilateral neck recipient vessel was found suitable.

Two patients had follow-up beyond 3 years, while 11 patients had been followed up for more than 6 months and 7 patients had a shorter follow-up.

Discussion

In contrast to acute post-RT changes, the late sequelae of adjuvant radiotherapy is stated to start beyond 6 months and continue for several years.[5] The incidence is reported to be around 10 to 15%.[6–8] Over long term, radiated tissue flaps can experience various significant changes, including fibrosis, volume reduction, osteoradionecrosis, plate exposure, and fistula.[4,5] These alterations in the flap's characteristics resulting from adjuvant RT can pose challenges both in terms of function and appearance (►**Fig. 2**).

Ionizing radiation primarily damages the deoxyribonucleic acid and alters the cellular microenvironment through free radicals.[9] The mechanism of underlying soft tissue damage due to radiation follows the principle that, cells with a higher rate of division are more vulnerable to radiation and suffer more damage compared with cells not actively dividing. Among these, endothelial cells found in arterioles and capillary networks are especially sensitive to

Table 1 Master char

No.	Age/Sex	Diagnosis	Primary reconstruction	Neck dissection	RT dose (Gy)	Indication for secondary soft tissue transfer	Secondary flap used	Time between adjuvant RT and secondary reconstruction (mo)	Recipient vessels A/V	Follow-up (mo)
1	60/M	CA BM	PMMC	Unilateral	60	ORN	RAFF	13	Contralateral FA and IJV	66
2	50/M	CA BM	FOCFF	Unilateral	60	Volume loss and contour irregularity	ALT	24	Ipsilateral FA and EJV	65
3	43/M	CA BM	FOCFF	Bilateral	60	Exposed implant, volume loss, and contour irregularity	RAFF	12	Contralateral FA and EJV	60
4	39/M	CA BM	FOCFF	Unilateral	60	Exposed implant with volume loss	RAFF	22	Contralateral FA, IJV, and EJV	52
5	47/M	CA lower alveolus	FOCFF	Unilateral	63	Exposed implant with contracted skin	DP	10		41
6	50/M	CA lower alveolus	FOCFF	Unilateral	60	Exposed implant with contracted skin	PMMC	6		40
7	62/M	CA lower alveolus	FOCFF	Bilateral	60	Exposed implant with volume loss	RAFF	84	STA and STV	31
8	71/M	CA upper alveolus	FOCFF	Bilateral	60	Exposed implant with contour irregularity	LD	14		36
9	47/M	CA BM	FOCFF	Unilateral	60	Exposed implant with contour irregularity	PMMC	27		32
10[a]	46/F	CA lower lip	RAFF	Bilateral	60	Volume loss with lower lip incompetence	RAFF	11	STA and STV, EJV	25
11	48/F	CA lower alveolus	FOCFF + RAFF	Unilateral	60	Exposed implant with orocutaneous fistula	DP flap	5		23
12	57/M	CA lower alveolus	FOCFF	Bilateral	60	Exposed Implant, fibrosed skin	RAFF	13	STA/STV and EJV	18
13	60/M	CA BM	FOCFF	Unilateral	60	Exposed implant with discharging sinus	DP Flap	10		6
14	55/M	CA lower alveolus	RAFF + DCIA	Unilateral	60	Fistula with fibrosed skin	ALT	15	STA and STV	14
15[a]	41/M	CA lower alveolus	FOCFF + ALT	Unilateral	60	Exposed implant, contour irregularity	ALT	75	STA and 2 STV	3
16[a]	72/F	CA lower alveolus	FOCFF	Bilateral	60	Orocutaneous fistula with ORN	RAFF	105	STA and STV, EJV	5
17	57/M	CA central upper alveolus	DCIA	Bilateral	60	Oronasal fistula, volume loss, and contour irregularity	RAFF	11	STA and STV, EJV	2

(*Continued*)

Table 1 (*Continued*)

No.	Age/Sex	Diagnosis	Primary reconstruction	Neck dissection	RT dose (Gy)	Indication for secondary soft tissue transfer	Secondary flap used	Time between adjuvant RT and secondary reconstruction (mo)	Recipient vessels A/V	Follow-up (mo)
18[a]	55/M	CA central upper alveolus	RAFF + DCIA	Unilateral	60	Volume loss and contour irregularity with incompetent upper lip	RAFF	30	STA and STV	1
19	42/M	CA lower alveolus	FOCFF	Bilateral	60	Flap volume loss, contour irregularity, and orocutaneous fistula	ALT	14	STA and STV	1
20	29/F	CA maxilla	Free LD	Unilateral	60	Exposed implant with contour irregularity	Forehead	8		4
21	60/M	CA lower alveolus	FOCFF	Bilateral		Exposed implant with orocutaneous fistula	RAFF	38	STA and STV	1

Abbreviations: ALT, anterolateral thigh flap; BM, buccal mucosa; CA, Carcinoma; DCIA, deep circumflex iliac artery flap; DP, deltopectoral flap; EJV, external jugular vein; F, female; FA, facial artery; FOCFF, fibula osseocutaneous free flap; IJV, internal jugular vein; LD, latissimus dorsi flap; M, male; ORN, osteoradionecrosis; PMMC, pectoralis major myocutaneous flap; RAFF, radial artery forearm flap; RT, radiation therapy; STA, superficial temporal artery; STV, superficial temporal vein.
[a]Illustrated cases.

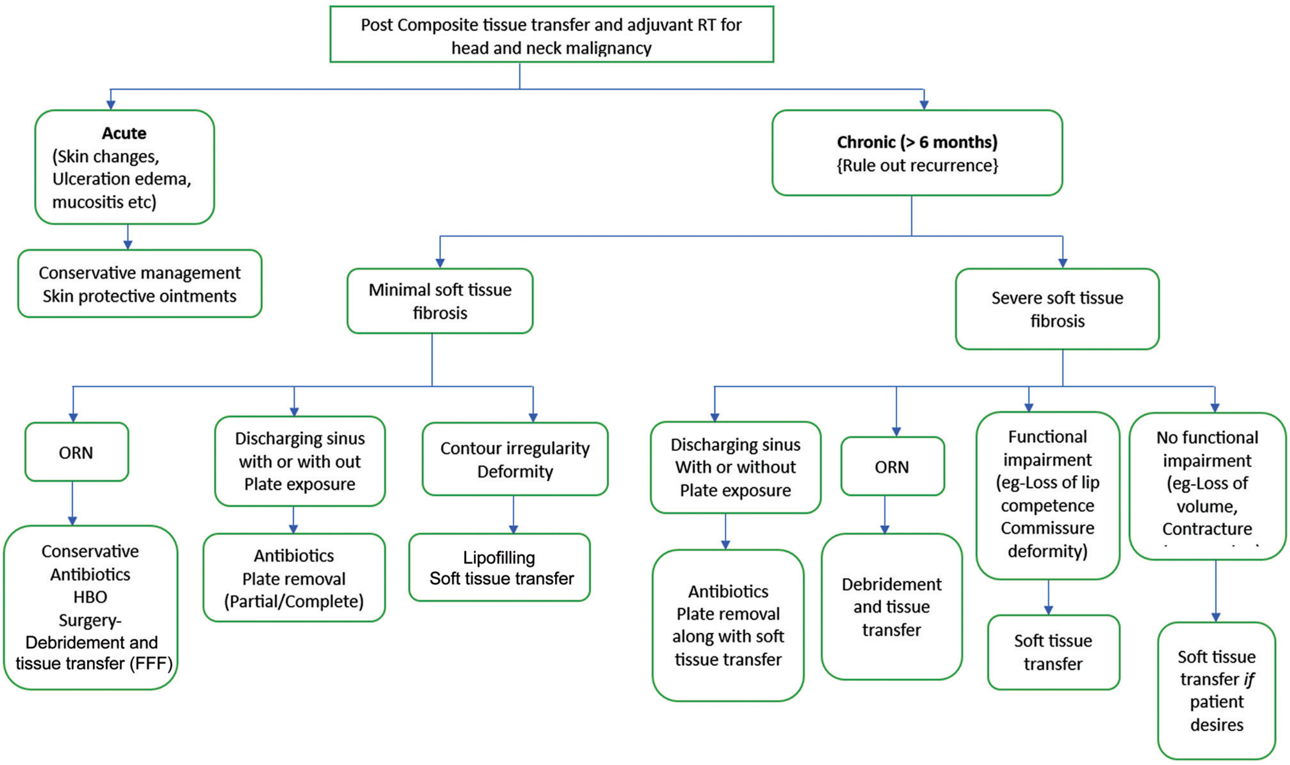
radiation in comparison to stromal cells. This sensitivity leads to obliterative endarteritis, which results in reduced oxygen supply to the tissue and characteristic fibrotic changes in the tissue's stroma that has been damaged by radiation.[2] However, in tissues with limited cell turnover, these processes are less influenced by cell division and are instead driven by chemokines and fibrotic cytokines. This leads to a latency period between radiation exposure and the onset of tissue damage, including tissue fibrosis, atrophy, or vascular injury.[9] This progression is like the chronic healing process. Although various factors contribute to the late sequelae of adjuvant radiotherapy, including treatment, patient, and tumor-related factors, Masuda and Kamiya have highlighted that certain patients may possess a genetic susceptibility to radiation-induced injury.[10]

Majority of late postradiation effects typically become apparent at approximately 1 year after treatment. For secondary procedures, a minimum of 6 months following adjuvant radiotherapy is generally considered "safe" with regard to wound healing.[4] The underlying vascular endarteritis makes an attempt "to repair" growing new capillaries, but these grow disorganized and underlying scarring and hypoxia persists.[1,11] In all but one of the 21 cases, the secondary procedures were performed after 6 months to as late as 10 years, following adjuvant radiotherapy.

Advancements in radiotherapy have evolved from utilizing Cobalt to photon-based techniques, enabling precise three-dimensional dose targeting with the application of IMRT. These innovations have indeed reduced the incidence of complications compared with earlier methods but have not eliminated them. Patients undergoing adjuvant radiotherapy through IMRT receive the highest radiation dose precisely focused on the excised area, which encompasses the reconstructed flap and its surrounding region, as visualized in the planning computed tomography. This approach ensures that a high dose is delivered to the targeted area while significantly minimizing radiation exposure to nearby healthy tissues.[12]

Patients typically seek medical attention only when there is a breach, discharging sinus with exposed hardware or bone, or when fistulas develop. Patients tend to disregard volume loss, pigmentary changes, and contour irregularities, possibly due to concerns about additional surgical procedures, associated discomfort, and costs. Management of plate exposure involves a conservative strategy, incorporating antibiotics and, subsequently, plate removal, either partially or entirely. This is suitable when the surrounding skin is pliable and can be readily closed primarily (**Algorithm 1**). However, in a specific subset of patients with plate exposure, the surrounding soft tissue will be firm, leathery, and not pliable, making it inadequate for proper closure. The skin might also be adherent to the underlying bone and any additional surgical undermining of this hypoxic tissue will further compromise its vascularity (►**Fig. 1**). The transfer of vascularized tissue to the radiated area offers pliable tissue that facilitates the closure of breached areas. Moreover, it enhances volume, aesthetics, and results in improved facial contour (►**Fig. 1**).

While addressing radiation-related changes an initial conservative approach may be initiated, using antibiotics,



Algorithm 1 Algorithm for management of postradiation sequelae.

proper nutrition, cessation of tobacco, and avoiding any pressure and trauma[8] (**Algorithm 1**).

Hyperbaric oxygen has been found to improve tissue oxygen over a course of 30 to 40 treatments. This may stimulate angiogenesis and improve granulation, resulting in a more elastic and less fibrotic tissue.[1] This may bring about improvement in 80% but the skin in no way returns to normal.[1]

Fat grafting has been coincidentally found to improve surrounding skin quality. Cell-assisted lipotransfer at radiated sites has been proposed.[15] This may be considered for minimal volume and contour irregularity when the skin is soft and pliable.[13] However, this approach may not be suitable when the overlying skin is fibrosed and scarred (►**Figs. 1** and **2**). Additionally, fat grafting is not effective in addressing pigmentary changes or substantial volume replacement. Use of fat grafting to prevent secondary changes in an irradiated bed is an area that needs exploration.[14]

Presently, it appears logical that replacement of the affected tissues, with a fresh vascularized composite tissue, would address this problem in a select group of patients where conservative measures fail (►**Fig. 2**).

The selection of flap was customized to address specific requirements and issues unique to each patient, particularly addressing the loss of tissue volume and color match. The decision was also influenced by factors, including the location and availability of suitable recipient blood vessels, the patient's preference regarding the donor site, and cost-related considerations. In the instances of free tissue transfer radial artery forearm flap was the choice, where volume requirement was minimal, and as it provided a thin, pliable skin, despite the drawback of a forearm scar. In cases where patients experienced substantial volume loss requiring additional bulk, anterolateral thigh free flap was employed. Among the pedicle flaps, the DP flap was the preferred option due to its color match, pliability, and cost-effectiveness, even though it required staging. Donor site of DP flap was closed primarily, resulting in a linear scar.

In 10 out of 21 patients (i.e., 48%), ipsilateral superficial temporal vessels served as the preferred recipient vessels. This choice was primarily based on their location outside the radiation field, avoiding exploring the irradiated neck. Initial surgical step involved exploring and verifying the suitability of the superficial temporal vessels, prior to flap harvest and transfer (►**Fig. 1**). For central defects where the contralateral neck was uninvolved, it was the preferred choice.

Wei et al have discussed second free flaps in the context of addressing complications such as volume loss resulting from insufficient planning and issues during the primary surgery. However, their work did not address post-RT soft tissue fibrosis.[15,16] It is logical that replacing a scarred hypoxic tissue with a well-vascularized tissue will address the progressive sequelae of RT.

The impact of radiation-induced alterations in skin and subcutaneous tissue is widely acknowledged, yet there has been a lack of objective analysis in this regard. Various factors, including the type and dose of radiation, the patient's primary disease status, nutritional condition, and genetic influences, can contribute to these changes.[10] While exploring primary preventive measures like overcorrecting soft tissue volume, interposing muscle or subcutaneous fat at the reconstruction site is an avenue which is in practice.[11] The quest to mitigate the adverse effects of radiation on soft tissue and the subsequent demands for reconstructive surgery, represent an ongoing and complex challenge in the field of radiation oncology and plastic surgery. Further research and clinical exploration are imperative to develop preventive and management strategies to address these late effects effectively and improving patient outcomes.

Conclusion

While a satisfactory reconstruction is typically accomplished during primary surgery, the delayed consequences of adjuvant radiotherapy, particularly those involving soft tissues, can sometimes lead to significant secondary deformities, potentially resulting in compromised functional and aesthetic outcomes. It is important to emphasize that not all soft tissue-related issues occurring post-adjuvant RT are a direct result of the radiotherapy itself. Rather, a specific subset of patients is affected by these radiation-induced effects on soft tissue. In those subsets of patients, these challenges can be effectively managed with a secondary flap procedure. This consideration should be integrated into the surgical treatment timeline, alongside patient counseling and motivation.

Conflict of Interest
None declared.

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