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Microvascular Free Tissue Reconstruction in the Patient With Multiple Courses of Radiation

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Objectives/Hypothesis: To assess the feasibility of microvascular free tissue transfer in the multiply irradiated patient.

Study Design: Retrospective cohort analysis of 48 patients in a tertiary care, private practice setting.

Methods: Inclusion criteria were defined as patients who received multiple courses of radiation and underwent subsequent free tissue reconstruction to manage treatment-related complications (n = 24) or defects following additional oncologic surgery (n = 24). The main outcome measures included total and partial flap necrosis, hardware exposure, and pharyngocutaneous fistula. The minimum follow-up was 6 months.

Results: One case of total flap failure, two cases of partial skin paddle necrosis, one case of poor wound healing of the surrounding tissue to the flap, six cases of hardware exposure, 11 cases of fistula with eight requiring operative intervention, three cases requiring and additional free flap to supplement reconstruction, and one stroke.

Conclusions: Microvascular free tissue transfer to the head and neck is expected to provide a successful reconstruction in patients who have received multiple courses of radiation and who develop second primary tumors, recurrence of disease, or who suffer from late complications of their radiation therapy.

Key Words: Microvascular free tissue transfer, complications of radiation therapy, pharyngocutaneous fistula, radionecrosis.

Level of Evidence: 4.

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INTRODUCTION

Many patients who have undergone primary or adjuvant external beam radiation therapy (EBRT) in the treatment of head and neck squamous cell carcinoma (HNSCC) go on to develop second primary tumors or recurrent cancer.[1] A subset of these patients will require a second round of full-dose radiation either as primary treatment or as an adjuvant to salvage surgery. These patients who have received two full courses of radiation remain susceptible to recurrence and second primary HNSCC.

Additionally, the rate of radiation-induced complications, such as soft tissue necrosis leading to nonhealing wounds, orocutaneous or pharyngocutaneous fistulae, dysfunctional laryngeal function, or osteoradionecrosis (ORN) remains high in the double-irradiated patient, with potential complications occurring long after treatment has concluded.[2–8]

In the double-irradiated patient, free tissue transfer is useful for reconstructing defects resulting from the above complications, as well as in cases of cancer recurrence where resection remains an option. To our knowledge, there have been no studies examining the efficacy of free flap reconstruction in patients who have received multiple courses of preoperative radiation. We performed this retrospective chart review to ascertain the feasibility of microvascular reconstructive surgery in the multiply irradiated patient.

MATERIALS AND METHODS

After appropriate institutional review board approval was obtained, a retrospective chart review was performed on all cases presenting to the senior author, practicing in a tertiary care private setting, between September 1997 and September 2012. Patients were studied who received multiple courses of EBRT, as well as patients who underwent salvage therapy using either EBRT and brachytherapy or EBRT and robotic radiosurgery. Criteria for inclusion comprised patients who completed at least twice the standard treatment dose of radiation (field of reirradiation encompassed the area of reconstruction in each case) and who then underwent surgical reconstruction using free tissue transfer, for either a complication of radiation or for cancer recurrence. Minimum follow-up was 6 months. Patients who received a simple EBRT boost after one formal full treatment dose were excluded.

Variables examined included the modality of radiation therapy (e.g., EBRT vs. brachytherapy vs. stereotactic radiosurgery), and whether radiation was used as an adjuvant to surgery. The use of chemotherapy at the time of primary oncologic treatment was also examined, either as induction therapy or concomitantly. Indications for surgery were noted, as well as postoperative complications, in the form of flap failure, exposure of hardware (when applicable), fistula formation, problems with

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TABLE I.
Patients' Radiation, Chemotherapy, and Surgical Treatments (N = 48).

Treatment	No. of Patients
Induction chemotherapy	6
Concurrent chemotherapy	25
Agent used	
Erbitux	8
Platinum-based agent	17
EBRT as adjuvant postoperative treatment	16
Radiosurgery	5
Two full courses of EBRT and robotic radiosurgery	3
Received second full round of EBRT	39
Received third round EBRT	1

EBRT = external beam radiation therapy,

wound healing, major bleeding events, the need for additional reconstructive surgery, and dependence on a gastrostomy tube for nutritional support.

RESULTS

Forty-eight patients met the inclusion criteria listed above. Of these, 31 were male (age range, 32–74 years; mean, 57.8 years) and 17 were female (age range, 36–77 years; mean, 60.2 years).

Radiation History

All 48 patients received EBRT as part of their initial oncologic treatment (Table I). Twenty-five patients were treated with concurrent chemotherapy, with eight patients receiving cetuximab and 17 patients receiving platinum-based agents. Five patients were treated with radiosurgery, such as Cyberknife or Novalis. Sixteen patients underwent primary surgical resection with postoperative EBRT.

Three patients received two full courses of EBRT as well as treatment with robotic radiosurgery. One patient underwent three courses of EBRT, though the first course was limited to only 15 treatments (the other two were full treatment length). Overall, 5-year disease-free survival in the reirradiation group was 43.5%.

Surgical Interventions and Complications

Reasons for surgery included ORN recalcitrant to hyperbaric oxygen therapy, debridement, and antibiotics (11 patients), recurrent carcinoma in the previously irradiated field with no evidence of distant metastases (24 patients), dysfunctional larynx with aspiration or airway compromise (nine patients), carotid exposure or major bleeding event, either in the form of a sentinel bleed or formal blowout (four patients) (Tables II and III).

In the group treated for ORN (11 patients), flaps utilized included eight osteocutaneous fibula free flaps (FFF), two scapular free flaps, and one osteocutaneous radial forearm free flap. There were no instances of total flap failure. One FFF demonstrated partial skin paddle necrosis. No instances of bony necrosis were noted. Recurrent hardware exposure was observed in four patients, with three patients experiencing multiple episodes of plate erosion despite intravenous antibiotics, plate exchange, and a viable free flap. The affected overlying soft tissues that broke down in all three cases were limited to external, native skin. All three of these patients were managed with a second flap, using radial forearm fasciocutaneous flaps (RFFF) in two patients and a pedicled pectoralis major flap in another.

In the group treated for dysfunctional larynx (n = 9), all patients had documented airway compromise, aspiration necessitating gastrostomy tube dependence, and poor voice. These patients all underwent total laryngectomy with RFFF reconstruction. Seven of these patients developed pharyngocutaneous fistulas (77.8%), and two of these patients were repaired with sternocleidomastoid flaps, two with pectoralis major flaps, and two closed with local wound care. One flap was lost after advanced cardiac resuscitation protocols were initiated, in the setting of cardiovascular collapse in a patient who experienced carotid blowout in the postoperative period. The patient was reconstructed with another RFFF. Two patients suffered sentinel carotid hemorrhage in the postoperative period without significant additional morbidity.

In the group treated for vascular complications, such as carotid exposure or sentinel bleeding event, a latissimus dorsi free flap was used for coverage in one patient, a rectus abdominis free flap (RAFF) in another patient, an anterolateral thigh free flap (ALTFF) in another, and an RFFF in the last patient. There were no instances of partial or total flap failure. One patient experienced major neurological injury secondary to a stroke suffered as a result of carotid blowout.

In the group treated for recurrent cancer, resections involved the larynx/hypopharynx (11 patients), the neck with overlying skin (three patients), the temporal bone (three patients), the oral cavity (three patients), and the oropharynx (four patients). Laryngectomy/laryngopharyngectomy defects were repaired with an RFFF in all 11 cases. There were four instances of pharyngocutaneous fistulae (PCF) in this subset, of which three were closed with pectoralis major flaps and one with local wound care. There were no instances of flap failure of any kind. Only four patients were able to resume adequate oral intake to allow for removal of their gastrostomy tubes.

Patients operated on for recurrence of cervical disease (n = 3) were reconstructed with an RAFF in two patients and an RFFF in one patient. There were no complications in these patients. Among the patients undergoing surgery for temporal bone disease (n = 3), two were reconstructed with an RAFF and one with an ALTFF. The patient who received the ALTFF endured problems with wound breakdown surrounding the flap for 12 months. There were otherwise no complications in this group.

Patients undergoing resection of oral cavity carcinoma (n = 3) were reconstructed with an FFF in all cases. One patient received an RAFF in addition to the FFF for reconstruction of the tongue. There was one

TABLE II.
Patients' Surgical Indications.

Surgical Indication	Type of Flap							Total
	FFF	Scapula	OCRFFF	RFFF	ALT	RA	Lat	
ORN (n = 11)	8	2	1	0	0	0	0	11
Dysfunctional larynx (n = 9)*	0	0	0	10	0	0	0	10
Vascular complication (n = 4)	0	0	0	1	1	1	1	4
Recurrent cancer (n=24)†	3	0	0	15	1	7	0	26
Location of recurrence								
Larynx/hypopharynx (n = 11)	0	0	0	11	0	0	0	11
Neck with skin excision (n = 3)	0	0	0	1	0	2	0	3
Temporal bone (n = 3)	0	0	0	0	1	2	0	3
Oral cavity (n = 3)†	3	0	0	1	0	1	0	5
Oropharynx (n = 4)	0	0	0	2	0	2	0	4

*One patient experienced total flap loss after cardiovascular collapse and was repaired with another RFFF.
†One patient received two flaps for primary reconstruction. Another patient needed an RFFF for hardware exposure postoperatively, resulting in 26 flaps for 24 patients. Both tumors were located in the oral cavity.
ALT = anterolateral thigh; FFF = fibula free flaps; Lat = Latissimus; OCRFFF = osteocutaneous radial forearm free flap; ORN = osteoradionecrosis; RA = rectus abdominis; RFFF = radial forearm fasciocutaneous flaps.

instance of partial skin necrosis in one FFF cutaneous paddle. Two patients experienced chronic hardware exposure, with plates in both patients eroding through the native facial skin rather than through the oral wound that had been repaired with the flaps. Both of these patients required plate exchange. A pectoralis major flap was used in one patient for soft tissue coverage, whereas an RFFF was used in the other.

Oropharyngeal defects included the tonsil and base of tongue in all patients (n = 4). Two patients underwent reconstruction with an RFFF and two with an RAFF. There were no complications relating to flap failure or wound healing in these patients. All patients, however, were dependent on nutritional support via their gastrostomy tubes.

The rate of major wound healing difficulties among all 48 patients, defined as total flap failure, recurrent hardware exposure, fistula requiring surgical intervention, or need for second flap repair was 40% (19 patients).

DISCUSSION

Morbidity of Reirradiation

Many patients who receive external beam radiation therapy for HNSCC will suffer either recurrence or second primary tumors. Treatment for these patients often includes a second full course of radiation, either in the form of EBRT, brachytherapy, or other modalities such as robotic radiosurgery.[2,9] Repeat radiation incurs a risk of complications beyond that of primary radiation alone.[2–8]

Additionally, patients undergoing salvage surgery for recurrent or second primary HNSCC after one course of primary radiation, followed by a second course of adjuvant, postoperative radiation, are at high risk for late complications, with ORN occurring in up to 16%, mucosal necrosis in 20%, and cervical fibrosis in 44%.[10]

TABLE III.
Patients' Complications.

Complication	Indication for Free flap				Total (n = 38)
	ORN (n = 11)	Airway (n = 10)	Vascular (n = 4)	Recurrence (n = 24)	
Total flap loss		1			1
Partial flap loss (skin)	1			1	2
Wound healing				1	1
Recurrent hardware exposure	4			2	6
Fistula requiring surgical intervention		5		3	8
Fistula healing with wound care		2		1	3
Permanent G-tube dependence				11	11
Sentinel bleeding event		2			2
Need for second flap repair	3				3
Stroke			1		1

G-tube = gastrostomy tube.

Role of Vascularized Tissue in Salvage Surgery Followed by Reirradiation

The use of pedicled flaps and free tissue transfer to mitigate the complications of salvage surgery followed by radiation in the previously irradiated patient with HNSCC has been studied. Stafford and colleagues noted an apparent reduction in difficulties with wound healing when locoregional soft tissue flaps were used to assist wound closure in the setting of Ir-192 brachytherapy.[11] All patients receiving flap reconstruction healed without complication.

An improvement in wound healing was also noted in patients undergoing salvage surgery with partial resection of HNSCC followed by brachytherapy (Ir-192 or I-125) with locoregional pedicled flaps compared with primary closure.[12] These authors noted a reduction in wound breakdown from 46% to 12% when pedicled flaps were utilized.

The use of microvascular free flaps further enhances the beneficial effects of flap reconstruction beyond those of locoregional flaps by transferring healthy, distant tissue into the surgical bed. Moscoso and others examined patients undergoing salvage surgery followed by brachytherapy (Ir-192 or I-125) who were closed with the aid of pedicled flaps in one group versus free flaps in the second group.[13] The locoregional flap group experienced an acute complication rate of 40% compared to a rate of 20% in the free flap group.

Suh and colleagues studied 12 patients who underwent salvage surgery for HNSCC after previous EBRT who were reconstructed with microvascular free tissue transfer and then underwent additional postoperative radiation therapy.[14] These authors noted no instances of flap loss. Severe late complications were seen in 33% of patients. These included glaucoma, dysphagia, mandibular ORN, or soft tissue necrosis leading to intraoral ulceration or orocutaneous fistula.

Experience With Free Tissue Reconstruction in the Multiply Irradiated Patient

Surgical reconstruction is often necessary in tissue beds that have received multiple courses of radiation, either in cases of recurrent or second primary HNSCC, where the maximum dose of radiation to the surrounding anatomic structures has been reached, leaving salvage surgery as the only option, or when problems with wound healing or late complications of radiotherapy in the doubly irradiated neck arise, such as fistula formation, soft tissue necrosis, or osteoradionecrosis.

Our retrospective cohort analysis suggests that free tissue transfer in the multiply irradiated patient is feasible, with an acceptable flap failure rate (<2%), which is comparable to overall flap success rates at other high-volume centers. Of note, the one case of total flap loss was likely due to cardiovascular collapse and not an intrinsic, flap-related problem. Other complications were related to problems with the surrounding irradiated tissue bed. Of the six patients who suffered hardware exposure in the postoperative period, five demonstrated erosion of hardware through the native tissues rather than through breakdown of the flap suture line.

PCF formation was a common problem. Of the 20 patients who underwent laryngectomy or laryngopharyngectomy for either dysfunctional larynx or recurrent carcinoma, 11 (55%) developed PCF. Eight of these required surgical intervention, whereas the other three healed with wound care alone. Interestingly, PCF was more common in laryngectomy performed for dysfunctional larynx (77.8%) versus oncologic resection (36.4%).

Role of Vascularized Reconstruction in the Salvage Laryngectomy

In the literature, the rate of PCF following salvage laryngectomy has been observed to be higher than that of primary laryngectomy,[15,16] with some studies noting much higher rates of fistula formation of up to 59%[17] and 77%.[18]

The timing of surgery, relative to radiation, has also been shown to be associated with wound healing complications. In a study by Dirven et al., the rate of fistula formation in patients undergoing salvage laryngectomy within 4 months of completion of radiotherapy was 75%, compared to 25% in those who underwent surgery >4 months after radiation.[16] When stratified in term of patients having surgery within a year of radiation, 48% of patients who underwent salvage surgery within a year of EBRT developed PCF, whereas no patients who were operated on more than a year after EBRT suffered PCF.

It has been suggested that pharyngeal closure after salvage laryngectomy should be bolstered with free tissue irrespective of the presence of adequate mucosa for primary closure. Fung and colleagues noted a reduction in fistulas requiring surgical management when free flaps were used to assist with pharyngeal closure compared to primary closure (0% vs. 11.1%), whereas the overall fistula rate was comparable (29% vs. 30%).[19] Major wound complications were reduced from 14.8% to 0% with the use of microvascular free tissue.

Withrow and investigators also noted an improvement in healing following salvage laryngectomy with a reduction in PCF from 50% with primary closure alone to 18% with primary closure and free flap overlay.[20] The vast majority of fistulas from both groups in this study were successfully treated conservatively. Additionally, there was a trend toward reduced rates of esophageal stricture formation as well as feeding tube dependence with free tissue repair, though these findings were not statistically significant.

Our rate of PCF (55%) is higher than the range of PCF formation found in the literature for salvage laryngectomy with free flap pharyngeal closure. We would expect the rate of fistula formation and wound breakdown to be higher in tissue that has received a greater total dose of radiation. We hypothesize that the use of free tissue in pharyngeal closure in the multiply irradiated patient would improve healing in a similar fashion to that seen in salvage laryngectomy cases. However, this current study does not supply sufficient data to confirm or refute this.

Several of the patients included in the study underwent prior regional flap reconstruction (e.g., pectoralis major flap) or free flap reconstruction during the course of their initial treatment. The appropriateness of microvascular free tissue transfer needs to be examined on a case-by-case basis and depends on a patient's prior surgical history, functional status, and anticipated survival, as well the patient's motivation. By performing this study, we are not advocating the use of free tissue for the reconstruction of all patients who have received high cumulative doses of radiation; rather, we are examining the feasibility of free flap surgery in this population and its expected rate of complication.

CONCLUSION

The use of free tissue transfer in double-irradiated tissue beds has not been specifically studied in the literature. It is clear that patients who have received high doses of radiation to the head and neck are at increased risk for wound healing complications. Microvascular free tissue transfer has shown promise in reconstructing defects in patients undergoing surgery following one course of radiation, as well as in salvage patients who will subsequently receive additional postoperative radiation. Although more data are needed to quantify the benefit of free flap reconstruction in patients with high cumulative doses of radiation, our retrospective analysis provides encouraging data suggesting that microvascular surgery can be successful in patients who have received multiple courses of radiation preoperatively.

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