Published in final edited form as:

Ann Surg Oncol. 2016 December ; 23(Suppl 5): 850–857. doi:10.1245/s10434-016-5492-9.

Impact of flap reconstruction on radiotoxicity after salvage surgery and reirradiation for recurrent head and neck cancer

Allen S. Ho, MD¹, Zachary S. Zumsteg, MD², Annika Meyer, MD², Nadeem Riaz, MD², Rahmatullah Rahmati, MD¹, Dennis H. Kraus, MD¹, Colleen McCarthy, MD³, Richard J. Wong, MD¹, Jatin P. Shah¹, and Nancy Y. Lee, MD^{1,†}

¹Head and Neck Service, Department of Surgery

²Department of Radiation Oncology

³Plastic and Reconstructive Surgical Service, Department of Surgery

Abstract

Background—Recurrent head and neck malignancies remain a therapeutic challenge. Tissue transfer, in addition to defect coverage and prevention of wound complications, may potentially decrease radiotoxicity. We evaluated radiation toxicity and survival outcomes of patients who underwent salvage surgery with reirradiation, comparing primary closure to flap reconstruction.

Methods—Retrospective outcomes analysis of recurrent head and neck squamous cell carcinoma (HNSCC) patients treated with curative intent by salvage surgery ($\pm$ flap reconstruction) and reirradiation from 1996–2011. Recurrent stage, reirradiation modality, chemotherapy use, and toxicities were evaluated.

Results—Of 96 patients, 59 had primary closure while 37 underwent flap reconstruction (26 free, 11 pedicled). Median radiation and reirradiation doses were 66Gy and 60Gy, respectively. Comparing non-flap and flap patients, there was no significant difference in acute mild toxicities (100% vs. 100%, $p=1.0$) or acute severe toxicities (33.9% vs. 37.8%, $p=0.83$). Non-flap patients experienced significantly greater incidence of both late mild toxicities (81.4% vs 54.1%, $p=0.006$) and late severe toxicities (47.5% vs 21.6%, $p=0.02$). Overall survival at 5 years was equivalent (33.1% vs. 34.7%, $p=0.88$). Free flap patients had greater delays to postoperative reirradiation and treatment package times compared to pedicled flap patients, but no meaningful difference in survival outcomes.

Conclusions—Vascularized tissue potentially helps offset late toxicities associated with a second radiation course in recurrent head and neck cancer patients. In these selected patients, flap coverage may confer functional benefits and improve the long-term radiotoxicity profile.

[†]Corresponding Author: Nancy Y. Lee, MD, Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065 USA, Telephone: (212) 639-3341, Fax: (212) 639-2417, leen2@mskcc.org.

Conflict of Interest Statement: None declared

INTRODUCTION

Salvage treatment of recurrent, previously irradiated head and neck squamous cell carcinoma (HNSCC) continues to pose a considerable challenge. For resectable disease, salvage surgery offers superior overall survival and locoregional control when compared to chemotherapy or reirradiation.^{1,2} However, in many cases patients are still at high risk for further recurrence after salvage surgery alone, warranting a second course of radiation.

Reirradiation with or without concurrent chemotherapy has shown promise in conferring locoregional control and survival benefits in head and neck cancer patients with resectable disease.^{3,4} It nonetheless poses the threat of escalated toxicity in previously damaged tissues⁵, and effects may be magnified in post-surgical patients with increased risk of wound complications. Flap reconstruction, although lengthy and complicated, reduces the risk of wound breakdown and fistula formation in poorly vascularized, previously irradiated tissue. Prior studies suggest that the addition of flaps is a robust means of wound closure^{6,7}, but it is unclear whether the interposition of well-vascularized, un-irradiated tissue affords protection from the deleterious effects of reirradiation.^{8,9} We examined the incidence of reirradiation toxicities after salvage surgery with and without flap reconstruction.

METHODS

Retrospective analysis of recurrent HNSCC patients undergoing reirradiation at Memorial Sloan Kettering Cancer Center (MSKCC) from October 1996 to April 2011 was performed. Eligible patients included those with recurrent or second primary HNSCC who had previously received a full course of head and neck radiation therapy (RT), underwent salvage surgery with curative intent, and had adjuvant reirradiation due to sufficiently high risk of locoregional recurrence based on surgical pathology. High-risk features included close or positive margins, invasion of local structures, perineural or vascular invasion, multiple positive lymph nodes, and extracapsular spread. Staging of the recurrent tumor was determined based on American Joint Committee on Cancer, 7th edition.¹⁰ To avoid accounting for symptoms resulting from recurrent disease or additional therapy, adverse events after reirradiation were censored on disease progression.

Special attention was paid to the reirradiation toxicity outcomes in patients who underwent primary closure of their surgical sites versus those who received flap reconstruction (pedicled or free flaps). In all cases the reirradiation fields coincided with or overlapped previous RT fields, and included the flap if present. Acute toxicities were defined as less than 90 days from completion of reirradiation, with late toxicities as greater than 90 days. Toxicities were assessed by patient-reported outcomes via questionnaire, using 1995 guidelines published by the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) (Table 1).¹¹ Retrospective review of records was used to confirm objective longitudinal sequelae. Those that existed prior to reirradiation, such as PEG dependence and tracheostomy dependence, were excluded from the analysis. Treatment package time was defined as the interval between the date of salvage surgery and the end of reirradiation.¹²

Exclusion criteria consisted of patients with distant metastatic disease, who did not complete the majority of their reirradiation course, who underwent RT for palliative intent, who received RT for non-cancers, and who received radiation in non-overlapping sites. Associations between variables and endpoints were assessed with Fisher exact test or Chi-square with Yates correction. Disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan-Meier method and analyzed using the log-rank test. All p-values were two-sided, with significance set at $p < 0.05$. Statistical analyses were performed using SPSS Version 20 (Chicago, IL).

RESULTS

Patient demographics

A total of 96 patients were included in the study: 59 patients underwent salvage surgery with primary closure, while 37 patients required reconstruction with tissue flaps at the time of salvage surgery (11 pedicled flaps, 26 microvascular free flaps) (Figure 1). Excluded patients comprised those with distant metastases prior to reirradiation ($n=38$), cutaneous malignancy diagnoses ($n=19$), lack of radiation site overlap ($n=16$), lack of primary or recurrent cancer diagnosis ($n=4$), and subtherapeutic reirradiation dose ($n=2$).

Collectively, median age was 62.0 years (95% CI, 59.8–64.2), and 83.3% had recurrent advanced stage (rStage 3–4) disease. The neck, oral cavity, oropharynx, and larynx were the most common sites of recurrence. In terms of recurrences prior to salvage surgery and reirradiation, 36.5% were local, 30.2% were regional, 20.8% were locoregional, and 12.8% were second primaries. The cohorts were well-matched in terms of patient and tumor characteristics, both when comparing primary closure vs. flap (Table 2) as well as comparing pedicled flap vs. free flap (Table 3).

Radiation characteristics

The median initial radiation dose was 66.0 Gy (95% CI, 64.8–67.2). The median reirradiation dose was 60.0 Gy (95% CI, 57.8–62.2). The majority of patients (72.9%) had intensity-modulated radiation therapy (IMRT) for their reirradiation. Before their full-course reirradiation, three patients received intraoperative radiation therapy and two received a brachytherapy boost. One-half (50.0%) of patients received concurrent chemotherapy with reirradiation. The median time interval between the date of salvage surgery and initiating reirradiation was 8.0 weeks. Median follow-up for surviving patients after reirradiation was 50.6 months (95% CI, 35.9–65.7). Median survival time after reirradiation was 19.5 months (95% CI, 12.7–26.3).

Non-flap vs. flap patients

The distribution of cancer histology, advanced stage (of initial and recurrent cancers), and disease-free interval (DFI) was not significantly different between groups. Reirradiation dosages, IMRT usage, and concomitant chemotherapy usage were similar. In the non-flap group, more laryngeal cancer cases (39.0% vs. 21.6%, $p=0.03$) and fewer oral cavity cases (22.0% vs. 43.2%, $p=0.04$) were observed. There were more local recurrences in the flap cohort (62.2% vs. 20.3%, $p<0.001$), while conversely there were more regional recurrences

in the non-flap cohort (40.7% vs. 13.5%, $p=0.006$). Recurrence rate and overall survival were not significantly different between groups. For non-flap vs. flap cohorts, 3-year OS was 38.2% vs. 36.8% ($p=0.53$), while 5-year OS was 33.1% vs. 34.7% ($p=0.88$). Flap patients did not demonstrate a higher rate or earlier rate of local re-recurrence compared to non-flap patients.

The incidence of acute mild toxic symptoms from reirradiation was 100% in both cohorts, with xerostomia, mucositis, and dermatitis being the most common side effects (Table 4). There was no significant difference in the incidence of acute severe toxicity after reirradiation (33.9% in the non-flap group vs. 37.8% in the flap group, $p=0.83$). Non-flap patients were significantly more likely to experience mild late toxicities (81.4% of non-flaps vs. 54.1% of flaps, $p=0.006$), as well as severe late toxicities (47.5% vs. 21.6%, $p=0.02$).

In terms of major sequelae after surgery and reirradiation, 18.6% of non-flap and 18.9% of flap patients developed wound dehiscence ($p=1.00$). Rates of osteoradionecrosis (8.4% vs. 5.4%, $p=0.70$) and fistula formation (8.4% vs. 10.8%, $p=0.73$) were similar between groups. Carotid blowout was noted in one patient (non-flap group), while treatment-related death occurred in one patient (flap group). There were no cases of flap breakdown or failure.

Long-term incidence of PEG dependence due to reirradiation was similar between non-flap and flap cohorts (18.6% vs 18.9%, $p=1.00$), as was tracheostomy dependence (20.3% vs. 21.6%, $p=1.00$). Despite the added recovery time presumably associated with flaps, there was no significant difference in time interval between salvage surgery and reirradiation (9.4 weeks vs. 8.7 weeks, $p=0.82$), the median salvage treatment package time (96.0 vs. 103.0 days, $p=0.88$), or the number that failed to complete their reirradiation course (3.4% vs. 13.5%, $p=0.10$).

Pedicled flap vs. free flap patients

On subset analysis between pedicled and free flaps, there were more laryngeal cancer patients in the pedicled flap group (45.5% vs. 11.5%, $p=0.04$). Regional recurrences were more likely to be found in the pedicled flap cohort (45.5% vs. 0%, $p=0.001$), but not so if combined with locoregional recurrences. Pedicled flap cases had significantly shorter postoperative intervals to begin reirradiation (8.1 vs. 8.9 weeks, $p=0.05$), as well as overall treatment package time (99.0 vs. 106.5 days, $p=0.04$). However, there were no substantial differences in total radiation doses or toxicity (Table 3), in functional sequelae (Table 4), median survival, or overall survival.

DISCUSSION

The impact of flap reconstruction on outcomes in the postoperative reirradiation scenario is unclear. Wound closure with nonradiated tissue could be expected to better withstand adjuvant reirradiation than previously irradiated tissue at the surgical site. However, flaps may require longer postoperative healing periods, delaying reirradiation and potentially compromising outcome. In this study, the application of nonradiated tissue via flaps during salvage surgery was associated with significantly fewer mild (54.1% vs. 81.4%, $p=0.006$) and severe long-term toxicities (21.6% vs. 47.5%, $p=0.02$) following postoperative

reirradiation. The cohorts were largely matched in terms of stage, suggesting that one group did not necessarily harbor more aggressive disease or sicker patients. Other indicators, such as reirradiation dose and proportion of patients receiving concomitant chemotherapy, were similar.

There are several plausible mechanisms by which flaps could be hypothesized to lead to decreased long term toxicity. Radiation has well-characterized deleterious effects on tissue vascularization.^{14,15} By delivering unirradiated, vascularized tissue to the site of reirradiation, we might expect flaps to be less compromised by radiation vasculopathy than previously radiated tissue. Flaps also provide more bulk and protection to the surrounding tissue during reirradiation than the native tissue, which can become atrophic and fibrotic following radiotherapy. These advantages of flap reconstruction are notwithstanding its fundamental importance in protecting radiated fields from wound breakdown in large defects, and in facilitating reirradiation delivery where affected skin must be sacrificed.

Notably, our results extend previous reports from other groups. For example, prior retrospective series examined flaps in the postoperative reirradiation setting but did not demonstrate differences in radiotoxicity.^{9,16} This may have been due to study design, small sample size, inclusion of noncurative or nonsurgical patients, or institutional selection criteria for salvage. In addition, a relatively high percentage of patients in our study received reirradiation via IMRT (72.9%). IMRT enables precise dose distribution, limits injury to adjacent organs, and may consequently improve reirradiation outcomes.^{17–19} The narrower treatment fields reduce side effects in a previously radiated setting, and may have helped allow the beneficial effect of flaps on late reirradiation toxicities to become apparent.

Multiple studies have suggested that reirradiation with chemotherapy may be beneficial, but significant concerns persist regarding toxicity. For example, both RTOG 96-10 and RTOG 99-11 prospectively demonstrated that reirradiation with concomitant chemotherapy is feasible, with survival rates superior to historical trials of chemotherapy alone, but 8% of patients experienced treatment-related deaths, and 32% enrolled in RTOG 99-11 experienced grade 4–5 toxicity.^{20,21} Additionally, Janot et al found that postoperative reirradiation with concomitant chemotherapy resulted in improved progression-free survival following surgical resection in previously irradiated fields. However, 8% of patients randomized to chemo-reirradiation experienced treatment-related death and 39% of those surviving 24 months had late grade 3–4 toxicity.¹³ Thus, the considerable side effects reported poses stiff barriers to treatment, even for patients with few other options. If flap reconstruction can offset adverse treatment sequelae, its use may meaningfully improve quality of life and favorably tilt the therapeutic ratio. This strategy may address the reluctance of clinicians to apply a second therapeutic course of radiation.

Even if flaps were able to improve the radiotoxicity profile, their use may be difficult to justify if they markedly delay treatment. Compared to pedicled flap patients, those with free flaps had a longer delay to start postoperative reirradiation (8.1 vs. 8.9 weeks, $p=0.05$), as well as a longer median treatment package time (99.0 vs. 106.5 days, $p=0.04$). These prolonged intervals are likely due to longer healing times associated with microvascular reconstruction. Ang et al suggested that prolonged treatment intervals led to lower

locoregional control and survival.²² Similarly, Rosenthal et al identified that a total treatment time of greater than 100 days was associated with poorer survival.¹² Such studies did not examine the reirradiation population, and in our study free flaps did not worsen survival. Nonetheless, the consequences of potential delays are worthy of consideration in determining management.

There are multiple caveats to this analysis, including its retrospective nature, with associated selection and referral bias. Flap coverage may not be necessary in all settings, or the only option in others. The heterogeneity of sites and the flaps placed also may impact the study's generalizability. For instance, larynx cancer patients tend to have improved survival outcomes compared to other sites^{2,23}, and comprised a higher percentage of the non-flap group. Finally, although we have shown no differences in stage, treatment dose, or treatment interval, flap patients may *a priori* harbor more extensive lesions, defects, and tissue compromise not completely captured by staging or treatment metrics. In this context, the mitigated toxicities found in flap patients are perhaps even more noteworthy.

CONCLUSION

Utilization of unirradiated, vascularized tissue in a previously radiated field may help offset the late toxicities of a second therapeutic dose of radiotherapy in HNSCC patients. Flap coverage potentially confers not only functional value but also oncologic benefit from reirradiation, albeit with additional recovery time. Prospective evaluation of flap closure to improve the toxicity profile in a population with few therapeutic options and high risk of sequelae from treatment is warranted.

References

1. Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? *The Laryngoscope*. 2000; 110(3 Pt 2 Suppl 93):1–18.
2. Ho AS, Kraus DH, Ganly I, Lee NY, Shah JP, Morris LG. Decision making in the management of recurrent head and neck cancer. *Head & neck*. 2014; 36(1):144–151. [PubMed: 23471843]
3. Fakhry C, Zhang Q, Nguyen-Tan PF, et al. Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2014; 32(30):3365–3373. [PubMed: 24958820]
4. Chen GB, Xu Y, Xu HM, Li MD, Zhu J, Lou XY. Practical and theoretical considerations in study design for detecting gene-gene interactions using MDR and GMDR approaches. *PloS one*. 2011; 6(2):e16981. [PubMed: 21386969]
5. Chen AM, Phillips TL, Lee NY. Practical considerations in the re-irradiation of recurrent and second primary head-and-neck cancer: who, why, how, and how much? *International journal of radiation oncology, biology, physics*. 2011; 81(5):1211–1219.
6. Kim AJ, Suh JD, Sercarz JA, et al. Salvage surgery with free flap reconstruction: factors affecting outcome after treatment of recurrent head and neck squamous carcinoma. *The Laryngoscope*. 2007; 117(6):1019–1023. [PubMed: 17545864]
7. Kostrzewa JP, Lancaster WP, Iseli TA, Desmond RA, Carroll WR, Rosenthal EL. Outcomes of salvage surgery with free flap reconstruction for recurrent oral and oropharyngeal cancer. *The Laryngoscope*. 2010; 120(2):267–272. [PubMed: 20013840]

8. Iseli TA, Yelverton JC, Iseli CE, Carroll WR, Magnuson JS, Rosenthal EL. Functional outcomes following secondary free flap reconstruction of the head and neck. *The Laryngoscope*. 2009; 119(5): 856–860. [PubMed: 19358194]
9. Suh JD, Kim BP, Abemayor E, et al. Reirradiation after salvage surgery and microvascular free flap reconstruction for recurrent head and neck carcinoma. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*. 2008; 139(6): 781–786. [PubMed: 19041503]
10. Greene, FLPD., Fleming, ID. American Joint Committee on Cancer (AJCC) Cancer Staging Manual. 7. New York: Springer; 2009.
11. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *International journal of radiation oncology, biology, physics*. 1995; 31(5):1341–1346.
12. Rosenthal DI, Liu L, Lee JH, et al. Importance of the treatment package time in surgery and postoperative radiation therapy for squamous carcinoma of the head and neck. *Head & neck*. 2002; 24(2):115–126. [PubMed: 11891941]
13. Janot F, de Raucourt D, Benhamou E, et al. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008; 26(34):5518–5523. [PubMed: 18936479]
14. Fajardo LF. Is the pathology of radiation injury different in small vs large blood vessels? *Cardiovascular radiation medicine*. 1999; 1(1):108–110. [PubMed: 11272350]
15. McCready RA, Hyde GL, Bivins BA, Mattingly SS, Griffen WO Jr. Radiation-induced arterial injuries. *Surgery*. 1983; 93(2):306–312. [PubMed: 6823669]
16. Iseli TA, Iseli CE, Rosenthal EL, et al. Postoperative reirradiation for mucosal head and neck squamous cell carcinomas. *Archives of otolaryngology--head & neck surgery*. 2009; 135(11): 1158–1164. [PubMed: 19917931]
17. Tanvetyanon T, Padhya T, McCaffrey J, et al. Prognostic factors for survival after salvage reirradiation of head and neck cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009; 27(12):1983–1991. [PubMed: 19289616]
18. Salama JK, Vokes EE, Chmura SJ, et al. Long-term outcome of concurrent chemotherapy and reirradiation for recurrent and second primary head-and-neck squamous cell carcinoma. *International journal of radiation oncology, biology, physics*. 2006; 64(2):382–391.
19. Sulman EP, Schwartz DL, Le TT, et al. IMRT reirradiation of head and neck cancer-disease control and morbidity outcomes. *International journal of radiation oncology, biology, physics*. 2009; 73(2):399–409.
20. Spencer SA, Harris J, Wheeler RH, et al. Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. *Head & neck*. 2008; 30(3):281–288. [PubMed: 17764087]
21. Langer CJ, Harris J, Horwitz EM, et al. Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007; 25(30):4800–4805. [PubMed: 17947728]
22. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *International journal of radiation oncology, biology, physics*. 2001; 51(3):571–578.
23. Ganly I, Patel SG, Matsuo J, et al. Results of surgical salvage after failure of definitive radiation therapy for early-stage squamous cell carcinoma of the glottic larynx. *Archives of otolaryngology--head & neck surgery*. 2006; 132(1):59–66. [PubMed: 16415431]

SYNOPSIS

Use of nonradiated, vascularized tissue in a previously radiated field may help offset the late toxicities of a second therapeutic dose of radiotherapy in selected patients. Flap coverage potentially confers not only functional value but also oncologic benefit from reirradiation.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

Treatment schematic of patients undergoing salvage surgery with or without flap reconstruction. HNC, head and neck cancer; ALT, anterolateral thigh.

Table 1

Grading Severity

Grade	Dysphagia
1	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing
2	Unable to take solid food normally; Swallowing semi-solid food; Dilatation may be indicated
3	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing; Dilatation required
4	Necrosis/Perforation; Fistula
Grade	Hoarseness
1	Hoarseness; Slight arytenoid edema
2	Moderate arytenoid edema; chondritis
3	Severe edema; Severe chondritis
4	Necrosis of larynx
Grade	Fibrosis
1	Slight induration (fibrosia) and loss of subcutaneous fat
2	Moderate fibrosis but asymptomatic; Slight field contracture; <10% linear reduction
3	Severe induration and loss of subcutaneous tissue; Field contracture; >10% linear measurement
4	Necrosis

Toxicities were as defined by the 1995 validated guidelines published by the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC).¹¹

Table 2

Patient and Tumor Characteristics

Category	Primary closure	Flap (pedicled and free)	p-value
Number of patients (n)	59	37	
Median age (yrs)	63.0	60.0	
% Male	81.4%	83.8%	
Cancer sites			
Oral cavity	22.0%	43.2%	0.04
Oropharynx	13.6%	21.6%	0.40
Larynx	39.0%	21.6%	0.03
% initial advanced stage (Stage 3–4)	49.2%	67.6%	0.09
% recurrent advanced stage (rStage 3–4)	81.4%	86.5%	0.58
Median DFI (mo)	21.8	27.8	0.32
>36 mo	39.0%	45.9%	0.53
Recurrence type			
Local	20.3%	62.2%	<0.001
Regional	40.7%	13.5%	0.006
Locoregional	23.7%	16.2%	0.45
Second Primary	15.3%	8.1%	0.36
Median interval (salvage surgery to re-RT) (wks)	9.4	8.7	0.82
Median treatment package time (days)	96.0	103	0.88
% >100 days	40.7%	51.4%	0.40
Radiation			
Median initial RT dose (Gy)	66.0	66.0	0.81
Median re-RT dose (Gy)	60.0	59.4	0.67
Median time between RT and re-RT (mo)	24.3	31.5	0.32
% receiving IMRT	69.5%	81.1%	0.24
% receiving adjuvant chemoRT	44.1%	59.5%	0.21
% completing re-RT course	96.6%	86.5%	0.10
Toxicities			
Acute mild toxicity	100.0%	100%	1.00
Acute severe toxicity	33.9%	37.8%	0.83
Late mild toxicity	81.4%	54.1%	0.006
Late severe toxicity	47.5%	21.6%	0.02
Median survival time after re-RT (mo)	20.1	15.1	0.43
Disease-free	49.2%	35.1%	0.21

SCC, squamous cell carcinoma; DFI, disease-free interval; IMRT, intensity modulated radiation therapy; re-RT, reirradiation therapy

Table 3

Flap Characteristics

Category	Pedicled flap	Free flap	p-value
Number of patients	11	26	
Median age	55.0	60.5	
% Male	90.9%	80.8%	
Cancer sites			
Oral cavity	36.4%	46.2%	0.72
Oropharynx	18.2%	23.1%	1.00
Larynx	45.5%	11.5%	0.04
% initial advanced stage (Stage 3–4)	72.7%	65.4%	1.00
% recurrent advanced stage (rStage 3–4)	90.9%	84.6%	1.00
Median DFI (mo)	21.2	38.1	0.30
<36 mo	63.6%	50.0%	0.50
Recurrence type			
Local	36.4%	73.1%	0.06
Regional	45.5%	0.0%	0.001
Locoregional	9.1%	19.2%	0.65
Second Primary	9.1%	7.7%	1.00
Median interval (salvage surgery to re-RT) (wks)	8.1	8.9	0.05
Median treatment package time (days)	99.0	106.5	0.04
%<100 days	54.5%	46.2%	0.73
Radiation			
Median initial RT dose (Gy)	70.0	64.7	0.87
Median re-RT dose (Gy)	59.4	60	0.81
Median time between RT and re-RT (mo)	23.2	41.1	0.29
% receiving IMRT	72.7%	84.6%	0.40
% receiving adjuvant chemoRT	90.9%	61.5%	0.12
% completing re-RT course	90.9%	80.8%	0.65
Toxicities			
Acute mild toxicity	100.0%	100.0%	1.00
Acute severe toxicity	36.4%	38.5%	1.00
Late mild toxicity	63.6%	50.0%	0.50
Late severe toxicity	45.5%	38.5%	0.73
Median survival time after re-RT (mo)	11.7	21.3	0.45
Disease-free	45.5%	30.8%	0.46

SCC, squamous cell carcinoma; DFI, disease-free interval; IMRT, intensity modulated radiation therapy; re-RT, reirradiation therapy

Table 4

Toxicities and Sequelae

Acute toxicities	No flap	Flap	p-value	Pedicle flap	Free flap	p-value
Xerostomia (Grade 1–2)	52.5%	32.4%	0.06	18.2%	38.5%	0.28
Mucositis (Grade 1–2)	42.4%	59.5%	0.14	54.5%	61.5%	0.73
Mucositis (Grade 3–4)	13.6%	16.2%	0.77	9.1%	19.2%	0.65
Skin (Grade 1–2)	67.8%	67.6%	1.00	81.8%	61.5%	0.28
Skin (Grade 3–4)	13.6%	5.4%	1.00	0.0%	7.7%	1.00
Fibrosis (Grade 1–2)	13.6%	5.4%	1.00	9.1%	3.8%	0.51
Fibrosis (Grade 3–4)	1.7%	5.4%	0.56	9.1%	0.0%	0.30
Dysphagia (Grade 1–2)	37.3%	24.3%	0.26	18.2%	26.9%	1.00
Dysphagia (Grade 3–4)	33.9%	54.1%	0.06	54.5%	53.8%	1.00
Hoarseness (Grade 1–2)	30.5%	18.9%	0.24	36.4%	11.5%	0.16
Nausea	15.3%	21.6%	0.42	18.2%	23.1%	1.00
Fatigue	32.2%	29.7%	0.83	45.5%	23.1%	1.00
Thrush	6.8%	8.1%	1.00	9.1%	7.7%	1.00
Trismus	6.8%	8.1%	1.00	0.0%	15.4%	0.30
Chronic pain	6.8%	2.7%	0.65	0.0%	15.4%	0.30
Late toxicities	No flap	Flap	p-value	Pedicle flap	Free flap	p-value
Xerostomia (Grade 1–2)	49.2%	16.2%	0.001	9.1%	42.3%	0.65
Mucositis (Grade 1–2)	6.8%	2.7%	0.65	0.0%	7.7%	1.00
Mucositis (Grade 3–4)	1.7%	0.0%	1.00	0.0%	0.0%	1.00
Skin (Grade 1–2)	8.5%	10.8%	0.73	0.0%	7.7%	1.00
Skin (Grade 3–4)	5.1%	0.0%	0.28	0.0%	0.0%	1.00
Fibrosis (Grade 1–2)	23.7%	21.6%	1.00	27.3%	15.4%	0.67
Fibrosis (Grade 3–4)	10.2%	2.7%	0.24	0.0%	7.7%	1.00
Dysphagia (Grade 1–2)	23.7%	10.8%	0.18	18.2%	11.5%	0.57
Dysphagia (Grade 3–4)	25.4%	40.5%	0.17	45.5%	34.6%	0.73
Hoarseness (Grade 1–2)	11.9%	2.7%	0.15	9.1%	0.0%	0.30
Nausea	1.7%	0.0%	1.00	0.0%	0.0%	1.00

Acute toxicities	No flap	Flap	p-value	Pedicle flap	Free flap	p-value
Fatigue	13.6%	13.5%	1.00	18.2%	11.5%	0.62
Thrush	5.1%	0.0%	0.28	0.0%	0.0%	1.00
Trismus	22.0%	29.7%	0.47	18.2%	34.6%	0.44
Chronic pain	15.3%	5.4%	0.19	0.0%	7.7%	1.00
Sequelae	No flap	Flap	p-value	Pedicle flap	Free flap	p-value
PEG dependence *	18.6%	18.9%	1.00	27.3%	15.4%	0.40
Tracheostomy dependence *	20.3%	21.6%	1.00	18.2%	23.1%	1.00
Wound dehiscence	18.6%	18.9%	1.00	18.2%	19.2%	1.00
Fistula	8.4%	10.8%	0.73	9.1%	15.4%	1.00
Stricture	10.2%	2.7%	0.24	9.1%	3.8%	0.51
Osteoradionecrosis	8.4%	5.4%	0.70	9.1%	7.7%	1.00
Temporal lobe necrosis	3.4%	0.0%	0.52	0.0%	0.0%	1.00
Flap atrophy	N/A	5.4%	N/A	0.0%	11.5%	0.54
Hardware removal	0.0%	2.7%	0.39	0.0%	3.8%	1.00
Major bleeding	1.7%	0.0%	1.00	0.0%	0.0%	1.00
Carotid blowout	1.7%	0.0%	1.00	0.0%	0.0%	1.00
DVT	3.4%	0.0%	0.52	0.0%	0.0%	1.00

PEG, percutaneous endoscopic gastrostomy; DVT, deep vein thrombosis

* Excludes patients who were PEG-dependent or tracheostomy-dependent prior to reirradiation