

Improved Head and Neck Free Flap Outcome—Effects of a Treatment Protocol Adjustment from Pre- to Postoperative Radiotherapy

Martin Halle, MD, PhD*†

Bjorn O. Eriksson, MD†§

Ann-Charlott Docherty Skogh,

MD, PhD*†

Pehr Sommar, MD, PhD*†

Lalle Hammarstedt, MD, PhD†§

Caroline Gahm, MD, PhD†§

Background: The impact of preoperative radiotherapy on microvascular reconstructive surgery outcome has been a subject of debate. However, data are conflicting and often dependent on local treatment protocols. We have studied the effects of radiotherapy in a unique, single-center setting where a treatment protocol change was undertaken from pre- to postoperative radiotherapy administration for microsurgical head and neck reconstructions.

Methods: A cohort study was conducted for 200 consecutive head and neck free flap cases, where 100 were operated on before and 100 after the treatment protocol adjustment in 2006. Only direct cancer reconstructions were included. Complication rates of anastomosis-related (flap necrosis) and flap bed-related (infection, fistula, and wound dehiscence) complications were compared between irradiated and nonirradiated patients. A multivariate analysis was performed to correct for treatment period.

Results: One hundred twenty-six patients had received radiotherapy before reconstruction due to cases of cancer recurrence. There were no significant differences in demographic data or risk factors between irradiated and nonirradiated cases. Irradiated cases had a higher rate of both flap loss (9.5% versus 1.4%; $P = 0.034$) and flap bed-related complications (29% versus 13%; $P = 0.014$). However, after multivariate analysis, there was only a significant relationship between preoperative irradiation and infection (odds ratio = 2.51; $P = 0.033$) and fistula formation (odds ratio = 3.13; $P = 0.034$).

Conclusions: The current single-center study clearly indicates that preoperative radiotherapy is a risk factor for both infection and fistula formation, most likely related to an impaired flap bed. We suggest postoperative radiotherapy administration whenever possible for oncological reasons, otherwise proper antibiotic cover and meticulous flap inseting to prevent radiation-related infection and fistula formation. (*Plast Reconstr Surg Glob Open* 2017;5:e1253; doi: 10.1097/GOX.0000000000001253; Published online 30 March 2017.)

From the *Department of Plastic and Reconstructive Surgery, Karolinska University Hospital, Stockholm, Sweden; †Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden, Stockholm, Sweden; ‡Department of Clinical Sciences Intervention and Technology, Karolinska Institute, Stockholm, Sweden; and §Department of ENT Head & Neck Surgery, Karolinska University Hospital, Stockholm, Sweden.

Received for publication November 26, 2016; accepted January 10, 2017.

M.H. is supported by the Cancer Research Funds of Radiumhemmet (Grant number 161072), the Swedish Society of Medicine (Grant number SLS-248851), and together with C.G. by the Stockholm County Council (Grant number 20140458).

Presented in part at the 26th Annual Meeting of European Association of Plastic Surgeons, EURAPS, May 28, 2015, Edinburgh, UK.

Copyright © 2017 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of The American Society of Plastic Surgeons. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/GOX.0000000000001253

BACKGROUND

Free flap reconstruction is today an integral part of head and neck cancer treatment for large tumors, where resection together with radiotherapy and chemotherapy are common treatment modalities.¹ However, no firm evidence exists to date as to whether pre-versus postoperative radiotherapy affects the oncological outcome.² The impact of preoperative radiotherapy on microsurgical complications has, on the other hand, been a subject of intense debate. Some studies have suggested that radiotherapy affects free flap complications,³⁻⁵ whereas others primarily describe general complications^{6,7} or no impact on complication rates at all.⁸ Conflicting data from previous publications are likely dependent on heterogeneous cohorts where the influence of local treatment protocols and technical factors cannot be foreseen. We have studied the effects of radiotherapy in a unique,

Disclosure: The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by M.H., supported by Funds of Radiumhemmet (Grant 161072).

single-center setting where a treatment protocol change was undertaken from pre- to postoperative radiotherapy administration for microsurgical head and neck reconstructions.

MATERIALS AND METHODS

A cohort study was conducted for 200 consecutive head and neck free flap cases. One hundred patients were operated on before and 100 after the treatment protocol adjustment in 2006. Before the protocol adjustment, patients underwent preoperative radiotherapy. After the adjustment in 2006, irradiation has instead been administered postoperatively when indicated. Only cases of immediate free flap reconstructions after tumor resection and neck dissection were included. Data were retrieved from hospital records and continuously registered in a prospectively maintained free flap database. Each case was registered separately with variables covering patient characteristics, surgical technique, pharmacologic treatment, and postoperative outcome. Complete flap necrosis and partial flap necrosis were recorded. Partial flap necrosis was defined as necrosis of more than 30% of flap volume in accordance with previous research.⁹ Infections were registered if any intervention had been performed, such as drainage of abscess or change in intravenous antibiotic therapy from standard cover due to local signs of infection. Delayed wound healing and fistula formation was registered if remaining at the reconstructed site 1 month after the reconstruction. Adverse outcomes were categorized as anastomosis-related (flap necrosis) and flap bed-related (infection, fistula, and wound dehiscence) complications and compared between irradiated and nonirradiated patients. The study was approved by the Ethical Committee of Stockholm and was performed in agreement with institutional guidelines and the principles of the Declaration of Helsinki.

Binary logistic regression was performed to evaluate the effect of radiotherapy on both the anastomosis- and flap bed-related complications. A multivariate analysis was performed to correct for treatment period. Logistic regression results are presented with odds ratios (ORs), 95% confidence intervals, and *P* values. A *P* value less than 0.05 was considered a significant result. SPSS version 22.0 (IBM Corp, Armonk, N.Y.) was used when performing the statistical analyses.

RESULTS

In total, 100 patients were operated on before (group 1; operated on between 1997 and 2006) and 100 after (group 2; operated on between 2006 and 2014) the treatment protocol adjustment 2006.

The mean age was 60.2 years (± 12.6), and there was a male to female preponderance (65% to 35% for group 1, 61% to 39% for group 2). Patients operated before 2006 were younger (58.3 versus 62.1 years; *P* = 0.034), and the prevalence of orally medicated diabetes was lower (0 versus 6; *P* = 0.029), otherwise there were no significant demographical differences between group 1 and group 2 (Table 1). The majority of the primary tumor sites were

Table 1. Demographic Data for Group 1 versus Group 2

Demographic Data	Before 2006	After 2006	<i>P</i>
Total	100	100	
Age*	58	62	0.034
Male	65	61	0.661
Female	35	39	0.661
Diabetes, insulin	1	2	1.0
Diabetes, oral	0	6	0.029
Cardiovascular disease†	13	12	1.0
Hypertension	19	26	0.309
Current smoking	37	24	0.064
Chemotherapy	5	13	0.134

*Mean (SD).

†Previous myocardial infarction, transient ischemic attack/stroke, peripheral arterial disease, coronary bypass surgery.

Table 2. Location of Tumors

Tumor Site	No. Patients	%
Oropharynx/oral cavity	173	86.5
Maxilla/midface	6	1.5
Scalp/facial skin	5	2.5
Mandible	5	2.5
Thyroid/parathyroid	3	1.5
Hypopharynx/larynx	8	4.0

Table 3. Types of Flaps

Flap Type	Irradiated	Nonirradiated	Total
RFF	101	36	137
Fibula	13	24	37
ALT	6	5	11
Other*	11	4	15

*Iliac crest, extended lateral arm, jejunum, latissimus dorsi, rectus abdominis, and scapular.

ALT, anterolateral thigh flap; RFF, radial forearm flap.

Table 4. Demographic Data for Irradiated versus Nonirradiated Patients

Demographic Data	Irradiated (%)	Nonirradiated (%)	<i>P</i>
Total	126	74	
Male	82 (65)	44 (59)	0.451
Female	44 (35)	30 (41)	0.451
Age*	59 (13)	63 (12)	0.018
Diabetes, insulin	2 (2)	1 (1)	1.0
Diabetes, oral	2 (2)	4 (5.5)	0.196
Cardiovascular disease	14 (11)	11 (15)	0.507
Hypertension	22 (18)	23 (32)	0.034
Current smoking	42 (34)	19 (26)	0.339
Chemotherapy	15 (12)	3 (4.1)	0.075

*Mean (SD).

located in the oropharynx (Table 2), and the most commonly used free flap was a radial forearm flap, followed by fibular and anterolateral thigh flaps (Table 3). In total, 126 patients had received radiotherapy before reconstruction. This is due to cases of cancer recurrence, which had also been irradiated, within the cohort after the treatment protocol adjustment. Further analyses were therefore performed to compare irradiated with nonirradiated cases. Irradiated cases had a higher mean age and more risk factors compared with nonirradiated cases (Table 4). However, despite this fact, irradiated cases still had a higher rate of both flap loss (9.5% versus 1.4%; *P* = 0.034) and flap

Table 5. Univariate versus Multivariate Analysis of Results for Flap Bed–related Complications

Complications	Odds Ratios for Irradiated Patients			
	Univariate OR (95% CI)	P	Multivariate OR (95% CI)	P
Infections*	2.72 (1.23–6.02)	0.014	2.51 (1.08–5.85)	0.033
Fistulas*	3.64 (1.34–9.90)	0.011	3.13 (1.09–8.93)	0.034
Wound*	2.16 (0.96–4.83)	0.062	1.98 (0.84–4.69)	0.119
Total necrosis†	7.69 (0.98–58.8)	0.034	5.49 (0.65–47.6)	0.118
Total + partial necrosis†	3.19 (0.89–11.5)	0.075	2.67 (0.69–10.3)	0.157

*Flap bed–related complications in relation to radiation status of the tumor site.

†Flap complications in relation to radiation status of the neck.

CI, confidence interval.

bed–related complications (29% versus 13%; $P = 0.014$). Flap bed–related complications consisted of localized postoperative infections (29.0% versus 13.0%; $P = 0.014$), fistula formations (22.1% versus 7.2%; $P = 0.009$), and cases of wound dehiscence (24.4% versus 13.0%; $P = 0.066$). Multivariate analysis performed to correct for treatment period did not detect a significant relationship between preoperative irradiation total flap loss ($P = 0.146$), but for infection (OR = 2.51; $P = 0.033$) and fistula formation (OR = 3.13; $P = 0.034$) when preoperative irradiation was compared with postoperative irradiation (Table 5).

DISCUSSION

The detrimental effects of radiotherapy on normal tissues have been reported as a result of vascular damage mainly confined to endothelial cell injury.¹⁰ Although this is a seemingly sound concept, it has not been unanimously supported by actual clinical experience of microvascular complications in free flap surgery.¹¹ Noteworthy, endothelial cell injury can, within this context, potentially affect both conduit vessels and the microcirculation with a variety of different complications.¹² The latter can, in fact, lead to impaired integration of the flap into the flap bed, that is, inosculation,¹³ which in its worst form could eventually lead to a “floating flap.”¹⁴ Decreased vascularization of the graft bed has been demonstrated histologically after preoperative radiotherapy.¹⁵ However, the pathology is not limited to endothelial cell injury only but rather a consequence of general cellular dysfunction of the irradiated bed.^{10,12} In support for this is a recent study, by Yoshida et al.¹⁶, showing that transplantation of adipose-derived stem cells to irradiated tissues may contribute to enhanced tissue blood flow and blood vessel density. In the current study, we have divided the effects of endothelial cell injury complications into 2 major types: anastomosis-related (flap necrosis) and flap bed–related (infection, fistula, and wound dehiscence) complications.

The current single-center study clearly indicates that preoperative radiotherapy is a risk factor for both infection and fistula formation, most likely related to impaired microcirculation of the flap bed. The effect of radiotherapy on larger conduit vessels (ie, the anastomosis) was related to the treatment period and may be associated with technical factors, such as the learning curve for free flap surgery. However, the inability to detect such a relationship could also be dependent on the limited sample size.¹⁷ Currently, the low frequency of microvascular complications,

together with relatively fewer cases in irradiated patients, makes it almost impossible to detect such a relationship even in larger studies. However, a recent meta-analysis by Herle et al.¹⁸ describes a significant relationship between preoperative radiotherapy and flap failure as well as fistula formation for head and neck reconstructions. The current study not only supports the data regarding fistula formation but also proposes infection as another important flap complication to be considered.

Limitations of the study need to be acknowledged. The low frequency of anastomosis-related complications is generally reported as problematic in attaining sufficient sample sizes and may explain why the outcome did not reach statistical significance in this study. The value of the current study lays instead in the results of flap bed–related complications and the fact that a treatment protocol adjustment was undertaken in 1 prospective cohort, where the results were controlled for treatment period. The multivariate analysis strengthens data regarding flap bed–related complications related to radiotherapy.

We conclude that the current single-center study clearly indicates that preoperative radiotherapy is a risk factor for both infection and fistula formation, most likely related to impaired microcirculation of the flap bed. The effect of radiotherapy on larger conduit vessels (ie, the anastomosis) was related to treatment period. We suggest postoperative radiotherapy administration whenever possible for oncological reasons, otherwise proper antibiotic cover and meticulous flap inseting to prevent radiation-related infection and fistula formation.

Martin Halle, MD, PhD

Department of Plastic and Reconstructive Surgery
Karolinska University Hospital
171 76 Stockholm, Sweden
E-mail: martin.halle@karolinska.se

ACKNOWLEDGMENT

The authors acknowledge the statistical analyses by Eva Hagel, LIME, Karolinska Institutet, Stockholm, Sweden.

REFERENCES

- Swiecicki PL, Malloy KM, Worden FP. Advanced oropharyngeal squamous cell carcinoma: pathogenesis, treatment, and novel therapeutic approaches. *World J Clin Oncol*. 2016;7:15–26.
- Wennerberg J. Pre versus post-operative radiotherapy of resectable squamous cell carcinoma of the head and neck. *Acta Otolaryngol*. 1995;115:465–474.

3. Fosnot J, Fischer JP, Smartt JM Jr, et al. Does previous chest wall irradiation increase vascular complications in free autologous breast reconstruction? *Plast Reconstr Surg.* 2011;127:496–504.
4. Tall J, Björklund TC, Skogh AC, et al. Vascular complications after radiotherapy in head and neck free flap reconstruction: clinical outcome related to vascular biology. *Ann Plast Surg.* 2015;75:309–315.
5. Benatar MJ, Dassonville O, Chamorey E, et al. Impact of preoperative radiotherapy on head and neck free flap reconstruction: a report on 429 cases. *J Plast Reconstr Aesthet Surg.* 2013;66:478–482.
6. Momeni A, Kim RY, Kattan A, et al. The effect of preoperative radiotherapy on complication rate after microsurgical head and neck reconstruction. *J Plast Reconstr Aesthet Surg.* 2011;64:1454–1459.
7. Frederick MJ, Lin AM, Neuman R, et al. Nipple-sparing mastectomy in patients with previous breast surgery: comparative analysis of 775 immediate breast reconstructions. *Plast Reconstr Surg.* 2015;135:954e–962e.
8. Chang EI, Liu TS, Festekjian JH, et al. Effects of radiation therapy for breast cancer based on type of free flap reconstruction. *Plast Reconstr Surg.* 2013;131:1e–8e.
9. Halle M, Bodin I, Tornvall P, et al. Timing of radiotherapy in head and neck free flap reconstruction—a study of postoperative complications. *J Plast Reconstr Aesthet Surg.* 2009;62:889–895.
10. Stone HB, Coleman CN, Anscher MS, et al. Effects of radiation on normal tissue: consequences and mechanisms. *Lancet Oncol.* 2003;4:529–536.
11. Bui DT, Cordeiro PG, Hu QY, et al. Free flap reexploration: indications, treatment, and outcomes in 1193 free flaps. *Plast Reconstr Surg.* 2007;119:2092–2100.
12. Straub JM, New J, Hamilton CD, et al. Radiation-induced fibrosis: mechanisms and implications for therapy. *J Cancer Res Clin Oncol.* 2015;141:1985–1994.
13. Glotzbach JP, Levi B, Wong VW, et al. The basic science of vascular biology: implications for the practicing surgeon. *Plast Reconstr Surg.* 2010;126:1528–1538.
14. Cheon YW, Lee MC, Kim YS, et al. Gluteal artery perforator flap: a viable alternative for sacral radiation ulcer and osteoradionecrosis. *J Plast Reconstr Aesthet Surg.* 2010;63:642–647.
15. Schultze-Mosgau S, Grabenbauer GG, Radespiel-Tröger M, et al. Vascularization in the transition area between free grafted soft tissues and pre-irradiated graft bed tissues following preoperative radiotherapy in the head and neck region. *Head Neck.* 2002;24:42–51.
16. Yoshida S, Yoshimoto H, Hirano A, et al. Wound healing and angiogenesis through combined use of a vascularized tissue flap and adipose-derived stem cells in a rat hindlimb irradiated ischemia model. *Plast Reconstr Surg.* 2016;137:1486–1497.
17. Halle M, Farnébo F. Does previous head and neck irradiation increase vascular complications in free autologous reconstruction? *Plast Reconstr Surg.* 2012;129:549e–550e; author reply 550e.
18. Herle P, Shukla L, Morrison WA, et al. Preoperative radiation and free flap outcomes for head and neck reconstruction: a systematic review and meta-analysis. *ANZ J Surg.* 2015;85:121–127.