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

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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 insetting 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.)

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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. 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 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).

| Demographic Data | Before 2006 | After 2006 | P |
|------------------|------------|------------|---|
| 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         | 0.004 |
| Chemotherapy     | 5          | 13         | 0.134 |

*Mean (SD).
†Previous myocardial infarction, transient ischemic attack/stroke, peripheral arterial disease, coronary bypass surgery.

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

| 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.

| Demographic Data | Irradiated (%) | Nonirradiated (%) | P   |
|------------------|----------------|-------------------|-----|
| 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 (5.3)           | 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).
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.\(^\text{10}\) Although this is a seemingly sound concept, it has not been unanimously supported by actual clinical experience of microvascular complications in free flap surgery.\(^\text{11}\) Noteworthy, endothelial cell injury can, within this context, potentially affect both conduit vessels and the microcirculation with a variety of different complications.\(^\text{12}\) The latter can, in fact, lead to impaired integration of the flap into the flap bed, that is, inosculation,\(^\text{13}\) which in its worst form could eventually lead to a “floating flap.”\(^\text{14}\) Decreased vascularization of the graft bed has been demonstrated histologically after preoperative radiotherapy.\(^\text{15}\) However, the pathology is not limited to endothelial cell injury only but rather a consequence of general cellular dysfunction of the irradiated bed.\(^\text{10,12}\) In support for this, by Yoshida et al.\(^\text{16}\), 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 treatment period. We suggest postoperative radiotherapy administration whenever possible for oncological reasons, otherwise proper antibiotic cover and meticulous flap insetting to prevent radiation-related infection and fistula formation.

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