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CLINICAL REVIEW

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# Controversies in free tissue transfer for head and neck cancer: A review of the literature

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**Abstract**

**Background:** Microvascular free tissue transfer provides superior functional outcomes when reconstructing head and neck cancer defects. Careful patient selection and surgical planning is necessary to ensure success, as many preoperative, intraoperative, and postoperative patient and technical factors may affect outcome.

**Aims:** To provide a concise, yet thorough, review of the current literature regarding free flap patient selection and management for the patient with head and neck.

**Materials and Methods:** PubMed and Cochrane databases were queried for publications pertaining to free tissue transfer management and outcomes.

**Results:** Malnutrition and tobacco use are modifiable patient factors that negatively impact surgical outcomes. The use of postoperative antiplatelet medications and perioperative antibiotics for greater than 24 hours have not been shown to improve outcomes, although the use of clindamycin alone has been shown to have a higher risk of flap failure. Liberal blood transfusion should be avoided due to higher risk of wound infection and medical complications.

**Discussion:** There is a wide range of beliefs regarding proper management of patients undergoing free tissue transfer. While there is some data to support these practices, much of the data is conflicting and common practices are often continued out of habit or dogma.

**Conclusion:** Free flap reconstruction remains a highly successful surgery overall despite as many different approaches to patient care as there are free flap surgeons. Close patient monitoring remains a cornerstone of surgical success.

**KEYWORDS**

free flap, head and neck cancer, microvascular surgery, reconstruction

## 1 | INTRODUCTION

Reconstructing complex head and neck defects requires thoughtful consideration, as the goal is not only to cover vital structures, but also to restore as much function as possible. Free tissue transfer has become the standard of care, with over 20 free flap donor sites available.[1,2] Although free tissue transfer is technically difficult, overall success rates are as high as 97%.[2] Among the most experienced microvascular surgeons, theories on proper management strategies in the preoperative, intraoperative, and postoperative period vary widely. With such a high overall success rate, it is often difficult to study and conclude with enough statistical power that one management strategy is superior to another. It is

  

therefore unsurprising that there is no available consensus on free tissue transfer strategies for head and neck surgery.

This paper will review and summarize the varying management options that have been studied, providing a concise and up-to-date reference for microvascular surgeons. Our goal is to provide a centralized, evidence-based resource on topics ranging from the evaluation of free flap candidates to the postoperative management. The authors recognize that this paper is not a comprehensive review of the literature, as each subtopic warrants its own systematic review, but rather is a succinct overview of many different topics we encounter in our daily practice.

## 2 | METHODS

PubMed and Cochrane databases were queried for publications pertaining to free tissue transfer or microvascular free flap management or outcomes. When possible, studies were selected based on relevance and study characteristics. Nearly all included were specific to head and neck cancer reconstruction, and studies included preferentially had larger patient populations with more definitive, statistically significant reported results. As this paper intends to discuss controversies in free flap reconstruction, papers with contradictory results were presented whenever possible and discrepancies in these results were analyzed to posit circumstances in which opposing strategies could each be beneficial.

## 3 | DISCUSSION

### 3.1 | Preoperative considerations

Head and neck reconstruction with free tissue transfer is a lengthy procedure, and thus preoperative selection of appropriate patients is extremely important. There is often hesitation in performing such a lengthy and complicated procedure on advanced aged patients. Many surgeons expect that malnutrition, cardiovascular disease (CVD), tobacco use, and diabetes mellitus (DM) will also negatively affect free tissue transfer outcomes. Furthermore, patients who have been radiated prior to their surgery may have poorer tissue from a wound-healing standpoint, increasing flap failure rates. Depending on which factors are present, surgeons may choose to select an approach that is theoretically safer but yields less-than-ideal functional outcomes, such as local flap. We reviewed the evidence behind which of these factors actually influences free tissue transfer outcomes.

#### 3.1.1 | Age

Age has not been found to be a negative predictor of free tissue reconstruction success. In a retrospective analysis of 288 patients who underwent head and neck free flap reconstruction, no variability in surgical complications were found across four different age groups (age <50, 51-60, 61-70, and >70), with overall flap success rate of 94%.[3] In fact, the lowest flap failure rate occurred in the oldest group, with a failure rate of only 4%. Two additional retrospective studies echoed these findings.[4,5] Older patients were more likely to have at least one significant preoperative condition (58% in patients older than 60 years) and, therefore, more postoperative medical complications and longer hospital stays.[5] Fagin et al found the only significant different in free flap patients greater than 90 years was a higher likelihood of discharge to a skilled nursing facility, but no difference in surgical complications or return to baseline functional status. The data showed a trend toward higher American Society of Anesthesiologists (ASA) classification and more postoperative medical complications; however, this did not reach significance, likely due to small sample size.[6] It is unsurprising that older patients overall tend to have more medical complications, but in this light, patients' biological—and not chronological—age is favored in patient selection for free flap reconstruction. It should be noted that the number of octogenarians and nonagenarians undergoing free flap reconstruction is low, and studies may be underpowered. However, proper surgical reconstruction should not be denied on the basis of chronologic age alone, as long as additional medical comorbidities do not preclude the ability to withstand a lengthy procedure.

#### 3.1.2 | Malnutrition

Due to their location in the upper aerodigestive tract, head and neck tumors often cause discomfort with eating and subsequently lead to malnutrition. It has been estimated that approximately a third of patients with head and neck cancer are malnourished, as defined as a prealbumin level less than 10 mg/dL.[7] A low prealbumin level is associated with free flap failure and with a slower rate of wound healing.[7,8] Specifically, fistula healing rates are improved when a patient's C reactive protein to prealbumin ratio is low; that is, lower levels of prealbumin is associated with significantly worse rates of fistula closure.[9] Presurgical malnutrition should be identified and addressed to help boost the patient's chance of success.

#### 3.1.3 | Cardiovascular/medical comorbidities

The ASA score summarizes the patient's degree of medical comorbidities. Although ASA score is associated with significantly more complications from surgery and longer hospital stay, there is no significant effect on free tissue transfer survival.[3,5,10] In a large retrospective analysis specifically analyzing the impact of patient comorbidities on

microvascular outcomes, no correlation was found between patient comorbidities and flap failure.[8]

As the success of a free flap depends on the integrity of the vessels, particular attention must be given to conditions known to affect the patient's microvasculature (eg, CVD, tobacco use, and diabetes). Lee et al examined the specific outcomes of anastomosing vessels that had evidence of calcification intraoperatively. This retrospective review identified 44 of 1329 flaps, with fibula flaps disproportionately affected. There was no significant difference in flap survival when compared to flaps without atherosclerotic vessels.[11]

### 3.1.4 | Tobacco use

Tobacco use is a known risk factor for CVD and atherosclerosis and a known vasoconstrictor. It is reasonable to assume that using tobacco products may compromise the pedicle and anastomosis, and lead to flap failure. However, large retrospective studies have shown that tobacco use does not independently increase the risk for free flap failure in head and neck reconstruction.[8,12]

Although smoking does not have a direct link to free flap failure, it has been associated with poor wound healing. Kuri and colleagues compared poor wound healing, as demonstrated by the need for debridement, resuture, or reconstruction, among five groups, categorized based on time between last cigarette and surgery. Current smokers and those who quit less than 3 weeks before surgery had a significantly higher risk of impaired wound healing, suggesting that patients should abstain from using tobacco products for at least 3 weeks before surgery.[13]

### 3.1.5 | Diabetes mellitus

DM is known to cause both macrovascular and microvascular complications. The correlation between flap failure and DM has been examined in various studies, with conflicting results.[8,13,14] One very large retrospective review and meta-analysis found the prevalence of DM in patients with failed free flaps to be 2.3 times higher than in the general population.[15] They reported a 1.76 increased risk of local postoperative complication in patients with DM.[15] Although this does not necessarily suggest a causative relationship of diabetes leading to flap failure, more patients with failed flaps are diabetic. Another study found that patients with postoperative hyperglycemia, particularly in the 24 hours immediately following surgery, were twice as likely to have infections at the flap site, although there was no higher risk of other postoperative complications, including arterial or venous thrombosis or flap loss.[16] Patients with DM must be selected carefully and managed diligently in the postoperative period.

### 3.1.6 | Radiation exposure

Radiated tissue is notorious for having poorer wound healing outcomes, and radiation is thought to induce inflammatory changes and a prothrombotic state.[17] In one retrospective review of 344 free flaps, flap loss was higher in the irradiated vs nonradiated patients.[17] This was corroborated by a meta-analysis comparing these patients with the relative risk of flap failure equaling 1.48 ($P = .004$) in the irradiated patients. This was particularly an issue in those who received a radiation dose in excess of 60 Gy.[18]

Despite these data, free flap reconstruction in previously irradiated patients is often the reconstructive option of choice for the purpose of introducing healthy and well-vascularized tissue into the wound bed. If the contralateral neck has not been exposed to preoperative radiation, and the flap pedicle provides adequate length, it may be prudent to use this nonirradiated side for the anastomosis.

## 3.2 | Intraoperative considerations

Intraoperative protocols vary widely, particularly regarding vessel selection, geometry, and number of vessels anastomosed. Careful handling of donor and recipient vessels is critical to free flap success, as the leading cause of failure is vascular thrombosis.[19] Surgeons tend to have a preference in which venous system they use, the technique used for anastomosis, and the geometry of the anastomosis. Aside from vessel selection and handling, some suggest that the use of intraoperative vasopressors or anticoagulants can impact flap success.

### 3.2.1 | Recipient vessel selection

Selection and preparation of the arterial and venous anastomosis is arguably one of the most important steps in free flap surgery. Selection may depend on the location and extent of the surgical defect, as well as prior surgery and treatment. The venous system used, number of veins anastomosed, and vessel configuration (ie, end-to-end vs end-to-side) are frequent topics of debate.

The internal jugular vein (IJV), its branches, and the external jugular vein (EJV) are the most commonly used recipient vessels. Some have found higher success when anastomosing to the IJ system (100% vs 92% success in EJV), theoretically because the IJV has a higher caliber size, increased blood flow, and has an associated negative pressure with respiration.[20] The EJV may be less optimal because its superficial location increases the susceptibility to external compression. However, a meta-analysis on this topic reviewed 1409 flaps, and no statistical difference was found in venous thrombosis rates (4.83% in IJV vs 5.25% in EJV).[21]

Direct anastomosis into the IJV through an end-to-side fashion has also been reportedly successful, reducing the risk of pedicle kinking and permitting multiple anastomoses of various sizes.[22,23] It is clear that there are many variations to venous selection, and that ultimately, the decision depends on vessel availability, vessel geometry, pedicle length, and surgeon preference.

### 3.2.2 | Preparing and performing the anastomosis

The use of antithrombotic agents as irrigation or as an intravenous bolus has been questioned. Most surgeons will irrigate the flap vessels with heparinized saline while preparing for anastomosis, although there is no clear evidence that this has an effect on the outcome.[24] Intraoperative heparin boluses have also been used in attempts to improve free flap outcomes and decrease thrombosis. One study compared 260 patients who received an intraoperative heparin bolus to 245 patients who did not, and did not find a difference in free flap outcome.[25] Notably, heparinized saline (10 units/mL) and papaverine were routinely used in both groups to flush the vessels prior to anastomosis. Other surgeons report using heparin boluses intraoperatively only if the anastomosis seems tenuous, although there is also no literature to support this practice.

Mechanical coupling devices have grown in popularity, especially for venous anastomosis. Proposed benefits include decreased operative time, decreased flap ischemia time, and fewer foreign bodies (ie, suture) in the vessel lumen.[26,27] When comparing thrombosis rate in hand sewn vs coupled veins, no significant difference has been found.[27] Mechanical coupling devices are also described for the arterial anastomosis, with zero flap failures reported in one study of 50 arterial anastomoses.[28] Challengers of this technique suggest that coupler devices may restrict arterial blood flow, as the arterial walls lack pliability and may be too thick to drape over the coupler pins. Although Ross et al demonstrated surgical success, they do suggest that the use of a coupler smaller than 2.5 mm in diameter may lead to reduced laminar flow and induce thrombosis.[28]

The number of veins to anastomose is also a topic of debate, as some suggest that multiple venous drainage pathways are superior in preventing flap congestion. In a recent meta-analysis of 3684 flaps, superior outcomes with double venous anastomosis were reported with significantly fewer thrombi and fewer surgical revisions compared to flaps with a single anastomosis.[29] However, Hanasono and colleagues would argue the opposite: they measured peak venous blood velocity in flaps with one vs two venous anastomoses, and found that those with one venous anastomosis had higher blood velocities.[30] They concluded that one venous anastomosis is the superior choice, as higher blood velocity will decrease the risk of venous stasis and thrombosis.

### 3.2.3 | Maintaining stable hemodynamics

During this lengthy procedure, anesthesia providers are burdened with balancing how much fluid to give and which medications are required to maintain hemodynamic stability while not compromising flow through the anastomosis. The concept of goal-directed hemodynamic therapy (GDHT) has been described by some as the ideal method of maintaining circulating volume while also avoiding fluid overload and flap edema.[31,32] Kim et al performed a randomized control trial comparing routine hemodynamic management to GDHT.[31] Aside from only assessing mean arterial pressure and urine output to direct resuscitation, the GDHT group had their stroke volume variation (goal: less than 12%) and cardiac index (goal: greater than 2.5 L/min/$m^2$) monitored to determine when fluid or vasopressors should be given. Those in the GDHT group had significantly better outcomes, with zero flap losses or "at risk" flaps, as compared to 1 flap failure and 5 "at risk" in the control group (n = 31 in each group).

The use of vasopressors during free tissue transfer is controversial, reportedly increasing the risk of vessel spasm, which could be catastrophic during and after anastomosis. Interestingly, there is little data to suggest that vasopressor use is associated with worse outcomes, regardless of intraoperative timing of vasopressor administration.[33,34] Perforator flaps have also been examined as a separate group, as their small-diameter pedicles may be especially sensitive to the effects of vasopressors, and again vasopressors did not lead to significantly more failed perforator flaps.[34]

## 3.3 | Postoperative considerations

The first 24-48 hours after a free tissue transfer are the most critical for monitoring the flap and identifying an impending failure. In our experience, frequent monitoring with hourly flap checks in the first 24 hours is ideal, and this frequency can decrease to every 4 hours for the subsequent 2-3 days. Although most surgeons agree that patients will require an intensive or intermediate care unit for close monitoring and frequent exams, methods of checking the flap vary greatly. Infection prevention with postoperative antibiotics is also frequently debated, as the clean-contaminated site of most of our reconstructions presents a risk for infection and subsequent flap failure.

### 3.3.1 | Flap monitoring

Early detection of flap problems increases the likelihood of flap salvage.[35] Flap color, temperature, capillary refill time,

and bleeding characteristics after pinprick are standard exam components, as well as the use of a handheld Doppler probe to assess the patency of the anastomosis. More recently, the advent of implantable Doppler (ID) devices has changed the paradigm of flap monitoring systems. Multiple centers have compared the sensitivity of ID to external Doppler (ED) and have found superior results with the ID.[36] Specifically, the arterial signal detected by the ID is highly reliable. Some series have reported increased false positive results if relying on the venous signal alone, leading to unnecessary flap exploration.[37] As surgeons and centers have become more apt at interpreting the ID, this false positive rate has reportedly diminished, and some of the busiest flap surgeons nationally rely solely on the ID with great success.[38] No monitoring method has been shown to be correlated with high rates of flap survival or salvage when compared to others; however, studies in which flaps cannot be monitored at all demonstrate decreased flap survival and decreased ability to salvage free flaps with complications.[35]

### 3.3.2 | Antibiotic type and duration

Inherent to the surgical location and presence of oral flora, head and neck reconstruction is always performed in a "clean-contaminated" setting, and thus the ideal time frame to use perioperative antibiotics is frequently discussed. This becomes even more important in the setting of free flap reconstruction, as an infected surgical field surrounding the flap pedicle will increase the risk of failure.[39] The antibiotic chosen is typically one that will cover gram-positive and gram-negative organisms, as well as provide anaerobic coverage. Our current hospital policy suggests ampicillin-sulbactam, or clindamycin for those allergic to penicillin, for perioperative antibiotic prophylaxis.

Although clindamycin has typically been accepted as the antibiotic of choice for patients allergic to penicillins, multiple studies have found an increase in flap or neck infections in patients treated solely with clindamycin.[39,40] Specifically in patients who underwent a free tissue transfer in the oral cavity or pharynx, clindamycin was associated with a four-time increase risk of surgical site infection, and this was even after controlling for confounders, such as tobacco use and prior radiation.[39] At our institution we have adopted the use of levofloxacin and metronidazole to provide additional coverage, instead of clindamycin alone. The duration of antibiotic treatment continues to be debated, although multiple studies, including a meta-analysis, have shown that 24 hours is sufficient and not associated with more infections when compared to patients treated with prolonged antibiotics, when accounting for type of antibiotic (ie, avoiding clindamycin alone).[39,41,42]

### 3.3.3 | Blood transfusions

As previously mentioned, the effect of intraoperative vasopressors on flap perfusion is a commonly debated topic. Postoperatively, patients with head and neck cancer are often transfused blood products to maintain hemodynamic stability. Predictors for needing a blood transfusion have been previously delineated, and blood transfusion is associated with higher T stage, low body mass index, low preoperative hemoglobin, osseous free flaps, and female sex.[43] Although blood transfusions have not been associated with free flap failure, there is concern that more than three blood transfusions after free tissue transfer increases risk of death and is associated with higher wound infection rates.[44] In addition, blood transfusions are associated with higher incidence of medical complications and higher risk of unplanned readmission.[45-47]

### 3.3.4 | Anticoagulants and antiplatelets

The key to free flap success is maintaining the patency of the anastomosis, and many surgeons also use postoperative antithrombotic medications to prevent thrombi, in additional to deep venous thrombosis prophylaxis. At our high volume free flap institution, the patient is loaded with a single dose of aspirin 300 mg at the conclusion of the case, followed by 3 to 4 weeks of aspirin 325 mg daily, as well as routine daily venous thromboembolism (VTE) prophylaxis while inpatient. One study demonstrated that VTE prophylaxis increases the risk of flap hematoma by 7.4% and showed that 25% of those flaps could not be salvaged. Cannady et al concluded that the morbidity and mortality of VTE outweighs the slightly increased risk of flap hematoma to warrant VTE prophylaxis in patients at risk for VTE.[35]

There have been a multitude of studies assessing the risks of antithrombotic medications after head and neck reconstruction and also the efficacy of such medications in preventing flap thrombosis. There is scant evidence that these medications improve outcomes, and there are even studies suggesting that no additional anticoagulation is necessary, other than the deep venous thrombosis prophylaxis.[35,48-50] Regardless, in 2007, approximately 76% of microvascular surgeons reported the use of postoperative aspirin, with the remainder using low molecular weight dextran or subcutaneous heparin.[51] Some have questioned whether antithrombotic agents will increase hematoma risk. The postoperative hematoma/hemorrhage rate is reportedly higher in patients who are treated with a heparin drip as compared to aspirin or no anticoagulation.[52]

In summary, close monitoring in the immediate postoperative period is of utmost importance to catch a failing flap early and also to prevent complications. Antibiotic use for longer than the perioperative 24 hour period does not seem to prevent infections, and although the majority of surgeons continue to use additional antithrombotic agents to improve

anastomosis patency, recent data do not suggest that this will improve or change the outcome.

## 4 | CONCLUSIONS

Head and neck reconstruction with free tissue transfer is a highly successful surgery with superior functional outcomes than other methods of reconstruction. Although rare, flap loss remains a devastating complication, requiring reoperation and prolonging hospitalization. The relatively low incidence of flap failure makes it difficult for single institutions to design randomized controlled trials comparing different interventions, and thus we aimed to summarize the most relevant and current evidence surrounding the management of head and neck free tissue reconstruction. It is clear that there are many conflicting studies reporting successful technique, thus complicating the ability to come up with a universal guideline, but it is also evident that some practices, such as postoperative anticoagulation, may continue to be performed simply out of habit. Regardless, proper surgical planning and meticulous monitoring continues to be the cornerstone of success.

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