RESEARCH ARTICLE

Multi-Disciplinary Surgical Approach to Esophageal Reconstruction: The Role of the Plastic Surgeon

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Abstract
Reconstruction of the esophagus is a highly interdisciplinary undertaking that involves a wide range of specialties in all phases of care. Esophageal reconstruction may be indicated for a number of reasons, which range from oncologic resection to traumatic injuries to congenital defects. The ultimate goals of esophageal reconstruction are to provide soft tissue coverage of the defect, restore continuity of the gastrointestinal (GI) tract, create a functional conduit, and allow for oral intake. This can be achieved through a number of different surgical techniques, which depend on the extent of the defect. For non-circumferential patch defects of the esophagus, local muscle flaps from the neck and trunk are commonly used. For shorter segmental defects, interposition small intestine free flaps or tubularized fasciocutaneous flaps from the extremities are employed. For longer segmental defects, sections of the native GI tract (such as stomach, colon, or jejunum) are recruited to reconstruct the esophagus. The most common complications of esophageal reconstruction include fistula formation, which can typically be managed conservatively, and conduit strictures, which may require serial dilation. Long-term outcomes are typically favorable, with good restoration of swallowing and speech and overall high quality of life in long-term survivors. New developments in tissue engineering involving the use of biological substitutes have also shown promise in esophageal reconstruction. These methods involve the placement of biologic matrices, autologous cells and/or growth factors to restore continuity of the esophagus. In this review, we discuss the role of plastic surgery in the reconstruction of the esophagus.

Keywords: esophageal reconstruction, multidisciplinary care, patch flaps, tubularized flaps, quality of life, bioengineering, plastic surgery

Introduction

Esophageal defects can be caused by a broad range of etiologies. Although they are most commonly due to oncologic resections, they can also be caused by traumatic, autoimmune, and congenital processes. Reconstruction of these esophageal defects poses a complex challenge for the plastic surgeon. The ultimate goal of reconstruction is to restore esophageal continuity and provide soft tissue coverage. The first esophageal reconstruction was described by Mikulicz in 1886, in which skin flaps from the neck were tubularized and used to connect the proximal and distal ends of a cervical defect.[1] Since that time, the options for reconstruction have expanded to include the use of both local and distant tissue with the latter involving the stomach, jejunum, and colon as pedicled or free tissue flaps. Microsurgical techniques in plastic surgery allow for additional reconstructive options through the technique of "supercharging," which augments the blood supply of a reconstructed conduit. Given the many reconstructive options- each of which entails certain benefits and potential complications – selecting the best reconstructive approach for a given patient is critical to ensuring a desirable outcome. Complications of dysphagia, gastro-esophageal reflux, aspiration, regurgitation, weight loss, and ongoing pain are common and need to be monitored to assess the impact on patients' quality of life.[2,3]

This review describes the roles of different surgical sub-specialties in esophageal reconstruction, with a focus on reconstructive options based on the length of the defect: patch, short segmental, and long segmental. Types of complications were found to be similar among all of the reconstructions used. While the current reconstructive options have been present since the 1900s, novel tissue engineering approaches are actively being developed.

Multidisciplinary Care in Esophageal Reconstruction

To optimize outcomes for patients undergoing esophageal resection and reconstruction, peri-operative management involves a highly multidisciplinary approach.[4] Diagnosis or further workup may involve Gastroenterology and Pathology. For oncologic causes, pre-operative planning in conjunction with Medical Oncology and Radiation Oncology to determine the optimal timing of surgery with respect to continued neoadjuvant or adjuvant chemotherapy and radiation therapy is required. Surgical planning for resection and reconstruction may involve Thoracic Surgery, Surgical Oncology, Otolaryngology, and Plastic Surgery. Patients should be evaluated by an anesthesiologist and have their co-morbidities medically optimized with their primary care physician prior to undergoing surgery. Post-operatively, the patient care team can include Psychiatry, nurses, nutritionists, pharmacists, physical therapists, and speech therapists.

The interaction between surgical sub-specialties during the perioperative period warrants closer attention, as multiple surgical teams are often involved in esophageal reconstruction. In general, esophageal reconstruction can be broken down into three intra-operative phases: resection of the lesion, exposure and preparation of the reconstruction, and anastomosis of the conduit.

Resection of the lesion is carried out by Otolaryngology, Thoracic Surgery, or Surgical Oncology, depending on the location and extent of the involved esophagus. In proximal cancers, such as laryngeal cancer, Otolaryngology or Surgical

Oncology may remove the larynx in conjunction with the cervical esophagus. For cancers distal to the larynx, Thoracic Surgery or Surgical Oncology may remove a portion of or the entire esophagus. This can be performed as an open or video-assisted thoracoscopic surgery, where the latter may provide improved visualization and mobilization of the intra-thoracic esophagus.

Exposure and preparation of the reconstruction involves the efforts of Surgical Oncology, Thoracic Surgery, and Plastic Surgery. If an intra-abdominal procedure is needed, Surgical Oncology will mobilize segments of the stomach or colon and provide the length of gastrointestinal (GI) conduit that is needed for a tension-free anastomois reconstruction. Due to the patient's nil per os status post-operatively, a nasogastric feeding tube is passed beyond the anastomosis and/or a distal feeding jejunosotomy tube is placed to help protect the anastomoses. Thoracic Surgery will prepare the proximal esophagus and thorax for reconstruction, which can involve partial resections of the manubrium, clavicle, and first rib to provide access to the internal mammary vessels if a supercharged intestinal flap is used. Simultaneously, Plastic Surgery will harvest the flap that is selected for the reconstruction and then transfer the flap to the esophagus for anastomosis. This may involve dissection in the extremities (for tubularized radial forearm or anterolateral thigh flaps) or in the abdomen (for jejunal flaps).[5]

Anastomosis of the conduit can require the involvement of all four surgical sub-specialties, depending on the location and the type of reconstruction. At our institution, the proximal esophago-jejunal or esophago-colonic anastomoses in the neck are typically performed by Thoracic Surgery or Plastic Surgery. If an intestinal reconstruction is used, the necessary bypasses for the remaining bowel are done by Surgical Oncology. If a microvascular anastomosis is needed, Plastic Surgery will expose the recipient vessels, as well as perform the vascular anastomoses between the flap to the recipient vessels. These situations arise for pedicled flaps that are supercharged (jejunum and colon) and free flaps (tubularized radial forearm or anterolateral thigh flaps).

Patch Defects

Non-circumferential patch defects typically require limited soft tissue coverage for reconstruction, for which a local flap is used. Some of the most common options include sternocleidomastoid muscle flap, supraclavicular artery island flap, trapezius flap, and pectoralis major muscle pedicled flap.[6–8] The benefit from these approaches include a relatively short operative time without the need to perform microvascular anastomoses, as well as their ability to be used as salvage flaps. The difficulties in using these flaps include prior surgical scars, possible injury to the flap blood supply during the esophageal resection or neck dissection, and poor tissue quality in the setting of prior radiation treatment.

Fig 1: A 51-year-old female with a history of Zenker's diverticulum resection that was complicated by stricture presented for reconstruction. A sternocleidomastoid (SCM) muscle flap was selected for esophagoplasty. A) Pre-operative photo with design of the incision. B) Exposure of the esophageal stricture performed by ENT. The posterior wall was repaired primarily and a bougie placed through the defect to demonstrate the anterior wall defect. Skin markings indicate the planned SCM myocutaneous flap. The muscle was detached from its clavicular attachments, the superior portion of the skin paddle de-epithelialized and the flap rotated medially while preserving its middle (superior thyroid) and inferior (transverse cervical) blood supply. C) Primary closure of the incision. D) Postoperative barium swallow study indicating successful passage of contrast across the repair site.

*Sternocleidomastoid muscle flap (**Fig 1**)*

The sternocleidomastoid muscle (SCM) is in close proximity to the cervical esophagus, making it a reasonable option for reconstructing a short segmental defect of the esophagus. It is a broad muscle that originates from the clavicle and manubrium and inserts from the tip of the mastoid process to the occiput.[9] The SCM has a segmental vascular supply, which allows a flap to be either superiorly- or inferiorly-based using the occipital artery or thyrocervical trunk, respectively. Ideally, the middle segment supplied by the superior thyroid artery should be preserved as a secondary blood supply to augment the primary blood supply. Either the entire muscle or just the anterior portion of the SCM can be used for reconstruction.[9,10] A skin paddle opposite to the vascular pedicle is used for the esophageal lumen, and the remaining skin is de-epithelialized and used to obliterate any dead space in the wound. A meta-analysis of the SCM flap showed that it is typically based on the superior blood supply with the most common complication being partial skin necrosis (21%) when used for closure of oro-, pharyngo-, and tracheocutaneous fistulae, facial reconstruction, reconstruction of mastoid defects, and reconstruction of the laryngotracheal complex.[10]

Supraclavicular artery island flap

The supraclavicular artery island flap (SCIA) was originally described in 1979.[11] It is a thin, hairless, fasciocutaneous flap harvested from the supraclavicular and deltoid regions that can be used in the anterior or posterior cervical regions.[11,12] The origin of the supraclavicular artery is primarily from the transverse cervical artery and secondarily from the subclavian artery.[11,12] The origin of the supraclavicular artery is found within a triangle defined medially by the posterior border of the SCM muscle, posteriorly by the external jugular vein, and inferior/anteriorly by the median portion of the clavicle.[12] The size of the skin paddle can range from 4-12 cm wide and 20-30 cm long. The donor site can typically be closed primarily but may require a skin graft if a very large flap is used.[12] The SCIA flap has been used for both partial and complete circumferential pharyngeal defects with 30% of patients developing pharyngeal leaks that all resolved without surgical intervention and 10% developing a stricture requiring balloon dilation.[13]

Trapezius muscle flap

The trapezius myocutaneous flap was originally described in 1975 for repair of an oral cavity defect and has since been used for a number of other indications, including patch defects of the esophagus.[14] It is a triangular muscle that extends from the occiput to the shoulders and upper back, with the blood supply typically from the superficial transverse cervical vessels.[14,15] The location of the skin paddle is centered on the acromioclavicular angle for a transversely oriented flap or between the vertebral column and medial scapula for a vertically oriented flap.[14] After elevation, the flap is rotated into the defect and the skin paddle is sutured to the mucosal defect. The muscle bulk from the trapezius can reinforce the suture line and help protect the carotid vessels that may be exposed.[15] In order to close the surgical site primarily, the width of the flap should not exceed 7 cm.

Pectoralis major muscle flap

The pectoralis major myocutaneous flap is one of the workhorse flaps for head and neck reconstruction. Its use was first reported in 1979, which included a description of anatomic findings from cadaver dissection.[16] The pectoralis major muscle is a thick, triangular muscle that originates from the clavicle, sternum, and costal cartilages and inserts on the humerus. The blood supply is primarily from the thoracoacromial artery, which is found on the undersurface of the pectoralis major muscle. A true island flap can be created to maximize the vascular supply, increase mobility, and decrease tension during inset.[18] A subcutaneous tunnel is created between the neck incision and the chest to transfer the flap into the defect.[17] Occasionally the tunnel may be too tight in which case, the skin is incised and a skin graft is used to cover the exposed muscle. The flap can be used in both a pedicled and a free fashion for head and neck reconstruction, although free pectoralis major flaps have a higher rate of requiring a salvage operation with another pedicled flap.[18]

Short Segmental Defects

Segmental defects can be non-circumferential or circumferential and involve only a portion of the esophagus. The advent of improved microsurgical techniques has made reconstruction of segmental defects possible using tubed fasciocutaneous flaps including the anterolateral thigh flap and the radial forearm free flap. These flaps are both excellent options, especially in the setting of a normal thoracic esophagus that might otherwise be sacrificed when using a pedicled reconstruction approach.

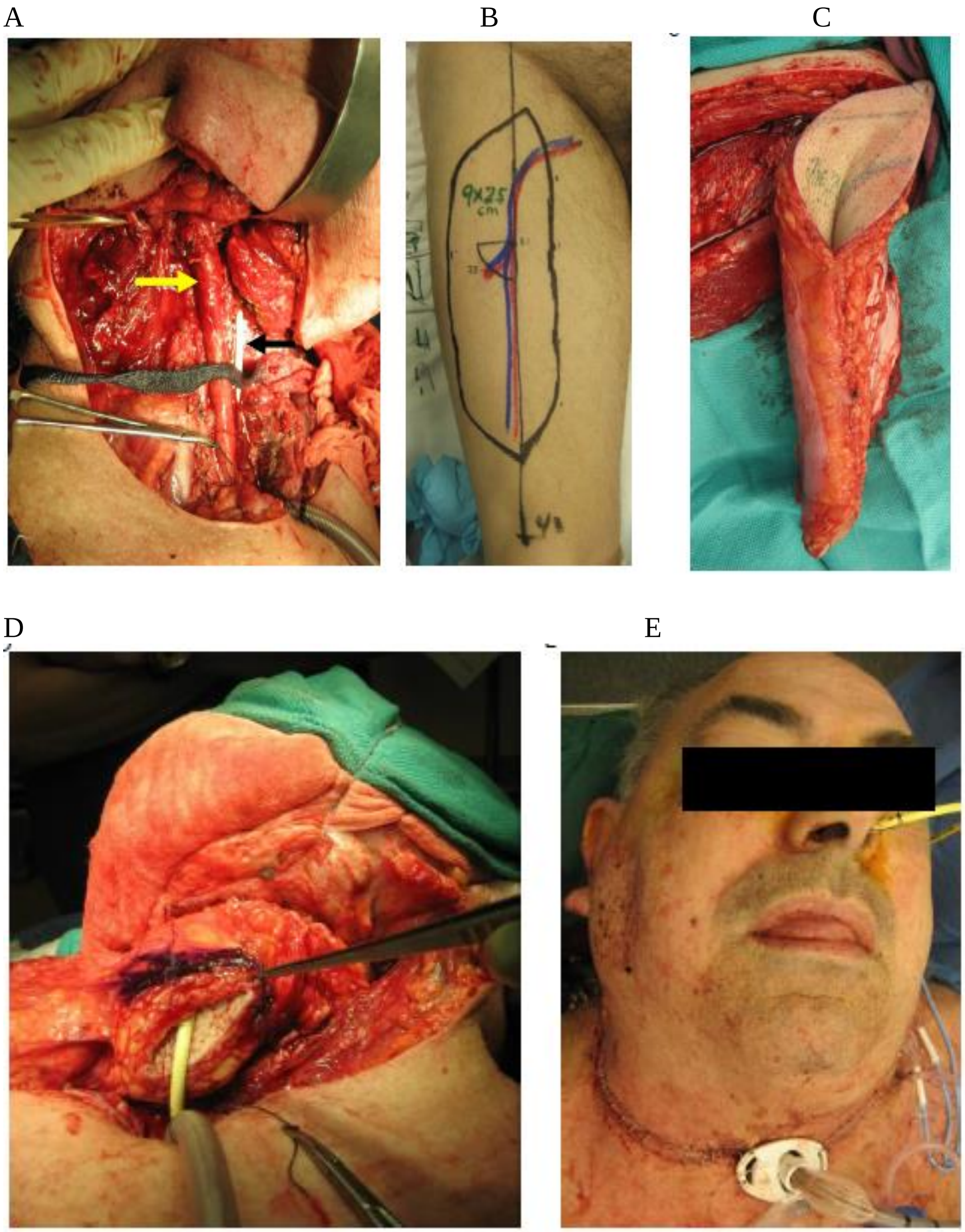

Fig 2: A 62-year-old male presented with airway obstruction and was found to have locally advanced laryngeal squamous cell carcinoma. He underwent complete laryngopharyngectomy with removal of tumor encasing the right internal and external carotid arteries by ENT and Vascular Surgery. A free anterolateral musculocutaneous flap was selected for reconstruction. A) Intra-operative view following laryngopharyngectomy with exposed internal carotid artery (yellow arrow) and nasogastric tube (black arrow) indicating laryngopharyngeal defect. B) Right thigh flap markings of skin paddle and descending branch of lateral femoral circumflex artery. C) In situ tubulization of ALT. Portion of harvested vastus lateralis visible posteriorly. D) Flap inset. Microvascular anastomosis performed to the left superior thyroid artery and vein. E) Immediate postoperative result.

Anterolateral thigh free flap (***Fig 2***)
The anterolateral thigh (ALT) flap is a fasciocutaneous flap that obtains its vascular supply from the descending branch of the lateral femoral circumflex artery. Since it was first described in the 1980s, it has become a true workhorse flap of plastic surgery due to its versatility and size.[19–21] The skin paddle of this flap can be made narrow or wide, depending on the circumference of the esophageal defect, and can be used for both patch and circumferential defects of varying sizes. Recipient vessels for micro-vascular anastomosis usually include the external carotid artery, transverse cervical artery or superior thyroid artery. The transverse cervical vein and internal jugular vein are commonly used as recipient veins. For circumferential defects, a 14 mm diameter Montgomery salivary bypass tube (Boston Medical Products, Westborough, Massachusetts) can be considered to reduce the risk of stricture or fistula. This is usually left for 2-6 weeks prior to removal. Donor sites of 8 cm or less can typically be closed primarily, resulting in a straight-line scar. If flap width exceeds 8 cm or there is excessive tension during closure, a skin graft can be taken from the contralateral thigh and used for donor site coverage. While the ALT donor site is favorable to that of the radial forearm due to location, its harvest can be more difficult, especially in obese patients.

Radial forearm free flap
The radial forearm free flap (RFFF) was initially described as a free flap in 1981.[22] It is a fasciocutaneous flap supplied by the radial artery and drained by the venae comitantes of the radial artery. The cephalic vein can be used when the venae comitantes outflow is insufficient. The donor site is routinely covered with a split thickness skin graft, resulting in a characteristic scar on the forearm. Average wrist circumference ranges from 10-15 cm. Thus, harvesting a 9 cm-wide flap to perform a circumferential esophageal reconstruction (assuming an average esophageal diameter of 3 cm) can result in a donor site scar up to 2/3 of the circumference of the wrist. When reconstructing defects of a shorter length, the flap can be rotated 90° during inset to reduce the width of the donor site scar. Benefits of the RFFF include its reliability and ease of harvest, as well as its pliability and relative ease of tubularization. Disadvantages include relatively higher rates of fistula and stricture when compared to the ALT, as well as the more significant donor site morbidity.

Long Segmental Defects
With longer, circumferential defects of the esophagus, other sections of the GI tract are recruited to replace the esophagus. Rather than using distant muscle or skin flaps, these reconstructions offer the advantage of GI structures that are already tubular and mucosalized, and can readily be interposed into the esophageal defect. Notably, the stomach, colon, and jejunum are most commonly used for these longer defects.

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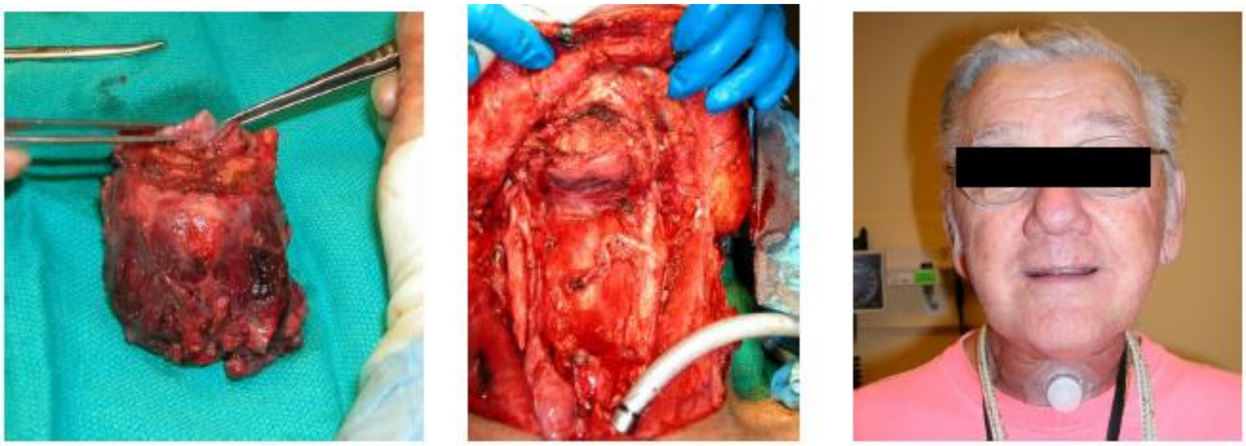

Fig 3: A 72-year-old male with hypopharyngeal cancer underwent total laryngectomy and cervical esophagectomy. Pharyngoesophageal reconstruction was performed with a free jejunal flap. A) Intra-operative photo of the excised specimen. B) Intra-operative view of the esophageal defect and recipient vessel preparation. The superior thyroid artery and internal jugular vein were chosen for micro-anastomosis. C) Postoperative result at 9 months

Gastric pull-up

The gastric pull-up technique was first described in 1920.[23] In this technique, the stomach is mobilized from its abdominal attachments, advanced into the posterior mediastinum as a tube, and anastomosed to the distal end of the remaining esophagus. The tubularized gastric segment is reliant upon the right gastroepiploic and right gastric arteries for blood supply. Notably, this technique uses donor tissue that is already in the correct anatomical position and requires a single anastomosis, thereby reducing the chance of anastomotic leak and breakdown. Additionally, the gastric pull-up has a robust and reliable blood supply. However, the interposed gastric segment can be prone to regurgitation and reflux symptoms. This option may also have insufficient length for a proximal reconstruction, or be unusable in patients who have had prior gastric surgery, or if the stomach is involved in the underlying disease process.

Colonic interposition flap

The colon can also be used to reconstruct longer defects of the esophagus and was first described in 1911.[24] A segment of the colon – oftentimes the descending colon due to the extended length from the sigmoid – is detached from its native location and interposed into the esophageal defect. The blood supply for a descending colon interposition is typically based on the middle colic artery, but this will vary based on the segment of colon used. This technique offers advantages of a longer length than can be achieved with a gastric pull-up, less regurgitation and reflux symptoms, and, in instances in which radiation is used for treatment of esophageal cancer, the recruitment of distant tissue that is outside of the irradiated field. However, this procedure requires three anastomoses (two for the neo-esophagus and one to reconnect the bowel) as compared to a single anastomosis for a gastric pull-up and can develop conduit redundancy over time, which leads to unpleasant sensations of fullness with oral intake.

*Jejunum flap (**Fig 3**)*

The jejunum represents another option to reconstruct long defects of the esophagus. This can be done as a free flap, especially for segmental cervical defects, or as a supercharged flap for longer defects. Similar to a colonic interposition, a jejunal flap involves a segment of jejunum that is detached from its native location, tunneled in a retrosternal fashion, and then anastomosed into the esophageal defect. The jejunum flap is typically based off of the 4th mesenteric jejunal branch of the SMA, which can be used for a free jejunum flap, while the 2nd and 3rd branches can be divided to provide length to reach the proximal esophagus. The pedicled jejunum flap technique was first described in 1907, although its use was limited due to the variable vascular anatomy of the small bowel reliant upon the mesentery and the subsequent risk for bowel ischemia and anastomotic breakdown due to insufficient blood supply.[25] In order to ensure adequate blood supply, the technique of "supercharging" was developed, in which the 2nd mesenteric vessel branches are anastomosed to the internal thoracic or cervical vessels while the 4th mesenteric jejunal branch remains intact.[26] A small segment of jejunum can be exteriorized to the chest wall and serve as a monitoring segment to ensure vascular anastomotic patency to the flap. This technique allows for reconstruction with a conduit that maintains the caliber and peristaltic nature of the native esophagus and can be used for both short and long defects.[5] However, this is a considerably more complex procedure than either gastric pull-up or colonic interposition that requires significant microsurgical experience.[27] The typical recipient blood vessel is the internal mammary artery and vein.

Clinical Outcomes

The primary goal for esophageal reconstruction is to reestablish continuity of the gastrointestinal tract and create a functional conduit that allows for swallowing and speech. In restoring swallowing, the goal is to allow patients to eat without dysphagia and allow for adequate nutrition through oral intake alone, without the aid of a feeding tube. The restoration of speech is beyond the scope of this article and has been well-described by others.[28] This section will focus on the clinical outcomes surrounding reconstruction of circumferential defects.

Fistula formation is one of the most common early complications following esophageal reconstruction. It causes significant morbidity and has been shown to increase hospital stay, prolong wound healing, and delay restoration of swallowing and speech. Risk factors for fistula development include prior radiation of the esophagus, poor tissue quality, significant tension at the anastomosis, and flawed surgical technique. Average, rates of fistula formation are 5-10% for all reconstruction methods, although rates as low as 3% and as high as 48% have been reported.[28–30] Small fistulas can often be managed conservatively with wound care and withholding oral intake, which allows spontaneous resolution within weeks. However, larger fistulas may require additional surgery to obliterate dead space and protect vital structures such as the carotid artery.

One of the most challenging late complications of esophageal reconstructions is stricture, which can lead to dysphagia. Strictures are more common following segmental reconstruction, due to the presence of circumferential anastomoses that can scar and subsequently constrict. It is more commonly seen in patients who had complications of an anastomotic leak, ischemic injury to the conduit, or fistula. Symptomatic strictures require dilation either with a bougie or an endoscopic balloon, but 30% of patients develop recurrent dysphagia within the first year and require serial dilations.[31] Severe cases may require placement of a feeding tube or surgical revision of the anastomosis. The rates of long-term stricturing and dysphagia are typically 5-25%, with variable rates based on the particular method of reconstruction, although some patients report spontaneous resolution of symptoms without dilatation.[32–34]

Patients may also develop dumping syndrome. This syndrome is hypothesized to occur when a hyperosmotic food load – which would typically be digested and slowly released by the pylorus in a patient with unaltered anatomy – is suddenly bolused into the intestines, causing rapid movement of fluids into the GI tract. This can result in both GI symptoms (bloating, diarrhea, nausea, and cramps) and also vasomotor symptoms (pallor, diaphoresis, fatigue, and syncope). A number of factors can contribute to dumping syndrome, including use of a denervated or devascularized esophageal conduit, diminished gastric capacity, and dysfunction of the pylorus. Some manifestation of dumping syndrome may be present in up to 50% of patients, but symptoms are only clinically relevant in approximately 5% of patients after esophageal reconstruction.[35] In most instances, these symptoms can be adequately managed with the assistance of a Clinical Nutrition team. Patients may require dietary modifications including eating multiple small meals, increasing the amount of complex carbohydrates, and restricting fluid intake around the time of meals.[36] In severe cases that are refractory to dietary changes, medications including octreotide, prednisolone, and verapamil have been shown to help relieve symptoms.[37–39]

A majority of patients who undergo circumferential reconstruction have restoration of swallowing, with rates ranging from 59% to 100%. Despite the occurrence of stricturing that results in dysphagia, most patients are able to rely on oral intake alone and do not require the use of feeding tubes. Patients with long-term survival report high levels of satisfaction with oral intake, with most patients free of dysphagia and regurgitation.[40] Reconstruction with a native gastrointestinal conduit (*i.e*. stomach, jejunum, and colon) also restores a degree of peristalsis to the neo-esophagus. However, this function is typically lost over time and ultimately results in passive conduits.[41] Other common long-term complaints include early satiety, diarrhea, and reflux, although these are generally well-tolerated. Ultimately, esophageal reconstruction provides a satisfactory ability to swallow and eat normally.

Mortality rates for esophageal reconstruction across all indications have historically been high, with immediate peri-operative mortality rates of 12% and five-year survival rates of less than 20%. Advances in the treatment and reconstruction of esophageal disease have improved the 90-day mortality of patients undergoing complex esophageal reconstruction to 2-10%[41,42], as well five-year survival rates in patients who have had colonic interposition to 66%[43], and supercharged jejunum to 30%.[41] However, the treatment and reconstruction of esophageal disease, particularly in instances of advanced cancer, remains a challenging topic for the plastic surgeon.

Future Innovations in Esophageal Reconstruction

Beyond the techniques described in this article, scientists and surgeon-scientists continue to explore, discover, and innovate new approaches for esophageal reconstruction. Given the complex properties required of a functional esophagus, it is not surprising that these efforts have been met with challenges and failures along the way. Previously tested approaches for esophageal reconstruction include the use of synthetic grafts (e.g., Teflon, Dacron), allogenic esophageal transplantation, and tissue autografts or allografts, each with their own shortcomings.[44] Synthetic grafts carry a risk for infection and foreign body reaction that results in fibrosis with anastomotic fistula and stricture formation.[45] Esophageal allografts are plagued by insufficient blood supply necessitating composite thyro-tracheo-esophageal grafting. The technical difficulty of this operation, coupled with the necessity for lifelong immunosuppression, have limited its clinical utility.[46] Tissue autografts and allografts from multiple sources have been tested for esophageal reconstruction and include pleural, pericardial, dermal, musculofascial, and aortic grafts. Unfortunately, in multiple animal models, these grafts were found to suffer from high stricture rates, requiring intermittent mechanical dilations and ultimately failing due to progressive fibrosis by 1 year post-implantation.[47–49] As a result of the challenges encountered with these various reconstructive modalities, research has increasingly shifted toward alternative methods of reconstruction.

Tissue engineering approaches involving the use of biological substitutes have shown promise in esophageal reconstruction. Typically, these methods involve the placement of biologic matrices, with or without autologous cells and growth factors, within the defect. Prior to implantation, these grafts may be incubated *in vitro* or within a host tissue such as the latissimus dorsi muscle or omentum. Several promising approaches using biological substitutes are reviewed here.

Cell sheets

Cell sheet technology involves culturing cells on a temperature-responsive polymer that changes its physical properties based on temperature.[50] For example, poly(*N*-isopropylacrylamide) is hydrophobic at 37°C or higher, allowing cells to attach and proliferate. Below 32°C, the polymer becomes hydrophilic,[51] which creates cell sheets with intact extracellular matrices and cellular morphology that allows implantation.[52] This modality allows for the reconstruction of superficial defects of the esophagus, such as those resulting from endoscopic submucosal dissection (ESD) when treating superficial esophageal malignancies. Following earlier validation in preclinical models,[53,54] this method was tested for safety and feasibility in humans.[55] Epithelial cell sheets grown from oral mucosal epithelium were transplanted into 10 patients with esophageal ulcers resulting from ESD. The authors reported re-epithelialization at an average of 3.5 weeks post-implantation, and a 10% (n=1) rate of stricture formation, which occurred in a patient who had a circumferential defect involving the gastro-esophageal (GE) junction.[56] A major limitation of this approach is the relative fragility of the cell sheets during transportation and transplantation. New endoscopic devices have been developed using 3D printing technology to improve cell sheet delivery,[57] culminating in a medical device recently approved by the Japanese Pharmaceuticals and Medical Devices Agency. Clinical trials utilizing this reconstructive technique are ongoing.

Synthetic and biologic scaffolds

Tissue engineering techniques using synthetic or biologic matrices are also being explored as a potential replacement for autologous reconstruction. Broadly speaking, matrices provide structural support and provide a scaffold for cellular ingrowth to promote the formation of a functional tissue construct. The ideal matrix is biodegradable, non-immunogenic, affordable, mechanically similar to the replaced tissue, and allows for eventual replacement by the host tissue.

Several synthetically produced matrices have been developed including polyester-based aliphatic polymers (polylactic acids [PLA], poly-L-lactic acid [PLLA], poly-caprolactone [PCL], polyglycolic acid [PGA], poly-DL-lactic acid [PLGA], and poly-L-lactide-co-caprolactone [PLLC].[58] Given their hydrophobic nature which can limit cell adhesion and integration, researchers have found that adding natural proteins to the matrix surface can ameliorate this disadvantage. In a recent study, Zhu *et al.* demonstrated that covalently adding collagen onto the surface of PLGA could improve proliferation and morphologic characteristics of esophageal smooth muscle cells.[59] The main disadvantage of these synthetic polymers remains their lack of biocompatibility that frequently results in foreign body reaction with fistula or stricture formation.

Biologic matrices are obtained from both human (allogenic) and animal (xenogenic) sources, and include acellular dermal matrix, small intestinal submucosa, urinary bladder matrix, esophageal acellular matrix, gastric acellular matrix, and amniotic membrane. Prior to storage and eventual use, they are de-cellularized via enzymatic processes to reduce graft rejection. As with synthetic matrices, biologic matrices can provide a scaffold for cellular ingrowth and tissue integration. A significant advantage of biologic matrices over synthetic matrices is their propensity to induce less inflammation and fibrosis, thus promoting a more regenerative phenotype.

Collagen matrices are similar to biological matrices but lack several of the extracellular structures. They can similarly be produced using collagen extracted from bovine skin or tendon. Collagen matrices have been used to reconstruct esophageal defects in several animal models including dogs[60] and rabbits.[61] Encouragingly, Takimoto *et al.* found that reconstruction of circumferential esophageal defects in dogs using a collagen matrix could lead to the histologic formation of highly regenerative esophageal tissue by 4 weeks.[60] Additionally, small intestinal submucosa has also been explored as a strategy for esophageal replacement in porcine[62] and rat[63] models. Unfortunately, these studies invariably resulted in chronic stricture, indicating the need for an alternative strategy.

Cell-seeded scaffolds

Increasingly, a hybrid approach using cell-seeded scaffolds appears to be the most promising approach toward engineering esophageal replacements.[64] The therapeutic benefit of stem cells for promoting tissue regeneration has been borne out in multiple studies and is attributed largely to their trophic and paracrine activity, which can result in improved neovascularization and reduced fibrosis and inflammation, as well as their ability to transdifferentiate into multiple cell types.[65–68] Spurrier *et al.* reported full regeneration of a murine esophagus by seeding esophageal units containing progenitor cells onto a PGA/PLA collagen-coated scaffold.[69] La Francesca *et al.* reported successful regeneration of esophageal tissue in a porcine model using synthetic polyurethane electro-spun grafts seeded with autologous adipose derived mesenchymal stem cells (aMSCs).[70] The polyurethane scaffolds were endoscopically removed, leaving behind regenerated esophageal tissue containing esophageal mucosa, submucosa, and smooth muscle layers with blood vessel formation.

In another recent study, Kim *et al.* created a 3D-printed two-layered tubular scaffold seeded with mesenchymal stem cells (MSCs) incubated either in an *ex vivo* bioreactor or *in vivo* in an omental rat model. Encouragingly, both bioreactor- and omentum-incubated scaffolds showed more than 80% mucosal regeneration without a fistula. Furthermore, the integrated scaffold was covered with layers of stratified squamous epithelium and demonstrated newly developed blood vessels. Finally, recent studies have also shown that differentiated, non-progenitor cells may also be used for esophageal reconstruction. For example, Nakase *et al.* created esophageal grafts in a canine model using human amniotic membrane sheeted onto PGA and seeded with oral keratinocytes, fibroblasts, and smooth muscle cells.[71] These constructs were wrapped around tubes and matured within omentum *in vivo.* The scaffolds developed into tubes containing stratified squamous luminal cells surrounded by a layer of smooth muscle tissue. These grafts were used to reconstruct esophageal defects and allowed dogs to tolerate an oral diet without stricture formation up to 420 days post-implantation.

As research in esophageal reconstruction continues to move forward, it is clear that the technologies described here will play a key role. Cell-sheet technology has shown promise in treating superficial lesions involving the esophageal mucosa. Alternatively, multiple studies have illustrated the regenerative synergy that can be achieved by combining novel bioscaffolds with progenitor cells. Despite the promising results from these small and large animal studies, further research investment will be needed to translate these treatment modalities to the clinical setting.

Conclusions

Esophageal reconstruction is a difficult yet rewarding challenge for the reconstructive plastic surgeon, with the ultimate goals of restoring gastrointestinal continuity and allowing patients to achieve oral intake. Successful reconstruction requires the participation and cooperation of a number of medical and surgical subspecialties. Several techniques have been developed to address the various types of esophageal defects, including local muscle flaps for patch defects, tubularized free flaps for short segmental defects, and interposed segments of native GI tract for long segmental defects. Outcomes for these reconstructions are generally favorable, particularly in long-term survivors, but patients still commonly experience fistulas and strictures. New developments in tissue engineering offer promising alternatives in cell sheets and cell-seeded scaffolds, but more research is needed before these techniques can be brought to the operating room. Ultimately, esophageal reconstruction requires a highly multidisciplinary team throughout the pre-, peri-, and post-operative period to ensure the best possible outcomes.

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