Tracheal replacement: state of the art and novel perspectives

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Abstract: Non-malignant and malignant obstruction of the tracheal airway causes significant morbidity and mortality. With increased use of artificial airways, benign and iatrogenic complications are increasing. A tracheal stenosis that is less than 5 cm in length can be resected with end-to-end anastomosis. Longer tracheal lesions can be treated in a palliative way by placement of a stent to secure airway lumen patency. The management of tracheal defects is an evolving field. Tracheal transplantation and tracheal regeneration may bring major treatment advances to cases with long-segment tracheal involvement. This review examines the current possibilities and future prospects in the area of tracheal transplantation and regeneration.

Keywords: Trachea; replacement; allotransplantation; immunosuppression; revascularization

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Immediate repair of long-segmental defects

Prosthetic tracheal repair

In recent years, most synthetic materials used for tracheal replacement have been tested in experimental animal research. From these studies, it became clear that definitive prosthetic replacement of the airway wall is not possible (1). To date, nearly all surgical prostheses that have been successful were observed in potentially sterile mesenchymal tissues. No example of successful prosthetic repair can be cited in the respiratory or gastrointestinal tract. The internal site of the airway tract belongs to the outside world, and bacterial contamination at the interface between the airway and prosthesis prevent its ingrowth (*Figure 1*). The complications of wound breakdown at the anastomoses can be temporarily delayed by wrapping the prosthesis in vascularized tissue, mostly transposed omentum.

Palliative treatment of long-segmental defects

Long-segmental tracheal defects, which result after removal of malignant tumors are extremely rare. The only possibility for immediate reconstruction of these defects is to reduce the length of the defect by inserting a silicone stent, which is sutured to the upper and lower margins of the defect. A free fasciocutaneous skin tube (lateral thigh flap, radial forearm flap) can be used to wrap the silicone stent as a temporary closure (*Figure 2*) (2).

Tracheal transplantation

Introduction

Experience with tracheal allotransplantation has been anecdotal because of the difficulties linked with restoration of the blood supply. The first case of a tracheal allotransplant was reported in *The Lancet* in 1979 (3). Donor trachea was implanted heterotopically in the sternocleidomastoid muscle of the recipient and transferred to the orthotopic position 3 weeks later. However, the recipient was not given immunosuppressive therapy, no evidence of allograft viability was reported, and no information about the long-term outcome was published. The original article stated that "the tracheal allograft has become integrated and it has functioned perfect for 9 weeks without any evidence of rejection, ischemia, or infection."

A second case of tracheal allotransplantation was reported in 1993 (4). The allotransplant was revascularized orthotopically under protection of immunosuppressive

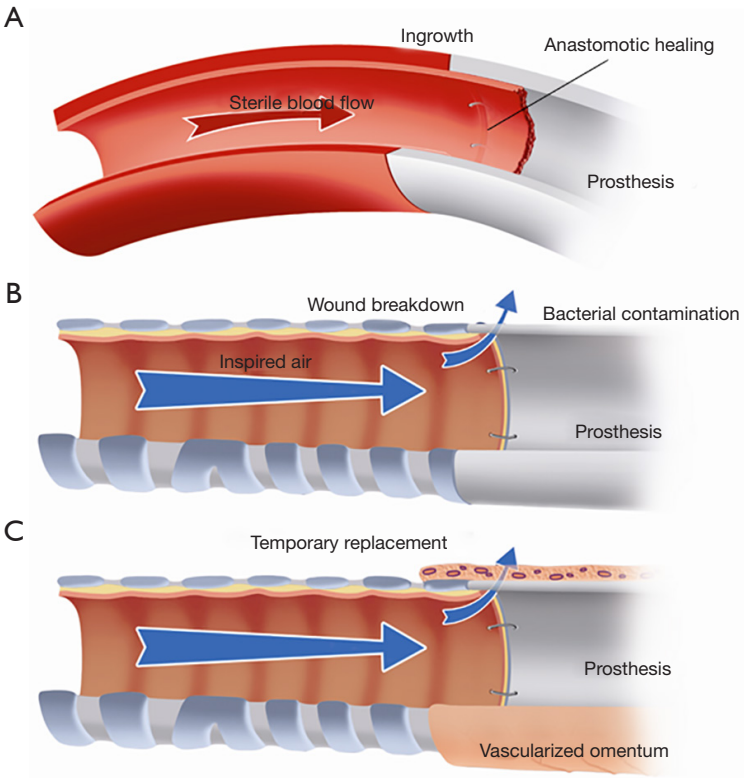

Figure 1 Prosthetic replacement: airway versus vascular conduits. (A) Blood vessel prosthesis. Endothelialization of the luminal surface of vascular grafts occurs only 1 to 2 cm into the graft from the anastomotic site. These endothelial cells are derived from adjacent, native endothelium and they enable the anastomosis to heal; (B) airway prosthesis. In the respiratory tract, the flow of inspired air will lead to bacterial contamination and wound breakdown at the anastomosis. The respiratory epithelium will not grow over the prosthesis-airway anastomosis; (C) airway prosthesis wrapped in vascularized tissue. A prosthesis may act as a temporary airway stent when it is wrapped by well-vascularized tissue (e.g., omentum). The vascularized tissue around the prosthesis may temporarily avoid the complications of wound breakdown at the anastomotic sites.

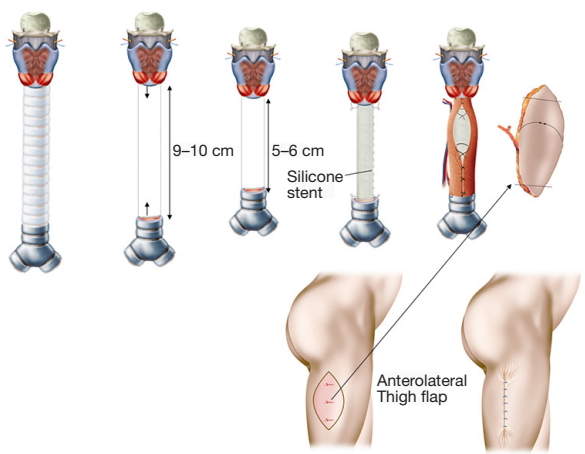

Figure 2 Palliative treatment of long-segment tracheal defects.

drugs. The graft appeared vital at the end of the second month, but signs of graft stenosis appeared by the end of the fourth month. However, the transplant was not visualized in the paper. Current knowledge suggests that orthotopic revascularization of a tracheal graft is completely impossible (*Figure 3*).

We began experimental animal research on tracheal allotransplantation in 1993 (5,6). In rabbits, the trachea was successfully transplanted in its orthotopic position after 2 weeks of heterotopical revascularization by wrapping in a vascularized fascia flap. From these studies, we learned that the trachea is subject to the same immunologic laws as all other allogeneic tissues. The most important component in tracheal rejection was lymphocyte-mediated, and the prime

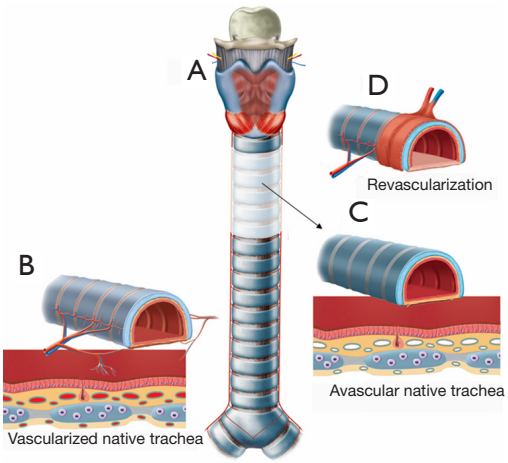

Figure 3 Blood supply and tracheal transplantation. (A,B) Blood supply in the healthy native trachea is ensured by a network of small blood vessels that penetrate the trachea between the cartilage rings. (C) Prelevation of a tracheal segment inevitably leads to interruption of its blood supply. Successful transplantation requires restoration of an adequate blood supply (as in B), which is an extremely difficult process. (D) De-vascularized tracheal segments can become revascularized in a heterotopic position. Direct orthotopic transplantation of the trachea is not possible regardless of whether the trachea is enwrapped with vascularized tissue. In humans, revascularization of the membranous trachea is difficult because the trachealis muscle forms a barrier for mucosal revascularization. Heterotopic tracheal revascularization safely occurs after excision of the membranous trachea (D).

target cell population was the allograft endothelium (6). In 2008, we attempted tracheal allotransplantation in the clinic.

Learning curve of tracheal allotransplantation

In 2008, we were confronted with a difficult clinical case of long-segment stenosis. Tracheal allotransplantation was considered as a possible solution for the patients' problem. Successful transplantation of a patch tracheal allograft was performed. The procedure involved the following key steps: (I) heterotopic revascularization of the cartilaginous trachea at the forearm under protection of immunosuppressive therapy; (II) replacement of the donor respiratory epithelium by recipient buccal mucosa; (III) withdrawal of immunosuppressive therapy; and (IV) orthotopic transplantation, with anastomosis of the radial vascular pedicle to blood vessels of the neck. Withdrawal of immunosuppressive drugs was possible because of the immune-privileged status of chondrocytes within the cartilage rings. As they are protected within a matrix, chondrocytes will remain vital if they are perfused by diffusion through recipient blood vessels from surrounding tissues (7,8).

Based on our experiences obtained in this first patient, we proposed the concept illustrated in *Figure 4* for subsequent patients (8,9).

This concept was applied in six patients, including five patients with long-segment stenosis and one patient with a low-grade tracheal chondrosarcoma (9,10). The patient with chondrosarcoma was a 63-year-old man whose tumor developed over a period of more than 10 years. His airway was preserved by placement of a silicone stent. Due to stagnation of secretions, he required periodical bronchoscopic cleaning of the stent. However, he developed acute episodes of stent blockage, which made definitive treatment necessary. Four months after implantation of a suitable allograft in the left forearm (*Figure 5*), the tumor was resected through an anterior cervical incision with a sternotomy extension (*Figure 6A,B,C,D*). The tracheal allotransplant was used to repair the laryngotracheal defect.

The potential for tumor progression while under immunosuppression for a low-grade malignancy was considered to be low. Computed tomography (CT) scan at the time of orthotopic transplantation demonstrated a nearly unchanged tumor bulk. Immunosuppressive medication was gradually phased out 11 to 12 months after orthotopic transplantation. The morphology of the transplant remained intact after withdrawal of immunosuppressive therapy (*Figure 6E,F,G,H*). Thus, it seems that mucosal repopulation of the transplant after cessation of immunosuppressants can occur with minimal loss of airway lumen.

Optimal tracheal allotransplantation concept

The major drawback of this transplantation concept is the long period of donor mucosal revascularization and regeneration. It takes 2 to 3 months before full mucosal regeneration is established. Moreover, both edges of the transplant are at risk of necrosis, with loss of some of the circumference of the cartilaginous trachea. In one of our patients, we made the seminal observation that the revascularization phase could be shortened from 2–3 months to 2 weeks when the luminal surface of the

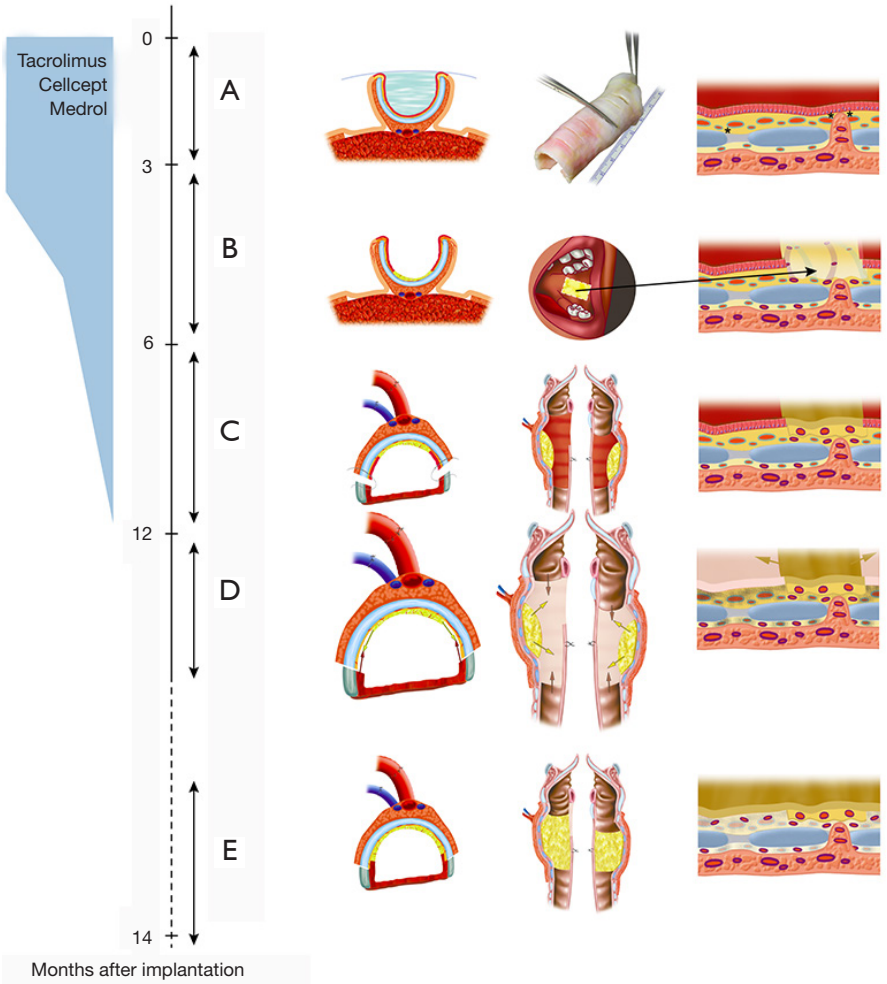

Figure 4 Time line for tracheal allotransplantation. Timeline for clinical procedure (left), key surgical steps (middle), and postulated processes of revascularization, tissue rejection, and regeneration (right). Timeline (in months) shows the principal procedural steps (A-E) and timing of immunosuppression (tacrolimus 9 mg/d, CellCept 2 g/d, medrol 24 mg/d). (A) Heterotopic allograft revascularization. Freshly harvested tracheal allograft is wrapped with fascia and subcutaneous tissue on the radial side of the forearm. Fibrin glue (light blue) on the luminal side prevents the mucosa from drying. Before implantation, partial incisions are made in alternating anterior intercartilaginous spaces. Recipient blood vessels (purple lining) from forearm tissues mediate vascular induction of donor blood vessels (blue lining) in the adventitia, which, in turn, mediate vascular induction of donor blood vessels in the submucosa, either through intact intercartilaginous ligaments (*) or direct contact in areas where ligaments are incised (**). Revascularization allows the donor respiratory mucosa to regenerate, a process that is complete within 3 months. (B) Implantation of recipient buccal mucosa. Once the graft is fully revascularized, the central portion of the respiratory donor mucosa is removed and replaced with a graft from the recipient's mouth mucosa (yellow). Angiogenesis occurs with ingrowth of recipient blood vessels from the surrounding forearm tissues into the mucosal space of the transplant, through intercartilaginous ligament incisions. (C) Orthotopic vascularized transplantation. After ingrowth of the recipient mucosal graft, the revascularized tracheal graft can be transplanted orthotopically with its newly created vascular pedicle to repair the airway defect (illustrated in a sagittal laryngotracheal view). Immunosuppressive medication is gradually phased out and stopped at 1 year (blue bar). (D) Allorejection of donor noncartilaginous tissues. Withdrawal of immunosuppression provokes immunologic rejection of residual donor mucosal tissues, with inflammatory infiltrates, vascular thrombosis, and necrosis of the mucosal layer. We postulate that the donor cartilage is immune-privileged and not susceptible to allorejection. Noncartilaginous tissues are replaced via outgrowth of the recipient buccal mucosa (yellow arrows) and recipient respiratory mucosa at the anastomotic sites (brown arrows). (E) Replacement of noncartilaginous recipient-type tissues. Situation after healing of rejected donor mucosal lining.

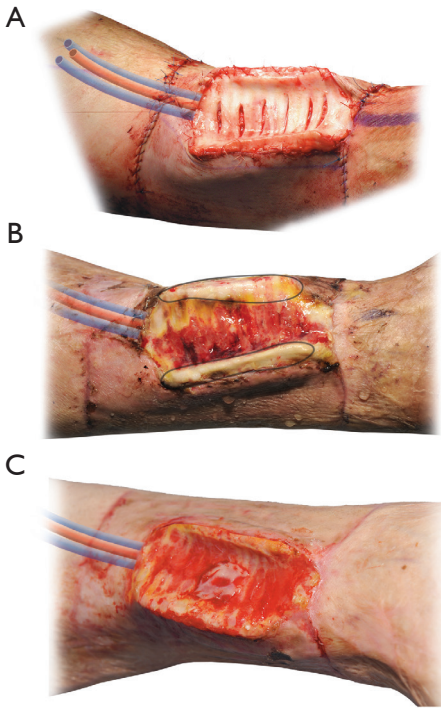

Figure 5 Heterotopic revascularization of the tracheal allograft. (A) At forearm implantation, incomplete incisions of the intercartilaginous ligaments are made to promote ingrowth of recipient blood vessels into the submucosal space of the transplant; (B) situation after 1 month. Mucosal revascularization and regeneration are apparent. Edges (black lines) of cartilaginous tracheal transplant are at risk of necrosis; (C) situation after 2 months. Buccal mucosal graft is sutured into midportion of transplant after removal of donor mucosa. Radial artery and veins at the proximal site of the transplant are depicted.

transplant was covered with well-vascularized tissue (*Figure 7*).

Our observation of the importance of covering the luminal site of the transplant with well-vascularized tissue led us to adapt our original transplantation concept. In subsequent patients, our goal has been to cover the luminal surface of the transplant as much as possible with the distal part of the radial forearm fascia flap (*Figure 8*).

Conclusions

We were the first to report a successful orthotopic allotransplant in 2010, using a novel protocol involving a controlled process of progressive vascularization, rejection of allogeneic mucosa, and preservation of the viability of the cartilage, which is otherwise immune-privileged. Our observations suggest that this unique vascularized transplantation technique with temporary immunosuppression generates a chimeric trachea, and that the immune-privileged nature of the cartilage has a central role of this process (7,8). The technique holds great promise for patients needing extensive airway reconstruction because the chimeric trachea graft does not require ongoing immunosuppression, a highly desired but elusive goal in the field of allotransplantation.

This technique was developed on the basis of animal research (6,7) and autotransplantation experience (11-13). It was further refined in a series of six patients (9,10). Through our experiences, we learned that vascular induction of the submucosal blood supply during graft revascularization is a different process from true angiogenesis (*Figure 3*) (9). Vascular induction of donor mucosal capillaries by recipient blood vessels around the transplanted tissue may occur through the intercartilaginous ligaments. In contrast, true angiogenesis with repopulation of the submucosal space by ingrowing recipient blood vessels is only possible in areas where the recipient blood vessels are in direct contact with the submucosal layer of the graft. Therefore, the most important adaptation was to allow for growth of recipient blood vessels in the submucosal space of the graft. This growth could be guaranteed by making partial incisions through the intercartilaginous ligaments. These incisions disrupted the barrier for angiogenetic outgrowth of recipient vessels and enabled ingrowth of recipient vessels into the submucosal space of the transplant (9).

Another important factor was the implantation of a recipient buccal mucosal graft in the central portion of the transplant (*Figure 3*). Buccal mucosa was chosen because respiratory mucosa is difficult to handle as a free graft. After ceasing immunosuppressive therapy, all donor respiratory epithelium will disappear, and the buccal mucosal graft will progressively grow and recover part of the surrounding transplant's inner lining. At transplant sites lined with nonciliated squamous epithelium, the loss of mucociliary clearance will be compensated through coughing.

With the intercartilaginous incisions and the recipient buccal mucosa, immunosuppressive medication could be safely tapered and stopped 9 to 12 months after forearm implantation (9). Cartilage tissue escaped immunologic rejection owing to the absence of blood vessels and the protection of chondrocytes within a matrix (8). After cessation of immunosuppressive therapy, the surviving recipient mucosal graft will allow for secondary healing of

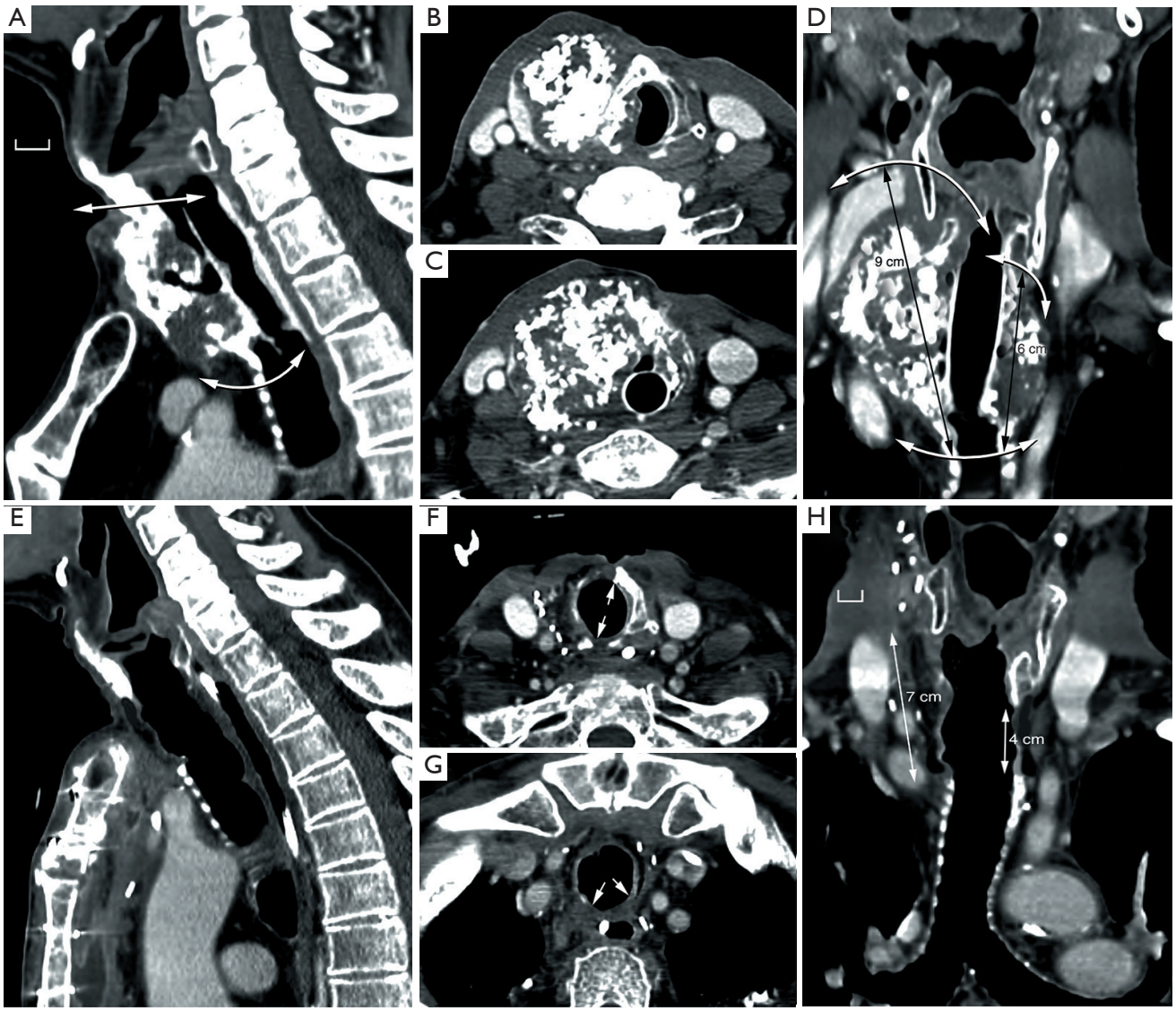

Figure 6 CT scan of tracheal chondrosarcoma before and after transplantation. Upper panel (A-D): before transplantation. Tumor extent is shown on sagittal (A), axial at subglottic (B), and tracheal (C) levels, and on coronal (D) section. Airway lumen is bridged by a silicone stent. Degree of resection is indicated with white two-headed arrows. Lengths of tracheal resection were 9 cm (right) and 6 cm (left) (scale: 1 cm). Lower panel (E-H): CT scans 2 years after orthotopic transplantation and 1 year after withdrawal of immunosuppressive drugs. Note the absence of cartilage calcification in the allotransplant (scale: 1 cm). (E) Sagittal reformatted CT scan. (F) Axial CT scan at laryngeal level. (G) Axial CT scan at level of cervical trachea. (H) Coronal reformatted CT scan. CT, computed tomography.

the necrotic areas of donor epithelial lining (9).

The trachea is transplanted as a composite tissue, but the cartilage structure is the critical functional element of the graft. Cartilage is avascular, relies on indirect nutrition from the surrounding tissues, and is well known to be immune-privileged (8). The ingenious revascularization procedure, along with carefully timed immunosuppression, takes advantage of these unique properties so as to preserve the tracheal cartilage tissue and structure, while noncartilaginous tissues are replaced by recipient tissues.

Going forward, our principal objective is to optimize the revascularization process, thereby reducing the heterotopic

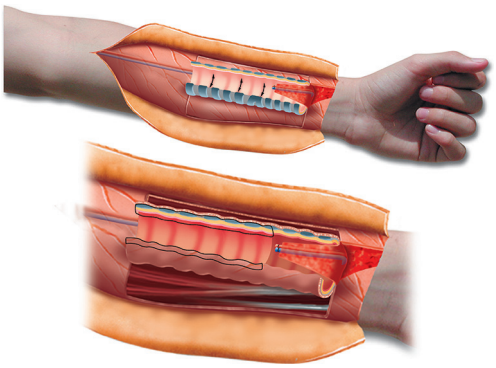

Figure 7 Coverage of distal segment of transplant with radial forearm fascia. (A) In one of our patients, the distal part of radial forearm fascia was dissected and turned over the distal part of the transplant. Double arrows indicate incised intercartilaginous ligaments; (B) distal part of tracheal allograft [2] showed full revascularization and donor mucosa regeneration after only 2 weeks. Middle and proximal sections of transplant [1] needed 2 months for full revascularization. Black lines indicate edges of transplant, which are at risk of necrosis.

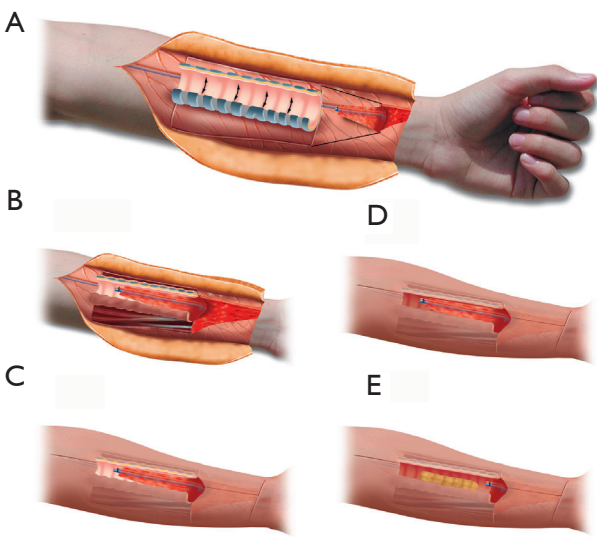

Figure 8 Optimal protocol for patch tracheal reconstruction. (A-C) Allotransplant is implanted in a more proximal position so that a larger amount of distal fascia becomes available for covering of the luminal site of the transplant. Double arrows indicate intercartilaginous incisions; (D) coverage of the luminal site of the transplant with well vascularized tissue guarantees a fast mucosal revascularization and regeneration; (E) after revascularization, a buccal mucosal graft from the recipient is implanted in the central portion of the allograft. After ingrowth of the buccal mucosal graft, the inside rotated portion of the fascia flap is removed from the luminal site of the transplant.

grafting and immunosuppression phases. Specifically, instead of using fibrin glue, we plan to cover the luminal site of the heterotopic trachea with the distal part of the radial forearm fascia flap.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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