Autologous tracheal replacement: From research to clinical practice

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Summary

Background > Despite numerous attempts, synthetic materials and heterologous tissues failed to replace durably the trachea. Autologous tracheal substitution (ATS) without synthetic material or immunosuppression was investigated to replace extended tracheal defect. We present our experience regards to this innovative challenge.

Method > After a previous research study, we developed a novel reconstruction technique for extended tracheal defects on animals. Through a single stage operation, a tube from a forearm free fascio-cutaneous flap vascularized by radial vessels is re-anastomosed to cervical vessels. This flap is reinforced by rib cartilages interposed transversely in the subcutaneous tissue. It provides also a reliable ATS. Twelve patients benefits from an extended tracheal resections, 7–12 centimeter (mean 11 cm) long. Indications were eight Primary tracheal Neoplasms (including 5 adenoid cystic carcinoma [ACC] and 3 squamous cell carcinoma [SCC]), three secondary tracheal neoplasms (including 1 thyroid carcinoma and 2 lymphoma) and one post-intubation tracheal destruction after long history of stenting. Daily bronchoscopy and transitory trachetomy was associated due to absence of mucociliary clearance.

Results > The research work leads to present the first described animal model for tracheal resection and replacement with an autologous conduit. It was constructed from costal cartilages and a pediculed cervical skin flap. From 2004 to 2012, 12 patients have had ATS with associated resections in four cases. All patients were extubated on the first postoperative days; eight patients are alive at 2 to 94 months (mean = 36) postoperatively, with no respiratory distress. The two patients with ATS after resection extended to the carina died due to pulmonary infection. No airway collapse has been detectable, either by endoscopy, dynamic CT scan or spirometry. Two patients still have a tracheotomy because performed too low at the level of the proximal anastomosis. One patient with a chronic severe respiratory insufficiency required recently a distal and short stent.

Conclusion > ATS is actually a good, durable tracheal substitute that can resist respiratory pressure variations because of their transverse rigidity without any immunosuppression. The limits of this technique are probably, chronic respiratory insufficiency and cartilage calcifications. Research to develop a method for lining the neo-trachea with ciliated respiratory epithelium is needed.
Primary tracheal neoplasms (including Adenoid Cystic Carcinomas [ACC], Squamous Cell Carcinomas [SCC] and other tracheal diseases) can be usually managed by tracheal resection with primary anastomoses [1]. The maximum length of tracheal resection that can be resected and repaired by end to end anastomosis is 6 cm. However, there are diseases that require resection of segments of trachea longer than 6 cm that require reconstruction with a tracheal substitute. Efforts to address the problem of > 6 cm tracheal resection with reconstruction have unsuccessfully employed prostheses [2]. Among the first such attempts was the prototype of Neville [3]. There being no safe and effective tracheal prosthesis, stents have been used seeking to provide an adequate airways [4,5]. However, stents are of limited value because they are associated with the risk of erosion into mediastinal and cervical blood vessels and catastrophic haemorrhage [6,7].

Another solution could be transplantation of heterologous tissue [8]. However, the need for long term immunosuppression would be a decided disadvantage to this approach. Although orthotopic tracheal allotransplantation with eventual withdrawal of immunosuppressive therapy might be good for patients with benign long-segment tracheal stenosis, this approach would not be attractive to treat patients with cancer [9]. Autologous tubular conduits constructed from small bowel, oesophagus, skin or the aorta generally become obstructed because they are not capable of withstanding the normal pressure variations of respiration [2]. When the aorta was used as a tracheal substitute, there was erosion into mediastinal structures such as the oesophagus and surrounding vessels [10, 11]. Moreover, previously tried autologous tracheal substitutes and stents have generally been associated with pooling of bronchial secretions and serious infections [12–14]. Nowadays, the attractive concept of bio-engineered tracheal replacements has not yielded a reliable solution [15].

After laboratory research on animals, we started tracheal replacement using reliable autologous free fasciocutaneous flaps reinforced with autologous cartilage struts. The flaps meet the requirement for an epithelial surface, and the cartilage provides transverse rigidity [16,17]. We report the first autologous tracheal substitution (ATS) without synthetic material or immunosuppression and report our experience.

Methods

Preliminary research

In a large-animal study, we previously report the development of an autologous tracheal substitute for long-segment tracheal resection that satisfies the criteria defined by Grillo. We demonstrate excellent short-term functional results [17]. Airway reconstruction was performed using autologous pedicled cervical skin flaps scaffolded with costal cartilages. This preliminary study demonstrates excellent respiratory function and short-term survival in pigs undergoing resection of more than 50% of their native trachea. Use of cervical skin flaps buttressed with costal cartilage seems also to be a promising solution for long-segment tracheal replacement, but the cervical skin flap is probably not suitable in clinical practice because the cervical skin in human subjects is less extensive than that in pigs, in which the neck area is larger and shorter. For human tracheal replacement, we plan to use a free skin flap with its own arterial and venous vascularization. The blood supply to this free flap will be carried by performing arterial and venous microvascular anastomoses with a cervical vascular pedicle. Also, in human subjects it can be a free forearm skin flap pedicled on the radial artery and vein. These small vessels could then be anastomosed to the cervical artery and vein.

Patient selection for ATS

Between August 2004 and September 2012, this single-center retrospective study consisted of 12 consecutive patients selected from a population of patients with an extended primary tracheal neoplasm, a secondary tracheal neoplasm or an extended tracheal destruction at Marie Lannelongue Hospital. Two surgical teams from Gustave Roussy Institute (Plastic and reconstructive surgery) and from Marie Lannelongue Hospital (Department of Thoracic and Vascular Surgery and Heart-Lung Transplantation) were associated for those operations. The medical records of these patients were reviewed retrospectively to determine the age, sex, histology, preoperative medical history, pulmonary function test, performance, laboratory tests, tumor location, vocal cords function, and cardiac function. The diagnostic staging modalities included bronchoscopy, computed tomography (CT) scanning, and positron emission tomography-computed tomography (PET-CT). These were performed initially and preoperatively, or whenever there was a suspicion of disease recurrence. The resection margin after tracheal resection was also determined (R0, no residual tumor; R1, microscopic residual disease; R2, macroscopic residual disease).

The immediate postoperative outcomes, namely the durations of postoperative mechanical ventilation, intensive care unit, and postoperative hospital stay, were obtained from hospital records. Data on the postoperative complications, 30-day mortality (surgical mortality), and 90-day mortality (in-hospital mortality), were also collected. Long-term outcomes were evaluated by respiratory function, vocal cords function, overall survival and recurrence. Overall survival (OS) was defined as the time from surgery to death due to any cause in patients who underwent surgery only for cancer. The probability of survival was estimated according to the Kaplan-Meier method. All statistical analyses were performed by using the Statistical Package for the Social
Science (SPSS, Chicago, IL) version 18.0. All tests were 2-sided, with 0.05 serving as the level of significance.

**Resectability**
Locoregional and distant metastatic disease before resection were assessed. Bronchoscopy was performed before resection to assess the presence and extent of luminal invasion. For SCC, patients with N2 disease were excluded for ATS using preferentially EBUS or mediastinoscopy. Tracheal resection was considered when complete resection of gross airway disease appeared feasible. Symptoms caused by airway obstruction or hemoptysis were an indication for resection. A tumor was considered unresectable when advanced metastatic disease was present or in case of invasion of vital adjacent organs. The length of involved airway at bronchoscopy precluded the ATS reconstruction that is limited to 12 centimeters.

**Extended tracheal resection**
Carcinologic tracheal resection was performed for primary and secondary tracheal neoplasms. When preoperative unilateral vocal cord paralysis was present, the contralateral recurrent nerve was firstly dissected. The invasion of both recurrent nerve leads to a laryngotracheal resection. For laryngotracheal resection, the tumor was removed with the larynx, and the entire trachea was reconstructed with ATS. Invasion of oesophageal muscle or mucosa was treated with resection of full-thickness wall. Intestinal substitution was performed after the ATS procedure if needed. Locoregional lymph nodes were resected. Absence of tumor at the airway margins was confirmed by frozen section unless the limits of resection had been reached and no additional trachea could be removed without sacrificing the larynx. The resection was judged to be complete when the airway margins were found to be free of disease, the soft tissue margins were not grossly involved with the tumor, and no statement in the operative note indicated that gross tumor remained.

**Tracheal reconstruction**
The neo-tracheal conduit is constructed from a large, rectangular fasciocutaneous flap harvested from the patient’s forearm. The skin of this flap is rotated around a silicone tube, the diameter of which is approximately slightly larger than that of the normal trachea. The tubular conduit, supplied by the radial artery and vein, is made of skin along its inner aspect and of fascia in its outer aspect. Before transforming the fasciocutaneous rectangle into a tube by suturing the main lengths together, several costal cartilage segments obtained from the patient’s rib cage are inserted between skin and fascia in the subcutaneous tissue to ensure the transverse rigidity of the tube. The flap pedicle will be divided only immediately after its final implantation in the chest cavity to minimise the flap ischemic time.

Before completing the construction of the neo-tracheal conduit, the damaged trachea is approached by cervicotomy and median sternotomy. The diseased trachea is resected on healthy margins and the autologous conduit sutured to the native tracheal stumps (ie, to the tracheobronchial bifurcation below and to the larynx above). If necessary, in addition to removing the trachea, partial or total resection of the oesophagus and removal of one of the recurrential nerves and possibly of the adjacent vascular structures can be necessary. Revascularisation of the flap is provided by microanastomoses. Careful calibration of the conduit proved necessary to counteract narrowing of the neo-tracheal lumen due to flap oedema and high inspiratory negative pressures generated by bronchial congestion and laryngeal oedema. In case of main bronchi involvement, ATS was performed using the same forearm free flap shaped with a bifurcation and reinforced with cartilage ribs on both sides.

**Postoperative course and follow-up**
During the first two weeks, the airway stent is removed by interventional bronchoscopy. In all instances, the flaps were endoscopically checked once daily for satisfactory healing of the anastomoses and viability. Frequent bronchoscopies were needed to clear retained secretions. Usually, a transitory tracheotomy was associated due to absence of muco-ciliary clearance. CT scan with dynamic axial and sagittal image reconstruction was performed to verify the patency of the flap blood supply, the viability of the cartilaginous framework and the resistance to airway collapse. Patients were followed and controlled with bronchoscopy at 1 month, 6 months, 1 year and every year. An adjuvant treatment was associated in case of R1 resection for ACC on the proximal and distal anastomosis.

**Results**
The characteristics of 12 patients are listed in table 1 according to the type of resection and ATS. Indications were eight primary tracheal neoplasms (including 5 ACC and 3 SCC), three secondary tracheal neoplasms (including 1 thyroid carcinoma and 2 tracheal lymphomas) and one post-intubation extended tracheal destruction after long history of stenting. With a mean age of 50.6 years (range from 37 to 68 years), the lengths of the tracheal involvement leads to mean length of tracheal resection of 10.5 cm (range from 8 to 12 cm). Full-length resection from the first cartilaginous ring to the carina was required in five patients with an extended circular tracheal resection (41.6%). For two patients, tracheal resection included the carina and both main bronchi; one of these patients also needed a right upper lobectomy (RUL). Total laryngectomy with ATS was performed in three cases. Two patients with extended TEF required complete removal of the membranous
<table>
<thead>
<tr>
<th>Table I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathology and resection type</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>(years)</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
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<td>10</td>
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<tr>
<td>11</td>
</tr>
<tr>
<td>12</td>
</tr>
</tbody>
</table>

ACC: adenoid cystic carcinoma; F: female; ICU: intensive care unit; M: male; SCC: squamous cell carcinoma; TOF: tracheo-oesophageal fistulae; TPLG: total pharyngolaryngectomy.
## Table II
Reconstruction and postoperative course

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Reconstruction procedure</th>
<th>Procedure date</th>
<th>Carinal reconstruction</th>
<th>Time to first extubation</th>
<th>ICU discharged</th>
<th>Major postoperative complications</th>
<th>Endotracheal stenting/tracheotomy</th>
<th>Survival (months)</th>
<th>Status</th>
<th>Adjuvant treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Double FFF for tracheal and oesophageal reconstruction (12 cm trachea)</td>
<td>Aug 2004</td>
<td>–</td>
<td>8 hours</td>
<td>10 days</td>
<td>–</td>
<td>No/No</td>
<td>101</td>
<td>Alive</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Reinforced FFF (8 cm trachea)</td>
<td>Sept 2006</td>
<td>–</td>
<td>12 hours</td>
<td>50 days</td>
<td>ARDS</td>
<td>No/No</td>
<td>75</td>
<td>Alive</td>
<td>Iodine 131</td>
</tr>
<tr>
<td>3</td>
<td>Reinforced ALFF (12 cm trachea)</td>
<td>July 2007</td>
<td>–</td>
<td>12 hours</td>
<td>40 days</td>
<td>ARDS</td>
<td>No/Yes</td>
<td>66</td>
<td>Alive</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Reinforced bifurcated FFF (10 cm trachea and both main bronchi)</td>
<td>March 2008</td>
<td>+</td>
<td>Not extubated</td>
<td>23 days</td>
<td>ARDS</td>
<td>No/No</td>
<td>0.8</td>
<td>Dead</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>Reinforced bifurcated FFF (8 cm trachea and both main bronchi)</td>
<td>Feb 2009</td>
<td>+</td>
<td>Not extubated</td>
<td>41 days</td>
<td>ARDS treated with a veno-venous ECMO</td>
<td>No/No</td>
<td>1.4</td>
<td>dead</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>Reinforced FFF (12 cm trachea)</td>
<td>Aug 2009</td>
<td>–</td>
<td>6 days</td>
<td>25 days</td>
<td>–</td>
<td>No/No</td>
<td>41</td>
<td>Alive</td>
<td>RT</td>
</tr>
<tr>
<td>7</td>
<td>Reinforced FFF (10 cm trachea) and TOF closure</td>
<td>March 2010</td>
<td>–</td>
<td>12 hours</td>
<td>40 days</td>
<td>ARDS</td>
<td>Yes/No</td>
<td>34</td>
<td>Alive</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>Reinforced FFF (12 cm trachea)</td>
<td>December 2010</td>
<td>–</td>
<td>12 hours</td>
<td>21 days</td>
<td>–</td>
<td>No/No</td>
<td>16</td>
<td>Dead</td>
<td>RT</td>
</tr>
<tr>
<td>9</td>
<td>Reinforced FFF (12 cm trachea)</td>
<td>March 2011</td>
<td>–</td>
<td>5 days</td>
<td>30 days</td>
<td>ARDS</td>
<td>No/No</td>
<td>20</td>
<td>Alive</td>
<td>RT</td>
</tr>
<tr>
<td>10</td>
<td>Reinforced FFF (10 cm trachea)</td>
<td>July 2011</td>
<td>–</td>
<td>5 days</td>
<td>80 days</td>
<td>ARDS</td>
<td>No/Yes</td>
<td>18</td>
<td>Alive</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>Reinforced FFF (12 cm trachea)</td>
<td>April 2012</td>
<td>–</td>
<td>2 days</td>
<td>24 days</td>
<td>Brachio-cephalic artery rupture</td>
<td>No/No</td>
<td>6</td>
<td>Dead</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>IMAP Flap</td>
<td>Sept 2012</td>
<td>–</td>
<td>8 hours</td>
<td>5 days</td>
<td>–</td>
<td>No/No</td>
<td>4</td>
<td>Alive</td>
<td>–</td>
</tr>
</tbody>
</table>

ALFF: antero lateral thigh free flap; ARDS: acute respiratory distress syndrome; ECMO: extra corporeal membrane oxygenation; FFF: Forearm free flap; ICU: intensive care unit; IMAP: intercostal mammary artery perforating; RUL: right upper lobectomy; TOF: tracheo-oesophageal fistulae.
part of the trachea and ATS. Overall results are summarized in table II.

Postoperative course and follow-up
All flaps remained viable; the cartilaginous framework prevented inspiratory collapse. All patients presented almost one pulmonary infection treated with antibiotics. Two patients suffered pneumonia and ARDS after replacement of the trachea and the main bronchi. One of them was treated with a venovenous ECMO. Even for this complicated cases, the flaps remained viable and functional until the patients died from respiratory infection and excessive bronchial congestion. Eight patients are currently alive, without respiratory dysfunction, living normal lives 101, 75, 66, 41, 34, 20, 18 and 4 months post-operatively. Two patients died of cancer recurrence at 6 months and of lung metastases at 16 months after surgery.

One patient with a chronic severe respiratory insufficiency required a distal and short stent and two others have a permanent tracheostomy. In one of them with a severe respiratory insufficiency, the lumen collapse is related to a break of the calcified rings of costal cartilage in the other one at the level of the postoperative tracheostomy which was performed through the upper airway anastomosis.

The two patients who complained of dysphagia before the procedure due to extensive esophago-tracheal fistulas were able to resume oral feeding after surgery. Repeat endoscopy and dynamic CT scan demonstrated satisfactory patency of the neo-trachea without inspiratory collapse both during the immediate postoperative period, when the respiratory cycle increases the endoluminal negative pressure, as well as at several years after the procedure (figure 1). The Kaplan-Meier Survival analysis for 11 patients with cancer indicates a 64.8% of survival at 5 years.

The viability of the cartilaginous structure of the neotrachea was confirmed by its uptake of iodinated contrast medium very early after surgery and at a post-surgical follow-up. Furthermore, three patients with adenoid cystic carcinoma underwent adjuvant radiotherapy with no adverse effect on the flap. One patient with thyroid carcinoma underwent adjuvant radioactive iodine ablation therapy. All living patients have complete remission of their cancers.

Discussion
Tracheal surgery remains the mainstay of therapy for several airway diseases. Management of both benign and malignant tracheal diseases often requires long-segment replacement of portions of the trachea. Therefore, transplantation of re-vascularized tracheas merits consideration [9]. With an active lung transplantation program, we have previously reviewed tracheal transplantation [8]. However, we believed that tracheal allotransplantation would be too difficult, and that the need for long-term immunosuppressive therapy mitigated against the use of tracheal transplantation [8,18]. Prosthetic and composite devices for tracheal substitution have been unsuccessfully tried since the 1960s leading to granulomas, airway obstruction, and fistula. They always become infected, and not infrequently they may eventually erode into the adjacent organs [19,20]. Arguably, stented fresh aortic allografts merit consideration [21–23]. Tsukada et al. reported tracheal replacement with a silicone-stented fresh aortic allograft in sheep [21]. Like Kim et al., Tsukuda et al. concluded that this type of tracheal substitute appears to be unsuitable for primary tracheal replacement because it is associated with important shortening of the tracheal graft area, at times up to 87.5% within one year [21,24]. The findings of Wurtz et al. similarly speak against the use of composite grafts that include fresh or banked aortic allografts [11]. They reported three of six patients whose aortic allograft tracheal replacements eroded into the oesophagus and one patient who suffered vascular erosion. Thus, we believe this technique, with a mortality of about 50%, should not be used for tracheal replacement [10,11,25]. In our opinion, as recommended by Dr Grillo, a satisfactory tracheal replacement must provide the following [26]:

- resistance to airway collapse. The cross sectional area of the graft conduit must be transversely rigid to resist negative intraluminal pressure generated by inspiration and positive intrathoracic pressure developed during expiration;

Figure 1
Computed Tomography Scan reconstruction at 1 year.
Extended tracheal resection and autologous tracheal substitution with free flap skin flap and costal cartilages (black arrows).
• immunologic tolerance. Autologous tissue is not rejected because of incompatibility between the host and the graft;
• mechanical tolerance by adjacent structures. A fasciocutaneous free flap structurally reinforced with costal cartilage that has an abundant blood supply fills the mediastinal gap that results from tracheal resection without inducing mediastinitis or eroding into the neighboring blood vessels or oesophagus. Furthermore, its ample blood may reduce risks from adjuvant radiation therapy when such is indicated;
• pliability of soft tissue in the graft. Free fasciocutaneous flaps are thinner than musculocutaneous flaps. When they come from the radial forearm they have a thinner layer of subcutaneous tissue as compared to fasciocutaneous flaps from the thigh. In addition, the long vascular pedicle of radial forearm flaps greatly enhances the ease and reliability with which the flap can be transferred into the narrow passage between the neck and the chest cavity;
• structural integrity to withstand airway pressure changes. Rigid transverse support to the fasciocutaneous tube is provided by rib cartilage rings implanted into the subcutaneous tissue as close as possible to the dermis so that the tissue layer located between the cartilage. The skin surface is too thin to be drawn into the lumen of the neo-trachea and it is not separated from the cartilage when the pressure drops during inspiration. This rigid transverse scaffolding located within the wall of the fasciocutaneous conduit can withstand both the external pressure applied during expiration and the pressure drop during inspiration. Conversely, scaffoldings located outside the tube, such as metallic grids, prevent tube collapse during expiration but offer no resistance against the inspiratory pressure drop. This results in the tracheal wall being drawn into the lumen. Intraluminal silicone-coated stents are foreign bodies and consequently carry a risk of infection; furthermore, crusting of the stent with dried secretions occurs, requiring repeated stent changes [19,27]. In our patients, during the immediate postoperative period, edema usually developed in the conduit, thus causing temporary narrowing of the lumen during inspiration, most notably when the cartilage rings in the subcutaneous tissue were located too far from the dermis. Consequently, the conduit should be fashioned to a diameter that is slightly greater than that of the normal trachea, and an intraluminal silicone-coated tube should be left in place for a few days until resolution of the edema and the development of mild subcutaneous tissue sclerosis;
• epithelium lining of the tracheal replacement. As all body surfaces in contact with the outside air or fluid medium, the tracheal replacement should be lined on its inner aspect by respiratory epithelium, which per se can play a crucial role against infection. Bronchial secretions must be swept up to the pharyngolaryngeal junction to be cleared by expectoration or ingestion. Therefore, the ideal neo-trachea should have a ciliated respiratory type epithelium allowing mucociliary clearance of bronchial secretions.

Limitations of the technique and future developments

The main limitation of the neo-trachea we have created is the absence of mucociliary clearance because of its lining by squamous epithelium. Recent experimental evidence seems to address the absence of mucociliary clearance by replacing the cutaneous epithelium with a ciliated lining obtained by cultures lines of nasopharyngeal epithelium [28].

Why did two of our patients die? We believe their fatal pneumonia may have resulted from their extensive replacement of the trachea and main bronchi and the absence of mucociliary clearance. Thus, for the time being we shall defer using this technique when the need for resection and replacement extend beyond the trachea itself. Moreover, the absence of mucociliary clearance within the neo-tracheas requires aggressive management of bronchial secretions. At times one must resort to a temporary inter crico-thyroid tracheotomy, in addition to daily fiberbronchoscopies, bacteriological sampling and postural drainage. We also believe that the tracheal replacement method we have successfully used for 6 patients should for the time being not be employed for patients who lack excellent diaphragmatic and respiratory mechanical function that makes them capable of effective coughing.

Conclusion

Preliminary research studies tend to find a highly resistant tracheal substitute. Advances in reconstructive surgery offers a novel field in surgery. The association between plastic and thoracic surgery tried to develop a totally autologous substitute. With his own vascularization, this ATS is also resistant to infection. It is transversally rigid to resist respiratory pressure variations. The major advantage is that there is no endoluminal stenting. On the other hand because of the absence of a mucociliary clearance of the skin epithelium, transitory tracheostomy and postural drainage are always mandatory. We have shown that extensive tracheal diseases previously not amenable to tracheal replacement can now be successfully managed with the use of totally autologous conduits made of fasciocutaneous free flaps reinforced by costal cartilages. This ATS has nearly all the qualities of the ideal tracheal substitute. The absence of a ciliated epithelial lining to provide mucociliary clearance remains a limiting aspect of this method. Whereas excellent results can be achieved with autologous neo-tracheal, fascio-cutaneous-cartilage supported sotologous tube grafts, we currently do not recommend this method to treat lesions that extend...
to the main bronchi or for patients with pulmonary and diaphragmatic dysfunction of sufficient magnitude to interfere with effective coughing. The limits of this technique are probably, chronic respiratory insufficiency and cartilage calcifications. Research to develop a method for lining the neo-trachea with ciliated respiratory epithelium is needed.

**Disclosure of interest:** the authors declare that they have no conflicts of interest concerning this article.

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## References


