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Tracheobronchial Replacement
A Systematic Review

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IMPORTANCE Tracheobronchial replacement remains a surgical and biological challenge despite several decades of experimental and clinical research.

OBJECTIVE To compile a comprehensive state-of-the-science review examining the current indications, techniques, and outcomes of tracheobronchial replacement in human patients.

EVIDENCE REVIEW A systematic review of the literature was conducted on July 1, 2024, to identify studies examining tracheobronchial replacement. This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines and the PRISMA 2020 statement. We selected the following 3 databases: (1) PubMed via the US National Library of Medicine's PubMed.gov; (2) Embase via Elsevier's Embase.com; and (3) the Cochrane Central Register of Controlled Trials (CENTER) via Wiley's Cochrane Library. An additional search was performed using the following clinical trials registers: the World Health Organization's International Clinical Trials Registry Platform and ClinicalTrials.gov, provided by the US National Library of Medicine.

FINDINGS The initial search produced 6043 results, with a total of 126 publications included in the final review. Only 1 prospective cohort study and 1 registry, both concerning the use of cryopreserved aortic allografts, were identified. Most publications were case reports and series. From July 1, 2002, to July 1, 2024, a total of 137 cases of tracheobronchial replacement were published. Tracheobronchial replacement was indicated for extensive neoplastic tumors (108 cases [78.8%]) or benign stenoses (29 cases [21.2%]). The most common malignancies were thyroid cancers and adenoid cystic carcinomas. The most frequent resections involved the upper half of the trachea, with reconstructions using muscle flaps, or, most notably, cryopreserved aortic allografts, which have shown promising outcomes and have become the most widely used method since 2022. In the only available registry, the 30-day postoperative mortality and morbidity rates were 2.9% and 22.9%, respectively. Long-term follow-up showed that mortality was related to local recurrences and metastases in patients with cancer.

CONCLUSIONS AND RELEVANCE This systematic review indicates that extensive malignant lesions are the primary indication for tracheobronchial replacement, with cryopreserved aortic allografts being the only scientifically evaluated surgical technique. Postoperative outcomes were comparable to other major thoracic surgical procedures, while long-term results depended on the underlying disease, especially in cancer cases.

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Supplemental content

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At a time when organ transplantation is routinely performed, tracheobronchial replacement remains a significant surgical and biological challenge, despite several decades of intensive experimental and clinical research. Tracheobronchial replacement can be indicated for patients with benign or malignant diseases who have reached a therapeutic dead end, either initially or after 1 or more interventions. In recent years, successive case reports and prospective or retrospective studies have documented the use of various innovative approaches, which have sometimes led to relative successes, but have also led to poor outcomes and significant ethical controversies.[1-12]

The advancement of tracheobronchial surgery has been made possible by the efforts of several teams worldwide.[1] Since the 1960s, resection with direct reconstruction by end-to-end anastomosis has become feasible for treating lesions up to 5 to 6 cm, approximately half the length of the trachea. For more extensive damage, tracheobronchial replacement using a substitute becomes essential. Hermes C. Grillo (of Massachusetts General Hospital and Harvard Medical School), the father of modern tracheal surgery, noted that at first glance, it might seem simple to replace a conduit intended primarily for the passage of gases to and from the lungs, but in reality, the challenge is far more complex.[1-12] The ideal substitute should be rigid radially but flexible longitudinally, airtight, and capable of integrating with surrounding tissues to prevent complications, such as inflammation, granulation tissue formation, and infection. It must prevent ischemia by promoting neovascularization. It must be biocompatible, nontoxic, nonimmunologic, noncarcinogenic, and durable, avoiding dislocation, erosion, or stenosis over time. It should also resist bacterial colonization, support epithelial resurfacing, and be a permanent solution. Immunosuppressive therapy is usually avoided due to several concerns, especially since tracheobronchial replacement is primarily indicated for advanced cancers. Additionally, the surgical technique must be both straightforward and reliably reproducible. Different substitutes have been proposed for tracheobronchial replacement, including synthetic prostheses, tubularized autologous tissues, tracheal allografts, cryopreserved aortic allografts, and tissue-engineered conduits. The objective of this systematic review is to examine the current indications, techniques, and outcomes of tracheobronchial replacement in human patients.

Key Points

Question What are the indications, techniques, and outcomes of tracheobronchial replacement?

Findings This systematic review of 126 articles found that tracheobronchial replacement is primarily used for extensive malignant lesions, with cryopreserved aortic allografts being the most implanted and scientifically evaluated grafts. The only available registry reports a 30-day postoperative mortality rate of 2.9%, with long-term mortality mainly due to cancer recurrences and metastases in patients treated for cancer.

Meaning Further research is needed to standardize the approach to tracheobronchial replacement in accordance with established recommendations for surgical innovation.

Methods

A systematic review of the medical literature was conducted on July 1, 2024, to identify studies examining the current indications, techniques, and outcomes of tracheobronchial replacement. This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines and the PRISMA 2020 statement. Three databases were selected for review: (1) PubMed via the US National Library of Medicine's PubMed.gov; (2) Embase via Elsevier's Embase.com; and (3) the Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley's Cochrane Library. The search strategy was initially developed in PubMed by 4 of the authors (E.M., X.C., O.H., and E.V.) using several combinations of the following key words connected by the Boolean "AND" operator: on one side, *tracheal*, *tracheobronchial*, *bronchial*, or *airway*, and on the other side, *replacement*, *transplantation*, *reconstruction*, or *engineering*. No filters based on human participation, publication date, or age were initially used in order not to potentially exclude relevant articles and to have a comprehensive view of all clinical applications carried out to date. The search strategy was then translated to the other databases. Results were entered in Rayyan (Rayyan Systems), a web-based software platform for systematic review development using artificial intelligence and natural language processing. After identification of the results, duplicates were removed by Rayyan and by hand. Articles were screened by the first and last authors (E.M. and E.V.). The remaining articles underwent full-text review to include or exclude publications according to our criteria. Quality of evidence was determined by the first and last authors (E.M and E.V.) and evidence was rated according to standards of the Oxford Centre for Evidence-Based Medicine. As recommended, an additional search was performed using the following clinical trials registers: the World Health Organization's International Clinical Trials Registry Platform and ClinicalTrials.gov, provided by the US National Library of Medicine.

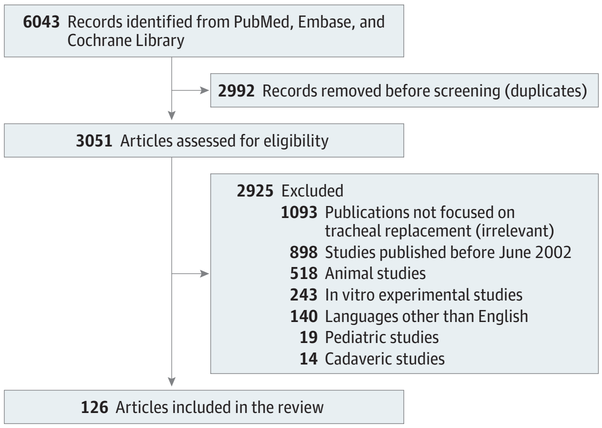
Results

A total of 6043 articles were initially identified; 126 remained after removing duplicates, irrelevant articles, and those that met exclusion criteria (**Figure 1**). Characteristics of included articles are described in **Table 1**. There were no randomized studies. There was only 1 prospective cohort study and 1 registry, both concerning the use of cryopreserved aortic allografts. Most articles were case reports (n = 28) and case series (n = 14). In the final list of 75 references cited in this systematic review, editorials and letters were mostly excluded. Those that provided valuable insights into the debated topic of tracheobronchial replacement were, nevertheless, retained. Clinical trials regarding tracheobronchial replacement are listed in **Table 2**. Among the 5 trials listed, the 3 that are completed or ongoing involve tracheobronchial replacement using a cryopreserved aortic allograft. From July 1, 2002, to July 1, 2024, a total of 137 cases of tracheobronchial replacement were published (eTable in Supplement 1).

Indications

The indication for tracheobronchial replacement is usually considered for extensive lesions that have reached a therapeutic dead end. The theoretical limit of 5 to 6 cm (half the length of the

Figure 1. PRISMA Flow Diagram



Note that older articles published before the review by Grillo (2002)[1] have been excluded from the review. Indeed, these articles are all referenced in Grillo's review and primarily focus on animal studies, with only few cases involving humans. Pediatric studies were also excluded, as the techniques used are most often very specific to children.

Table 1. Summary of the Literature Included in the Final Review by Type of Articles and Ratings of the Quality of Articles (1 to 5) According to the Oxford Centre for Evidence-Based Medicine

Reference type	No. Articles (n=126)	Quality ratings
Case report and case series	42	NA
Case report	28	5
Case series	14	4
Review	33	NA
Narrative review	26	5
Systematic review	7	1
Original investigation	18	4
Letter	18	5
Editorial	8	5
Retrospective cohort (registry)	3	3
Retraction of publication	2	NA
Bibliometric study	1	NA
Prospective cohort	1	2

Abbreviation: NA, not applicable.

trachea) can be significantly reduced depending on age, anatomical characteristics, the type of lesion, and previous treatments (eg, multiple interventions or radiotherapy). This systematic review revealed that tracheobronchial replacement was performed for neoplastic tumors in most cases (108 of 137 [78.8%]) but also for benign stenoses (29 of 137 [21.2%]). The most common malignancies were thyroid cancers invading the trachea (n = 42) and adenoid cystic carcinomas (n = 32), followed by lung carcinoma (n = 12), squamous cell carcinoma (n = 8), and mucoepidermoid carcinoma (n = 3). The most frequent benign etiologies were stenoses related to intubation or tracheotomy (n = 9), trauma (n = 7), and trachea-esophageal fistula (n = 7). The different indications are detailed in **Table 3**.

Surgical Treatment

Surgical Techniques

The most frequent type of resection was that of the upper half of the trachea (n = 69). Muscle flaps (n = 64) and cryopreserved aortic allografts (n = 51) were the most commonly used grafts. The implantation of tracheal allografts, tissue-engineered conduits, and revascularized allografts was only performed in 7, 4, and 1 case, respectively. Since 2022, the cryopreserved aortic allograft has been the most widely used, in 42 of the 44 published cases (eTable in Supplement 1). The different types of resections and grafts are detailed in Table 3. Schematically, surgical techniques were based on the use of 5 types of grafts.[1-12] Surgical approaches were performed according to the type of resection (**Figure 2**).[16]

Synthetic Prostheses | Made from materials like metal, glass, and various plastics, synthetic prostheses have been tested in animals and occasionally in humans. However, due to complications like migration, infection, vascular erosion, and death, this research has largely been abandoned.[1-12] This systematic review showed that no cases of synthetic prosthesis use have been reported since June 1, 2002.

Tubularized Autologous Tissues, Reinforced or Not With Cartilage | Various autologous tissues, such as skin, local muscle, and forearm or tibial flaps, have been used in tubularized reconstructions, sometimes reinforced with cartilage.[17-38] A group affiliated with Marie Lannelongue Hospital reported a series of 16 cases using forearm flaps with costal cartilage reinforcement.[28] A 2015 study highlighted the advantage of no need for immunosuppression.[30] However, drawbacks include stent maintenance, lack of epithelial regeneration, donor site morbidity, and prolonged intensive care unit stays due to the complexity and duration of the procedure. These challenges have prevented the development of a standardized clinical application.[17-38]

Tracheal Allografts | After previous failures, research was revived by a team from the Leuven Tracheal Transplant Group with a 2-stage tracheal allograft procedure.[39-42] The first stage involves revascularization in the recipient's forearm under immunosuppression for 2 to 4 months, followed by graft transfer to the orthotopic position. Despite initial enthusiasm, only 6 cases were performed, the latest in 2014 with no comprehensive long-term follow-up. Another team's attempt led to a fatal hemorrhage.[43] A more recent approach from Mount Sinai Hospital in New York showed favorable results in a reported case, but challenges like donor availability, the need for immunosuppression, and procedure complexity could limit its use.[44-47] This review showed that only 8 cases of tracheal allografts have been published, with none in the last 3 years.

Cryopreserved Aortic Allografts | After an experimental phase (from 1997-2008, conducted at the Alain Carpentier Foundation in Paris) and a few clinical cases, a prospective study (at the Assistance Publique–Hôpitaux de Paris [AP-HP] in Paris) demonstrated the feasibility of tracheobronchial replacement using cryopreserved aortic allografts in 13 patients.[13,48-55] This was confirmed by other groups and the prospective TRITON-01 registry, with 35 patients (AP-HP) showing rates of mortality (2.9%) and morbidity (22.9%) comparable to those of major thoracic surgical procedures.[14,15,56-62]

Table 2. Clinical Trials Regarding Tracheobronchial Replacement

Clinical trial	Clinical trial No.	Investigator, center (country)	Recruitment status	Date		Patients, No.	Source (No. of patients)
				First posted	Last update		
Replacement of the Airways and/or the Pulmonary Vessels Using a Cryopreserved Arterial Allograft (TRACHEO BRONC-ART)	NCT01331863	Martinod/Vicaut, Assistance Publique-Hôpitaux de Paris (France)	Completed	April 8, 2011	September 9, 2020	20	Martinod et al,[13] 2018 (13)
A Study to Assess the Safety, Tolerability and Potential Efficacy of a Tracheal Replacement Consisting of a Tissue-engineered Tracheal Scaffold With Seeded Mesenchymal Cells	NCT02949414	Birchall, University College London (UK)	Suspended	October 31, 2016	March 29, 2018	0	No
Tracheobronchial Bioengineering Using Aortic Matrices for Airway Reconstruction (TRITON)	NCT04263129	Martinod/Vicaut, Assistance Publique-Hôpitaux de Paris (France)	Recruiting	February 10, 2020	October 18, 2022	49 (Personal data)	Martinod et al,[14] 2022 (35)
Feasibility of Tracheobronchial Reconstruction Using Bioengineered Aortic Matrices	NCT04850742	Chen, National Taiwan University Hospital (Taiwan)	Recruiting	April 2, 2021	May 11, 2021	1	Hung et al,[15] 2024 (1)
Feasibility study of porcine dermal acellular matrix in artificial trachea replacement based on in-vivo bioreactor	ChiCTR2200056696	Tan, Shanghai Chest Hospital, Shanghai Jiao Tong University (China)	Pending	February 10, 2022	September 4, 2023	0	No

Mid- and long-term complications, mainly stent-related granulomas, required minimally invasive treatment using rigid bronchoscopy. Regeneration of epithelial and cartilaginous tissue allowed stent removal after 18 months in some patients. Additional research is being conducted with specialized laboratories in respiratory, cartilage, and immunology fields to better understand the mechanisms of regeneration, which remain controversial.[63] Other matrices, like alloderm and xenogeneic conduits, have been tested in a few cases.[64-66]

Tissue-Engineered Conduits | Between 2008 and 2017, there was international enthusiasm for this method following clinical applications by a team at the Karolinska Institute in Sweden. Subsequently, convictions for scientific and ethical fraud led to the retraction of publications and the cessation of this otherwise-promising line of development and have significantly slowed clinical research on tracheobronchial replacement in recent years.[67-70] This method could potentially restart with new foundations in the near future.[71] Indeed, tracheobronchial tissue engineering aims to develop a functional airway replacement that does not require immunosuppression or stents. Both natural and synthetic scaffolds offer potential, especially with stem cell and coseeding techniques, although revascularization and scaffold biocompatibility remain challenging. Further studies in large animal models are crucial before human clinical applications.

Anesthesia and Perioperative Care

Tracheobronchial replacement poses a significant threat to life, requiring careful planning and assessment by a multidisciplinary team. Patients scheduled for tracheobronchial replacement should undergo comprehensive evaluations, including pulmonary function tests and cardiovascular assessments, prior to surgery. Special attention must be given to airway management, as the induction of anesthesia can be particularly hazardous. The risk of cardiopulmonary collapse is high during induction, and positive pressure ventilation may be more effective in such cases. General anesthesia should be administered using total intravenous anesthesia, and the use of muscle relaxants may be necessary.[72] Depending on the location of the lesion, 1-lung ventilation or jet ventilation may be required.[73] For surgical procedures involving the lower trachea or carina, percutaneous venovenous extracorporeal life support provides a safe approach to anesthesia management.[72,74] Hemodynamic management should use a calibrated cardiac output monitoring device capable of beat-to-beat assessment of left ventricular stroke volume, especially in situations involving changes in intrathoracic pressure. This approach is preferred over arterial area under the curve analysis devices, which are less reliable under these conditions. The strategy is to extubate patients as early as possible after surgery, ideally while still in the operating room. In the postoperative period, patients should be closely monitored in an intensive care unit to prevent life-threatening complications, such as hemorrhage, sepsis, pneumonia, or acute respiratory distress syndrome.[75] Early rehabilitation, including mobilization and lung physiotherapy, should be routinely implemented to support recovery. Currently, most of the literature on this topic consists of case reports or case series, limiting the evidence base to expert opinion.

Outcomes and Prognosis

Postoperative mortality, as well as medium- and long-term follow-up, is difficult to study due to the prevalence of case reports and case series and the resulting heterogeneity of the data. Only 4 deaths were reported within 30 days of 137 cases, resulting in a postoperative mortality rate of 2.9% (eTable in Supplement 1). In the only available prospective cohort, the 90-day postoperative mortality was 7.7% (1 of 13 cases).[13] Major 90-day morbidity events occurred in 4 patients (30.8%), including laryngeal edema, acute lung edema, acute respiratory distress syndrome, and atrial fibrillation. In the only available registry, the 30-day postoperative mortality and morbidity rates were 1 of 35 cases (2.9%) and 8 of 35 cases (22.9%), respectively.[14] Most patients (18 of 35 [52.9%]) developed stent-related granulomas necessitating a bronchoscopic treatment. The actuarial 2- and 5-year survival rates (Kaplan-Meier estimates) were 88% and 75%, respectively.

These results appear comparable to those observed in major thoracic surgery for advanced lung cancer, esophageal neoplasms, and transplantation.[14] As shown in the eTable in Supplement 1, complications reported in other cases were also associated with the operation (acute respiratory distress syndrome, multiple organ failure, and mediastinitis), the graft (brachiocephalic artery or vein erosion, stenosis, and anastomotic dehiscence), the stent (granulomas, obstruction, recurrent pneumonia, and trachea-esophageal fistula), or other causes (hemoptysis, pulmonary embolism, acute anterior spinal cord ischemia, and hypercalcemia). At long-term follow-up, mortality was associated with local recurrence and metastasis in the group of patients who underwent surgery for cancer. The implantation of tissue-engineered conduits has been consistently associated with mortality in all cases due to multiple complications related to the grafts.[68-70]

Discussion

This systematic review is mainly composed of case reports and small case series. However, for the evaluation of cryopreserved aortic allografts, there was a prospective cohort study and an ongoing registry, which included 35 cases in 2022, with a maximum follow-up duration of 13 years.[13,14] To date, no randomized clinical trial has yet been conducted in this field, which remains a highly debated topic. This confirms the need to establish surgical research according to usual guidelines.[54,76] According to idea, development, exploration, assessment, and long-term follow-up (IDEAL) recommendations, the feasibility of a novel technique may be assessed in animal models or simulation before full evaluation in human patients. Schematically, surgical research must proceed through the following steps: structured cases (stage 1, idea); prospective development studies (stage 2a, development); feasibility studies (stage 2b, exploration); randomized controlled trials (stage 3, assessment); and registry (stage 4, long-term studies). It is essential to prevent further controversies in this field; the scientific approach must be beyond reproach.

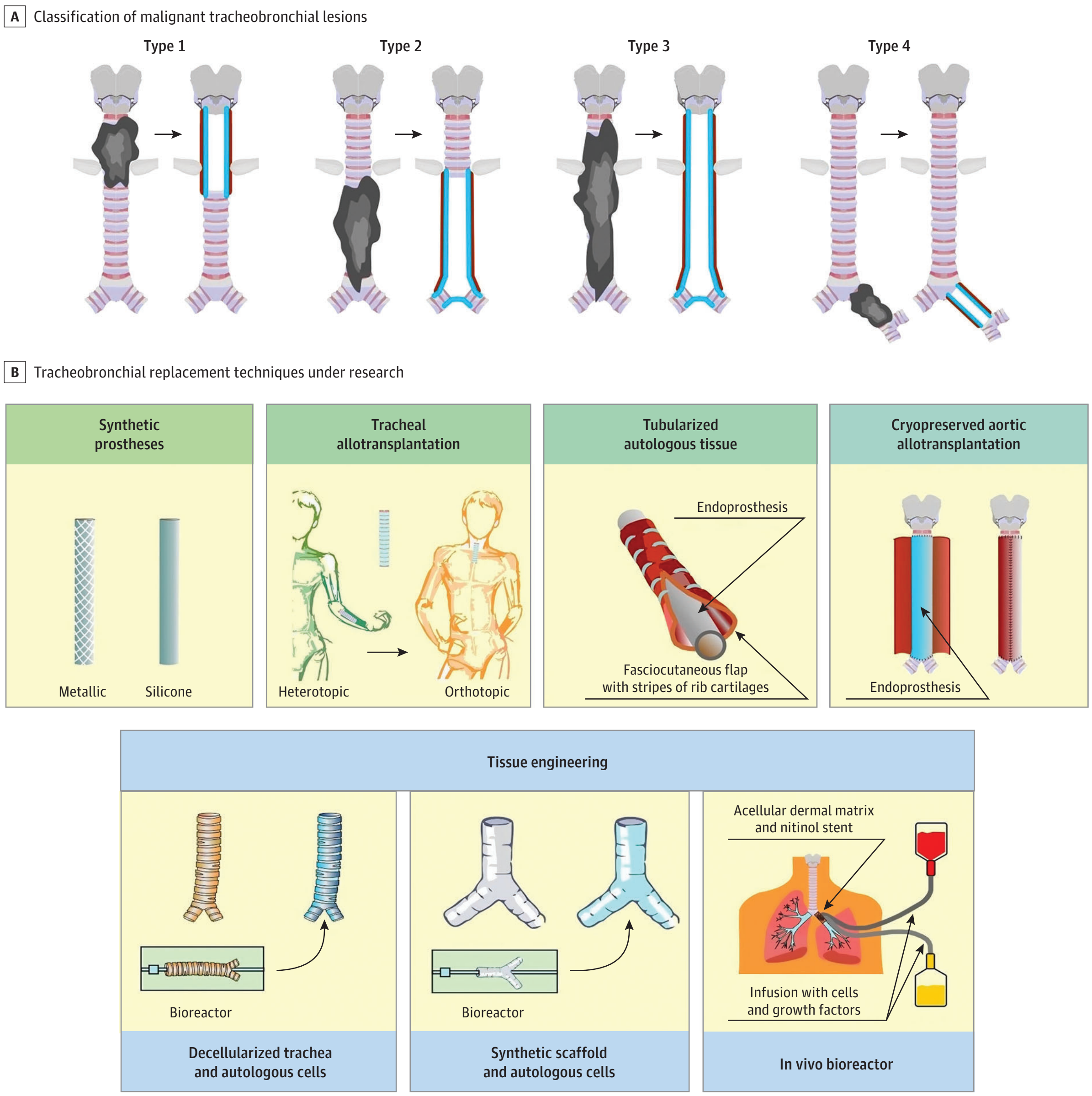
This systematic review shows that tracheobronchial replacement was performed for cancer lesions in most cases. The most common malignancies were thyroid cancers invading the trachea and adenoid cystic carcinomas, followed by lung carcinoma, squamous cell carcinoma, and, finally, mucoepidermoid carcinoma. The prognosis for differentiated thyroid cancers with tracheal involvement relies on complete surgical resection, as other treatments are not curative. Radical surgery, potentially supported by tracheal replacement, is critical for managing locally invasive T4 tumors and improving outcomes.[14,25,33,35,61] Primary tracheal cancers are rare, with squamous cell carcinoma and adenoid cystic carcinoma being the most common types. Surgery significantly improves survival, particularly when complete resection with negative margins is achieved, and tracheobronchial replacement may increase the likelihood of successful resections and better outcomes. This systematic review also shows that tracheobronchial replacement may have other valuable indications, particularly in avoiding pneumonectomy for certain proximal lesions (whether cancerous or not) in the main bronchi or in benign stenoses of various origins (postintubation or tracheotomy, traumatic, etc), which were often subject to multiple surgical procedures or stenting.[13,14,40,52]

This systematic review establishes that muscle flaps and cryopreserved aortic allografts were the most commonly used grafts; that the implantation of tracheal allografts, tissue-engineered conduits, and revascularized allografts were only performed in 7, 4, and 1 cases, respectively; and that the cryopreserved aortic allograft has been the most widely used, in 42 of 44 published cases since 2022 (eTable in Supplement 1). The different techniques have been extensively detailed herein. Interest in tissue-engineered conduits surged in 2008 but was halted due to ethical misconduct.[67-70] There is potential for reviving this research on stronger foundations.[71] On the other hand, some investigators have highlighted whether tracheal resection is circumferential or not, but this point has limited significance.[2-12] What truly matters is whether the surgical treatment resolves the issue. Indeed, the primary goal is effective treatment of the lesion, even if the resection is only partial, rather than achieving a specific type of resection.

Table 3. Tracheobronchial Replacement Indications, Type of Reconstruction, and Type of Graft

Variable	Cases, No.
Indications	
Neoplastic tumors, No./total No. (%)	108/137 (78.8)
Thyroid carcinoma	42
Adenoid cystic carcinoma	32
Lung carcinoma	12
Squamous cell carcinoma	8
Mucoepidermoid carcinoma	3
Paragangliomma	2
Carcinoid tumor	2
Chondrosarcoma	1
Parathyroid carcinoma	1
Inflammatory myofibroblastic tumor	1
Undetermined tumor	4
Benign, No./total No. (%)	29/137 (21.2)
Stenoses related to	
Intubation or tracheotomy	9
Trauma	7
Tracheo-esophageal fistula	7
Tuberculosis	2
COVID-19	1
Lung transplantation	1
Ischemia	1
Undetermined causes	1
Type of resection (n = 137 patients)	
I	69
II	30
III	21
IV	17
Type of graft (n = 137 patients)	
Muscle flaps	64
Local flap with or without cartilage	20
Free flap with or without cartilage	44
Forearm	30
Tibial	14
Cryopreserved aortic allograft	51
Allotransplantation	7
Autologous pulmonary tissue flap	5
Tissue-engineered conduits	4
Xenogenic matrices	3
Revascularized allograft	1
Alloderm conduit	1
Aortic autograft	1

Figure 2. Different Types of Tracheobronchial Replacement and Ways of Research



A, Classification of tracheobronchial (malignant) lesions according to Martinod and colleagues.[16] The surgical approach is based on the type of tracheobronchial replacement schematically as follows: transverse cervicotomy with or without extension into partial sternotomy (manubriotomy) for type I; right posterolateral thoracotomy in the fourth intercostal space for type II; extended cervicotomy with (partial) sternotomy for type III; and posterolateral thoracotomy in the fourth intercostal space for type IV. B, Different ways of research for tracheobronchial replacement.

Finally, there are no standardized recommendations regarding anesthesia and perioperative management. Postoperative mortality and morbidity are comparable to those of other major thoracic surgical procedures. Long-term survival largely depends on the underlying pathology, particularly in cancer cases.

Limitations

This review has several limitations. First, the number of selected articles is limited. Second, the available medical literature consists predominantly of case reports and case series. Finally, a robust scientific methodology has been applied to only 1 technique: the use of cryopreserved aortic allografts.

Conclusions

In conclusion, the results of this systematic review suggest that the primary indication for tracheobronchial replacement is represented by extensive malignant lesions. To date, the only surgical technique that has undergone scientific evaluation, including a prospective feasibility study and a registry, is the use of cryopreserved aortic allograft. Postoperative outcomes were similar to those of other major thoracic surgical procedures. Long-term outcomes were dependent on the underlying pathology, particularly in case of neoplastic diseases. Concerning the use of cryopreserved aortic allografts (the most commonly performed technique), reproducibility must be demonstrated in a larger number of cases and at different centers. The ideal time frame and objective assessment for stent removal remain to be determined and are partially guided by the feasibility of removing the stent in the long term due to de novo cartilage generation.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Martinod, Radu, Onorati, Chapalain, Peretti, Chouahnia, Duchemann, Juvin, Galvaing, Chadeyras, Tronc, Kuczma, Tresallet, Venissac, Beloucif, Huet.
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