# Surgery in Tracheal Tumors

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## Abstract

**Background:** The trachea is an anatomical structures of 10 cm to 12 cm of length in adults, which could appear just a simple conduit that brings the air to the lungs, but it is a very complex organ with a lot of functions and is supplied by many arterial branches arising from inferior thyroid artery, bronchial, intercostal arteries or direct branches from discending aorta, that create a vascular reticulum entering inside and feeding the ciliated pseudostratified columnar epithelium.

**Methods:** The literature search has been made by using as a keywords "Tracheal tumors", "Trachea surgery", "Carina surgery", "Engineered trachea". We selected 74 articles from 15191 papers.

**Results:** According to the literature search, we can say that, because of its own structure, it's not simple to resect and reconstruct the trachea by direct end to end anastomosis, especially for more than 50% of its length and it cannot be easily replaced or transplanted. Although surgery is not the only possible therapy, the radiotherapy and the endoscopic treatments are so far from guarantee an adequate survival, and they are usually employed as adjuvant therapies after surgery or they are reserved to non-surgical patients for medical problems or oncological criteria.

**Conclusion:** To overcome the surgical limits in direct reconstruction, have been developed different autogenic or allogenic grafts and nowadays there are different vascularized biocompatible scaffolds till the tissue engineered neotrachea, but more studies are still needed to standardize a valid reconstructive system for tracheal major resections or transplantation.

**Keywords:** Tracheal tumors; Trachea surgery; Carina surgery; Engineered trachea

## Introduction

Over the last 50 years the problem of tracheal resection and reconstruction has been dealt with increasingly interest, given also the importance of respiratory intensive medicine (by the use of the invasive ventilation systems) developed at the same time.

Since the dog experiment of Dr Hermes Grillo, it has progressively shown it was possible to resect and reconstruct the trachea by a direct end to end anastomosis, till the 50% of its length [1,2].

With the aim to repair and keep the trachea open to the air flow, a lot of materials have been studied and tried in animal and human models: steel wire, tantalum, marlex, PTFE, Dacron and Teflon and silicone [3-10]. More recently, the science has moved to the new horizons of regenerative medicine, with the project of tissue engineered neotrachea transplantation [11].

So, by this analysis, we tried to focus on the critical points of oncological tracheal resections, limits and pitfalls, and reflect about the future possibilities.

## Methods

### Step 1

The literature search was performed in PUBMED, EMBASE, and COCHRANE the search was restricted to publications in English, in Human series using as a key word "Tracheal tumors", "Trachea surgery", "Carina surgery", "Engineered trachea". We found 15191 papers.

### Step 2

By reading the titles and the abstracts, we eliminated duplicated articles, cases reports, comments, letters to the editor, and publications about infective pathologies (search result, 931 papers).

### Step 3

We selected at the end the references with surgical interest and the publications about engineered tissue, bioscaffold with clinical impact and finally we arrived to our 74 references.

# Results

The trachea starts just inferior to the cricoids and extends to the carina. It's is about 10 cm to 12 cm in adults in length and 1.5 cm to 2.5 cm in width. Trachea is partially in the cervical region (extra-thoracic trachea) and partially in mediastinum (intra-thoracic trachea). The anterior portion is made of c-shaped cartilaginous rings and the posterior portion is composed by a membranous tissue. A tracheal mucosa (ciliated pseudostratified columnar epithelium) covers the anterior cartilage and the posterior membrane. The inferior thyroid artery (arising from the subclavian artery) supplies upper trachea (generally by a first, second and third branch). The inferior two thirds receive blood from bronchial or intercostal arteries arising directly from the aorta. The vessels enter the lateral surfaces of the trachea and they create the anterior and posterior vascular reticulum that supplies the mucous tissue, with lateral longitudinal anastomosis which connects the branches of inferior thyroid artery with those of superior and middle bronchial arteries [12].

Tracheal primary tumors represent 0.1% to 0.4% of all the malignancies; they are really less frequent than supraglottic tumors [13-15]. The frequencies of malignant and benign neoplasms are different according to the age. In adults 90% of the tracheal tumors are malignant, in children only 10% to 30%. In adults the more represented histotypes are the squamous carcinoma (although is more represented in larynx and in the bronchi), the adenoid cystic carcinoma, adenocarcinoma, large cell undifferentiated carcinoma, neuroendocrine tumours (carcinoid), muco-epidermoid carcinoma, soft tissue sarcoma, chondrosarcoma; the benign tumors are papilloma, pleiomorphic adenoma, fibroma, haemangioma glomous tumour, chondroma) [16-20].

In children the benign tumors include hemangioma (that is the only histotype not requiring surgery, but which can be treated with medical therapy: propranolol), papilloma, leiomyoma, lipoblastoma, chondroma; the malignancies are carcinoid, mucoepidermoid carcinoma, adenoid cystic carcinoma, rhabdomyosarcoma, leiomyosarcoma [21-24].

When we evaluate the carinal tumors, we have also to consider the non-small cell lung cancer T4 or N2 invading the carina or the inferior third of the trachea [25].

The most frequent signs and symptoms of tracheal tumors are dyspnoea, wheezing, and stridor, cough and haemoptysis, but these are a specific and because of it the diagnosis is often delayed. Indeed, we have to remember that at 8 mm of residual diameter can appear exertional dyspnoea and just under 5 mm at rest dyspnoea [20,26].

In tracheal tumors the surgery is the most important treatment and is represented by a resection/anastomosis of the segment of trachea interested by the tumor [27-31].

In rare case the tumorectomy is an adequate treatment and generally is reserved to the benign lesions especially in children [32]. The transtracheal access is generally employed for posterior tracheal injuries, repairing the laceration without thoracotomy trough the cervical incision and longitudinal median tracheotomy [33].

The choice of surgical access depends on the tumor site. For the upper third of the trachea the neck-collar incision is the first step, but it can be extended with a manubriotomy or mini-sternotomy. The longitudinal median sternotomy or the right thoracothomy are used for the inferior two thirds and for carinal resection. As in adults, also in children upper trachea is approached with a transverse cervical incision, with or without manubriotomy, and lower trachea by the sternotomy or right thoracotomy [32,34].

Obviously all these standard surgical approaches could be integrated and modified by a video thoracoscopic experiences to limit the invasiveness of the access [35,36].

The sternal approach requires the anterior and posterior pericardiotomy, to increase the intercavo-aortic space moving laterally ascending aorta and superior vena cava and vertically right main pulmonary artery (especially for carinal anterior approach).

Sometimes it could be necessary section of left anonymous vein or heart apex gentle mobilization with ionotropic support, according to need of space and surgeon's experience the reconstructive techniques after carinal resection depend obviously on the anatomy, stump distance, quality of tissues, structures mobilization. All these aspects should not be assumed especially after neoadjuvant integrated treatments. The most important anastomosis are: end to end right main bronchus with trachea; end to side left main bronchus with intermedius; end to end right main bronchus with trachea; end to side left main bronchus with trachea; end to end left main bronchus with trachea; end to side right main bronchus with trachea [25].

For carinal and origin of main bronchi tumors, parenchyma-saving or sparing procedures, such as sleeve resections or bronchoplasties, are the best techniques, especially in children to avoid chronic functional limitations, obviously if the oncological radicality allows to do it [37].

The carinal resections without resection of pulmonary parenchyma and the left-sided carinal pneumonectomies are approached through a median sternotomy. Sometimes it could be necessary to combine left thoracotomy or left thoracoscopy, especially for posterior adhesions, for pulmonalis ligamentum section or for left pulmonary vein section.

Indeed, the right carinal penumonectomy requires right muscle sparing thoracotomy. The critical point of the carinal pneumonectomy is represented by the intubation of the controlateral bronchus after airway section. Gonfiotti et al., [37] described a type of intra-operative ventilation such as e preoxygenation and hyperventilation with 100% oxygen ($O_2$) to reach arterial $PO_2$ and $PCO_2$ levels of at least greater than 450 and 28 to 35 before the airway section and then controlateral bronchus intubation for a continuous ventilation with low breathing pressure (0 mmHg to 1 mmHg) [38-43].

Evaluating all the tracheal resections, Macchiarini et al., [42] reports as absolute contraindications to surgery: the presence of many positive lymph nodes, the involvement of more than 50% of the trachea in adults and 30% to 40% in children, the mediastinal invasion of unresectable organs, the presence of a mediastinum that has received the maximum radiation dose of more than 60 Gy or has been operated on, and distant metastases of squamous cell carcinoma [38-40,44].

In tracheal and carinal surgery, the releasing maneuvers recommended are: the laryngo-tracheal, inferior U-shaped hilar, pericardiophrenic (with separation of the pericardium and the diaphragm between both phrenic nerves) [31,34,41,45].

To support the surgery, other therapies can help to treat tracheal malignancies. In non surgical diseases or as a bridge to surgery, the endoscopic procedures are interesting treatments, but they cannot

consider radical therapies for the survival [46-49].

Radiotherapy is useful for inoperable patients or as adjuvant treatment to surgery till 68 Gy to 70 Gy for tumor residuals [50-52].

## Comment

The cut-off of the maximal length for the resection, the complex vascular supply of the trachea and the excessive anastomotic tension due to the structure fixity, represent the anatomical limits of the resection and of end to end anastomosis. Sometimes these aspects can lead to reduce the length of resection not for choice but for need, especially in adenoid cystic carcinomas where postoperative radiotherapy can treat the microscopical residuals, avoiding excessive anastomotic risks and severe complications till death [53,54].

For long stenosis, especially in benign pathologies such as post-intubation or post-tracheotomy stenosis, the length problem has been tried to be solved by the slide-tracheoplasty, describe in 1989, that is a procedure which divides the trachea in the midpoint of the stenosis and approximate the two ends by sliding one on the other [55]. This kind of surgery has great limits in oncological fields for obvious reasons.

With to aim to get oncological radicality, when it's not possible the direct reconstruction by end to end anastomosis, or with the aim to avoid palliative stenting or definitive tracheostomy (sometimes necessary also for benign stenosis), have been developed different reconstructive systems: autologous or allogenic tissues and more recently tissues engineering to getting the complete tracheal transplantation.

According to the vascular anatomy of trachea, the tissue engineering requires a biocompatible, non oncogenic, vascularized scaffold and this is not simple.

Autologous reconstructive techniques include many vascularized scaffolds: vascular graft scaffold of Hemashield filled with a vascularized forearm flap, free radial forearm fasciocutaneous flap with rib cartilage, a corticoperiostal flap from femur and saphenous flap, a corticoperiosteal-cutaneous flap from medial femoral condyle and an auricular cartilage prelaminated flap in radial forearm, though there was already in the 90s a study about tracheal autograft in greater omentum [56-61].

With the aim to realize the allogenic trachea transplantation, have been also developed allogenic reconstructive models: the human allotrachea of donor implanted in sternocleidomastoid muscle of the recipient; the first human one-stage tracheal allotransplantation with omentopexy; the acellular tracheal omograft with allogenic trachea (prepared by immersion in methiolate and alcohol); the tracheal allograft revascularization in omentum of the recipient; tracheal allograft revascularized by heterotopic wrapping in radial forearm fascia and with epithelium replacement with buccal mucosal grafts of the recipient; the allogenic aorta wrapped in pectoralis muscle [62-70].

From the limits analysis of the allogenic tracheal transplantation, the science has moved to tracheal tissue engineering tree-dimensional vascularized biocompatible neo-trachea.

Macchiarini et al., [71] performed a tracheal human transplantation, with a donor decellularized trachea, and filled it with autologous differentiated condrocytes and with autologous respiratory epithelial cells in rotational bioreactor, decellularizing the scaffold with specific enzymes to avoid immunosuppressive chronic therapy. The decellularized scaffolds have been realized in different ways for the trachea transplantation by Elliot and Jungebluth-Macchiarini, also by the use of omental flap and TGF-beta and recombinant erythropoietin to promote the cellular differentiation and the angiogenesis [64,70-72].

These models could be considered as an evolution of acellular biosynthesized polypropylene reinforced mesh of Omori, who was the first human employment in human of this kind of acellular scaffold filled with autologous blood [73,74].

With the tracheal resection and transplantation, has been completed an evolution from the "multidisciplinary" to a real "multisciences" therapeutic approach, beyond the limits of medicine, immunology, technical surgical skills till the nanotechnology, molecular biology applied to clinical practice to face problems too big to be simply solved with technical improvements such as better releasing or new types of anastomosis, because they are due to anatomy and biology of the tracheal tissue, and to its complex vascular support.

More studies are necessary in tracheal tumors because the reconstructive improvements allow to perform a more radical and extended surgery, but more studies are also needed in benign tracheal diseases to give adequate quality of life to patients with definitive tracheostomy or endotracheal stenting or prosthesis.

Indeed, in these non-cancer patients we have to be very careful because, with an unnecessary surgery to survival, we could create life threatening complications to patients who could have lived a lot of time, although with limitations.

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