What Is the Best Management Strategy for Adenoid Cystic Carcinoma of the Trachea?

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Background

Adenoid cystic carcinoma (ACC) is a relatively rare disease, and most general thoracic surgeons encounter it only a few times in their careers. Consequently, many unique management protocols have been presented at medical conferences. In one such example, a patient with ACC underwent sleeve resection of the trachea. However, a microscopically negative stump was not achieved, and tracheal resection was, therefore, repeated. This increased the distance between the two margins, making end-to-end anastomosis impossible. The surgeon then performed a total laryngectomy and terminal tracheostomy despite a pathologically positive finding at the tracheal margin, and the patient subsequently lost his voice. In 2002, the Annals of Thoracic and Cardiovascular Surgery published an article by Kanematsu1 in which the author described that 5 patients with microscopic residual tumor who received postoperative radiotherapy survived without recurrence for 3 to 17 years. This evidence suggests that a pathologically negative stump might not be always required, but in such cases, it is essential to add postoperative radiotherapy.

Another team also reported a patient who underwent aggressive management, in which self-expandable metallic airway stents (SEMSs), namely, Ultraflex stents and Gianturco Z stents, were placed to treat airway stenosis due to ACC. After radiotherapy, the stricture improved; however, granulation tissue formation around the stents produced further stenosis. The authors unsuccessfully attempted to remove the SEMSs under bronchoscopy. They performed surgery to resect the destroyed left lung and remove the SEMSs embedded in the main bronchus under extracorporeal circulation. It is extremely difficult to remove SEMSs, especially Gianturco Z stents, as the metal spikes are embedded in the tracheal mucosa.

The present editorial describes historical and recent management of ACC.

Surgery

Indications for surgical treatment of ACC are determined based on the location and local extension in the trachea. Standard surgery is sleeve resection of the trachea with primary tracheal anastomosis.1–5) When ACC is located in the upper trachea, tracheal resection combined with total laryngectomy is sometimes necessary, after which terminal tracheostomy is required. When ACC involves the carina and main bronchi, there are a variety of carinal resections and reconstructions requiring more difficult techniques.2)

Grillo2) described 60 patients with resected ACC, and stressed the role of prophylactic irradiation even when margins are histologically negative, as pathological diagnosis of the tracheal stump is not always reliable. Grillo reported operative death in eight patients (13.3%) and tumor death in 12 patients; however, 40 resected patients were alive and tumor-free at the time of the manuscript submission in 1990. The operative death rate of 13.3% reported by Grillo indicates that this surgery is extremely complicated and requires a cautious survey and meticulous surgical technique.

A successor to Grillo, Honings,3) reported 108 cases of ACC in 2010. Although a macroscopically positive margin was found in nine patients (8.3%) and a microscopically positive result was seen in 59 patients (55%), a negative result was found in 40 (37%). Postoperative radiotherapy was administered to 89 patients (82%) with
positive or negative findings. Median overall survival in patients with negative margins (40 patients) was longer than that in patients with positive margins (68 patients) (20.4 vs. 13.3 years, \( P = 0.007 \)). Disease-free survival after resection in patients with negative airway margins was also longer than that in patients with positive margins (16.6 vs. 9.3 years, \( P = 0.005 \)). The 5- and 10-year survival rates with macroscopically positive, microscopically positive, and negative margins were 56%, 75%, and 86% and 28%, 65%, 71%, respectively.

Maziak and Pearson\(^4\) reported their experience treating 38 patients with ACC. They performed surgery in 32 patients, and experienced three operative deaths (9.3%). They adopted four Marlex mesh prostheses. The mean survival in 14 patients who underwent complete resection was 9.8 years, and that in 15 patients who underwent incomplete resection was 7.5 years. The 10-year survival rate in patients who underwent complete and incomplete resection was 69% and 30%, respectively. In contrast, 6 inoperable patients treated with only radiation had a mean survival of 6.2 years. Kanematsu\(^7\) reported 16 cases of ACC. He performed 11 resections; six patients had microscopic residual tumor, of whom five received postoperative radiotherapy. Five patients with unresectable lesions received radiotherapy. The rates of 5- and 10-year survival without local recurrence were 91% and 76% in the resected group and 40% and 0% in the unresected group, respectively. The present author\(^5\) reported two patients with ACC. Both underwent sleeve resections of the trachea and postoperative radiotherapy even though they exhibited negative margins. Both patients remained alive for more than 10 years without recurrence; recently, one patient was confirmed to be alive without disease 20 years after surgery.

Although tracheal resection and reconstruction are difficult, the operative death rate has decreased following the accumulation of operative experiences such as releasing the trachea from surrounding organs, lessening anastomotic tension, and interposing an autograft, such as the patient’s own muscle, between the anastomosis and large vessels. The reported postoperative results demonstrate acceptable prognoses. Therefore, tracheal resection and reconstruction is the main management strategy for ACC whenever possible. The question remains, however, of how thoracic surgeons can select patients who are eligible for surgery and determine the type of reconstruction.

Important information is obtained from imaging modalities, such as computed tomography, magnetic resonance images (including 3-dimensional displays), bronchoscopy, and endobronchial ultrasonography. Lymph node metastases and invasion of adjacent organs are not always contraindications for surgery,\(^3\) because even in such cases, complete resection, if possible, can provide an acceptable prognosis. As mentioned above, although a pathologically negative tracheal stump is desirable, microscopically positive margins can still provide a good long-term prognosis.\(^1\)\(^-\)\(^3\) However, a trachea invaded too far longitudinally by the tumor cannot be reconstructed after an extensive resection. Safe reconstruction might be achieved if less than eight tracheal cartilages are excised, as the anastomotic tension would not be excessively high.\(^3\)

### Artificial Prosthesis and Transplantation

For patients requiring a more extensive resection, tracheal prosthesis is necessary in order to maintain the airway wall. As mentioned above, Maziak and Pearson\(^4\) used Marlex mesh prostheses in four patients. One patient sustained a trachea-innominate artery fistula and another patient died after a dehiscence at the anastomosis. In 2010, Wurts\(^6\) used an aortic allograft for tracheal defects in six patients with salivary gland-type carcinoma, including five with ACC. Three patients had major complications such as fistulas between the esophagus and graft. Before Wurts’s report, Kato and Ishihara\(^7\) moved a canine esophagus anteriorly to a defect of the resected trachea. A Montgomery T-tube passing through the a autoplasted esophagus was used to maintain the rigidity of the airway. Reconstruction using an esophageal autograft seems to be safe, as the rejection response can be completely ignored. Although this technique is not yet utilized in any clinical applications, it seems to be the most reliable and effective maneuver currently available.

### Radiotherapy

The preceding chapter suggests that additional postsurgical radiation to the residual tumor or radiotherapy for unresectable ACC could control the growth of tumors. After the report by Grillo,\(^2\) many surgeons added radiation to the anastomosis even if the stump was pathologically negative. Maziak\(^4\) demonstrated the efficacy of radiation in six unresectable patients. Bittner\(^5\) described the effectiveness of fast neutron radiotherapy for 19 unresectable ACC patients, and reported a 5-year actuarial survival rate of 89.4%, a median survival of 97 months, and a 5-year actuarial locoregional control rate of 54.1%.
However, the supplementary high-dose brachytherapy boost did not improve their results.

**Chemoradiotherapy**

In addition, some case studies have reported that the combination of radiation and chemotherapy was successful for the treatment of unresectable patients. Radiation therapy with concurrent carboplatin and paclitaxel, or with concurrent nedaplatin and 5-fluorouracil, might be an effective treatment for ACC.

**Airway Stents**

For a patient with suffocation due to ACC, placement of an airway stent is an attractive option because it promptly dilates the tracheal stenosis. In particular, SEMS can be easily placed using flexible bronchoscopy and fluoroscopy. However, SEMS fracture is not uncommon in patients with tracheobronchial stenosis, and SEMS can induce the formation of granulation tissue, which causes further stenosis. Removal of SEMS under bronchoscopy can also be extremely troublesome due to the incorporation of the metal into the tracheal mucosa, especially when the stent is fractured. Secure tracheal surgery seems to become impossible just after insertion of SEMS due to the damage to the deep tracheal mucosa. Thoracic surgeons should evaluate whether the patient can undergo tracheal surgery before placement of the SEMS, and SEMS placement should be considered only when all other therapeutic options are depleted. In contrast, silicone stents are the “gold standard” because they can be removed after they become useless or harmful. A disadvantage of silicone stents is that their placement requires a rigid bronchoscope, which is more difficult to manipulate than a flexible bronchoscope. In addition, silicone stents also induce the formation of granulation tissue, and laser therapy cannot be used to remove granulation tissue when a silicone stent is in place because the silicone may burn upon contact with the laser.

**How Should Thoracic Surgeons Manage ACC?**

The strategy for treatment of ACC of the trachea depends on the precise data regarding the local extension of ACC in the trachea. Surgeons should collect this information using imaging modalities, even if they take time to perform. If complete resection is performed, long survival time can be achieved. Therefore, surgical therapy should be considered first. When a patient presents with suffocation, and when the doctor considers the possibility of ACC, SEMS should not be placed immediately because, as mentioned above, SEMS may negatively impact the safety of surgery due to damage to the tracheal wall. Until surgery is ruled out completely, temporary tracheal intubation should be performed.

Radiotherapy and chemoradiotherapy have been performed in unresectable patients, and some investigators have reported excellent outcomes, suggesting that radiotherapy and chemoradiotherapy might replace surgical management in the future.

**Future of ACC Management**

Previous reports on ACC patients reveal a wide variety of tumor characteristics, including malignant behavior, pattern of intra- and extratracheal extension, and sensitivity to radiotherapy. In 1988, Nomori and Ishihara grouped 12 cases of ACC into three histological categories: tubular, cribriform, and solid. The authors also identified three gross infiltrating types: entirely intraluminal, predominantly intraluminal, and predominantly extraluminal. Each histological group might have individual characteristics and show different responses to treatment. Analysis of accumulated cases of ACC in the literature might contribute to the development of new classification and management strategies.

**References**


