Review Article

Tracheal Cancer: A comprehensive Review

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Abstract

Primary malignant neoplasms of the trachea are very rare, making up only 0.1-0.4% of all respiratory malignancies. Limited data exists on management and evidences guiding the treatment are gained from single-institution reports and a few epidemiologic studies. Surgical resection combined with postoperative radiotherapy is the main treatment option. Early diagnosis, access to interventional bronchoscopy, and surgical treatment in specialist units may improve survival.

At present, no clear knowledge exists on the role of chemotherapy, chemo radiation and targeted therapy in the postoperative and advanced setting. Therefore, collaborative effort and multicenter studies are needed.

ABBREVIATIONS

SEER: Surveillance, Epidemiology and End Results; SCC: Squamous Cell Carcinoma; ACC: Adenoid Cystic Carcinomas; HPV: Human Papilloma Virus; CT: Computed Tomography; MR: Magnetic Resonance; RT: Radiotherapy; OS: Overall Survival; DFS: Disease-Free Survival; Cth: Chemotherapy.

INTRODUCTION

Primary cancer of the trachea is particularly rare [1] and accounts for only 0.1-0.4% of all newly diagnosed respiratory tract cancers, which corresponds to 2.6 new cases per 1,000,000 individuals annually worldwide [2,3].

The largest reported series comes from a Surveillance, Epidemiology, and End Results (SEER) analysis of 578 cases identified over a 31-year period [1]. In that series, 56% of patients were male and the mean age was 63 years. Similar results were reported in population-based studies from tumor registries in Finland, Denmark, Netherlands and England [4-7], where the mean age at presentation was approximately 60 to 65 years, and most of cases (60 to 70%) occurred in males.

HISTOLOGY

Primary tracheal tumours can arise from the respiratory epithelium, salivary glands, and mesenchymal structures.

In adults, 90% of primary tracheal cancers are malignant. Squamous cell carcinoma (SCC) represents the most frequent histology (44–63%), while adenoid cystic carcinomas (ACC) accounts for 7–16% of cases. ACCs arise from the mixed seromucinous glands of the tracheobronchial sub mucosa and are characterized by a prolonged clinical course.

The remaining part are distributed widely in a heterogeneous group, covering adenocarcinoma, undifferentiated carcinoma, and neuroendocrine tumors, including small cell cancer [1,8].

In addition to primary tumors, secondary tracheal involvement can occur from tumors of surrounding tissues such as thyroid, oesophagus, larynx and lung cancer, and mediastinal lymphomas.

The absence of lung masses and/or of extensive mediastinal or hilar lymph node enlargement and absence of distant metastasis may be suspected for primary tracheal lesion.

Common benign tracheal lesions include chondromas, hemangiomas and papillomas.

Risk factors

Smoking remains the major risk factor for SCC, but it does not seem to affect the incidence of ACC [9].

Depending upon histology and location, tracheal tumors may overlap with primary lung or head and neck cancers. In addition, given the strong association with smoking, 40% of patients with airway SCC develop synchronous or metachronous head-and-neck or lung cancers [10].

No other risk factors have been associated to tracheal malignancies. Of note, tracheal papillomatosis, a benign condition characterized by papillomatous growth of the bronchial epithelium, is a result of infection with human papilloma virus (HPV) 6 and 11. Malignant transformation to SCC does occur.

Clinical manifestation

The commonest clinical presentation is with exertional

dyspnoea (71%), cough (40%), hemoptysis (34%), wheeze (19.5%), and stridor (17.5%) [11]. Because of the tracheal functional reserve, tumours do not cause symptoms until they occlude 50–75% of the luminal diameter [8].

Moreover, delay in diagnosis can occur because the pulmonary fields remain normal on a chest radiograph [11]. In presence of hemoptysis, which is frequent in SCC, a diagnosis is more likely to be made because bronchoscopy will be performed, even in the presence of a normal chest radiograph.

Upper airway obstruction can be interpreted as adult onset asthma, thus evading timely diagnosis [12-16]. Consequently, a significant number of patients may present with advanced disease [17] and beyond the window of curative treatment.

In 15% of cases diagnosis was delayed by 2 or more months after initial clinical presentation and in 10% of patients the diagnostic delay exceeds six months. In 40% of patients the diagnosis is established following an emergency admission and only occasionally, tracheal tumors manifest with fatal airway obstruction [4].

Patients with more advanced disease may experience dysphagia and hoarseness, which usually indicates that the cancer has spread beyond the trachea. Oesophageal involvement is found in 2% of patients, while distal bronchi and lung parenchyma extension in 28% of cases. Metastases develop in 22% of patients over the course of the disease [4].

Staging

Imaging studies usually precede bronchoscopy, unless the patient arrives in respiratory distress. Patients presenting with respiratory symptoms undergo chest x-ray at first, which usually shows normal lung fields. Studies have shown that chest radiograph identifies only a minority (18%-28%) of tracheal tumor [18,19]. Diagnostic clues on chest radiographs include tracheal narrowing, post-obstructive atelectasis or pneumonia, or abnormal calcification.

Computed Tomography (CT) is a more sensitive diagnostic toll and is regarded as the standard imaging technique for diagnosis, the assessment of tumour extension and its relation with adjacent structures. CT may demonstrate a tracheal or bronchial mass but underestimates the extent of submucosal invasion. Newer software algorithms allow three-dimensional and luminal evaluation by CT (virtual bronchoscopy), but lack the detail of real bronchoscopy and do not reliably determine tumor length [20].

Magnetic resonance (MR) provides no clear advantage over CT in the assessment of tracheal tumours, except for adenoid cystic lesions, because of its ability of evaluate submucosal involvement. In addiction, MR is now being applied to better evaluate extension into tissue planes and vascular anatomy.

Flexible tracheobronchoscopy remains the gold standard for diagnosis because it provides definitive assessment of the airways, gives anatomical considerations, and can obtain a tissue for pathological diagnosis. In case of acute respiratory distress or when the mass show bleeding tendency, flexible bronchoscopy could aggravate the obstruction of the airway: in these cases the use of rigid bronchoscopy is advised.

Endoscopic ultrasound (EBUS) can also help to establish the depth of tracheal invasion, tracheal wall thickness and mediastinal lymph-node metastasis.

Mediastinoscopy is an important exam for staging potentially resectable lung cancers: however the natural history of primary tracheal malignancies and the few data of Literature do not allow drawing similar conclusions for cancers arising from the trachea.

No data exist regarding the role of PET-CT scan in tracheal cancer staging. However with the aim of differentiating primary tracheal neoplasm from metastasis of pulmonary or other intra/extrathoracic cancers, PET/CT can be a reliable useful tool, especially in case of squamous cell or small cell cancers.

Pulmonary function tests can detect obstruction in the upper airway. Flow-volume loops with characteristic flattening of both inspiratory and expiratory phases can also be identified, providing further evidence of a fixed upper-airway obstruction.

The cancers of the trachea have no specific TNM classification but it commonly follows lung cancer staging.

Treatment

Evidence in tracheal cancer treatment is based mostly on small retrospective series, which enrolled patients during long (two, three decades) periods. Obviously, because of the long time interval, treatment and diagnostic modalities have changed. Due to the absence of guidelines based on randomized clinical trials, the choice of treatment modalities and their optimal sequence remain an open-ended question.

Treatment can be either palliative, which aims to restore airway patency, or therapeutic [21].

In early stage disease, primary treatment includes surgery with optional postoperative radiotherapy (RT). With the combined treatment the 5-year overall survival (OS) rate reaches up to 52% in ACC and 39% in SCC [22,23]. Endoscopic resection by various techniques can also play a role.

Surgery

Surgery represents a curative treatment for benign and low-grade malignant tumours, achieves long-term survival in tracheal carcinomas, provides pathological confirmation of complete tumour removal and relieves airway obstruction permanently. Epidemiological studies found a survival advantage with surgical resection [6], thus suggesting that it represents a curative treatment option. The decision to resect depends on several factors and it is influenced particularly by tumor length, neck mobility, histology, patients' comorbities and preferences. The extent of the tumor determined by imaging and the bronchoscopic appearance, as well as patient characteristics and available services, determines the best approach. The role of mediastinal lymphadenectomy for ACC or SCC tracheal cancers is not clear; in a recent national review of the incidence and treatment of primary tracheal cancer in England between 1996 and 2011, lymphadenectomy was performed in only 1.8% of cases [4].

Furthermore, anaesthesia for tracheal procedures offers distinct challenges and requires careful coordination between the surgical and anaesthesia teams during airway excision and anastomosis [24].

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Up to 70% of patients can be treated with surgical excision of the trachea or carina followed by RT, which results in superior long-term survival compared with palliative therapy [23,25]. Even bulky SCCs may be resectable and surgery generally offers the best chances of longer term survival when feasible [1,6,7].

Conversely, in case of locally advanced or metastatic disease, as well in patients medically unfit for surgery, there are minimal data to define a standard of care [26].

The resectability evaluation should be made by an experienced surgeon. Surgical treatment may involve segmental tracheal or cricotracheal resection and re-anastomosis, wedge and sleeve resection, biological, or prosthetic grafts. Challenges exist in intraoperative and postoperative management, including wound healing and preservation of blood supply.

In specialized tracheal centres resection rates of up to 70% and perioperative mortality rates as low as 3% have been reported [23,27], while 30-days mortality is 7–11% [28].

Disease-free survival (DFS) after resection is limited more by distant metastasis and regional disease rather than by local recurrences. Data from larger series indicates that negative airway margins and adenoid cystic histology are associated with longer DFS.

As ACC exhibits a limited response to chemotherapy (CTh) and RT, surgical resection with negative margins is an extremely important prognostic factor. Unfortunately, ACC tends to infiltrate along the airways, thus it is often incompletely resected (complete resection rate ranges from 42 to 57%) and prone to recur locally [29]. Interestingly, incomplete resection seems not to negatively affect survival. The median DFS and OS after incomplete or complete resection were 84 and 119 months and *vs* 98 and 121 months, respectively in the Kanematsu experience. However, this result was not consistent with the outcome in similar reports [30].

Postoperative treatments

Multidisciplinary treatment including RT and CTh may be necessary to obtain lower recurrence rate and better prognosis.

Complete surgical resection followed by postoperative RT, is considered the standard treatment since it seems to offer the best chance of achieving long-term cure [7,30-34].

However, although RT seems to improve local control [3,22,25], no significant differences in OS and DFS have been demonstrated with or without postoperative RT [3,30].

In the experience of Maziak et al. [3], the 5 and 10 year survival rate was 79% and 51% respectively in 32 patients with ACC treated with primary resection followed by adjuvant RT. Interestingly, a mean survival of 6.2 years was reached in six patients who received RT alone.

Few publications with larger series of patients and long term follow-up data after adjuvant RT and CTh are available. Therefore, no definitive conclusion can be drawn.

Palliative treatments

RT plays a significant role as a part of radical combined treatment as well as a palliative approach [35,36]. Given the lack of a uniform staging system, comparison of treatment results across studies remains difficult. However, a general consensus supporting the use of RT exists, and some Authors have recommended primary therapy with radiation alone for early-stage lesions [37].

RT can be used as initial treatment, but with dismal survival as compared to surgery. In one series, median survival was 11 months with a 5-year survival of only 11% [7].

RT can also be used for unresectable lesions, particularly after palliative procedures, including stents, have relieved airway obstruction.

Although sparse, literature data suggest that a dose of higher than 60 Gy given as 30 fractions over 6 weeks, and preferably in the order of 70 Gy given as 35 fractions over 7 weeks, is needed for local tumour control in most patients with unresectable SCC [18,36-43] and in ACC [44-46].

Recently, palliative endotracheal brachytherapy has emerged as a new option. In a prospective series by Nguyen and Colleagues, the mean overall survival and symptom-free survival were 5 and 6.8 months, respectively. After brachytherapy, 88% of patients experienced symptomatic improvement with minimal toxicity (only one grade 1 tracheal stenosis was reported) [47].

There is little defined role for CTh as primary or post operative treatment in the context of tracheal neoplasm. Available reports have focused mainly on advanced and recurrent disease.

In advanced stage disease, including transcartilaginous or extratracheal extension, consideration may be given to combined CTh and RT, very much akin to treatment of advanced laryngeal cancer.

Only case studies have reported the use of CTh in patients with ACC [48-50] and the combination of RT and CTh (with carboplatin and paclitaxel, or with concurrent nedaplatin and 5-fluorouracil) for advanced disease. The combined therapy was successful for the treatment of unresectable disease [48].

However, the effectiveness of combined treatment modality has not yet been prospectively assessed and the role of RT and CTh is far from finally settled. Decisions about the operative strategies should depend on the size, location, and local invasion of the lesion, experience of the surgeon, and diverse accompanying conditions.

Recently, the role of tyrosine kinase inhibitors imatinib and sunitinib [51-53] in advanced ACC has been explored with dismal results.

Endobronchial therapies

For the patient in respiratory distress, rapid relief is provided by endobronchial debulking.

Debulking with laser, electron cautery, argon plasma coagulation, cryotherapy, or photodynamic therapy via rigid tracheobronchoscopy may rapidly relieve airway obstruction. Although used in a palliative setting, these treatments have the advantage that can be repeated and/or used as a bridge to surgery or RT. Unfortunately; these modalities are not widely available [54].

These measures should never be attempted with curative intent, because they rarely offer long-term survival. Local therapy can be curative only in the setting of early and superficial SCC, while surgical removal is a better treatment option for ACC, since it has a great propensity for submucosal spread.

Laser therapy has been used to relieve malignant major airway obstruction if a patent distal airway exists and there is intrinsic airway disease rather than extrinsic compression. Laser therapy is particularly useful in symptomatic patients for whom surgical options were excluded.

Disadvantages include the difficulty in predicting the extent of penetration into deeper tissues. Possible complications include perforation, rupture, fistula formation, and haemorrhage. Air embolism has also been described.

Placement of airway stents must be avoided as long as surgical resection remains an option; since it can damage the normal tracheal wall, thus impairing healing of tracheal anastomosis [32]. In addiction, self-expanding stents are almost impossible to remove once placed, thus life expectancy should be limited to a few months at the time of insertion in order to avoid secondary complications. Conversely silicon stents, which can be easily removed, may be very helpful in getting patients through radiation as there is often significant swelling initialy.

Prognosis

The published studies carried out until now indicate some well defined prognostic factors such as histological subtype, early stage disease, complete resection and negative surgical airway margins [22,55]. In the study by Chen, performance status and RT were identified as independent prognostic factors for DFS and OS at both the univariate and multivariate levels [56]. The available data clearly indicate the negative impact of positive nodal disease on OS, as it diminished survival by greater than 50% when compared to lymph node negative disease.

Reported survival rates for primary SCC are remarkably poor, typically exhibiting median survivals of less than 6 months and 5-year survival rates of less than 10% [6,57]. Some series reported better outcome, with 5-year survival rates of 35% and 47%. These difference mainly reflect differences of stage at diagnosis [25,28].

Survival rates for ACC are substantially higher than that of other tracheal malignancies, with 5-year survival rates ranging from 66% to 100% and 10-year survival rates ranging from 51% to 62% [45,58]. Regional nodal involvement is rare in ACC, but approximately 50% may eventually have hematogenous metastases [3,45].

DISCUSSION AND CONCLUSION

Primary tracheal cancers are rare and still represent a challenge for clinicians because of the absence of defined treatment guidelines. Early detection along with improved surgical and interventional techniques can impact on patients' outcome.

Surgery followed by adjuvant RT remains the treatment of choice for most patients. However, there are still many unsolved issues and further data are required to define the role of chemotherapeutic agents, combination therapies, and novel surgical and endoscopic techniques.

More robust evidence-based studies would be required to provide robust evidence but the rarity of disease will likely prevent it from ever being studied prospectively in single institutions.

Therefore, collaborative efforts and multicenter studies will be necessary.

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