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REVIEW ARTICLE

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Tracheal cancers

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ABSTRACT

Primary tracheal tumors are very rare and the literature on this subject is limited. Due to their rarity and diversity, the provision of patient care in terms of optimal management poses a considerable challenge. There are no unequivocal guidelines concerning the treatment in patients with local or distant disease. The most common types of primary tracheal tumors are squamous cell carcinoma and adenoid cystic carcinoma. Squamous cell carcinoma of the trachea is 2–4 times more common in men than in women and develops primarily in the sixth and seventh decades of life. It is strongly associated with tobacco smoking. Adenoid cystic carcinoma of the trachea occurs with similar frequency in men and women, and is most common in the fourth and fifth decades of life. The etiology of this type is unknown, however it is not associated with tobacco smoking. Adenoid cystic carcinoma is characterized by submucosal and perineural spread. Treatment of patients with primary tracheal tumors requires a multidisciplinary approach. Optimal treatment of localized tumors is based on surgery or radiotherapy. If distant metastases are present the therapeutic palliative methods are: chemotherapy, palliative radiotherapy or palliative surgery. The prognosis of patients with primary tracheal tumors is determined by several factors. Histological diagnosis of adenoid cystic carcinoma, good performance status, and complete resection have been identified as favorable prognostic factors. Despite intensive treatment, the 5-year survival rate for primary tracheal tumors is not satisfactory.

Keywords: tracheal tumors, tracheal cancers, adenoid cystic carcinoma of the trachea, squamous cell carcinoma of the trachea, treatment

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Epidemiology

Primary tracheal tumors are rare. They account for 0.2% of all respiratory tract cancers and 0.02% to 0.04% of all malignant tumors [1]. The annual incidence is approximately 0.1 cases per 100,000 individuals. About 90% of primary tracheal tumors in adults are malignant. In comparison, malignant tumors account for 10–30% of cases in children [1]. Squamous cell carcinoma (SCC) and adenoid cystic carcinoma (ACC) both represent over two-thirds of primary tracheal tumors in adults [2]. In a large epidemiological study on primary tracheal tumors using data from the SEER (Surveillance, Epidemiology, and End Results) database, among 578 cases from 1973 to 2004, SCC was the dominant histological type (44.8%), followed by ACC (16.3%), unspecified or undifferentiated carcinoma (12.8%), small cell carcinoma (9.7%), adenocarcinoma (5.9%), large cell carcinoma (3.8%), and sarcoma (3.8%) [3].

Squamous cell carcinoma

Macroscopically, SCC typically appears as multiple and often ulcerating lesions growing into the lumen of the trachea. These lesions vary in the degree of cellular differentiation and may or may not exhibit keratinization [4]. Histologically, SCC of the lung and trachea are identical [5]. The tumor can affect any part of the trachea, and in one-third of patients at the time of diagnosis,

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there are metastatic lesions in the mediastinum or lungs [2]. It occurs 2 to 4 times more frequently in men than in women, primarily in the 6th and 7th decades of life [2, 5–7]. The etiopathogenesis is closely linked to tobacco smoking [5, 6]. In 30–40% of cases, SCC coexists with a metachronous or synchronous second primary tobacco-related tumor in the oral part of the throat, larynx, or lungs [2, 5].

Adenoid cystic carcinoma

Adenoid cystic carcinoma of the trachea is most commonly observed in the 4th and 5th decades of life [5–7]. It occurs 2 to 4 times more frequently in men than in women, primarily in the 6th and 7th decades of life [2, 5–7]. The etiology of the tumor is unknown, and unlike SCC, it is not associated with tobacco smoking [5, 6, 8].

This tumor originates from small salivary and serous glands present in the submucosal membrane of the trachea, and the morphological picture of ACC corresponds to primary salivary gland tumors [9]. Macroscopically, ACC often grows as an exophytic tumor, leading to the narrowing of the tracheal lumen [2]. The morphological picture is characteristic, with two types of cells: ductal cells with scant cytoplasm and hyperchromatic angular nuclei that stain positive for cytokeratin (CK7) and flattened myoepithelial cells that stain positive for myoepithelial markers (p63, SMA, calponin). The biphasic appearance highlighted by immunohistochemistry is crucial for differential diagnosis. Cells form cribriform, tubular, and solid patterns [10]. The percentage of solid areas determines the degree of histological differentiation. In cases of uncertainty, immunohistochemical staining with MYB antibody can be performed — a positive result indicates the MYB gene translocation characteristic of ACC, which can be confirmed by fluorescence in situ hybridization (FISH) [11, 12]. Submucosal and perineural spread characterize ACC [13]. At the time of diagnosis, regional lymph node metastases or distant metastases are present in only about 10% of patients [2]. Although the growth rate of ACC is often slow, in some cases, it may present a more aggressive course with a tendency for local invasion and metastasis. Furthermore, even after a very long disease-free period, local or systemic recurrences can occur [2, 5].

Other histological types

Primary tracheal tumors other than ACC and SCC are rare and histologically diverse. They are not easily classified and are usually reported together with ACC and SCC [3, 5, 14, 15]. In one of a few studies focusing on other histological types of tracheal tumors, 33 different histological diagnoses were made among 90 patients [16]. Diagnoses were divided into 5 groups, including benign tumors, carcinoids, other salivary gland-type tumors (including mucoepidermoid carcinoma; MEC), sarcomas, and non-squamous cell carcinomas. Malignant tracheal tumors were diagnosed in 62% of patients. The diagnoses involved 54 men and 36 women with an average age of 43 years (range 4–81 years). In another study, 23 different histological types of malignant tracheal tumors were presented with an analysis of the age at which peak incidence occurs among selected types [7]. In yet another study, among other malignant tracheal tumors, carcinoids, lymphomas, melanomas, MEC, non-squamous cell carcinomas, and sarcomas were distinguished [5].

Clinical presentation

Clinical symptoms of tracheal tumors can result from airway obstruction (shortness of breath, wheezing, stridor), irritation and ulceration of the mucous membrane (cough, hemoptysis), or direct invasion of neighboring structures (nerve paralysis, dysphagia). The disease is often diagnosed late due to the large functional reserves of the tracheal lumen. Initial symptoms only appear when the tracheal lumen is narrowed by 50–75%. Exertional dyspnea occurs when the tracheal lumen narrows to 8 mm (resting dyspnea at 5 mm) [2, 5]. The presented symptoms are nonspecific and can lead to a misdiagnosis of asthma, chronic obstructive pulmonary disease, or bronchitis. The most common symptom of tracheal SCC is hemoptysis. The occurrence of hemoptysis usually leads to early diagnosis of the tumor. However, hemoptysis is present in fewer than 25% of patients at early stage of the disease. The absence of symptoms often leads to a delay in diagnosis, sometimes by several months [2]. The development of hoarseness and dyspnea typically indicates advanced disease. Wheezing and stridor are the most common symptoms in the case of ACC.

Diagnosis

Conventional chest X-ray only detects abnormalities in 18–28% of patients, and it is not recommended for the diagnosis of tracheal tumors [9]. The standard imaging method for evaluating tracheal tumors and assessing their extent, including the involvement of adjacent and distant structures, is computed tomography (CT). Magnetic resonance imaging (MRI) may have an advantage in the case of ACC [2]. Most SCCs show high fluorodeoxyglucose uptake in positron emission tomography-computed tomography (PET-CT), but ACC exhibits variable uptake depending on the degree of differentiation [17].

Diagnosis is based primarily on bronchoscopic examination, which allows for precise localization of the lesion, assessment of the extent of the disease, and the collection of tissue samples for pathological examination [18].

Staging

Tracheal tumors, due to their rarity, are not included in the TNM classification system for malignant tumors. There are only proposals for classification, which have not been prospectively confirmed, describing the anatomical extent of the disease [2, 6, 14, 19–21]. Assessing the anatomical extent of the lesions can help decide on the choice and feasibility of a particular treatment method and may have prognostic value. In a study published in 2022, a collection of publications proposing a method for determining the stage of primary tracheal cancer was presented, and attempts were made to examine the prognostic significance of TNM in patients with primary tracheal tumors [22].

Treatment

Radical surgical treatment

Radical surgical treatment, if the extent of the disease allows, is the treatment of choice. The type of surgery depends on the location and size of the primary tumor as well as the involvement of adjacent structures [2]. Tracheal tumors are considered resectable if the affected tracheal segment can be safely removed and reconstructed with a primary anastomosis. This depends not only on the extent of the disease but also on the patient's age, body mass, neck mobility, and comorbidities [5]. Older patients with limited neck mobility may not be candidates for resections longer than 2–4 cm, while in younger and taller individuals, over 6 cm of the trachea can be removed [5, 23]. This assessment also depends on the operator's experience. Nowadays, precise preoperative planning and improved reconstruction techniques allow for the safe removal of even more than 50% of the tracheal length in selected cases [6]. Routine extensive lymphadenectomy is not recommended due to the risk of compromising blood flow to the remaining part of the trachea and hindered anastomotic healing [2, 5, 23]. Removal of clearly enlarged and altered lymph nodes is only recommended [24].

Tracheal SCC resection aims to achieve microscopically radical excision (R0) while preserving good postoperative function. This is achieved in approximately two-thirds of surgeries in large centers [25]. Intraoperative histological analysis using frozen section evaluation helps determine margin status and potentially increases the scope of the operation unless safe reconstruction limits have been reached, and additional resection is ruled out [5]. Non-radical resection is more common in ACC due to its characteristic growth pattern. This tumor spreads submucosally and along the course of nerve trunks beyond the visible tumor boundaries. Positive surgical margins are found in 40–50% of patients undergoing resection for ACC [25]. Most patients, after non-radical resections, receive adjuvant radiotherapy [5, 25].

Palliative surgical treatment

Palliative surgical treatment aims to restore the lumen of the narrowed part of the airways when radical treatment is not possible or serves as a bridge to radical treatment in patients with severe symptoms caused by airway obstruction. Restoration of the airway can be achieved through various endoscopic techniques, including mechanical endoscopic dilation, laser vaporization, electrocoagulation, cryotherapy, photodynamic therapy, or argon coagulation [2, 26]. In most cases, these methods provide improvement but often require repeated procedures and do not guarantee a permanent effect. In non-operative cases, airway patency improvement can be achieved using stents. Satisfactory palliative results can be achieved in 80–90% of properly selected patients [2]. However, literature reports indicate that despite efforts to improve the material used to create a functional scaffold, the limitation of the method is granulation within the tracheal lumen caused by the foreign body, which can lead to an increase in the length of the constriction. Other drawbacks include stent migration and the esophageal and vascular fistulas [5]. Self-expandable metal stents can be used in patients with an expected survival of 3–6 months [5]. They are not suitable for non-operative patients diagnosed with ACC. In these patients, long-term survival is observed despite advanced disease. Some authors prefer silicone stents in such cases. However, both techniques should be reserved for patients for whom future surgery is not planned [26].

Postoperative radiotherapy

The discussion regarding the use of adjuvant radiotherapy (RT) remains inconclusive. Postoperative RT is often used despite limited evidence of its effectiveness in all patients [7]. Treatment begins when the surgical anastomosis is fully healed. The effect of tracheal wall tension may persist for some time, and treatment typically starts around 2 months after surgery or later in cases where there are significant concerns about the risk of anastomotic leakage [5]. The standard total dose in adjuvant

treatment is 54–60 Gy in conventional fractionation (2 Gy per fraction) [2, 5]. In cases with larger residual tumor masses, the dose may be increased to 68-70 Gy (2 Gy per fraction) [2]. Postoperative RT planning should be based on the preoperative CT scan [27]. Patients who have undergone limited resection due to the length of the involved trachea and reconstructive possibilities are eligible for treatment [5]. In most studies, adjuvant RT is also recommended for microscopically incomplete resections although this is not based on prospective randomized studies. Fifty-nine percent of ACC patients treated at the Massachusetts General Hospital had "positive" surgical margins, compared to 18% of SCC patients [5]. Other factors considered in adjuvant RT include local tumor advancement, invasion beyond the lymph node capsule, and perineural or vascular invasion. In a retrospective "matched-pair" analysis conducted by Xie et al. [28] based on the SEER database, an attempt was made to determine the impact of RT on improving outcomes in patients with malignant primary tracheal tumors. Patients who received RT were matched to patients with similar demographic characteristics, tumor histology, disease extent, and surgical resection. RT improved survival, especially in patients diagnosed with SCC ($p < 0.0001$) and regional disease ($p = 0.030$). In a study by Wen et al. [21] based on data from 405 patients from the SEER database, nomograms predicting overall survival (OS) were created. Using the propensity score matching method, the authors found a favorable effect of adjuvant RT only in cases of SCC. It should be noted that the nomograms did not include surgical margin status. In their discussion, the authors pointed out the lack of this information in the SEER database. On the other hand, a retrospective analysis of patients treated at the MD Anderson Cancer Center did not show a statistically significant OS improvement after adjuvant RT [6].

In the case of tracheal ACC, therapeutic decisions are complicated by additional factors. This tumor exhibits low radiation sensitivity, but its specific growth pattern often results in "positive" margins. Additionally, late local recurrences of ACC are observed even after radical resections [29]. Available literature data are inconclusive — some centers recommend postoperative RT for all patients, while others use radiation therapy in cases with "positive" surgical margins or do not recommend adjuvant RT due to its lack of impact on overall survival [29].

The decision about postoperative RT should be made individually in each case.

Radical radiotherapy

The standard of care for patients with tracheal tumors should involve radical resection, which is applied to fewer than 25% of patients eligible for radical treatment [30]. For the remaining patients, radical radiotherapy is considered an alternative therapeutic option [31]. Indications for RT include locoregional disease, where radical surgical treatment is not feasible [25]. Radical RT is also used in patients who do not qualify for resection due to non-oncologic reasons or do not consent to surgery. Patients in good overall condition after a thorough assessment of the tumor extent are eligible for radiation therapy. The required dose to achieve local control is 70 Gy (35 fractions over 7 weeks) [5, 25]. RT should be planned using conformal techniques, preferably with intensity-modulated radiation therapy (IMRT) [27]. However, there are limited data on modern RT methods using precise radiation techniques, such as image-guided radiation therapy (IGRT) and IMRT, as well as proton therapy or carbon ion (C12) radiation [25, 32].

Intraluminal brachytherapy (8–15 Gy) has shown an impact on improving local tumor control when combined with external beam RT (60–68 Gy) in the radical intraluminal treatment [2]. Further research is needed to determine the maximum and optimal intraluminal brachytherapy dose as a method to increase the total dose in combination with external beam RT [2].

Palliative radiotherapy

Palliative radiation therapy is used to relieve symptoms caused by local tumor growth in patients who are not eligible for radical treatment. The most common indications include hemoptysis, pain, dyspnea, and cough. A good palliative effect can be achieved in 75% of treated patients. In the group treated with palliative intent at the Bydgoszcz Oncology Center, an improvement in presented symptoms was observed, which correlated with an objective response in the irradiated tumor area. The average response time was 12.5 months [33].

Radiochemotherapy

The combined radiochemotherapy (RCTH) approach is an established method for the radical treatment of many locally advanced cancers. The biological basis for combining both methods lies in increasing the effectiveness of local and regional cures while reducing the risk of distant metastases. Radiochemotherapy is also used as part of organ-sparing procedures (as an alternative to very extensive surgical procedures). Concurrent RCTH with cisplatin is the treatment of choice for patients with locally advanced head and neck cancers. Concurrent and sequential RCTH has been shown to be superior to standalone RT in the treatment of locally advanced lung cancers and is the standard of care in such cases. Data regarding the combination of chemotherapy (CTH) and RT for tracheal tumors are very limited. There are only individual case reports and retrospective studies involving very small groups of patients. Published studies

have used RCTH in both concurrent and sequential forms. Most studies focus on concurrent treatment, which includes CTH using carboplatin (AUC 2) and paclitaxel (50 mg/m^2) administered weekly, combined with conventional fractionated conformal RT to a total dose of 60–66 Gy [31, 34–36]. Other centers prefer cisplatin (80 mg/m^2 on days 1 and 28) with vinorelbine (12.5 mg/m^2 on days 1, 8, and 15) with concurrent RT with a dose of 60 Gy, followed by an additional 2 cycles of CTH [25]. Sequential treatment CTH regimens include carboplatin (AUC 5) and paclitaxel (175 mg/m^2) given every 21 days or the PELF regimen consisting of cisplatin, etoposide, leucovorin, and fluorouracil. In the PELF regimen, 2 cycles of induction CTH are administered, followed by 2 additional cycles with RT at a dose of 60 Gy in 30 fractions [31, 37]. Toxicity most commonly involves acute esophageal reactions.

Systemic treatment

The clinical course of ACC is characterized by relatively slow growth, and regional lymph node metastases are rare. In the early years of observation, local treatment is highly effective (with 5-year disease-free survival rates ranging from 50% to 75%). However, in subsequent years of observation, there is an increased number of patients with local recurrences or distant metastases. Approximately 10–15% of patients remain disease-free after 15 years of follow-up [38]. Distant metastases most commonly occur in the lungs [10, 39]. Patients with lung metastases tend to have a better prognosis than those with metastases in other organs [38]. Lung metastases typically grow expansively and often remain asymptomatic for many years [40]. Among a large group of patients (62) treated at the Mayo Clinic between 1972 and 2002, distant metastases were observed in 40.5% of cases [10]. Fifteen patients with ACC had distant metastases primarily to the lungs, brain, chest wall, and liver [10]. Advanced disease at diagnosis is described very rarely. In another study, non-operable patients accounted for 23% (8), with only 3 having stage IV disease at the outset [41]. In two other studies, patients at clinical stage IV at the time of diagnosis accounted for 8.3% (1) and 10% (3), respectively [11, 40]. Adenoid cystic carcinoma has limited chemosensitivity. There are limited data in the literature regarding systemic treatment for tumors located in the trachea. In the study mentioned above, attempts were made to use CTH in patients with stage IV disease [41]. The first patient received a regimen of gemcitabine and cisplatin, but the disease progressed due to the enlargement of the primary lesion and mediastinal lymph nodes after two cycles of treatment. The second patient received vinorelbine and cisplatin, which reduced symptoms and stabilized the disease on imaging studies. In patients who experienced disease progression during the observation period, only one showed a response to treatment with paclitaxel and cisplatin [41]. Another study described the effectiveness of combining carboplatin and paclitaxel, as well as one case of the effectiveness of uracil-tegafur and cisplatin in combination with RT [29, 34]. In two of the largest studies that evaluated systemic treatment in patients with ACC of the head and neck region, the limited role of CTH was confirmed, with a low frequency and short duration of responses. In patients with unresectable recurrences or ACC metastases, CTH may only be considered in the case of rapid progression; in patients with clinical symptoms, it can be considered after ruling out the possibility of using local treatment methods (palliative RT, resection of a single metastatic lesion). Monotherapy is preferred for its lower toxicity in the event of a decision to administer chemotherapy. Drugs that have shown objective responses include mitoxantrone, vinorelbine, and epirubicin [38, 42]. For head and neck ACC, research is ongoing into the use of systemic and targeted therapies [43–47]. New molecularly targeted drugs are being evaluated. In one study, whole-genome sequencing was used to better understand the genetic changes underlying metastatic ACC and identify potential therapeutic targets [43]. The analysis was based on material from five patients with ACC (including 2 cases of ACC originating in the trachea). The analysis revealed a small number of mutations, consistent with findings from other studies. Each patient had potential therapeutic targets identified. Based on the results, three patients received dedicated molecularly targeted treatment in phase I and II clinical trials. Two of them achieved disease stabilization. The identification of molecular targets in ACC may lead to potentially effective systemic treatment.

There are no established systemic treatment regimens for advanced SCC of the trachea. Only individual case reports, mainly concerning combination therapy, are available. In daily practice, regimens adapted from the treatment of squamous cell carcinomas of the head and neck, and lung are most commonly used. The most frequently cited combinations in the literature include platinum-based chemotherapy with paclitaxel or vinorelbine [25, 31, 35]. In one available case report, RT was combined with systemic treatment consisting of fluorouracil, leucovorin, oxaliplatin, and cetuximab, achieving complete regression [48].

Immune checkpoint blockade has become a therapeutic option for many patients with cancer. Immune checkpoint inhibitors have demonstrated effectiveness in some cancer types. The greater efficacy of immunotherapy refers to tobacco-related cancers, which may be related to the high number of somatic mutations observed in cancer cells, potentially carrying a high mutational load [49]. Tracheal SCC appears to be closely associated with tobacco smoking, in contrast to ACC. In one study, a retrospective review of medical

records of 23 patients with primary tracheal tumors was conducted. Available paraffin blocks were immunohistochemically assessed to determine the expression of programmed death-ligand 1 (PD-L1). Among the cases identified were 14 (61%) ACC cases and 4 (17%) SCC cases. PD-L1 expression was observed in 3 (75%) SCC cases, while it was not observed in ACC cases. PD-L1 expression was significantly higher in SCC tumors than in salivary-type tumors ($p = 0.001$) [50]. Two case reports regarded immunotherapy for tracheal SCC. In the first case, recurrent tracheal SCC with PD-L1 expression of 95% was treated with pembrolizumab (200 mg every 3 weeks) for 11 months. Complete remission was achieved in the third month of treatment, with no treatment-related toxicities observed [51]. Another case involved treatment with nivolumab (3 mg/kg every 2 weeks). A follow-up bronchoscopy after 7 months of treatment showed complete regression. The patient experienced a significant improvement in overall condition, reduced dyspnea, and resolution of dysphagia. The patient reported only mild fatigue throughout the treatment period.

Summary

Primary tracheal tumors constitute a rare and relatively poorly understood group of cancers. Due to their rarity, diverse morphology, and clinical presentation, it is challenging to accurately predict the course of the disease. Current literature mainly consists of retrospective analyses and case series. However, in recent years, several larger studies and reviews have expanded our knowledge in this area. Over the past decade, there have been six original studies based on large population databases [3, 21, 24, 28, 52, 53] and ten studies that mostly obtained data from single institutions. These studies predominantly focused on the diagnosis of ACC in the Asian population and included patient groups ranging from 10 to 88 [11, 15, 32, 39–41, 54–57]. In 2019, the first systematic review was published, involving 342 articles and 733 patients with tracheal tumors [7]. In addition to case reports, five Polish original studies from 2022, 2016, 2010, 1998, and 1990 included patient groups of 89, 58, 50, 23, and 15, respectively [15, 20, 22, 33, 58].

Evaluating and comparing these results is challenging due to the rarity and diversity of tracheal tumors. Furthermore, there is a lack of clear criteria for classifying tumors as originating primarily in the trachea, especially in the case of SCC (primary or secondary to previously diagnosed head and neck or lung cancer). Adenoid cystic carcinoma is predominantly located in the trachea, likely due to the distribution of glandular cells in the bronchial tree (the presence of glandular cells decreases in the bronchial tree as the bronchi branch). The incidence of ACC arising in peripheral lung is very low [29]. Squamous cell carcinoma and other histological types are more challenging to diagnose, and careful comparison of radiological documentation with pathological reports is necessary to differentiate between metastatic and primary tracheal involvement. Additionally, some patients may present with 2 or 3 tobacco-related tumors. Clear treatment guidelines for primary tracheal tumors are still lacking. Prognosis for these tumors may depend on several factors. Positive prognostic factors include a histological diagnosis of ACC [3, 6, 14–16, 19–21, 33, 59–63], good overall patient condition [15, 20, 64–66], and radical surgical treatment [6, 7, 10, 14, 20, 40, 59, 62, 67]. Authors have also highlighted the significance of tumor stage and sex [22, 68].

Despite aggressive treatment approaches, reported 5-year survival rates are disappointing. Squamous cell carcinoma of the trachea, in particular, exhibits a very poor prognosis, with average survival rates of around 6 months and 5-year survival rates of approximately 10% [3, 14–16, 20, 62, 63]. However, some studies reported 5-year survival rates as high as 39% and 47% [59, 60]. In contrast, ACC generally has a much better prognosis, with 5-year survival rates ranging from 40.2% to 89.4% and 10-year rates between 29% and 62.3% [3, 15, 19–21, 59–61]. A meta-analysis confirmed significantly better survival for ACC compared to SCC (165 months *vs.* 14 months, respectively; $p < 0.001$) [7]. Despite ongoing improvements in RT and surgical techniques, there has been no significant breakthrough in improving the survival of patients with primary tracheal tumors. Given the rarity and complexity of this disease, patients should be treated in highly specialized centers experienced in managing these rare tumors. Collaboration within multidisciplinary teams, including surgical oncologists, clinical oncologists, radiation therapists, pathologists, and radiologists, is crucial. Additionally, efforts should be made to include patients with primary tracheal tumors in multicenter clinical trials, as their results may form the basis for developing standardized care protocols.

Article Information and Declarations

Author contributions

A.Piórek: writing — original draft preparation; A.Plużański, M.K.: supervision; all authors: conceptualization, writing — review and editing.
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Supplementary material

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