

Prognostic significance of sex in patients with primary tracheal tumors – a retrospective, single-center study

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Introduction. We aimed to assess the prognostic significance of the sex of patients with primary tracheal tumors based on our own results as well as the literature review.

Material and methods. We carried out a retrospective analysis of 89 patients with primary tracheal tumors treated at the Maria Skłodowska-Curie National Research Institute of Oncology in Warsaw, Poland, between January 2000 and December 2016. Men and women were compared in terms of overall survival, disease-free survival, and progression-free survival.

Results. In the entire study group, the median overall survival was 61.30 months in women and 8.55 months in men ($p < 0.0001$). 5-year overall survival rates were 2.1% in men versus 50.6% in women ($p < 0.0001$). Among those receiving radical treatment, women had improved survival rates compared with men. Sex was an independent prognostic factor in both the total study population and among those undergoing radical treatment.

Conclusions. According to our results, women with primary tracheal tumors have significantly better survival than men. Because female sex is an independent prognostic factor in patients with primary tracheal tumors, the ratio of women to men should be taken into consideration in reports comparing the outcomes of different treatments.

Key words: tracheal tumors, adenoid cystic carcinoma of the trachea, squamous cell carcinoma of the trachea, sex

Introduction

Primary tracheal tumors are rare, and therefore remain poorly understood. They represent 0.2% of all respiratory cancers and 0.02–0.04% of all malignancies [1], with an annual incidence of approximately 0.1 per 100 000 people. The most common types are squamous cell carcinoma (SCC) and adenoid cystic carcinoma (ACC), which together account for more than two-thirds of primary tracheal tumors in adults [2].

Squamous cell carcinoma of the trachea usually presents as multiple and often ulcerative lesions growing into the tracheal lumen, with histology identical to that of SCC of the lung [3]. Squamous cell carcinoma can occupy any part of the trachea, and a third of patients have mediastinal or pulmonary metastases at diagnosis [2]. 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 [2–5]. It is strongly associated with tobacco smoking [3, 4], and 30–40% of patients with SCC of the trachea have concurrent metachronous or synchronous primary smoking-related cancer of the oropharynx, larynx, or lung [2, 3].

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 [2–5]. The etiology of ACC is unknown; however, unlike SCC, it is not associated with tobacco smoking [3, 4, 6]. Adenoid cystic carcinoma is characterized by submucosal and perineural spread [7]. It often develops slowly, but can be more aggressive in some cases, with a tendency to local infiltration and, less frequently, lymph node metastases. Moreover, local or systemic recurrences may occur beyond 10 years after primary treatment [2, 3].

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The prognosis of patients with primary tracheal tumors is determined by several factors. Histological diagnosis of ACC [4, 8–20], better performance status [14, 16, 21–23], and radical surgery [4, 5, 8, 16, 17, 19, 24–26] have been identified as favorable prognostic factors. Literature on the influence of sex on overall survival (OS) in different tumors has been increasing. An Australian study showed that men had lower 5-year OS than women for all cancers (47.1% [95% confidence interval (CI): 46.9–47.4] versus 52.0% [95% CI: 51.7–52.3]). Specifically, poorer survival for men was observed for 11 cancers (head and neck, esophagus, colon, pancreas, lung, bone, melanoma, mesothelioma, kidney, thyroid, and non-Hodgkin lymphoma) [27]. Several studies on the most common respiratory cancer – non-small cell lung cancer – have shown that women have a lower risk of disease progression and death than men [28–31]. Better prognosis for women with lung cancer has also been shown in Polish studies [32, 33]. In an American study based on the Surveillance, Epidemiology, and End Results (SEER) database, women with ACC of the head and neck had better OS than men in multivariate analyses (HR 0.73; 95% CI: 0.65–0.82) [34]. Data on the influence of sex on the survival of patients with primary tracheal tumors are lacking. In this study we therefore aimed to examine the prognostic significance of sex in patients with primary tracheal tumor.

Material and methods

This retrospective analysis included patients with primary tracheal tumors treated at the Maria Skłodowska-Curie National Research Institute of Oncology in Warsaw, Poland, between January 2000 and December 2016. Patients were identified by searching the institution's cancer registry. We enrolled adults (≥ 18 years) diagnosed with primary tracheal tumors for whom complete data were available. Patients with tumors that may have originated from the larynx, main bronchus, or other organs (e.g., thyroid or esophagus) were excluded.

Overall, the records of 89 actively treated patients with primary tracheal tumors were included. Data on demographics, clinicopathological variables (symptoms, smoking history, performance status, histological diagnosis, location, and extent of the tumor), and type of treatment were extracted from traditional (paper-based) and electronic medical records. The follow-up ended on December 31, 2019.

Differences in distribution were determined using one-way analysis of variance for normally distributed variables and the Kruskal-Wallis test for other continuous variables. Fisher's exact test was applied to assess the independence between categorical variables.

The Kaplan-Meier estimator, log-rank test, and Cox proportional hazards model were used to analyze survival. For all tests, statistical significance was set at $p < 0.05$. Variables for which the p value was less than 0.10 were included in the multivariate Cox models.

OS was defined as time from diagnosis to death from any cause. Disease-free survival (DFS) was defined as time from initiation of radical treatment to recurrence or death from any cause, and progression-free survival (PFS) as time from initiation of palliative treatment to disease progression or death.

Results

Clinicopathological characteristics

Among the total study population ($n = 89$), men slightly predominated (48 men and 41 women). The median age at diagnosis was 62 years. SCC was the most common histological type, identified in 50 (56.2%) of 89 patients. 19 patients were diagnosed with ACC (21.3%). The remaining histological findings were classified for statistical purposes as "other". Men were more frequently diagnosed with SCC (66%), whereas ACC predominated among women (73.7%). The majority (78%) of patients with SCC were over 60 years of age and none were under 35 years of age. ACC was diagnosed in all age groups (36.8% of patients were under 35 years of age). Among the 43 patients for whom data on smoking history were available, 100% of those diagnosed with SCC were current or former smokers. Only women were never-smokers. The most commonly reported symptoms were dyspnea (37.1%) and hemoptysis (36%). 68% of women and 56% of men had a WHO performance status of 0–1. Among the patients who underwent radical treatment, 28 (62.2%) were women and 17 (37.8%) were men, compared with 13 (29.5%) women and 31 (70.5%) men among those receiving palliative treatment. 13 (28.9%) of 45 patients receiving radical treatment underwent surgical resection, of whom 11 (85%) were women and two (15%) were men.

Survival analyses

For the entire study group, the median OS was 61.30 months in women and 8.55 months in men ($p < 0.0001$). 5-year OS rates were also significantly higher in women than in men (50.6% vs. 2.1%) (fig. 1). Among those who underwent radical treatment, 5-year OS rates were 5.9% in men, compared with 70.6% in women ($p < 0.0001$). Median OS in this group was 16.9 months in men versus 129.4 months in women ($p < 0.0001$) (fig. 2). 5-year DFS rates were 10.9% in men versus 33.6% in women ($p = 0.0023$). Sex was an independent prognostic factor in both the total study population and among those receiving radical treatment. We found no differences in OS and PFS between sexes in patients receiving palliative treatment.

Discussion

Data on the influence of sex on the survival of patients with tracheal tumors are scarce and inconsistent. In a retrospective analysis of 30 patients with ACC of the trachea, 5-year OS rates were 92% in men and 77% in women ($p = 0.345$) [25]. Moreover, the only available meta-analysis did not identify a statistically significant effect of sex on PFS or OS [5]. Another study showed that women had better disease-specific survi-

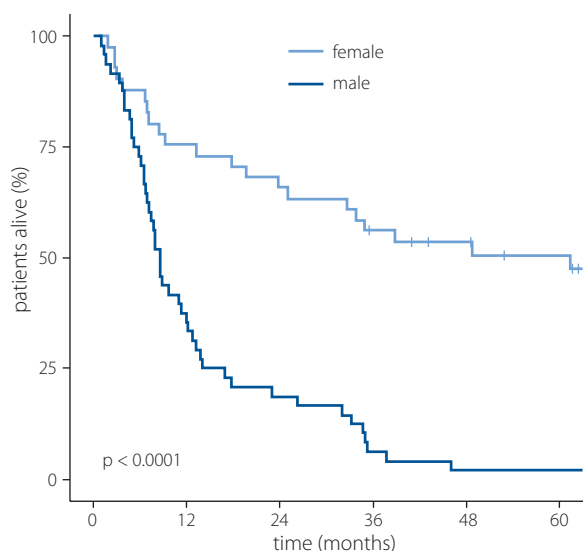


Figure 1. Cumulative probability of overall survival by sex in the total study group

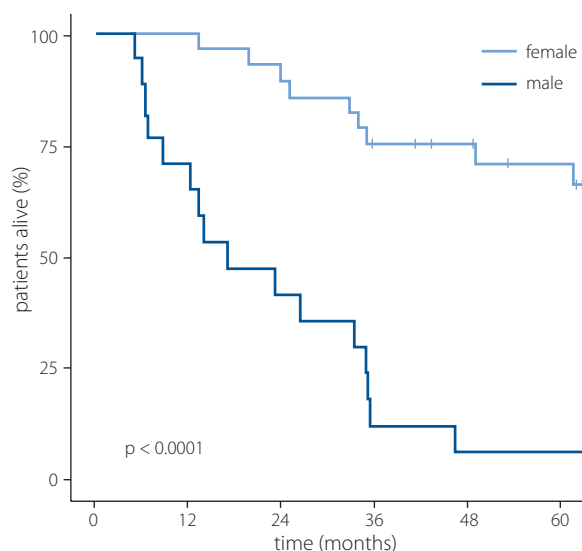


Figure 2. Cumulative probability of overall survival by sex in patients receiving radical treatment

val, defined as time from the initiation of treatment to death from the tracheal tumor ($p = 0.044$); however, no effect on OS was identified ($p = 0.467$) [10]. In a study of surgically treated patients with ACC of the trachea, female sex was a favorable prognostic factor for DFS, but not for OS [35]. Only one study, by Hetnal et al. [16] reported a favorable OS for women compared with men (5-year OS rates of 7% in men versus 32% in women, $p = 0.04$); however, multivariate analysis did not confirm sex to be an independent prognostic factor.

In our study, female sex was associated with favorable OS. OS and DFS benefits were also seen for women among patients who underwent radical treatment. Sex was an independent prognostic factor in both the overall study population and among those who underwent radical treatment. Various factors were considered to identify the underlying causes of such profound differences in survival by sex.

Analysis of other favorable prognostic factors in men and women showed that, in many cases, women predominated among groups with favorable characteristics. We found that:

- the group of never-smokers consisted of only women,
- the proportion of women and men who had a WHO performance status of 0/1, T1, and N0 were as follows: 68% vs. 56%, 39% vs. 19%, and 61% vs. 33%,
- 73.6% of patients with ACC were women,
- 62% of women were eligible for radical treatment compared with 38% of men,
- among those undergoing primary surgical treatment, 11 (85%) were women and two (15%) were men.

Attention was also paid to the difference between male and female life expectancy. Women live longer than men. According to Statistics Poland, the average life expectancy was 73.8 years for men in 2018, compared to 81.7 years for women. Few studies (and none on tracheal tumors) have taken life

expectancy into account. A study on surgically treated patients with non-small cell lung cancer that accounted for expected lifetime found that women had better survival than men [36].

Other factors that may be associated with the above relationship include the patient's age at diagnosis of the tumor and comorbidities. A study in small-cell lung cancer indicated that the relationship between the patient's sex and age was important. A favorable prognostic effect of female sex was observed in younger patients, whereas prognosis in men was independent of age. The median OS in patients under 60 years was 13.3 months for women and 10.1 months for men ($p = 0.0001$); however, no significant difference between sexes was seen in older patients ($p = 0.12$) [37]. Another study also demonstrated improved prognosis in younger individuals (especially among women) [33]. In our study population, 100% of patients under 35 years of age were women. We found no data in the literature on the correlation between the survival of patients with tracheal tumors and their sex and age.

Sex-specific differences in comorbidities may translate into differences in survival between women and men. Some studies suggest that men have more comorbidities than women at cancer diagnosis and that there is a relationship between comorbidities and poor survival (e.g. in lung cancer) [38]. We did not analyze the presence of comorbidities in our study, nor did we find any data concerning the influence of comorbidities on OS in patients with tracheal tumors in the literature.

Other studies evaluating the effect of female sex on survival highlighted that women seek health care more often and sooner than men, which contributes to earlier diagnosis of cancer [39, 40]. Women may also be more likely than men to take the proposed treatment. Furthermore, women more frequently adhere to the treatment plan and better tolerate treatment [34, 41].

Differences in molecular, endocrine, and metabolic abnormalities may be another factor. In other cancers, men and women were found to vary in terms of genetic disorders. For example, the *EGFR* mutation in non-small cell lung cancer is more common among women than men [42, 43]. Studies on the aforementioned factors could provide relevant information regarding differences in the biological behavior of tracheal cancers and explain disparities in survival.

Conclusions

This study suggests that women with primary tracheal tumors have significantly better survival than men, in both univariate and multivariate analysis. Since female sex is an independent prognostic factor for tracheal tumors, the ratio of women to men should be taken into consideration in reports comparing the outcomes of different treatments. The reasons why women with tracheal tumors live longer than men remain unexplained. Studies on genetic, hormonal, and metabolic factors could help explain sex-specific differences in survival rates.

Conflict of interest: none declared

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