Cohort Study

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A SEER database cohort of 868 patients with primary tracheal cancers: characteristics and outcomes and the role of bronchoscopic interventions

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Introduction: Primary tracheal cancers have a yearly prevalence of 2.6 cases per million people. Because of their rarity there is a lack of studies investigating them. In this study, we investigate the clinical characteristics and outcomes of primary tracheal cancers using a large population database.

Methods: The Surveillance, Epidemiology and End Results (SEER) database was queried between 1973 and 2016 to identify a retrospective cohort of patients with primary tracheal cancers. Demographic information, tumor characteristics, treatments administered, and survival in months were investigated.

Results: Eight hundred sixty-eight cases were analyzed. The majority of the patients were male (56.8%) with an average age of 62.13 (±15.67). Squamous cell carcinoma (SCC) was the predominant subtype (42.9%) followed by adenoid cystic carcinoma (ACC) (18.1%). Five-year survival was 21.6% and median survival was 12 months. Patients with ACC had more localized tumors, received surgery more often and had longer survival than patients with SCC ($P < 0.01$). Both groups had best outcomes when treated with surgery. Bronchoscopic intervention was associated with favorable outcomes for ACC. For SCCs, bronchoscopic interventions followed by adjuvant therapy had better outcomes than radiotherapy alone. Cox proportional hazards identified advanced age and stage, radiotherapy and chemotherapy as negative predictors of outcome. Whereas ACC and sarcoma histology and diagnosis between 2010 and 2016 were positive prognosticators.

Conclusions: Tracheal cancers have poor outcomes with a median survival of 12 months and 5-year survival of only 21.6%. Surgical resection should be the treatment of choice wherever feasible. In patients with ACCs who are not surgical candidates bronchoscopic interventions may provide appropriate treatment and palliation and improved survival. For SCCs, bronchoscopic intervention wherever possible with adjuvant therapy may be favorable to radiotherapy alone.

Keywords: Trachea, Tracheal cancers, Bronchoscopy, Adenoid cystic carcinoma, Squamous cell carcinoma

Primary tumors of the trachea are a rare entity. Reports estimate an approximate incidence of 0.1% for every 100000 people[1–4] and an approximate prevalence of 2.6 cases per million people every year[5–9]. They account for only 0.1%–0.4% of all malignant neoplastic diseases[7–16] and represent about 2% of all airway malignancies[17–20].

Primary tracheal tumors are overwhelmingly malignant in adult patients and usually benign in children[21–23]. Squamous cell carcinoma (SCC) and adenoid cystic carcinoma (ACC) are the 2 most common histologies and represent about two thirds of these tumors in adults[15,21,24,25]. They are followed by other rarer neoplasms such as mucoepidermoid carcinoma, sarcomas, lymphomas, and melanomas[17].

Because of their rarity, there are no randomized controlled trials to determine a standardized approach for their management. Surgical resection is generally considered the treatment of choice if feasible; however, most are not amenable to primary resection. Their low occurrence also means that to acquire a big enough sample size, patients from multiple institutions over many years would need to be recruited to effectively comment on their characteristics. We, therefore, decided to utilize a population-based data set to analyze their clinical characteristics and outcomes.

Methods

Study population

This retrospective cohort study is fully compliant with the STROCSS criteria[26]. It has been registered at Research Registry

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We identified a retrospective cohort using the Surveillance, Epidemiology and End Results (SEER) database, a registry sponsored by the National Cancer Institute[27]. The SEER database was established in 1973 and is a set of extensive population-based cancer registries that cover ~28% of the US population (Alaska Native Tumor Registry, Connecticut, Georgia Center for Cancer Statistics, San Francisco-Oakland, San Jose-Monterey, Greater California, Hawaii, Idaho, Iowa, Kentucky, Los Angeles, Louisiana, Massachusetts, New Mexico, New York, Seattle-Puget Sound, Utah). We queried the November 2018 submission from 1973 to 2016. Using the *International Classification of Disease, Third Edition* (ICD-O-3) codes, we queried for Primary site "Trachea" (ICD-O-3 C33.9). Patients with multiple primaries were removed from our cohort. Since data in the SEER database is deidentified, our study is exempt from ethical review.

Selection of variables

Details were collected on the year of diagnosis, patient demographics (age at diagnosis, sex, race and marital status), tumor characteristics (histology, stage, grade, and tumor size), treatments administered and survival in months and patient status at the end of follow-up period.

Treatment groups were divided into bronchoscopic interventions (photodynamic therapy, laser ablation, electrocautery, cryosurgery, polypectomy), surgery, radiotherapy and chemotherapy. The race was recorded as white, black, Asian, and other. Tumor histology was grouped into SCC, ACC, adenocarcinoma, large cell carcinoma, small cell carcinoma, sarcoma, lymphoma, and other.

Survival was recorded in months from the time of diagnosis to the point of last contact or the date of death in cases where the patient was deceased. Patient status at the end of follow-up period was recorded as alive or dead.

Statistical analysis

Data extracted from the SEER database was imported on to the statistical package for the social sciences (SPSS) version 23 IBM Corp, USA for further analysis. Both descriptive and inferential analysis was conducted. Characteristics of our sample population were described using frequencies, percentages, means, and medians. Survival was estimated using the Kaplan-Meier method. Survival differences between variables were compared using the log-rank test. In cases where the median overall survival (OS) could not be calculated due to a high number of censored cases, mean OS was used. A *P*-value of <0.05 was considered significant. Confidence intervals (CI) were set at 95%. Multivariate Cox-regression was used to study the relationship between various patient and disease-specific factors and survival. Subgroup analysis between SCC and ACC was conducted as well.

Results

Between 1973 and 2016, the SEER database recorded 1413 cases of primary tracheal cancers. After removing patients with multiple primary cancers, we were left with 868 patients in our cohort.

Patient characteristics

Our patients had an average age of 62.13 (± 15.67). The majority of the patients were males (56.8%), white (81.0%) and diagnosed between the years 2000 and 2009 (35.4%).

Tumor characteristics

SCC was the predominant subtype (42.9%) followed by ACC (18.1%). The majority of the patients had the regional disease (35.4%) and poorly differentiated, grade III (20.6%).

Patient and tumor characteristics are summarized in **Table 1**.

Treatment

Table 2 summarizes the treatments received by the patients in our cohort. The most common treatment received was radiotherapy (62.1%), either alone or in combination with other therapies. Surgery was performed in 22.9% of cases, most of whom received adjuvant radiation or chemoradiation. Bronchoscopic treatment was performed in 15%. There were 168 (19.4%) patients who did not undergo any treatment.

Table 1

Patient demographic and clinical characteristics (n = 868).

Demographics	n (%)
Age, mean ± SD (y)	62.13 ± 15.67
Sex	
Male	571 (56.8)
Female	375 (43.2)
Race	
White	703 (81.0)
Black	92 (10.6)
Asian	35 (4.0)
Other	38 (4.4)
Decade of diagnosis	
1970–1979	74 (8.5)
1980–1989	156 (18.0)
1990–1999	151 (17.4)
2000–2009	307 (35.4)
2010–2016	180 (20.7)
Tumor characteristics	
Tumor histology	
Squamous cell carcinoma	372 (42.9)
Adenoid cystic carcinoma	157 (18.1)
Small cell carcinoma	58 (6.7)
Adenocarcinoma	41 (4.7)
Lymphoma	34 (3.9)
Sarcoma	33 (3.8)
Large cell carcinoma	24 (2.8)
Other	149 (17.2)
Tumor stage	
Localized disease	240 (27.6)
Regional disease	307 (35.4)
Distant disease	165 (19.0)
Unstaged	156 (18.0)
Tumor grade	
Well differentiated; grade I	51 (5.9)
Moderately differentiated; grade II	155 (17.9)
Poorly differentiated; grade III	179 (20.6)
Undifferentiated; grade IV	54 (6.2)
Unknown	429 (49.4)

Table 2

Treatments administered to patients.

	n (%)
Bronchoscopy	130 (15)
Bronchoscopy only	46 (5.3)
Bronchoscopy plus radiotherapy	45 (5.2)
Bronchoscopy plus chemotherapy	5 (0.6)
Bronchoscopy plus chemoradiotherapy	34 (3.9)
Surgery	199 (22.9)
Surgery only	68 (7.8)
Surgery plus radiotherapy	106 (12.2)
Surgery plus chemotherapy	3 (0.3)
Surgery plus chemoradiotherapy	22 (2.5)
Radiotherapy	539 (62.1)
Radiotherapy only	206 (23.7)
Chemoradiotherapy	126 (14.5)
Chemotherapy	229 (26.4)
Chemotherapy only	39 (4.5)
No treatment	168 (19.4)

Survival

Median OS was 12 months (CI: 9.89–14.11). One-year, 3-year, and 5-year survival was 46.7%, 28.7%, and 21.6%.

When stratified by tumor histology, patients with large cell carcinoma had the lowest median OS of 4 months (CI: 1.71–6.29) and 1-year, 3-year, and 5 survival of 17.4%, 4.3%, and 0%, respectively. While patients with ACC had the longest median OS of 101 months (CI: 55.05–146.95) and 1-year, 3-year, and 5 survival of 84.1%, 69.4%, and 54.8%, respectively. Patient survival outcomes according to tumor histology are summarized in **Table 3**.

Stratification according to treatment received demonstrated that patients who did not undergo any treatment had the lowest median OS of 1 month (CI: 0–2.01) and 1-year, 3-year, and 5-year survival of 21%, 8.8%, and 6.3%, respectively. Patients who underwent surgery only had the longest median OS of 195 months (CI: 135.86–254.14) and 1-year, 3-year, and 5-year survival of 77.9%, 64.7%, and 51.5%, respectively. Patient survival outcomes according to treatment received are summarized in **Table 4**.

Table 3

Median overall survival and 1-year, 3-year and 5-year survival according to tumor type in months.

	Median Overall Survival	1-Year Survival (%)	3-Year Survival (%)	5-Year Survival (%)
Squamous cell carcinoma (n = 372)	7 (5.61–8.40)	32.5	14.2	8.9
Adenoid cystic carcinoma (n = 157)	101 (55.05–146.95)	84.1	69.4	54.8
Small cell carcinoma (n = 56)	10 (7.56–12.45)	35.7	14.3	7.1
Adenocarcinoma (n = 38)	6 (3.06–8.94)	34.2	21.1	18.4
Lymphoma (n = 34)	42 (33.08–50.92)	61.7	44.1	26.5
Sarcoma (n = 33)	74 (0–235.83)	66.7	51.5	42.4
Large cell carcinoma (n = 23)	4 (1.71–6.29)	17.4	4.3	0
Other (n = 130)	12 (9.89–14.11)	46.9	24.6	22.3

Table 4

Median overall survival and 1-year, 3-year and 5-year survival according to treatment type.

	Median Overall Survival	1-Year Survival (%)	3-Year Survival (%)	5-Year Survival (%)
Bronchoscopy only (n = 46)	85 (33.72–136.28)	60.9	52.2	43.5
Surgery only (n = 68)	195 (135.86–254.14)	77.9	64.7	51.5
Radiotherapy only (206)	7 (5.56–8.44)	33.0	15.5	8.7
Chemotherapy only (n = 39)	11 (8.99–13.01)	38.5	17.9	10.3
Bronchoscopy plus Radiotherapy (n = 45)	76 (26.89–125.11)	66.7	53.3	37.8
Bronchoscopy plus chemotherapy (5)	42	60.0	25	0
Bronchoscopy plus chemoradiotherapy (n = 34)	17 (9.29–27.71)	47.1	23.5	14.7
Surgery plus radiotherapy (106)	95 (52.51–137.49)	77.4	58.5	51.9
Surgery plus chemotherapy (3)	9	100	0	0
Surgery plus chemoradiotherapy (22)	24 (0.94–47.06)	68.2	36.4	31.8
Chemoradiotherapy (126)	10 (7.86–12.14)	41.3	16.7	9.5
No treatment (n = 143)	1 (0–2.01)	21	8.8	6.3

Multivariate analysis

We further investigated the correlation between overall survival and other covariates in a Cox regression analysis. Multivariate analysis with surgery only as indicator variable demonstrated significantly poor survival with radiotherapy only hazard ratio (HR: 2.34, 95% CI: 1.28–4.27, $P < 0.01$), chemotherapy only (HR: 2.60, 95% CI: 1.11–6.10, $P < 0.05$), bronchoscopy plus radiotherapy (HR: 2.28, 95% CI: 1.08–4.82, $P < 0.05$) and no treatment (HR: 4.66, 95% CI: 2.42–8.95, $P < 0.001$). In addition, advanced age, regional and distant extension of disease were associated with poor outcomes ($P < 0.001$), while cases diagnosed between 2010 and 2016, ACC and sarcoma histology were significant prognosticators for good outcomes ($P < 0.01$) (**Table 5**). Sex, race, and tumor grade did not have a significant association and were omitted from **Table 5**.

Subgroup analysis

Patients with SCC were older than patients with ACC (mean age: 64.81 ± 12.08 vs. 52.56 ± 15.86; $P < 0.001$). There was a male predominance in patients affected with SCC (male vs. female: 64.2% vs. 35.8%). Whereas patients with ACC had a more uniform sex distribution (male vs. female: 45.2% vs. 54.8%). Distant spread was more common in patients with SCC (23.9% vs. 8.3%) while localized disease was more common in patients with ACC (39.5% vs. 20.2%). A higher proportion of patients with ACCs received surgery for their disease than those with SCCs (58% vs. 14.5%; $P < 0.001$). Patients with SCC had

Table 5

Clinical and pathologic characteristics with associated hazards ratio based on Cox regression multivariate analysis of overall survival in patients with primary malignant tracheal tumors.

Variables	Hazards Ratio	95% Confidence Interval	*P*
Age, mean (y)	1.03	1.02–1.04	**<0.001**
Decade of diagnosis			
1970–1979	1		
1980–1989	0.71	0.46–1.09	0.12
1990–1999	0.90	0.57–1.41	0.63
2000–2009	0.71	0.46–1.08	0.12
2010–2016	0.41	0.24–0.69	**<0.01**
Tumor histology			
Squamous cell carcinoma	1		
Adenoid cystic carcinoma	0.31	0.16–0.60	**<0.01**
Adenocarcinoma	0.86	0.52–1.43	0.56
Large cell carcinoma	1.26	0.72–2.19	0.42
Small cell carcinoma	0.81	0.47–1.40	0.45
Sarcoma	0.31	0.14–0.65	**<0.01**
Lymphoma	0.45	0.06–3.38	0.43
Other	0.71	0.47–1.05	0.09
Tumor stage			
Localized	1		
Reigional by direct extension or lymph node involvement	1.91	1.37–2.65	**<0.001**
Distant site(s)/node(s) involved	3.11	2.14–4.52	**<0.001**
Unstaged	1.32	0.86–2.01	0.20
Treatment			
Surgery alone	1		
Bronchoscopy alone	1.19	0.55–2.57	0.66
Radiotherapy alone	2.34	1.28–4.27	**<0.01**
Chemotherapy alone	2.60	1.11–6.10	**<0.05**
Bronchoscopy plus radiotherapy	2.28	1.08–4.82	**<0.05**
Bronchoscopy plus chemotherapy	2.38	0.51–11.17	0.27
Bronchoscopy plus chemoradiotherapy	1.44	0.67–3.11	0.35
Surgery plus radiotherapy	1.22	0.61–2.43	0.58
Surgery plus chemotherapy	0.01	0–2.28	0.96
Surgery plus chemoradiotherapy	1.34	0.57–3.17	0.50
Chemoradiotherapy	2.29	1.22–4.30	**<0.05**
No treatment	4.66	2.42–8.95	**<0.001**

Statistical significance *P* values are in bold.

significantly shorter overall survival than patients with ACC (**Table 3**). Both SCC and ACC had best outcomes when treated with surgery (**Table 6**) ($P < 0.001$). For patients with ACCs, the bronchoscopic intervention had better survival outcomes than radiotherapy alone ($P < 0.05$), whereas for patients with SCCs, bronchoscopic intervention plus adjuvant therapy had better survival than radiotherapy alone ($P < 0.05$).

Discussion

Primary malignant tracheal tumors are rare. Previous literature comprises primarily of anecdotal studies with a few large case series. The availability of a large national cancer database therefore is invaluable for the evaluation of these tumors. The SEER database provides multi-institutional data and represents the practice across the United States. Several investigators have previously made use of the SEER database to study tracheal tumors. However, ours is the only study that comments on the use of a bronchoscopic intervention for the management of tracheal cancers.

Table 6

Treatment-specific survival for squamous cell carcinoma and adenoid cystic carcinoma.

	Mean Overall Survival	Median Overall Survival
Squamous cell carcinoma		
Surgery only	59.65 (21.01–98.30)	35 (2.21–67.79)
Bronchoscopy only	6 (2.78–9.22)	3 (0.16–5.84)
Radiotherapy alone	15.13 (10.32–19.95)	6 (4.52–7.47)
Surgery plus adjuvant	87.33 (48.64–126.03)	20 (8.71–31.29)
Bronchoscopy plus adjuvant	39.44 (18.11–60.78)	12 (10.89–13.11)
Adenoid cystic carcinoma		
Surgery only	226.83 (148.36–305.30)	218 (109.11–326.89)
Bronchoscopy only	173.33 (117–229.67)	—
Radiotherapy alone	66.06 (47.50–84.62)	68 (50.66–85.34)
Surgery plus adjuvant	151.61 (119.93–183.33)	141 (80.38–201.62)
Bronchoscopy plus adjuvant	150.75 (87.17–214.33)	101 (61.84–140.16)

Another significant factor to consider is the coexistence of multiple primary cancers. Agrawal et al[9] published a retrospective analysis of 958 patients from the SEER database. Their study, however, did not mention excluding patients with multiple primary cancers of other areas. This can be a significant confounding factor when assessing patient survival. Our study takes this into account and patients in whom tracheal cancer was the single primary malignancy were included only.

In our analysis, SCCs and ACCs were the 2 most common histologic subtypes. ACCs, as expected had significantly better survival outcomes than SCCs. This is most likely due to the natural course of these tumors. ACCs are slow-growing tumors with an indolent history and late-onset of metastases. Previous reports have indicated 50% of patients developed metastases at 10 years after diagnosis[8]. ACCs also demonstrated a higher number of localized tumors as compared with SCCs. This may explain why a higher proportion of these patients were treated with surgery.

Our study emphasizes the important role of surgery in patients with primary malignant tracheal tumors. It is important to note that while surgery is associated with the best survival outcomes, only 22.9% of patients underwent any kind of surgical treatment. This apparent under the utility of surgery may be due to the lack of a standardized approach to these tumors or it may be due to late diagnosis and unresectability. Should the latter be the case, there's a need to expand the pool of surgical candidates. This may be done by developing appropriate tracheal substitutes and grafting material so that more extensive tracheal resection can be performed and patients with larger tumors can benefit from surgical therapy.

Previous studies have also demonstrated the role of radiotherapy including the study by Xie and colleagues, who used the SEER database to suggest a survival benefit for the use of radiotherapy for all patients with tracheal cancers. Our results in patients receiving radiotherapy do not encourage its use and generally demonstrated poor survival. A large proportion of patients, however, received radiotherapy and radiotherapy only was the most common treatment strategy in this cohort. This may again be either due to lack of standardization of treatment or it

may represent a significant selection bias where patients receiving radiotherapy only represent a subgroup with advanced disease not amenable to surgery.

Our study is unique as it demonstrates that bronchoscopic debulking or ablative techniques might be a feasible option for primary tracheal cancers. Our results show good survival outcomes with bronchoscopic interventions. In patients with ACCs, bronchoscopic interventions achieved a mean OS of 173.33 (117–229.67) months compared with 226.83 (148.36–305.30) months in patients treated with surgery alone. Bronchoscopic interventions were also preferable to radiotherapy which demonstrated a mean OS of 66.06 (47.50–84.62) in these patients. This may suggest that patients with ACCs who are not candidates for surgery may be treated with bronchoscopy.

Our study also shows that for nonsurgical patients with SCCs bronchoscopic interventions combined with radiotherapy have improved survival compared with radiotherapy alone.

On multivariate analysis, we observed a positive trend in patient survival for decades of diagnosis with statistical significance achieved in the 2010–2016 group. This may be due to a better understanding of the disease process as well as improvements in imaging technology and bronchoscopy equipment. The multivariate analysis also demonstrated and understandably so, the negative survival effect of increasing age and regional and distant spread of tracheal cancers.

Our study has several limitations. Being a retrospective study, some degree of selection bias is inherent. Secondly, the SEER database does not contain information on patient comorbid conditions. These may be an important confounding factor when looking at survival outcomes. Also important is the fact that due to a lack of standardized staging algorithm for tracheal cancers, tumor size, and nodal status is not reported for many cases. Tumor stage, however, grouped as local, regional, and distant disease served as a useful alternative.

Conclusions

We utilized a large population-based database to demonstrate the clinical characteristics and outcomes of primary tracheal tumors. We observed that tracheal cancers have poor outcomes with a median OS of 12 months and 5-year survival rates of only 21.6%. SCCs were the most common histologic subtype followed by ACCs. Surgical resection should be the treatment of choice wherever feasible. In patients with adenoid cystic carcinomas who are unfit for surgery or have unresectable tumors, bronchoscopic debulking or ablation may provide appropriate treatment and palliation. For SCCs bronchoscopic interventions with adjuvant therapy provide better outcomes than radiotherapy alone.

Ethical approval

Our study utilizes de-identified data from a publicly accessible database; therefore, our study is exempt from ethical review.

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Author contribution

This work was carried out in collaboration between all authors. M.Z.B., C.P.C., and F.Y.B. designed the study and wrote the protocol. M.Z.B. and J.F.W. wrote the first draft of the manuscript. M.Z.B. managed the literature searches. All authors read and approved the final manuscript.

Conflict of interest disclosures

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Statement of nonduplication

I, Faiz Y. Bhora, certify that this manuscript is a unique submission and is not being considered for publication, in part or in full, with any other source in any medium.

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Guarantor

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