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Demography, patterns of care and survival outcomes in patients with malignant tumors of trachea: A systematic review and individual patient data analysis of 733 patients

Supriya Mallick[a,1], Rony Benson[a,1], Prashanth Giridhar[a,*], Angel Rajan Singh[b], Goura K Rath[a]

[a] Department of Radiation Oncology, All India Institute of Medical Sciences, New Delhi, India
[b] Department of Hospital administration, All India Institute of Medical Sciences, New Delhi, India

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ABSTRACT

Background: Malignant tumors of the trachea (MTT) account for 0.01-0.4% of all cancer cases. The rarity of the tumor along with different histologies makes it is a great challenge on how to optimally treat tracheal tumors and most of the available data is from small retrospective data series. We performed a systematic review and individual patient data analysis to evaluate the patterns of care and survival outcomes in patient with MTT.

Methodology: A comprehensive search in Pub Med and Google scholar was done to find all possible publications related to malignant tumors of the trachea. The data on patient demograpphy, treatment, survival and recurrence pattern of individual patient was collected from the published data and was entered in a predesigned proforma. Progression free survival [PFS] and overall survival [OS] was calculated from the date of diagnosis to the date of documented progression and death respectively. Kaplan- Meier method was used for survival analysis and uni-variate analysis was performed using log rank test. SPSS v16 was used for all statistical analysis.

Results: 733 patients were included in this analysis. The most common histology was adenoid cystic carcinoma (ACC) followed by squamous cell carcinoma (SCC). The gender ratio was 4.43: 1[male: female] in patients with SCC while it was 0.85:1[male: female] in ACC. Smoking and age > 50 years were associated with worse OS. The estimated median overall survival for entire cohort was 96 months. Survival was significantly better in patients with ACC than in patients with SCC [165 vs. 14 months, $p < 0.001$]. The use of definitive surgery was associated with a significantly better survival of 180 months when compared to 48 months with radiation as local therapy, [$p < 0.001$]. The radiation dose used also affected survival in patients with SCC with a better median OS of 24 months in patients who recieved more than 60 Gy vs 6 months in whom the dose was less than 60 Gy although not statistically significant ($p = 0.011$).

Conclusion: ACC and SCC are the most common MTT. ACC has better prognosis compared to SCC. Surgery seems to provide better outcomes than radiation for ACC and sarcoma. Role of definitive radiotherapy versus surgery in SCC needs to be further studied.

1. Introduction

Malignant tumor of the trachea (MTT) is a rare disease [1,2] comprising around 0.01-0.4% of all cancer cases. In the US, incidence of these tumors is less than 0.2 per 1, 00,000 population [3,4]. Frequently, these tumors are diagnosed late as they present with non-specific symptoms and are often mis-diagnosed as asthma or other respiratory disorder. A wide range of histological subtypes has been described in the literature adding to the heterogeneity of presentation, treatment and outcome of these tumors. Surgery is considered the cornerstone of therapy. Due to the peculiar anatomy and need for plastic surgical techniques achieving a clear surgical margin is often difficult and adjuvant radiation has been used by many clinicians to improve outcome especially in patients with close/positive margins after resection. But the exact benefit from adjuvant radiation has not been established. There are also a group of inoperable patients in whom definitive radiotherapy has been advocated. However, owing to the rarity, most of the data is derived from institutional practice, case reports or small case series with wide range of bias. Hence, we embarked on to do an individual patient data analysis of published literature to find patient

* Corresponding author.
E-mail address: prashanth.jipmer@gmail.com (P. Giridhar).
[1] Supriya Mallick and Rony Benson has equal contribution and should be considered common First author.

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characteristics, patterns of care, survival outcomes and impact of various prognostic factors in this rare tumor. We also planned to do a subset analysis of major histology with regard to various treatment strategies and survival outcomes. In addition, we aimed to look into "Whether adjuvant radiotherapy has a role in the management of these tumors".

2. Search methodology

A comprehensive search of the PubMed, and Google scholar with Mesh terms: "Tracheal Carcinoma; Tracheal AND carcinoma; Trachea AND carcinoma; Tracheal tumor; Trachea AND treatment; Trachea AND Melanoma; Trachea AND Sarcoma; Trachea AND Lymphoma; Trachea AND Carcinoid; Trachea AND adenocarcinoma; Trachea AND plasmacytoma; Trachea AND histiocytoma" to find all possible publications related to malignant tumors of the trachea was done independently by 2 authors. Duplications were eliminated by mutual discussion.

3. Eligibility criteria

All patients with primary tracheal malignant tumors from the systematic search were screened. The patients diagnosed after an autopsy were excluded. Studies that provided only pathological information or details on surgical techniques without data on patient survival outcome were excluded from the survival analysis.

Data extraction and critical appraisal:

Search for all possible publications related to malignant tumors of the trachea was done independently by 2 authors. Duplications were eliminated by mutual discussion. Attempt to acquire missing data from various case reports was done by communicating with corresponding authors via mail. In cases where entire manuscript/report was not available abstracts were used to get maximum possible information. Our search had an English language filter. Information on base line patient characteristics, histological subtype, surgery, type of surgery [R0 vs. R1/2], adjuvant treatment received, survival outcomes, patterns of recurrence and salvage treatment were recorded in a predesigned proforma. The data was later counterchecked by 2 individual authors and possible duplications removed. The PRISMA chart (Fig. 1) explains the data synthesis from the eligible studies.

4. Statistical analysis

The data was analyzed and categorical variables were summarized by frequency and percentage and quantitative variables by the median and range. Progression free survival (PFS) and overall survival (OS) was calculated from the date of diagnosis to the date of documented progression and death respectively. The Kaplan-Meier method was used for survival analysis. Uni-variate analysis using log rank test was used to find out the impact of age, gender, location, histology, surgery, use of radiation, on survival outcome. A p value of < 0.05 was taken as significant. SPSS v16 was used for all statistical analysis.

5. Results

5.1. Quantity of evidence

360 articles were screened out of which 342 were eligible for quantitative data synthesis. Detail for eliminating 18 articles is summarized in PRISMA chart (Fig. 1). 733 individual patient data was used for statistical analysis.

5.2. Quality of evidence

Data obtained is from retrospective data of case reports, case series and correspondence with contributing authors. No prospective or randomized data with individual patient data was available for inclusion in analyses.

5.3. Patient characteristics

Clinical and demographic data of 733 patients with tracheal malignant tumor were retrieved. The most common histology was adenoid cystic carcinoma (n = 247, 33.7%) followed by squamous cell carcinoma (n = 228, 31%). The distribution of tracheal malignant tumors as per histology is summarized in Fig. 2. The gender distribution of the entire cohort was skewed towards males with a male to female ratio of 1.49:1. The gender ratio was 4.43: 1 in patients with squamous cell carcinoma (SCC) while adenoid cystic carcinoma (ACC)showed a female preponderance, with male to female ratio of 0.85:1.Median age at diagnosis for the entire cohort of malignant tracheal tumors was 54 years (Range: 2–93 years) years. However, median age of presentation of squamous cell carcinoma was 62 years (Range: 12–84 years) while for adenoid cystic carcinoma it was 47 years (Range: 15–84 years). Incidence of different histology varied with age significantly. Incidence of different malignant tracheal tumors affecting various age groups has been depicted in Fig. 3. Information regarding smoking history was available in 107 patients out of which 61(57%) were smokers. Of those who had information on smoking, histology wise, 82% of SCC patients were smokers while only 33% ACC were smokers. MTT were found more commonly in the distal trachea than proximal trachea (Defined as more or less than 5 cm below larynx), the ratio being 2.25:1. This trend was seen in both SCC and ACC. Histology wise demographic profile has been summarized in Table 2.

5.4. Treatment characteristics

Surgical intervention to resect MTT was attempted and documented in 305(41.6%) patients. Due to incomplete description, data on extent of resection could be discerned properly only in 40 patients. Of these, incomplete resection was documented in 18 (45%) patients out of which 10 received adjuvant radiotherapy. Radiotherapy was part of initial treatment in 276 (37.6%) patients. 137[18.7%] patients received radiotherapy with curative intent. Brachytherapy by interstitial implant or seed implant as part of radical radiotherapy was performed in 18 patients. Adjuvant radiotherapy was delivered in 54(17.8%) patients while pre-operative radiotherapy was used in only 6 (2%) patients. Palliative radiotherapy was used in 14 patients. The intent of radiotherapy was not specified in 80 patients. Median dose of radical radiation (External beam alone) was 70 Gy (Range: 10 Gy – 80 Gy) while the most common schedule used when brachytherapy was also part of treatment was 50 Gy external beam radiotherapy followed by four fractions (each fraction 5 Gy) of brachytherapy boost. Median dose of adjuvant radiotherapy was 60 Gy (Range: 30–105 Gy).Chemotherapy was part of treatment in 50 (6.8%) patients. The other treatment modalities used in treatment were LASER, cryotherapy, photodynamic therapy and tracheal stenting.

5.5. Survival analysis

Median follow up for the entire cohort was 22.5 months [Range: 0.1–324 months].The median PFS was 72 months [95% CI 54.2–89.7]. Patients who had undergone a surgery had significantly better outcome in terms of PFS with a median survival of 132 months in those who underwent surgery vs. 43 months in those who did not undergo surgery [$p < 0.001$]. Patients who underwent radiation as a local therapy had a median PFS of 36 months versus 132 months for surgical cohort [$p < 0.001$]. Age, sex, location of the tumor and use of adjuvant radiotherapy were not found to be significant factors affecting progression free survival [Fig. 4].

The estimated median OS was 96 months [95% CI 71.5–120.4]. The median OS was significantly better for patients less than or equal to 50

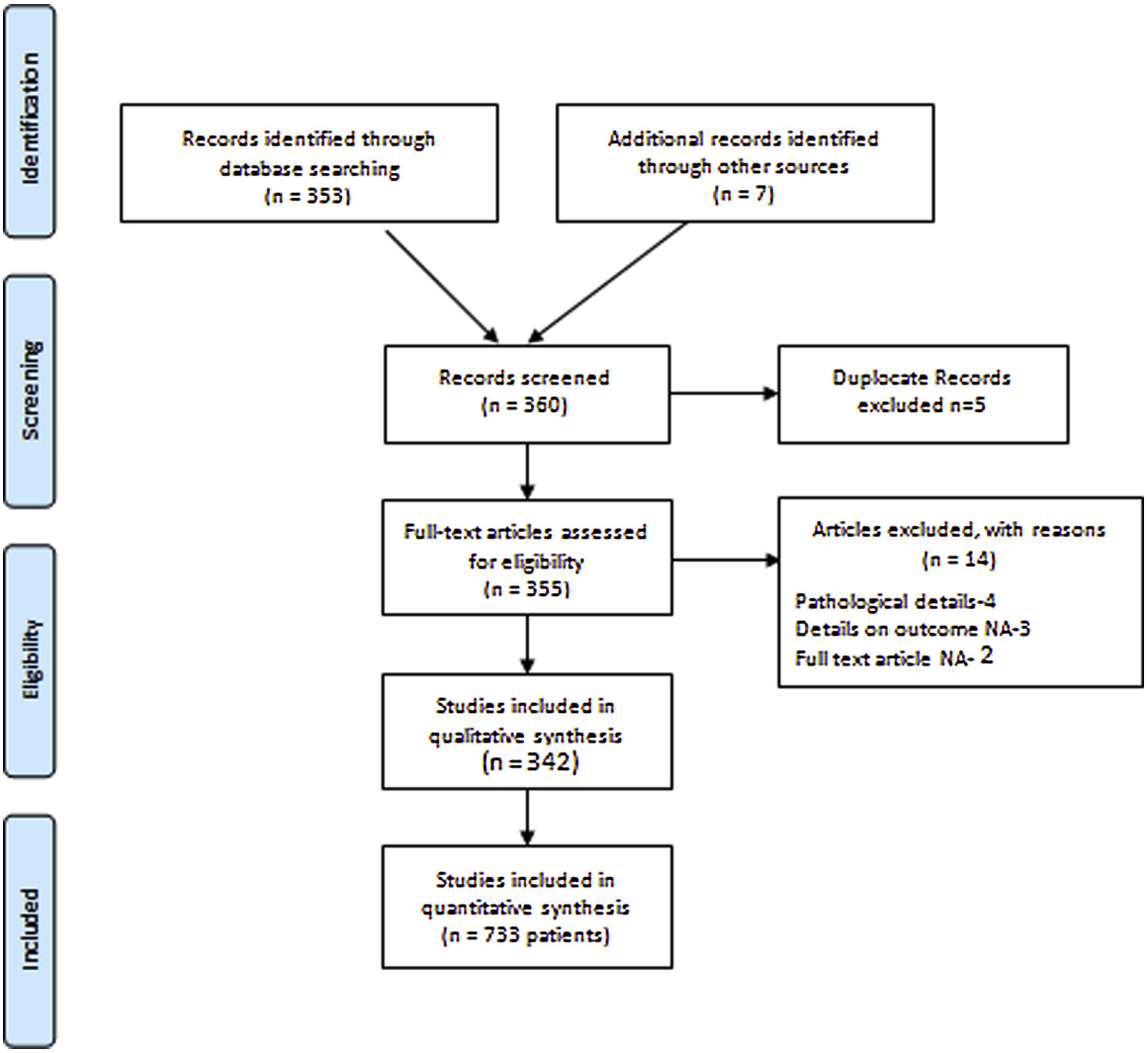

Fig. 1. PRISMA chart depicting the selection and exclusion of articles for the present analysis.

years [118 vs 51 months, p -0.001]. Patients who had undergone a surgery had significantly better OS with a median survival of 180 months vs. 36 months only in those who did not undergo surgery [$p < 0.001$].Patients who underwent radiation as a local therapy had a median survival of 48 months versus 180 months for surgical cohort [$p < 0.001$]. Sex, location of the tumor and use of post-operative radiotherapy were not found to be significant factors affecting overall survival [Fig. 5]. The effect of various factors on OS has been summarized in Table 1.

5.6. Histology wise analysis of effect of prognostic factors on OS

Median OS varied across different histology. OS was significantly better in patients with Adenoid Cystic Carcinoma (ACC) with a median OS of 165 months vs only 14 months in patients with squamous cell carcinoma (SCC) [$p < 0.001$] [Table 3]. The median OS in patients with sarcoma was 168 months [Table 3]. Other histology had inadequate data to perform meaningful analyses. Among patients with ACC, those who underwent surgery had numerically better OS in comparison to those who underwent radiation (Median OS: 180 months vs 108 months respectively) [Table 3]. Among patients with SCC, those who underwent radiotherapy had numerically better OS in comparison to those who underwent surgery (Median OS: 29 months vs 23 months respectively) [Table 3]. Median OS was higher in patients of SCC who received > 60 Gy dose of radiotherapy (24 months vs 6 months; p value = 0.011). Among patients with sarcoma, median OS was significantly better in patients who underwent surgery versus those who underwent radiotherapy (Median OS: 168 months vs 35 months; p value = 0.034). No clear effect of adjuvant radiotherapy on OS could be found on analysis for ACC, SCC or sarcoma. Smoking history or gender had no effect on OS when analyzed histology wise. The histology wise effect of treatment on OS is summarized in Table 3.

5.7. Recurrence patterns and salvage

The median time of progression was 22.5 months (Range: 1–268 months). Recurrence was documented in 120 (16.4%) patients. Distal progression was documented in 30 (4.1%) patients while only local recurrence was seen in 8 patients. The location of progression was not documented in rest of the patients. Histology wise, of the patients who recurred 48 were ACC and 43 were SCC. Sites of distal recurrence included lung, bone, liver, brain, epidural lesions, ileum and nose.

6. Discussion

Epidemiology of MTT is poorly described in available literature. Most of the information is derived from periodic SEER data base analysis which is often restricted by geographical bias and limited information about treatment and survival [5]. The present analysis aimed to present a global overview about the demography, patterns of care,

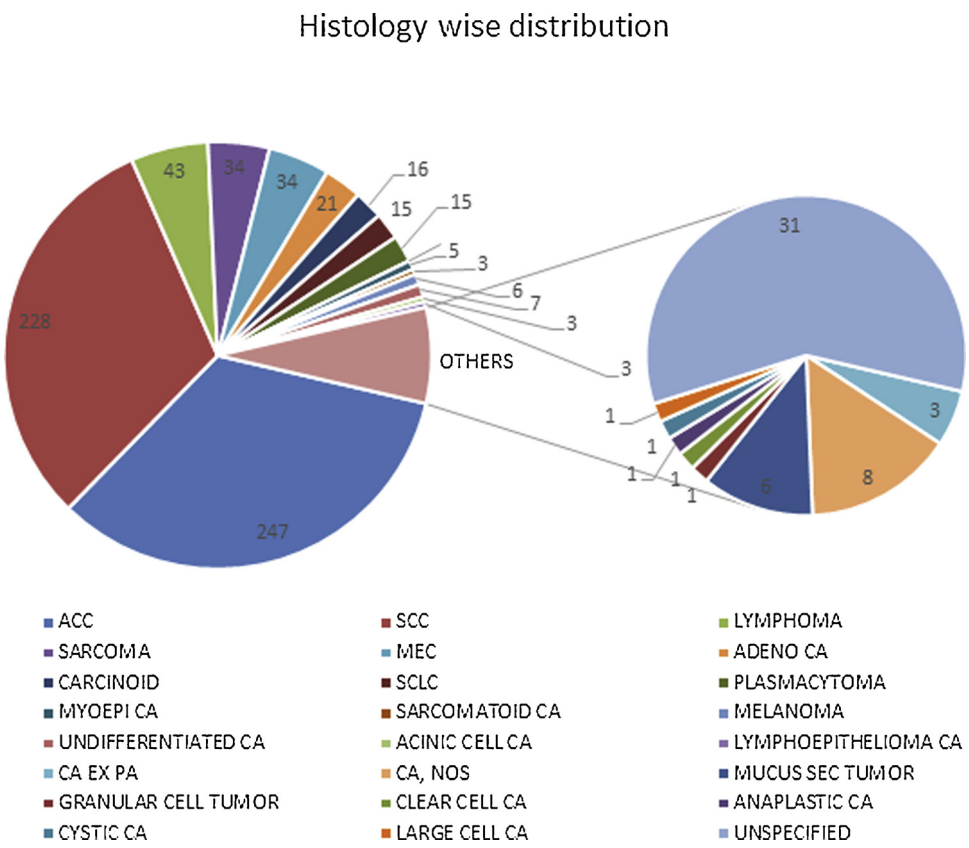

Fig. 2. Pie-Chart depicting histology wise distribution of malignant tracheal tumors [ACC: Adenoid Cystic Carcinoma; SCC: Squamous cell Carcinoma; MEC: Mucoepidermoid Carcinoma, SCLC: Small Cell Lung Carcinoma; CA Ex PA: Carcinoma Ex-Pleomorphic Adenoma; NOS: Not otherwise Specified].

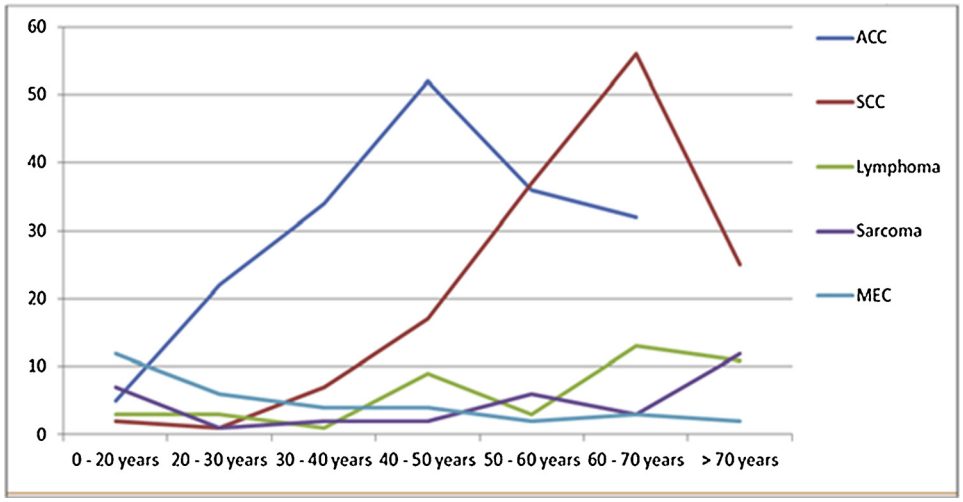

Fig. 3. Age wise distribution of malignant tracheal tumors [[ACC: Adenoid Cystic Carcinoma; SCC: Squamous cell Carcinoma; MEC: Mucoepidermoid Carcinoma].

survival outcomes and effect of possible prognostic factors of 733 cases of malignant tracheal tumors from across the globe representing the real world scenario.

MTT though rare, has been described to present with various types of histology [6]. Our analysis identified 23 different histology of MTT. In the present analysis, ACC is the commonest tracheal tumor (n = 247, 33.7%) followed by squamous cell carcinoma (n = 228, 31%). This is in contrast to the previously published SEER report [5] where only 16% patients were ACC. This could represent a geographical variation in histological distribution of malignant tracheal tumors or reporting bias with ACC being reported more commonly due to supposed rarity of it. For the entire cohort, median age at presentation is 54 years. The earlier SEER database analysis [5] reported a median age of 59 years which closely corroborates with the finding of the present analysis. It is seen that the incidence of ACC and SCC increase with age with ACC peaking in the fourth decade and SCC two decades later in our study. Interestingly, the incidence of mucoepidermoid carcinoma decreases with age in the present analysis. In contrast to earlier reports of equal prevalence among both genders, the present analysis points toward a male preponderance. SCC was four times more common in males with strong association with smoking history. More than four fifths of patients of SCC had a positive smoking history. ACC on the other hand is seen more commonly in females with only one third of patients having a smoking history. A similar strong association of SCC with smoking

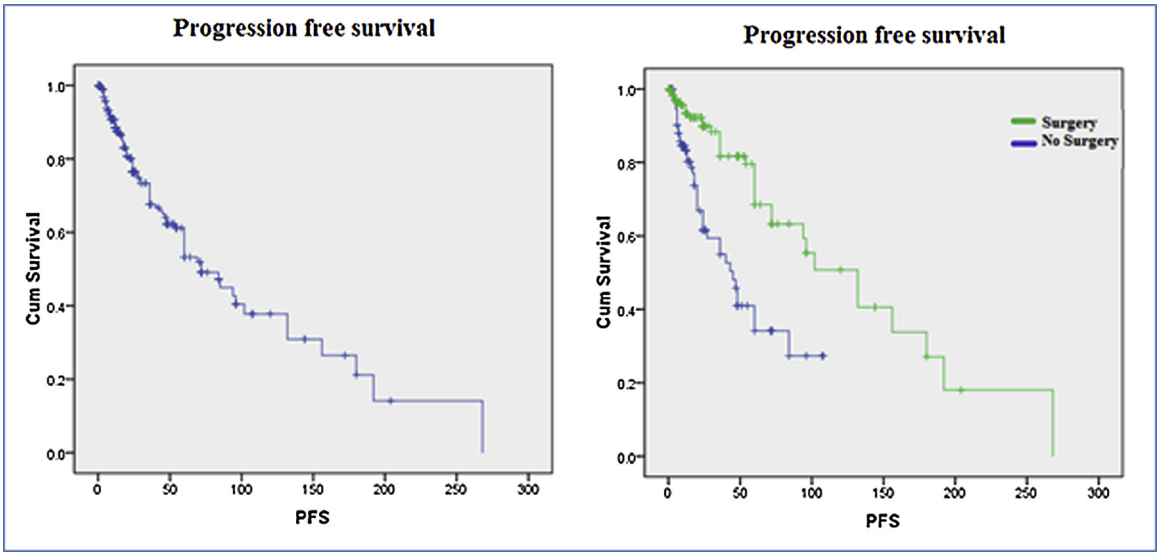

Fig. 4. Kaplan-Meier survival graph depicting PFS of the entire cohort [A]; impact of Surgery on PFS [B].

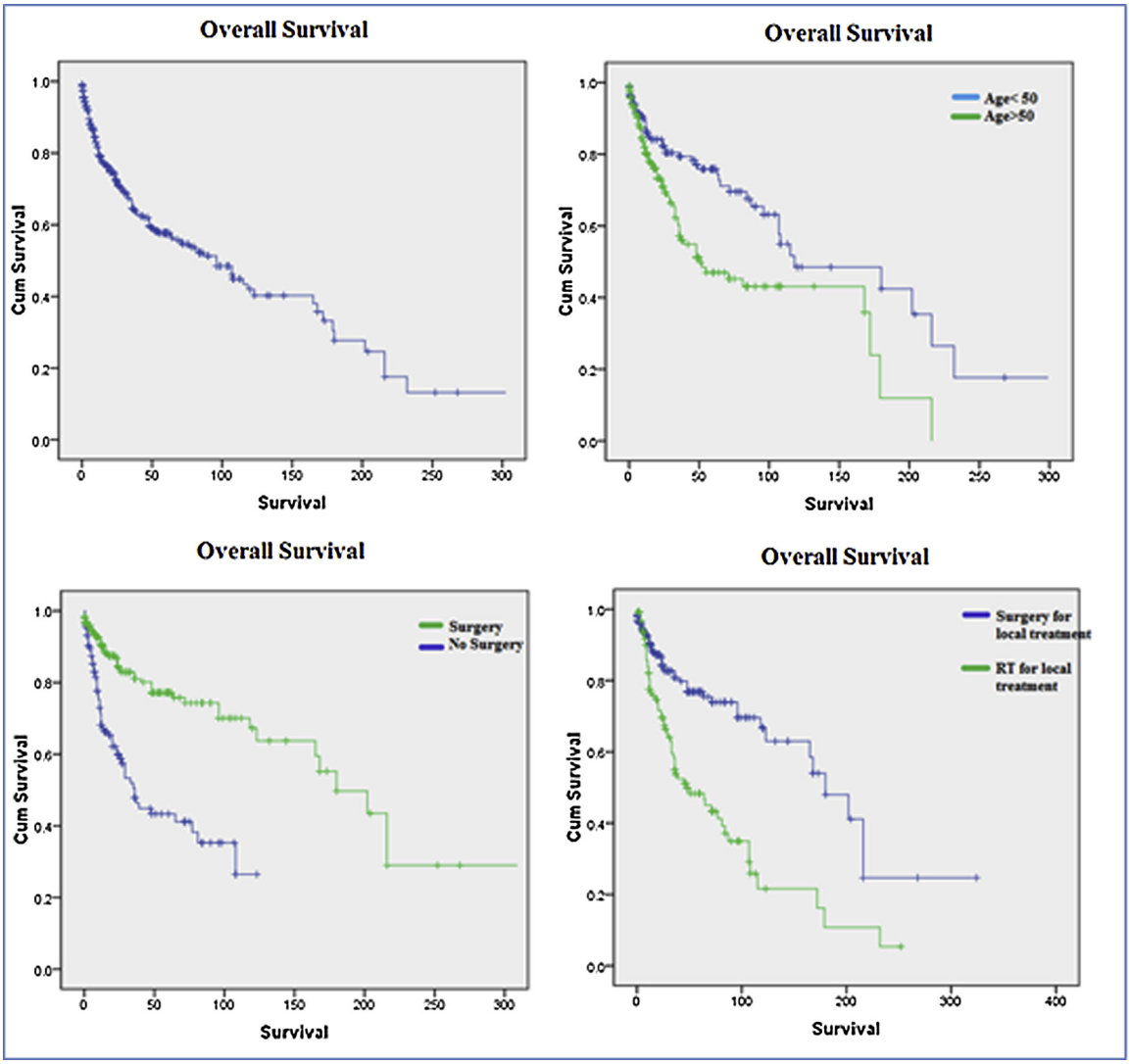

Fig. 5. Kaplan-Meier survival graph depicting OS of the entire cohort [A]; impact of age on OS [B]; impact of surgery on OS [C]; impact of treatment modality on OS [D].

Table 1
Effect of different prognostic factors on OS.

Factor (n = 733)		Median OS	P value	Remarks
Location	Proximal	Not Reached	0.789	No effect of location on OS
	Distal	118 Months		
Smoking	Yes	Not Reached	0.139	Smoking history marginally worsens OS
	No	179 Months		
Surgery	Yes	180 months	< 0.001	Surgery improves OS
	No	36 months		
Post op RT	Yes	Not Reached	0.595	No effect of PORT on OS
	No	202 Months		
Surgery vs Radiation	Surgery	180 months	< 0.001	Surgery better than radiotherapy
	Radiation	48 months		

was reported by chart review of tracheal tumor patients by researchers in MDACC [8].

The present analysis suggests that age > 50 years and SCC histology are poor prognostic factors for OS. Patients of older age tend to have multiple co-morbidities, tolerate radical surgery less and are more likely to have SCC histology. The above factors could have contributed to poorer prognosis in older patients. Patients with ACC had a median survival of 165 months while those with SCC had only 14 months. Inherent difference in biology between the two histologies with ACC known to have a slow and indolent progression in contrast to SCC which is more aggressiveand associated smoking in SCC patients making them less tolerant to thoracic surgery possibly contributed to this huge difference in survival. In light of this finding, future experimental therapies in the adjuvant or radical setting should specifically target SCC histology.

The present analysis highlights that surgery is associated with better survival outcomes as the primary treatment modality compared to radiation in ACC and sarcoma. But it is also possible that definitive radiotherapy is associated with inferior outcomes as patients undergoing radiotherapy possibly had more advanced disease not amenable to surgical resection or had a poor performance status being unfit for surgery. Most case reports fail to mention the exact extent of primary disease or patient performance status making a more balanced comparison difficult. Interestingly, patients with SCC who underwent radiotherapy instead of surgery had slightly better OS. In view of rarity, conducting prospective studies comparing radiotherapy and surgery is not feasible. Matched pair analysis after nullifying effect of histology and stage between the above two interventions is warranted but difficult to perform in view of incomplete data. In the absence of better quality data, it seems prudent to consider surgery as first line treatment in ACC and sarcoma. Patients with SCC should be enrolled into trials to compare radiotherapy and surgery.

The debate on addition of adjuvant radiotherapy remains unresolved especially with close or positive postoperative margins. In a retrospective study by Honings et al [9] on ACC trachea, grossly positive margins were found in less than 10% cases while microscopic positive margins were found in about half the cases. Margin positivity was found to have a negative impact on OS in that study. In our study, margin status was documented in 40 cases out of which 18 cases were positive (45%). 55% of margin positive patients received adjuvant radiotherapy in our study in comparison to only 17% for the entire cohort. This trend does show that radiation oncologists around the world tend to favor adjuvant radiotherapy in cases of positive margins though the evidence supporting adjuvant radiotherapy is scarce. In a study by Wen et al [10], a nomogram predicting OS was created using data of 405 patients in the SEER database. Using the PSM method, the authors conclude that a favorable impact of adjuvant radiotherapy may be seen in SCC. Interestingly, the nomogram does not include margin status in survival prediction. The authors in their discussion do point out that there was lack of data regarding margin status even in the SEER database thus preventing them from performing a meaningful analysis pertaining to margin status. We also faced a similar issue during our analysis. In a matched pair analysis by Xie at al [7], post-operative radiotherapy significantly improved OS with lower incidence of death due to tracheal cancer. The MDACC retrospective analysis, on the other hand could not provide statistically significant association between adjuvant radiotherapy and OS [8]. No conclusive evidence for adjuvant radiotherapy could be created in the present analysis and in light of contradicting results from previous studies decision regarding adjuvant radiotherapy should be tailored.

This analysis has many limitations. All the publications included in the analysis are retrospective that brings into question various sources of bias. Information regarding extent of disease, treatment interventions including extent/ variations of surgery and indication and quality of post-operative radiotherapy was incomplete in most reports. But being a rare tumor very little data is available comparing outcomes with surgery and radiotherapy and effect of post-operative radiotherapy. With such rare diseases, it is difficult to get good quality data and a randomized controlled trial is very difficult to conduct. Our study tried to provide demographic profiling of MTT and find answers to pertinent questions related to treatment interventions. Though not conclusive, our findings will provide directions to physicians to make treatment decisions till better quality data comes up. The use of individual patient characteristics for analysis may be considered as one of the merits of this work. This work highlights the difficulty of managing these patients and underlines the need to centralize it per country in a limited number of expert centers. The quality of the data would then be more reliable and would probably allow better comparisons. This work also highlights the need for a central database for primary MTT so that good homogenous data can be generated and unanswered questions answered.

7. Conclusion

ACC and SCC are the most common malignant tracheal tumors. ACC presents two decades earlier than SCC and has better prognosis. Smoking is strongly associated with SCC trachea. Surgery remains the first line treatment for malignant tracheal tumor with radical radiotherapy showing inferior survival outcomes in ACC and sarcoma. Radiotherapy seems non-inferior to surgery for patients with SCC. Role of post-operative radiotherapy remains undefined.

Disclosures

The authors have nothing to disclose.

Table 2
Histology wise demographic profile distribution.

Histology	No. Patients	Location Proximal vs Distal		Median age (Yrs)	Gender M vs F		Smoking (%)
ACC	247	14	36	47	79	93	33.3
SCC	228	17	29	62	133	30	82.1
Sarcoma	34	1	0	58	24	8	50
MEC	34	1	11	26	17	16	33.3

Table 3
Histology wise effect of treatment on overall survival.

Histology	Median OS	Surgery vs No surgery (Median OS)	P value	PORT vs No PORT (Median OS)	P value	Surgery vs RT (Median OS)	P value	RT > 60 Gy vs < 60 Gy (OS)	P value
ACC (n = 247)	165 months	**180 months vs 108 months**	0.257	Not reached vs 180 months	0.148	**180 months vs 108 months**	0.381	Not reached vs 108 months	0.824
SCC (n = 228)	14 months	23 months vs 20 months	0.965	Not reached	0.696	**23 months vs 29 months**	0.486	**24 months vs 6 months**	**0.011**
Sarcoma (n = 34)	168 Months	**168 months vs 35 months**	**0.034**			**168 months vs 35 months**	**0.034**		

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Not presented

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None.

Compliance with ethical standards

- Disclosure of potential conflicts of interest: The authors have no conflict of interest
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- Informed consent: Not applicable

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References

[1] G. Morency, J. Chalaoui, L. Samson, et al., Malignant neoplasms of the trachea, Can. Assoc. Radiol. J. 40 (1989) 198–200.
[2] P. Schneider, J. Schirren, T. Muley, et al., Primary tracheal tumours: experience with 14 resected patients, Eur. J. Cardiothorac. Surg. 20 (2001) 12–18.
[3] F.L. Ampil, Primary malignant tracheal neoplasms: case reports and literature radiotherapy review, J. Surg. Oncol. 33 (1986) 20–23.
[4] A.Y. Rostom, R.L. Morgan, Results of treating primary tumors of the trachea by irradiation, Thorax. 33 (1978) 387–393.
[5] A.I. Urdaneta, Wilson L.D. Yu JB, Population based cancer registry analysis of primary tracheal carcinoma, Am. J. Clin. Oncol. 34 (2011) 32–37.
[6] D.J. Howard, V.V. Haribhakti, Primary tumours of the trachea: analysis of clinical features and treatment results, J. Laryngol. Otol. 108 (1994) 230–232.
[7] L. Xie, M. Fan, N.C. Sheets, et al., The use of radiation therapy appears to improve outcome in patients with malignant primary tracheal tumors: a SEER-based analysis, Int. J. Radiat. Oncol. Biol. Phys. 84 (2012) 464–470.
[8] B.D. Webb, G.L. Walsh, D.B. Roberts, et al., Primary tracheal malignant neoplasms: the University of Texas MD Anderson Cancer center experience, J. Am. Coll. Surg. 202 (2006) 237–246.
[9] J. Honings, H.A. Gaissert, A.C. Weinberg, E.J. Mark, C.D. Wright, J.C. Wain, D.J. Mathisen, Prognostic value of pathologic characteristics and resection margins in tracheal adenoid cystic carcinoma, Eur. J. Cardiothorac. Surg. 37 (June (6)) (2010).
[10] J. Wen, D. Liu, X. Xu, D. Chen, Y. Chen, L. Sun, J. Chen, M. Fan, Nomograms for predicting survival outcomes in patients with primary tracheal tumors: a large population-based analysis, Cancer Manag. Res. 10 (2018) 6843–6856 Dec 11.