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ORIGINAL ARTICLE

Radiotherapy in Patients with Trachea Tumours: A Retrospective Study and Literature Review

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OBJECTIVE

In this study, we aimed to evaluate our patients with tracheal tumours treated with primary or adjuvant radiotherapy (RT) and to review the current literature on the subject.

METHODS

Between 1998 and 2017, eight patients underwent RT. Their median age was 37 years (15–53). The diagnosis was adenoid cystic carcinoma in five patients, squamous cell carcinoma in three patients and mucoepidermoid carcinoma in one patient. Resection type was R0 (1), R1 (4), R2 (1), and biopsy (2). The median tumour size was 2.6 cm (2–5). Median 59.4 Gy RT (32.4–66.6) was given, and weekly cisplatin was administered to four patients concomitantly.

RESULTS

With a median follow-up of 85 months (4–189), five patients were alive. The 5-year overall and disease-free survival rates were 83% and 67%, respectively. There was no local recurrence in any patient. In one patient who had a complete response with curative chemo-RT, dilatation was performed five times in 10 years because tracheal stenosis developed at 60 months.

CONCLUSION

Trachea tumours are rare, and the primary treatment is surgery. Adjuvant RT is controversial in R0 cases. In unresectable cases, RT is the primary treatment modality. We believe that our treatment results will contribute to the literature on the subject.

Keywords: Local control; radiotherapy; survival; trachea tumor.

Introduction

Primary malignant tumours of the trachea are very rare and account for <0.5% of all tumours and 2% of all upper airway tumours.[1,2] The male–to–female (M/F) ratio is 2/1, and it occurs predominantly in the distal third of the trachea. Symptoms are often misdiagnosed as those of asthma or chronic bronchitis. While haemoptysis and cough symptoms are observed in all patients, inspiratory dyspnoea in the cervical location and expiratory dyspnoea and chest pain in the thoracic location have been reported.[1,3] Squamous cell carcinoma (SCC, 60% –90%) is the most common histology worldwide; adenoid cystic carcinoma (ACC), mostly observed in non-smokers and young people, is the second-most common tumour type.[1] However, in a recent review of 733 cases, the most common histologies were ACC (34%) and SCC (31%).[4] It has

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also been reported that ACC patients were younger (47 vs 62), and the M/F ratio was 0.8/1 for ACC and 4.4/1 for SCC in this study. Less common histologies include adenocarcinoma, neuroendocrine carcinoma, mucoepidermoid carcinoma (MEC), carcinoid, carcinosarcoma, neurogenic tumours, chondrosarcoma, and lymphoma.

The standard treatment approach for these tumours is tracheal resection with adequate margins and end-to-end anastomosis. Resectability depends on the tumour length, location, comorbid factors, and patient age. Survival increases with negative resection margins and the absence of lymph node (LN) involvement.[5] The staging systems proposed by Battacharyya in 2004 and Macchiarini in 2006 were used for surgical suitability.[2,6,7] However, a more accurate classification system is needed for prognosis prediction and treatment management. A new staging system was created in 2017 with SEER analysis, and the prognosis was shown to be associated with histology, tumour size, location, and invasion of the surrounding organ.[8]

Although 50% of the patients were suitable for surgery, the complete resection (R0) rate was 24%.[9] Postoperative or adjuvant radiotherapy (RT) is recommended for all patients for whom complete resection was not possible (R1, R2); however, the recommendation for R0 resected cases is controversial. The presence of perineural invasion (PNI) and invasion of the mediastinal structures are reported as risk factors for recurrence, and adjuvant RT is recommended in such patients. For unresectable/inoperable disease, RT is the primary treatment option. In patients not eligible for curative surgery, endoscopic procedures (such as electrocoagulation, cryotherapy, laser excision, photodynamic therapy), stenting, and brachytherapy are used to obtain a biopsy and keep the airway open; palliation can be achieved in 80%–90% of these patients.[6,10] Although the benefit of chemotherapy alone (CHE) has not been demonstrated for localized disease, concurrent chemo-RT is believed to improve the results due to the radiosensitizing effects, similar to the approach in lung cancer patients.[1] Local recurrence is a major cause of failure. While 40%–50% of distant metastasis and more distant LN involvement are observed in ACC cases, patients with SCC are characterized with 10%–20% distant metastasis, 30% paratracheal LN involvement, and early recurrence.[1,3,6,11,12] The reported median overall survival (OS) was 37 months for ACC and 6–12 months for SCC.[1]

In this study, we aimed to retrospectively evaluate our patients with tracheal tumours treated with primary or postoperative RT in our department and to conduct a review of the current literature on the subject.

Materials and Methods

Between February 1998 and April 2017, eight patients with tracheal tumours underwent RT in our department. The median patient age was 37 years (15–53), and the median M/F ratio was 3/5 (Table 1). Most patients presented with dyspnoea (75%) and inspiratory stridor and wheezing (37%) symptoms at a median time of four months (3–24). The presenting symptoms were dysphagia in one case (7%) and haemoptysis and tracheal perforation in another case (7%). Four patients (50%) had multiple symptoms. Thorax computed tomography (CT) and/or magnetic resonance imaging (MRI) and positron emission tomography (PET/CT) were used for establishing the diagnosis. Histopathological diagnosis was ACC in five cases, SCC in three cases, and MEC in one case. The presence of PNI was evaluated in two patients with ACC, and one patient tested positive. The resection type was R0 (1), R1 (4), R2 (1), and biopsy (2). The tumour location was the cervical-upper third of the trachea in three patients, middle-third in one patient, and lower-third in four patients. One patient had undergone paratracheal nodal dissection after laser excision and showed poorly differentiated SCC metastasis. The other two patients with ACC who had undergone R0 and R1 resection were staged as N0 using regional nodal dissection. In 62% (5/8) of the patients, the tumour originated from the lateral wall. The median interval between diagnosis and surgery was seven days (0–25) for five patients who underwent surgical/laser excision. The interval from diagnosis to RT was 58 days (0–91) and that from surgery to RT was 61 days (51–91). The median tumour diameter was 2.6 cm (2–5). Patients were classified as a stage (s) II (3), sIII (3), and sIV (2) as per the classification given by Bhattacharyya and into sI (3), sII (1) and sIII (4) according to Macchiarini staging. Staging compliance was 37.5%. Three patients had a family history of cancer. Comorbidity was present in four cases, one patient had epilepsy, one patient had psychiatric disease-breast surgery, one patient had asthma-osteoporosis-carpal tunnel syndrome, and one patient had undescended testicle surgery.

Between 1998 and 2008, RT was performed with a photon energy of 6–25 MV as two dimensions with antero-posterior and oblique boost areas. In addition, elective nodal irradiation (ENI) was used, covering the

Table 1 Clinical characteristics

Case	Age	Sex	Symptoms	Location	Surgery	Histology	Bhattacharyya staging	Macchiarini staging	RT Gy	Concomitant cisplatin mg/m²/wk	Status	OS months
1	46	F	Dyspnea, stridor	Middle 1/3	bx	ACC	T3N0M0-sIII	T3N0M0-sIIIA	66.6	30/6 weeks	Lost to follop up	190
2	26	M	Dyspnea, wheezing	Cervical	R1	ACC	T2N0M0-sIII	T3N0M0-sIIIA	59.4	30/5 weeks	Alive	175
3	53	F	Dyspnea	Cervical	bx	SCC	T2N0M0-sII	T1aN0M0-sIA	32.4		Dead	4,5
4	25	F	Dyspnea	Lower 1/3	R0	ACC	T2N0M0-sII	T2N0M0-sIB	55.8		Alive	130
5	37	M	Dyspnea	Lower 1/3	R1	ACC	T4N0M0-sIV	T3N0M0-sIIIA	59.4		Alive	115
6	53	F	Dysphagia	Lower 1/3	R2	SCC	T3N0M0-sIII	T3N0M0-sIIIA	56	30/3 weeks	Dead	8
7	51	F	Dyspnea, wheezing	Cervical	R1	SCC	T2N1M0-sIV	T2N1M0-sIIA	63	70/5 weeks	Alive	87
8	15	M	Hemoptysis, perforation	Lower 1/3	R1	MEC	T2N0M0-sII	T2N0M0-sIB	62		Alive	21

paracervical, paratracheal and subcarinal nodes. After June 2008, the tumour/tumour bed and the involved nodes were irradiated with three-dimensional conformal RT. The radiotherapy field was created with a 1-cm margin on the anterior-posterior and lateral sides of the tumour, with a 2-cm for SCC and a 5-cm margin for ACC at the superior-inferior margins and included only involved nodes. The median 59.4 Gray (Gy) RT (32.4–666.6) was given to all patients, and concomitant weekly cisplatin CHE (30–70 mg/m^2) with median 5 cycles (3–6) was administered to four patients.

The response was assessed in the first month with thorax CT. The patients were followed up with thorax CT and/or bronchoscopy every three months for two years, every six months for five years, and annually thereafter. Treatment–related adverse effects were evaluated using the "Common Terminology Criteria for Adverse Events, v.4".[13] In patients who developed recurrence/progression or metastasis, surgery, CHE, or supportive treatment was administered.

Statistical analyses were performed using SPSS v.21 in December 2017. Overall and disease–free survival (DFS) were calculated from the time of diagnosis till the time of death, progression, or last follow up. Survival was analysed using the Kaplan–Meier method. P-values were ≤0.05 were considered significant. Univariate and multivariate analyses were not performed because of the small sample size.

Results

Two patients died, one patient was lost to follow-up and five patients were alive in December 2017 with an average follow-up period of 85 months (4–189). Tracheostomy was performed because of respiratory distress during RT in one patient who had undergone biopsy; this patient was able to receive only 32.4 Gy RT. This patient died due to lung infection, and survival duration was 4.5 months from diagnosis. Another patient who had undergone R2 resection with tracheostomy during RT received 56 Gy and died at four months after RT due to lung infection. The survival duration for this patient was eight months from the time of diagnosis. Both patients were diagnosed with SCC, and we believe that lung infection developed because of multiple causes.

Grade 1-2 acute complications, such as skin erythema (4), dysphagia (2), nausea-vomiting (1), and hoarseness, (1) developed in four patients. Acute grade 3 leucopoenia was observed only in two patients who were receiving concomitant cisplatin with RT. Symp-

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tomatic and radiological response (70%) was achieved in one patient who had undergone biopsy and was treated with 45 Gy RT and concurrent weekly cisplatin (30 mg/m^2). In this case, surgical intervention was not considered because of comorbidites; total curative 66.6 Gy RT and simultaneous CHE were administered for six weeks. In the first month after treatment, complete response was observed on thorax CT (Fig. 1). This patient underwent dilatation five times in 10 years because of tracheal stenosis, starting at the 60 months; the patients was lost to follow up after 190 months of survival.

Median and 5-year OS and PFS were found 118 months (4.5–190), 83% and 87 months (0–190), 67%, respectively (Fig. 2). The median OS was 130 months (118–190) in ACC, eight months (4.5–87) in SCC, and 21 months in one patient with MEC. No local recurrence occurred during the follow-up period. A patient with R1 resection and ACC histology had developed lung metastasis at 22 months, treated with surgery and

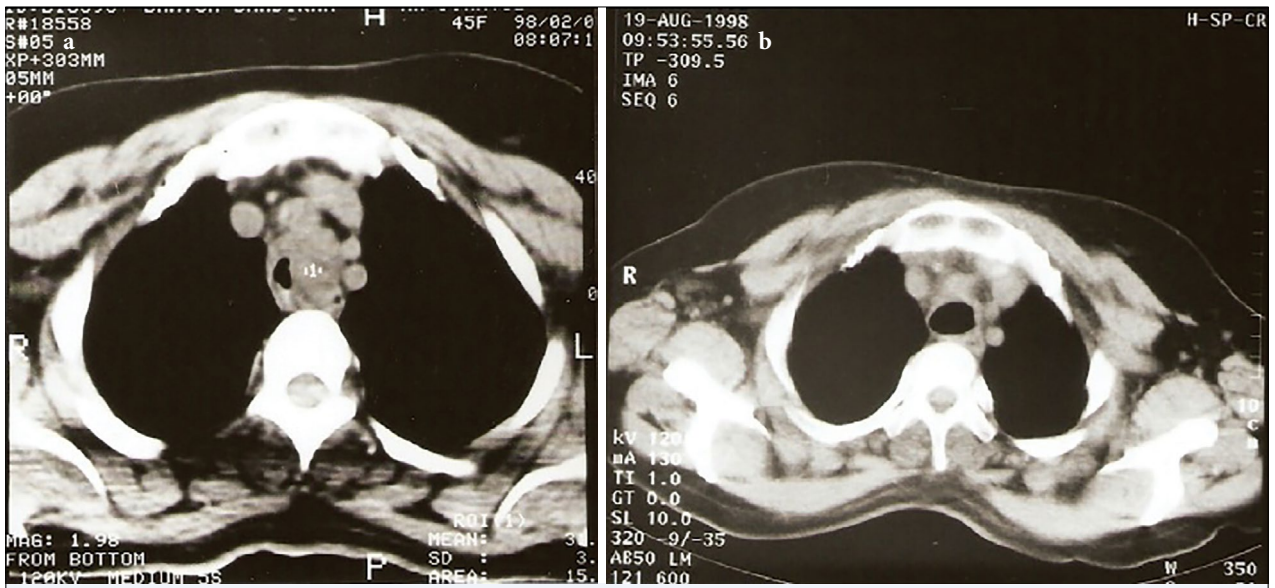

Fig. 1. Complete response in a patient treated with curative chemo-RT. (a) Thorax CT shows a tumor that narrows the trachea. (b) Thorax CT shows complete response at 4 months with 66.6 Gy RT and concurrent weekly cisplatin in same patient.

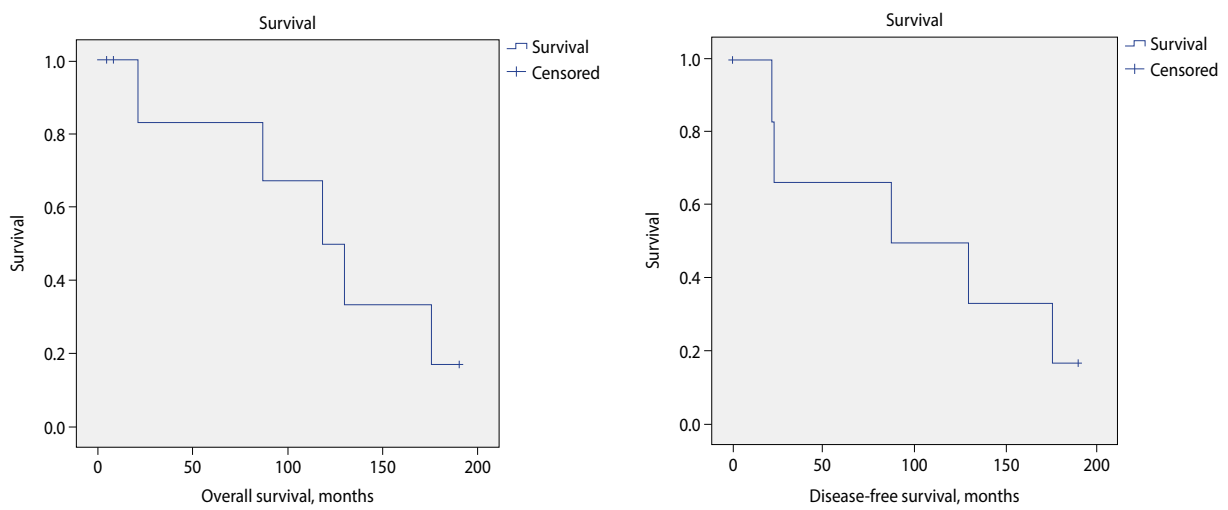

Fig. 2. Overall and disease-free survival.

adjuvant six cycles of CHE. This patient was alive as on 115 months from diagnosis and 90 months after salvage treatment.

Discussion

The trachea is a fibrocartilagenous structure between the cervical 6–7 and the thoracic 4–6 vertebrae and is approximately 12 cm long. The cervical or upper-third part of the trachea is considered 3 or 5 cm below the cricoid cartilage. The lower-third of the trachea is considered up to 3 cm above the carina, and the part between the proximal and distal third is defined as the middle-third of the trachea.[4,14] Primary malignant tumours of the trachea are rare and peak at the 5th decade of age.[1] The tracheal lumen may be obstructed by 70% before the onset of any symptoms or signs. Yang et al. reported that 60% of the tumours originate from the anterior-lateral wall of the trachea.[11] ACC tends to occur in the upper third of the trachea and extends beyond the trachea with three times more frequency than in SCC.[1,11] While the intraluminal part and extramural extension of the tumour is better evaluated using CT, MRI is the most important method to determine its length along the mucosa. Endoscopic evaluation is necessary for a decision regarding resectability, biopsy, diagnosis, and treatment of airway obstruction.

The most common symptoms are cough (72%), dyspnoea (66%), stridor (39%), haemoptysis (39%), and dysphonia (31%) in patients with trachea tumours.[1] It is reported that the diagnosis is delayed by >6 months in one-third of the cases, and this is thought to be an indicator of the slow growth of these tumours.[11]

Many studies have reported that the histology, tumour size, stage, age, type of resection, thyroid gland invasion, lymphatic invasion, and PNI are significant prognostic factors (PFs) for tracheal tumours.[1] Staging systems created by Battacharyya and Machiarini have been used to date (Table 2).[2,6] However, there is a need for a more accurate estimation of prognosis and a more accurate classification for better treatment management. In their SEER study, He et al. established a new staging system in 2017.[8] In this study, most of the 287 patients had adenocarcinoma and SCC, and the prognosis was associated with age, histology, tumour size, and extension to the adjacent organs. In this classification, every 1 cm of tumour size was found to be significant, and the median and 5-year OS was 57 months and 49% in patients if the tumour size was <4 cm. However, in the Bhattacharyya study for 99 cases, median and 5-year OS was 30 months and 40%, respectively, and the 5-year OS was 53% for those with tumour size <2 cm.[2,8] He et al. emphasized the importance of subgroup staging based on the extension and size in addition to the T stage. According to the extension, the 3-year OS was 75% for stage E1 patients with tumour size <4 cm; however, in stage E1 and patients with tumour size >4 cm or E2-3 cases and those with tumour size <3 cm, the 3-year OS was 57%, similar to each other. For stage E2, and patients with tumor size >3 cm as well as for E4 cases, the 3-year OS rates were 28% and 9%, respectively (Table 2). In addition, it was reported that the prognosis of patients with SCC or N2 was worse than that of others. The 5-year OS was 60%, 45%, 20%, and 0% for N0, Nx, N1, and N2 cases, respectively. The limitations of this study were that the anatomical location was not considered, and they did not include ACC cases.

In a cohort study conducted at the Yale University, 45% of the 578 patients were diagnosed with SCC and 16% were diagnosed with ACC. The local, regional, and metastatic disease rates were 24%, 37%, and 19%, respectively.[15] Although 70% of the patients underwent RT, the 5-year OS was 27% and there was no apparent benefit of RT. The results are attributable to the selection bias introduced given that patients referred for RT had more local aggressive disease and positive surgical margins or were treated for palliative purposes. In a retrospective analysis, Xie et al. report on the survival benefit obtained with RT, especially in patients with SCC, regional disease, or patients who did not undergo resection.[16] Wen et al. established a nomogram according to histology, tumour size, age, nodal stage, presence of metastasis and treatment type in the analysis of 405 cases, most of them had SCC (40%) and ACC (24%).[17] In this study, the nomogram accuracy was 81% for survival prediction, and an increase in the OS was demonstrated using postoperative RT in patients with SCC (5–year OS, 61% vs 23%, $p<0.05$). However, the importance of surgical margin status concerning results could not be evaluated in this study. In a cohort study of 549 patients of the National Cancer Institute, it was reported that ACC and R+ patients received more adjuvant RT because of difficulty in performing surgery due to submucosal spread. However, they also emphasized that there was no level 1 evidence for the adjuvant RT decision.[18]

Levy et al. evaluated 31 ACC patients with 41% R0 resection treated with adjuvant or curative RT.[19] In this study, the 5-year OS, PFS, as well as local and distant recurrences rates were 88%, 61%, 10%, and 26%,

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Table 2 Staging systems

Bhattacharyya 2004

Primary tumor (T)

Tx	Unknown or cannot be assessed
T1	Primary tumor confined to trachea; size <2 cm
T2	Primary tumor confined to trachea; size >2 cm
T3	Spread outside the trachea but not to adjacent organ or structures
T4	Spread to adjacent organs or structures

Regional lymph nodes (N)

Nx	Unknown or cannot be assessed
N0	No evidence of regional nodal disease
N1	Positive regional nodal disease

Anatomic stage/Prognostic groups

I	T1N0
II	T2N0
III	T3N0
IV	T4 or N1

He 2017, SEER

Primary tumor (T)

T1	Primary tumor was confined to trachea, size <4 cm
T2	Primary tumor was confined to trachea, size >4 cm; Spread outside the trachea but not to adjacent organs; Spread to adjacent organs, size <3 cm
T3	Primary tumor spread to adjacent organ sor structure, size >3 cm
T4	Further contiguous extention

Regional lymph nodes (N)

Nx	Lymph node involvement unknown
N0	No regional lymph node involvement
N1	Regional lymph node involvement (mediastinal, paratracheal, pretracheal, tracheoesophagial nodes)
N2	Distant lymph node involved

Extension

E1	Primary tumor was confined to trachea
E2	Primary tumor spread outside the trachea but not to adjacent organs
E3	Primary tumor spread to adjacent organs or other structures including: Arch of aorta, Azygos vein, Brachiocephalic vein, Carotid sheath, Common carotid artery, Jugular arch, Phrenic nerves, Pretracheal fascia, Recurrent laryngeal nerve, Subclavian artery, Vagus nerve, Cricoid cartilage, esophagus, Pleura, Main bronchi (originated from trachea), Sternum, Thymus, Thyroid gland, Vertebral coulmn, et al.
E4	Further contiguous extension

Prognostic groups

5-year OS

Group 1	E1, <4 cm	----------	T1.	E1 <4 cm	75%
Group 2	E1, >4 cm	----------	T2.	EI >4 cm	57%
Group 3	E2, <3 cm	----------		E2 <3 cm	
Group 4	E3, <3 cm	----------		E3 <3 cm	
Group 5	E3, >3 cm	----------	T3.	E3 >3 cm	28%
Group 6	E4	----------	T4.	E4	9%

Macchiarini 2006 *

Primary tumor (T)

Tx	Cannot be assessed
Tis	Any tumor without invasion
T1a	< 3 cm limited to mucosa
T1b	≥ 3 cm limited to mucosa
T2*	Any tumor that invades cartilage or adventitia
T3	Any tumor that invades ctrachea or larynx
T4a	Any tumor that invades carina or main bronchus
T4b	Any tumor that invades neighbouring structures

Regional lymph nodes (N)

Nx	regional lymph nodes cannot be assessed
N0	No evidence of node metastasis
N1	Local nodes positive (N1a<3 cm; N1b≥3 cm)
Upper third	Highest mediastinal nodes; upper paratracheal nodes; prevascular and retrotracheal
Middle third	Upper paratracheal nodes; prevascular and retrotracheal; Lower paratracheal nodes; paraaortic nodes (ascending aorta or phrenic)
Lower third	Upper paratracheal nodes; prevascular and retrotracheal; subaortic nodes (aorto-pulmonalis window)
N1A	<3 cm, 1-3 positive nodes in upper third
N1B	≥3 cm, >3 positive nodes in upper third
N2	Regional nodes positive
Upper third	Lower paratracheal nodes; subaortic nodes (aorto-pulmonalis window)

Table 2 Cont.

Middle third	Highest mediastinal nodes; subaortic nodes (aorto-pulmonalis window)
Lower third	Upper paratracheal nodes; pulmonary ligament
Distant metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Metastasis to nodes othar than N1 and N2
M2	Distant metastasis (e.g. lung)
Anatomic stage/Prognostic groups	
0	TisN0M0
Ia	T1aN0M0
Ib	T1b-2N0M0
IIa	T1b-2N1M0
IIb	T1b-2N2M0
IIIa	T3N0M0
IIIb	T3N1-2M0
IVa	TN1-2M1
IVb	TN1-2M2

*The MDACC system denotes "arising from but extending outside of trachea" as T3 disease and does not use T4 (from Webb 2006)

respectively. Advanced age (≥50 years), presence of PNI and RT dose (≤60 Gy) were reported as significant PFs. In their study on 32 patients, Song et al. reported that MEC patients accounted for 1% of all tracheobronchial cancers, and their median age was 28 years. [20] Histology, stage, grade, inadequate resection, and adjuvant RT and CHE were reportedly associated with the prognosis. The 5-year OS was 81% for all patients, while all high-grade cases recurred and had a 5-year OS rate of 29%.

Surgery is the first choice in the treatment of primary malignant tracheal tumours. However, at the time of diagnosis, most patients may not be suitable for surgery due to the invasion of surrounding structures. Honnings et al. reported that peritracheal invasion was present in 67% of the 59 patients with SCC if the tumour diameter was >2 cm.[21] Napieralska et al. demonstrated the need for additional surgery in 15%–26% of the cases.[22] In a survey of 50 cases, Honnings et al. recommended that multidisciplinary treatment decision was 24% resection, 58% RT, 12% endobronchial therapy, and 6% observation; however, resection decision increased to 56% if a second surgeon's opinion was obtained.[9] Gaissert et al. emphasized that with the development of surgical technique, complete resection rates increased from 68% to 82%, and the mortality decreased from 21% to 3%.[10]

Table 3 shows the results of treatment based on the literature. Adjuvant RT is recommended in all patients because most relapses are local, and these tumours are sensitive to irradiation. Grillo and Mathisen reported that survival increased with surgery and adjuvant RT compared with RT alone based on a study of 150 patients.[5] However, it was emphasized that selection bias due to the recommendation of curative RT for invasive cases may have influenced the results. In a 22-case study by Chow et al., surgery+RT was found to be superior to surgery or RT alone (median OS: 61, 16, and 21 months, respectively).[23] Regnard et al. showed improved survival with adjuvant RT in both R0 or R+resected SCC patients.[12] Maziak et al. reported that 50% of the 32 patients with ACC who underwent surgery were R+because of submucosal spread beyond the visible tumour ≥1cm.[24] Although there was no difference in the survival with adjuvant RT in this study (R0 and no RT; 131 vs R0/R+and RT; 88 months), only 13% had local recurrence, and RT was reportedly useful in preventing local recurrence. In the SEER study by He et al., only 39 % of the patients received RT. It is demonstrated that survival significantly improved in univariate analysis with RT (p=0.001) in this study. [8] In the current series of 733 cases by Mallick et al., PFS (132 vs 36 months, p<0.001) and OS (180 vs 48 months, p<0.001) were better with surgery than with curative RT, and this difference was demonstrated in all the histological groups.[4] In this study, a statistically insignificant increase in survival was reported with adjuvant RT (Table 3). The absence of significant survival difference with adjuvant RT may be attributable to the low reporting rate for surgical margin status and given that only 55% of them were recommended to undergo adjuvant RT.

In the literature, the prognostic significance of nodal involvement is controversial, and it is reported

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Table 3 Trachea tumors–treatment results based on literature

Study	Histology (n)	Treatment	Median OS (months/% for 5-year)	p
Grillo-Mathisen, 1990	SCC (70)	Surgery±RT (44)	34	
		RT (26)	10	
	ACC (80)	Surgery±RT (60)	118	
		RT (20)	28	
Chow, 1994	22	Surgery (4 SCC, 1 unclassified)	16	
		RT (7 SCC, 2 ACC, 2 adenocarcinoma 1 small cell carcinoma)	26	
		Surgery+RT (1 SCC, 3 ACC, 1 adenocarcinoma)	61	
Regnard, 1996	SCC (79)	R0+RT (31)	74	Insignificant
		R0 (27)	53	
		R1, 2+RT (15)	47	<0.05
		R1, 2 (6)	0	
	ACC (62)	R0 (36)	82	Insignificant
		R1, 2±RT (26)	63	
Mallick, 2019	733	Surgery	180	<0.001
		RT	48	
		Surgery±RT	Not reached 202	Insignificant
	SCC (228)	Surgery	23	Insignificant
		RT	29	
		Surgery±RT	Not reached	Insignificant
	ACC (247)	Surgery	180	Insignificant
		RT	108	
		Surgery±RT	Not reached 180	Insignificant

that even with cervical nodal involvement, the results do not worsen, and ENI is not required.[1,11] Nodal irradiation is recommended in cases of radiological or pathological nodal involvement and in the presence of poor pathological PFs.[9] In the SEER study, the prognostic significance of each nodal stage is demonstrated, and it is emphasized that tumour size, extension, histology, and anatomic location should be considered, similar to that in esophageal cancers.[8] In a study of 263 cases with tracheobronchial ACC, LN metastasis was reported to be present in 28% of the patients.[25] In this study, tumours <3 cm in size and of tracheal origin rather than bronchial origin had less nodal metastasis, and if the number of examined LNs was >10 and the metastatic LN ratio was ≤0.07, the disease-specific survival increased. Although there was no difference in survival with surgery with or without RT in this study, further studies are needed to determine the importance of the total number of metastatic LNs concerning adjuvant RT decision due to lack of reporting PFs that may affect the results, such as the surgical margin, surgical type, PNI, RT dose and comorbidity.

RT is the primary treatment option in unresectable cases. Rostom-Morgan reported that in 19 local–stage cases treated with curative 50–70 Gy RT was obtained 58% complete response, and 26% of those was recurred locally in the median 26 months.[26] Makarewicz et al. showed that a 78% response that lasted 12 months and median survival of 9.5 months was achieved in 23 patients treated with curative 50–60 Gy or palliative 20–30 Gy.[27] Recurrence/progression of 50%, distant metastasis of 25% and treatment complications of 17% were reported in this study, and complete response and >60 Gy RT dose were significant for all results. In the review by Mallick et al., the PFS and OS rates were 36 and 48 months, respectively; the OS rate was 108 months in ACC and 29 months in SCC patients treated with curative median 70 Gy RT.[4] Additionally, the

prognosis was reportedly worse in patients aged >50 years because of decreased surgical tolerance due to comorbidities in addition to SCC histology. It was emphasized that OS was increased in SCC and in patients administered >60 Gy RT; further, there was a 16% progression at a median of 22 months in all patients. Napieralska et al. evaluated 58 patients who received adjuvant or curative RT.[22] Poor performance status, presence of haemoptysis and absence of RT reported as significant PFs for OS in the multivariable analysis. In this study, it was emphasized that local relapse developed in 49% of the patients at 17 months and distant relapse in 37% at 12 months.

The effects of the RT dose on local control (LC) have been shown. At least 60 Gy has been recommended after R0 resection and additional doses are prescribed for high-risk SCC.[1] The importance of dose concerning response, LC, and OS has been shown in patients treated with curative RT. In a study on 18 patients treated with curative RT by Fields et al., increased complete was demonstrated in patients receiving doses >60 Gy (86% vs 9%).[28] Mornex et al. studied 84 patients and reported that the 5-year OS was better in patients receiving >56 Gy RT (12% vs 5%).[29] Mallick et al. reported that the median OS was increased with >60 Gy in patients treated with curative RT (24 vs 6 months).[4] However, Chow et al. emphasized the increase in the rate of serious complications in patients receiving >60 Gy RT.[23] To overcome this, the combination of external RT with brachytherapy has been proposed.[1] Fuwa et al. reported that the 5-year LC was 65%, and the 3-year OS was 55% in 40 patients treated with a median 91 Gy with external RT and brachytherapy; however, one patient who received total 113 Gy died due to complications.[30] In a study of 25 cases by Harms et al., they reported 88% symptom palliation, 44% LC with 60 Gy external RT, and an additional 15–18 Gy brachytherapy dose. 5-year OS was 26% in those with SCC and 86% for those with ACC; 8% Grade 3–4 complications were observed in this study.[31] Je et al. reported that local recurrence developed in 67% and distant metastasis in 78% at 24 months in nine patients with ACC despite curative RT.[32] The 5-year local progression-free survival (100% vs 0%) and OS (83% vs 33%) were significantly increased in patients receiving additional doses with brachytherapy (77.1 vs 66 Gy). In this study, 10% complication of tracheal stenosis was reported. The QUANTEC study reports that the risk of stenosis is low if the central airways receive ≤80 Gy.[33] It is recommended that optimal doses should be determined in multicentric studies in patients with favourable PFs.

The planning target volume should be created by adding 1–2 cm at the anterior-posterior and medial-lateral direction to the visible tumour for curative RT and preoperative tumour volume after surgery and 3–5 cm in the cranial-caudal direction for ACC patients; the involved lymph nodes should also be included.[1,19,32] It is recommended that the LC be increased and adverse effects are decreased with the use of PET/CT for planning and intensity-modulated RT (IMRT) or volumetric arc therapy in treatment. Chang et al. reported that IMRT application after curettage in a patient with ACC is less invasive and achieves better prognosis than R0 resection.[34] To increase the LC, the use of radiosensitizer agents simultaneously with RT is recommended, as in lung cancers.[1,35] 2-year PFS has been reported for unresectable SCC patients receiving chemo-RT with combined agents containing cisplatin.[36,37] Furthermore, the immune system control inhibitors may play a role in patients with unresectable, recurrent, or residual tracheal cancer. Tapias et al. reported that there was programmed cell death receptor expression and CD8+ infiltration in 75% of the SCC–diagnosed trachea tumours.[38] Maller et al. demonstrated complete response and 1-year PFS to immune control inhibitors in a patient with SCC who had an invasion of the trachea and was resistant to other treatments, including RT.[39]

Conclusion

Of the eight patients with tracheal cancer who underwent primary or adjuvant RT, 83% OS and 67% PFS were obtained with 85 months of follow-up in our study. No local recurrence was observed in any patient. A patient who had developed distant metastasis was alive and free of disease after salvage therapy at 90 months of follow-up. The limitation of the present study is the small sample size. Future research should focus on the clinicopathological features and treatment results in more subjects using a multicentric study design and evaluate these subjects in light of the current data.

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