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REVIEW

Treatment and Outcomes of Primary Tracheal Adenoid Cystic Carcinoma: A Systematic Review

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Abstract: Primary tracheal adenoid cystic carcinoma (TACC) is a rare malignant tumor. This systematic review describes the treatment strategies and oncological outcomes in patients with TACC. Full-text English manuscripts published from January 1st 1960, to December 31th 2023, were included. Data on demographics, treatment, and outcomes were also collected. A pooled analysis of 5-year overall survival (OS) was performed. Nineteen articles and 1488 patients met the inclusion criteria. The first-choice treatment strategy was surgery (74.5%), whereas adjuvant radiotherapy was administered to 56.7% of the patients. The follow-up range was 6–390 months. A total of 552 deaths were recorded, 98.7% of which were cancer related. The 5-year OS rate ranged from 28.6% to 100.0%; in the pooled analysis, it was 65% (range, 32%–96%). Surgery remains the mainstay of treatment for TACC. Adjuvant radiotherapy is commonly administered to patients with positive margins, and survival estimates are good overall but heterogeneous.
Keywords: adenoid cystic carcinoma, trachea, treatment, survival

Introduction

Adenoid cystic carcinoma (ACC) is a kind of primarily salivary gland tumor, which may also occur in other sites such as the paranasal sinuses, larynx, and trachea.[1] ACC is the second-most common primary malignant tracheal tumor, ranked after squamous cell carcinoma (SCC), with an incidence of 0.04–0.2%.[2] It is a rare slow growing tumor that arises from secretory glands in the trachea, with late distant metastasis. It has not been found to be associated with smoking or alcohol consumption.[3] The sex incidence of tracheal adenoid carcinoma (TACC) is fairly even, and the age incidence predominates in the fourth and fifth decades. The management of TACC involves surgical resection and reconstruction, with the recommendation of adjuvant radiotherapy for controlling microscopic disease or as salvage treatment for unresectable disease.

In recent decades, oncological treatment modalities have considerably improved. However, the infrequency of this tumor impedes the establishment of treatment standards, and survival analyses may be biased by the small size of published series. In addition, larger cohorts occasionally gather tumors from different sites, with limited detailed data for the trachea site origin. Therefore, we performed a systematic review of TACC to describe the treatment strategies and outcomes of this rare tumor.

Materials and Methods

Objectives

The primary objective was to define the survival outcomes in patients diagnosed with TACC. The secondary objective was to describe the treatment modality used.

Search Strategy

This systematic review was performed and reported in accordance with the Preferred Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist and statement recommendations.[4] A comprehensive search on PubMed, Web of

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Science and MEDLINE was conducted on February 28th, 2024, using the following queries: "(adenoid cystic carcinoma) AND (tumor*OR neoplasm*OR malignancy) AND (Tracheal)".

Selection Criteria

Only original papers published in English in a peer-reviewed journal from January 1st, 1960, to December 31th, 2023, were included. Exclusion criteria were: 1) impossible to extrapolate specific data on treatments and survival of patients with TACC; 2) pediatric cohorts; 3) series with less than or equal to 5 patients; 4) non-human studies.

Two authors (YS and SX) independently screened all titles and abstracts. Full text was obtained for publications that fulfilled the inclusion criteria. The references of all the selected articles were reviewed to identify additional relevant articles. Disagreements were resolved by discussion with the senior author (JZ).

Data Extraction

The relevant features of each study (publication year, country, study design, and period of observation) were collected along with demographics (age at presentation, sex), pre-operative imaging, tumor features (site and subsite, TNM classification, perineural invasion [PNI], lymphovascular invasion [LVI], grading, and margin status), treatment modality and post-operative complications, mean follow-up, death, recurrence rate (local or distant), 5- and 10-year overall survival (OS), disease-free survival (DFS), local recurrence free survival (LRFS), and distant recurrence free survival (DRFS). Two authors (YS and SX) independently extracted data from the eligible articles and created a dedicated database. Data analyses were performed using Microsoft Excel. A pooled analysis of the 5-year OS extracted from the selected articles was performed to obtain a general estimate of the outcome.

We have not used any generative AI tools in this research.

Results

General Features

The initial search returned 1888 articles. The identification, screening, inclusion, and exclusion criteria are shown in Figure 1. Nineteen articles, all based on a retrospective series of 1488 patients, were included in the present systematic review (Table 1). The age range of the patients was 18–93 years old.

Demographics and Tumor Characteristics

The demographic and tumor characteristics are summarized in Table 2. Clinical features were reported for all 1488 patients. The male-to-female ratio was 1:1.38. There were 63 patients with T stage disease, 275 with negative lymph node invasion, 7 with distant metastasis, and 37 with perineural invasion. Excluded 1056 (71.0%) of patients with no specific subsite documented, the most common anatomical region of origin was distal/carinal trachea (149/10.0%), followed by cervical trachea (130/8.7%) and middle trachea (100/6.7%). The TNM classification has been reported in a few articles,[2,13,17–19,21,22] and tumor grading has rarely been reported (Bhattacharyya's staging system was adopted[23]). Lymph node involvement was reported in seventy-two cases, and metastasis status was reported in seven cases. PNI was reported in 2.5% (37/1488) of the cases, and LVI has not been reported. The resection margin status was detailed for 690 patients who were surgically treated, with 178 cases with negative margins, 255 with positive margins (not otherwise specified), 249 with microscopically positive margins (R1), and 8 with macroscopic positive margins (R2). Among 690 cases, 36.1% (249/690) presented with a confirmed R1 margin status and only 1.2% (8/690) with a confirmed R2 margin status and 25.8% (178/690) with negative margin.

Treatment

The treatment modalities are described in all studies and are detailed in Table 3. Surgery was the most common treatment option. One thousand one hundred and nine patients (74.5%) were treated with different surgical procedures according to the tumor site. Tracheal surgery was performed in 416 patients, and when the distal trachea was involved, tracheal resection was associated with lobectomy or pulmonary resection in two and 55 patients, respectively. About 57.6% (639/

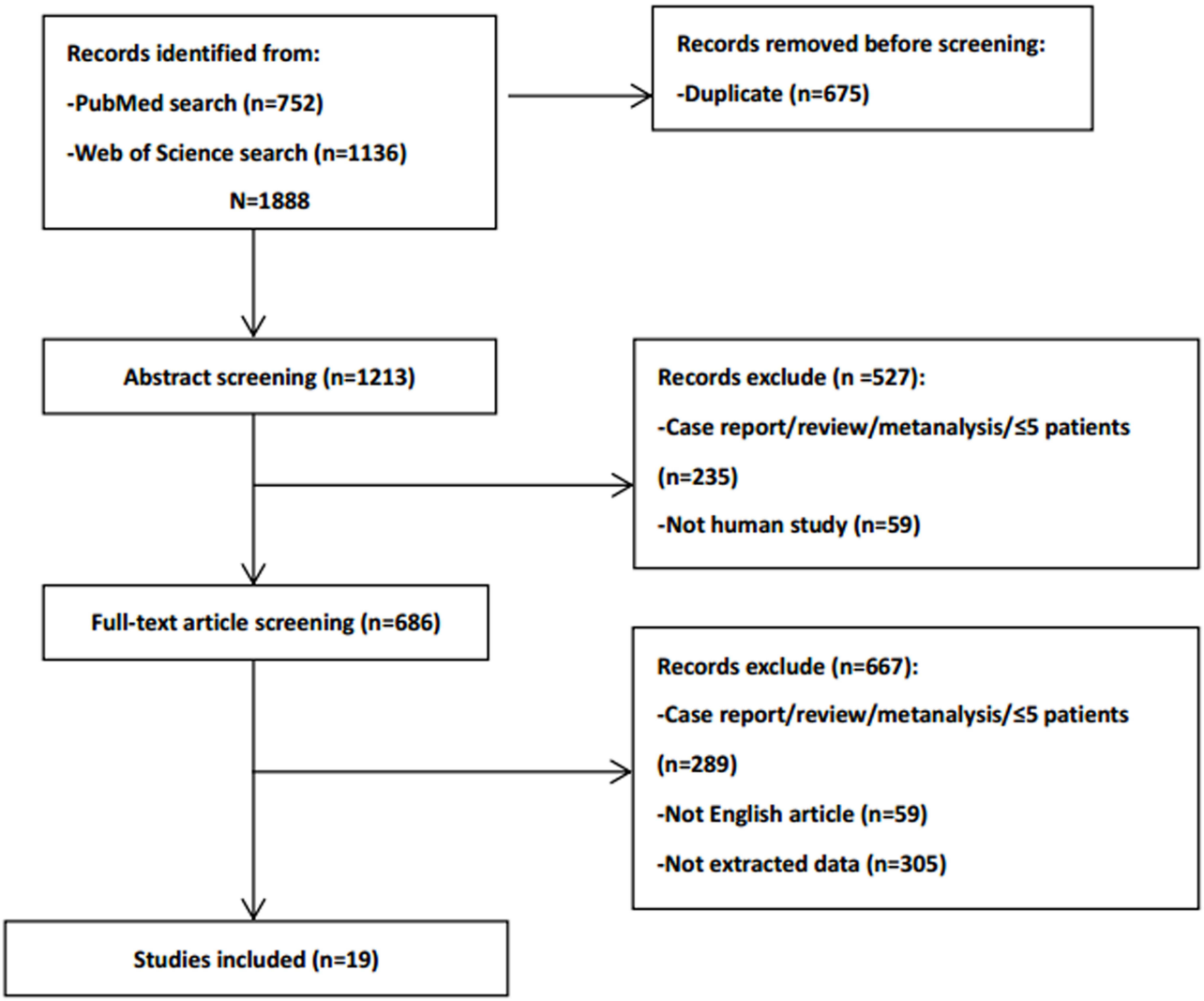

Figure 1 Identification of studies via database and registers.

1109) was managed with adjuvant radiotherapy (RT), 4.1% (46/1109), and 0.3% (3/1109) were managed by adjuvant chemoradiotherapy and chemotherapy, respectively. Almost all patients who received adjuvant radiotherapy were treated with photons, whereas only one patient was treated with carbon-ion radiotherapy (CIRT). Neoadjuvant therapy was administered to 2 patients.[22]

Post-operative complications were described in 40 patients who underwent surgery, including 6.4% of non-fatal complications and 11 deaths due to anatomical problems (Table 4).

Follow-up and Outcomes

The follow-up time was available for 1416 patients (range, 6–390 months). Patient status was available for 1364 patients. Five-hundred fifty-two patients died, with the most frequent cause of death being disease-related (98.7%). During the follow-up period, 139 patients reported recurrence. Survival estimates for 5-years and 10-years DFS, LRFS, and DRFS were frequently unavailable (Table 5). According to the data collected, 5-year OS ranged from 28.6% to 100.0%.[2,5–15,17–22] The better survival rate (5-year OS 100.0%) was reported by Hazama et al,[7] while the worse 5-year OS (28.6%) was described by Yang et al.[9] Due to the relative lack of available data in the published documents, we aimed to obtain an average of 5-year OS was 65%. The 95% CI for 5-year OS was calculated by a weighted mean based on the inverse of the standard errors derived from individual study proportions, resulting in an estimated range of 32%–96%.

Table 1 General Features of the Articles Included in the Systematic Review

First Author	Publication year	Country	Study design	Observation Period	No. of Patients	Data Type	Site	Age (year)
Taraneh[5]	1998	USA	Retrospective	1971–1996	6	single-center	trachea	(28–63)range
Harms[6]	2000	Germany	Retrospective	1984–1997	8	multi-center	trachea	median: 46 (32–59)range
Hazama[7]	2003	Japan	Retrospective	1979–2000	8	multi-center	trachea	mean: 49
Henning[8]	2004	USA	Retrospective	1962–2002	135	single-center	trachea	mean: 49
Yang[9]	2005	Taipei, China	Retrospective	1990–2002	7	single-center	trachea	median: 35 (21–55)range
Honings[10]	2006	Netherland	Retrospective	1989–2002	21	NCR	trachea	mean: 60 (38–93)range
Zhengjaiang[11]	2007	China	Retrospective	1981–2002	35	single-center	trachea	–
Bittner[12]	2008	USA	Retrospective	1989–2005	20	single-center	Trachea	median: 46 (24–67)range
Ahn[13]	2009	Korea	Retrospective	1989–2006	9	single-center	Trachea	median:41 (29–66)range
Honings[14]	2010	USA	Retrospective	1962–2007	108	single-center	Trachea	median: 48 (24–80)range
Yang[15]	2015	China	Retrospective	1995–2014	109	single-center	Trachea	median: 46 (21–70)range
Chen[16]	2015	China	Retrospective	1995–2012	52	multi-center	Trachea	median: 44 (18–77)range
Je[17]	2017	Korea	Retrospective	1994–2008	22	single-center	Trachea	–
Högerle[2]	2019	Germany	Retrospective	1991–2017	38	single-center	Tracheal	median: 51 (19–80)range
Benissan-Messan[18]	2019	USA	Retrospective	2004–2015	149	NCDB	Trachea	median: 54 (44–63)range
Yang[19]	2020	USA	Retrospective	1998–2014	132	NCDB	Trachea	–
Baig[20]	2020	USA	Retrospective	1973–2016	157	SEER	Trachea	53 ±16
Behbahani[21]	2021	USA	Retrospective	2004–2016	394	NCDB	Trachea	median: 56 (IQR:45–66)
Li[22]	2022	China	Retrospective	2000–2020	78	single-center	Trachea	49 ±12

Abbreviations: NCR, Netherland Cancer Registry; NCDB, National Cancer Database; SEER, the Surveillance, Epidemiology and End Results database.

Table 2 Demographics and Tumor Features

Characteristics	Total
No. of patients	1488
Age, years (mean)	51
Gender	
Male	562
Female	776
Subsite	
Trachea NOS	1056
Cervical trachea	130
Middle trachea	100
Distal/carinal trachea	149
Intrathoracic trachea	53
pTNM, (no. of patients surgically treated with available data)	
T3-T4	63
N0	275
N+	72
M0	47
M1	7
PNI-LVI,(no. of patients surgically treated with available data)	
PNI+	37
LVI+	/
Margins,(no. of patients surgically treated with available data)	
R0	178
R+	255
R1	249
R2	8

Notes: no. of patients surgically treated with available data: the number of patients who were surgically treated and provided with available data.
Abbreviations: NOS, not otherwise specific; PNI, perineural invasion; LVI, lympho-vascular invasion; N+, lymph node positive; R+, margins positive (not otherwise specified); R1, microscopically positive; R2, macroscopic positive.

The 5-year DFS was described in four articles[12,14,15,17] and ranged from 28.4% to 67.0%. The 5-year DRFS was reported in only two articles and ranged from 52.6% to 69.0%.[2,17]

The 10-year survival outcomes were available in 11 studies and ranged from 14.3% to 100.0%. The 10-year LRFS and DRFS rates were reported in two studies, ranging from 70.2% to 83.0% and 33.5% to 53.0%, respectively.[2,17]

In most studies, patients with surgery treatment resulted in a better survival rate than in patients without surgical treatment. However, Högerle et al found that patients treated with radiotherapy alone seemed to present with better outcome of 5-year OS (100%) than patients treated with surgery (with/without RT) (90.0%).[2] In the subgroup of patients

Table 3 Treatment Strategies in the Reported Series of Patients

First author	No. of Patients	Site	Surgery	TS	TS+ Lobectomy	TS+ Pulmonary Resection	Adjuvant Therapy
Taraneh[5]	6	trachea	5	5	0	0	3RT
Harms[6]	8	trachea	5	3	0	2	5RT
Hazama[7]	8	trachea	7	6	1	0	3RT
Henning[8]	133	trachea	101	83	0	18	71RT
Yang[9]	7	trachea	3	2	0	1	3RT
Honings[10]	21	trachea	11	–	–	–	8RT
Zhengjaiang[11]	35	trachea	28	–	–	–	17RT
Bittner[12]	20	trachea	9	–	–	–	9RT
Ahn[13]	9	trachea	4	–	–	–	–
Honings[14]	108	trachea	108	96	0	12	89RT
Yang[15]	109	trachea	109	105	0	4	73RT
Chen[16]	52	trachea	48	35	0	13	12RT,12CRT
Je[17]	22	trachea	13	7	1	5	13RT
Högerle[2]	38	trachea	20	–	–	–	12RT, 1CIRT
Benissan-Messan[18]	137	trachea	137	–	–	–	–
Yang[19]	132	trachea	132	–	–	–	95RT
Baig[20]	157	trachea	–	–	–	–	–
Behbahani[21]	394	trachea	295	–	–	–	182RT,33CRT,1C
Li[22]	78	trachea	74	74	0	0	43RT,1CRT,2C

Abbreviations: TS, tracheal surgery; RT, radiotherapy; CRT, chemoradiotherapy; CIRT, carbon-ion radiotherapy; C, chemotherapy.

Table 4 Post-Operative Complications

Author	No. Surgical Patients	Post-Operative Complication		
		Death	Yes	Non-Fatal Complications
Taraneh[5]	5	0	–	–
Harms[6]	5	0	1	Fistula(1)
Hening[8]	135	10	–	–
Yang[9]	3	0	–	–
Bittner[12]	9	0	–	–
Honings[14]	108	0	–	–
Yang[15]	109	1	24	Unilateral recurrent laryngeal nerve palsy (9), anastomotic stenosis (4), postoperative dyspnea (2), granulation stenosis (2), permanent tracheostomy (2), pneumonia (2), empyema (1), tracheoesophageal fistula (1), incision infection (1)
Li[22]	78	–	4	–

Table 5 Oncologic Outcomes

First Author	No. of patients Follow-up	Follow-up Period	All Treated Patients							
			5-year (%)				10-year (%)			
			OS	DFS	LRFS	DRFS	OS	DFS	LRFS	DRFS
Taraneh[5]	6	Range: 6–252m	75.0	–	–	–	–	–	–	–
Harms[6]	6	–	85.7	–	–	–	–	–	–	–
Hazama[7]	7	Median: 53.6m	100.0	–	–	–	100.0	–	–	–
Henning[8]	129	–	48.8	–	–	–	27.1	–	–	–
Yang[9]	7	–	28.6	–	–	–	14.3	–	–	–
Honings[10]	21	–	61.0	–	–	–	61.0	–	–	–
Zhengjaiang[11]	35	–	40.2	–	–	–	–	–	–	–
Bittner[12]	20	Median: 62m(10–121)m, range	89.4	28.4	–	–	–	–	–	–
Ahn[13]	9	Mean: 56.3m(16–205)m, range	45.7	–	–	–	–	–	–	–
Honings[14]	71	Mean: 8.6y(0–32.5)y, range	78.0	67.0	–	–	65.0	53.0	–	–
Yang[15]	83	101.9±35.0 m, (56 −181) m, range	88.7	62.0	–	–	43.2	20.0	–	–
Je[17]	22	Median: 123m,(13–232) m, range	81.8	47.8	85.7	52.6	54.2	28.7	70.2	33.5
Högerle[2]	38	Median: 74.5m	95.0	–	96.0	69.0	81.0	–	83.0	53.0
Benissan-Messan[18]	149	Median: surgery [72.6m]; non-surgery [65.8m]	74.1	–	–	–	–	–	–	–
Yang[19]	132	–	82.1	–	–	–	64.1	–	–	–
Baig[20]	157	–	54.8	–	–	–	–	–	–	–
Behbahani[21]	394	–	70.0	–	–	–	47.5	–	–	–
Li[22]	78	Median: 35.5m	87.1	–	–	–	59.3	–	–	–
First author	**No.of Patients follow-up**		**Surgery**					**Non-surgery**		
			5-year		**10-year**			**5-year**		**10-years**
			OS		**OS**			**OS**		**OS**
Hazama[7]	7		100.0		100.0			–		–
Henning[8]	129		54.2		33.3			33.3		9.1
Yang[9]	7		33.3		33.3			25.0		25.0
Ahn[13]	9		50.0		–			50.0		–
Honings[14]	108		78.0		65.0			–		–
Yang[15]	83		88.7		43.2			–		–
Högerle[2]	38		90.0		77.2			100.0		83.0
Yang[19]	132		82.1		64.1			–		–
Behbahani[21]	394		77.0		53.4			43.0		28.5

(*Continued*)

Table 5 (Continued).

First author	No.of Patients follow-up		Surgery+RT							
			5-year				10-year			
			OS	DFS	LRFS	DRFS	OS	DFS	LRFS	DRFS
Ahn[13]	9		100.0	–	–	–	–	–	–	–
Yang[15]	61		88.4	67.8	–	–	37.6	14.1	–	–
Je[17]	22		92.3	67.7	100.0	67.7	76.9	42.3	100	42.3
Högerle[2]	38		92.0		100.0	61.0	82.0		100.0	61.0
Benissan-Messan[18]	95		80.0	–	–	–	–	–	–	–
Behbahani[21]	182		76.2	–	–	–	52.5	–	–	–

Abbreviations: OS, overall survival; DFS, disease free survival; LRFS, local recurrence free survival; DRFS, distant recurrence free survival.

who underwent surgery combined with adjuvant RT, seemed to present with better outcome of 5-year OS, ranged from 76.2% to 100.0%.

Discussion

Due to the rare prevalence of TACC, the published literatures are mostly retrospective, in the form of relatively small cohort studies or even case reports. This leads to evidence in the literature that is of low quantity and quality. Consequently, data on treatment and outcomes are biased by the features of the reviewed studies, resulting in poor generality. In this systematic review, we aimed to present an overview of TACC with a focus on treatment strategies and oncological outcomes.

Our review included 1488 patients with a slightly higher proportion of females (1:1.38) and peak diagnosis in adulthood. It is seen that the sex distribution presents with an equal distribution, and the incidence increases with age and peaks in the fourth decade.[24] Meanwhile, Mallick et al reported that TACC is seen more commonly in females.[25] This is consistent with the findings of our review. Patients with TACC typically have a delay in diagnosis, one reason is that the nature of the indolent nature and slow growth and the other is that symptoms usually mimic other respiratory diseases, such as asthma, chronic obstructive pulmonary disease, or pneumonia. Radiological imaging, particularly computed tomography (CT), can assess the primary tumor location, extraluminal involvement, and regional/distant metastasis.[26] Irrespective of anatomical origin, one of the most outstanding features of ACC is its tendency to invade nerves. For tumors in the paranasal sinuses or oral cavity, perineural spread is usually along the second and/or third branch of the trigeminal nerve.[27] Here, only 49 cases were reported with PNI status (among them, 37 cases were positive), and rare reports of PNI in TACC have been described.[14] Hornings et al also found that the presence of perineural growth decreased both long-term survival and DFS.[14] Considering its importance, researchers recommended to include a statement regarding perineural growth in the pathology reports.

Excluded for 1056 cases with no specific subsite, the distal/carinal trachea was the most common region. Montenegro et al reported that distal/carinal trachea was the most involved subsites, as well.[28] TNM stage was reported in a small portion, with 7 distant metastasis cases.

In our review, the most common intervention was surgery (74.5%) with or without post-operative RT. Surgical procedures differed according to the site of involvement. A positive resection margin status was reported in 72.2% of the patients. Owing to the delay in diagnosis and its growth pattern with submucosal and perineural spread along the airways, performing a complete resection of TACC and achieving negative surgical margins can be difficult.[29–31]

A series of case reports and small single-center studies suggest that a combination of surgery and adjuvant (post-operative) RT is beneficial for patients with TACC.[16,30,32–36] However, there is limited evidence to support this treatment strategy. The efficiency of adjuvant RT is still debated and is generally recommended in the case of incomplete

resection.[37] Chen et al, followed 37 patients with incomplete resection, found that patients with adjuvant RT were associated with improved DFS and OS.[16] Behbahani et al reviewed 394 patients, and they found that the 5-year OS and 10-year OS in patients with surgery alone were 77.5% and 65.9%, respectively, but 76.2% and 52.5%, respectively, in patients underwent surgery with RT.[21] Meanwhile, Yang et al reported that patients with negative margin did not present with a better 5-year survival compared with patients with positive margin, and adjuvant radiation therapy to patients with positive margins was not associated with improved 5-year overall survival.[19] Surgery treatment and surgical resection of small tumor size were the favorable factors to the OS.[2,21]

According to our data, more than half of patients who underwent surgery were treated with adjuvant RT. Conventional photon therapy was mostly used, with only one patient treated with CIRT. Therefore, reliable data on the effectiveness of RT as an adjuvant therapy for TACC need to be further researched.

Intervention with RT alone or CRT without surgery is rare and is usually managed in patients with unresectable tumors or distant metastases at diagnosis. The clinic value of systemic treatment in patients with recurrent or metastatic tracheal ACC has not been well demonstrated owing to the limited number of clinical trials published to date. ACC has been regarded as a histotype that presents with poor sensitivity to chemotherapy. Combined therapy with cisplatin may improve the response rate, but not more than 33% of patients.[38] In our review, very few patients were treated with chemotherapy. With an improved understanding of the molecular mechanism of carcinogenesis in ACC, opening up new therapeutic perspectives, a series of trials have been designed to evaluate the efficiency of molecular therapeutic targets. According to the results of studies on the inhibition of the c-KIT pathway[39–41] and the EGFR pathway,[42–44] these two pathways are not able to modify the natural history of ACC. Dovitinib, a small molecular inhibitor of fibroblast growth factor receptor 1(FGFR1), produced few objective responses but suppressed the tumor growth rate with progression-free survival (8.2 months) and OS (21 months) compared favorably with other targeted agents.[45] Other agents targeting the NOTCH signaling pathway have been studied, including Brontictuzumab and AL101. Brontictuzumab, a monoclonal antibody targeted Nothch1, showed partial response and prolonged disease stabilization.[46] ACCURACY trial demonstrated AL101 was the potential anti-tumor activity of Notch pathway inhibition, based on clinical benefit response rate of 67.5% in patients with ACC-bearing activating NOTCH mutations.[47] The NISCAHN trial observed the 8.7% partial response and 56% of stable disease in ACC patients treated with nivolumab.[48]

The follow-up range was 6–390 months. The natural history of ACC features slow tumor progression yet carries a substantial risk of late recurrence, potentially occurring 10 to 20 years after initial therapy. These distinctive biological characteristics warrant cautious interpretation of the presented survival outcomes.

There is a consensus that radical surgical resection is associated with better survival outcomes in patients with TACC. Based on the data collected, surgery had a better impact on the outcomes (Table 5), mainly in terms of the 5- and 10-year OS. Interestingly, Högerle et al retrospectively analyzed the outcomes of 38 patients and found that patients who received radiotherapy alone seemed to have better survival outcomes than those who underwent surgery.[2]

Given the limited scope of tracheal resection and the tendency of TACC to spread in submucosal tissue, complete resection is not always achievable, with a 59–63% positive resection margin.[49] So, adjuvant RT is usually recommended for TACC with positive resection margins. In this review, surgery associated with adjuvant RT presented a good outcome, mainly in terms of 5- and 10-year LRFS (100%), which indicated that adjuvant RT may help in delaying local recurrence.[2,17] However, Behbahani et al found that surgical treatment was an independent predictor of OS, rather than surgery combined with adjuvant RT.[21] Therefore, whether adjuvant RT or alternative options should be managed upfront should be studied further for those with positive margins.

In order to obtain an estimate of the 5-year OS rate, we performed a pooled analysis, yielding a value of 65% (ranging from 32% to 96%). The same statistical analysis was not applicable to other outcomes because of the lack of precise data.

This systematic review has some limitations. Considering all the articles included, due to the rarity of this type of malignancy, and the time span in which these series studies were frequently collected, we were not able to acquire complete oncologic outcomes. The pooled analysis was applicable only to the 5-year OS, as very little data were available for other statistical analyses. The results should be interpreted with caution, as the majority of the literature reported OS at 5-and 10-years, which is not long enough to conclude an indisputable answer to TACC outcomes.

Conclusion

TACC is a very rare malignancy, often present in the fourth decade of life, and its diagnosis is often delayed. To date, no guidelines have been established for the treatment of TACC. Surgery is the most common first-choice treatment; adjuvant RT is frequently managed for patients with positive margins, while survival still presents with heterogeneity. Distant metastases may occur for more than 5 years, even after treatment. To improve oncological outcomes, large-scale prospective studies with extended longitudinal follow-up and more detailed data including OS, DFS, LRFS, and DRFS are required to better understand the nature of the disease and to better define treatment strategies.

Abbreviations

TACC, tracheal adenoid cystic carcinoma; OS, overall survival; SCC, squamous cell carcinoma; PNI, perineural invasion; LVI, lymphovascular invasion; DFS, disease free survival; LRFS, local recurrence free survival; DRFS, distant recurrence free survival; R1, microscopically positive; R2, macroscopic positive margins; RT, radiotherapy; CIRT, carbon-ion radiotherapy; CI, confidence interval; CRT, chemoradiotherapy; TS, tracheal surgery; C, chemotherapy.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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