Systematic Review

Secondary tracheal tumors: a systematic review

Maria Lucia Madariaga, Henning A. Gaissert

Division of Thoracic Surgery, Department of Surgery, Massachusetts General Hospital, Boston, MA, USA

Correspondence to: Henning A. Gaissert, MD. Founders House, Massachusetts General Hospital, 265 Charles Street, Boston, MA 02114-2621, USA. Email: hgaissert@partners.org.

Background: Secondary tracheal tumors arise from mural invasion by primary tumors in adjacent organs, metastatic lymph nodes or blood-born metastasis from distant sites. This systematic review aims to assess the presentation, management options, and clinical outcomes of these uncommon non-tracheal malignancies.

Methods: Electronic searches of the MEDLINE database were performed to identify case series and individual case reports of tracheal invasion by primary non-tracheal tumors or metastatic disease. All English-language studies with available abstracts or articles containing primary data were included.

Results: From 1978 to 2017, a total of 160 case reports or case series identified 2,242 patients with invasion of the trachea by tumors of adjacent organs (n=1,853) or by metastatic lymph nodes or hematogenous spread (n=389). Common primary sites of origin were thyroid, esophagus, and lung, and the most common presentation was metachronous (range of interval: 0 to 564 months) with dyspnea, neck mass, voice change and/or hemoptysis. A majority of patients in case reports (77.9%) and case series (66.0%) underwent resection and the most common reported operation was segmental tracheal resection. Fewer patients underwent bronchoscopic intervention (21.7%) and radiation was used in 32.2% of patients. Complications after bronchoscopic treatment included bleeding, granulation tissue, and retained secretions, while anastomotic leak, unplanned tracheostomy, and new recurrent laryngeal nerve paralysis were observed after surgical resection. The rate of 30-day mortality was low (0.01–1.80%). Median survival was higher in patients with thyroid malignancy and in patients who underwent surgical management. Follow-up time ranged from 0.03 to 183 months.

Conclusions: Patients with tracheal invasion by metastatic or primary non-tracheal malignancies should be assessed for symptoms, tumor grade, tumor recurrence and concurrent metastases to decide on optimal surgical, bronchoscopic or noninterventional therapy. Clinical experience suggests that palliative endoscopic intervention for tracheal obstruction by metastasis-bearing lymph nodes is underreported.

Keywords: Endotracheal metastasis; secondary tracheal tumors; systematic review

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Introduction

Secondary tracheal tumors are defined as tumors in, but not of the trachea and comprise a wide spectrum of tumor histologies and stages. There are no population-based data for these tumors, and in clinical practice these lesions are probably more common than primary neoplasms. A thoracic surgeon probably encounters tracheal obstruction by metastatic lymph nodes more often than invasion by adjacent primary tumors. Since natural history and prognosis are related to the tumor of origin, their management and prognosis may differ considerably from primary tracheal neoplasms; a correct diagnosis with attribution to the original tumor is therefore important. Tracheal invasion by metastasis may further be categorized as metachronous when the diagnosis is made after a disease-free interval, in contrast to synchronous diagnosis when primary malignancy coincides with tracheal invasion.

Secondary tracheal tumors may arise from hematogenous or lymphatic sites of metastasis, or by direct extension from adjacent structures including thyroid or esophagus.

A useful and detailed classification of tracheobronchial metastases was proposed by Kiryu and associates based on the relationship of the primary tumor to the trachea (1). Type 1 tumors are direct metastases to the bronchus; type 2, invasion by an adjacent parenchymal lesion; type 3, invasion by lymph nodes; and type 4, peripheral lesion extending proximally along the airway wall. Most of the studies that we reviewed below reported type 1 tumors from extrapulmonary sites or type 2 tumors from the thyroid. We suspect, however, that invasion by adjacent lymph nodes metastatic from lung, esophageal, head and neck or other cancer is the most frequent form of metastasis; this type would be less represented in reports because the trachea is not the sole focus of attention in progressive disease and the survival of patients after diagnosis is short.

The true incidence of secondary tracheal tumors is unknown. One of the earliest cases of endotracheal metastasis was reported in 1954 in a case of colon cancer metastatic to the trachea (2). Existing epidemiological studies mainly focus on endobronchial metastases and contain different exclusion criteria. In an autopsy study of 1,000 consecutive cases of malignant neoplasms of epithelial origin from 1943 to 1947, six endotracheal metastases originated from primary sites of lung (3), larynx (1) and breast (1); however, this study excluded cases of direct extension to adjacent organs (4). Another study analyzing 1,359 consecutive autopsies from 1968 to 1971 found a 2% incidence of endobronchial metastases and 0.8% of endotracheal metastasis from primary thyroid cancer (1) and melanoma (1); cases of lymphoma, central nervous system tumors and primary lung neoplasms were excluded (3). A literature review from 1966 to 2002 found 204 confirmed cases of endobronchial metastases from extrapulmonary solid tumors, while 4% were located in the trachea (5).

We are unaware of any prior collective analysis of secondary tracheal tumors. In this study, we conduct a systematic review of secondary tracheal tumors based on studies available in the MEDLINE database to analyze the evolution of practice patterns and assess the relative merits of nonoperative, bronchoscopic and surgical therapy. The aim of this study is to provide a guide to multidisciplinary management of patients presenting with airway obstruction from secondary tracheal tumors.

Methods

Literature search strategy

A systematic review was performed. MEDLINE was searched for original published studies using the terms: "tracheal metastasis" OR "secondary tracheal tumors" OR "endotracheal metastasis" OR "tracheobronchial tumors".

Eligibility criteria

Studies eligible for this systematic review included patients with metastatic disease to the trachea or primary tumors secondarily involving the trachea. We included individual case reports, single institutional case series and multi-institutional case series while excluding reviews, editorials, expert opinions and studies that lacked abstracts. Several reports collected primary and secondary tracheal tumors, or tracheal and bronchial tumors; the data regarding secondary tracheal tumors were specifically extracted and included in this study. For repeated publications reporting similar patients from the same institution, the most recent data set was included [e.g., (6-8)].

Data extraction and critical appraisal

One reviewer (ML Madariaga) reviewed each included study and extracted data from text, tables and figures. Another author reviewed the extracted data (HA Gaissert). All data were entered into a standardized database.

Statistical analysis

Results will be presented as means and ranges where applicable. Kaplan-Meier survival analysis was performed for treatment groups of ≥10 patients derived from individual studies.

Outcome measures

The primary endpoints included symptom relief, overall survival, disease recurrence and 30-day postoperative or post-procedure complications. Secondary endpoints included tumor histology, location of tracheal tumor, and treatment.

Surgical technique

Techniques to resect tracheal invasion were classified as window resection (resection of the anterior tracheal wall only), shave resection (partial thickness resection of the trachea), segmental tracheal resection (circumferential full-thickness resection), exenteration (resection of trachea,

esophagus, larynx and other cervicomediastinal structures), and debulking (less than complete resection), the latter by endoscopic or open methods.

Results

Quantity of evidence

After applying our search criteria, 2,866 studies were identified. Manual evaluation of abstracts and full-length articles identified 160 relevant publications. There were 64 individual case reports and 96 case series (consisting of more than one case). Of the 96 case series, 17 series contained enough details to extract individual patient data; these 110 patients were analyzed with the individual case reports (8-24). Forty-five case series reported exclusively on tracheal invasion by thyroid cancer (*Table S1*). A total number of 2,242 patients were included in this study, 174 patients in individual case reports and 2,068 patients in case series.

Quality of evidence

All were retrospective, observational series, and there were no randomized controlled or prospective trials. Thirty retrospective case series included bronchial as well as tracheal lesions, or primary in addition to secondary tracheal tumors, but only provided outcome measures based on the general study population (*Table S1*). Where possible, data relevant to secondary tracheal tumors were specifically extracted. However, to facilitate interpretation of the general outcome measures in case series, the number of patients with tracheal tumors was compared with the total number of patients in the study (*Tables S2,S3*). Data unavailable for extraction were left blank in the accompanying tables.

Patient demographics

Among 2,242 patients, mean age of patients was 58.5 years and 58.4% were female. The most common histologic types were well-differentiated thyroid cancer (74%), unspecified esophageal cancer (5.93%), and squamous cell carcinoma of the lung (2.77%) (*Table 1*). In 9.5% of patients, the tumor was not otherwise specified or there was a mix of tumor histology not defined for each patient (*Table 1*).

Symptoms

The presence of symptoms was recorded for 50.4% (n=1,130) of included cases (*Table 2*). Among 95.2% of patients, the leading symptoms were dyspnea (31.8%), neck mass (19.5%), voice change or hoarseness (15.0%), and hemoptysis (13.7%), while 4.8% were asymptomatic.

Concurrent metastases

Among case series of well-differentiated thyroid cancer, lung metastases were present in 13.8% (range, 6.5% to 20.0%) of patients at the time of or prior to diagnosis (7,25-31) and esophageal involvement in 29.0% (range, 4.9% to 62.0%) (6,25,29,31-36). Lung metastases were also present at or prior to secondary tracheal tumor diagnosis in patients with renal cell carcinoma (22%), rectal cancer (85%), melanoma (16.7%), esophageal cancer (3%), colon cancer (33.3%), carcinoma with thymus-like differentiation (CASTLE; 12.5%) and breast cancer (40%) (*Table S1*). Individual patients with liposarcoma and hepatocellular carcinoma also had lung metastasis (37,38).

Interval between initial diagnosis and secondary tracheal tumor presentation

The time interval between initial tumor diagnosis and secondary tracheal involvement was known in 622 (27.7%) patients, as shown in *Table 3*. Two thirds of patients presented with delay after diagnosis of the primary tumor. Patients with renal cell carcinoma had the longest median metachronous interval (90.0 months), followed by ovarian (84.0 months) and breast cancer (72.0 months). The shortest median metachronous interval was observed in squamous cell carcinoma of the lung (14.5 months), esthesioneuroblastoma (15.0 months) and adenocarcinoma of the lung (16.5 months). In one study collecting data from patients with various secondary tracheal tumors, the median metachronous interval was 7.3 months (121).

Assessment of treatment

Data regarding treatment was available for 1,527 patients in case series and 170 patients in individual case reports (detailed in *Tables S2,S3*). Altogether, 21.7% of patients underwent bronchoscopic management, 32.2% of patients underwent radiation and 76.8% of patients underwent surgery.

In case series, data about treatment and outcome was available in 1,527 patients. The follow-up interval ranged from 12.0 to 97.7 months. Treatment included

Table 1 Demographics of patients with secondary tracheal tumors (n=2,242)

Tumor histology	Number of patients	%	Mean age (years)	Female (%)
Thyroid cancer well-differentiated	1,659	74.00	58.1	68.1
Other/mixed	213	9.50	60.5	39.0
Esophageal cancer NS	133	5.93	60.0	16.7
Lung squamous cell carcinoma	62	2.77	58.6	27.2
Lung cancer NS	36	1.61	63.9	16.8
Esophageal squamous cell cancer	22	0.98	58.4	20.7
Thyroid cancer NS	18	0.80	61.1	26.7
Colon cancer	9	0.40	61.2	64.0
Renal cell carcinoma	9	0.40	56.3	25.5
Thyroid cancer poorly differentiated	9	0.40	62.0	69.2
CASTLE	8	0.36	56.5	0.5
Lung carcinoma small cell	8	0.36	58.0	55.9
Lung adenocarcinoma	7	0.31	58.3	31.9
Rectal cancer	7	0.31	71.4	57.1
Melanoma	6	0.27	52.5	33.3
Breast cancer	5	0.22	55.8	100.0
Thymoma	5	0.22	8.0	18.0
Prostate cancer	4	0.18	68.8	0
Ovarian adenocarcinoma	3	0.13	48.7	100.0
Esthesioneuroblastoma	2	0.09	45.5	50.0
Larynx squamous cell carcinoma	2	0.09	67.0	0
Thyroid squamous cell carcinoma	2	0.09	78.0	0
Carcinoid	1	0.04	–	–
Endometrial cancer	1	0.04	–	100.0
Hepatocellular carcinoma	1	0.04	80.0	0
Liposarcoma	1	0.04	53.0	100.0
Lung large cell carcinoma	1	0.04	–	–
Nasopharyngeal carcinoma	1	0.04	68.0	0
Parathyroid carcinoma	1	0.04	40.0	0
Seminoma	1	0.04	–	0
Thymic cancer	1	0.04	59.0	100.0
Thymoma	1	0.04	10.0	0
Thyroid adenoma	1	0.04	79.0	100.0
Thyroid carcinosarcoma	1	0.04	55.0	0
Tongue squamous cell carcinoma	1	0.04	61.0	0

NS, not specified; CASTLE, carcinoma showing thymus-like element of the thyroid.

Table 2 Symptoms reported during presentation for secondary tracheal tumor (n=1,130)

Symptom	# of patients	%
Cough	56	5.0
Dysphagia	39	3.5
Dyspnea	359	31.8
Hemoptysis	155	13.7
Neck mass	220	19.5
Stridor or wheeze	80	7.1
Voice change/hoarse	170	15.0
Asymptomatic	54	4.8

bronchoscopic management alone in 19%, bronchoscopy and chemotherapy/radiation in 2%, surgical management alone in 50.6%, surgical management and chemotherapy/radiation in 27.3%, and chemotherapy/radiation alone in 0.9%. Surgical therapy consisted of circumferential resection in 41.9%, shave resection in 36.6%, window resection in 11.1%, exenteration in 4.5%, debulking in 1%, and other procedures in 2% (*Table S2*).

In individual case reports, data regarding treatment and outcome was available in 170 patients. The median follow-up interval was 21 months (range, 0.03–183 months). Treatment was characterized as bronchoscopic alone in 16.5%, bronchoscopy with chemotherapy/radiation in 6.5%, surgical management alone in 32.9%, surgical management with chemotherapy/radiation in 28.3%, combined surgical and bronchoscopic management in 2.4%, chemotherapy/radiation alone in 11% and in 2.4%, a combination of resection, bronchoscopy and chemotherapy/radiation. Surgical therapy for tracheal invasion included circumferential resection in 65%, exenteration in 14.2%, window resection in 5.4%, shave resection in 2.7%, and debulking in 2.7%. The average length of resected circumferential trachea measured 3.7 rings or 3.8 cm (*Table S3*).

We are not aware of any combined resections of trachea and the entire esophagus with successful reconstruction of tracheal continuity. In the literature of invasive thyroid cancer, there was one case of laryngotracheoesophagectomy with reconstruction of the digestive tract with a forearm free flap (109). There were 28 cases of circumferential tracheal and partial-thickness or partial-circumference esophageal resection with reconstruction (6,8,10,25,29) and in addition two cases of combined partial resection of trachea and esophagus (25). One series reported concomitant unspecified esophageal resection with tracheal shave (n=5), tracheal window resection (n=2) and circumferential tracheal resection with reconstruction (n=1) (31). Two series of aerodigestive tract invasion by thyroid cancer reported patients who underwent partial to circumferential tracheal and esophageal resections, but did not specify how many patients had concomitant resections (33,36). There was one patient with esophageal cancer who underwent tangential tracheal resection, spiral tracheoplasty and esophagectomy (19) and two patients with esophageal cancer who underwent partial esophagectomy with partial tracheal resection and muscle flap reconstruction (15).

Six case series of thyroid cancer invading the trachea directly analyzed survival associated with different treatment options. One study from China with 156 patients with thyroid cancer showed that 5-year survival was 100% with 0 cancer recurrence after circumferential resection compared to 5-year survival of <10% with 54% cancer recurrence after tracheal shaving (29); circumferential tracheal resection showed improved survival over tracheal shaving in other studies as well (31). However, other studies did not demonstrate significant difference in survival outcomes between tracheal shave and circumferential resection (122,123). In one study from Japan containing 114 patients, those undergoing shave resection had better 5-year survival (99%) than those undergoing circumferential resection (71%) (124); this result was also seen in a study of 65 patients from Korea (35); there was no analysis of survival beyond 5 years in these slow-growing tumors.

Assessment of complications

Data regarding complications after treatment were available in 54.4% of patients from case series and are detailed in *Table 4* and *Tables S2,S3*. The rate of complications ranged from 12.5% to 16.7% for bronchoscopic management with chemotherapy/radiation, 0.0% to 58.0% for bronchoscopy alone, 0.0% to 78.0% for resection alone and 0.0% to 61.0% for surgery with chemotherapy/radiation.

The most common complications after bronchoscopic intervention was bleeding (range, 17–33%), formation of granulation tissue after stent insertion (range, 17–58%), retained sputum (range, 11–33%) and stent migration (8%) (*Table 4*). Death during hospitalization occurred in 0.01% to 0.04%.

Following resection, the most common complications

Table 3 Time interval between initial tumor diagnosis and secondary tracheal involvement (n=622)

Cancer histology	Reference(s)	Synchronous (n)	Metachronous (n)	Metachronous median [range] (months)
Breast cancer	(39-42)	0	3	72.0 [65.0–120.0]
CASTLE	(14,20,43)	6	2	62.0 [13.0–111.0]
Colon cancer	(18,44-52)		5	54.0 [12.0–120.0]
Esophageal cancer NS	(12,53-55)	16	12	–
Esophageal squamous cell cancer	(15,19,56-60)	12	1	–
Esthesioneuroblastoma	(61,62)	–	2	15.0 [12.0–18.0]
Hepatocellular carcinoma	(38)	–	1	–
Liposarcoma	(37)	–	1	–
Lung carcinoma NS	(53)	9	26	–
Lung adenocarcinoma	(13,63,64)	–	2	16.5 [7.0–26.0]
Lung carcinoma small cell	(65,66)	–	1	–
Lung squamous cell carcinoma	(13,67,68)	–	6	14.5 [8.0–52.0]
Melanoma	(69-72)	1	4	36.0 [24.0–48.0]
Mixed	(1,73-79)	–	12	17.0 [2.0–38.0]
			98	7.3.0 [0.0–51.0]
Nasopharyngeal carcinoma	(80)	–	1	–
Ovarian adenocarcinoma	(81-83)	–	3	84.0 [32.0–86.0]
Parathyroid carcinoma	(84)	–	1	–
Prostate cancer	(85-91)	1	3	48.0 [18.0–65.0]
Rectal cancer	(18,48,92-97)	–	6	58.0 [12.0–132.0]
Renal cell carcinoma	(45,98-105)	1	4	90.0 [48.0–204.0]
Thymic cancer	(106)	1	–	–
Thymoma	(107)	1	–	–
Thyroid adenoma	(108)	–	1	–
Thyroid cancer well-differentiated	1980–1999 (7-10,31,36,55,109-111) and 2000–2017 (6,11,17,19,21-24,27,30,33,34,112-120)	146	30	52.8 [1.0–564.0]
			32	79.0 [11.0–384.0]
			166	–
Thyroid squamous cell carcinoma	(68)	1	1	–
Tongue squamous cell carcinoma	(16)	–	1	–

NS, not specified; CASTLE, carcinoma showing thymus-like element of the thyroid.

Table 4 Percentage of complications extracted from 26 case series expressed as range [individual case reports were excluded (6-8,17,36,53,58,73,121,125-134)]

Complications	Bronchoscopic therapy (%)	Surgery (%)
Anastomotic leak	–	0.04–23.8
Arrhythmia	0.04–5	–
Bleeding	17–33	3
Chyle leak	–	4.3–22
Death	0.01–0.04	0.02–1.4
Dysphagia	–	0.15–100
Esophageal fistula	2	5–6
Granulation tissue	17–58	–
Mucostasis	11–33	–
New recurrent laryngeal nerve paralysis	–	0.04–55
No complications	–	–
Not recorded	–	–
Other	2.6	–
Respiratory failure/prolonged intubation	0.04–16.7	10
Stent migration	8	–
Tracheal stenosis	–	5
Unplanned permanent tracheostomy	–	4.3–50
Wound infection	–	1.4–11

were anastomotic leak (range, 0.04–23.8%), chyle leak (range, 4.3–22%), new recurrent laryngeal nerve paralysis (range, 0.04–55%), esophageal fistula (5–6%), unplanned permanent tracheostomy (range, 4.3–50%), respiratory failure or prolonged intubation (10%), tracheal stenosis (5%) and wound infection (range, 1.4–11%). In one study of thyroidectomy, lymph node dissection and shave resection of the trachea with radioactive iodine and selected adjuvant external beam radiation, all patients experienced dysphagia after radiation (125). Hospital mortality ranged from 0.02% to 1.4% in this group.

Data on complications were available for 70% of individual case reports (121 of 174 patients). There were no complications in 70% of all cases with available data. The most frequent complications were anastomotic leak in 9.0%, tracheal stenosis in 3.3% and unplanned permanent tracheostomy in 3.3%. Additional complications included respiratory failure or prolonged intubation in 2.5%, new recurrent laryngeal nerve permanent paralysis in 2.5%, esophageal leak or fistula in 2.4%, dysphagia in 2.5% and hospital death in 2.5%.

Assessment of survival

In our review of case series, 95% of patients had data regarding survival outcomes as shown in *Table S2*. Following surgical therapy, 5-year survival ranged from <10% to 100% and 10-year survival ranged from 15% to 90%. Reported median survival after bronchoscopic management ranged from 0.3 to 75.0 months, whereas median survival in the surgery treatment group ranged from 3 to 207 months. In the case series, median survival in patients with non-thyroid malignancy ranged from 1 to 18 months and in thyroid malignancy from 8.0 to 112.8 months. Median 5-year survival in patients with thyroid malignancy was 74.2% [range, <10% after shave resection (29) to 100%].

The 174 patients in individual case reports were grouped by treatment modality, cancer histology and available survival outcomes data to conduct Kaplan-Meier survival analysis (*Table S3*). Overall 5-year survival was 80% after resection alone (n=47), 75% after resection with chemotherapy/radiation (n=44), 25% after bronchoscopic intervention with or without stent placement (n=19) and less than 20% after bronchoscopy with chemotherapy/radiation (n=10). Overall 5-year survival was 42% in patients with non-thyroid and 78% in thyroid malignancy; overall 10-year survival was 42% in patients with non-thyroid and 55% in thyroid cancer.

Assessment of recurrence

Data on recurrence were extracted from 13 case series identified for collective analysis (7,17,27,29,33,35,73,124,126,135-138) and nine individual case reports (14,15,17,44,56,61,81,98,139) and are listed in *Table S4*. The disease-free interval ranged from 1 to 58 months. Among patients with thyroid cancer who underwent bronchoscopic intervention, the incidence of recurrence ranged from 17% to 82%. Recurrence after segmental tracheal resection for thyroid cancer ranged from 0% to 34% and after tracheal shave resection from 4.7% to 54%. One study comparing shave and segmental tracheal resection for thyroid cancer found the local recurrence higher after shave resection [54% versus 0%, (29)]. Data on recurrence in patients with other cancer histology were too few to draw meaningful conclusions.

Discussion

Few individual centers amass a meaningful clinical experience in the management of tracheal tumors, and far fewer yet in secondary tracheal malignancy. The extraction of information from data useful to the clinical surgeon is therefore difficult and requires critical reading between the lines. Case reports often emphasize perceived successes, while palliative intervention in patients with advanced, progressive malignant disease is probably underreported. There are, however, several principal findings and conclusions we consider central to the understanding of secondary tracheal malignancy.

(I) The distinction between invasion by a primary tumor of a structure adjacent to the trachea and a lymphatic or hematogenous metastasis is important for treatment and the assessment of prognosis;

(II) Obtaining the histologic diagnosis is valuable even after the distinction outlined by point I) is made, since more than one tumor type may arise from organs or lymph nodes adjacent to the trachea;

(III) Even when considering the guarded prognosis of most unreported secondary tracheal malignancies, segmental tracheal resection is successful in patients who are carefully selected for favorable histology and limited airway involvement;

(IV) While secondary tracheal tumors often require the coordinated deployment of multiple modalities, a tracheal surgeon experienced in segmental resection is a key member of this group;

(V) Oncologically doubtful interventions on the trachea, specifically shave and window resections, have no proven value in treatment with curative intent. Neither windows nor shaves permit the reliable assessment of margins and persist in use only because the consequence of incomplete resection is not discovered for many months or years. Since the tumors often occur in younger patients, observation of survival should extend to 20 or even 30 years to capture meaningful adverse events;

(VI) Cervical exenteration involves resection of both trachea and esophagus, but does not result in end-to-end tracheal reconstruction. An important consequence of esophageal resection is the loss of tracheal blood supply as the vascular arcades on either side are disrupted. Even though any resection of the esophagus above the carina inevitably renders the trachea ischemic, no sequelae occur in absence of a tracheal anastomosis. The addition of a tracheal anastomosis to complete esophageal resection poses a high risk of failure even with only modest tension due to ischemia.

The major limitation of this study is its reliance on case studies or case series that have incomplete or heterogeneous information. Most studies examined patients with endobronchial metastases, where cases of endotracheal metastases are few; other studies presented outcomes based on mixed tumor histology of secondary tracheal tumors. We mitigated this bias by extracting outcomes values pertinent to secondary tracheal tumors where possible. Comparison of survival outcomes after different treatment modalities is rare because tumor histology and stage are not controlled. A more homogeneous data set would allow us to assess the relative utility of therapeutic interventions and their specific

impact on morbidity and mortality. The interpretation of complications is challenging in a collective review as patient selection and operative standards vary widely among institutions. Complications were reported in half of all case reports and may have inspired publication. Similar limitations were noted by a review of laryngotracheal invasion by thyroid carcinoma from 1971 to 1990 that included 595 patients from 20 studies with airway invasion (140) and a review of endobronchial metastases from extrapulmonary solid tumors from 1962 to 2002 (5).

In conclusion, this comprehensive systematic review of secondary tracheal tumors highlights common presentations, modes of treatment and general outcomes. Patients with secondary tracheal tumors should be assessed for overall prognosis and impediments to quality of life. An individualized treatment approach involving surgical, bronchoscopic and medical therapies can then be utilized to optimize clinical outcomes.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Selected case series

Case series	References
Case series reporting exclusively on tracheal invasion by thyroid cancer [1980–1999]	(7-10,31,36,109,122,123,127,135,141)
Case series reporting exclusively on tracheal invasion by thyroid cancer [2000–2009]	(6,11,14,17,19,25,27-29,117-119,136,142-144)
Case series reporting exclusively on tracheal invasion by thyroid cancer [2010–2017]	(20-24,30,32-35,124-126,137,138,145)
Case series including bronchial as well as tracheal lesions, or primary in addition to secondary tracheal tumors, but only provided outcome measures based on the general study population [1970–1999]	(26,55,58,109,128-131)
Case series including bronchial as well as tracheal lesions, or primary in addition to secondary tracheal tumors, but only provided outcome measures based on the general study population [2000–2017]	(1,17,29,32,33,60,73,74,76,118,119, 121,126,133,134,137,138,143,145-147)
Case series showing concomitant lung metastases [1970–1999]	(7,26,36,42,148)
Case series showing concomitant lung metastases [2000–2009]	(1,17,18,25,27,28,40,80,93)
Case series showing concomitant lung metastases [2010–2017]	(21,23,29,30,43,47,49,50,52,72,73,76,94,96,97,100,103,114)

Table S2 Surgical technique and outcomes data from 68 case series

Reference	Number of patients	Bronchoscopic technique	Surgical technique	Other	% complications	Complications ((reported as % or number of patients))	% alive	5-year survival (%)	10-year survival (%)	Median survival time	Follow-up time
(142)	3	Laser	–	Chemo, XRT, RAI	–	–	–	–	–	6–10 months	–
(73)	24	Coring, cryo	–	XRT	12.5	Atrial fibrillation and R mainstem clots [1], early death from massive tracheal bleeding [1], early death from pneumonia and respiratory failure [1]	–	–	–	16.0 (0.7–75.0) months	–
(128)	6	Laser, stent	–	XRT	16.7	One patient had acute dyspnea from edema and exudate at treatment site requiring emergency bronchoscopic debridement and further laser	–	–	–	52 days	–
(17)	3	Coring, laser, stent	–	–	–	Migration [4], retained secretions [4], granulation tissue overgrowth [8], infection [1], tumor overgrowth [6], tumor ingrowth [1]; supraglottic stenosis from edema or temporary bilateral vocal cord paralysis requiring tracheostomy [1] or minitrach [4]	–	–	–	8 months	56 months
(53)	51	Coring, laser, stent, balloon	–	–	12	Pneumothorax (6%), arrhythmia (2%), tracheoesophageal fistula (2%), septic shock (2%)	–	–	–	3.4 (1.6–7.3) months	–
(133)	14	Coring, stent	–	–	32	Sinus bradycardia (3.3%), hypotension (3.3%), bleeding (26.0%)	0	–	–	3 months	–
(73)	2	Cryotherapy	–	–	–	–	–	–	–	1.1 months (10 days to 4 years, 8 months)	–
(149)	19	Emergency laser	–	–	0	–	–	–	–	4.7 months	–
(150)	5	Laser	–	–	–	–	20	–	–	1–8 months	–
(129)	1	Laser	–	–	1–27	Rigid bronch 27% (PTX, laryngospasm, heart block), flex bronch 1%: PNA	–	–	–	–	–
(134)	65	Laser, APC, cryo, stent	–	–	10.8	Arrhythmias, restenosis, hypoxia	27.6	–	–	–	–
(134)	12	Laser, APC, stent	–	–	5–17	Bleeding (17%), granulation (17%), mucostasis (11%), bradycardia (5%)	–	–	–	4.1 (0–29.5) months	–
(121)	98	Laser, stent	–	–	2.7	In-hospital death	–	–	–	5.6 (0–51.0) months	–
(143)	3	Laser, stent	–	–	–	–	–	–	–	–	18 months
(142)	7	Laser, stent	–	–	–	–	–	–	–	–	–
(132)	8	Stent	–	–	8–58	Granulation (58%), retained secretions (33%), bleeding (33%), tumor regrowth (8%), halitosis (8%), migration (8%)	33	–	–	4.5 (1–50.0) months	–
(146)	5	–	Resection	Chemo, XRT	–	–	60	–	–	–	–
(131)	10	–	Resection	Chemo, XRT	4.8–24.0	24% RLN palsy, 14% anastomotic leak, 9.5% tracheal ischemia, 4.8% PNA, 4.8% wound infection	–	38	–	–	–
(76)	1	–	Resection	Chemo, XRT	–	–	–	–	–	16.1 months (after treatment 17.4 months, supportive care 12.4 months)	–
(58)	11	–	Resection	Neoadjuvant chemo XRT	61	11% chyle leak, 11% RLN palsy temporary, 11% wound infection, 5% TEF, 1% abscess drainage	–	–	–	4–18 months	–
(126)	52	–	Exenteration	RAI	3–55	Dysphagia (3%), vocal cord paralysis (55%), hypocalcemia (12%)	–	–	–	–	77 months
(29)	21	–	Resection, exenteration	RAI	19–52	Air leak (23.8%), lymphatic fistula (19.0%), temporary dysphagia (52.0%), temporary hypoPTH (43.0%)	–	100	–	–	5 years and 7 months (1–10 years)
(125)	35	–	Shave	RAI	–	–	–	–	–	–	43 months
(123)	6	–	Resection	RAI, XRT	0	–	100	–	–	–	–
(30)	7	–	Resection	RAI, XRT	14	14% chyle leak, sepsis, death; 14% aspiration requiring PEG	–	–	–	3–24 months	–
(29)	103	–	Shave	RAI, XRT	1.9–29	Air leak (1.9%), lymphatic fistula (22.0%), temporary dysphagia (20.4%), temporary hypoPTH (29.0%)	–	<10	–	–	–
(141)	127	–	Shave	XRT (15%)	–	–	–	–	–	–	90.3 months
(125)	21	–	Shave	XRT and RAI	–	Dysphagia (100%), dermatitis (100%)	100	–	–	43 [4–145] months	44 months
(122)	15	–	Debulking	XRT, RAI	–	–	–	60	50	–	–
(33)	4	–	Window	XRT, RAI	32%	Respiratory failure (10.0%), tracheostomy unplanned (1.4%), 28.0% permanent tracheostomy, esophageal fistula (6.0%), dysphagia (6.0%), chyle leak (4.3%), hematoma (3.0%), wound infection (1.4%)	–	71	–	–	58 months [7–129 months]
(32)	3	–	Exenteration	–	78	Permanent tracheostomy	–	–	–	4.3 months	–
(7)	13	–	Exenteration, resection	–	0–15	Operative mortality (0%), anastomotic dehiscence (15.4%)	–	38	15	5.6 years	–
(7)	69	–	Exenteration, resection	–	1.4–4.3	Operative mortality (1.4%, from glottic edema), anastomotic dehiscence (4.3%), permanent tracheostomy (4.3%), dysphagia (4.3%)	–	38	15	–	–
(6)	31	–	Exenteration, resection	–	6–39	Anastomotic leak (6%), bilateral RLN palsy (39%), unilateral RLN palsy (35%)	77.4% 5-year survival, 67% 10-year survival	77.4	67	–	89.4 months (6 months–20 years)
(31)	6	–	Laryngotracheal step	–	33	Prolonged intubation [1], aspiration PNA [1]	66	–	–	–	60 months
(7)	27	–	Resection	–	37	In-hospital death (2 from nonhealing anastomosis and respiratory failure), tracheal necrosis [1], suture granuloma [1], air leak [1], new unilateral vocal cord paralysis [1], dysphagia [4]	5-year survival 59%, 10-year survival 50%	59	50	69 [1–172] months	–
(6)	12	–	Resection	–	–	–	83	–	–	>60 [3–62] months	–
(136)	6	–	Resection	–	–	–	100	–	–	–	7 years
(31)	5	–	Resection	–	20	Prolonged ICU stay [1]	60	–	–	–	34 months
(127)	60	–	Resection	–	1.5–5.0	Anastomotic stenosis (5.0%), dysphagia (5.0%), tetany (3.0%), temporary vocal cord edema (1.7%)	5-year survival R0 resection 78%; R1 resection 44%; 10-year survival R0 resection 78%; R1 resection 24%	78	78	–	–
(124)	72	–	Resection	–	–	–	–	99	84	–	–
(33)	7	–	Resection	–	–	–	–	–	–	–	–
(33)	10	–	Resection	–	–	–	–	–	–	–	–
(117)	2	–	Resection	–	–	–	–	–	–	–	–
(137)	5	–	Resection	–	–	–	71	–	–	54.3 [1.0–207.0] months	–
(130)	7	–	Resection	–	–	–	56	–	–	10 [2–48] months	–
(1)	5	–	Resection	–	–	–	–	–	–	9 [1–66] months	–
(35)	37	–	Resection or window	–	–	–	–	90	85	–	97.7 (7.0–235.0) months
(122)	34	–	Resection or window	–	–	–	–	85	90	–	–
(151)	1	–	Resection, tracheocutaneous fistula, prosthetic	–	32.5	–	–	–	–	–	–
(118)	10	–	Resection, window	–	–	–	–	–	–	21.5 months	28.8 months
(36)	46	–	Resection, window, tracheocutaneous fistula, mesh prosthesis	–	19	Mesh extrusion [1], carotid artery perforation [2], poor wound healing [5], death on POD1 [1]	–	>50	–	–	63.5 months (1 day to 30 years)
(122)	75	–	Shave	–	–	–	–	90	80	–	–
(26)	4	–	Shave	–	–	–	–	–	–	–	28.8 months
(31)	17	–	Shave	–	47	Pneumothorax [1], infection [4], tracheal necrosis [1], tracheostomy [1], flap necrosis [1]	47	–	–	–	53 months
(35)	18	–	Shave	–	–	–	100	–	–	–	70 [12–192] months
(124)	42	–	Shave	–	–	–	–	99	84	–	
(28)	22	–	Shave	–	–	–	–	93	41	–	61 months
(33)	13	–	Shave	–	–	–	–	–	–	6–30 months	–
(117)	11	–	Shave	–	–	–	–	–	–	–	
(126)	39	–	Shave	–	–	–	–	–	–	–	
(135)	6	–	Shave, resection, window or exenteration	–	–	–	83% alive	–	–	–	1–5 years
(31)	6	–	Window	–	66.6	Tracheoesophageal fistula [1], RLN palsy [1], tracheostomy and innominate artery fistula with death [1], plexus injury [1], cerebral convulsion [1]; 50% with permanent tracheostomy	16	–	–	–	19 months
(34)	41	–	Window	–	–	–	–	–	–	–	43 months
(27)	12	–	Window	–	33	2 bilateral RLN complete palsy s/p tracheocutaneous fistula creation, 1 esophageal fistula, 1 re-intubation	–	87.5	73	–	60 months
(74)	2	–	–	Chemo, XRT	–	–	–	–	–	18 [4–84] months; 27 if treated, 13 if palliation	–
(25)	8	–	–	XRT	–	–	75	–	–	–	39–85 months
(144)	4	–	–	RAI, XRT	–	–	25	–	–	–	–

Window, resection of anterior tracheal wall; shave, shave resection of trachea (partial thickness); wedge, wedge resection of trachea (full-thickness); resection, circumferential trachea resection (extent of tracheal resection if known); exenteration: trachea and other structures (not including larynx or thyroid); chemo, chemotherapy; LND, lymph node dissection; RAI, radioactive iodine; RLN, recurrent laryngeal nerve; XRT, radiation therapy; PTX, pneumothorax; PNA, pneumonia; APC, argon plasma coagulation; TEF, tracheoesophageal fistula; PEG, percutaneous endoscopic gastrostomy tube.

Table S3 Surgical technique and outcomes data from 174 individual case reports

References	Age (years)	Sex	Bronchoscopic therapy	Surgical therapy	Other therapy	30-day complications	Survival	Follow-up time (months)
(23)	49	F	–	Window, non-vascularised composite nasal septal graft, re-resection cricoid for positive margin	XRT	None	Alive	24
(23)	62	M	–	Window, non-vascularised composite nasal septal graft + completion thyroidectomy, LND	RAI	Wound subcutaneous emphysema	Alive	18
(23)	55	F	–	Window, non-vascularised composite nasal septal graft	XRT	None	Alive	24
(9)	17	F	–	Window, myoperichondrial flap + total thyroidectomy, LND	RAI	None	Alive	96
(9)	30	F	–	Window, myoperichondrial flap + total thyroidectomy, LND	–	–	Alive	50
(9)	35	M	–	Window, myoperichondrial flap + subtotal thyroidectomy, LND	–	None	Alive	72
(8)	79	F	–	Wedge	–	None	Dead	108
(110)	76	M	–	Tracheostomy	XRT	None	Alive	28
(8)	59	M	–	Total thyroidectomy, partial laryngectomy	–	Air leak	Alive	44
(14)	62	F	–	Total thyroidectomy	Chemo, XRT	–	Alive	21.6
(10)	–	–	–	Thyroidectomy, tracheostomy (refused tracheal surgery)	–	–	Dead	1.5
(104)	61	M	–	Thoracotomy, open endotracheal mass removal and anterior mediastinal mass removal	–	None	–	–
(19)	65	F	–	Tangential tracheal resection, spiral tracheoplasty	–	None	–	–
(20)	75	M	–	Shave	–	–	Alive	113
(114)	66	F	–	Shave	–	–	–	–
(10)	74	M	–	Resection, tracheostomy + total thyroidectomy, LND	RAI	Decannulated	Dead	47
(10)	82	M	–	Resection, tracheostomy + total thyroidectomy, LND	–	Decannulated	Dead	24
(152)	72	M	–	Resection, myocutaneous flap, free costal cartilage graft	–	–	–	–
(8)	68	M	–	Resection, cutaneous tube + total thyroidectomy		Revision stoma	Dead	24
(8)	17	F	–	Resection + total thyroidectomy, LND	RAI	Vocal cord paralysis	Alive	75
(11)	54	M	–	Resection + total thyroidectomy, LND	RAI	None	Alive	183
(11)	58	M	–	Resection + total thyroidectomy, LND	RAI	None	Alive	179
(11)	35	F	–	Resection + total thyroidectomy, LND	RAI	None	Alive	155
(11)	50	F	–	Resection + total thyroidectomy, LND	RAI	None	Alive	41
(11)	22	F	–	Resection + total thyroidectomy, LND	RAI	None	Alive	14
(11)	68	F	–	Resection + total thyroidectomy, LND	RAI	None	Alive	71
(11)	50	F	–	Resection + total thyroidectomy, LND	RAI	Anastomotic leak	Alive	48
(11)	78	F	–	Resection + total thyroidectomy, LND	RAI	Anastomotic recurrence, airway obstruction requiring tracheostomy	Alive	39
(9)	50	M	–	Resection + total thyroidectomy + laryngectomy	–	Permanent tracheostomy for stenotic anastomosis	Alive	60
(9)	65	F	–	Resection + total thyroidectomy + laryngectomy	–	Permanent tracheostomy	Alive	60
(9)	77	M	–	Resection + total thyroidectomy + laryngectomy	–	None	Dead	12
(8)	69	F	–	Resection + total thyroidectomy	XRT	None	Dead	20
(8)	54	F	–	Resection + total thyroidectomy	–	Dehiscence, death	Dead	–
(8)	39	M	–	Resection + total thyroidectomy	–	None	Alive	105
(10)	–	–	–	Resection + total thyroidectomy	–	–	Alive	2
(10)	–	–	–	Resection + total thyroidectomy	–	–	Alive	14
(10)	–	–	–	Resection + total thyroidectomy	–	–	Alive	75
(8)	50	M	–	Resection + thyroidectomy	RAI	None	Alive	23
(8)	66	F	–	Resection + thyroidectomy	RAI	None	Alive	21
(24)	48	F	–	Resection + thyroidectomy	RAI	None	–	–
(24)	42	M	–	Resection + thyroidectomy	RAI	None	–	–
(106)	59	F	–	Resection + thymectomy, LND	XRT	–	Alive	8
(111)	66	F	–	Resection + residual thyroidectomy + laryngectomy	–	Permanent tracheostomy	Alive	84
(108)	79	F	Laser	Resection + partial thyroidectomy	–	None	Alive	24
(8)	34	M	–	Resection + partial thyroidectomy	XRT	None	Dead	20
(8)	67	M	Laser	Resection + partial laryngectomy	–	None	Alive	28
(8)	36	M	–	Resection + partial laryngectomy	XRT	None	Alive	74
(8)	67	M	–	Resection + laryngectomy	–	Respiratory failure, pulmonary emboli, atrial fibrillation	–	–
(68)	87	M	–	Resection (thyroid cartilage, cricoid cartilage, rings 1–3) + partial thyroidectomy, LND	XRT	Vocal cord paralysis	Dead	11
(21)	46	M	–	Resection (rings 2–4) + total thyroidectomy	RAI	–	Alive	24
(21)	67	M	–	Resection (rings 2–3) + thyroidectomy, LND	RAI	Bleeding requiring reintervention, prolonged intubation, readmission for air leak	Dead	30
(21)	67	F	–	Resection (rings 2–3)	–	Postoperative bleeding (12.5%), air leak (25%), transient hypoPTH (37.5%)	Alive	67
(21)	63	F	–	Resection (rings 1–4)	–	–	Alive	70
(21)	61	F	–	Resection (rings 1–4)	–	–	Alive	22
(21)	31	M	–	Resection (rings 1–3)	–	–	Alive	10
(21)	68	M	–	Resection (rings 1–2)	–	–	Alive	3
(21)	33	M	–	Resection (rings 1–4)	–	Air leak	Alive	25
(93)	59	F	–	Resection (cricoid to 3rd tracheal ring) + total thyroidectomy + total parathyroidectomy, LND	–	None	Alive	26
(17)	61	F	Laser, endoscopic resection	Resection (8 rings) + total laryngectomy	–	None	Alive	17
(153)	52	M	–	Resection (8 cm), fasciocutaneous flap with autologous cartilage struts	RAI	ARDS	Alive	75
(154)	34	M	–	Resection (7 cm), LND, forearm flap	–	None	Alive	24
(22)	53	M	Laser	Resection (6 cm)	XRT	Anastomotic stenosis	Alive	20
(22)	50	F	–	Resection (5 cm), myocutaneous flap, T tube	RAI, XRT	Esophageal fistula, anastomotic dehiscence	Alive	6
(22)	68	M	–	Resection (5 cm)	RAI	None	Alive	30
(115)	90	F	–	Resection (4 rings) + partial thyroidectomy, LND	–	None	Alive	22
(22)	55	F	–	Resection (4 cm)	XRT	None	Alive	23
(22)	32	M	–	Resection (4 cm)	XRT	None	Alive	55
(22)	42	F	–	Resection (4 cm)	XRT	None	Alive	30
(22)	65	F	–	Resection (4 cm)	XRT	Bilateral RLN paralysis, anastomotic dehiscence	Alive	6
(22)	49	M	–	Resection (4 cm)	RAI	None	Alive	6
(22)	49	F	–	Resection (4 cm)	–	None	Alive	15
(22)	62	M	–	Resection (3.5 cm)	XRT	None	Alive	9
(22)	69	M	–	Resection (3 cm)	RAI	None	Alive	19
(22)	67	M	–	Resection (3 cm)	–	Dysphagia, esophageal fistula	Dead	3
(22)	48	F	–	Resection (3 cm)	–	None	Alive	11
(22)	68	F	–	Resection (2.5 cm)	RAI	None	Alive	26
(22)	30	F	–	Resection (2.5 cm)	RAI	None	Alive	2
(22)	56	M	–	Resection (2.5 cm)	–	None	Alive	29
(22)	61	F	Laser	Resection (2 cm)	RAI	Bilateral RLN paralysis	Alive	33
(22)	51	F	–	Resection (2 cm)	–	None	Alive	31
(22)	71	F	–	Resection (2 cm)	–	None	Alive	29
(155)	–	–	–	Resection	XRT	–	Alive	36
(8)	63	M	–	Resection	–	Granuloma at suture line	Dead	80
(8)	73	F	–	Resection	–	None	Alive	1
(20)	48	F	–	Resection	–	–	Alive	38
(20)	70	F	–	Resection	–	–	Alive	34
(92)	77	M	–	Resection	–	–	–	–
(13)	53	M	–	Resection	–	–	Alive	16
(84)	40	M	–	Parathyroidectomy, thyroidectomy	XRT	None	Alive	132
(107)	10	M	–	None	–	–	Dead	0.07
(46)	44	F	–	Laryngomicrosurgery	Chemo XRT	–	–	–
(17)	53	F	Laser, endoscopic resection	Exenteration	–	None	Dead	6
(10)	66	F	–	Exenteration	XRT	Not decannulated	Alive	11
(10)	66	F	–	Exenteration	XRT	Decannulated	Alive	114
(8)	55	M	–	Exenteration	XRT	None	Dead	31
(15)	67	M	–	Exenteration	chemo	R subclavian vein thrombosis	Alive	8
(120)	65	M	–	Exenteration	–	None	Alive	36
(8)	49	M	–	Exenteration	–	Transient hemiplegia, stomal separation	Dead	23
(8)	65	F	–	Exenteration	–	Dysphagia	Alive	20
(8)	62	M	–	Exenteration	–	Stomal stenosis	Alive	24
(8)	78	F	–	Exenteration	–	Dysphagia	Alive	21
(112)	55	F	–	Exenteration	–	Tracheal dehiscence 2 months postop, treated with antibiotics	–	–
(8)	69	M	–	Exenteration	–	None	Alive	6
(8)	69	F	–	Exenteration	–	Duodenal ulcer perforation, esophageal leak, death	Dead	–
(56)	52	M	–	Exenteration	–	Wound infection, ileus	Dead	6
(15)	57	M	–	Exenteration	–	None	Dead	4
(19)	65	M	–	Exenteration	–	–	–	–
(54)	56	M	Laser, stent	Esophagectomy	Chemo XRT	None	Alive	18
(14)	49	M	–	Debulking thyroidectomy	–	–	Alive	30
(113)	67	M	Photodynamic therapy	Debulking	RAI	None	Alive	12
(14)	43	M	–	Debulking	XRT	–	Alive	72
(43)	47	M	–	Debulking	–	–	Alive	66
(90)	59	M	–	Bilateral orchiectomy	–	None	Alive	12
(52)	69	M	Stent	–	XRT	None	Dead	8
(57)	75	F	Stent	–	–	None	Dead	4
(62)	41	M	Laser, XRT via tracheotomy	–	–	None	Alive	12
(12)	40	M	Laser, stent	–	XRT	None	Alive	1.8
(38)	80	M	Laser, stent	–	XRT	–	Alive	3
(61)	50	F	Laser, stent	–	Chemo XRT	None	Dead	30
(41)	71	F	Laser, stent	–	Chemo	None	Dead	6
(20)	58	F	Laser, stent	–	–	–	Dead	8
(12)	65	F	Laser, stent	–	–	None	Dead	1.7
(12)	65	M	Laser, stent	–	–	None	Dead	0.73
(12)	69	F	Laser, stent	–	–	None	Alive	1.13
(17)	52	M	Laser, endoscopic resection	–	–	None	Alive	78
(17)	77	F	Laser, endoscopic resection	–	–	None	Alive	46
(17)	88	F	Laser, endoscopic resection	–	–	None	Alive	42
(97)	76	F	Laser, argon plasma coagulation	–	–	–	–	–
(49)	66	M	Laser	–	XRT	None	Alive	15
(83)	40	F	Laser	–	chemo	None	Dead	6
(44)	73	M	Laser	–	–	–	Dead	12
(18)	69	F	Laser	–	–	–	Dead	14
(18)	73	F	Laser	–	–	–	Dead	5
(96)	70	F	Laser	–	–	–	Alive	11
(156)	28	M	Laser	–	–	–	–	–
(157)	54	M	Laser	–	–	–	Dead	2
(70)	58	M	Laser	–	–	–	–	–
(72)	64	M	Endoscopic resection, argon plasma coagulation	–	–	None	Dead	0.3
(85)	71	M	Endoscopic resection, argon plasma coagulation	–	–	None	Dead	5
(42)	35	F	Endoscopic resection	–	–	–	–	–
(50)	46	F	Endoscopic resection	–	–	–	–	–
(71)	50	F	Endoscopic resection	–	–	None	–	–
(100)	53	M	Endoscopic resection	–	–	–	–	–
(12)	64	F	Emergent intubation, laser, stent	–	XRT	None	Dead	2.8
(12)	64	M	Emergent intubation, laser, stent	–	XRT	Stent migration	Dead	0.73
(12)	51	M	Emergent intubation, laser, stent	–	–	None	Dead	1.2
(81)	45	F	Electrosurgery, endoscopic resection	–	Chemo XRT	None	Alive	54
(65)	45	F	Electrosurgery	–	–	Death	Dead	0.1
(102)	–	F	Electrosurgery	–	–	–	–	–
(37)	53	F	Electrosurgery	–	–	–	–	–
(64)	57	F	Cryotherapy	–	Chemo	None	Alive	–
(69)	61	F	Argon plasma coagulation via tracheotomy	–	–	None	Dead	3
(59)	–	–	–	–	XRT, steroids	None	Dead	–
(116)	40	M	–	–	XRT	None	Alive	6
(47)	73	F	–	–	XRT	None	–	–
(13)	60	M	–	–	XRT	–	Alive	9
(13)	68	M	–	–	XRT	–	Alive	–
(13)	53	M	–	–	XRT	–	Alive	9
(13)	64	M	–	–	XRT	–	Alive	11
(82)	61	F	–	–	XRT	None	Alive	6
(16)	67	M	–	–	XRT	–	–	–
(80)	68	M	–	–	XRT	None	Alive	24
(158)	–	M	–	–	XRT	–	–	–
(16)	61	M	–	–	XRT	–	–	–
(10)	–	–	–	–	RAI, XRT	–	Dead	21
(67)	51	M	–	–	Chemo XRT	–	–	–
(40)	54	F	–	–	Chemo	None	Alive	16
(94)	76	M	–	–	Chemo	–	–	–
(13)	66	M	–	–	Chemo	–	Alive	10
(86)	64	M	–	–	Chemo	–	–	–
(87)	81	M	–	–	Anti-androgen	None	Alive	–
(66)	59	F	–	–	–	None	Dead	1
(105)	48	M	–	–	–	–	–	–
(103)	62	M	–	–	–	Death	Dead	0.03

Window, resection of anterior tracheal wall; shave, shave resection of trachea (partial thickness); wedge, wedge resection of trachea (full-thickness); resection, circumferential trachea resection (extent of tracheal resection if known); exenteration, trachea and other structures (not including larynx or thyroid); LND, lymph node dissection; RAI, radioactive iodine; RLN, recurrent laryngeal nerve; XRT, radiation therapy; ARDS, acute respiratory distress syndrome.

Table S4 Recurrence data. In case series, numerical values are reported as mean or percentages. N is the study population in case series. Thyroid cancer is well-differentiated unless otherwise specified

References	Cancer histology	Year	N	Age (years)	Sex	Tracheal treatment	Recurrence incidence	DFI (months)
(14)	CASTLE	2003	–	49	M	Debulking thyroidectomy	Yes	Unknown
(44)	Colon cancer	1991	–	73	M	Laser bronchoscopy	Yes	1
(61)	Esthesioneuroblastoma	1998	–	50	F	Laser, chemo, stent, XRT	Yes	30
(56)	Esophageal squamous cell carcinoma	1990	–	52	M	Total laryngoesophagectomy, thyroidectomy, LND; reconstruction with gastric tube and mediastinal tracheostomy with pec major flap	Yes	Unknown
(15)	Esophageal squamous cell carcinoma	2006	–	57	M	Trachea resection (5 rings), partial esophageal resection, LND, tracheostomy	Yes	3
(81)	Ovarian adenocarcinoma	2006	–	45	F	Electrocautery, snare, XRT, chemo	Yes	58
(98)	Renal cell carcinoma	2013	–	74	M	Stent	Yes	Unknown
(139)	Thyroid	1983–1998	–	68	F	Resection + total thyroidectomy, LND, RAI	Yes	Unknown
			–	78	F	Resection + total thyroidectomy, LND, RAI	Yes	39
(17)	Thyroid	1996–2006	–	52	M	Coring out, laser, interval repeat laser	82%	Unknown
			–	77	F			
			–	88	F			
			–	53	F			
			–	61	F			
(7)	Thyroid	1964–1991	27	61.3	47	Resection with reconstruction	8%	–
			7			Resection without reconstruction, end-tracheostomy		–
(135)	Thyroid	1968–1983	12	58	58.3	Resection, thyroidectomy, LND	17%	–
(136)	Thyroid	1987–2004	127	55	86	Shave + electrocautery to carcinoma remnants (16%), XRT (15%)	4.70%	–
(31)	Thyroid	1990–1998	17	58.6	–	Shave + thyroidectomy	–	19
			6	63.8		Window + thyroidectomy		12
			5	66.4		Resection + thyroidectomy		8
			6	54.3		Laryngotracheal step operation + thyroidectomy		37
(35)	Thyroid	1990–2010	65	60.5	66	Tracheal shave excision (n=18), tracheal resection (n=37) and total laryngectomy (n=10)	60%	–
(124)	Thyroid	1993–2009	42	–	68.8	Shave	21%	–
		1993–2009	72		60.4	Resection	34%	–
(27)	Thyroid	1994–2005	12	59	59	Window	16%	–
(138)	Thyroid	1995–2014	30	56	61	Shave (20%), partial excision (30%), resection (50%)	39%	–
(17)	Thyroid	1996–2006	35	70	88.5	Mechanical debulking, laser, stent	17%	–
(33)	Thyroid	1997–2006	69	62	49	Resection + thyroidectomy, LND, EBRT (99%), RAI (42%); 28% permanent tracheostomy, 56% esophageal resection	33%	–
(73)	Mixed	2001–2013	24	56	16	Cryotherapy; XRT (50%)	–	38
(29)	Thyroid	2004–2014	21	60	76	Resection (4–8 rings), RAI (57%), partial esophageal wall resection (9.5%)	0	–
			103	57	80.5	Shave, RAI (29%), XRT (71%)	54%	–
(126)	Thyroid	2005–2012	96	55	64	Exenteration, RAI	25% (5% local, 9% distant, 16% nodal)	–
(137)	Thyroid poorly or undifferentiated	1985–2013	5	56.8	71.4	Thyroidectomy, XRT	18%	–

CASTLE, carcinoma showing thymus-like element of the thyroid; DFI, disease free interval; LND, lymph node dissection; RAI, radioactive iodine; RLN, recurrent laryngeal nerve; XRT, radiation therapy; EBRT, external beam radiation therapy.

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