


# Radiotherapy for Primary Tracheal Carcinoma: Experience at a Single Institution

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## Abstract

**Background:** There is limited understanding of tracheal carcinoma (TC) because of its rarity. We examined the efficacy of radiotherapy (RT) for patients with primary TC. **Methods:** We analyzed the records of 32 patients with primary TC who received RT at our center between November 1996 and December 2016. **Results:** Thirteen patients received adjuvant RT and 18 received definitive RT. Eight patients achieved complete remission (CR) after definitive RT. Among all patients, the 5-year overall survival (OS) rate was 46.9% and the locoregional progression free survival (LRPFS) rate was 68.1%. Univariate analysis indicated the 5-year OS was better in those with adenoid cystic adenocarcinoma than squamous cell carcinoma ( $P = 0.001$ ); the 5-year LRPFS was better in patients who received surgical resection than those who did not (92.9% vs 46.4%,  $P = 0.013$ ) and in patients who received postoperative RT than in those who received definitive RT (91.7% vs 50.1%,  $P = 0.038$ ). A sub-group univariate analysis indicated the 5-year PFS was better for those who received at least 68 Gy of radiation (44.4% vs 13.0%,  $P = 0.044$ ). Patients who achieved CR had a better 5-year PFS than those who did not (57.1% vs 10%,  $P = 0.006$ ). No patients had a toxicity of grade 3 or more. **Conclusions:** Adjuvant and definitive RT are safe and effective treatments for TC. Patients who received dosages of 68 Gy or more and who had complete tumor regression following definitive RT seemed to have better long-term survival.

## Keywords

tracheal carcinoma, radiotherapy, dose, IMRT, survival

## Abbreviations

ACC, adenoid cystic adenocarcinoma; ADC, adenocarcinoma; CI, confidence interval; CR, complete remission; CTV, clinical target volume; DMFS, distant metastasis free survival; F, female; GTV, Gross tumor volume; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; LP, Locoregional progression; LRPFS, locoregional progression free survival; M, male; NP, not provided; OAR, organs at risk; OS, overall survival; PD, progressive disease; PFS, progression free survival; PORT, postoperative RT; PR, partial remission; PTV, planning target volume; RECIST, Response Evaluation Criteria in Solid Tumors; Rsct, resection; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SCC, squamous cell carcinoma; TC, tracheal carcinoma; 2DRT, 2-dimensional radiotherapy; 3DCRT, 3-dimensional conformal radiotherapy

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## Introduction

The incidence of primary tracheal carcinoma (TC) is extremely low, and this cancer accounts for only about 0.1% of all malignancies.<sup>1</sup> The most common histological type is squamous cell carcinoma (SCC) followed by adenoid cystic adenocarcinoma (ACC).<sup>2,3</sup> Because there are no specific symptoms, diagnosis typically occurs in patients with advanced tumors. There is no definitive staging system and no comprehensive treatment guidelines due to the rarity of this cancer. Bhattacharyya *et al* proposed a TNM staging system,<sup>3</sup> but this system has not

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been widely accepted. Because the study is based on the result of the SEER database. As it is a survey database, problems with missing data may be encountered. In addition, the staging system lacks the subdivision of N staging and does not include M staging, which leads to difficulties in comparison between different studies.

Surgery is considered the main treatment. Radiotherapy (RT) plays an important role as a postoperative adjuvant treatment because the surgery margin may be insufficient.<sup>4-11</sup> For this reason, most clinicians administer postoperative RT after resection for locally advanced tumors, even in the absence of any prospective evidence. There is no evidence from clinical trials regarding the optimal approach for patients who are inoperable or unsuitable for surgery, and clinicians typically propose definitive RT for these patients.<sup>4-6,12</sup> Data on long-term complete remission suggest that outcome is related to radiation dose.<sup>4,6</sup> Although there are some reports on the use of different RT regimens, there is little information on this topic, and it is difficult to develop personalized RT planning and dosages.

The purpose of this study is to evaluate our institutional experience with RT, either as adjuvant or definitive treatment, on the outcome of patients with primary TC, and to compare our results with previous studies of this cancer.

## Materials and Methods

### Subject Selection and Data Collection

Following approval by our Institutional Review Board, we identified patients by searching the institutional tumor registry of our Cancer Center for all patients with neoplasms of the trachea from 1996 to 2016. Eligible patients had primary TC confirmed by pathology and received RT at our institution. Patients were excluded if they had benign tumors, tumors that might have arisen from other sites, did not receive anti-tumor therapy or RT at our institution, or had distant metastases at diagnosis.

The medical charts were reviewed to collect clinical and demographic data, including age, sex, carcinogen exposures, presenting symptoms, histologic information, tumor location and size, treatment modality, and outcome.

### Treatment

The surgical approach was endoscopic resection or open surgical resection. Open surgical resection included tracheal resection, laryngotracheal resection, stent implantation, and tracheotomy. Tumor resection was not performed for the latter 2 methods.

The goal of the surgical resection was complete resection. The main objectives were to protect the blood supply of the trachea and to perform safe reconstruction by avoiding excessive anastomotic tension. The eligibility for surgical resection was determined via a multidisciplinary clinical conference after review of the patient's condition and analysis of tumor

characteristics, including size and location. Contraindications to resection of the major airways were respiratory failure and presence of a major co-morbidity. The surgical approach that was used depended on the surgeon's experience.

RT was administered with a linear accelerator using a 6 MV X-ray beam. Adjuvant RT was usually initiated 4-6 weeks after surgery, and the total dose was 50-54 Gy. A boost dose was administered if there was microscopic residual tumor or an insufficient surgical margin. The definitive RT dose was 60-70 Gy. The dose per fraction was 180-200 c Gy, 5 times per week.

Gross tumor volume (GTV) was defined as all gross visible disease based on imaging and endoscopy. The clinical target volume (CTV) was usually expanded 3-5 cm longitudinally and 1-2 cm axially from the tumor bed or primary tumor, and adjacent lymph node stations were also included. The planning target volume (PTV) was generally expanded 1 cm beyond the CTV. Dose constraints were implemented for organs at risk (OAR), such as the spinal cord, esophagus, and lung.

RT techniques have changed during the 20-year period of this analysis. Thus, patients received 2-dimensional radiotherapy (2DRT), 3-dimensional conformal radiotherapy (3DCRT), or intensity-modulated radiotherapy (IMRT).

Chemotherapy was combined with RT as concurrent or adjuvant chemotherapy in some cases. The most common therapeutic regimen was 1-7 cycles of cisplatin.

### Evaluation Standards

Response evaluation and routine follow-up was performed by use of CT imaging and bronchoscopy with or without biopsy after treatment. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.<sup>13</sup> The Radiation Therapy Oncology Group (RTOG) toxicity grading system was used to score acute and chronic complications.<sup>14</sup>

### Statistical Analysis

The primary endpoints were overall survival (OS), locoregional progression free survival (LRPFS), progression free survival (PFS), and distant metastasis free survival (DMFS). OS was measured from the date of treatment to the date of death or last follow-up. LRPFS, PFS, and DMFS were measured from the date of treatment to the date of each event, death, or last follow-up.

The survival rate was calculated using the Kaplan-Meier survival analysis method. Univariate and multivariate analyses of prognostic factors were performed using the log rank and Cox's regression methods, respectively. Variables associated with a  $P$  value  $< 0.2$  were included in the multivariate analysis. All tests were two-sided and  $P$ -values of less than 0.05 were considered to indicate statistical significance. SPSS Statistics 17.0 software was used for the survival analysis.

**Table 1.** Characteristics of Patients and Treatments.

Patients	No. (%) or median (Range)	Treatments	No. (%) or median (Range)
Age, years	48 (28-68)	Surgery	19 (59.4)
Sex		Type	
Male	23 (71.9)	Endoscopic rsct	3 (3/19,15.8)
Female	9 (28.1)	Tracheal rsct	9 (9/19,47.3)
Histologic type		Laryngotracheal rsct	4 (4/19,21.1)
SCC	18 (56.3)	Stent implantation	2 (2/19,10.5)
ACC	10 (31.2)	Tracheotomy	1 (1/19,5.3)
Undifferentiated	3 (9.4)	Rsct margin status	
Adenocarcinoma	1 (3.1)	R1	7 (7/16,43.8)
Smoking status		R0	9 (9/16,56.3)
Never	19 (59.4)	Radiotherapy	32 (100)
Ever	13 (40.6)	Type	
Location		PORT	13 (40.6)
Cervical	7 (21.9)	Definitive RT	18 (56.3)
Thoracic	25 (78.1)	Palliative RT	1 (3.1)
Extension		Technique	
Carina	10 (31.3)	2DRT	9 (28.1)
Nodal involvement	5 (15.6)	3DCRT	12 (37.5)
Esophagus	3 (9.4)	IMRT	11 (34.4)
Main stem bronchus	3 (9.4)	Median dose, Gy	
Thyroid	1 (3.1)	PORT	54.0 (50-60)
Presenting symptoms		Definitive RT	67.5 (60-70)
Hemoptysis	12 (37.5)	Chemotherapy	12 (37.5)
Dyspnea	9 (28.1)	Induction	3 (9.4)
Stridor	6 (18.8)	Concurrent	7 (21.9)
Cough	5 (15.6)	Adjuvant	2 (6.3)

Abbreviations: Rsct, resection; SCC, squamous cell carcinoma; ACC, adenoid cystic carcinoma; PORT, post-operative radiotherapy; RT, radiotherapy; 2DRT, 2-dimensional radiotherapy; 3DCRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

## Results

### Patient and Treatment Characteristics

We initially reviewed the records of 96 patients who had diagnoses of tracheal neoplasms, and excluded 11 patients with benign tumors and 29 patients who had tumors that might have arisen from other sites. Among the 56 patients with primary malignant neoplasms of the trachea, 8 patients did not receive anti-tumor therapy at our institution and 16 patients did not receive RT or had distant metastases before treatment. Thus, we ultimately examined the records of 32 patients.

Analysis of the characteristics of the 32 patients (Table 1) indicated that most lesions were in the thoracic trachea (78.1%), and 22 patients had extra-tracheal invasion. The most common presenting symptoms were hemoptysis (37.5%) and dyspnea (28.1%). Twenty-three patients (71.9%) were male, and SCC (56.3%) and ACC (31.2%) were the predominant histological types. Sixteen patients with SCCs had histories of smoking, but none of the patients with ACCs had histories of smoking.

Sixteen patients (50.0%) received surgical resection, 13 of whom received open surgical resection and 3 of whom received endotracheal resection. Evidence of microscopic residual tumor (R1 at the resection margin) was present in 7 patients after resection. Two patients received stent implantation and 1

patient received a tracheotomy for palliation, but none of these 3 patients received any form of tracheal resection.

All patients who received open surgical resection received postoperative RT (PORT), and all patients who received endoscopic resection received definitive RT. Resection and definitive RT was not possible in 1 patient because the tumor was too large; thus, palliative RT (dose: 56 Gy) was applied after tracheotomy in this patient. The mean duration of adjuvant RT was 5.5 weeks and the mean dose was 55.2 Gy (median: 54.0 Gy; range: 50 to 60 Gy). The mean duration of definitive RT was 6.6 weeks and the mean dose was 66.5 Gy (median: 67.5; range: 60 to 70 Gy).

Twelve patients received 3DCRT, 11 patients received IMRT, and 9 patients received 2DRT (Table 1).

Twelve patients received chemotherapy, 7 of them were treated with cisplatin as a single-drug regimen for concurrent chemotherapy combined with radiotherapy. Three patients who received induction chemotherapy before and 2 patients who received adjuvant chemotherapy after surgical resection used the PF regimen (Cisplatin plus 5-fluorouracil).

### Tumor Response and Pattern of Failure

Patients were evaluated for short-term efficacy at 3 months after the end of RT. Among the 18 patients who received

**Table 2.** Patient and Treatment Characteristics of Definitive RT Group.

Sex	Age (yrs)	Histologic type	Size (cm)	Dose (Gy)	RT technique	Chemotherapy type	RESP		T-LP		T-DM (mo.)	Cause of death
							LP	(mo.)	DM	(mo.)		
F	41	ACC	1.8	67	2D-RT	/	PR	-	+	92	DM	
F	38	ACC	2.0	68	3DCRT	/	CR	-	+	23	DM	
M	39	ACC	4.5	70	IMRT	/	CR	-	-		Alive	
F	32	ACC	1.0	66	IMRT	/	CR	-	-		Other	
M	50	SCC	4.2	68	3DCRT	Induction	CR	-	-		Alive	
M	60	SCC	3.5	70	3DCRT	Concurrent	CR	-	-		Alive	
M	36	SCC	4.0	64	IMRT	Concurrent	PR	+	13	-	LP	
M	56	SCC	3.8	63	IMRT	Concurrent + adjuvant	PR	-	+	5	DM	
F	38	SCC	6.0	68	3DCRT	/	CR	+	30	-	LP	
M	52	SCC	2.9	66	2D-RT	/	CR	+	14	-	LP	
M	68	SCC	3.5	60	2D-RT	Concurrent + adjuvant	PR	+	6	-	LP	
M	57	ADC	6.5	68	2D-RT	Concurrent	PR	+	7	-	LP	
M	39	SCC	2.5	68	2D-RT	Concurrent	PR	-	+	12	DM	
M	57	SCC	3.2	66	2D-RT	Induction	PR	+	10	-	LP	
M	65	ACC	4.1	68	3DCRT	/	CR	-	-		Alive	
M	53	SCC	3.3	66	2D-RT	/	PR	-	+	56	DM	
M	59	SCC	1.6	70	IMRT	Concurrent + adjuvant	PR	+	48	-	LP	
M	44	SCC	2.0	63	IMRT	/	PR	+	22	-	LP	

Abbreviations: ADC, adenocarcinoma; F, female; M, male; ACC, adenoid cystic carcinoma; SCC, squamous cell carcinoma; RT, radiotherapy; 2DRT, 2-dimensional radiotherapy; 3DCRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; RESP, initial response after RT; CR, complete remission; PR, partial remission; LP, local progression; DM, distant metastasis; T, time since start of treatment; mo., months.

definitive RT, 8 (44.4%) achieved complete remission (CR) and 10 (55.6%) achieved partial remission (PR) (Table 2). None of the 32 patients experienced progressive disease (PD) during the initial response evaluation, and the overall response rate was 100%.

Locoregional progression (LP) occurred in 9 patients (28.1%) during the follow-up period, and 8 of these patients received definitive RT. Seven patients (21.9%) developed distant metastases (4 with lung metastases and 3 with bone metastasis).

### Survival and Prognostic Factors

We followed up patients by telephone and clinical visits. The median follow-up duration was 60 months (range: 7 to 202 months) and 20 patients (62.5%) died during the follow-up period. No patients were lost to follow up. The cause of death was LP in 9 patients, lung metastasis in 4 patients, bone metastasis in 2 patients, and was unrelated to cancer in 5 patients. Analysis of survival data indicated the 5-year OS was 46.9%, the LRPFS was 68.1%, the DMFS was 77.6%, and the PFS was 47.9%.

Univariate analysis (Table 3) indicated that histologic type (ACC vs SCC) was significantly associated with OS and LRPFS, and that surgical resection (yes vs no) and RT type (PORT vs Definitive RT) were significantly associated with LRPFS. The 5-year OS rate was better for patients with ACC than SCC (80.0% vs 29.4%,  $P = 0.001$ ; Figure 1) and the 5-year LRPFS rate was 100% in patients with ACC and 44.2% in patients with SCC ( $P < 0.001$ ). The 5-year LRPFS rate was

**Table 3.** Univariate Analysis of the Relationship of Clinical and Treatment-Related Factors With OS and LRPFS.

Factors	Comparison	P-value	
		OS	LRPFS
<b>Clinical factors</b>			
Sex	Male vs female	0.689	0.594
Age	≤ 40 years vs > 40 years	0.361	0.681
Smoking history	Never vs ever	0.184	0.575
Histologic type	SCC vs ACC	0.001	<0.001
Location	Cervical vs thoracic	0.170	0.056
Tumor size	≤ 4 cm vs > 4 cm	0.102	0.389
Extension	Yes vs no	0.545	0.608
<b>Treatment-related factors</b>			
Surgical resection	Yes vs No	0.823	0.013
RT type	PORT vs definitive RT	0.324	0.038
RT technique	3DCRT/IMRT vs 2D-RT	0.193	0.062
Chemotherapy	Yes vs No	0.543	0.189
Tumor response	CR vs PR	0.160	0.205

Abbreviations: SCC, squamous cell carcinoma; ACC, adenoid cystic carcinoma; RT, radiotherapy; PORT, post-operative radiotherapy; 2DRT, 2-dimensional radiotherapy; 3DCRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; OS, overall survival; LRPFS, locoregional progression free survival.

better for patients who received surgical resection than those who did not (92.9% vs 46.4%,  $P = 0.013$ ; Figure 2), and the 5-year LRPFS rate was better for patients who received PORT than those who received definitive RT (91.7% vs 50.1%,  $P = 0.038$ ; Figure 3).

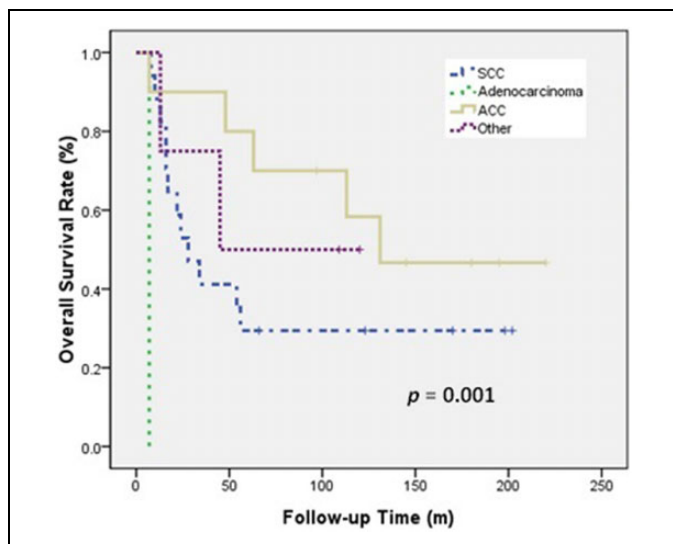


Figure 1. OS of patients with SCC, ACC, and other histology.

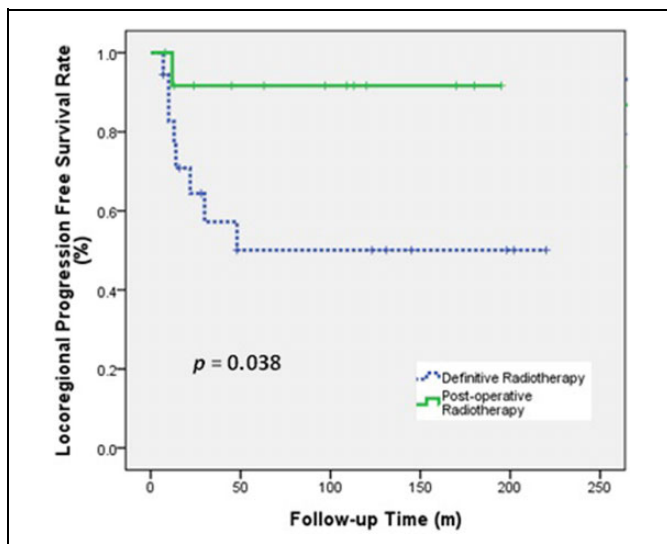


Figure 3. LRPFS of patients who received post-operative radiotherapy or definitive radiotherapy.

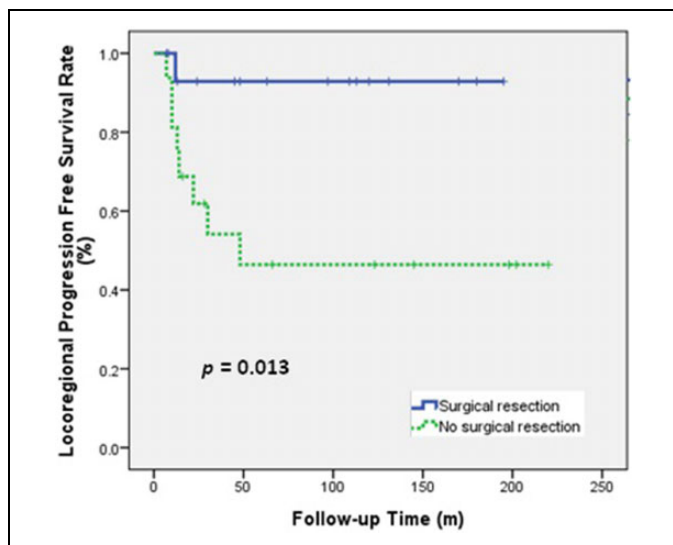


Figure 2. LRPFS of patients who received or did not receive surgical resection.

For OS the smoking history, histological type, tumor size, location, RT technique and tumor response enter to multivariate analysis. For LRPFS the histological type, location, surgical resection, RT type, RT technique and chemotherapy enter to multivariate analysis. However, no factor could reach statistical significance for both (Table 4).

Sub-group analysis of patients who received definitive RT indicated the 5-year OS was 33.3%, the LRPFS was 50.1%, the DMFS was 67.7%, and the PFS was 29.8%.

Univariate analysis indicated that RT dose and tumor response were associated with PFS (Table 5). The 5-year PFS was 44.4% for patients who received at least 68 Gy during RT, but was 13.0% for those who received less than 68 Gy

Table 4. Prognostic Factors for OS and LRPFS in Multivariate Analysis.

	HR	95% CI	P-value
<b>OS</b>			
Smoking history	0.478	0.166-1.379	0.172
Histologic type	0.800	0.513-1.248	0.325
Location	0.821	0.264-2.547	0.733
Tumor size	0.532	0.167-1.701	0.287
RT technique	0.941	0.296-2.821	0.876
Tumor response	1.429	0.493-4.138	0.511
<b>LRPFS</b>			
Histologic type	0.254	0.053-1.224	0.088
Location	0.297	0.055-1.620	0.161
Surgical resection	1.033	0.020-52.370	0.987
RT type	0.335	0.011-9.799	0.526
RT technique	0.876	0.196-3.906	0.862
Chemotherapy	1.857	0.292-11.831	0.512

Abbreviations: HR, hazard ratio; CI, confidence interval; OS overall survival; LRPFS local progression free survival; RT radiotherapy.

( $P = 0.044$ ; Figure 4). In addition, patients who achieved CR had a better 5-year PFS than those who did not (57.1% vs 10%,  $P = 0.006$ ; Figure 5). In multivariate analysis, no factor could reach statistical significance for OS and PFS (Table 5).

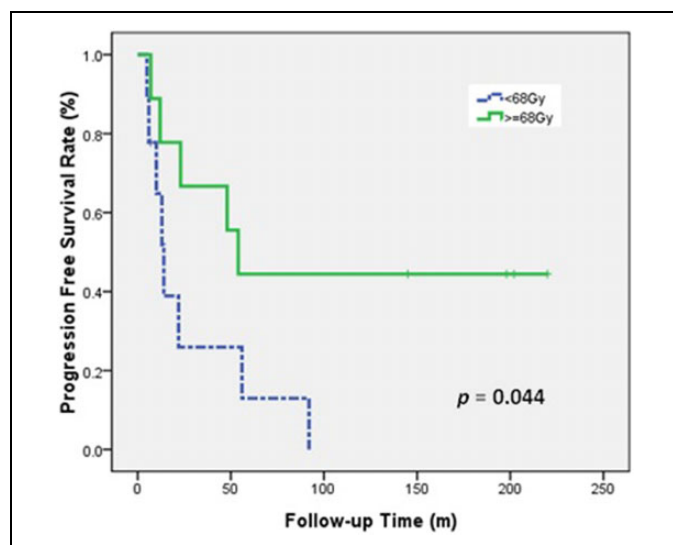
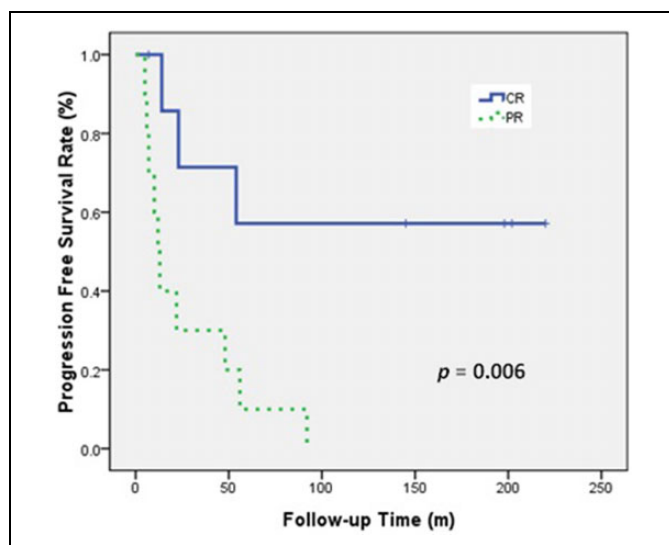
### Treatment-Related Complications

Analysis of complications during RT (data not shown) indicated that they were mainly non-severe (grade 1 or 2), and included odynophagia (n = 19), esophagitis (n = 6), radiation-induced lung fibrosis (n = 3), and tracheal stenosis (n = 2). The patients with odynophagia were able to tolerate eating after taking analgesics. None of the patients had esophageal stenosis or perforation after treatment.

**Table 5.** Univariate and Multivariate Analysis of the Relationship of Treatment-Related Factors With 5-Year OS and PFS in Definitive RT Group.

Factors	Description	Univariate		Multivariate			
		%, <i>P</i> -value		HR (95% CI)		<i>P</i> -value	
		OS	PFS	OS	PFS	OS	PFS
RT technique	3DCRT/IMRT vs 2D-RT	36.4% vs 28.6%	40.4% vs 14.3%	0.828 (0.205-3.351)	0.896 (0.211-3.807)	0.792	0.881
RT dose	≥ 68 Gy vs <68Gy	44.4% vs 22.2%	44.4% vs 13.0%	0.638 (0.118-3.450)	0.951 (0.202-4.471)	0.602	0.949
		0.128	0.053				
Tumor response	CR vs PR	50.0% vs 20.0%	57.1% vs 10.0%	1.959 (0.388-9.903)	4.741 (0.843-26.654)	0.416	0.077
		0.067	0.044				
		0.065	0.006				

Abbreviations: RT, radiotherapy; HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression free survival; 2DRT, 2-dimensional radiotherapy; 3DCRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CR, complete remission; PR, partial remission.

**Figure 4.** PFS of patients who received high-dose and low-dose definitive RT.**Figure 5.** PFS of patients who received definitive RT and achieved or did not achieve CR.

## Discussion

During the 20-year history of this major cancer center in South China, only 56 patients were diagnosed with primary TC. We analyzed 32 of these patients, after exclusion of 8 patients who did not receive anti-tumor therapy at our institution and 16 patients who did not receive RT or had distant metastases before treatment. The sex, age, histologic type, and carcinogen exposures were similar among our 32 patients and among patients in most other series.<sup>4-6,8,9</sup> In particular, most of our patients were male and the main histological types were SCC and ACC. In addition, SCC was associated with a history of smoking, but ACC was not. Most patients tolerated their treatments, and there was a low rate of complications.

The thoracic trachea was the most common tumor location among our patients. Patients with tumors in this location are often misdiagnosed. Thus, we suggest that primary TC be included in the differential diagnosis when a patient presents

with symptoms of hemoptysis, dyspnea, and stridor, particularly when the patient has a history of smoking.

The length of a tumor, the presence of extracapsular extension, and the difficulty in performing reconstruction are often responsible for insufficient surgical margins. Thus, most clinicians agree on the necessity for PORT following resection for locally advanced tumors.<sup>4,12</sup> Definitive RT remains important for patients with unresectable tumors. In our study, the 5-year OS rate was 46.9% in the entire group. Other large series reported 5-year OS rates of 15% to 73%.<sup>3,8,9,15,16</sup> However, it is difficult to directly compare these results because there are no agreements regarding the staging system and treatment strategies.

Previous studies of primary TC have reported longer survival times for patients with ACC than SCC. In particular, the 5-year OS rate ranged from 40% to 88% for ACC and 13% to 45% for SCC.<sup>7-10,16,17</sup> Our results are consistent with these previous results. In fact, none of our patients with ACC experienced LP during the follow-up, regardless of the receipt of

**Table 6.** Previous Studies That Examined the Effect of RT on Primary TC.

Author	Year	Patients, n (PORT/DRT)	Histology SCC/ACC	Dose (Gy) PORT/DRT	CR, %	Survival
Fields <sup>4</sup>	1989	24 (6/18)	13/4	<40-70	86(6/7)	5-year OS: 25%
Makarewicz <sup>5</sup>	1998	23 (NP/8)	13/7	>60	75	Mean survival: 26 months
Chao <sup>6</sup>	1998	42 (9/32)	28/3	10-64	50 (4/8)	Median survival: 5.7 months
Bhattacharyya <sup>3</sup>	2004	92 (39/21)	41/19	NP	NP	Mean survival: 63.3 months
Webb <sup>8</sup>	2006	45 (10/18)	26/7	29.8-70/18-130	NP	5-year DSM: 72.9%
Honing <sup>16</sup>	2007	293 (23/156)	156/21	NP	NP	5-year OS: 15%
Xie <sup>9</sup>	2012	78 (46/30)	33/12	NP	NP	5-year OS: 42.3%
Je <sup>11</sup>	2017	22 (13/9)	All ACC	50.4/60-66	11.1 (1/9)	5-year OS: 81.8%
Levy <sup>10</sup>	2018	31 (22/9)	All ACC	45-65/66-70	NP	5-year OS: 88%

Abbreviations: PORT, post-operative radiotherapy; DRT, definitive radiotherapy; SCC, squamous cell carcinoma; ACC, adenoid cystic carcinoma; CR, complete remission; DSM, disease-specific mortality; NP, not provided.

PORT or definitive RT. This might be because ACC tends to be well-differentiated and slow-growing, although previous research reported the appearance of metastases after 10 years.<sup>11,12</sup> One of our patients with ACC developed distant metastases during the first decade after treatment.

We observed only one patient who received PORT after surgical resection who had LP, although 7 (43.8%) patients who received surgical resection had R1 resections and 4 (25.0%) others had surgical margins less than 1 cm. This result suggests that adjuvant RT provides an important benefit. In the definitive RT group, 44.4% (8/18) of the patients had LP. This indicates that surgery may be important for local control, even if the tracheal tumor cannot be completely removed. Our study also showed that the 5-year LRPFS was significantly longer in patients who received surgical resection than those who did not, and that the 5-year LRPFS was better in the PORT group than in the definitive RT group (Figure 3).

Our sub-group analysis of the definitive RT group indicated that patients treated with high RT doses ( $\geq 68$  Gy) had better long-term progression-free control than those receiving low doses ( $<68$  Gy), and this difference was marginally significant in univariate analysis ( $P = 0.044$ ). Selection of the most appropriate RT dose for unresectable TC can be difficult. Several previous retrospective studies examined the effect of RT on the outcome of patients with primary TC (Table 6). The available literature indicates that an RT dose of at least 60 Gy was associated with improved outcome.<sup>3-6,8-11,16</sup> Makarewicz *et al*<sup>5</sup> reported that RT doses of 60 to 70 Gy are needed to achieve CR.

However, some reports showed that higher RT doses led to increased complications and did not improve survival.<sup>17,18</sup> We believe that this discrepancy may be related to the use of different RT technologies. When a tumor is near a natural air cavity, the RT dose may be insufficient for the gross tumor volume (GTV), due to electronic disequilibrium around the air-tissue interfaces. Joshi *et al*<sup>19</sup> demonstrated that the magnitude of dose reduction in water near the air-water interface increases with photon energy and the number and size of the radiation beam. They also demonstrated no interface dose reductions when using 3DCRT. Use of Monte Carlo simulation may provide better estimates of the doses delivered at these interfaces.<sup>20</sup> In our

study, 77.8% (7/9) of patients received 68 Gy or more by 3DCRT or IMRT, and 2 patients (22.2%, 2/9) received 68 Gy by 2DRT. The 3DCRT/IMRT group had a better 5-year PFS than 2DRT group, but this was not statistically significant ( $P = 0.053$ ). The effect of conformal technology on increasing the dose for tracheal tumors requires further research.

All of our patients who received definitive RT also received at least 60 Gy, and this group had a high remission rate (100%; CR: 44.4%). Those with complete tumor regression had a significantly better 5-year PFS. Fields *et al*<sup>4</sup> reported that CR was significantly related to dose. In particular, 6 of their 7 patients (86%) who received more than 60 Gy achieved CR, but 1 of 11 (9.0%) who received less than 60 Gy achieved CR ( $P < 0.001$ ). Although the association between CR and RT dose needs verification, CR was reported as a favorable prognostic factor for survival in several case series.<sup>4,5,21</sup>

We found that the major pattern of distant failure was lung metastasis, regardless of whether surgery or high-dose definitive RT was administered. The development of systemic therapeutics in this setting seems to be important.<sup>22</sup> Concurrent or adjuvant chemotherapy tends to prolong survival, but provided no significant effect in our group. Thus, further studies are needed to determine the benefit of chemotherapy. In addition, it is meaningful to analyze different chemotherapy regimens, cycles and combination modes if we expand the sample size in follow-up research. The search for genetic mutation targets is also a priority for future research.

We examined patients in our cancer center with primary TC who received RT over a period of 20 years. This is a retrospective analysis of a relatively small group of patients, which affects the reliability of the results. Need to expand the sample size to further confirm. The RT techniques have changed substantially over this period, and this could have led to bias. The lack of a standardized staging system and the rarity of this cancer make comparisons among studies difficult.

## Conclusions

In conclusion, our retrospective analysis of patients with primary TC indicated that RT was a safe and effective adjuvant or

definitive method of treatment. Patients who received dosages of 68 Gy or more and who had complete tumor regression following definitive RT seemed to have better long-term survival. Further studies are needed to evaluate the use of modern RT techniques, including conformity, dose distribution, and protection of organs at risk.

### Authors' Note

Ruifang Zeng and Hanyu Wang contributed equally to this work. This study was approved by Ethics Committee of Cancer Center Integrated Hospital of Traditional Chinese Medicine (No. NFZXY20170618). The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.


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