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Thyroid Carcinoma Showing Thymus-Like Differentiation (CASTLE) with Tracheal Invasion: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 49-year-old
Final Diagnosis: Thyroid carcinoma showing thymus-like differentiation (CASTLE)
Symptoms: Hoarseness
Medication: —
Clinical Procedure: Thyroidectomy
Specialty: Surgery

Objective: Rare disease

Background: Thyroid carcinoma showing thymus-like differentiation (CASTLE) is a rare disease entity. It arises from ectopic thymic tissue in the thyroid gland. Patients usually present with enlarging neck mass and hoarseness.

Case Report: A 49-year-old man presented to our clinic with hoarseness and a right thyroid mass. Ultrasound showed a 6-cm right thyroid tumor and computer tomography confirmed invasion into the trachea. He received total thyroidectomy together with excision of one-third of the tracheal wall. No gross tumor was left behind. The tracheal defect was repaired using a pedicled right sternocleidomastoid muscle flap. He had a good recovery and was discharged 2 days after surgery. Histology revealed carcinoma showing thymus-like differentiation (CASTLE). The patient had regular follow-up and showed no clinical evidence of recurrence 18 months after surgery.

Conclusions: Thyroid carcinoma showing thymus-like differentiation (CASTLE) is a rare yet potentially extensive disease with favorable prognosis. Imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), is helpful in aiding diagnosis and operative planning. Surgical resection is currently the treatment of choice, with generally favorable outcomes. The role of adjuvant therapies such as radiotherapy and chemotherapy require further studies.

MeSH Keywords: Endocrine Surgical Procedures • Thyroid Neoplasms • Trachea

Abbreviations: **Bcl2** – B cell lymphoma 2 gene; **CD5** – cluster of differentiation 5; **CT** – computed tomography; **LCA** – leukocyte common antigen; **MRI** – magnetic resonance imaging; **PAX8** – paired-box gene 8; **RLN** – recurrent laryngeal nerve; **SETTLE** – spindle epithelial tumors with thymic-like differentiation; **CASTLE** – thyroid carcinoma showing thymus-like differentiation; **TTF-1** – thyroid transcription factor 1

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/919208

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Background

Thyroid carcinoma showing thymus-like differentiation (CASTLE) is a rare type of malignant thyroid tumor. The first report in the literature was reported by Miyauchi et al. in 1985 as "intrathyroid epithelial thymoma". It originates from ectopic thymus tissue within the thyroid gland or branchial pouch remnants along the thymic line [1]. It is rare, with around 110 patients reported in the literature to date. Patients typically presented with neck mass and hoarseness [2]. Here, we report the case of a patient with CASTLE with tracheal invasion.

Case Report

A 49-year-old man presented to our clinic with hoarseness and a right thyroid mass. The bedside ultrasonography with high-frequency 10-MHz linear array probe revealed a large 6-cm heterogenous solid tumor occupying almost the entire right thyroid gland, with concomitant slightly-enlarged lymph nodes in the right cervical chain (Figure 1). Indirect laryngoscopy confirmed the presence of a vocal cord paresis on the side of the tumor. The left thyroid gland appeared unremarkable. Panendoscopy confirmed right tracheal wall invasion involving one-third of the circumference. Contrast computed tomography (CT) demonstrated a heterogeneous contrast-enhancing irregular mass centered in the right lobe of the thyroid gland, measuring 4.4×3.5×6.0 cm, with invasion into the trachea at the level of the thoracic inlet causing about 4–5% tracheal stenosis (Figures 2, 3). There was also encroachment of the esophagus medially. Blood tests, including thyroid function test, bone profile, carcinoembryonic antigen, and calcitonin, were all normal. Fine-needle aspiration cytology of the thyroid mass with a 23-G needle confirmed malignancy, while the cytology of the right neck lymph nodes only revealed reactive changes.

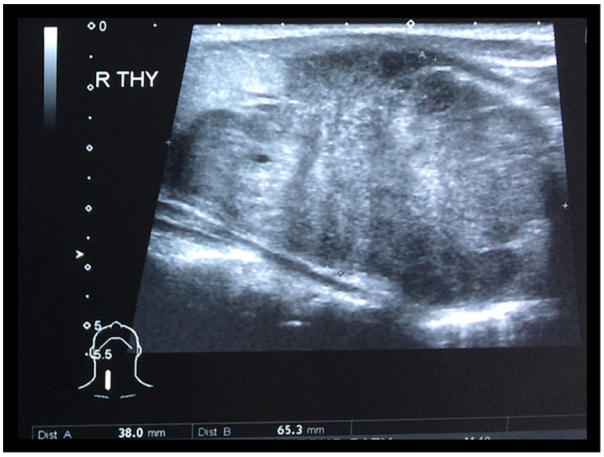

Figure 1. Ultrasound image showing large right thyroid tumor (longitudinal view).

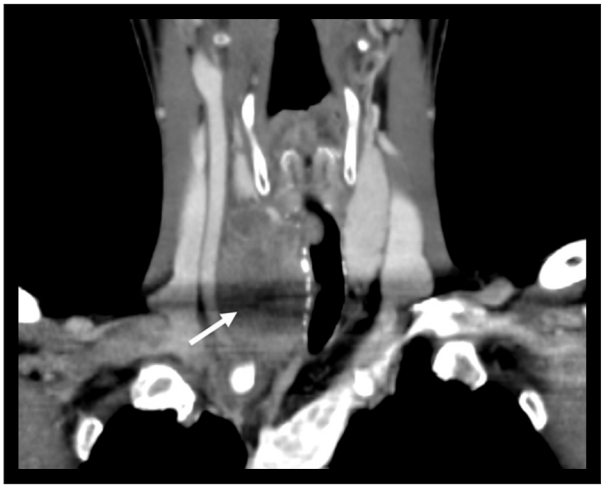

Figure 2. CT image (coronal view) showing large right thyroid tumor with tracheal invasion (arrow).

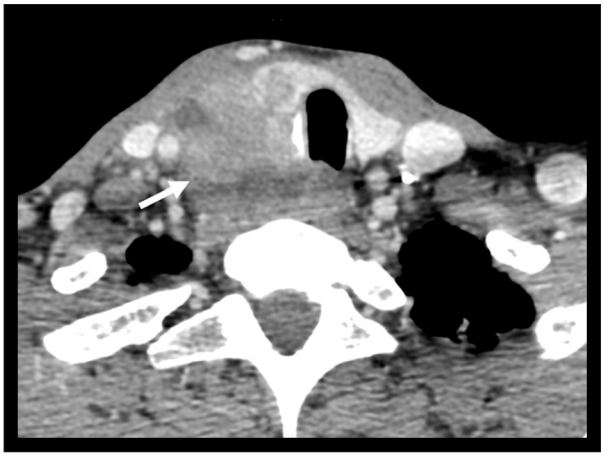

Figure 3. CT image showing large right thyroid tumor with tracheal invasion (arrow).

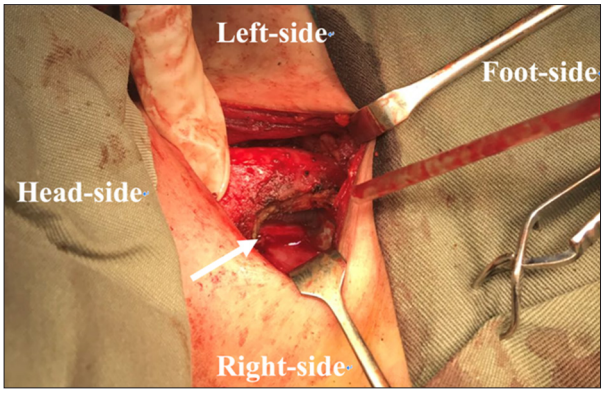

Figure 4. Operative photo showing tracheal defect after tumor removal (arrow).

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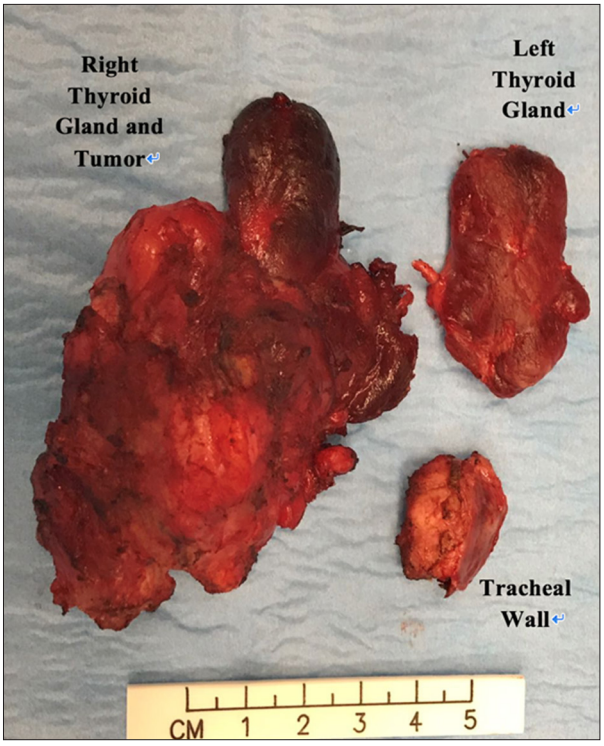

Figure 5. Operative specimen.

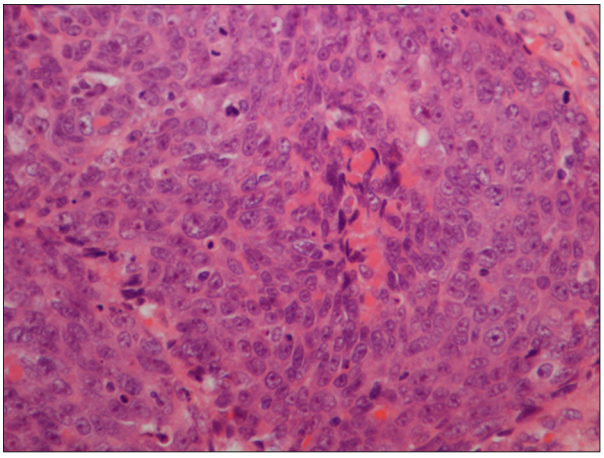

Figure 6. Histological slide showing indistinct cell borders, large vesicular nuclei, and prominent nucleoli.

Surgical excision was performed shortly thereafter. Intra-operatively, the thyroid tumor was locally advanced with invasion of one-third of the circumference of the tracheal wall. The right recurrent laryngeal nerve (RLN) was invaded by the tumor bulk and had to be sacrificed. The left thyroid gland and RLN were normal. Intra-operative recurrent laryngeal nerve monitoring confirmed normal functioning of the left RLN. The right common carotid artery was adhered to but not invaded by the tumor. Total thyroidectomy together with excision of one-third of the tracheal wall was performed (Figures 4, 5). No gross tumor was left behind. The tracheal defect was

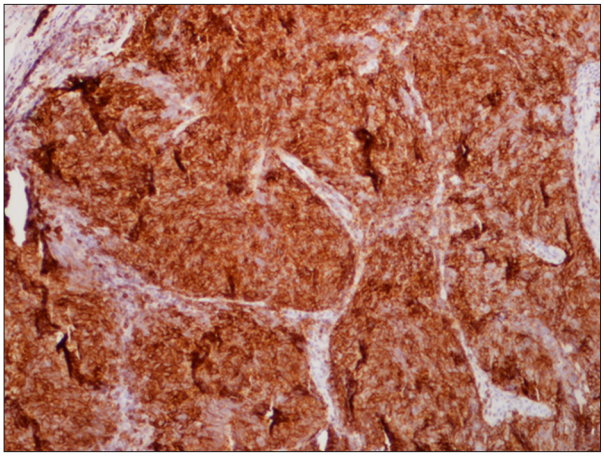

Figure 7. Tumor cells are positive for CD5.

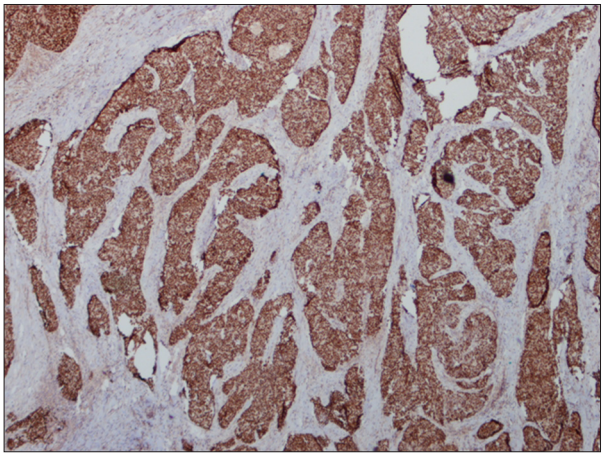

Figure 8. Tumor cells are positive for p63.

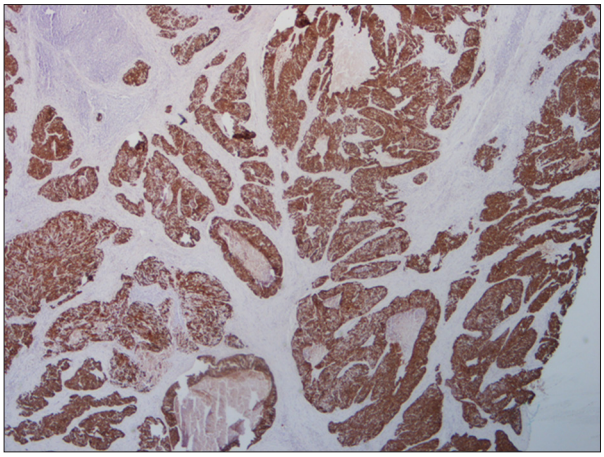

Figure 9. Tumor cells are positive for MNF116.

repaired using a pedicled right sternocleidomastoid muscle flap on the same occasion. Right selective neck dissection was performed as well. He had a good recovery and was discharged 2 days after surgery. Histology of both the tumor and right neck level II and III lymph nodes revealed diffuse

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replacement of thyroid tissue by irregular nodular aggregates of tumor traversed by fibrous tissue (Figure 6). The tumor cells had ill-defined cell borders with vesicular nuclei and conspicuous nucleoli. There was no definite squamoid or glandular differentiation. The tumor was extensively positive for MNF116, p63 gene, Cluster of differentiation 5 (CD5), B cell lymphoma 2 gene (Bcl2) and Paired-box gene 8 (PAX8); focally positive for AE1/3 and p53 (Figures 7–9). It was negative for thyroid transcription factor 1 (TTF-1). Scattered leukocyte common antigen (LCA)-positive lymphocytes were found. The overall features were consistent with carcinoma showing thymus-like differentiation (CASTLE). CD 5 marker was reported to be highly specific for the diagnosis of CASTLE. PAX 8, a member of the paired-box gene family, was found to be expressed in thymic epithelial tumors and was especially overexpressed in thymic squamous cell carcinoma, and this had a role in the diagnosis of CASTLE. Other marker such as p63 gene, Bcl 2, and p53 indicated that they may be involved in the tumorigenesis and progression of CASTLE and were reported to be biomarkers for CASTLE [3,4].

The patient received a course of adjuvant radiotherapy (total of 66 Gray) after the operation. He had regular follow-up and showed no clinical evidence of recurrence at 18 months after surgery.

Discussion

Carcinoma showing thymus-like differentiation (CASTLE) is a rare type of thyroid tumor. It was first reported in the literature by Miyauchi et al. in 1985 [1]. It was classified by Chan and Rosai et al. into 4 types according to its clinical and pathological features: ectopic hamartomatous thymoma, ectopic cervical thymoma, spindle epithelial tumors with thymic-like differentiation (SETTLE), and carcinoma showing thymic-like elements (CASTLE). The first 2 types were considered benign in nature, while the latter 2 were considered malignant [5]. According to the World Health Organization classification of tumors of endocrine organs, CASTLE is considered to be an independent clinicopathological entity of thyroid tumors. CASTLE patients in the literature have heterogeneous features and their characteristics are summarized in Table 1.

CASTLE affects both sexes similarly, most commonly during the fourth to fifth decades of life (25–79 years old). The majority of patients present with neck masses (48.78–88%) and hoarseness (11–15.85%) secondary to RLN involvement. It has a higher tendency to be found in the lower pole of the thyroid (73–92%) [2]. Lymph node involvement is common, occurring in up to 37.4–60% of patients, and is probably related to its non-specific features and late presentation. Trachea and esophagus involvement are rarely reported in the literature [6,7].

Pre-operative diagnosis of CASTLE is generally difficult, not only due to its non-specific clinical features, but also due to the lack of characteristic radiological features. Ultrasound features reported by Yamamoto et al. include heterogeneously solid tumors without cystic components or calcification, and the central part of the tumor was reported to be slightly hyperechoic compared with the peripheral part of the tumor [8]. On non-contrast CT scans, the tumors are ill-defined and nodular, with uniform density. They share similar attenuation to adjacent muscles without calcification. Cystic changes of the tumor are rare. On contrast CT scans, the tumors generally show mild heterogeneous enhancement only [9]. MRI scan are advocated in cases of uncertain FNAC [10]. T1-weighted images display homogeneous isointensity, while T2-weighted images show hyperintensity. Wu et al. suggested that MRI is a more sensitive tool for distinguishing tumor from normal thyroid tissue and hence could guide clinicians through the relationship between tumor and thyroid tissues [9]. Very few reports in the literature have discussed the role of PETCT scan as a staging scan. Reports by Iyamu et al. and Jackson et al. showed that both primary tumor and metastatic lesions demonstrated hypermetabolic ^{18}F-FDG avid uptake. They suggested the potential role of PETCT scan in staging, prognosis, and monitoring response of CASTLE to adjuvant radiotherapy [11,12]. Fine-needle aspiration cytology can be used for diagnosis of CASTLE. Typically, cytology shows tight clusters and sheets of round tumor cells with high nucleus-to-cytoplasm ratios, vesicular nuclei, prominent nucleoli, and amphophilic cytoplasm, with lymphocytic background [13].

Surgery is the mainstay of treatment for CASTLE. More than half of patients present with regional lymphatic metastasis; hence, the majority of patients in the literature underwent total thyroidectomy with selective lymph node dissection as curative surgery [4–6,9,11,13–39]. Our patient had clinically detectable lymph node involvement on presentation; therefore, we directly proceeded with selective lymph node dissection without use of sentinel lymph node dissection in the hope of enhancing accurate staging and achieving tumor clearance. Complete resection was deemed crucial to the long-term survival and local recurrence rate. Outcome for surgical patients tended to be favorable, with loco-regional recurrence rate of 14% and 5- and 10-year cause-specific survival rates of 90% and 82%, respectively [33,40]. The role of radiotherapy in CASTLE is controversial due to lack of data in the literature. CASTLE is a type of radiosensitive tumor. Some studies demonstrated favorable outcome with use of adjuvant radiotherapy, with significant decrease in local and regional recurrence [33], and the effect is more profound in patients with positive or unknown nodal status. Many authors have suggested surgery alone would be sufficient without need for adjuvant radiotherapy or chemotherapy for patients with lymph node-negative disease due to the low recurrence risk [35]. Some studies

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Table 1. A summary of cases reported in the literature.

Reference	Patients	Sex (M: F)	Age (average)	Tumor	Lymph node +ve	Treatment	Recurrence	Follow up	Outcome
Cui XJ et al. 2017 [19]	7	1: 2.5	65.6	Intrathyroid: 6 Extrathyroid: 1	4	–	1	–	All alive
Marini A et al. 2016 [6]	1	M	76	Intrathyroid	0	Surgery	–	–	–
Liang J et al. 2015 [28]	6	–	–	–	–	Surgery: 1 Surgery+RT: 5	0	-	All alive
Wu B et al. 2016 [9]	10	1.5: 1	46.4	Intrathyroid: 7 Extrathyroid: 3	4	–	–	–	–
Liu SM et al. 2015 [29]	1	F	67	Extrathyroid	0	Surgery	0	12 months	Alive
Hanamura T et al. 2015 [23]	1	–	–	–	0	Chemotherapy alone	–	–	Alive
Iyamu I et al. 2015 [11]	1	M	30	Intrathyroid	1	Surgery+ chemotherapy+ RT	1	4 months	Die of disease
Noh JM et al. 2015 [33]	3	1: 2	62	Intrathyroidal: 3	0	Surgery+RT: 3	0	29 months (median),	All alive
Wang YF et al. 2015 [4]	10	1: 1.5	47.6	Intrathyroid: 10	2	Surgery: 5 Surgery+RT: 5	2	38 months (median)	All alive
Abeni C et al. 2014 [14]	1	M	26	Intrathyroid	1	Surgery, chemotherapy, radiotherapy	1	3 months	Alive
Zhang G et al. 2015 [39]	1	M	27	Extrathyroid	0	Surgery	1	36 months	Alive
Hsu HT et al. 2014 [24]	1	F	50	Intrathyroid	0	Surgery	–	–	–
Huang C et al. 2013 [25]	1	F	41	Intrathyroid	0	Surgery, RT	1	12 months	Alive
Liu Z et al. 2013 [31]	8	1.6: 1	56	Intrathyroid: 8	5	Surgery: 1 Surgery+RT: 7	0	12 months (median)	All alive
Geraci G et al. 2013 [22]	1	M	63	Intrathyroid	0	Surgery+RT	0	–	–
Kakudo K et al. 2013 [26]	15	1: 1.2	49.9	Intrathyroid: 15	6	Surgery+RT: 15	–	4 years (median)	Alive: 11 Dead: 4
Chang S et al. 2012 [13]	1	F	34	Intrathyroid	1	Surgery	0	27 months	Alive
Sun et al. 2011 [36]	7	1.3: 1	48	Intrathyroid: 7	1	Surgery: 1 Surgery+wRT: 6	2	34 months (median)	All alive
Liu X et al. 2011 [30]	8	1: 1	48.8	Intrathyroid: 8	–	Surgery: 8	2	4–55 months	Alive
Youens KE et al. 2011 [38]	1	F	52	–	–	–	–	–	–
Chan LP et al. 2008 [17]	1	M	54	Intrathyroid	0	Surgery	0	36 months	Alive

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Table 1 continued. A summary of cases reported in the literature.

Reference	Patients	Sex (M: F)	Age (average)	Tumor	Lymph node +ve	Treatment	Recurrence	Follow up	Outcome
Yamazaki M et al. 2008 [37]	1	M	62	Extrathyroid	0	Surgery	–	–	–
Rodrigues TA et al. 2008 [34]	1	M	52	Intrathyroid	0	Surgery+ chemotherapy+ RT	0	13 months	Alive
Chow SM et al. 2007 [18]	3	2: 1	51.3	Intrathyroid: 3	0	Surgery + chemotherapy + RT: 3	0	30 months (median)	All alive
Roka S et al. 2004 [35]	2	1: 1	39.5	Extrathyroid: 2	2	Surgery: 1 Surgery + radioiodine treatment: 1	2	63.5 months (mean)	All alive
Dorfman DM et al. 1998 [21]	5	1: 4	48.8	Intrathyroid: 5	2	Surgery: 5	2	164 months (median)	Alive: 4 Dead: 1
Ahuja AT et al. 1998 [15]	1	F	67	Extrathyroid	1	Surgery+RT	–	–	–
Mizukami Y et al. 1995 [32]	2	1: 1	65	Extrathyroid: 2	1	Surgery: 2	1	15 months (mean)	Alive: 1 Dead: 1
Chan JK et al. 1991 [5]	2	1: 1	56	Extrathyroid: 2	–	Surgery: 1 Surgery+RT: 1	1	111 months (mean)	Alive
Damiani S et al. 1991 [20]	1	M	47	Extrathyroid			–	17 months	Dead
Kakudo K et al. 1988 [27]	1	M	59	Extrathyroid		Surgery+RT	1	17 months	Dead
Asa SL et al. 1988 [16]	1	M	35	Extrathyrioid		Surgery	1	192 months	Dead
Miyauchi A et al. 1985 [1]	5	1: 4	48.8	Intrathyroid: 2 Extrathyroid: 3	3	Surgery+RT: 5	1	85 months (median)	All alive
	111	1: 1.08	50.8 (average)	Intrathyroid 83 (80.6%) Extrathyroid 20 (19.4%)	37.4%	–	26%	–	–

demonstrated that radiotherapy alone had a role in long-term control with shrinkage of the tumor; however, regrowth of the remaining viable tumor does occur [7]. The role of chemotherapy in CASTLE is unclear. Kakudo et al. reported minor response with a regimen consisting of doxorubicin, cyclophosphamide, and nimustine [26]. Roka et al. reported 2 patients with disease progression despite use of cisplatin and epirubicin as first line treatment followed by doxorubicin, irinotecan, and docetaxel as second-, third-, and fourth-line therapy [35]. Further clinical studies and investigations are required to establish the role of chemotherapy in CASTLE.

In general, CASTLE patients have a satisfactory prognosis. Recurrence rates of 14% to 21% have been quoted in the literature. Local invasion with trachea and esophagus involvement did not show significant a difference in overall prognosis [6,7]. Five- and ten-year cause-specific survival rates reached 90% and 82%, respectively in patient with curative surgery [33]. However, long-term observation and follow-up with reassessment imaging (e.g., regular ultrasound neck with interval CT scans every 1–2 years) was recommended as recurrence can occur up to 10 years of disease-free interval after treatment [7].

Conclusions

We reported the case of a patient with locally extensive CASTLE requiring tracheal reconstruction. CASTLE is an uncommon type

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of thyroid malignancy with non-specific clinical and radiological characteristics. Our literature review found that curative resection and selective neck dissection remain the mainstay of treatment, with generally good outcomes. Radiotherapy had a potential role in disease control, while role of chemotherapy is unclear. Long-term follow-up and surveillance are recommended.

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