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Potential Role of Adjuvant Radiation Therapy in Cervical Thymic Neoplasm Involving Thyroid Gland or Neck

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Purpose
The purpose of this study is to assess the clinicopathologic features, treatment outcomes, and role of adjuvant radiation therapy (RT) in cervical thymic neoplasm involving the thyroid gland or neck.

Materials and Methods
The medical and pathologic records of eight patients with cervical thymic neoplasm were reviewed retrospectively. All patients underwent surgical resection, including thyroidectomy or mass excision. Adjuvant RT was added in five patients with adverse clinicopathologic features. The radiation doses ranged from 54 Gy/27 fractions to 66 Gy/30 fractions delivered to the primary tumor bed and pathologically involved regional lymphatics using a 3-dimensional conformal technique.

Results
Eight cases of cervical thymic neoplasm included three patients with carcinoma showing thymus-like differentiation (CASTLE) and five with ectopic cervical thymoma. The histologic subtypes of ectopic cervical thymoma patients were World Health Organization (WHO) type B3 thymoma in one, WHO type B1 thymoma in two, WHO type AB thymoma in one, and metaplastic thymoma in one, respectively. The median age was 57 years (range, 40 to 76 years). Five patients received adjuvant RT: three with CASTLE; one with WHO type B3; and one with WHO type AB with local invasiveness. After a median follow-up period of 49 months (range, 11 to 203 months), no recurrence had been observed, regardless of adjuvant RT.

Conclusion
Adjuvant RT after surgical resection might be worthwhile in patients with CASTLE and ectopic cervical thymoma with WHO type B2-C and/or extraparenchymal extension, as similarly indicated for primary thymic epithelial tumors. A longer follow-up period may be needed in order to validate this strategy.

Key words
Thyroid neoplasms, Carcinoma, Thymus-like differentiation, Neck, Radiotherapy

Introduction

Thymic epithelial tumor is a rare neoplasm arising from the thymic gland, which is derived from the branchial pouches. During the migration of the thymic primordia to the anterior mediastinum, aberrant migration or remnants could occur along the descending passage [1]. Ectopic cervical thymoma, originating from the aberrant thymic tissue, is an extremely rare tumor, which is sometimes misdiagnosed as thyroiditis, anaplastic carcinoma, or malignant lymphoma of the thyroid [2-4]. Carcinoma showing thymus-like differentiation (CASTLE), which is also a rare tumor involving the thyroid gland, was first reported by Miyauchi et al. [5]. According to the classification by Chan and Rosai [6], CASTLE belongs to the class of tumors that develop in the soft tissue of the neck and thyroid gland, along with ectopic hamartous thymoma, ectopic cervical

thymoma, and spindle epithelial tumors with thymic-like differentiation. CASTLE is histologically similar to squamous cell carcinoma (SCC), however, the biological behavior and prognosis of CASTLE is more favorable than that of primary SCC of the thyroid or metastatic SCC from other organs [7-9]. According to the World Health Organization (WHO) classification, both ectopic cervical thymoma and thyroid CASTLE are independent clinicopathologic entities [10].

Most of these tumors have been documented only by case reports, thus, the optimal management strategy is still unclear [4,11]. A few studies have reported on treatment outcomes of CASTLE [9,11], while there have been no reports on ectopic cervical thymoma [4]. Surgical resection seems to be the treatment of choice, and a certain portion of patients receive adjuvant radiation therapy (RT). Patients with neck lymph nodes or extrathyroidal extension might be candidates for adjuvant RT [12,13]; however, the definite indication of adjuvant RT has not been clearly determined.

In this study, we retrospectively reviewed the clinicopathologic features and treatment outcomes of cervical thymic neoplasm involving the thyroid gland or neck at a single institution, and the optimal treatment strategy including the indication of adjuvant RT was discussed.

Materials and Methods

We searched the pathological reports of patients who underwent surgical resection for thyroid or infrathyroid neck mass using the following terms: "thymoma," "thymus," or "thymic." Eight patients were found to have ectopic cervical thymoma or CASTLE between October 1994 and February 2013 at Samsung Medical Center. After approval by the Institutional Review Board (2013-07-023), the medical, pathologic, and RT records were reviewed retrospectively. All patients underwent surgical resection including total thyroidectomy (n=3), mass excision (n=3), subtotal thyroidectomy (n=1), and hemithyroidectomy (n=1). To confirm the diagnoses, all pathologic slides were reviewed by three experienced pathologists (S.Y.H., Y.L.O., and J.H.). After surgical resection, microscopic involvement of the resection margin was found in one patient.

The decision to apply adjuvant RT was based on the institutional practice policy for primary thymic epithelial tumor, as previously reported [14]. Consequently, five patients with extraparenchymal extension received adjuvant RT. The primary tumor bed and pathologically involved regional lymphatics were included in the RT target volume. Three-dimensional conformal RT with 4-15 MV photon beams was used in four patients: 54 Gy in 27 fractions in three patients with negative resection margins, and 60 Gy in 30 fractions in one patient with a positive margin (Fig. 1A). Another patient who had CASTLE with metastatic regional lymph nodes received helical tomotherapy at a dose of 66 Gy in 30 fractions (Fig. 1B).

Results

The clinicopathologic characteristics of eight patients are summarized in Table 1. There were two men and six women, with a median age of 57 years (range, 40 to 76 years). According to the WHO classification [15], type B1 (Fig. 2A), AB, B3 (Fig. 2B), and metaplastic thymoma were found in two, one, one, and one patient, respectively. One patient with WHO type B1 thymoma and a patient with metaplastic thymoma have previously been reported [2,16]. There were three patients with CASTLE (Fig. 2C). On immunohistochemistry, two cases with CASTLE were positive for CD5, a marker for carcinoma of thymic origin (Fig. 2D) [8,9,17]. The remaining case of CASTLE without immunoreactivity to CD5 was positive for cytokeratin and negative for thyroid transcription factor 1. The case of WHO type B3 thymoma did not show immunoreactivity to CD5.

The median follow-up period, calculated from the date of surgical resection, was 49 months (range, 11 to 203 months). During the follow-up period, no tumor recurrence was observed in five patients who received adjuvant RT. There also was no tumor recurrence among the three patients who had WHO type B1 or metaplastic thymoma confined to the capsule and who did not receive adjuvant RT.

Discussion

More than 50 cases of CASTLE have been reported in the literature worldwide [11]; of these, four cases have been reported from Korea [18]. Most previous publications are case reports regarding the diagnostic cytopathology [18,19], except for two studies from Japan and China, which reported treatment outcomes [9,11]. In the study by Ito et al. [9], among 22 patients with CASTLE, ten patients received adjuvant RT, and nine had extrathyroidal extension. No locoregional recurrence occurred in the patients who received RT, while three locoregional recurrences occurred in those who did not receive RT. The absence of nodal metastasis and tumor extension were suggested as indicators of favorable prognosis. In the study by Sun et al. [11], six of

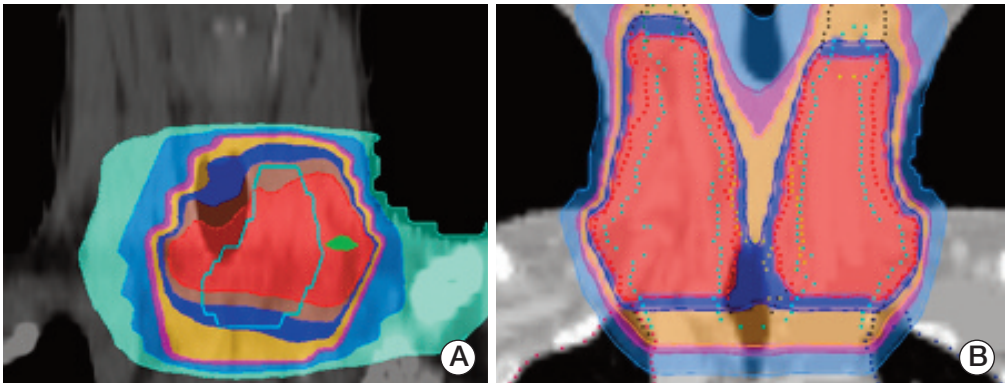

Fig. 1. Representative dose distributions of three-dimensional conformal radiotherapy (A) and helical tomotherapy (B). The areas filled with red, brown, blue, yellow, pink, and light blue refer to 100%, 97%, 95%, 85%, 75%, and 50% of the prescribed dose, respectively. The clinical target volumes are delineated in sky blue.

Table 1. Clinicopathologic characteristics of eight patients with cervical thymic neoplasm involving the thyroid gland or neck

No.	Age (yr)	Gender	Location	Pathologic diagnosis	EPE	Adjuvant radiotherapy	Follow-up (mo)
1[a]	69	F	Left lower lobe of thyroid	B1	No	No	203
2	66	F	Left lobe of thyroid	B1	No	No	116
3	40	M	Left infrathyroid area	AB	Yes	Yes	59
4[b]	43	F	Anterior neck below thyroid	Metaplastic thymoma	No	No	52
5	76	M	Right lobe of thyroid	CASTLE	Yes	Yes	41
6	44	F	Left infrathyroid area	B3	Yes	Yes	47
7	54	F	Left lobe of thyroid	CASTLE	Yes	Yes	29
8	59	F	Left lobe of thyroid	CASTLE	Yes	Yes	11

EPE, extraparenchymal extension; F, female; M, male; CASTLE, carcinoma showing thymus-like differentiation. [a]Previously reported [2], [b]Previously reported [16].

seven patients received adjuvant RT; among these, there was one event of local recurrence after 22 months. Sun et al. [11] suggested that curative surgery followed by adjuvant RT should be considered for improvement of local control.

Ectopic cervical thymoma of the thyroid gland or infrathyroid neck has been reported less frequently than CASTLE [1,3,4,20]. The previous case reports mainly focused on the cytologic features, and the treatment outcomes and indication of adjuvant RT were not adequately addressed. The current study included three cases of CASTLE and five cases of ectopic cervical thymoma of the thyroid gland or infrathyroid neck. Five patients with either bad histologic features or local invasiveness received adjuvant RT following surgery. The remaining three patients with WHO type B1 thymoma or metaplastic thymoma confined to the capsule did not receive adjuvant RT. The fact that no recurrence was observed regardless of application of adjuvant RT might suggest that there is a role for RT in patients with adverse clinicopathologic features. Notably, there was one case of WHO type B3 thymoma, which has been reported only once in ectopic cervical thymic tissue [4].

In the absence of established guidelines, the decision to apply adjuvant RT should be based on the clinical practice guideline for primary thymic epithelial tumor. Masaoka stage II refers to transcapsular or surrounding fatty tissue invasion [21], which corresponds to extraparenchymal extension of ectopic cervical thymoma or CASTLE. In patients with WHO type B2-C and stage II thymoma, adjuvant RT is usually indicated for improvement of local control [14,22,23]. As seen in the previous reports and the current study, application of these indications seems feasible in terms of local control in patients with CASTLE or ectopic cervical

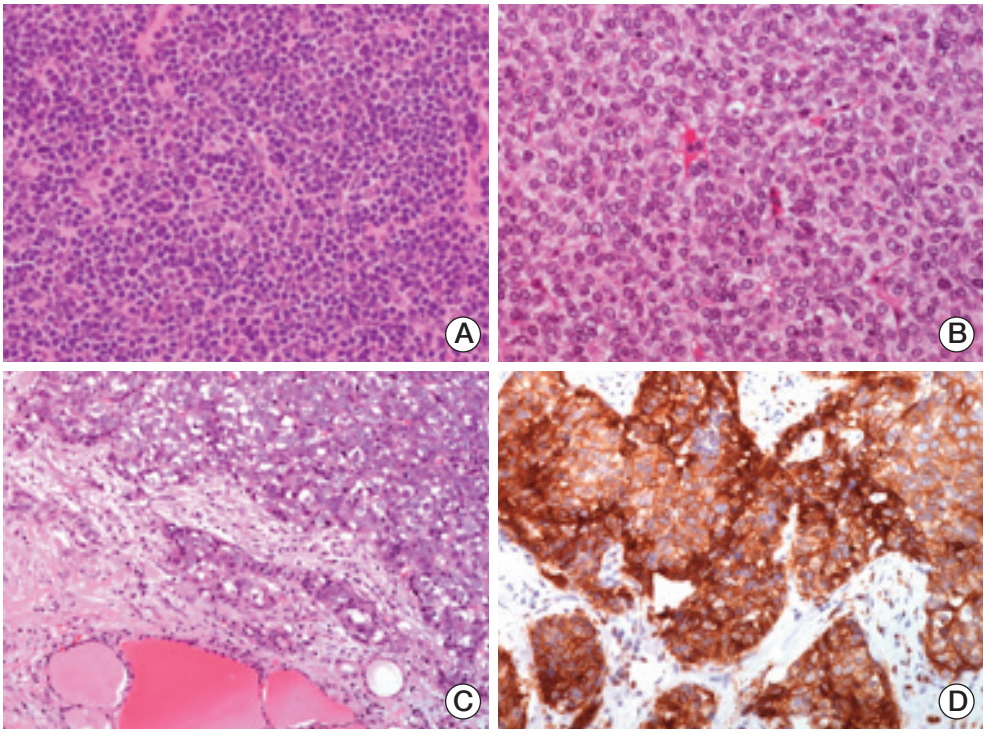

Fig. 2. Representative photographs of cervical thymoma World Health Organization (WHO) type B1 (A), WHO type B3 (B), and carcinoma showing thymus-like differentiation (CASTLE) (C, D). (A) Cervical thymoma WHO type B1 is predominantly composed of immature lymphocytes, resembling the normal thymic cortex. (B) Cervical thymoma WHO type B3 is predominantly composed of medium-sized round or polygonal epithelial cells with mild atypia. (C) CASTLE is located in the thyroid gland and tumor cell nests are surrounded by fibrous stroma. Tumor cells show vesicular nuclei and prominent nucleoli (A-C, H&E staining, ×200). (D) CD5 is diffusely positive in tumor cells of CASTLE (×200).

thymoma [9,11]. Although this was a retrospective study with a small number of patients, application of this strategy resulted in excellent treatment outcomes.

For selection of an appropriate treatment modality, accurate pathologic diagnosis is crucial in patients with CASTLE or ectopic cervical thymoma, which should be distinguished from other differential diagnoses, such as malignant lymphoma, anaplastic carcinoma, or primary or metastatic SCC of the thyroid gland, because the biological behavior and prognosis are quite different [2-4,7-9]. Immunoreactivity to CD5 is a distinctive feature of CASTLE, with 82% and 100% sensitivity and specificity, respectively [9]. In the current study, two of three cases of CASTLE also showed positive immunohistochemical staining to CD5. In addition, high molecular weight keratin and p63 can be helpful in differential diagnosis of CASTLE from other thyroid malignancies [8]. Negativity to the markers of thyroid-derived tumor, such as thyroglobulin, thyroid transcription factor-1, and calcitonin could be diagnostic clues [11].

Conclusion

In conclusion, adjuvant RT after surgical resection should be considered in patients with cervical thymic tumors involving the thyroid gland or neck, as similarly indicated for primary thymic epithelial tumors. Longer follow-up duration may be necessary in order to validate this strategy, and decisions regarding the treatment strategy should be preceded by the exact pathologic diagnosis.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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