Dear Editor,

Thymoma is the most common type of thymic tumors, whereas thymic carcinomas are very rare tumors with poor prognosis and an incidence of 0.05% and were first reported by Shimosato et al. [1] in 1977. Surgery is the mainstay of therapy in resectable cases. Multimodal approach plays a crucial role in partially resectable or non-resectable cases. However, due to the rare nature of these tumors, there have been no extensive studies on pre- and post-operative chemoradiotherapy and dose selection for chemotherapy regimens and radiotherapy. Here, we describe the case of a patient with partially resectable locally advanced thymic carcinoma in whom 40% reduction was achieved after concurrent chemoradiotherapy.

A 35-year-old male patient presented to the clinic with chest pain that had persisted for 1 month. Posteroanterior chest radiography result revealed a mass in the middle mediastinum. Pre-operative magnetic resonance imaging (MRI) results revealed the soft-tissue density mass lesion, with a few millimetric calcification foci (approximately 84×75 mm), adjacent to the left upper lobe paramediastinal area in the anterior mediastinum (Fig. 1). Partial resection of the mediastinal mass was performed with the left thoracotomy. On gross pathological examination, the tumor was a 3 cm diameter, non-encapsulated solid mass lacking broad fibrous septae on the cut surface. Surgical margin was positive because of incomplete resection due to proximity to the big vessels. Microscopically, the tumor was composed of sheets of cohesive non-keratinizing squamous cells displaying invasion to the lungs. Immunohistochemical studies support the diagnosis of thymic carcinoma with positive CD5, CD117, CK5/6, and P63 staining. Positive CD5 and CD117 indicate a thymic origin. Negative TTF-1, CK7, and CK20 ruled out metastasis. No lymphovascular or perineural invasion was observed (Fig. 2a-d). The Masaoka stage was identified as IVa. There was no evidence to indicate myasthenia gravis. Following partial resection, chemoradiotherapy was administered. Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² on days 1-5 and 29-33; and radiotherapy at a total dose of 59.4 Gy at 1.8 Gy/fraction helical tomotherapy for 33 days were planned. When the mass shrank at 39.6 Gy, adaptive planning was applied, and the radiotherapy doses administered to the lung and heart were reduced. Chest
surgery following induction chemotherapy followed by radiotherapy, the neoadjuvant chemotherapy setting for eight patients consisted of cisplatin (75 mg/m^2 on day 1), epirubicin hydrochloride (100 mg/m^2 on day 1), and etoposide (120 mg/m^2 on days 1, 3, and 5) repeated 3 times every 3 weeks; the induction chemotherapy regimen for the remaining patients consisted of cisplatin (50 mg/m^2), adriblastin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) repeated 3 times every 3 weeks. A dose of 40 Gy was usually administered to patients undergoing complete resection and 50-60 Gy to those undergoing partial resection; the mediastinum or residual tumor areas were irradiated in 3-5 weeks with five fractions per week.[2] In a majority of reported cases, cisplatin is a key agent for chemotherapy against thymic tumors and was included in all of the reported regimens.

MRI performed 2 months after the chemoradiotherapy revealed that the mass had shrunk by 40% (Fig. 3). The patient is stable at the 6th year follow-up.

Thymic carcinoma is a rare aggressive neoplasm. It is usually diagnosed at the advanced stage of III or IV according to the Masaoka staging system. Although complete surgical resection is the main treatment modality, it is not always feasible due to invasion of the neighboring vessels, lung tissues, pericardium, and pleura. Alternatively, several treatment modalities, such as surgery following induction chemotherapy and surgery following chemoradiotherapy, are available. There is no standard treatment due to the uncommon nature of the disease. Some studies have shed light on the use of induction chemotherapy regimen.[2-4] In a study that reported an overall survival rate of 78% with surgery following induction chemotherapy followed by radiotherapy, the neoadjuvant chemotherapy setting for eight patients consisted of cisplatin (75 mg/m^2 on day 1), epirubicin hydrochloride (100 mg/m^2 on day 1), and etoposide (120 mg/m^2 on days 1, 3, and 5) repeated 3 times every 3 weeks; the induction chemotherapy regimen for the remaining patients consisted of cisplatin (50 mg/m^2), adriblastin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) repeated 3 times every 3 weeks. A dose of 40 Gy was usually administered to patients undergoing complete resection and 50-60 Gy to those undergoing partial resection; the mediastinum or residual tumor areas were irradiated in 3-5 weeks with five fractions per week.[2] In a majority of reported cases, cisplatin is a key agent for chemotherapy against thymic tumors and was included in all of the reported regimens.
Adriamycin/cisplatin/vincristine/cyclophosphamide or
cisplatin/etoposide,[3] cisplatin/epirubicin/etoposide
or cisplatin/adriamycin/cyclophosphamide, and adri-
amycin/cisplatin/cyclophosphamide/prednisone.[4]

Theoretically, induction chemotherapy with concurrent
radiotherapy seems to be ideal for these cases similar to
that for other malignancies; however, limited prospec-
tive or retrospective studies and case reports are avail-
able. Therefore, we selected cisplatin 50 mg/m² on days
1, 8, 29, and 36 and etoposide 50 mg/m² on days 1-5 and
29-33 with concurrent radiotherapy for induction treat-
ment, although the supporting evidence is currently
limited. In our case, as only partial resection was pos-
sible due to vascular invasion, concurrent chemoradio-
therapy was actually planned for induction purposes.
Therefore, the initial planned dose of radiotherapy was
59 Gy. We reassessed the possibility of surgery with
chest MRI at 50.4 Gy (day 28 of radiotherapy). Since it
was considered unrectactable based on the decision of
the chest surgery clinic, we completed radiotherapy at
a dose of 59 Gy concurrently with chemotherapy. Thus,
we demonstrated the efficacy of chemoradiotherapy
with the use of cisplatin and etoposide in our case.

Paclitaxel is another preferred induction chemo-
therapy agent. It is a new agent that induces excessive
polymerization of tubulin and has demonstrated clin-
ical activity in a wide variety of malignancies, includ-
ing ovarian, breast, head-and-neck, and lung cancers.
Morio et al.[5] reported a case of Stage IVb thymic
carcinoma with lymph node metastasis and achieved
complete resection after induction therapy with weekly
paclitaxel plus cisplatin and concurrent radiotherapy
(total dose 40 Gy). Another case of advanced thymic
carcinoma treated with induction docetaxel, which is
also a new agent classified as a taxan-like paclitaxel,
plus cisplatin, and concurrent radiotherapy (total dose
40 Gy) also achieved complete resection.[6]

Although systemic workups did not detect any dis-
tant metastases, the patient was diagnosed as Stage IVb
according to the Masaoka staging system[7] because
of mediastinal lymph node metastasis. Two cycles of
chemotherapy consisting of paclitaxel (180 mg/m², 3 h)
and cisplatin (80 mg/m², 1 h) on day 1 were adminis-
tered every 3 weeks.

Anthracycline-based regimens are the current stan-
dard of care for thymic carcinomas according to the
results of various Phase II clinical trials, but they have
not been tested in a Phase III study. Fornasiero et al.[8]
reported their 13 years of experience in treating 37 pa-
tients with Stages III and IV thymic carcinoma with cis-
platin, doxorubicin, vincristine, and cyclophosphamide
combination. The ORR was 91.8%; with 43% achieving
CR, but the median survival time was only 15 months.
Loehrer et al.[9] reported a 50% ORR with 10% of pa-
tients achieving CR and a median survival patient with
thymic carcinoma with metastatic or locally progressive
 recurrent disease were treated with paclitaxel. There is
another Phase II study using a multidisciplinary ap-
proach with induction chemotherapy followed by sur-
gical resection, radiation therapy, and consolidation
chemotherapy for unresectable thymoma. In this Phase
II study; 22 patients received induction chemotherapy
with PAC plus prednisone for three cycles. The authors
reported that induction chemotherapy resulted in a 14% CR and a 63% PR rate. However, anthracyclines are
known to be associated with cardiomyopathy, especially
when combined with radiotherapy. Therefore, non-an-
thracycline regimens may be preferable for patients
treated with chemoradiotherapy.[4]

The European Organization for Research and Treat-
ment of Cancer conducted a study in which 16 patients
with advanced or recurrent thymoma were treated
with cisplatin and etoposide. In this trial, five patients
achieved CR and four achieved PR (ORR, 56%).[10] On
the basis of a single agent activity of ifosfamide in
thymoma, 20 patients with advanced thymoma and
eight patients with thymic carcinoma were treated with
etoposide, ifosfamide, and cisplatin in an intergroup
trial conducted by ECOG. An ORR of 35% and 25%
was reported in patients with thymoma and thymic
carcinoma, respectively.[11] Grassin et al.[12] reported
similar poor results (PR, 25%) in a study of 16 patients
treated with etoposide, ifosfamide, and cisplatin. Th-
ese cisplatin plus etoposide-based regimens produced
apparently inferior response rates to those previously
reported for anthracycline-based regimens.[13] As anthracycline-based chemotherapy can cause cardiac toxicities and cardiomyopathy, etoposide plus cisplatin is a potential alternative if radiotherapy is also to be administered. Furthermore, etoposide plus cisplatin combined with radiotherapy is the standard treatment for patients with localized advanced non-small-cell lung cancer[14,15] and local small-cell lung cancer[16] and has generally been well-tolerated by such patients.

In summary, combined cisplatin plus etoposide for thymic carcinoma is effective and reasonably well-tolerated, particularly with concurrent radiotherapy. Despite the limited evidence to support the use of cisplatin plus etoposide as a treatment for advanced thymic carcinoma, it is an alternative chemotherapy when anthracycline-based regimens cannot be used. Given the rarity of this tumor, prospective randomized trials are unlikely. Cumulative data, however, suggest that anthracycline-based regimens should remain the standard of care for these patients. However, for patients who can be treated with concurrent radiotherapy, etoposide plus cisplatin is a potential chemotherapy regimen for this malignancy.

References