Original Article

The role of postoperative radiotherapy for stage I/II/III thymic tumor—results of the ChART retrospective database

Qianwen Liu[1*], Zhitao Gu[2*], Fu Yang[3], Jianhua Fu[1], Yi Shen[4], Yucheng Wei[4], Lijie Tan[5], Peng Zhang[6], Yongtao Han[7], Chun Chen[8], Renquan Zhang[9], Yin Li[10], Keneng Chen[11], Hezhong Chen[12], Yongyu Liu[13], Youbing Cui[14], Yun Wang[15], Liewen Pang[16], Zhentao Yu[17], Xinming Zhou[18], Yangchun Liu[19], Jin Xiang[20], Yuan Liu[2], Wentao Fang[2]; Members of the Chinese Alliance for Research in Thymomas[a]

[1]Department of Thoracic Surgery, Guangdong Esophageal Cancer Institute, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, China; [2]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [3]Department of Thoracic Surgery, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai 200080, China; [4]Department of Thoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao 266001, China; [5]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China; [6]Department of Endocrinology, Tianjin Medical University General Hospital, Tianjin 300052, China; [7]Department of Thoracic Surgery, Sichuan Cancer Hospital, Chengdu 610041, China; [8]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou 350001, China; [9]Department of Thoracic Surgery, First Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [10]Department of Thoracic Surgery, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450008, China; [11]Department of Thoracic Surgery, Beijing Cancer Hospital, Beijing 100142, China; [12]Department of Cardiothoracic Surgery, Changhai Hospital, Shanghai 200433, China; [13]Department of Thoracic Surgery, Liaoning Cancer Hospital, Shenyang 110042, China; [14]Department of Thoracic Surgery, First Affiliated Hospital of Jilin University, Changchun 130021, China; [15]Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu 610041, China; [16]Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai 200032, China; [17]Department of Esophageal Cancer, Tianjin Cancer Hospital, Tianjin 300060, China; [18]Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, China; [19]Department of Thoracic Surgery, Jiangxi People's Hospital, Nanchang 330006, China; [20]Department of Pathology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, China

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*These authors contributed equally to this work.

Correspondence to: Jianhua Fu. Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, 561 Dongfeng Road East, Guangzhou, Guangdong 510060, China. Email: fujh@sysucc.org.cn; Wentao Fang. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 Huaihai Road West, Shanghai 200030, China. Email: vwtfang12@shchest.org.

Background: Postoperative radiotherapy (PORT) for thymic tumor is still controversial. The object of the study is to evaluate the role of PORT for stage I to III thymic tumors.

Methods: The Chinese Alliance for Research in Thymomas (ChART) was searched for patients with stage I to III thymic tumors who underwent surgical resection without neoajuvant therapy between 1994 and 2012. Univariate and multivariate survival analyses were performed. Cox proportional hazard model was used to determine the hazard ratio for death.

Result: From the ChART database, 1,546 stage I to III patients were identified. Among these patients, 649 (41.98%) received PORT. PORT was associated with gender, histological type (World Health Organization, WHO), thymectomy extent, resection status, Masaoka-Koga stage and adjuvant chemotherapy. The 5-year and 10-year overall survival (OS) rates and disease-free survival (DFS) rates for patients underwent surgery followed by PORT were 90% and 80%, 81% and 63%, comparing with 96% and 95%, 92% and 90% for patients underwent surgery alone (P=0.001, P<0.001) respectively. In univariate analysis, age, histological type (WHO), Masaoka-Koga stage, completeness of resection, and PORT were associated with OS. Multivariable analysis showed that histological type (WHO) (P=0.001),

Masaoka-Koga stage (P=0.029) and completeness of resection (P=0.003) were independently prognostic factors of OS. In univariate analysis, gender, myasthenia gravis, histological subtype, Masaoka-Koga stage, surgical approach, PORT and completeness of resection were associated with DFS. Multivariate analysis showed that histological subtype (P<0.001), Masaoka-Koga stage (P=0.005) and completeness of resection (P=0.006) were independent prognostic factors for DFS. Subgroup analysis showed that patients with incomplete resection underwent PORT achieved better OS and DFS (P=0.010, 0.017, respectively). However, patients with complete resection underwent PORT had the worse OS and DFS (P<0.001, P<0.001, respectively).

Conclusions: The current retrospective study indicates that PORT after incomplete resection could improve OS and DFS for patients with stage I to III thymic tumors. However for those after complete resection, PORT does not seem to have any survival benefit on the whole.

Keywords: Thymic tumor; postoperative radiotherapy (PORT); overall survival (OS)

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Introduction

Thymic tumors, including thymoma and thymic carcinoma, are the most common primary malignancies located in anterior mediastinum. They are relatively rare and usually grow indolently. The incidence of thymic tumors in the USA is 0.13 per 100,000 person-years according to the Surveillance, Epidemiology, and End Results (SEER) database (1). More than 30% of thymic tumors may be accompanied with myasthenia gravis (2). Surgical resection is the most important treatment for thymic tumors. Complete resection of the entire tumor has consistently been found to be an independent prognostic factor (3-6). The International Thymic Malignancy Interest Group (ITMIG) recommended that en bloc resection of the entire thymus gland and surrounding areolar tissue for complete resection (7). Local recurrence is the major failure pattern after surgery (3,5,8,9). The recurrence rate was lower for patients received complete resection than those received incomplete resection, resulted in a better survival in the former group (10). Chemotherapy has been used commonly, especially at the induction setting. Preoperative chemotherapy has been reported to increased R0 resection rate (7). Postoperative chemotherapy is not recommended for thymoma after complete resection. Chemotherapy is adopted in inoperable or gross residual disease after local treatment (11,12). Postoperative radiotherapy (PORT) is usually administrated in Masaoka-Koga stage IV thymoma for the purpose of local control (5,8,13). Indications of PORT for complete resected Masaoka-Koga stage I to III thymic tumors are controversial, although it has been used frequently in clinical practice. Most authors suggested that complete resection alone be adequate for Masaoka-Koga stage I to III thymic tumors, although some studies indicated potential survival benefits from PORT (4,5,9,14-21). Most of the knowledge on thymic tumors comes from retrospective, single-institutional studies. No randomized prospective trial has ever been conducted to date to evaluate the effect of PORT on thymic malignancies. The Chinese Alliance for Research in Thymomas (ChART) was founded in 2012, with the purpose of improving treatment for thymic tumors through collaborative studies. A retrospective database was established, gathering data from 18 tertiary referral centers in China. Our objective was to investigate the role of PORT in patients who underwent surgery for stage I to III thymic epithelial tumors using the ChART registry.

Materials and methods

Records of surgical patients between 1994 and 2012 in ChART database were retrospectively reviewed. Patients were included in the analysis if there was complete information on tumor stage, surgery and radiation therapy. Patients who received neoadjuvant treatment, who had history of other malignance, and who underwent a biopsy alone were excluded. All cases were restaged according to Masaoka-Koga staging system (22). Histological subtypes were classified according to World Health Organization (WHO) criteria published in 2004 (23).

Statistical analysis was performed with SPSS statistical software package version 19.0 (SPSS Inc, Chicago, IL).

Continuous data variables were analyzed using Student's *t*-test. Nominal data were analyzed using crosstabs and Pearson's chi-square test. Kaplan-Meier survival curves were constructed and compared using the log-rank test. Multivariate analysis was performed according to the Cox proportional hazard model. Significance was set at a probability value less than 0.05. Because only de-identified data were used for the study, informed consent was waived by IRB.

Results

We From the ChART database 2,159 patients with Masaoka-Koga stage I to III thymic epithelial tumors were identified. Among them, 1,546 patients with complete data on staging, radiation therapy, and surgery made the final study cohort. There were 717 patients classified as Masaoka-Koga stage I, 318 patients as stage II, and 511 patients as stage III. Patients' baseline characteristics were presented in *Table 1*. These included 649 patients (41.98%) who received PORT and 897 patients (58.02%) who received surgery alone. Significant differences were found in gender, WHO histological subtype, tumor size, thymectomy extent, complete resection, Masaoka-Koga stage and adjuvant chemotherapy between the two groups of patients.

The 5-year and 10-year overall survival (OS) rates and disease-free survival (DFS) rates for patients having surgery followed by PORT were 90% and 80%, 81% and 63%, comparing with 96% and 95%, 92% and 90% for patients having surgery alone (P=0.001, P<0.001) respectively *(Figures 1,2)*. In univariate analysis, age, WHO histological subtype, Masaoka-Koga stage, completeness of resection, and PORT were associated with OS (*Table 2*). Multivariate analysis showed that WHO histological type (P=0.001), Masaoka-Koga stage (P=0.029) and completeness of resection (P=0.003) were independently prognostic factors for OS, while PORT was not (*Table 3*). In univariate analysis, gender, myasthenia gravis, WHO histological type, Masaoka-Koga stage, surgical approach, PORT and completeness of resection were associated with DFS (*Table 4*). Multivariate analysis again showed that only WHO histological type (P<0.001), Masaoka-Koga stage (P=0.005) and completeness of resection (P=0.006) were independently prognostic factors for DFS (*Table 5*). Subgroup analysis showed that patients with incomplete resection underwent PORT achieved better OS and DFS (P=0.010, 0.017, respectively) than those having surgery alone. However for patients with complete resection, PORT was associated with worse OS and DFS (P<0.001, P<0.001, respectively). And no survival difference was detected between patients with or without PORT in the majority of stage or histology categories, except in stage II disease where PORT was associated with a worse DFS (*Tables 6,7*).

Discussion

The role of PORT in thymic tumors remains controversial. Local recurrence is the most common pattern of failure in thymic tumors after surgery. It has been suggested that PORT may reduce the recurrence rate from about 30% to below 5% (24,25). Given the rarity of the thymic tumors, their indolent natural history, and the large number of patients died from unrelated causes, no prospective randomized study has ever investigated the true benefit of PORT.

In this large multicenter study, a total of 1,546 patients with Masaoka-Koga stage I to III thymic tumors were elected from the ChART database. Unfortunately, PORT was not found to be associated with improved OS. The 5- and 10-year OS rates for patients who underwent surgery followed by PORT were 90% and 80%, comparing with 96% and 95% for patients who underwent surgery alone (P=0.001), respectively. This may be attributed to the higher proportion of patients with thymic carcinoma, stage III disease, and palliative surgery in the PORT group. However, PORT was significantly associated with improved OS in patients having palliative surgery.

The available data suggested that Masaoka-Koga stage, completeness of resection and histological classification were the independent prognostic factors (3,4,8). No significant differences in survival were noted among subgroup of thymoma, which was consistent with the result of the meta-analysis conducted by Detterbeck *et al*. (3). We also demonstrated that complete resection alone was sufficient to achieve a satisfactory outcome in the thymoma, saving the patients from the potential side effects caused by mediastinal radiation. These would include radiation pneumonitis, chronic pulmonary fibrosis, hematopoietic malignancies, esophageal malignancies, restrictive cardiomyopathy and pericardial effusion (26-30). A retrospective study by Mangi *et al*. found that most patients with stage III disease could undergo complete resection, and the addition of radiation therapy for patients receiving complete resection did not reduce the recurrence rate (21). The use of adjuvant radiation after complete resection of stage III thymoma

Table 1 Patients' baseline characteristics

Characteristics	Surgery alone, N (%)	Port, N (%)	P value[a]
Gender			0.000
Male	425 (52.3)	387 (47.7)	
Female	472 (64.3)	262 (35.7)	
Age	51.69	50.53	0.075
Myasthenia gravis			0.161
Yes	231 (61.1)	147 (38.9)	
No	666 (57.0)	502 (43.0)	
WHO classification			0.000
A	83 (83.0)	17 (17.0)	
AB	318 (78.9)	85 (21.1)	
B1	159 (72.9)	59 (27.1)	
B2	135 (55.8)	107 (44.2)	
B3	114 (40.1)	170 (59.9)	
C	74 (28.0)	190 (72.0)	
NETT	14 (40.0)	21 (60.0)	
WHO classification (combined)			0.000
A+AB	401 (79.7)	102 (20.3)	
B1+B2+B3	408 (54.8)	336 (45.2)	
C+NETT	88 (29.4)	211 (70.6)	
Thymectomy extent			0.000
Partial	182 (47.6)	200 (52.4)	
Total	714 (61.5)	447 (38.5)	
Completeness of resection			0.000
R0	854 (61.1)	543 (38.9)	
R1	27 (43.5)	35 (56.5)	
R2	16 (18.4)	71 (81.6)	
Tumor size (cm)	6.58	7.04	0.008
Masaoka-Koga stage			0.000
I	535 (72.6)	182 (27.4)	
II	190 (59.7)	128 (40.3)	
III	172 (33.7)	339 (66.3)	
Adjuvant chemotherapy			0.000
No	854 (63.9)	482 (36.1)	
Yes	32 (18.2)	144 (81.8)	

[a], χ test. WHO, World Health Organization; NETT, neuroendocrine thymic tumor; PORT, postoperative radiotherapy.

needs to be re-addressed. For thymoma in WHO types A, AB, B1, as well as those classified as having Masaoka-Koga stage I and II disease, Utsumi *et al.* insisted that complete resection alone was sufficient treatment strategy (19). Furthermore, there was no significant difference in survival noted with regard to the status of PORT among the patients classified as stage III/IV, and WHO types B2/B3 (19). Kondo *et al.* reviewed 1,320 patients with stage II and III thymomas, and their finding revealed that local recurrence rates were not significantly decreased by PORT,

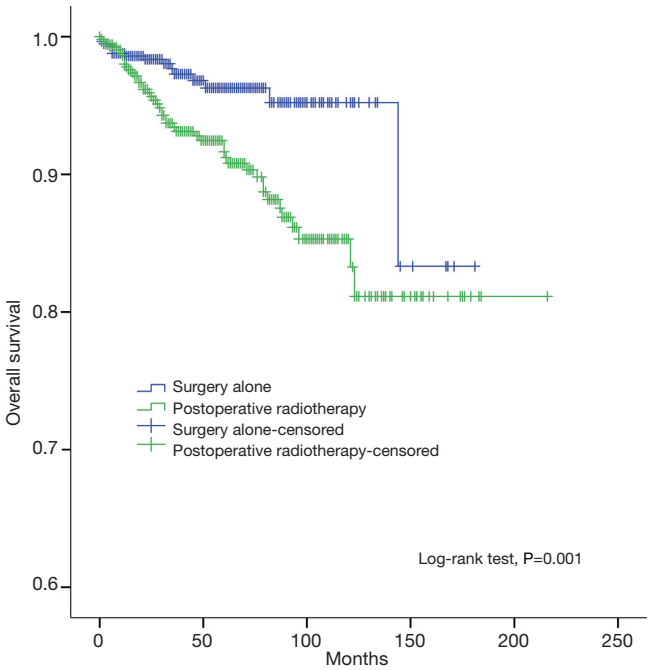

Figure 1 Kaplan-Meir overall survival curve of patients treated with surgery alone, and those treated with PORT. PORT decreased OS of stage I/II/III thymic epithelial tumor (P=0.001).

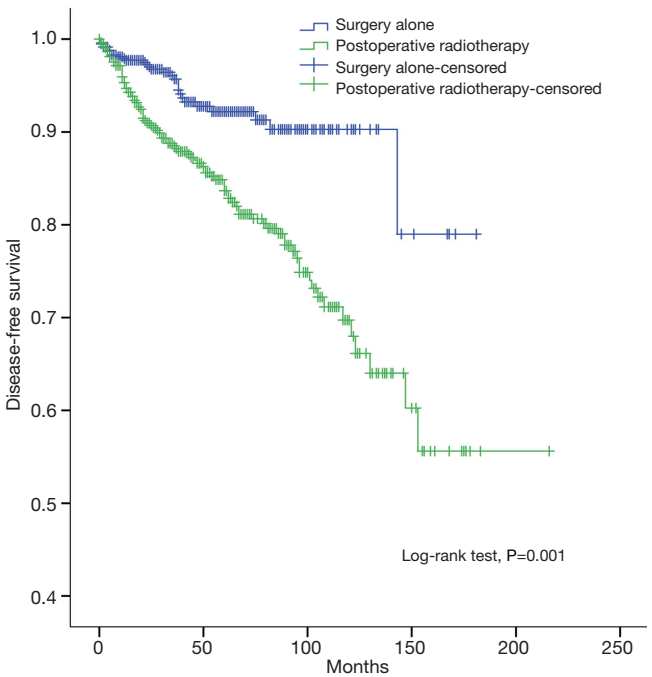

Figure 2 Kaplan-Meir disease-free survival curve of patients treated with surgery alone, and those treated with PORT. PORT decreased DFS of stage I/II/III thymic epithelial tumor (P<0.001).

Table 2 Univariate analysis of factors affecting overall survival

Characteristics	P value
Gender (MaleMale/FemaleFemale)	0.072
Age (≥50/<50)	0.050
Myasthenia gravis (Yes/No)	0.081
Tumor size (≤5 cm/>5 cm)	0.524
Histological type (WHO) (A or AB/B1 or B2 or B3/C)	0.000
Masaoka-Koga stage (I/II/III)	0.000
Surgical approach (VATS/Open)	0.107
Thymectomy extent (Partial/Total)	0.159
PORT (No/Yes)	0.001
Completeness of resection (R0/R1+R2)	0.000

WHO, World Health Organization; VATS, video-assisted thoracic surgery; PORT, postoperative radiotherapy.

Table 3 Multivariate analysis of factors affecting overall survival

Characteristics	P value	OR
Gender (Male/Female)	0.994	1.002
Age (<50/ ≥50)	0.165	1.518
Myasthenia gravis (No/Yes)	0.811	1.117
Histological type (WHO) (A or AB / B1 or B2 or B3/ C)	0.001	
B1+B2+B3	0.073	3.226
C	0.001	8.631
Masaoka-Koga stage (I/II/III)	0.029	
II	0.124	2.425
III	0.008	3.901
PORT	0.338	0.726
Completeness of resection (R0/R1+R2)	0.003	0.381

WHO, World Health Organization; PORT, postoperative radiotherapy.

and the prognosis of invasive thymoma were not improved by PORT (5). Complete resection was the most important factor in the treatment of thymic epithelial tumors. A meta-analysis by Korst *et al*. reviewed no statistically significant reduction in recurrence after adjuvant radiotherapy for patients with completely resected stage II or III thymic epithelial tumors (20). Weksler *et al*. reported a retrospective study using SEER database. This large population-based study demonstrated that adding PORT to surgery was associated with improved disease-specific survival. However, in multivariate analysis, postoperative

Table 4 Univariate analysis of factors affecting disease-free survival

Characteristics	P value
Gender (Male/Female)	0.008
Age (≥50/<50)	0.254
Myasthenia gravis (Yes/No)	0.002
Tumor size (≤5 cm/>5 cm)	0.094
Histological type (WHO) (A or AB/B1 or B2 or B3/C)	0.000
Masaoka-Koga stage (I/II/III)	0.000
Surgical approach (VATS/Open)	0.027
Thymectomy extent (Partial / Total)	0.629
PORT (No/Yes)	0.000
Completeness of resection (R0/R1+R2)	0.000

WHO, World Health Organization; VATS, video-assisted thoracic surgery; PORT, postoperative radiotherapy.

Table 5 Multivariate analysis of factors affecting disease-free survival

Characteristics	P value	OR
Gender (Male/Female)	0.675	0.914
Myasthenia gravis (No/Yes)	0.099	0.517
Histological type (WHO) (A or AB / B1or B2 or B3/ C)	0.000	
B1+B2+B3	0.001	4.909
C	0.000	10.194
Masaoka-Koga stage (I/II/III)	0.005	
II	0.014	2.549
III	0.001	3.056
Surgical approach (VATS/Open)	0.447	1.601
PORT (No/Yes)	0.971	0.991
Completeness of resection (R0/R1+R2)	0.006	0.513

WHO, World Health Organization; VATS, video-assisted thoracic surgery; PORT, postoperative radiotherapy.

Table 6 Stratified disease-free survival analysis of the role of PORT

Characteristics	Patients, N (%)	DFS		P value
		5-year	10-year	
R0	1,027			0.000
PORT	457 (44.50)	0.86	0.70	
Surgery alone	570 (55.50)	0.96	0.95	
R1+R2	99			0.017
PORT	78 (78.79)	0.60	0.39	
Surgery alone	21 (21.21)	0.35	0.35	
A+AB	365			0.646
PORT	89 (24.38)	0.99	0.90	
Surgery alone	276 (75.62)	0.98	0.98	
B1+B2+B3	549			0.053
PORT	285 (51.91)	0.89	0.66	
Surgery alone	264 (48.09)	0.93	0.90	
C+NETT	212			0.702
PORT	161 (75.94)	0.61	0.39	
Surgery alone	51 (24.06)	0.67	0.67	
Stage I	513			0.096
PORT	155 (30.21)	0.97	0.81	
Surgery alone	358 (69.79)	0.98	0.97	
Stage II	243			0.003
PORT	108 (44.44)	0.85	0.66	
Surgery alone	135 (55.56)	0.99	0.99	
Stage III	370			0.728
PORT	272 (73.51)	0.71	0.51	
Surgery alone	98 (26.49)	0.70	0.70	

PORT, postoperative radiotherapy; NETT, neuroendocrine thymic tumor; DFS, disease-free survival.

adjuvant radiation therapy was not significantly associated with improved overall survival (18). Based on the current results and existing literature, it seems that future studies on PORT for thymomas after resection should be focused on patients at high risk of developing local recurrence.

Thymic carcinoma consists the most aggressive subtype of thymic neoplasms,. Surgery provides the best chance of cure for resectable thymic carcinoma. Patients who received complete excision had a significantly better prognosis than those who did not received surgical therapy. Due to the rarity of this disease, lack of high level of evidences, the role of chemotherapy and radiation after surgery are not well established. Using SEER database, Weksler *et al*. studied 290 patients with thymic carcinoma. They found that PORT could not improve the overall survival for patients after complete resection, and complete resection was the preferred primary treatment for thymic carcinoma (31). We also found that PORT did not improve the prognosis for patients with thymic carcinoma in this study. However, Hsu *et al*. suggested that PORT seemed to improve the prognosis for patients with thymic carcinoma, although the difference was not statistically significant (32). Omasa *et al*. also reported that PORT did not increase RFS or OS for stage II or III thymoma but increased RFS for stage II

Table 7 Stratified overall survival analysis of the role of PORT

Characteristics	Patients, N (%)	OS		P value
		5-year	10-year	
R0	1023			0.000
PORT	454(44.38)	0.93	0.87	
Surgery alone	569(55.62)	0.98	0.98	
R1+R2	96			0.010
PORT	77(80.21)	0.75	0.51	
Surgery alone	19(19.79)	0.59	0.30	
A+AB	365			0.285
PORT	89(24.38)	0.99	0.90	
Surgery alone	276(75.62)	1.00	1.00	
B1+B2+B3	547			0.280
PORT	285(52.10)	0.92	0.91	
Surgery alone	262(47.90)	0.95	0.95	
C+NETT	207			0.930
PORT	157(75.85)	0.80	0.53	
Surgery alone	50(24.15)	0.85	0.76	
Stage I	511			0.067
PORT	153(29.94)	0.97	0.91	
Surgery alone	358(70.06)	0.99	0.99	
Stage II	243			0.537
PORT	108(44.44)	0.94	0.89	
Surgery alone	135(55.56)	0.98	0.98	
Stage III	365			0.717
PORT	270(73.97)	0.84	0.69	
Surgery alone	95(26.03)	0.85	0.79	

PORT, postoperative radiotherapy; NETT, neuroendocrine thymic tumor; OS, overall survival.

and III thymic carcinoma (33). Ahmad *et al*. reported that radiation therapy was associated with improved OS and longer RFS for patients with thymic carcinoma (34).

Radical resection, WHO histology classification, and Masaoka-Koga stage were revealed as t independent prognostic factors for thymic malignancy in the current study. Our results also showed that PORT could not bring any survival benefit to patients with completely resected stage I, II and III diseases. PORT should be administrated to the patients with palliative surgery, as it did improve the outcomes in these patients. However, because of the retrospective nature of this study and that the radiation field and dosage were highly varied, prospective randomized trials aiming at patients at high risk of developing recurrent disease should be conducted to evaluate the true effect of PORT in thymic epithelial tumors.

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Footnote

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