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Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II-III thymic epithelial tumors：the Japanese Association for Research on the Thymus Database Study

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Running title; PORT for thymic carcinoma and thymoma

Abbreviations;

Radiotherapy (RT)

The International Thymic Malignancy Interest Group (ITMIG)

Japanese Association for Research on the Thymus (JART)

Overall survival (OS)

Relapse free survival (RFS)

Confidence intervals (CI)

European Society of Thoracic Surgeons (ESTS)

Hazard ratio (HR)

Postoperative radiotherapy (PORT)

Precis

Postoperative radiotherapy increased RFS for stage II and III thymic carcinoma.

Postoperative radiotherapy did not increase RFS or OS for stage II and III thymoma.

CONFLICT OF INTEREST DISCLOSURE

None

FUNDING SUPPORT

None

Abstract

Background

The efficacy of postoperative radiotherapy (PORT) for thymic epithelial tumors is still controversial. This study aims to clarify the efficacy of PORT for Masaoka stage II and III thymic carcinoma and thymoma using the Japanese Association for Research on the Thymus (JART) database.

Methods

The JART database registered the records of 2,835 patients collected from 32 Japanese institutions from 1991 to 2010. Thymic carcinoma and thymoma at stage II or III were extracted. Efficacy of PORT on relapse-free survival (RFS) and overall survival (OS) was evaluated using the Kaplan-Meier method and the Cox regression analysis.

Results

A total of 1265 patients were consisted of 155 (12.3%) thymic carcinoma and 1,110 (87.7%) thymoma cases; 895 (70.8%) at stage II and 370 (29.2%) at stage III; 403 (31.9%) cases had PORT. PORT for stage II and III thymic carcinoma was associated with increasing RFS (hazard ratio, 0.48; 95% confidence interval, 0.30-0.78; P=0.003), but not with OS (hazard ratio, 0.94; 95% confidence interval, 0.51-1.75; P=0.536). PORT for stage II and III thymoma was not associated with RFS or OS (P=0.350).

Subgroup analysis for stage III thymoma showed no factor associated with the efficacy of PORT.

Conclusion

In this study, PORT did not increase RFS or OS for stage II and III thymoma, but increased RFS for stage II and III thymic carcinoma.

Key words; thymic carcinoma, thymoma, postoperative radiotherapy, Masaoka stage II, Masaoka stage III, relapse-free survival, adjuvant radiotherapy

INTRODUCTION

Thymic epithelial tumors are relatively rare neoplasms that originate from thymic epithelial cells[1]. They are chiefly divided into thymic carcinoma and thymoma, with the former accounting for 15–20% of thymic epithelial tumors[2]. Masaoka staging[3] and Masaoka–Koga staging[4] have been widely used for the classification of thymic epithelial tumors. An official uniform classification system, however, has not yet been established[5]. The mainstay treatment for thymic epithelial tumors remains surgical resection[6]. Radiotherapy (RT) has also been applied as a palliative or adjuvant therap[6] because of the radiosensitive nature of the tumors[7], but the efficacy of postoperative radiotherapy (PORT) for thymic epithelial tumors remains unclear. An optimal chemotherapy regimen has not yet been determined[8, 9].

The International Thymic Malignancy Interest Group (ITMIG) provided radiation therapy definitions and reporting guidelines for thymic malignancies, but did not comment on the guidelines for PORT[10], and thus the indication for PORT for thymic epithelial tumors is still left up to the individual judgments of respective institutes.

We undertook this database study to clarify the efficacy of PORT for Masaoka stage II or III thymic carcinoma and thymoma using the Japanese Association for Research on the Thymus (JART) database.

MATERIAL AND METHODS

Data Sources

The JART, established by Akira Masaoka and colleagues in 1982, is a nonprofit research organization that contributes to the development of research on thymic epithelial tumors. A nationwide project to create a database for surgically treated thymic epithelial tumors was conducted by the JART in 2012. The records of 2,835 patients collected from 32 leading Japanese institutions from January 1991 to December 2010 were registered in the JART database. The Masaoka staging system was applied to the classification of thymic epithelial tumors in this database. Institutional Review Board approval was obtained from each institution.

Patient Selection

Eligibility criteria were as follows: (1) histologically confirmed thymic carcinoma or thymoma; and (2) Masaoka stage II or III. Exclusion criteria consisted of: (1) thymic neuroendocrine tumor, (2) macroscopic gross residual tumor (>20% of tumor volume), and (3) lack of PORT information.

Patient clinical and demographic information (gender, age, associated myasthenia gravis (MG), resection completeness, tumor size, affected organs, WHO histological classification, postoperative chemotherapy, recurrence, and prognosis) was

extracted from the JART database.

Statistical analysis

Age and maximum tumor diameter were summarized using mean ± standard deviation and median (range), whereas the categorical variables were summarized using counts and percentages. For continuous variables, the Wilcoxon rank-sum test was used, and for categorical variables, the chi-square test or Fisher's exact test was applied as appropriate, to compare the patient backgrounds with or without the PORT. Relapse-free survival (RFS) and overall survival (OS) were calculated from the date of surgery. Time-to-event curves for RFS and OS were estimated by the Kaplan-Meier method, and differences in time-to-event curves with and without PORT were evaluated by the log-rank test. The hazard ratio (HR) and corresponding 95% confidence intervals (CIs) were calculated using the Cox proportional-hazards model controlling for Masaoka staging, histology, and completeness of surgery. All P-values were two-sided and P-values < 0.05 were considered as statistically significant. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

This study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (E1904). The study was also approved by each participated institutional review board.

RESULTS

Patient characteristics

The scheme of the study population of the 2,835 patients in the JART database is shown in Figure 1. A total of 1,265 patients with 574 males (45.4%) and a median age of 59 (range 18–86) years were analyzed. The diagnoses consisted of 155 (12.3%) thymic carcinoma and 1,110 (87.7%) thymoma cases; 895 (70.8%) of the cases were stage II, and 370 (29.2%) were stage III. Further, 403 (31.9%) cases had undergone PORT. The characteristics of these patients are reported in Tables 1a and 1b. The median follow-up period was 1,704 (range 0–7,741) days.

Overall results

The 5-year RFS proportions of the PORT group (n = 403) and the no PORT group (n = 862) for stage II/III were 78.0% and 83.5% respectively. Although PORT tended to show an adverse effect (P = 0.056*)* on RFS, the HR of PORT to no PORT by Cox regression analysis adjusted for covariates (histology, staging, and residual tumor)

showed no significant difference between the two groups (HR, 0.76; 95% CI, 0.58-1.01; P=0.116; Supplements 1, 2).

Relapse-free survival for stage II and stage III thymic carcinoma

The 5-year RFS proportions of the PORT group (n = 25) and the no PORT group (n=27) for stage II thymic carcinoma were 91.3% and 68.1% (Fig. 2a). For stage III thymic carcinoma, the 5-year RFS proportions of the PORT group (n=51) and the no adjuvant RT group (n=44) were 50.5% and 26.1% (Fig. 2b). The RFS HR of PORT for stage II and III thymic carcinoma as analyzed by Cox regression analysis adjusted for Masaoka stage and residual tumor was 0.48 (95% CI, 0.30–0.78; P=0.003; Table 2).

Relapse-free survival for stage II and stage III thymoma

The 5-year RFS proportions of the PORT group (n = 196) and the no PORT group (n=615) for stage II thymoma were 93.4% and 92.3% (Fig. 2c). The 5-year RFS proportions of the PORT group (n=119) and the no PORT group (n = 143) for stage III thymoma was 62.0% and 69.3% (Fig. 2d).

The RFS HR of PORT as analyzed by Cox regression analysis adjusted for Masaoka stage and residual tumor was 0.98 (95% CI, 0.70–1.37; P = 0.905; Table 2).

Subgroup analyses comparing PORT to no PORT for patients with stage III thymoma

No factors were associated with the efficacy of PORT for stage III thymoma cases in

the subgroup analyses: i.e., WHO histological type, affected organ, tumor size, presence of MG, and completeness of resection. Any subgroup containing fewer than 50 cases was excluded from these analyses. Each HR and 95% CI by subgroup is shown in Figure 3 as a forest plot.

Overall survival for stage II and III thymic carcinoma and thymoma

The 5-yaer OS proportions of the PORT group (n = 25) and the no PORT group (n=30) for stage II thymic carcinoma were 91.1% and 86.8% (Fig. 4a). The 5-year OS proportions of the PORT group (n = 55) and the no PORT group (n = 44) for stage III thymic carcinoma were 65.0% and 64.0% (Fig. 4b).

The 5-year OS proportions of the PORT group (n=199) and the no PORT group (n=637) for stage II thymoma were 96.5% and 96.2% (Fig. 4c). The 5-year OS proportions of the PORT group (n=122) and the no PORT group (n=147) for stage III thymoma were 92.9% and 89.7% (Fig. 4d).

PORT for stage II and III thymic carcinoma or thymoma was not statistically significantly associated with OS. The HR for combined stage II and III thymic carcinomas as analyzed by Cox regression analysis adjusted for Masaoka stage and residual tumor was 0.94 (95% CI, 0.51–1.75; P = 0.850; Table 3). The HR for combined stage II and III thymomas as analyzed by Cox regression analysis adjusted

for Masaoka stage and completeness of resection was 0.78 (95% CI, 0.47–1.31; P = 0.350; Table 3).

DISCUSSION

Although adjuvant RT has traditionally been performed for thymoma, many reports have reconsidered its supposed benefit in recent years[11-13]. However, retrospective cohort studies of the efficacy of PORT for thymic epithelial tumors have not resulted in a consensus[5, 11, 14-16].

The efficacy of PORT for stage II and stage III have historically been discussed separately because the former is considered an early-stage tumor with a low risk of recurrence, whereas the latter is an advanced-stage tumor with a relatively high risk of recurrence. Generally, for completely resected stage II thymoma, PORT is considered to have only minor efficacy[11, 12, 14, 17]. The conclusions for stage III thymic epithelial tumors are less agreed upon. One meta-analysis and a large-scale cohort study from Japan concluded that there was no statistically significant reduction in recurrence after RT[11, 18]. On the other hand, a systematic review and another large-scale cohort study from Europe both supported adjuvant therapy[16, 17]. The heterogeneity of the populations and the adjustments for covariates (or lack thereof) may have been responsible for the disparate results among these studies.

Analyzing thymic carcinomas and thymomas as a whole may present misleading results, because thymic carcinomas, not being associated with autoimmune diseases[19, 20], behave more aggressively than thymomas that actually have a lower 5-year survival proportion[18, 19]. This inevitably leads to a necessity for separate analyses of adjuvant therapy for thymic carcinomas and for thymomas. However, few systematic studies have been reported regarding thymic carcinoma alone[21-26]. Although little benefit of PORT for thymic carcinoma had been reported[21, 23], a cohort study using the European Society of Thoracic Surgeons (ESTS) database recently reported a contribution of PORT to survival for thymic carcinoma without identifying the group who gain the benefit[26].

In Japan, the indication of PORT for thymic epithelial tumor is left up to the judgment of individual institutions because an integrated consensus concerning this issue does not exist. Within our database, about a quarter of stage II thymoma patients (23.8%) and half of stage III thymoma patients (45.6%) were irradiated postoperatively throughout the study period (1991 - 2010). The frequency of PORT, however, tended to decrease over time. The proportion of irradiated patients for stage II thymoma in the second half of the period (2001 to 2010) was notably lower than in the first half (1991 to 2000; 17.2% vs. 44.0%). Similarly, the proportion of irradiated patients for stage III

thymoma in the second half of the period was lower than in the first half (41.0% vs. 56.1%). These decreasing trends of PORT incidence may be attributable to practice changes in the wake of a nationwide Japanese cohort study by Kondo *et al.* in 2003, which questioned the validity of PORT[18].

However, in the Japanese article[18] mentioned above, the data were analyzed without adjusting for covariates. As the results of a comprehensive review showed[14, 27], PORT seemed to adversely impact recurrence for advanced thymoma. Our analysis before adjusting for covariates (Supplement 2) also showed a similar result. This is because the results of meta-analyses are influenced by any bias in the population if the data are not adjusted for covariates. In contrast, the analysis using the ESTS database[16] adjusted for propensity score showed favorable efficacy of adjuvant therapy for thymic epithelial tumors. However, because these statistically reliable results were for all staged thymic epithelial tumors, it is difficult to identify the group whom adjuvant therapy would benefit the most.

We analyzed the efficacy of PORT using the JART database, which is a Japanese nationwide database, with emphasis on histology and Masaoka staging. The advantages of our analysis are the large scale of the cohort study, and the use of Cox regression analysis with adjustment for covariates. The RFS and OS of all eligible

patients in this study, when adjusted for staging, histology and surgical completeness, showed high HRs for stage III, thymic carcinoma, and incomplete resection (Supplement 2). With these results and the reasons mentioned before, thymic carcinomas and thymomas should be analyzed separately and that analyses should be stratified by the strong confounding factor, Masaoka staging (stage II vs. stage III).

Although the RFS curve for stage II thymic carcinoma with or without PORT showed no significant difference by the log-rank test, upon visual inspection the two curves appeared to differ (Fig. 2a). We speculate that this statistical result was caused by a shortage of cases. The HR of RFS for combined stage II and III thymic carcinomas adjusted for staging and surgical completeness was very low. From this result, we conclude that PORT improved RFS for stage II and III thymic carcinomas. The treatment after relapse of thymic carcinoma varies widely among institutes because there is no consensus on the efficacy of chemotherapy for thymic carcinoma[8, 9]. This high variability among follow-up treatment methodologies may cause difficulty to use OS as a measure of prognosis, and RFS is more appropriate measure to evaluate PORT for thymic carcinomas. An additional analysis of the RFS HR of PORT for stage II and III thymic carcinomas adjusted for the variables listed in Table 2 and postoperative chemotherapy revealed that the HR and P-values were nearly identical to

those in Table 2 (Supplement 3). Most patients with thymic carcinoma (84.4% [124/147]) were completely resected in our study. Thus, the HR of RFS for those patients was 0.36 (95% CI, 0.20-0.65; P < 0.001; Supplement 4), which was almost identical to the result including the patients with residual tumors (<20% of tumor volume) (HR, 0.48; 95% CI, 0.30-0.78; P = 0.003; Table 2) . Despite the non-standardized follow-up schedule in the JART database, we believe that the effect of PORT on RFS cannot be overestimated. The reason is that PORT patients need to visit the hospital for more frequent and routine examinations than patients that do not receive PORT. On the basis of these results, we conclude that PORT had a positive impact on stage II and III thymic carcinomas.

Our results for the RFS and OS of stage II thymoma were similar to those of the past study.[11, 12] In contrast, regarding the adjuvant therapeutic effect for stage III thymoma—*i.e.*, the controversial category—we applied additional subgroups (affected organ, WHO histological type, tumor size, residual tumor, and associated MG) to the analysis because of the lack of any significant improvement in RFS or OS in response to PORT. None of the subgroup analyses showed a favorable effect on RFS by PORT. We conclude, therefore, that PORT for stage III thymoma does not contribute to survival. Our results support the declining trends of PORT for stage II and III thymoma

in Japan.

Study Limitations

Since this is a database study, some limitations are inherent in the retrospective data collection. Follow-up schedules were not standardized, possibly resulting in bias towards null hypotheses. Further, the JART database lacks specific details of radiotherapy treatments and does not include information on any treatments performed after relapse; hence, we could not fully evaluate treatment efficacy after relapse.

In addition, we could not evaluate the influence of postoperative chemotherapy because there were only a few patients who underwent it. A future prospective study whose population receives a consistent type of postoperative therapy for thymic carcinoma is essential.

CONCLUSION

In this database study using the JART database, PORT did not increase relapse-free survival or overall survival for stage II and III thymoma, but did increase relapse-free survival for stage II and III thymic carcinoma.

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TABLE 1a. Patient Characteristics of Thymic carcinoma

	No. (%)		
Variables	**with PORT (n=80)**	**without PORT (n=75)**	**p-value**
Gender			0.621
Male	49 (61.3)	49 (65.3)	
Female	31 (38.8)	26 (35.7)	
Age (y)			0.842
mean ± SD	60.3±11.5	59.9±12.3	
median (range)	61.5 (36-79)	60 (23-86)	
Tumor size on imaging (cm)			0.440
mean ± SD	5.3±2.3 *	5.6±2.3 **	
median (range)	5.3 (0-10) *	5.6 (1.8-11) **	
Masaoka stage			0.314
Stage II	25 (31.3)	30 (40.0)	
Stage III	55 (68.8)	45 (60.0)	
Completeness of Surgery			0.048
macroscopic total	69 (86.3)	72 (96.0)	
subtotal	11 (13.8)	3 (4.0)	
Residual tumor			0.290
microscopic	8 (10.0)	10 (13.3)	
macroscopic	8 (10.0)	0 (0.0)	
no	64 (80.0)	65 (86.7)	
Myasthenia gravis			1
yes	1 (1.3)	1 (1.3)	
no	79 (98.8)	74 (98.7)	
Postoperative chemotherapy			0.011
yes	17 (21.3)	5 (6.7)	
no	62 (77.5)	70 (93.3)	
missing	1 (1.3)	0 (0.0)	

PORT = postoperative radiotherapy, SD = standard deviation

subtotal; surgically resected >80% tumor volume

Data are shown as mean ± standard deviation

* Data available for 77 patients

** Data available for 74 patients

TABLE 1b. Patient Characteristics of Thymoma

Variables	No. (%) with PORT (n=323)	No. (%) without PORT (n=787)	p-value
Gender			0.649
Male	144 (44.6)	332 (42.2)	
Female	179 (55.4)	454 (57.7)	
missing	0	1	
Age (y)			<0.001
mean±SD	54.0±12.7	58.4±13.5	
median (range)	55 (21-82)	60 (18-86)	
Tumor size on imaging (cm)			0.017
mean ± SD	5.6±2.5 *	5.2±2.5 **	
median (range)	5 (0-18) *	5 (1-30) **	
WHO histological type			<0.001
Type A	15 (4.6)	57 (7.2)	
Type AB	67 (20.7)	231 (29.4)	
Type B1	68 (21.1)	181 (23.0)	
Type B2	106 (32.8)	207 (26.3)	
Type B3	67 (20.7)	111 (14.1)	
Masaoka stage			<0.001
Stage II	200 (61.9)	640 (81.3)	
Stage III	123 (38.1)	147 (18.7)	
Completeness of Surgery			<0.001
macroscopic complete	306 (94.7)	782 (99.4)	
subtotal resection	17 (5.3)	5 (0.6)	
Residual tumor			<0.001
microscopic (+)	35 (10.8)	17 (2.2)	
macroscopic(+)	7 (2.2)	2 (0.3)	
no	281 (87.0)	768 (97.6)	
Myasthenia Gravis			0.482
yes	80 (24.8)	179 (22.7)	
no	242 (74.9)	605 (76.9)	
missing	1 (0.3)	3 (0.5)	
Postoperative chemotherapy			0.282
yes	10 (3.1)	16 (2.0)	
no	311 (96.3)	767 (97.5)	
missing	2 (0.6)	4 (0.5)	

SD = standard deviation

PORT = postoperative radiotherapy, WHO = World Health Organization

Data are shown as mean ± standard deviation

subtotal; surgically resected >80% tumor volume

* Data available for 305 patients, ** Data available for 749 patients

TABLE 2. Analyses of relapse-free survival in thymic carcinoma and thymoma

	Thymic carcinoma		**Thymoma**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
PORT (yes/ no)	0.48 (0.30 0.78)	0.003	0.98 (0.70 1.37)	0.905
Masaoka stage (stage III/ stage II)	3.51 (1.86 6.65)	< 0.001	4.54 (3.27 6.32)	< 0.001
Residual tumor (yes/ no)	1.93 (1.09 3.42)	0.023	2.01 (1.22 3.29)	0.006

RFS; relapse free survival

HR; hazard ratio

CI; confidential interval

PORT; postoperative radiotherapy

TABLE 3. Analyses of overall survival in thymic carcinoma and thymoma

	Thymic carcinoma		**Thymoma**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
PORT (yes/ no)	0.94 (0.51 1.75)	0.850	0.78 (0.47 1.31)	0.350
Masaoka stage (stage III/ stage II)	3.08 (1.37 6.94)	0.007	3.31 (2.03 5.41)	<0.001
Residual tumor (yes/ no)	1.32 (0.65 2.70)	0.446	1.48 (0.64 3.40)	0.355

OS; overall survival

HR; hazard ratio

CI; confidential interval

PORT; postoperative radiotherapy

Figure Legends

Figure 1. Scheme of study population.

Figure 2. Kaplan–Meier plots and the log-rank P-value comparing PORT to no PORT. (a) Relapse-free survival for stage II thymic carcinoma. (b) Relapse-free survival for stage III thymic carcinoma. (c) Relapse-free survival for stage II thymoma. (d) Relapse-free survival for stage III thymoma.

Figure 3. Forest plot of subgroup analyses comparing PORT to no PORT for patients with stage III thymoma. The squares represent the hazard ratio of each factor. Each hazard ratio represents the ratio comparing PORT to no PORT. The horizontal bars running through each square represent the 95% confidence interval. Factors with <50 cases were excluded. HR: hazard ratio, CI: confidence interval.

Figure 4. Kaplan-Meier plots and the log-rank P-value comparing PORT to no PORT. (a) Overall survival for stage II thymic carcinoma. (b) Overall survival for stage III thymic carcinoma. (c) Overall survival for stage III thymoma. (d) Overall survival for stage III thymoma.

Figure 1

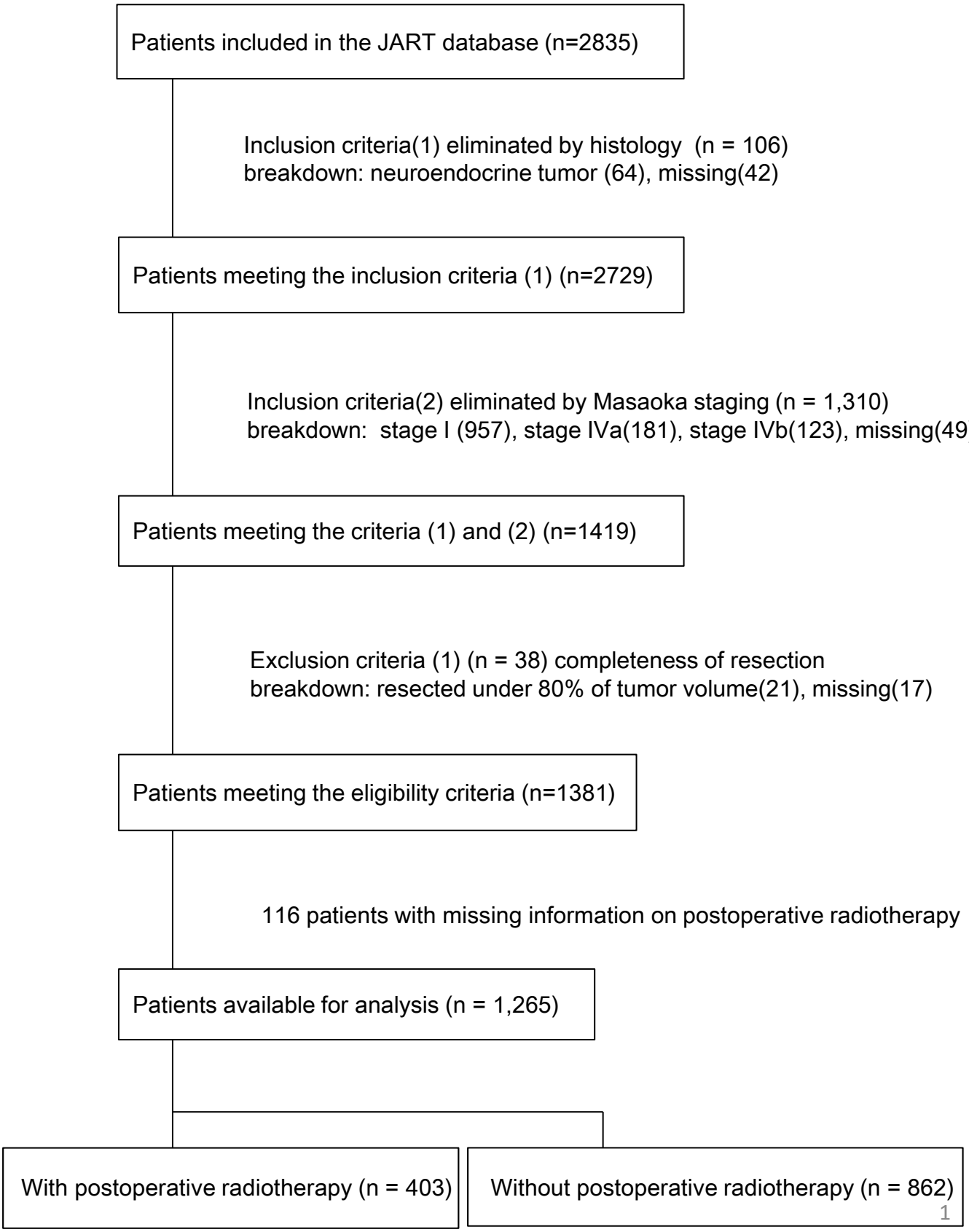

Patients included in the JART database (n=2835)
Inclusion criteria(1) eliminated by histology (n = 106)
breakdown: neuroendocrine tumor (64), missing(42)
Patients meeting the inclusion criteria (1) (n=2729)
Inclusion criteria(2) eliminated by Masaoka staging (n = 1,310)
breakdown: stage I (957), stage IVa(181), stage IVb(123), missing(49)
Patients meeting the criteria (1) and (2) (n=1419)
Exclusion criteria (1) (n = 38) completeness of resection
breakdown: resected under 80% of tumor volume(21), missing(17)
Patients meeting the eligibility criteria (n=1381)
116 patients with missing information on postoperative radiotherapy
Patients available for analysis (n = 1,265)
With postoperative radiotherapy (n = 403)
Without postoperative radiotherapy (n = 862)

Figure 2

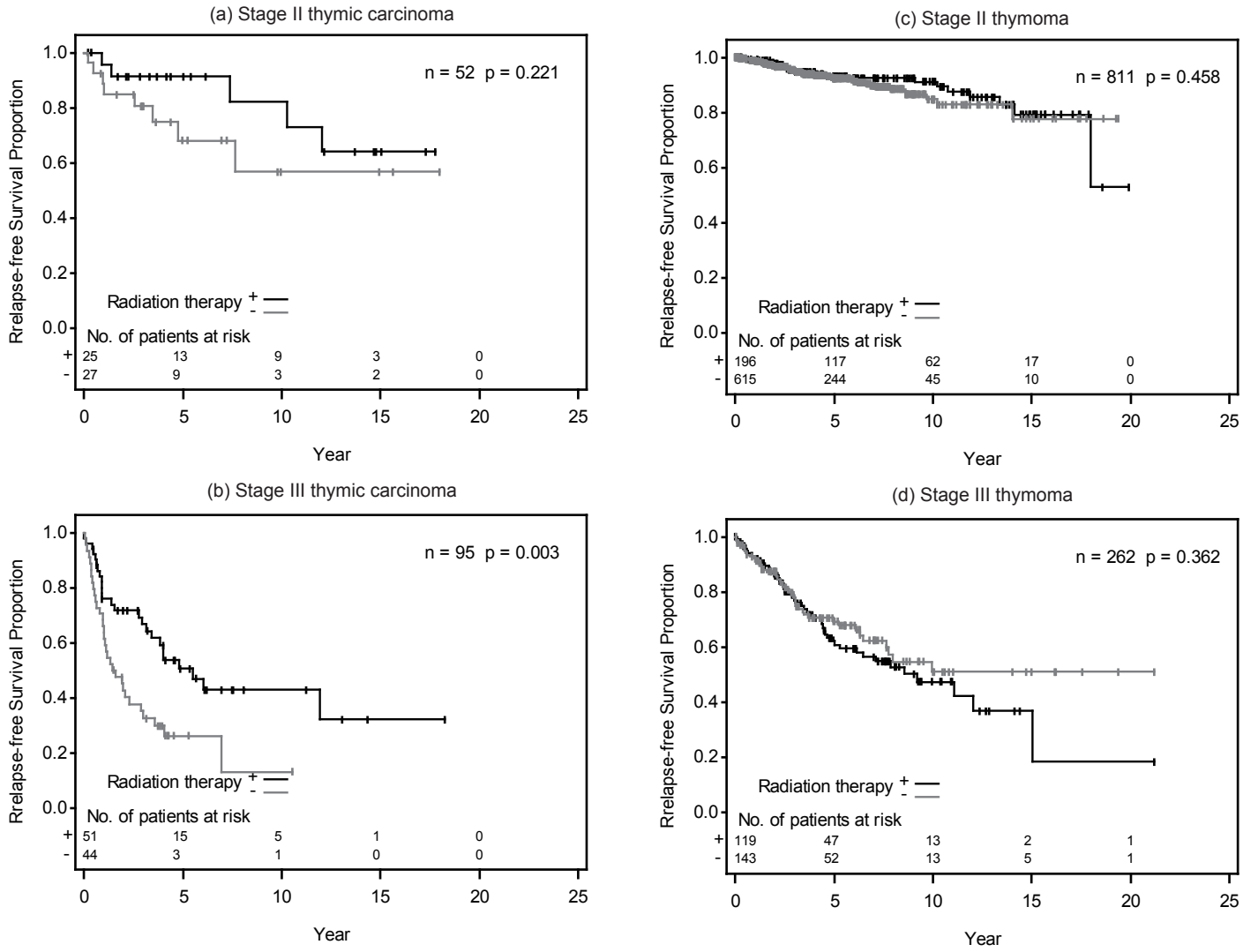

(a) Stage II thymic carcinoma
n = 52 p = 0.221
Rrelapse-free Survival Proportion
Radiation therapy + -
No. of patients at risk
+ 25 13 9 3 0
- 27 9 3 2 0
Year
(c) Stage II thymoma
n = 811 p = 0.458
Rrelapse-free Survival Proportion
Radiation therapy + -
No. of patients at risk
+ 196 117 62 17 0
- 615 244 45 10 0
Year
(b) Stage III thymic carcinoma
n = 95 p = 0.003
Rrelapse-free Survival Proportion
Radiation therapy + -
No. of patients at risk
+ 51 15 5 1 0
- 44 3 1 0 0
Year
(d) Stage III thymoma
n = 262 p = 0.362
Rrelapse-free Survival Proportion
Radiation therapy + -
No. of patients at risk
+ 119 47 13 2 1
- 143 52 13 5 1
Year

Figure 3

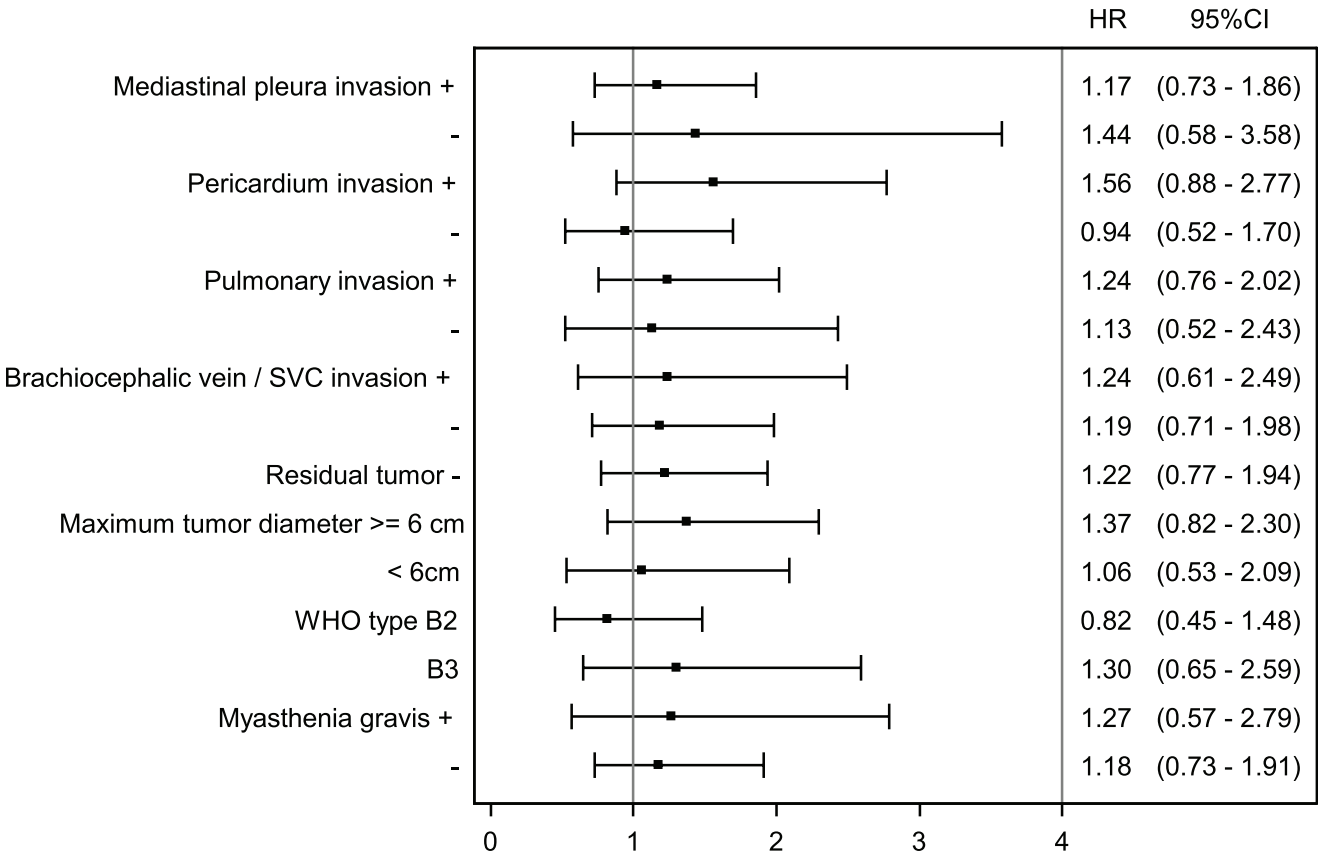
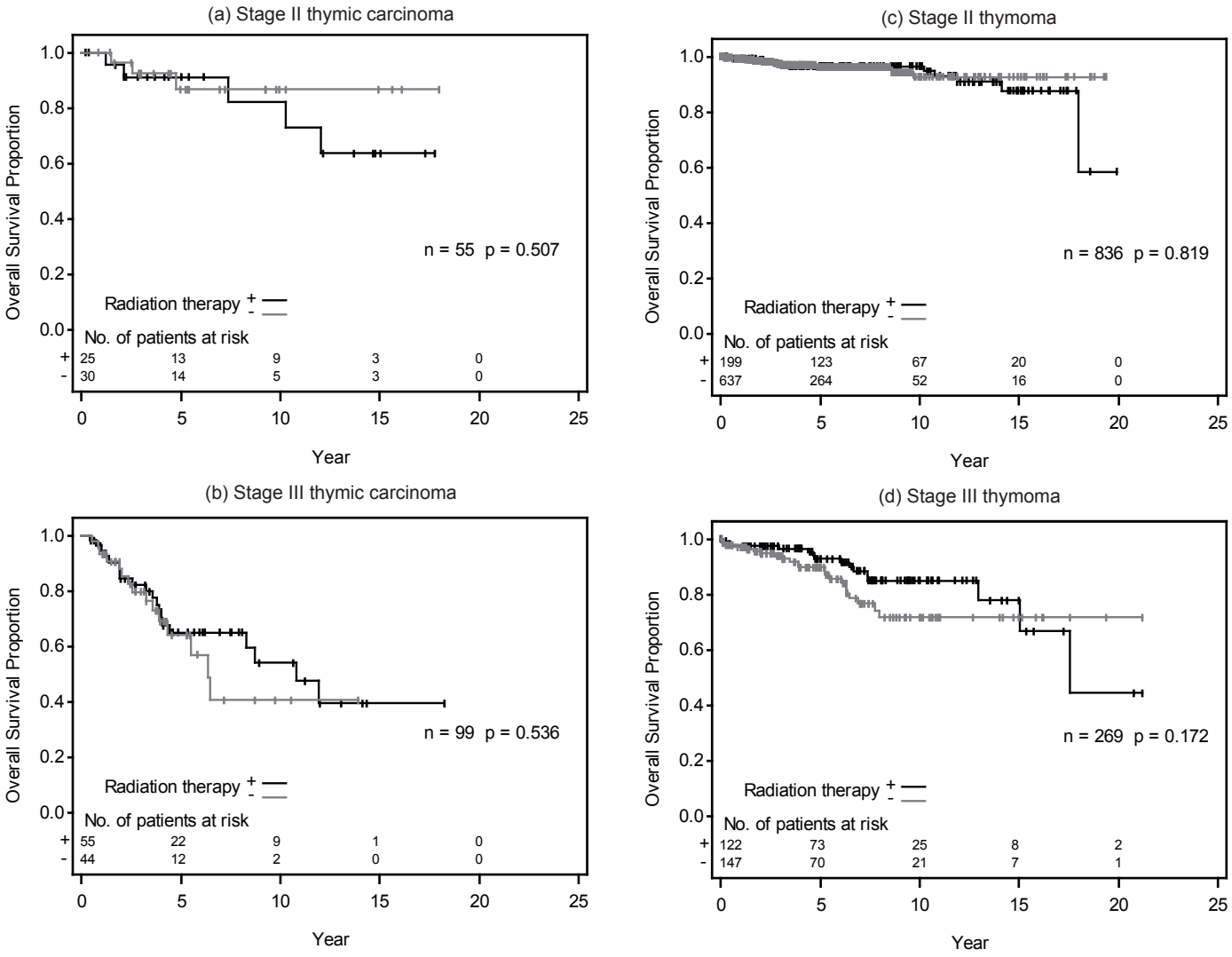
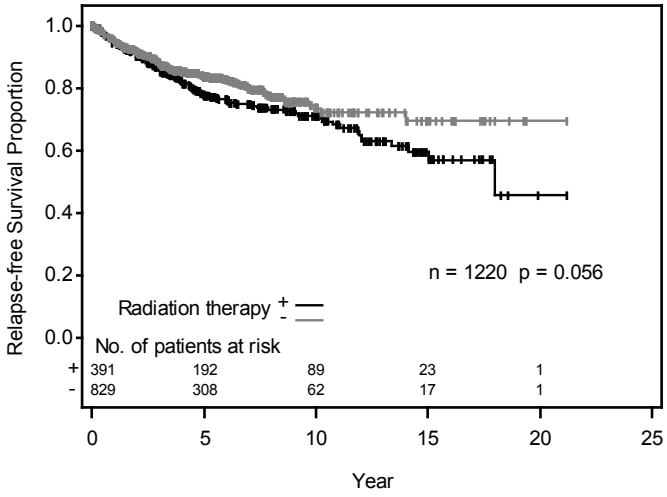

HR
95%CI
Mediastinal pleura invasion +
1.17 (0.73 - 1.86)
-
1.44 (0.58 - 3.58)
Pericardium invasion +
1.56 (0.88 - 2.77)
-
0.94 (0.52 - 1.70)
Pulmonary invasion +
1.24 (0.76 - 2.02)
-
1.13 (0.52 - 2.43)
Brachiocephalic vein / SVC invasion +
1.24 (0.61 - 2.49)
-
1.19 (0.71 - 1.98)
Residual tumor -
1.22 (0.77 - 1.94)
Maximum tumor diameter >= 6 cm
1.37 (0.82 - 2.30)
< 6cm
1.06 (0.53 - 2.09)
WHO type B2
0.82 (0.45 - 1.48)
B3
1.30 (0.65 - 2.59)
Myasthenia gravis +
1.27 (0.57 - 2.79)
-
1.18 (0.73 - 1.91)
0
1
2
3
4

Figure 4


(a) Stage II thymic carcinoma
Overall Survival Proportion
1.0
0.8
0.6
0.4
0.2
0.0
n = 55 p = 0.507
Radiation therapy + -
No. of patients at risk
+ 25 13 9 3 0
- 30 14 5 3 0
0 5 10 15 20 25
Year
(c) Stage II thymoma
Overall Survival Proportion
n = 836 p = 0.819
Radiation therapy + -
No. of patients at risk
+ 199 123 67 20 0
- 637 264 52 16 0
Year
(b) Stage III thymic carcinoma
Overall Survival Proportion
n = 99 p = 0.536
Radiation therapy + -
No. of patients at risk
+ 55 22 9 1 0
- 44 12 2 0 0
Year
(d) Stage III thymoma
Overall Survival Proportion
n = 269 p = 0.172
Radiation therapy + -
No. of patients at risk
+ 122 73 25 8 2
- 147 70 21 7 1
Year

Supplement 1

Supplement 1. Relapse-free survival for stage II/III thymic carcinoma and thymoma comparing PORT to no PORT.



Supplement 2

Supplement 2; Cox regression analysis for RFS adjusted for pathology, Masaoka staging and residual tumor

Parameter	HR (95% CI)	p-value
PORT (yes/ no)	0.76 (0.58 1.01)	0.116
Pathology (Thymic carcinoma/ Thymoma)	2.51 (1.87 3.38)	< 0.001
Masaoka stage (stage III/ stage II)	4.46 (3.33 5.99)	< 0.001
Residual tumor (yes/ no)	2.14 (1.49 3.09)	< 0.001

HR; hazard ratio

CI; confidential interval

PORT; postoperative radiotherapy

Supplement 3

Supplement 3; Cox regression analysis for RFS of thymic carcinoma adjusted for pathology, Masaoka staging, residual tumor and postoperative chemotherapy

Parameter	HR (95% CI)	p-value
PORT (yes/ no)	0.48(0.29 0.78)	0.003
Masaoka stage (stage III/ stage II)	3.32(1.74 6.36)	< 0.001
Residual tumor (yes/ no)	1.99 (1.11 3.55)	0.020
Postoperative chemotherapy (yes/ no)	1.21 (0.59 2.45)	0.607

HR; hazard ratio

CI; confidential interval

PORT; postoperative radiotherapy

Supplement 4

Supplement 4; Cox regression analysis for RFS of completely resected thymic carcinoma adjusted for pathology, Masaoka staging

	HR (95% CI)	p-value
PORT (yes/ no)	0.36 (0.20 0.65)	< 0.001
Masaoka stage (stage III/ stage II)	3.72 (1.93 7.17)	< 0.001

HR; hazard ratio

CI; confidential interval

PORT; postoperative radiotherapy