In the name of God

Survival and treatments in patients with incompletely resected thymoma

M.Sabuhi
F.Ghahremani

Introduction

Although a proportion of patients undergoing thymectomy for thymoma unexpectedly end up with a incomplete resection, there is little literature to date on survival and treatment in those with incompletely resected thymomas. Complete resection of thymoma has been reported as a significant favorable factor in overall survival, while in patients with incomplete resection, adjuvant treatments can offer comparable overall survival.

Previous reports have discussed the role of adjuvant treatments following either complete or incomplete resection for advanced thymoma, emphasizing postoperative adjuvant Radiotherapy, while adjuvant chemotherapy alone has not been recommended.

The aim of this study was
to investigate overall survival and progression-free survival following thymectomy in patients with completely resected thymomas and those with incompletely resected thymomas,and more importantly to investigate any potentially relevant factors associated
with improved overall survival or progression-free survival in patients with incompletely resected thymomas.

Patients and methods

Between January 1991
and December 2012, 156 consecutive patients with thymoma, who underwent thymectomy with curative intent at Kyoto University Hospital, were evaluated by a retrospective chart review. Preoperative evaluation included physical examination, laboratory workup, serum levels of ach-receptor antibody (in cases of myasthenia gravis), staging, and chest computed
Tomography,PET and MRI were performed at the discretion of the evaluating surgeon. Operative procedures were carried out or supervised by board-certified Japanese thoracic surgeons, either in an open approach or a minimally invasive approach (video-assisted thoracoscopic surgery or roboticassisted thoracoscopic surgery).

Postoperative follow-up,
which was undertaken by thoracic surgeons,
typically included a physical examination and chest computed tomography. In patients with completely resected thymomas, the follow-up interval was every 6 months in the first 5 years and yearly thereafter for Masaoka stage III or higher. For Masaoka stage II or lower, the interval was every 6 months in the first year and yearly thereafter. In patients with incompletely resected thymoma, the interval tended to be shorter than in those with complete resection.

The primary outcome was overall survival following thymectomy, and the secondary outcome was progression-free survival following thymectomy.

Overall survival and progression-free survival were calculated from the date of surgery, and progression-free survival was defined as from the date of surgery to radiological evidence of tumor progression.

In patients with incompletely resected thymomas, potentially relevant factors for overall survival and progression-free survival were analyzed using Cox proportional-hazard models:

age, sex, operative approach ,mediastinal LND, Masaoka stage, WHO histology, myasthenia gravis, neoadjuvant treatment preoperative steroid use, location of residual disease, macroscopic or microscopic residual disease, and adjuvant

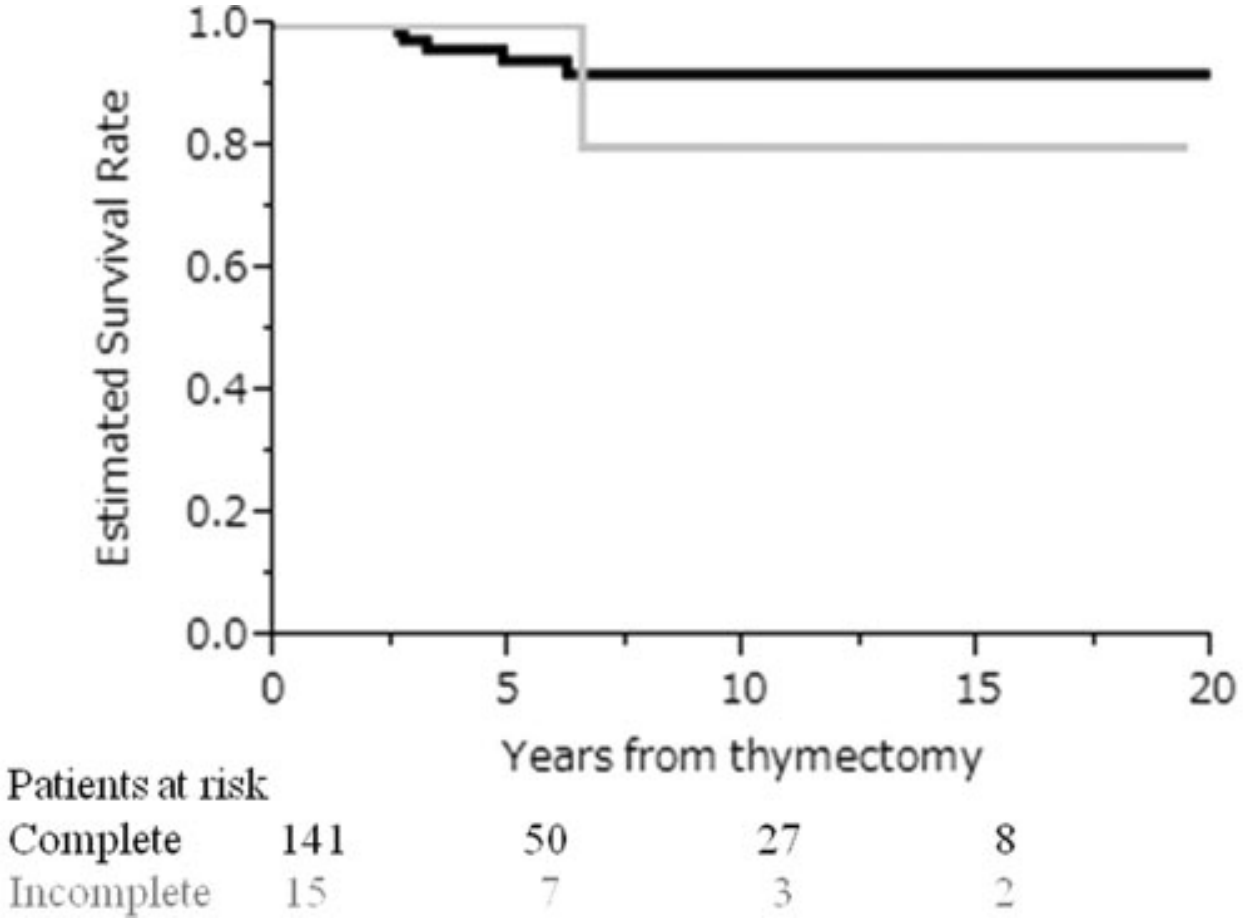
Postoperative complications and treatment for tumor progression that were considered to potentially relate to the primary and secondary outcomes, were also analyzed and documented.

Overall survival and progression-free survival were estimated by the Kaplan-Meier method, and compared using Cox proportional-hazard models.

A p value <0.05 was considered statisically significant . .
If the p value was <0.15 in univariate analysis, it was included in multivariate analysis.

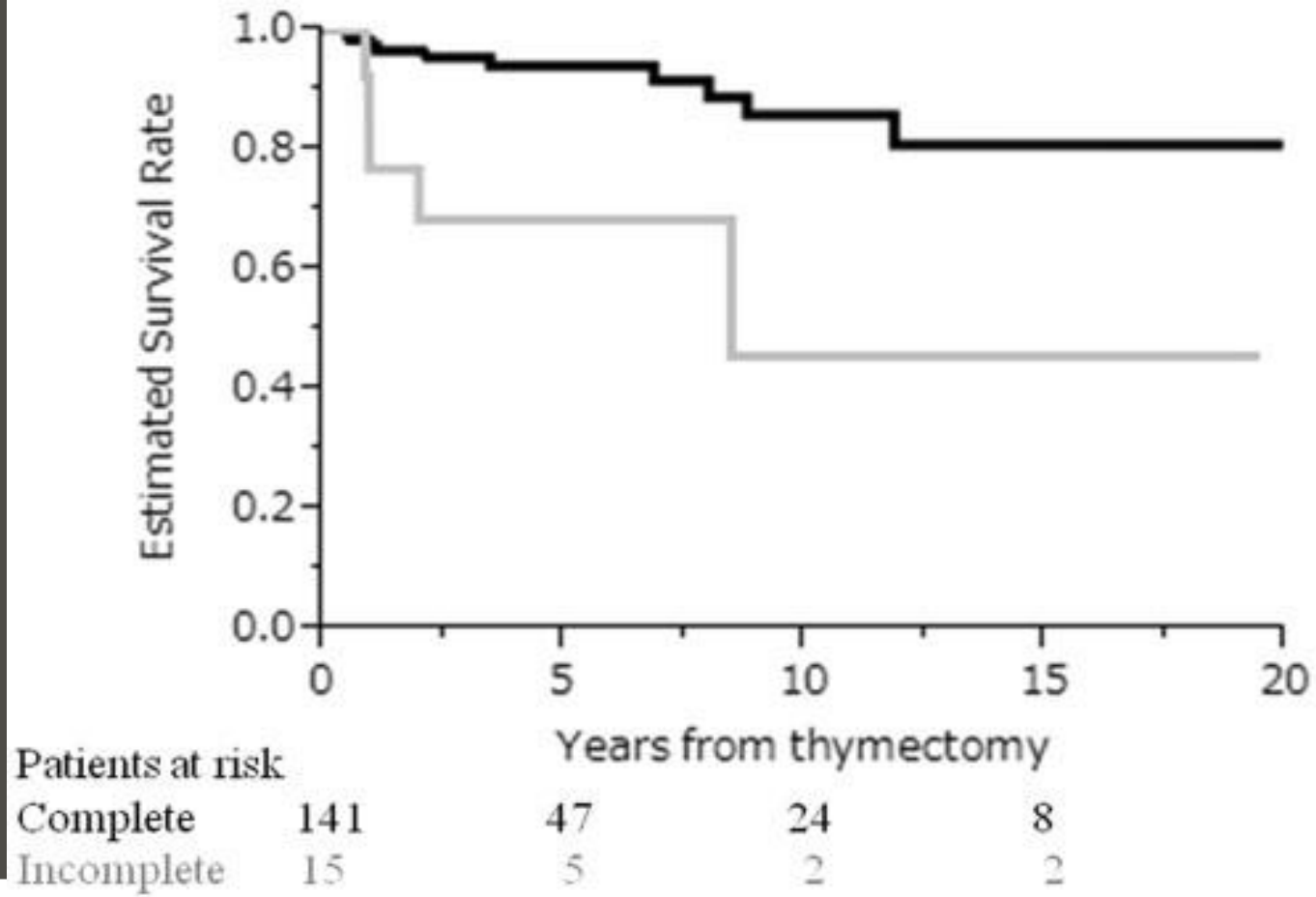
Results

Complete resection versus incomplete resection in overall survival and progression free survival:
The duration of follow-up ranged from 0.3 to 239 months (median 39 months).
There was no significant difference in overall survival (hazard ratio 1.64, 95%confidence interval: 0.086–10.2, p=0.638;),
but there was a significant difference in progressionfree survival following thymectomy confidence interval: 1.68–)(hazard ratio 5.4,95% 15.2, p=0.0012;
between patients with completely resected thymomas (n=141) and those with incompletely resected thymomas (n=15).



Kaplan-Meier survival curves for overall survival following thymectomy in the completely resected group (black line) and the incompletely resected group (gray line).

Figure 1



Kaplan-Meier survival curves for progression-free survival following thymectomy in the completely resected group (black line) and the incompletely resected group (gray line).

Figure 2

Preoperative staging and neoadjuvant treatments in patients with incompletely resected thymoma:

Preoperative staging was consistent with the final (pathological) staging in 9 (60%) patients, and lower than the final staging in 6 (40%). Of the 4 patients in preoperative stage III, 2 received neoadjuvant radiotherapy.
(3000 cGy and 4310 cGy). Of the 4 patients in preoperative stage IVA, one received neoadjuvant chemoradiotherapy
(2 cycles of a platinum-based regimen
and 3000 cGy) and another received neoadjuvant chemotherapy (1 cycle of paclitaxel only).

Postoperative complications and potential relevant factors in patients with incompletely resected thymoma:

No mortality was seen.
Five (33%) patients had postoperative complications: persistent high output from a chest tube in 1, congestive heart failure in 1, arrhythmiain 1, prolonged air leak in 1, and myasthenia crisis in 1.
All postoperative complications were treated conservatively.
The postoperative complication rate was significantlyhigher in patients with incompletely resectedThymomas.

In univariate analysis limited to patients with incompletely resected thymomas,size (p=0.10) and preoperative steroid use (p=0.12) showed tendencies for postoperative complications, but age (p=0.88), sex (p=0.49), maximal standard uptake value on PET(p=0.34),neoadjuvant chemotherapy (p=0.60), neoadjuvant radiotherapy (p=0.67), surgical approach (p=0.30), lymph node dissection (p=0.62), final Masaoka stage (p=0.21), WHO histology (p=0.47), microscopic or macroscopic residual disease (p=0.25), pleural disseminated disease (p=0.70), pericardial disseminated disease (p=0.46), residual disease in a lung (p=0.67), residual disease in the mediastinum (p=0.18), and myasthenia gravis (p=0.26) were not significant.

Extents and location of residual diseases:

Six (40%) patients had microscopic residual disease and 9 (60%) had macroscopic residual disease.

There was no significant difference in overall survival or progression-free survival between patients with macroscopic residual disease and those with microscopic residual disease.

Adjuvant treatment for patients with incompletely resected thymoma

One (6.6%) patient underwent adjuvant chemoradiotherapy, 5 (33.3%) had adjuvant chemotherapy only, and 5 (33.3%) had adjuvant radiotherapy only, while 4 (26.8%) did not undergo any adjuvant treatment.

Adjuvant chemotherapy was a platinum-based multidrug regimen.

Adjuvant radiotherapy ranged from 3000 to 6040cGy.

Adjuvant chemotherapy was given significantly more often to patients with macroscopic disease ($p=0.028$), but there was no difference in the frequency of adjuvant radiotherapy in patients with macroscopic or microscopic disease ($p=0.14$).

Survival and treatments in patients with disease progression:
Five (33.3%) patients had disease progression during fallow-up.
Of these 5 patients, one underwent debulking surgery, chemotherapy and radiotherapy ,2underwent debulking surgery and chemotherapy.
one had debulking
surgery only, and the other did not undergo treatment
but received best supportive care; 4 were alive at 2, 10,
56, 60 months from progression.

Overall survival following incomplete resection and potential prognostic factors;
Five- and 10-year overall survival following incomplete resection was 100% and 80%, respectively. In univariate
analysis, no relevant factors were significant for improved overall survival following thymectomy, but younger age (p=0.073) showed tendency for better overall survival. Five- and
10-year progression-free survival following incomplete resection was 68.4% and 45.6%, respectively. In univariate
analysis, no relevant factors were significant for improved progression-free survival following thymectomy,
but adjuvant chemotherapy (p=0.071) showed a tendency for improved progression-free survival.

discussion

Progression free survival following incomplete resection and potential prognostic factors:

With or without neoadjuvant treatment, a proportion of thymectomies for thymoma result in incomplete resection. Final (pathological) Masaoka stages and complete resection of thymoma are most often reported to be significant factors in overall survival or progression-
free survival. On the other hand, incomplete resection can offer comparable overall survival if combined
with adjuvant treatment, especially radiotherapy. Incomplete resection includes debulking
surgery and biopsy only, but these two procedures appear to have different goals and outcomes.

Inclusion of both debulking cases and biopsy cases in the incomplete resection group, as seen in previous reports, would make this group relatively heterogenous. Instead, we included in the incomplete resection group, only patients who underwent maximal debulking, not biopsy-only patients. That might be the reason why our analysis resulted in no significant difference in overall survival between the complete and incomplete resection groups, in spite of a tendency in the incomplete resection
group to include more advanced-staged thymomas.

Because our data did not identify preoperative patient characteristics, except for higher preoperative (radiological) Masaoka stages, which were predictive of incomplete resection vs. complete resection, it is hardly possible to predict incomplete resection preoperatively.
Radiological workup apparently has a limitation, given the fact that in our series, 4.8% of preoperative (radiological) stage I patients ended up with incomplete resection. Adding PET to routine chest computed tomography may help to predict thymoma histology or stage, but it does not appear to help in predicting complete or incomplete resection.

How aggressively we should debulk extensive or disseminated
disease has been controversial. In fact,
3 patients in our series had unsuspected disseminated disease found in the operating room and maximally debulked. Previous reports on incompletely resected thymoma, all of which were published earlier than 2007, differ in the value of maximal debulking vs. biopsy only. We have no data to compare maximal debulking with biopsy only, but based on the findings in this study, we would be inclined towards
maximal debulking to achieve a survival rate comparable
to complete resection.

It remains to be discussed extensively what adjuvant treatment should be administered to patients with incompletely resected thymoma. In locally advanced thymoma, completely or incompletely resected, neoadjuvant chemotherapy proved to be a significant favorable factor in overall survival and progression-free survival, while the role of adjuvant chemotherapy has not been not widely discussed.17,18 Postoperative adjuvant treatment has most often been mediastinal radiotherapy, which was found to be a significantly favorable factor in overall survival in incompletely resected thymoma. Our results suggest that in cases of incomplete resection, adjuvant chemotherapy should be favored over adjuvant radiotherapy, although adjuvant chemotherapy did not reach statistical significance.

Incomplete resection is a risk factor for recurrence or progression of disease. To achieve improved overall survival in patients with incompletely resected thymoma, management of recurrent or progressed disease should also be discussed. Of note, most locations of recurrence or progression are outside the mediastinum, and this suggests that adjuvant chemotherapy could be effective in managing potential microscopic metastatic disease at the time of debulking surgery, as reported by Kim and colleagues.

Progression of disease also depends on the biology of the tumor. In our series, all the treated patients underwent reoperative surgery on progression, and a few of them achieved satisfactory overall survival following
progression. Surgical resection of a localized recurrent or progressed lesion has been reported to be beneficial and associated with better overall survival. Our patients with progressed diseases appeared to have achieved satisfactory overall survival with multimodality treatments including surgery, but due to the small number, the treatment strategy for progressive cases following debulking surgery plus adjuvant treatment is difficult to establish.

The limitations of our study include the retrospective study design and the relatively small number of patients, although the rarity of thymoma and its indolent
nature make a prospective randomized study challenging.
Our follow-up interval was relatively short.
There are missing data regarding WHO histology in patients early in the series. Preoperative radiological staging was not consistent throughout the study period because PET or MRI was also performed in more recent patients. Our neoadjuvant and adjuvant treatments were not protocol-based but influenced by time period and attending physician.

Operative indications
for advanced thymoma and progressive disease were also influenced by surgeon bias and experience.
However, we concluded that satisfactory 5- and 10-year survival and progression-free survival were
achieved in patients with incompletely resected thymoma. Adjuvant chemotherapy for incompletely
resected thymoma tended to improve progression-free
survival following thymectomy.


Thank You