Thymoma needs a new staging system

Hisao Asamura\textsuperscript{a,*,} Kazuo Nakagawa\textsuperscript{a}, Yoshihiro Matsuno\textsuperscript{b}, Kenji Suzuki\textsuperscript{a}, Shunichi Watanabe\textsuperscript{a}, Ryosuke Tsuchiya\textsuperscript{a}

\textsuperscript{a}Division of Thoracic Surgery, National Cancer Center Hospital, 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan
\textsuperscript{b}Division of Pathology, National Cancer Center Hospital, 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan

Received 16 April 2003; received in revised form 9 October 2003; accepted 11 November 2003

Abstract

Despite the wide use of the Masaoka staging system for thymoma, the distribution of survival by stage group is not well balanced. The new staging systems for testing were defined as follows: stage I was created by merging Masaoka’s stages I and II, and stage IV remained unchanged. Stages II and III were defined as thymomas with invasive growth and the following combinations of tumor diameter and number of involved structures/organisms. Scheme I: stage II included tumors less than 10 cm in diameter and involving one neighboring structure/organ. Stage III included tumors with all combinations of diameter and number of involved structures/organisms other than those in stage II. Scheme II: stage II included tumors of all combinations other than those in stage III. Stage III included tumors 10 cm or more in diameter and involving two or more structures/organisms. The survival curves were assessed for 138 patients treated at the National Cancer Center, Tokyo. The 10-year survival rates for each stage according to the Masaoka, Scheme 1, and Scheme 2 systems were as follows: stage I (100%, 100%, 100%), stage II (100%, 86%, 83%), stage III (70%, 64%, 34%), and stage IV (34%, 34%, 34%), respectively. The survival curves for Scheme 1 gave the most balanced distribution of survival in each staging group. By considering both tumor diameter and number of involved structures/organisms, Masaoka’s stages I–III could be rearranged with more balanced distribution of survival.

© 2003 Published by Elsevier B.V.

Keywords: Thymoma; Thymectomy; Mediastinal tumor; Surgery; Pathology

1. Introduction

Thymoma is a neoplasm that arises from the epithelial cells of the thymus [1]. Due to their low incidence, wide range of histological appearance, and unique biologic behavior, their histological classification and a suitable staging system have been the subject of controversy for many years [2–4]. In 1999, a new histological classification was promulgated by WHO, in which thymic epithelial tumors were defined as types A, AB, B1, B2, B3, and C [5]. Type ‘C’ is thymic carcinoma with apparent cytological atypia. Our previous study on 130 resected thymomas demonstrated that this WHO histologic classification is an important indicator of the prognosis [6].

The TNM staging system has been applied to most malignant tumors, with an exact definition of the T- (tumor), N- (lymph node), and M- (distant metastasis) denominators. The purpose of this approach is to identify a relatively homogeneous group of patients with a similar prognosis, a ‘stage group’, to help determine a suitable treatment strategy [7]. There is currently no authorized staging system available for thymic epithelial tumors. The degree of tumor invasion described by the surgeon has long been respected as the single most important factor in predicting the patient’s prognosis [8]. In clinical practice, the Masaoka system [9], which is based on the degree of ‘invasiveness’ into the capsule and neighboring structures, has been used either tentatively or conventionally. However, several problems have become apparent with this system. Recent advances in treatment strategies for thymic epithelial tumors highlight the need for a TNM-type staging system in this field.

In this retrospective study, we proposed two staging systems based on the tumor diameter and number of structures/organisms involved by the tumor. Their suitability for predicting the prognosis was assessed by comparing the survival curves for the Masaoka system and our proposed systems.
2. Material and methods

2.1. Patients

From 1962 to 2000, 152 patients with thymoma were treated at the National Cancer Center Hospital, Tokyo. Thirteen patients who underwent an initial surgery at another hospital and for whom there were not enough tissue specimens for pathological review were excluded from the present study. One additional patient for whom there were not enough clinical data was also excluded. Therefore, a total of 138 patients with thymoma was considered for the present study. The patients’ clinical features were retrospectively studied by an extensive review of their medical records with regard to any allied disease, mode of operation, perioperative therapy, mode of recurrence, and prognosis.

The 58 men and 80 women (male to female ratio, 0.72) ranged in age from 15 to 83 years (mean age, 54 ± 14 years). As for allied diseases, myasthenia gravis (MG) and pure red cell aplasia (PRCA) were seen in 12 and 2%, respectively. Among the 138 patients, 131 underwent surgical resection regardless of its completeness, and the remaining seven were treated with non-surgical therapy such as chemotherapy and/or radiation because of the extent of the disease. As for the mode of operation for thymoma, thymectomy (resection of the tumor only), thymophymectomy (total thymectomy including the thymoma and neighboring structures if necessary), and exploration were performed in 53, 42, and 5%, respectively. The resection subtype was 'complete (no macroscopic/microscopic residual tumor)' in 95% of 131 resections. Tumors were smaller than 10 cm in diameter in 112 patients (81%), and 10 cm and more in diameter in 26 patients (19%). The histological subtype was determined according to the 1999 WHO classification as type ‘A’ (n = 19), ‘AB’ (n = 57), ‘B1’ (n = 18), ‘B2’ (n = 32), and ‘B3’ (n = 12) using hematoxylin-eosin-stained formalin-fixed paraffin sections of surgically resected or biopsy specimens of the tumor. Patients with thymic carcinoma (‘C’ by the WHO classification) or thymic neuroendocrine tumor were excluded from this study. Nodal involvement was not seen in any one of the patients.

2.2. Clinical stage

The Masaoka system has most commonly been used to stage thymoma [9]. This system is summarized as follows: stage I, macroscopically completely encapsulated tumors without microscopic capsular invasion; stage II, tumors with microscopic invasion into surrounding fatty tissue or mediastinal pleura, or tumors with microscopic invasion into capsule; stage III, tumors with macroscopic invasion into neighboring structures/organ(s); stage IV, tumors with pleural or pericardial dissemination or with lymphogenous/hematogenous metastases. To establish a staging system which better characterizes the extent of the disease in terms of the prognosis in each stage category, new schemes were introduced based on the results of our previous multivariate analysis [6], where the tumor diameter (10 cm cut-off) had a significant association with the prognosis. Two new staging systems, Scheme 1 and Scheme 2, were established as shown in Table 1. Briefly, in both systems, stage I was defined as tumors without any invasion into other structures/ organs regardless of capsular involvement, and stage IV was identical to that in Masaoka’s system. Tumors that invaded into neighboring structures/organ were defined as either stage II or III based on a combination of tumor diameter and number of involved structures/organ. In Scheme 1, stage II included tumors that were less than 10 cm in diameter and involved only one neighboring structure/organ. All other combinations of diameter and number of involved structures/organ were included in stage III. In Scheme 2, stage II included tumors that were 10 cm or more in diameter and involved two or more structures/organ. All other combinations of diameter and number of involved structures/organ were included in stage II.

2.3. Statistical analyses

Survival was measured from the day of the operation until death or the last follow-up visit. For patients without surgical treatment, the initial date of any treatment was defined as the first day of treatment. The Kaplan–Meier method was used to estimate the time to death from thymoma-related causes and its 95% confidence interval. Death due to the worsening of MG was included as a thymoma-related death. Differences in survival were evaluated by the log-rank test. Significance was defined as a P-value less than 0.05.

3. Results

3.1. Distribution of stage

The distributions of stages of 138 patients according to the Masaoka, Scheme 1, and Scheme 2 systems are as follows: stage I (40, 94, 94), stage II (54, 10, 22), stage III (28, 18, 6), stage IV (16, 16, 16), respectively. Since all tumors limited to within the mediastinal compartment were newly defined as stage I regardless of capsular involvement, the percentage of stage I was more than that in the Masaoka system.

3.2. Prognosis

There were 19 recurrences after the treatment out of 131 patients who underwent surgery. The most common mode of recurrence was pleural dissemination in 11, followed by local regrowth of the tumor in four, pulmonary metastasis in three, and unknown site in one. The number of patients with recurrence by stage (Masaoka, Scheme 1, Scheme 2) was as
follows: stage I (2, 4, 4), stage II (2, 2, 8), stage III (10, 8, 2), and stage IV (5, 5, 5), respectively. There was no special trend in the mode of recurrence according to the stage of any staging system. For all 138 patients, the 5- and 10-year survival rates were 89 and 87%, respectively. The survival curves according to the Masaoka, Scheme 1, and Scheme 2 staging systems are shown in Figs. 1–3, respectively. In the Masaoka system (Fig. 1), the survival curves for stages I and II were completely superimposed throughout the entire course of observation, which indicated that capsular invasion had no impact on survival. Since there were no events in stages I and II, we could only evaluate the difference in survival between stages III and IV: this difference was significant (P = 0.027). In Scheme 1, the survival curves for stages I–IV varied, with the prognosis worsening from stage I to IV (Fig. 2). The differences in survival according to the stage were as follows: between stages II and III (P = 0.13), stages II and IV (P = 0.012), and stages III and IV (P = 0.18). In Scheme 2, the survival curves of stages III and IV were almost superimposed (Fig. 3). The differences in survival according to the stage were as follows: between stages II and III (P = 0.003) and stages II and IV (P = 0.003).

4. Discussion

Thymoma is a tumor that arises from thymic epithelial cells and has unique clinicopathological properties [1,2]. In the earlier phase of the disease, tumors are well encapsulated with dense fibrous tissue, and behave like benign tumors. In the later phase, however, they break the capsule and invade neighboring structures. Nevertheless,
stages I and II have repeatedly been reported [6,11]. These facts clearly indicate that capsular invasion does not affect survival, and thus should not be used to define stage groups.

Another issue is the heterogeneous prognosis of patients with stage III thymoma. By definition, thymomas with only slight invasion into the pericardium are considered stage III, and they can be resected easily with a potentially favorable prognosis. On the other hand, huge tumors with aggressive invasion into the lung, great vessels, etc. are also considered stage III, and they might be unresectable with an unfavorable prognosis. Therefore, although these two tumors are in the same stage group, the appropriate therapeutic strategies are considerably different. Due to the wide range in the extent of the disease and the prognosis, different treatment plans could be applied, which would contradict the original purpose of 'staging'. These two issues regarding stages I–III seem the most crucial defect of the Masaoka system, and should be addressed.

Thus, we proposed two staging systems, and assessed the distribution of the prognosis among the four stage groups in comparison with those in the Masaoka system. In the new systems, we merged Masaoka’s stages I and II to create a new stage I, which was defined as tumors limited to within both the mediastinal pleurae regardless of capsular invasion. Furthermore, to create new stages II and III from Masaoka’s stage III, we considered both the tumor size and number of involved structures/organs. The prognostic significance of tumor size has been previously demonstrated by two important studies. Blumberg and colleagues showed that patients with large thymomas (>10 cm) had a significantly decreased (P = 0.0006) survival, with a 5-year survival rate of only 58% compared with 84% for patients with smaller (5–11 cm) thymomas [12]. Similarly, Lewis and colleagues showed that patients with thymomas 15 cm or more in diameter had a significantly worse prognosis than those with smaller thymomas (P < 0.0001) [13]. Our previous multivariate analysis of 130 resected thymomas also indicated that the size of the tumor was a significant prognostic factor [8].

The number of involved structures/organs might affect the resectability and, therefore, can be expected to relate to the choice of treatment and survival.

Among the three staging systems assessed, Scheme I gave the most balanced distribution of survival according to stage, although the limited number of case in this study made the statistical demonstration of 'balanced distribution of survival curves' difficult. The 10-year survival rates in stages I–IV worsened in a stepwise manner: 100, 86, 64, 34%, respectively. According to the Scheme 1 system, for example, a thymoma of 9.6 cm in diameter invading the lung parenchyma would be considered stage II, and could be expected to have a favorable survival rate of around 86% at 10 years with curative resection. However, due to the possibility of local recurrence, postoperative radiation might be indicated. Thus, we think that this new staging system can provide more practical information regarding the treatment plan and prognosis.

TNM-type staging systems have previously been reported by Yamakawa [14] (for thymoma) and Tsuchiya [15] (for thymic carcinoma). Due to the large difference in pathobiological properties and prognosis, two different stage groupings are defined for thymoma and other thymic malignancies. Due to the rarity of thymic carcinoma and neuroendocrine tumors, further accumulation of data and prognostic simulation are indispensable for establishing an appropriate stage grouping.

Acknowledgements

References