Introduction

The role of adjuvant radiotherapy in thymic tumors has not been explicitly defined. Since epithelial thymic tumors are relatively radiosensitive, many clinicians advocate the use of adjuvant radiation therapy in all cases, in addition to those cases where there is extension beyond the capsule [1-4]. Justification for adjuvant radiation is based on studies showing decreased recurrence rates for stage II disease with adjuvant therapy from 30% to 5% [5, 6]. Other groups suggest that, due to the low incidence of local recurrence after complete resection of stage II thymomas, radiation therapy should be reserved for selected patients [7-10]. Schmidt-Wolf [11] proposed that adjuvant external-beam radiotherapy should be considered only for stages II and III disease where there were extensive adhesions between tumor and pleura, microscopic pleural infiltration, or macroscopic invasion of the pericardium, large vessels, or lung. In addition, Chen [12] noted that completely resected stage II thymomas of WHO subtype A, AB, and B-I may not require adjuvant therapy. There is general agreement, however, that incompletely resected or primary unresectable thymomas of all stages should be treated with radiation with or without chemotherapy [13, 14].

Although surgery remains the first choice of treatment for stage I to III thymomas [15-17], there is still controversy concerning the optimum adjuvant treatment of thymoma after complete resection. For stage I thymoma, most studies report no or very few relapses after surgery without any adjuvant therapies [5, 6, 18]. Nevertheless, it has been reported that local recurrence occurs as frequently as pleural dissemination, even after complete resection of thymoma [5, 19, 20]. Postoperative mediastinal irradiation seems to be the most effective adjuvant therapy for reducing the risk of local recurrence and prolonging survival in patients with locally advanced thymoma [21, 22].

Stage I

Stage I thymomas have an excellent prognosis after complete resection. Most groups accept that there is no need for irradiation after surgery for stage I thymomas. In the Memorial Sloan Kettering experience, 25 stage I patients underwent complete resection with one recurrence and 95% 5-year survival and 86% 10-year survival rates [23]. Fujimura and colleagues [17] reported no recurrences in 31 stage I thymomas after total resection alone. Ten-year survival rate was 74.3%. The Massachusetts General Hospital experience between 1939 and 1990 included 52 stage I patients who were all treated with thymectomy alone. No patient relapsed or died of thymoma [24]. In 1988, Curran and colleagues [5] reported no recurrences in 43 stage I thymomas after total resection, with only 1 patient receiving neoadjuvant radiotherapy. Despite a relapse-free survival of 100%, the 5-year survival was only 67% due to a high frequency of severe myasthenia gravis in this patient population.

In the MD Anderson experience, between 1962 and 1987, Pollack and colleagues [25] presented 11 stage I patients who underwent total resection (5 patients who received postoperative radiotherapy, 50 Gy at standard fractionation, and 6 who did not). There were two recurrences (one in each group). A series from Osaka University Medical School presented 38 stage I patients, 26 who underwent irradiation, and 12 who were not radiated [22]. There were no recurrences in the radiated group, but one recurrence (8%) in the nonradiated group.

In a study by Masayuki [26], no recurrence was observed in patients with stage I thymoma after surgery with or without mediastinal irradiation. These results suggest that routine postoperative mediastinal irradiation is not indicated for patients with stage I thymoma after complete resection. However, 21.6% and 25% of stage II and stage III patients respectively suffered from recurrences. In those groups mediastinal irradiation did not have a significant effect on
recurrence rate when stratified by the clinical stage. These results suggest that it is very hard to select the patients who need the additional therapy based solely on clinical staging. Local invasion has been recognized as the most important clinical parameter for thymoma, particularly in stage II patients [19, 27]. To avoid the disadvantages of clinical staging, Masayuki proposed classification based on pleural and pericardial invasion [6]. Data from Singhal et al. [10] re-inforces the trend to refrain from radiating patients with completely resected stage I thymoma. It documents a single recurrence out of 27 stage I patients treated by resection alone and no significant difference between patients treated by resection alone versus resection plus irradiation. For stage I thymoma complete resection by an experienced surgical team is sufficient to maintain local control.

Stage II

It is well accepted that factors influencing prognosis in thymoma are completeness of the surgical resection, Masaoka stage, and WHO histological classification. The prognostic significance of these factors has been largely demonstrated in some recent series in the international literature [1, 18, 28-31]. Although completely resected, about 10% of stage II thymoma manifest local or pleural recurrence even after many years [28-30]. This observation and the demonstrated relative high sensitivity of thymoma to radiation therapy leads to recommendations advocating radiation therapy for all patients with stage II thymoma irrespective of resection status. The consistency of such recommendations is not clear [32]. Whereas the true indication of radiation therapy for stage II thymomas is still controversial, late local morbidity associated to mediastinal and lung irradiation are well-known (cardiac morbidity such as valve fibrosis, pericarditis with pericardial effusions, increased frequency of coronary artery disease; radiation pneumonitis and chronic pulmonary fibrosis; esophageal strictures, dismotility and malignancies; mediastinal fibrous and hematopoietic malignancies) [33-36].

During the past decades, some authors have advocated postoperative radiation therapy [5, 21, 37] whereas few studies have argued against it [23, 38]. Nakahara et al. [22] in 1988 reported a 29% (2 of 7) recurrence rate for patients with stage II thymoma submitted to surgery only, whereas 8% (2 of 25) patients have disease relapse after surgery and postoperative radiotherapy. The patients in this cohort received between 30 Gy in 3 weeks and 50 Gy in 6 weeks. Ogawa and colleagues [37] presented 61 Masaoka stage II patients who underwent postoperative mediastinal radiotherapy. Despite all patients receiving radiotherapy, 6 patients (10%) still experienced recurrence (2 mediastinal and 4 pleural). Their conclusion was that radiotherapy prevents mediastinal recurrence for patients with completely resected thymoma but is insufficient to avoid pleural-based recurrence. Blumberg et al. [23] reported about 30 patients submitted to surgery and irradiation (n = 17) or to surgery alone (n = 13): the recurrence and survival rates were similar for the two groups.

In some cases, the association of radiation therapy to surgery for the treatment of stage II thymomas seems to negatively affect long-term survival. Quintanilla-Martinez et al. [24] in 1994 presented 32 stage II patients submitted to surgery. Seven of them received postoperative irradiation. Recurrence rates were 28% and 8% for patients undergoing surgery and radiotherapy and surgery alone, respectively (difference was not significant). In a previous study, Ruffini et al. [38] showed a significantly lower recurrence rate in a cohort of patients treated with surgery alone compared with patients who underwent surgery and irradiation (the difference was significant p = 0.02): the effect of postoperative radiotherapy seemed potentially harmful. A significant portion of the literature does not perform disease-free or disease-specific survival analysis for stage II thymoma; most concentrate on overall survival.

The evaluation of the real impact of radiotherapy on long-term survival of completely resected stage II thymoma patients is difficult due to the relative indolent natural history of these tumors. The use of overall survival data as an endpoint in the literature has falsely lowered the expected long-term survival of thymoma patients. Progression-free survival and disease-related death seem to be better endpoints in the evaluation of this disease due to the long natural history and confounding factors such as the high incidence of myasthenia gravis.

More recently, two papers focused on the value of postoperative radiotherapy in stage II completely resected thymomas. Mangi et al. [39] updated their 27-year experience and presented 49 completely resected stage II patients. Thirty-five patients were submitted to surgery alone, whereas 14 patients underwent surgery and irradiation. The addition of adjuvant irradiation did not affect long-term disease control. Disease-specific survival for stage II thymoma patients was 100% with and without RT (p = 0.87).

Between February 1992 and 2002, Singhal et al. [10] performed 167 resections for thymoma. Of these, 70 patients were believed to have tumors in stage IIb or less intraoperatively, and all of these patients un-