Editorial

Thymic tumors with parathymic syndromes: good or bad?

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Padda *et al.* (1) published the largest multi-continent study about the relationship between thymic malignancies and parathymic syndrome. Thymic malignancies are very rare tumors of the anterior mediastinum frequently associated, in particular thymomas, with the so called parathymic syndromes. The most frequent of these is the myasthenia gravis (MG). Despite this association, it's been known for many years that different clinical, pathological and prognostic factors are still in a gray zone and further investigations are needed to clarify the binomial thymic tumors and parathymic syndromes. In recent years, the International Thymic Malignancy Interest Group (ITMG) collected data from different centers all over the world, which became a paradigm for performing research in rare malignancies such as thymic tumors. The authors in this paper had access to the retrospective ITMG database of 6,297 identified patients operated from 1951 to 2012 because of thymic tumors with their paraneoplastic or autoimmune thymic (PN/AI) status at the initial diagnosis. That's obviously is the first "pregio" of the present study. They focused their attention on the baseline and treatment characteristics of this cohort of patients associated with PN/AI syndromes, then they investigated the prognostic role of PN/AI syndrome for patients with thymic malignancies.

We already know that some factors are statistically related with the overall survival and disease-free survival, the strongest of these are histology, Masaoka-Koga stage, R resection status, tumor dimension, age, adjuvant radiotherapy. Padda and coworkers obtained the same results in multivariate analysis and moreover confirm the strict relationship between recurrence and survival (2).

Patients with thymic tumors and PN/AI syndromes are younger, more frequently female, with smaller lesion and diagnosed in earlier stage compared to patients without PN/AI. In older reports, parathymic syndromes were considered a risk factors for worse prognosis, even myasthenic patients (3,4). The reason for that could be explained with less knowledge about PN/AI syndromes and the limited therapeutic strategies at that time. The patients died not for cancer related causes but for the complications of MG or other PN/AI. Today for patients with MG the treatment is well defined and effective, limiting complications and myasthenic crisis that were the most frequent cause of death in the postoperative and follow-up period after thymectomy in the past. In the present study, this aspect is really clear, indeed the OS advantage for patients with PN/AI is evident only in the most recent time period of the database. The sentence "myasthenia, thymic tumor and worse prognosis" today is completely reversed. Patients who complain of myasthenic symptoms receive the diagnosis of thymic tumors earlier in less advanced stage with smaller lesions, indeed all patients with new diagnosis of MG must be studied to exclude the presence of an anterior mediastinal lesion. The diameter of the tumor is considered an important prognostic factor in many studies despite the new TNM staging system not including this aspect in T staging (5). In the future, the diameter of the lesion should be considered for T stratification. Moreover PN/AI syndromes give an advantage in terms of treatment time from diagnosis influencing favorable overall survival and disease-free survival. However, the time aspect is not sufficient to explain the better survival for patients with MG and thymic tumors, histology and cancer biology may be different between patients with and without MG. This

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aspect is still not clear, but some evidences are in favor of that. For instance, we know that in thymic carcinoma or B3 histology, PN/AI manifestation are rarer, so MG might represent a phenotype of thymoma with a less aggressive histology.

If a favorable outcome is related with MG, the same is not demonstrated for other PN/AI such as pure red cells aplasia or hypogammaglobulinemia. These PN/AI disorders are very rare and it's difficult to achieve sufficient evidence with such small numbers, but probably the time advantage and biological factors, are less favorable in these severe syndromes.

If MG associated with thymic tumors seems to give an advantage in term of early diagnosis, it seems to give also some advantage for the choice of the surgical procedure. Today the gold standard surgical intervention for thymic tumors is radical thymectomy and thymomectomy that include the *en bloc* resection of all mediastinal fatty tissue. Padda *et al.* (1) confirmed also in their work that radical thymectomy and thymomectomy are performed much frequently in patients with PN/AI in particular MG. The reasons for that could be multiple, first of all as we show before patients with PN/AI syndrome are younger and thus surgeons are more comfortable to perform such demolitive and aggressive surgery than in older patients. Second, we learned from thymectomy for MG that to achieve good results and complete remission of the syndrome is of paramount importance to remove all the mediastinal fat because containing very frequently gross or microscopic ectopic thymic tissue. In case of thymic tumor associated with MG the surgeons are more inclined to perform extensive mediastinal tissue resection because in those cases the primary objective is to remove radically the tumor and resolve the clinical symptoms of MG (6).

In older patients with early stage thymic tumors without MG the surgeons can be satisfied performing thymomectomy with partial thymectomy. Indeed, previous reports shown similar disease-free survival compared with radical thymectomy in this subgroup of patients. Padda *et al.* (1) reported a significant lower recurrence rate in PN/AI positive group compared to PN/AI negative group as well as better overall survival, but at the multivariate model, the PN/AI factor was not independently associated with recurrence rate and OS. If it's a confounding factor, it's not clear, but the tendency to perform limited resections in PN/AI negative patients and other factors such as higher rates of complete R0 resection, smaller tumors, earlier Masaoka stage in PN/AI positive patients probably have a statistically significant impact on follow-up results. Therefore, surgeons should be motivated to perform radical thymectomy and thymomectomy even in PN/AI negative patients (7). The authors didn't analyze the surgical access used to perform the operation. Today, in early stage thymic tumors it's considered justified to use minimally invasive approaches such as VATS or RATS. In the near future it will be required to associate a more or less radical lymphadenectomy of the anterior and profound mediastinal stations in particular in advanced stage and aggressive histology tumors. Indeed, patients with pN1–2 thymic tumors have a worse prognosis than pN0 patients (2,7). Therefore, surgical strategies to achieve complete R0 resection and adequate lymphadenectomy could change over the next years. So, again, patients with PN/AI syndromes, in which usually the diagnosis is made in early stage with smaller tumors and may be favorable histology, could be further encouraged to receive also a minimally invasive approach compared to patients without PN/AI syndromes. Even if it was not the mainstay of this work, Padda *et al.* (1) shown that curative chemotherapy was independently associated with worse OS. Nevertheless, there is a very limited data about curative or adjuvant chemotherapy in thymic tumors, there are no randomized trials comparing different therapeutic strategies or drugs regimens and some debate about the pathological stage who benefit more for adjuvant chemotherapy and even radiotherapy in particular Masaoka-Koga stage IIb (2). Meantime adjuvant therapy after surgery is mainly radiation treatment, that also in this study is an independent factor associated with decreased recurrence rate and improved OS. Induction therapy seems to be effective in advanced stages and to achieve more R0 resection, but further, may be, randomized studies on large series are needed.

In conclusion, until today many of landmark papers published about thymic tumors are based on very small series of patients (8), an example on all, less than a hundred patients were used to validate the most validated staging system by Masaoka *et al.*, still used in the majority of the countries.

The working method introduced by the ITMG and the creation of a large database is the key to thoroughly study these rare neoplasms. Padda *et al.* (1), basing their research on such huge database gives us a further confirmation of different prognostic factors: tumor stage, histology, tumor dimension, age, etc. In particular, they've shown that MG parathymic syndrome should be considered a positive prognostic factor for all the reasons described above. It's still not clear if other parathymic syndromes have the same

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prognostic values, but surely a future specific revaluation of this database with further cases enrolled could help us obtain concrete answers on the matter. Unfortunately, nowadays there still is a significant heterogeneity in the surgical approach and treatment, the ITMG group and papers like this will have to concentrate their efforts to validate the gold standard procedure for these patients on the basis of the staging system. The latter is experiencing a wind of change where the size of the tumor, the presence of PN/AI syndromes and the role of lymphadenectomy could become important factors in deciding the correct therapeutic strategy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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