this is the reason that the vast majority of our patients are myasthenic. The neurologists refer the patients to us.

Regarding the neurological follow-up, after the first operation, of these 43 patients, 29 experienced a partial or complete response of myasthenia symptoms, but in this group only 5 had a complete pharmacological remission.

It’s a low incidence, but it’s common in this series.

At the time of the second relapse, in this group of 29 patients, only 8 also had a relapse of symptoms, and after the operation, the disease remained stable. So it is not an exciting response to myasthenia in this thymoma group, but this is not at variance with the literature.

Dr Lucchi: I have a concern about the inclusion of the initial stage IVA thymoma. In stage IVA thymoma, recurrence is not rare. I think it’s quite natural. I would like to suggest excluding that kind of patient. Can you comment on that?

Dr Margaritora: Yes, you are right. You ask the question: Why do you include these patients? I can turn the question around: Why not? These 10 patients were not stage C, so nonthymic carcinoma, with small implants in the pleura, radically resected, and so I don’t think that these selected cases could be a bias in this study, but from a theoretical point of view, you are right.

Dr Lucchi: The last question is a little bit surprising by the high percentage of upgrading, 60%, but particularly I’m surprised that you found 6 type C thymomas at recurrence. I am reminded of a very famous American pathologist told me 2 years ago, that if your pathologist does 3 sections, he will say B1, B2 tumour, and if he does 10 sections, he will say B3 or maybe also type C. So there is lot of heterogeneity inside the single thymoma, but from thymoma A or B to type C there is a lot of difference. Can you comment on that?

Dr Margaritora: From the beginning, all cases of thymoma in our institution have been reviewed by a single pathologist. I must trust him. I have no other elements to say why. The data on survival (I mean that the upgrading does not affect survival) is very strange, and I think that has to be validated by a multicentre study. With a 43-patient series, I don’t think that we can make a conclusion.

Dr C. Choong (Melbourne, Australia): Obviously a lot of time has been put into this study and it is one of the largest series that we would have seen in the literature.

Firstly, I have a comment. Your paper is an important reminder to all of us that following up on these patients is very important in the long term because of the risk of recurrence. I have a simple question. What is your follow-up protocol in terms of doing X-ray every 6 months and a CT scan once a year? What is your suggestion?

Dr Margaritora: Well, after operation, the follow-up is performed on our patients by the neurologists, because you’ll see that 90% have myasthenia. The neurologists follow-up these patients. For patients who had radiotherapy after operation, the follow-up is made by the oncologists. In general, we adopted a follow-up policy as for lung cancer, which is intensive for the first 5 years and then yearly with a CT scan.

Dr P. Van Schil (Antwerp, Belgium): Were there any patients who had recurrent symptoms as the first sign of recurrent thymoma?

Dr Margaritora: Yes, but it was at the same time, because you have to consider that when a patient has a worsening of symptoms, he goes to the neurologist, so at the same time we had the diagnosis. In all cases there was a very early diagnosis of recurrent disease.

Dr G. Leschber (Berlin, Germany): I want to continue with this discussion. You said that most of the patients who had a relapse are myasthenia gravis patients. These are the ones that are followed by your neurologists. On the other hand, you pointed out that a lot of these recurrences happen pretty late, years and years thereafter. So isn’t it possible that a lot of patients actually have a small recurrence that we do not know of because after 5 years or so they are not followed anymore?

Dr Margaritora: Yes, it can happen in the nonmyasthenic patients, but the patient with myasthenia usually goes to the neurologist once a year.

Dr Leschber: No, I’m talking about the nonmyasthenics, but probably—

Dr Margaritora: Yes, but in this selected group we have only 3 nonmyasthenic patients.

Editorial comment

Recurrence of thymoma

Keywords: Thymoma; Thymic recurrence; Surgery

Despite the fact that recurrence of thymoma has been the object of a number of studies dating back to more than 20 years, the published series have provided conflicting results.

In fact, when viewing the impressive literature on thymomas, one cannot help noticing how virtually each study on thymoma suffers from the same methodological flaw: the lack of randomization. Thymomas are rare neoplasms with a tendency of a slow-growing progression and this implies that controlled randomized clinical trials are unlikely to be funded and supported because of the rarity of the disease, of the limited number of participating centers involved, and of the required long-term follow-up. In 2008, Davenport and Malthaner [1] published a systematic review of the literature to provide some evidence-based recommendations about the role of surgery in the management of thymomas. Among others, the authors tried to answer the question whether surgery is a useful treatment option in recurrent thymomas. The authors found six retrospective case series dealing with the role of surgery in the treatment of recurrence of thymoma. Since the completion of their literature search (June 2007), five additional reports have been published. The conclusions of the authors and the more recent series indicate that re-resection of recurrent thymoma seems reasonable, although the data on which such a recommendation is based are methodologically weak. A further source of confusion arises when considering that non-surgical recurrence treatments (chemotherapy, radiotherapy, or a combination of both) resulted in reasonable intermediate-term survivals (35–65% 5-year survival rates) [2].

As a consequence, there is still confusion among centers dealing with thymic malignancies about optimal management in case of thymoma recurrence. A recent survey among the European Society of Thoracic Surgeons (ESTS) members [3] indicated that most centers agree that recurrence should be removed when resection is feasible; some centers reported to perform multiple subsequent resections in case of repeated recurrence; several centers pointed out that they proceed to resection only when complete resection may be anticipated.

Having said that, a major issue is how we may reduce the recurrence rates and improve survival rates in recurrent
thymomas. It may be hypothesized that a stricter follow-up may detect a recurrence earlier, thus providing an increased survival, and this is currently being employed by some centers (annual computed tomography scan for life [4], but it may be hardly applicable worldwide due to the different health-care systems and the associated costs. Second, as survival rates are highly dependent upon the completeness of resection, surgery of thymoma recurrence should ideally be performed in centers with high volume of thymoma cases and with a great experience in major thoracic procedures, including extrapleural pneumonectomy and resection/reconstruction of intrathoracic great vessels. Third, a close cooperation with dedicated medical and radiation oncologists is essential in dealing with thymoma recurrences. Promising results have been published in reducing recurrence rates after thymoma resection using tyrosine kinase inhibitors (imatinib) [5].

To accomplish all the aforementioned guidelines, a major effort by the scientific community to work in close cooperation is crucial.

Major credit should be given to the International Thymic Malignancy Interest Group (ITMIG) [6], which recently defined a standard set of definitions for recurrence: (1) the term ‘recurrence’ is appropriate if all disease has been potentially eradicated (R0 resection); (2) recurrences are classified as local (anterior mediastinum), regional (intrathoracic not contiguous with the thymus), and distant (intrapulmonary and extrathoracic); and (3) the freedom-from-recurrence outcome indicator should be used for any study on recurrence after R0 resection, and 5- and 10-year outcomes should be reported in every series.

The series from Margaritora and associates [7] published in the current issue of the European Journal of Cardio-thoracic Surgery complies with most of the ITMIG requirements, and the authors deserve credit for that. Although retrospective, the series covers a long-time experience of one of the most authoritative centers performing thymic surgery. Out of 315 R0 resections in a 37-year period, 43 patients developed recurrence. Of them, 30 patients were deemed amenable to surgical resection of the recurrence (70% resection rate). The pattern of relapse according to ITMIG definitions was local (28%), regional (58%), and distant (14%). Of the 30 resected recurrences, a complete resection was achieved in 22 (73% complete resection rate). Surgery was performed safely in these patients (0% perioperative mortality, 27% morbidity). Survival rates in R0 patients was excellent, while similar poor survival (35% at 5 years) was observed in patients receiving either R+ resection or non-surgical treatments. In multivariate analysis, R0 resection and surgical treatment of recurrence were significant prognostic factors. The study has some points of interest, in particular the different time-to-progression in B3 tumors as compared with B1/B2, the uselessness of incomplete resection in favor of non-surgical therapies, the potential significance of the number of localizations, and the histologic shift in the recurrence as compared with the primary thymoma. These are surely points of interest, which will deserve consideration for collaborative studies where a large number of cases may be collated and analyzed.

The future of the clinical research in thymic malignancies seems therefore to lie in the building up of a collaborative multi-institutional effort, which should include international dedicated organizations such as ITMIG and the International Association for the Study of Lung Cancer (IASLC) and regional dedicated organizations including the ESTS and European Association for Cardio-thoracic Surgery (EACTS) thymic working groups, as well as the Japanese Association for Research on the Thymus (JART) in a global project to redesign a common set of definitions, a retrospective and prospective collection of data, and a validated staging system. A great deal of work is currently under way aiming at the provision of a new staging system for thymic malignancies, which should be approved by the Union Internationale Contre le Cancer (UICC) and the American Joint Commission on Cancer (AJCC) for the 8th edition of the TNM staging manual, expected in 2017. If the task is accomplished, it will surely represent a major step forward in the understanding of these rare, although unique, malignancies.

References


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