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Review

Surgical treatment of pleural recurrence from thymoma

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Summary

A complete surgical resection represents the cornerstone of the therapy of the thymic tumours. Pleural disease may already be present at the diagnosis representing an advanced stage thymoma (Masaoka IVA) or it may appear during the follow-up, representing a pleural recurrence. The treatment of Stage IVA thymoma is quite examined in the medical literature; however just a few reports analysed the surgical treatment of thymoma recurrences, whose exclusive pleural recurrences represent more than 90%. Our aim was to review the literature laying the stress on the incidence, diagnosis, treatment options and prognosis of this highly selected group of patients with pleural recurrence from thymoma.

Keywords: Thymoma; Pleural relapse; Surgery; Multimodality treatments; Survival

1. Introduction

Thymomas are neoplasms arising from the epithelial thymic cells. These tumours rarely metastasise, but they can frequently show pleural implants at the diagnosis or during the follow-up [1]. Data in literature show that pleural implants can also occur several years after thymoma resection, both encapsulated and invasive [2—6]. Unfortunately scanty medical literature is available about the treatment of recurrences of thymoma [3—7] and only a few reports focus on the pleural implants [8—10]. The treatment of the pleural implants ranges from immunosuppressive therapy [11] to platinum based chemotherapy regimens [12—13], to surgical removal of the pleural implants with intrapleural hyperthermic chemotherapy [8,14], to extended resections as the pleuro-pneumonectomy [15].

The aim of our work was to review the medical literature about the treatment of pleural recurrences in terms of incidence, treatment and prognosis in a highly selected group of patients.

2. Definition and incidence

Pleural recurrence from thymoma should be labelled as the appearance of pleural implants during the follow-up of a radically resected thymoma patient. In patients with initial Stage IVA thymoma, the term of pleural recurrence has to be considered with caution for two reasons: (1) the radicality of the first surgical treatment has to be regarded questionable and (2) the probability of a pleural relapse is really high. For this reason, we ruled out this subset of patients from the review.

Despite a complete resection, recurrence of thymoma can occur in 10—30% of patients for a long period after the operation. The overall frequency of haematogenous metastasis is low (0—10%) [1], while the majority of the recurrences appear as pleural dissemination (≃90%), mediastinal relapse (≃5%) or both [3,6,16].

3. Diagnosis

Pleural relapse of resected thymomas can also occur after many years. Analysing the treatment of recurrent thymoma in the medical literature, the mean disease-free period is between 60 and 80 months [3,5,6]. This data highlights that lifetime follow-up is necessary in order to detect recurrences of thymoma also in the early stage thymomas [3,5].

Development or deterioration of myasthenia gravis, as well as other thymus-related syndromes, may raise the suspicion of a recurrence [17]. Pleural relapse is often asymptomatic and found incidentally during the follow-up. In the presence of a pleural effusion, chest pain or dyspnoea represent the most common symptoms.

Chest CT is the main diagnostic tool and it should be performed at least every year during the follow-up in resected thymoma patients. Pleural implants can appear

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everywhere in the pleural cavity or in the pulmonary scissures, but they are more frequently in the mediastinal pleura (along the phrenic nerve), in the vertebral douche or over the diaphragm.

Similarly to the primary thymoma they are usually homogeneous and enhance with intravenous contrast, but they can occasionally show calcifications, cystic components and areas of necrosis. Chest CT is able to delineate the number, site and size of implants and overall presence or absence of local invasion. Regarding the number of pleural implants, CT usually underestimates it because the implants can be too small or hidden in anatomical regions not easily explorable. This issue lays the stress on the relevance of a careful exploration of the pleural cavity during surgery.

4. Pathological and staging classification

The World Health Organization histologic classification system seems to match the oncologic behaviour of thymoma [18–20], with most of the pleural recurrences occurring in type B3 thymoma. Until now no evidence is present in literature regarding the WHO classification as a prognostic factor whenever the survival rate is calculated from the occurrence of the pleural relapse itself.

The pleural implants usually maintain the same histological characteristics of the primary thymoma, even though they can be a little bit more undifferentiated. In an already-resected patient for a thymoma, the tissue diagnosis of a pleural implant is rarely necessary. Imaging (CT) easily leads to the diagnosis and, whenever the pleural implants are judged resectable surgery is indicated as primary therapy regardless of the histological diagnosis. On the contrary, large tumours, requiring extensive surgical procedures or neoadjuvant chemotherapy, require a histological confirmation.

In this case the available techniques are the fine-needle aspiration (FNA) cytology or, much better, a core needle biopsy or a thoracoscopy.

There is no standard staging system for thymoma, however the Masaoka staging has been accepted worldwide [21] and most of the authors do not advocate a tumour-node-metastasis (TNM) staging system. The presence of pleural implants from the beginning or during the follow-up of resected thymomas constitutes a 'Masaoka Stage IVA'.

Pleural implants may occur after the resection of a thymoma regardless of the clinical stage of the primary thymoma, however incidence of recurrence increases in relation to the clinical stage and the disease-free interval decreases according to the clinical stage [3,6].

A useful addendum to the Masaoka surgical–pathological staging of the initial thymoma was done by Haniuda et al. [22] in 1996. The author proposed a pathological approach based on the relation among thymoma and parietal pleura (pleural factor, p) and pericardium (pericardial factor, c). He reported that patients with fibrous adhesion (p1/c1) or microscopic invasion to the mediastinal pleura or pericardium (p2/c2) were at increased risk for recurrence.

The author confirmed this data in another report showing a statistically significant recurrence rate (>50%) for p2/c2 thymomas [6].

5. Surgical options

Except for widely metastatic disease, surgery is the cornerstone of therapy even in cases of recurrent thymoma. It is commonly accepted that a complete resection represents the critical factor in determining long-term survival even if the results in literature are controversial. Most series report that partial resection is associated with improved survival compared with biopsy [23–25]. On the contrary some series [26] reported no benefits by debulking surgery. The role of debulking surgery should be more extensively investigated before stating that extensive and jeopardising surgical procedures are really necessary.

Regarding the value of surgery in the treatment of pleural recurrences from thymoma, there is no scientific evidence that surgical treatment is superior to the chemotherapy with or without radiotherapy. Papers comparing patients who underwent surgery with patients who underwent radiotherapy are really few. Except for Haniuda's study [6], the majority of the papers are in favour of the surgical group [3,5]. However in all the studies, surgery was reserved to resectable recurrent tumours in patients with good clinical conditions; this clinical selection bias invalidates the scientific value of hypothetical superiority of the surgical treatment.

In theory, a complete resection of a recurrent thymoma should offer the best chance of long-term survival, but the judgement on a so-called radical resection in case of a pleural disease may be '*philosophical*' and surgeons can differ on the way to obtain the radicality.

When the pleural implants are minimal, usually in the costodiaphragmatic recess, or on the diaphragm, the resection is easy and it can be approached by a thoracotomy. A sternotomy can be indicated only in case of an associated relapse in the mediastinum. In case of massive pleural dissemination and massive involvement of the diaphragm, pulmonary hilum, and the chest wall, surgery may become challenging.

In these cases a radical pleurectomy or, better, a pleuro-pneumonectomy, with replacement of the diaphragm, should be considered. A few case reports were published about pleuro-pneumonectomy in the treatment of advanced stage thymic tumours. Lately it was published a paper by Wright [15] which emphasised this issue. He reported five patients with pleural Stage IVA B3 thymomas (two recurrent and three de novo) who were treated by a pleuro-pneumonectomy, as part of a multimodality treatment, with no operative mortality and only one major complication. Wright emphasised the selection criteria for pleuro-pneumonectomy: extensive pleural disease with pre-existing nerve paralysis in young patients with excellent cardiopulmonary function and a well-controlled myasthenia gravis, if present.

The hypothesis that pleuro-pneumonectomy, a procedure usually reserved for malignant pleural mesothelioma, can be useful for thymoma is supported by surgeons who believe in the positive prognostic value of radical surgery in this slowly evolving disease. On the other hand there are also authors who dissuade from performing a pleuro-pneumonectomy for thymoma pleural recurrence because of a high perioperative mortality [6] and good survival rates achievable by hemithorax radiation [9].

In order to achieve a better local control, some authors tried to add intraoperative perfusion thermochemotherapy to maximal achievable resection. The efficacy of hyperthermia in the treatment of malignant neoplasms has been already shown in several papers [8,14,27—28]. Intrapleural cisplatin-based chemotherapy has shown a local pharmacologic advantage exposing the tumour to a higher concentration of the drug with a reduced number of toxic systemic effects [27]. The synergism between hyperthermia and cisplatinum has been used for the treatment of thymic malignancies with pleural spread by Refaely et al. [8]. He reported 15 cases of thymic malignancies with pleural spread, 6 of these were intrapleural recurrent thymomas treated by resection and hyperthermic intrapleural chemotherapy. Operations ranged from extended extrapleural pneumonectomy to parietal pleurectomy or tumour resection without pleurectomy.

The treatment was feasible, without mortality, with low morbidity and achieved an excellent 5-year survival rate for the thymoma patients (70% survival rate). Furthermore, all the survivors and one patient who died for other causes did not have ipsilateral pleuropulmonary relapse. Cytoreductive surgery and intraoperative hyperthermic intrathoracic perfusion chemotherapy (HITHOC) with cisplatin and adriamycin were performed in a further three cases in The Netherlands Cancer Institute. De Bree et al. [14] reported nil mortality, low surgical and medical morbidity and all thymoma patients were alive and free of disease after a mean follow-up period of 18 months. The same authors recently [28] performed a study and the conclusion was that intrathoracic chemotherapy with doxorubicin and/or cisplatin could be used for primary and secondary pleural malignancies, even immediately after extensive thoracic surgery.

6. Other treatments

In case of pleural implant, most authors reserve medical treatment only for patients in poor condition or with extensive disease. In literature there are some papers, mainly case reports, reporting partial response or tumour regression with non-surgical treatments [11,13,29—30].

First, we should recall the value and effectiveness of corticosteroids for invasive thymomas [30], especially if thymus-related syndromes coexist. There is general agreement that the epithelial cells represent the tumour cells and the lymphocitic cells are considered benign infiltrating cells. So the effectiveness of corticosteroids could be due to their lympholytic action. Lately Taguchi et al. [11] published a case report showing tumour regression of disseminated pleural implants (implants which appeared 20 years after the thymoma resection), after combined therapy with corticosteroid and tacrolimus.

Thymomas have shown a good response rate to systemic chemotherapy [31—32]. Particularly in the neoadjuvant setting, the combination of cisplatin, doxorubicin and cyclophosphamide (PAC), the combination of cisplatin, doxorubicin, vincristine and cyclophosphamide (ADOC), and the combination of cisplatin, etoposide, and epidoxorubicin have reported objective response rates ranging from 77% to 100% [33—35]. Such excellent results have not been confirmed in the adjuvant or palliative setting. Reporting a 10-year experience on the systemic treatment of malignant thymoma and strictly adopting the RECIST criteria, Giaccone et al. [12] found a 31% response rate to chemotherapy administered for advanced or recurrent thymoma. In the same paper, Giaccone showed that the association of octreotide with prednisone was the only treatment producing objective remissions after first-line chemotherapy. Indeed he confirmed the preliminary experience of Palmieri et al. [29,36] and the experience of the Eastern Cooperative Oncology phase II trial by Loehrer et al. [37].

In order to decrease the toxicity of systemic chemotherapy and to achieve a better local control, Terada and colleagues [12] have successfully treated two cases of pleural recurrences by means of transarterial infusion of chemotherapy through the intercostal arteries and subphrenic artery.

Thymomas are tumours very sensitive to radiation [38]. The radiation has been used alone or in combination with chemotherapy for unresectable thymoma. Its role as an adjuvant treatment after surgical resection is controversial and it could be useful at doses of 45—55 Gy to reduce the mediastinal relapse rate only in really invasive Stage III [39—41].

However, adjuvant radiotherapy cannot decrease the incidence of pleural relapses as the implants are set out of the radiation field.

Low-dose entire hemithorax radiotherapy (EHRT) for pleural dissemination or relapse has been described for the first time by some authors [9,42] and, recently, by Sugie et al. [43]. The author treated eight pleural disseminations and four pleural relapses with surgery and EHRT at an average dose of 14.1 Gy. He experienced only one grade 4 pneumonitis and concluded that EHRT is safe and could contribute to control of the pleural dissemination.

New radiation techniques like intensity-modulated radiation therapy (IMRT), already used in malignant pleural mesothelioma [44], could improve the outcome by increasing the dose and reducing the toxicity. Until now, however, there is no report about IMRT in the treatment of pleural relapse from thymoma.

7. Conclusions

Thymoma are exceptionally rare tumours, consequently no randomised study was ever performed with any treatment modality in this disease. Pleural relapses are even rarer and a discussion about their treatment has to be based on small reported experiences.

The diagnosis of a pleural implant, with or without a mediastinal relapse, represents by itself a Stage IVA thymoma and its treatment should be considered inside a multimodality treatment, according to the new trends for advanced stage thymomas [34—35].

The reason of the appearance of pleural implants, so called 'droplet metastases', after many years of the resection of a non-invasive thymoma is not clear. Somebody could speculate that it is due to the seeding of tumoural cells during the manipulation of the tumour, particularly if the mediastinal pleura have been opened. This problem should stimulate a discussion about the appropriateness of resecting

small and well-capsulated thymomas using VATS or robotic technology [45—46]. A long-term follow-up is necessary to exclude the possibility that minimally invasive techniques can expose the patients to a higher risk of pleural relapse.

Even if the treatment of pleural recurrence of thymoma is not standardised, surgical treatment, especially if radical, is commonly believed the best option and, as a matter of fact, only resected patients are long-term survivors.

In case of single or few pleural implants the surgical resection is quite simple and the resection can be also judged '*radical*'; on the other hand a massive pleural recurrence and the involvement of major structures could require extensive resections and in this case the radicality becomes questionable. In these cases a multimodality approach including surgery should be preferred. Corticosteroids in the preoperative setting should be always administered to achieve a lympholytic effect and to control the possible thymus-related disorders. In case of microscopic or macroscopic residual disease, it is not clear which is the best adjuvant treatment to achieve a good local control, but low-dose entire hemithorax radiotherapy (EHRT) and intraoperative hyperthermic intrathoracic perfusion chemotherapy (HITHOC) are promising.

Systemic chemotherapy [12] or long-term therapy with octreotide analogue [37] is advisable if the patient is young, in good condition and the risk of recurrence is high.

After the treatment of a pleura recurrence from thymoma, a subsequent new relapse is probable, so that a strict radiological follow-up is mandatory in this subset of patients.

Whenever a new pleural relapse is found, an iterative resection should be considered [47].

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