

Pleural recurrences of thymoma: role and effectiveness of intrathoracic chemohyperthermia

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Thymoma is a rare tumor of the anterior mediastinum characterized by a relatively indolent behavior. Surgery is the cornerstone in the treatment of this tumor and completeness of resection is the main prognostic factor (1). However, despite a complete resection, recurrence of thymoma can occur in 10–30% of patients, following a mean disease-free period that ranges between 60 and 80 months (2). The most established risk factors for tumor recurrence are advanced Masaoka stage and WHO histotype (3,4).

Thymic carcinomas, on the other hand, are usually considered a distinct clinical entity with a more aggressive behavior and a higher relapse rate.

The most common site of relapse (46% to 80% of all recurrences) is the pleural space both on the visceral or parietal pleura as a droplet metastasis, followed by the mediastinum and, finally, by distant metastases (5).

The optimal management strategy for recurrent thymoma is still matter of debate. Treatment options include surgical resection, chemotherapy, multimodality approaches or even observation. Most surgical series report favorable outcomes in patients undergoing re-resection with 5- and 10-year overall survival rates after recurrence of 70.9%±16.2% and 49.6%±27.4%, respectively (6,7). These survival rates compare favorably with those obtained with nonsurgical management; however, they must be interpreted with caution, as retrospective case-series are inherently biased by the selection of patients for surgery, which is usually reserved to subjects with more limited

disease and better performance status.

More recently, several groups have independently adopted a new combined treatment modality, consisting in surgical resection of pleural thymoma recurrences followed by intrathoracic chemohyperthermia (ITCH) (8-10).

This treatment, initially developed and proposed in the multidisciplinary approach to mesothelioma, relies upon the pharmacologic advantage of exposing the tumor to higher concentrations of drugs than it would be possible with systemic therapy.

Hyperthermia has a synergistic effect, because local tissue/perfusate concentrations tend to be greater after hyperthermic perfusion than after normothermic perfusion, as demonstrated by pharmacokinetic studies (11,12).

Published studies reporting the use of ITCH for the treatment of recurrent thymoma, so far, include small cohorts of patients frequently characterized by heterogeneity in patients' selection, including those with pleural recurrence of thymoma but also patients with de novo IVa thymomas and thymic carcinomas with pleural spread, who are characterized by a different prognosis.

The recent report by Maury *et al.*, including 19 subjects, represents the largest homogeneous cohort of patients with pleural relapse of thymoma treated with surgery and ITCH (8). Notably, de novo stage IVa thymomas and thymic carcinomas were excluded from the study. All patients were re-operated with radical intent, by means of subtotal pleurectomy, lung wedge resections, diaphragmatic

and/or pericardium resection. Extrapleural pneumonectomy was performed only in one case. The ITCH protocol consisted in 25 mg/m² mitomycin and 50 mg/m² cisplatin, infused through two chest drains into the pleural cavity for over 90 minutes, with a mean maximal inflow temperature of 42 °C. There was no perioperative mortality and a 26% morbidity rate, with three patients (16%) experiencing toxicity from chemotherapy. After a median follow-up of 39 months, median disease-free survival was 42 months. Five patients died during follow-up; median overall survival was 63 months and 5-year survival was 86%. The authors concluded that ITCH is a feasible option, which clearly provides long local control, without major safety issues, to be discussed in specific multidisciplinary boards.

This paper adds a substantial contribute to the literature in regards to the feasibility of ITCH for treatment of recurrent thymoma; however, there are several questions, in common with other similar studies, that still remain unanswered.

First, the number of enrolled patients in these single-center studies is still too low to allow a reliable appreciation of morbidity rates. In particular, chemotherapy-related complications after ITCH, which occurred in three cases (16%) in the paper by Maury *et al.*, are a matter of concern. It is unclear whether previous chemotherapy, received at any point of the treatment of the initial thymoma or its relapses, might cause a higher toxicity rate at the time of ITCH, and thus represent a potential contraindication for this procedure. Second, survival outcomes for these patients are difficult to interpret, or to compare to case-series of surgically resected pleural relapses of thymoma. In fact, due to the relatively indolent course of the disease, these patients usually experience relatively good survival rates after re-resection alone (70.9%±16.2% 5-year overall survival after recurrence, according to a recent meta-analysis) (6). Thus, a higher number of patients would be needed to detect any statistically significant difference between the two treatment options (surgery alone or surgery with ITCH). For the same reason, the follow-up of 39 months reported in the paper by Maury *et al.* seems largely inadequate for the purpose of survival outcome analysis in patients affected by thymoma. Third, the optimal chemotherapy regimen in the setting of ITCH remains to be defined, as each published study employed different treatment protocols. The impact of this factor on morbidity rates or on survival outcomes is unknown. Fourth, there is still no consensus regarding the extent of resection in the field of surgery for thymoma with pleural involvement. While in the majority of published

studies the resection is limited to the portion of pleura with the underlying diaphragm, pericardium or lung involved, some authors have described the use of total pleurectomy or extrapleural pneumonectomy (13,14). The choice of the surgical procedure might be relevant not only for its impact in morbidity and mortality, but also, more specifically, because of its association with ITCH, as the presence of a portion of intact pleura might increase the absorption area and the serum levels of chemotherapeutic agents (10).

In conclusion, surgery and ITCH for the treatment of pleural localization of thymoma is a promising new therapeutic option, and the pharmacokinetic principles on which it is based seem valid. However, several open questions remain concerning its associated morbidity, inclusion criteria and the optimal treatment protocol. Moreover, long-term data on survival are lacking. It is the authors' opinion that, given the rarity of the disease, a large multi-center study, with a standardized protocol and longer follow up period, is needed in order to clarify some of these points. Until then, ITCH is bound to remain an experimental technique, which the treating physicians should be aware of, and which should be discussed in a multidisciplinary setting and on an individual basis. Referral to specialized, high-volume centers is fundamental in order to guarantee the most effective treatment option in patient with thymoma, and to facilitate the collection of data for scientific purposes.

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Footnote

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

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