Letter to the Editor

The valuable role of extended pleurectomy decortication and HITHOC for disseminated pleural thymoma

Laurens J. Ceulemans[1,2]^, Tom Vandaele[1,2]^

[1]Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium; [2]Department of Chronic Diseases and Metabolism, Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), KU Leuven, Leuven, Belgium

Correspondence to: Professor Dr. Laurens J. Ceulemans, MD, PhD. Department of Thoracic Surgery, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium; Department of Chronic Diseases and Metabolism, Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), KU Leuven, Leuven, Belgium. Email: laurens.ceulemans@uzleuven.be.

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Treatment for advanced-stage thymoma with pleural dissemination [Masaoka Stage IVa–TNM stage IVA (TNM 8th edition)] (TPD) is rapidly evolving and remains a topic of debate within the surgical/medical community. Due to the low incidence of TPD, and heterogeneous literature with a wide variety of therapeutic protocols, no clear consensus is reached on its treatment (1,2).

Foremost, when assessing and managing TPD it is crucial to recognize a stage IVA thymoma as locally advanced disease and treat it accordingly. Therefore, proper oncological staging is required. We propose that every patient would be staged by whole-body positron emission tomography-computed tomography (PET-CT) and chest magnetic resonance imaging (MRI), to rule out distant metastasis and assess local invasion (e.g., ingrowth in the thoracic wall or mediastinal vessels). We believe PET-CT should become standard practice for thymomas/thymic carcinomas as it helps with the differentiation between the two (3), helps with the detection of distant metastasis, and decreased fluorodeoxyglucose (FDG) uptake might even be associated with superior outcomes (4). Additionally, a functional assessment (e.g., ergospirometry, ventilation/perfusion scintigraphy, cardiac ultrasound, myocardial scintigraphy), should be performed to ensure the patient's fitness and estimate the operative risk.

Although thymomas are highly chemo-and radiosensitive, the cornerstone for treating TPD, in patients with good functionality, should be obtaining complete cytoreduction (R0-resection), as this is directly associated with favorable oncological outcomes (1,2,5-7). The value of surgery in TPD was prominently emphasized in the 2017 European Society of Thoracic Surgeons (ESTS) working group paper by Moser *et al.* (6). In two recent reviews, Ruffini *et al.* and Aprile *et al.* highlight that complete surgical resection is an important predictor for good oncological outcome (2,6,7).

However, since debulking surgery can vary from partial pleurectomy to extra-pleural pneumonectomy, and the type of procedure is not always well-defined in literature, it is challenging to determine the preferred surgical approach for TPD (2,6,7).

Based on our experience with mesothelioma-surgery, the optimal surgical approach to achieve complete resection of the thymoma and all pleural implants (macro- and microscopically) is extended pleurectomy decortication (ePD) in combination with hyperthermic intra-thoracic chemotherapy (HITHOC) (1,2). Our ePD procedures follow a standardized technique involving a complete parietal pleurectomy, visceral decortication, and lymph node resection, followed by hemo-and aërostasis, and finally the construction of a neopleura, as described in malignant pleural mesothelioma surgery (8). Regarding the visceral decortication, we create a plane between the visceral pleura and the lung parenchyma, then peel/strip the visceral pleura outwards without damaging underlying lung parenchyma.

^ ORCID: Laurens J. Ceulemans, 0000-0002-4261-7100; Tom Vandaele, 0000-0002-2120-2002.

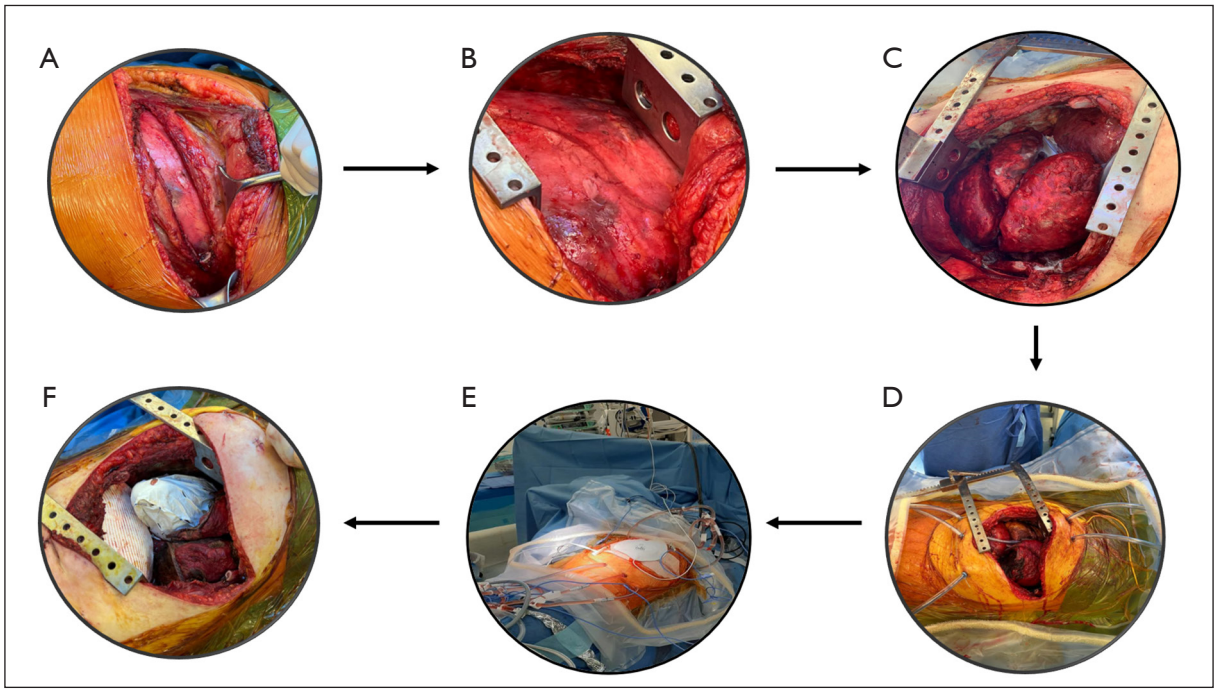

Figure 1 Visualization of our extended pleurectomy decortication with hyperthermic intrathoracic chemotherapy procedure. (A,B) Thoracotomy with resection of the 6th rib to achieve proper exposure; (C) status after parietal pleurectomy and visceral decortication; (D) installation of the HITHOC setup; (E) during HITHOC perfusion; (F) after reconstruction of the diaphragm and pericardium. HITHOC, hyperthermic intra-thoracic chemotherapy.

Thereafter, aërostasis is achieved by suturing major air leaks and constructing a neopleura using an absorbable polyglycolic acid sheet (Neoveil) and polymeric hydrogel sealant (Progel) (*Figure 1*).

Despite meticulous surgery and maximal resection, microscopic residual disease may be inadvertently left in the thoracic cavity (2). HITHOC has emerged as a novel intra-operative treatment modality, drawing inspiration from its abdominal counterpart, hyperthermic intraperitoneal chemotherapy (1,2,7). During HITHOC, the thoracic cavity is irrigated with heated chemotherapy to enhance local disease control by targeting residual microscopic disease. The mechanism of HITHOC is based upon two main principles: (I) hyperthermia increases the penetration depth of the chemotherapeutic agents and enhances the permeability of tumoral cells to these drugs; (II) during HITHOC high concentrations of cytotoxic agents can be presented to the target tissue (1). The main oncological benefit of HITHOC is seen in improving local disease-free survival, as highlighted in a review by Aprile *et al.* (2). According to Ruffini *et al.*, the use of HITHOC in the treatment of stage IVA thymomas can achieve long-term overall survival rates ranging from 67% to 89% (7).

It is crucial that the treatment approach is tailored to the patient, and disease (6). The most suitable indication for ePD + HITHOC would be a patient meeting the following criteria: (I) unilateral disease confined to the pleural cavity, (II) a tumor sensitive to chemotherapy, and (III) a functionally fit patient. Nevertheless, in case of stage IVA disease with a limited number of well-localized pleural droplet metastases (≤3), an ePD may be deemed excessive, and a local resection of the pleural implants might be sufficient as a first stage (6,7). This aligns with previous findings, indicating that the number of pleural implants was inversely correlated with positive oncological outcomes (7). Furthermore, it is essential to distinguish between *de novo* stage IVA thymoma (DNT) and thymoma with pleural relapse (TPR), because the outcomes might differ between both groups (6).

There is also no consensus on the preferred HITHOC protocol for TPD (1). Many protocols incorporate a platinum derivative, typically cisplatin, as their primary agent (1,2). Some protocols also include a secondary agent, usually anthracycline or mitomycin C (1,2). In

our institutional HITHOC protocol the patient typically receives 400 mg/m^2 5-FU and 20 mg/m^2 leucovorin intravenously one hour before HITHOC. During HITHOC the thoracic cavity is rinsed with 460 mg/m^2 of oxaliplatin at a temperature of <43 ℃ for 45 minutes (1). Our preference for oxaliplatin as primary agent is justified by its favorable systemic safety profile, improved renal tolerance compared to cisplatin, and the synergetic effect of hyperthermia and oxaliplatin. Despite the heterogeneity in HITHOC protocols, our systematic review on the topic (capturing 171 cases) concluded that HITHOC is a safe and feasible procedure with very low complication rates, irrespective of the choice of chemotherapeutic agents, temperature, and duration of perfusion (1).

In three of our recent cases—a DNT in a 60-year-old male, a TPR in a 23-year-old female, and a TPR in a 33-year-old male—our ePD/extrapleural pneumonectomy (EPP) + HITHOC protocol was used, resulting in favorable short-term oncological outcomes. All patients remained disease-free with the longest follow-up being three years. Similar findings from recent studies looking at ePD/EPP + HITHOC for TPD underscore the efficacy of this approach, with local recurrence rates of 30% and disease-free intervals ranging from 6 to >88 months (1). Beyond thymoma cases, the application of ePD + HITHOC is expanding to other rare thoracic malignancies such as thoracic pseudomyxoma (9), pleural yolk sac tumor (10), Ewing sarcoma, etc.

In conclusion, we would like to propose an International Thymic Malignancy Interest Group (ITMIG) working group to formulate a consensus statement on the work-up and treatment of stage IVA thymomas. This consensus statement should encompass a thorough oncological and functional work-up for every patient, offer guidance on the choice of debulking surgery, and outline a detailed HITHOC-protocol including the choice-and dosage of chemotherapeutic agents.

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