



# Mediastinal lymphadenectomy for thymic malignancies: the time has come

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## Introduction

In a recent issue of the *Journal of Thoracic and Cardiovascular Surgery*, Dr. Wentao Fang and Colleagues reported the results of a prospective observational trial concerning intentional lymphadenectomy during thymectomy for thymic malignancies on 275 patients (1). This remarkable study was devised and developed by the Chinese Alliance for Research in Thymomas (ChART) and follows a retrospective study on 1,617 patients (2). In the prospective study, a “lymphadenectomy minimum” was mandatory (at least 1 anterior mediastinal lymph node station should have been harvested). And here comes the first surprising result: the incidence of nodal metastases rises from 2.2% to 5.5% when compared with retrospective series. This “nodal upstaging” was not related to differences in stage and histology (which proved to be similar between the two groups) but to lymphadenectomy itself. The study underlines another somehow unexpected result: video-assisted thoracoscopic surgery (VATS) thymectomy allowed more stations to be harvested and yielded more lymph nodes than open approaches (3.30 vs. 2.84;  $P=0.017$  and 5.31 vs. 4.46;  $P=0.05$ ). On the other hand, VATS approach was hardly associated with bilateral node dissection (5% vs. 22.8%). The study also confirms some results which have been foreshadowed by retrospective series. In particular high-grade malignancies (carcinoid and carcinomas) and advanced stage lesions presented with higher incidence nodal metastases. Neuroendocrine thymic tumors (NETT) in particular, showed a tendency towards multistation and bilateral nodal involvement. Basing on these observations,

the authors proposed a model for prediction of nodal metastases according to locoregional extension (T), WHO classification, and type of dissection. These results were conveniently employed to produce a nomogram, providing a predictive tool for nodal spread “at a glance”.

## Incidence of nodal involvement in retrospective

The issue of nodal involvement has become more and more important after the introduction of a standardized staging, that would conform existing staging systems, basing essentially on the work of Masaoka, to TNM classification (3). To date, Yamakawa and Masaoka themselves proposed an *in nuce* stadiation that would include a separate descriptor for nodal involvement (4). It was defined as follows: anterior mediastinal nodes (surrounding the thymus gland, generally removed during a standard extended thymectomy), intrathoracic nodes (paratracheal, subaortic, hilar, intrapleural nodes) and extrathoracic nodes. In a subsequent retrospective analysis of 1,320 patients, Kondo and Monden (5) substantially validated the nodal staging. They observed an overall incidence of nodal disease in 1.8% of thymomas, 27% of carcinomas and 28% of carcinoids. Survival was strongly affected by nodal involvement, especially for carcinomas and carcinoids. Although N involvement was a prognostic factor for thymomas, no difference in survival was observed between N1 and N2. Upon the contrary, a significant difference in 5-year survival according to N status was observed in carcinomas and carcinoids (56% for N0, 42.1% for N1, 29.3% for N2). Concurrently, incidence of nodal

involvement varies between 25% and 37% in retrospective series (6). Thus, nodal involvement seems to be a clinical issue for more aggressive tumors. Fang and colleagues confirmed this trend, showing an incremental incidence of nodal metastases from B2 to C and NETT. According to the new insights provided by the work of Fang and colleagues, given the incidence of lymph nodal involvement, relapse should happen mainly in the mediastinal region for thymic carcinomas and NETT, whereas thymomas typically relapse within the chest cavity. In a retrospective analysis on 179 thymomas (including carcinomas, but excluding NETT), Wright and colleagues reported 2 relapses in the mediastinum (1.1%), and 16 pleural implants (7). More recently, Hwang *et al.* (8) have investigated the prognostic impact of nodal involvement in 131 thymic malignancies undergoing nodal dissection. Incidence of lymphatic involvement was higher in carcinomas (8/32; 25%, *vs.* 5/99; 5% for thymomas). When limiting the analysis to carcinomas and NETT undergoing any form of nodal dissection, incidence of N disease resulted 33% for carcinomas and 62% for NETT in a study from SEER database (9).

### Anatomical issues and relapse patterns

Park *et al.* reported their experience on lymph node dissection in 37 patients with thymic carcinomas. They performed nodal dissection in 29 patients, with an incidence of nodal involvement of 24.1% (10). They observed that right paratracheal nodes were constantly involved in case of N2 metastases, concluding that, in case of carcinomas, lymphadenectomy of at least 10 nodes should be performed, encompassing right paratracheal nodes. This work helps us understand the invasive nature of carcinomas (and NETT as well). Lymphatic diffusion apparently spreads from the anterior mediastinum (N1 nodes) to intrathoracic nodes (N2) following a right route. Intriguingly, it recalls some ancient experiments concerning the topographic anatomy of mediastinum as well.

Luigi Condorelli, full professor of Internal Medicine in Rome, in 1934 introduced a technique that allowed a precise topographical study of the mediastinum (11). By employing cadaveric models, he was able to localize an anterior region and a posterior region. The anterior region harbors the thymic gland and surrounding fat, while the visceral region contains the pericardium, great vessels, trachea and pulmonary hila. Condorelli identified a direct connection between the visceral region and the neck. This primordial division of the mediastinum laid the basis for Thomas Shield's classical division of the Mediastinum in anterior and visceral

compartments (12). More importantly, a direct diffusion of dye was constantly observed along the azygos arch, interesting the right paratracheal space (Baretty's space). Although some of these findings were later rejected, it is clear that in case of aggressive thymic tumors, the possibility of nodal diffusion from anterior to posterior mediastinum is likely. To date, Fang and coworkers identified eight cases of N2 metastases (53.3%). In six cases there was a simultaneous N1–N2 involvement, while in two cases a direct N2 was found.

### Surgical approaches to mediastinal nodes in case of thymic tumors

Now we shall consider all cases of aggressive thymic tumors ("advanced B", C and NETT) as potentially involving lymph nodes. What is more, involvement of N2 nodes is likely. New techniques may provide a more straightforward route to deep mediastinal nodes. Fang reports that patients undergoing minimally invasive thymectomy (MIT) had a greater number of N2 dissections and more lymph nodes removed (1). Although it isn't clear which is the best MIT approach (unilateral, bilateral, subxiphoid), it is possible that surgeons with expertise in minimally invasive lobectomy and lymphadenectomy for lung cancer may have easily endorsed the idea of N2 dissection for thymic tumors. MIT has been progressively adopted in the last decade, especially for early stage thymomas. Two meta-analyses (13,14) concluded that open and MIT displayed similar outcomes in terms of recurrence-free survival. Traditionally, MIT has been reserved to small thymomas, since dimension of 5 cm or more may lead to prolonged tumor manipulation and risk of seeding (15). New technologies, in particular robotic surgery, may help extending the boundaries of MIT (16). Given the enhanced visualization, major maneuverability of instruments, CO<sub>2</sub> inflation, it may eventually provide invaluable tools for nodal dissection.

### Future perspectives

The recent work of Fang and coworkers duly points out the need for lymph node assessment in case of "advanced" thymomas (B2–B3), Carcinomas and NETT. In these cases, a surgical approach which encompasses lymphadenectomy should be considered. However, discrimination between thymoma subgroups is not always straightforward, and preoperative biopsy shall be limited due to the risk of dissemination. PET-CT scan with dedicated imaging algorithms (tumor/mediastinum ratio and volumetric

indicators such as tumor volume above 45% of SUVmax) could provide a useful tool in both localizing nodal metastases and in predicting histological type, and thus be included in routine preoperative workup (17,18). Suspicion of advanced thymomas (B2-3, C) or NETT suggests the need for lymphadenectomy in case of upfront surgery. Given the possible role of induction therapy, the role of invasive staging [mediastinoscopy and endobronchial ultrasound (EBUS)] in case of thymic carcinomas and NETT should be further investigated.

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