What is the role of lymph nodal metastases and lymphadenectomy in the surgical treatment and prognosis of thymic carcinomas and carcinoids?

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Abstract

A best evidence topic in thoracic surgery was written according to a structured protocol. We looked at the clinical relevance of lymph node involvement and nodal (N) stage in thymomas, thymic carcinomas and carcinoids. The possible role of lymphadenectomy in addition to thymectomy was also evaluated. A total of 605 papers were found, of which nine represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers were tabulated. In the Yamakawa–Masaoka classification, based on 226 patients, lymph nodes were classified as anterior mediastinal (N1), defined as nodes surrounding the thymus gland; intrathoracic (N2), all nodes within the thorax excluding N1; and extrathoracic nodes (N3). Kondo validated the Yamakawa–Masaoka classification in a multicentric cohort of 1320 patients. Thymomas presented nodal involvement in 1.8% of cases, carcinomas in 27% of cases, and carcinoids in 28% of cases. The role of nodal status in defining the stage was even more emphasized in the staging system developed by Tsuchiya for thymic carcinomas. In the Istituto Nazionale Tumori classification, thymomas with N1 or N2 were considered as locally advanced disease with a 95-month disease-free survival rate for locally advanced disease of 46.9 vs 98.6% for locally restricted disease (absence of nodal involvement). Weissferdt and Moran, on a series of 65 thymic carcinomas, underlined the clinical relevance of nodal involvement. Positive lymph nodes were associated with significantly worse survival (P = 0.01070). Okuma, in a series of 68 advanced stage thymic carcinomas, showed that curative-intent surgical treatment was related to prolonged survival (P = 0.03). In particular, IVb tumours due to node-only involvement had better survival when radical resection was achieved when compared with IVb due to distant metastases (P = 0.03). Sung et al. showed the importance of harvesting 10 or more lymph nodes and dissecting intrathoracic lymph nodes to ensure a more complete staging of thymic carcinomas. The results underline the clinical relevance and prognostic value of nodal involvement in thymic carcinomas and carcinoids. In these cases, lymphadenectomy is desirable to allow the real definition of N status.

Keywords: Review • Thymoma • Thymic carcinoma • TNM classification • Lymph node metastases • Lymphadenectomy • Prognosis

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is described in the ICVTS [1].

THREE-PART QUESTION

In [thymic epithelial tumors], does [nodal stage and lymphadenectomy] affect the [prognosis]?

CLINICAL SCENARIO

A 63-year-old man underwent extended thymectomy for a 4-cm thymic mass. Pathological evaluation demonstrated a B3 thymoma with a metastatic perithymic lymph node. Afterwards, you wonder about the prognostic value of nodal involvement in thymic epithelial tumors (TET), and whether or not a lymphadenectomy should be performed in addition to extended thymectomy.

SEARCH STRATEGY

Combined results of two searches using Medline 1990–2013 was performed using the PubMed interface

(i) [thymic carcinoma OR thymoma] AND [staging]
(ii) [thymic carcinoma OR thymoma] AND [lymphadenectomy].

SEARCH OUTCOME

Five hundred and eighty-three and 22 papers were found, respectively, and 9 papers provided the best evidence to answer the question (Table 1).
<table>
<thead>
<tr>
<th>Study type (level of evidence)</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective analysis (level 3)</td>
<td>226 patients (207 thymomas, 13 thymic carcinomas and 6 thymic carcinoids)</td>
<td>Nodal involvement rate and N stage</td>
<td>N+: 5 cases 3 patients (1.4%) at the time of surgery; 2 developed N+ during the follow-up Sites of N involvement were mediastinal lymph nodes in 4 cases, neck lymph nodes in 2 cases, retroperitoneal lymph nodes in 1 case (2 patients had multiple station involvement)</td>
<td>This tentative TNM classification showed little advantage over conventional staging for thymomas</td>
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<td>Kondo et al. (2003), Ann Thorac Surg, Japan [3]</td>
<td>Multicentre study from 115 institutes: 1093 thymomas, 186 thymic carcinomas and 41 thymic carcinoids</td>
<td>Nodal involvement rate and N stage</td>
<td>N+: 1.8% of cases (73% N1, 27% N2, no N3)</td>
<td>The N factor was one of the predictors of survival in thymoma and thymic carcinoma. M factor showed less influence on survival than T or N factors</td>
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<td>Tsuchiya et al. (1994), Pathol Int, Japan [4]</td>
<td>16 patients (9 males, mean age 53.6 years) with carcinomas, selected between June 1964 and March 1990</td>
<td>Nodal involvement rate and N stage</td>
<td>N+: 28% (11/40) of cases (27.5% N1 only, 50% N2, 22.5% N3)</td>
<td>Carcinomas and carcinoids: N0 56%; N1 42.1%, N2 29.3%, N3 18.8%</td>
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<td>Bedini et al. (2005), Ann Thorac Surg, Italy [5]</td>
<td>123 patients (61 males and 62 females), selected from 1972 to 1995</td>
<td>Nodal involvement rate and N stage</td>
<td>N+: disease observed in 5/16 (31%) of cases (3 N1, 1 N2 and 1 N3) 43 and 34.4%</td>
<td>Carcinomas showed a major propensity for nodal involvement</td>
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Table 1:  (Continued)

<table>
<thead>
<tr>
<th>Author, date, journal and country</th>
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<tr>
<td>Weissferdt et al. (2012), Am J Clin Pathol, USA [6, 7]</td>
<td>Retrospective analysis (level 3)</td>
<td>65 patients with thymic carcinoma (43 men and 22 women; 19–81 years old)</td>
<td>Lymphadenectomy rate</td>
<td>30/65 patients underwent intrathoracic lymphadenectomy</td>
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<td>Nodal involvement rate</td>
<td>Lymph node metastasis was identified in 11 cases (37%)</td>
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<td>Survival analysis</td>
<td>Tsuchiya classification: N0: 19 cases, N1: 5 cases, N2: 6 cases</td>
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<td>Impact of nodal stage on prognosis</td>
<td>Positive nodal status was associated with significantly worse survival ($P = 0.01070$)</td>
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<td>Survival analysis</td>
<td>Significant survival differences between the proposed stages ($P = 0.04178$)</td>
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<tr>
<td>Okuma et al. (2014) Lung Cancer, Japan [8]</td>
<td>Retrospective analysis (level 3)</td>
<td>68 patients with thymic carcinoma</td>
<td>1-, 5- and 10-year survival</td>
<td>76.3, 36.0 and 6.2%, respectively</td>
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<td></td>
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<td>Impact of radical-intent surgery on prognosis</td>
<td>In univariate analysis, surgery with radical intent resulted in a favourable prognostic factor even in advanced stages (0.03)</td>
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<td></td>
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<td>Survival analysis</td>
<td>Radical surgery for patients with lymph nodal metastases resulted in a better survival than IVb due to organ metastases</td>
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<tr>
<td>Sung et al. (2013), Ann Thorac Surgery, Korea [9]</td>
<td>Retrospective analysis (level 3)</td>
<td>37 patients (23 males and 14 females, mean age 60 years), with resected thymic carcinomas</td>
<td>Lymph node dissection rate</td>
<td>29 patients (78.4%)</td>
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<td>Lymph node dissection results</td>
<td>21 patients had lymphadenectomy of anterior mediastinal nodes; the mean number of nodes removed was 4.6 (range, 1–14). Metastasis was confirmed in 4 patients</td>
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<td>21 patients had lymphadenectomy of intrathoracic nodes; the mean number of nodes removed was 12 (range, 1–45). Metastasis was confirmed in 3 patients (right paratracheal nodes constantly involved)</td>
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</table>

Lad (including intrathoracic nodal involvement) may benefit from surgery as part of multimodality treatment.

The authors confirm the importance of nodal involvement in the prognosis and the possible role of intrathoracic lymph node sampling for definition of prognosis.

This recent study confirms the observation that, in thymic carcinomas, lymph nodal involvement should be spared from other IVb subsets (distant metastases) and should be managed by radical surgery when possible. However, the extent and type of lymphadenectomy is not described.

Although the limited number of patients prevents from drawing general guidelines on the topic, the study provides some indications for further speculation: definition of lymph node stations to be harvested and minimum number of lymph nodes required to achieve oncological adequacy.
RESULTS

The incidence and prognostic value of lymph nodal involvement in case of thymic malignancies have been reported in a few studies. However, at the present time, there are no guidelines about the role and extent of lymphadenectomy in the course of thymectomy for thymic neoplasms.

Yamakawa et al. [2] defined nodal involvement as follows: anterior mediastinal (N1: nodes surrounding the thymus gland, generally removed during standard extended thymectomy); intrathoracic (N2: bilateral paratracheal, subaortic, hilar, intra-pleural lymph nodes, all nodes excluding anterior mediastinal), and extrathoracic (N3). Kondo and Monden [3] validated the Yamakawa–Masaoka TNM in a cohort of 1320 patients. Thymomas presented nodal (N+) involvement in 1.8% of cases (73% N1, 27% N2, no N3), carcinomas in 27% (49/183) of cases (39% N1, 20.4% N1 + N2, 6% N1 + N3; 4% N1 + N2 + N3; 10.2% N2; 20.4% N3), and carcinoids in 28% (11/40) of cases (27.5% N1 only, 50% N2, 22.5% N3). For thymomas, the authors observed a significant difference in 5-year survival between N− and N+ patients (P < 0.0001), although no difference between N1 and N2 was found. A significant difference in 5-year survival according to N status was observed in carcinomas and carcinoids (N0 56%; N1 42.1%, N2 29.3%, N3 18.8%).

Tsuchiya et al. [4] developed a classification with similar N descriptors, but different grouping. Stage I included encapsulated T1 or minimally invasive T2 (without diffusion to neighbouring organs) N0, Stage II T1–2 N1, all N2–N3 were considered IVb, while M+ were grouped in the novel IVc group. This classification allowed a better separation of survival curves between Stage I and III or IV, and between III and IV, indicating the importance of nodal involvement in prognosis. Istituto Nazionale Tumori (INT) classification identifies three stages: RD (radically treatable by surgery), LAD (requiring multimodality therapy) and SD (generally treated with chemo-radiotherapy). The N3 descriptor was limited to supraclavicular and prescalenic nodes only (other extrathoracic nodal metastases were considered M1b). N1 or N2 disease was considered LAD independent from the T descriptor, showing a worse prognosis when compared with RD (T1N0: no invasion of capsule, T2N0: microscopic invasion/minimal diffusion to mediastinal fat; without nodal involvement).

Positive nodal status was associated with significantly worse survival (P = 0.01070) in the reports of Weissferdt and Moran [6, 7]. They proposed a three-stage system based on the data of 33 patients. Presence of any kind of intrathoracic lymph nodal metastases was defined as N1 and was considered as Stage III (the differentiation between N1 and N2 was not followed). Statistically significant differences in survival emerged between the proposed stages (P = 0.04178) but not between Masaoka or Tsuchiya stages (P = 0.07762, P = 0.09081).

Therefore, nodal involvement seems to have clinical relevance mainly in thymic carcinomas and carcinoids. Okuma et al. [8], in a retrospective study about curative-intent treatment for thymic carcinoma in a cohort of 68 patients, showed that radical surgery was the only favourable prognostic factor (P = 0.03). In the IVb group, lymph node involvement without other distant metastases was a favourable prognostic factor. The author concludes that lymphatic metastases may be responsive to curative-intent surgery. Park et al. [9] evaluated the role of lymphadenectomy in a group of 37 thymic carcinomas. They divided the patients into four

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<tr>
<td>5-year DFS</td>
<td>The proportion of lymph node metastasis was significantly higher in cases of tumours invading neighbouring organs (T1/2*: 0% vs T3*: 35.2%; P = 0.028)</td>
<td>No lymphadenectomy (Nx): 75%</td>
<td>No metastases after lymphadenectomy of less than 10 nodes (N0a): 48.1%</td>
<td>*According to Yamakawa–Masaoka classification [2]</td>
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<td>Impact of nodal status on prognosis</td>
<td>No metastases after lymphadenectomy of more than 10 nodes N0b: 90%</td>
<td>Nodal metastases (N1): 33.3%</td>
<td>The DFS rate of the N0b subgroup (removed 10 or more lymph nodes) was significantly better than that of the N1 subgroup (P = 0.02)</td>
<td>In case of intrathoracic nodal involvement, right paratracheal nodes were constantly affected by metastases</td>
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groups: no lymphadenectomy (Nx) in 8 cases, ‘pathologic N0 by limited dissection’ (<10 nodes harvested) or N0a in 13, ‘pathologic N0 by extensive dissection’ (>10 nodes) or N0b in 10 cases and presence of nodal metastasis (N1) in 6 cases. Lymphadenectomy was thus performed in 29 patients with a mean of 9.4 nodes removed. Anterior-only mediastinal lymphadenectomy was performed in 21 cases. Metastases to anterior nodes (N1) were found in 4 cases. Intrathoracic lymph node dissection (N2) was performed in 21 patients. The sites of lymphadenectomy were para-tracheal (15 cases), sub-carinal (3), para-aortic (5), subaortic (5) and hilar (4) nodes. Intrathoracic metastasis was confirmed in 3 patients, constantly in the right para-tracheal nodes. In 1 case, there was a concomitant sub-carinal involvement. The 5-year DFS was 75% in Nx, 48.1% in N0a, 90% in N0b and 33.3% in N1. N0b showed a better prognosis than N1 patients (90 vs 33.3%). The authors concluded that a lymphadenectomy (including 10 or more nodes) should be performed in case of thymic carcinomas, to allow a correct prediction of prognosis.

CLINICAL BOTTOM LINE

These results underlined the clinical relevance and prognostic value of nodal involvement in thymic carcinomas and carcinoids. In these subsets of TET, a TNM-based staging system should be employed to define prognosis better. As a consequence, the surgical approach should include a form of lymphadenectomy (encompassing both anterior mediastinal and intrathoracic nodes, such as right paratracheal) to allow nodal staging. The International Thymic Malignancy Interest Group (ITMIG) suggested the need of systematic sampling of intrathoracic lymph nodes in case of Stage III thymomas and in all cases for thymic carcinoma [10]. ITMIG is also developing a consensus-based node map for thymic malignancy in which two main mediastinal regions are identified (anterior and deep region) [11]. This map will certainly provide a fundamental basis for further clinical investigations.

Conflict of interest: none declared.

REFERENCES


eComment. Inclusion of information on a lymphadenectomy and lymph node involvement in databases for thymic epithelial tumors

Author: Masatsugu Hamaji
Kyoto University, Kyoto, Japan
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I read with great interest the article by Viti et al. [1]. It is a nice review article focusing on the role of a lymphadenectomy and lymph node involvement in thymic epithelial tumours. As compared with thymoma, which has a more indolent behaviour and a more favourable prognosis, thymic carcinoma and carcinoid tumours are more frequently affected by positive thoracic lymph nodes [2]. Interestingly, on the other hand, the pattern of recurrence in thymic carcinoma is more frequently distant than that in thymoma [3]. Therefore, a lymphadenectomy or a lymph node dissection should be performed for a diagnostic, rather than a therapeutic, purpose. As discussed in this article, Park et al. emphasized an aggressive lymph node dissection in thymic carcinoma to predict its prognosis [4].

From a practical points of view, several questions arise: Has adjuvant chemotherapy or radiotherapy been recommended for patients with thymic epithelial tumours with positive lymph nodes? Also, in thymoma patients, who are more frequently encountered than those with thymic carcinoma and mentioned in this clinical scenario, has a lymphadenectomy or lymph node dissection been recommended for a prognostic purpose? These questions may be answered by routinely including lymph node information in current databases on thymic epithelial tumours.

Conflict of interest: none declared.

References