Staging for Thymoma and Thymic Carcinoma

6

Introduction

The staging of thymomas – just as its classification – is a rather controversial topic as there is not a universally accepted staging system for these tumors. In addition, often one of the proposed staging systems presented for thymomas has been adapted for thymic carcinomas, which has obscured even more the issue of thymoma and thymic carcinoma. It is very important to highlight the issue that thymoma is not the benign counterpart of thymic carcinoma nor is thymic carcinoma the malignant counterpart of thymoma. Those two thymic epithelial tumors represent two different clinicopathological entities; unfortunately, there is a tendency by some to try to lump both of these tumors into one category, while in reality the clinical behavior and treatment for those two tumors are rather different.

It is interesting and important to highlight the issue that even in the early large series of thymomas, the authors did not present a staging system, and the focus in those series was more on the histological classification of thymomas. An example of this is the focus by Bernatz and colleagues [1] when addressing the issue of classification, stating "some prognostic significance could be gained through study of cell types," basically assessing the issue of separating these tumors by the percentage of cell types into predominantly lymphocytic, predominantly epithelial, mixed types, and spindle cell type. However, even though the authors did not present a formal staging system, they emphasized the issue that, in their experience, three fourths of these tumors are noninvasive. Nevertheless, the authors also identified that regardless of their specific cell type, such findings did not correlate with the invasiveness of the tumors, as all the cell types were seen to be noninvasive and invasive. The authors clearly stated that they found no differences between the histological features of invasive and noninvasive neoplasms. On the contrary, larger series of thymic carcinomas are few and also focused on the clinicopathological aspects of the tumor rather than on the staging [2]. More recently different reviews addressing not only the historical aspects of the different schemas but also addressing their pitfalls and shortcomings have been presented [3–5]. Also important to highlight is that, even in larger series of cases, the authors have decided to lump together thymomas and thymic carcinomas as well as neuroendocrine carcinoma [6].

In this chapter, we will analyze each one of the proposed staging systems for thymoma and thymic carcinoma. However, since we consider these two tumors to represent different clinicopathological entities, a distinction in the staging system will be discussed with the hope that not only will it help in daily practice when dealing with these tumors but also that it may provide better triaging of patients for treatment purposes.

Staging of Thymoma

Sometime after Bernatz and colleagues [1] presented their views regarding the histological classification of thymomas, once again these same authors [7] presented a study of 181 patients diagnosed with thymomas over a period of 20 years, from 1949 to 1969. This study emphasized "factors influencing prognosis." In this group of patients, the authors found that 44% had thymomas associated with myasthenia gravis, while 36% of the tumors were grossly invasive. The average age was 50 years; however, patients with myasthenia gravis were 13 years younger than those without such an association. In addition, no significant gender distribution was noted. Needless to say, patients with invasive tumors had poor survival, and the presence of invasion was more important than the association with myasthenia gravis. One important feature that the authors identified was that myasthenia in invasive tumors did not alter the prognosis, contrary to the presence of myasthenia in noninvasive tumors where it may shorten survival. Important to highlight is that all histological

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types were identified among the invasive and noninvasive tumors. Similarly significant is that the presence of distant metastases was a rare event and was found in only 2 out of 181 patients, both cases with metastatic disease to the liver.

In 1979, Bergh and colleagues [8] presented a series of 43 patients with thymoma, corresponding to 20 women and 23 men between the ages of 17 and 73 years. All the thymomas were classified according to the Bernatz histological classification [1] into lymphocyte-rich, epithelial-rich, and mixed. The authors defined the three stages as follows:

- Stage I – Intact capsule or growth within the capsule
- Stage II – Pericapsular growth into the mediastinal fat
- Stage III – Invasive growth into the surrounding organs, intrathoracic metastases, or both

Based on this "staging system," the authors documented that tumor removal was possible in 25 patients in stages I or II and in 14/18 patients in stage III. Pleural metastases were observed in patients in stage III. It is of interest to highlight that, in this particular series of cases with the proposed staging system, the authors were able to identify only one patient with tumor relapse in stage II and five patients in stage III. In addition, the authors noted a "considerable" difference in survival between stages II and III and suggested not lumping these together. The authors also added that the association of superior vena cava syndrome appeared to be indicative of poor prognosis. However, the emphasis of this series of cases was on the accomplishment of complete surgical resection, as the authors noted low recurrence and high survival for stages I and II. Interestingly, the authors concluded that the diagnosis of thymoma might be questioned in patients with lymph node metastasis. In a separate report of 103 patients with thymoma, Wilkins and Castleman [9] staged the patients using the Bergh approach with "minor" modifications:

- Stage I – Intact capsule or growth within the capsule
- Stage II – Pericapsular growth into the mediastinal fat tissue or adjacent pleura or pericardium
- Stage III – Invasive growth into the surrounding organs, intrathoracic metastases, or both

It is obvious that the "minor" modifications took place in stage II, as the authors added involvement of pleura and pericardium. Even though there is not a specific explanation for the addition of two different structures to stage II, it is possible that such an argument is due to the survival noted by the authors in stages I and II, which documented only 1 of 18 patients in stage II who died due to complications of myasthenia gravis (MG). However, the authors also concluded that the presence of MG is not an adverse factor affecting survival. More interestingly, by 1991, Wilkins and associates [10] reported 85 cases of thymoma from 1972 to 1989, 32 of these patients with history of MG; however, in this report, the authors used the Masaoka staging schema, recommending that all patients to be followed for a minimum period of 10 years and that patients in Masaoka's stages II and III to receive postoperative radiotherapy. The authors also added that the presence of MG is no longer considered an adverse factor in survival.

In 1981 in a study of 96 cases of thymoma, Masaoka proposed what has been the most popular staging system for thymoma [11]. The emphasis in this staging system is on the macroscopic and microscopic aspects of the tumor. The proposed system is as follows:

- Stage I – Macroscopically completely encapsulated and microscopically no capsular invasion
- Stage II:
  1. Macroscopic invasion into the surrounding fatty tissue or mediastinal pleura
  2. Microscopic invasion into the capsule
- Stage III – Macroscopic invasion into the neighboring organ, i.e., the pericardium, great vessels, or lung
- Stage IVa – Pleural or pericardial dissemination
- Stage IVb – Lymphogenous or hematogenous metastasis

The patients were 56 men and 40 women between the ages of 8 months and 67 years. Histologically, all tumors were grouped according to the Bernatz classification [1], and all the different types were seen in the different staging systems proposed. Based on this proposed staging system, 50 patients were in stages I and II, while 46 patients were in stages III and IV. However, closer breakdown of the different stages shows that only 11 patients were in stages IVa and IVb, while 32 were in stage III, which accounts for 93 patients and not the 96 stated in the manuscript. However, the authors provided a 5-year survival rate of each clinical stage as follows: 92.6% for stage I, 85.7% for stage II, 69.6% for stage III, and 50% for stage IV. Interestingly, the authors point out that only 89 thoracotomies were evaluated at their center and that two patients refused the operation. Also important to highlight in this study is that all the histological subtypes of thymomas were seen in all the different stages proposed.

Based on this proposal for staging thymomas, there are several issues that deserve attention:

1. The authors observed a thymoma in an 8-month-old child. One would have to wonder if that in fact might have been a thymoma or a different thymic neoplasm.
2. Even though the manuscript states that the study contained 96 cases, in fact there were only 86 thoracotomies evaluated, and, as the authors point out, in at least two patients, surgical resection did not take place. Thus, one

would have to wonder about the "true staging" of those patients.
3. For stage I – What happens with tumors that may be "macroscopically" encapsulated but the microscopic evaluation reveals invasion?
4. How is it possible in stage II-1 to evaluate macroscopic invasion of the surrounding fat in a case that may be only "minimally invasive?"
5. For stage II-2, microscopic invasion into the capsule does not represent invasive thymoma.
6. For stage II-1 and stage IVa, regarding pleural involvement: there is a play of words, and one wonders what the authors meant exactly by "invasion" and/or "dissemination." One could easily move a patient from stage II-1 to stage IVa.
7. It is very likely that statistically there is not a significant difference between stage I and stage II. That is highly important for treatment purposes and possibly impacts long-term survival.

In 1994, Koga and associates [12] reviewed 79 thymomas and modified the previously proposed schema of Masaoka [10]. The modifications introduced by Koga and associates [11] are essentially in stage II of the Masaoka staging system. The system is as follows:

- *Original Masaoka*
- Stage II
  1. Macroscopic invasion into the surrounding fatty tissue or mediastinal pleura
  2. Microscopic invasion into the capsule
- *Koga's modifications*
- Stage II
  1. Microscopic transcapsular invasion
  2. Macroscopic invasion into the thymic or surrounding fatty tissue, or grossly adherent to but not breaking through the mediastinal pleura or pericardium

Even though in this review of Masaoka's schema the issue of transcapsular invasion is clarified, the authors technically introduced additional problems:

1. There are some thymomas that invade the thymic tissue, and yet the tumors are encapsulated, thus posing some problems for this stage.
2. Tumor "grossly adherent to the pleura but not breaking through it": Does this mean that if the tumor breaks through, it becomes stage III? If so, then stage III needs some modification. In addition, the tumor may be adherent to the pleura and/or pericardium as it is commonly seen but without actual invasion. Thus, there is no pleural invasion, which raises the issue of the actual significance of "grossly adherent."

In 1991, Pescarmona and associates [13] analyzed 83 patients with thymoma by age, sex, presence of MG, staging, and histological subtype. Important to mention in this study is that the authors used a different histological typing of tumors – cortical, medullary, and mixed. Based on their analysis, the authors concluded that age, sex, and presence of MG did not prove to represent significant prognostic factors. However, the authors stated that clinical stage and histological type had "significant" prognostic value. The patients evaluated corresponded to 44 women and 39 men ages 21–83 years. Histologically, 34 thymomas were cortical, 13 medullary, and 36 mixed. Clinically, using the Masaoka proposed schema [11], 23 patients were in stage I, 26 patients in stage II, 26 patients in stage III, and 8 patients in stage IV. It is of interest to note that none of the patients was further categorized in stages II-1, II-2, IVa, or IVb, and this raises the possibility that those features were either not important or ignored. The authors arrived at an important conclusion and that is that "medullary-type tumors are, in most cases, fully benign." Furthermore, the authors concluded that (1) stages I and II medullary-type and stage I mixed-type thymomas have an excellent prognosis; (2) stages I and II cortical-type thymoma and stages II and III mixed thymomas have an intermediate prognosis; and (3) stages III and IV cortical-type thymoma have the least favorable prognosis. It is of interest to highlight that the authors arrived at one important conclusion regarding the "benign" nature of "medullary thymoma" by having examined only 13 cases of this type of tumor, and, according to the authors, "most of those cases" were in stage I. Further studies of this particular type of thymoma have demonstrated that it is very likely that such an assumption is incorrect [14, 15]. Numerous other series of thymomas using the proposed Masaoka's schema for staging have been presented in the literature. Blumberg and coworkers [16], in a study from 1949 to 1993, retrospectively evaluated 118 patients with thymoma with the goal of determining independent factors to predict survival. The authors concluded that patients in stage I require no further therapy after complete surgical resection and that, for patients with invasive disease and large tumor, neoadjuvant therapy should be considered. Regnard and coworkers [17] presented their experience with 307 thymoma cases in which the authors observed that complete surgical resection should be taken into account in clinical-pathologic staging, as the authors observed that patients in Masaoka's stage III had a significantly higher survival rate if those patients had complete surgical resection of the tumor. In addition, the authors did not find any significant difference between patients who received postoperative radiation therapy and those who did not. Based on their findings, the authors proposed a modification to the Masaoka's schema in which most of the wording of the stages was essentially kept but the authors added the surgi-

cal resectability of the tumor: complete or incomplete resection. Safieddine and coworkers [18] presented their experience with 262 patients with the goal of determining prognostic factors for cure, recurrence, and long-term survival after surgical resection of thymoma. One interesting variable in this study is that the authors also used the histological schema proposed by the World Health Organization (WHO); however, the authors essentially concluded that complete surgical resection is associated with good prognosis while advanced staging is associated with poor prognosis. Demirci and coworkers [19], in a study of 47 patients with thymoma and thymic carcinoma using also the WHO histological schema for subtyping thymoma, concluded that the most important prognostic factor for overall survival was the extent of resection. Contrary to previous experiences reported by others with large series of cases, Cardillo and coworkers [20], in a report of 61 patients including 18 patients with thymic carcinoma, concluded that complete surgical resection, "Masaoka stage," induction chemotherapy, and histological WHO subtyping are independent predictors of survival in locally advanced thymoma/thymic carcinoma. Interestingly, more recently the International Thymic Malignancy Interest Group (ITMIG), stating that no official staging schema has been defined, introduced their own modification to an already "not so clear" Masaoka's schema. One of those "modifications" was to introduce an already known term: "minimally invasive." The remainder of the Masaoka schema was kept [21]. Even Dr. Masaoka himself has provided his own follow-up regarding his own staging schema [22]: in a review of 211 thymomas, Masaoka concluded that his staging schema remains a valuable prognostic factor. However, he also added that the combination of stages I and II and the separation of stage III into subgroups are not recommended, while, for patients in stage IVb, it is best to include positive lymph nodes. While some of his suggestions seem to be appropriate, combining his own proposed schema and mixing it with a TNM system does not seem appropriate but rather misleading.

In a departure from the Masaoka staging schema [11], Yamakawa in collaboration with Masaoka and others [23] presented a "tentative tumor-node-metastasis" classification of thymoma. The authors evaluated 207 patients with thymoma and stated that lymphogenous and hematogenous metastases were infrequent and that lymphogenous metastases were present in "few cases." However, the authors also concluded that TNM classification of thymomas had little advantage over conventional clinical staging. It is of interest, however, to highlight that the authors also evaluated the TNM system in 13 cases of thymic carcinoma and 6 cases of thymic carcinoid, stating that in these tumors, the TNM classification was more useful. Nevertheless, the authors advanced the following TNM schema:

- *T-factor*
  - T1 – macroscopically completely encapsulated and microscopically no capsular invasion
  - T2 – macroscopically adhesion or invasion into the surrounding fatty tissue or mediastinal pleura, or microscopic invasion into the capsule
  - T3 – invasion into neighboring organs, such as the pericardium, great vessels, and lung
  - T4 – pleural or pericardial dissemination
- *N-factor*
  - N0 – no lymph node metastasis
  - N1 – metastasis to anterior mediastinal lymph nodes
  - N2 – metastasis to intrathoracic lymph nodes except anterior mediastinal lymph nodes
  - N3 – metastasis to extrathoracic lymph nodes
- *M-factor*
  - M0 – no hematogenous metastasis
  - M1 – hematogenous metastasis

It is evident by the descriptions that the TNM proposal is based on the early definitions of Masaoka's schema with the same recurrent problems of "invasion into the capsule" and "invasion and dissemination in pleura or pericardium." Most puzzling about the definitions of the T-factor are the T1 and T2: how can a tumor be called T2 while it is both an encapsulated tumor (invasion into the capsule) and at the same time has macroscopic adhesion or macroscopic invasion into surrounding fatty tissue? The T2 definitions in this TNM schema are ambiguous at best if not plainly incorrect. In addition, the N-factor requires that the surgeon provides an extensive lymph node sampling, which has essentially been more recently found to likely be not correct.

Following this trend, Kondo [24], stating that system for all thymic epithelial tumors is desirable (including thymic carcinoma and carcinoid), also supported the TNM system. Kondo also added that the N and M factors influence the prognosis more than the T-factor. However, one has to wonder how is it that the author was able to properly address the proposed Yamakawa TNM schema [23] with the pitfall and shortcoming already mentioned, or, perhaps, as it was concluded by their own proponents of the TNM proposal, the system works better for thymic carcinoma and not very well for thymoma. Following the same concept of the TNM system, Bedini and coworkers [25] proposed their own interpretation of the TNM system, which the authors called the INT (Istituto Nazionale Tumori). Their INT system is as follows:

- T1 – no capsular invasion
- T2 – microscopic invasion into the capsule or extracapsular involvement limited to the surrounding fatty tissue or normal thymus
- T3 – direct invasion into the mediastinal pleura and/or anterior pericardium

- T4 – direct invasion into the neighboring organs, such as the sternum, great vessels, and lung; implants to the mediastinal pleura or pericardium, only if anterior to phrenic nerves
- N0 – no lymph node metastasis
- N1 – metastasis to anterior mediastinal lymph nodes
- N2 – metastasis to intrathoracic lymph nodes other than anterior mediastinal
- N3 – metastasis to prescalene or supraclavicular nodes
- M0 – no hematogenous metastasis
- M1a – implants to the pericardium or mediastinal pleura beyond the sites defined in the T4 category
- M1b – hematogenous metastasis to other sites or involvement of lymph nodal stations other than those described in the N categories

Regarding this proposal, the authors not only kept ambiguous terms such as invasion into the capsule or extracapsular involvement for the same stage, but they also added new ambiguous issues. For instance, similar definitions are provided for T4 and M1a with the caveat of "beyond the sites defined in the T4 category." What are those sites? Is there any other site besides the lung, great vessels, and possibly heart that were already mentioned in the T4? If the tumor goes below the diaphragm, then it will be M disease. Furthermore, even in the larger series of cases and in those which proposed the TNM system, it was stated that the number of cases that involve lymph nodes is not large; needless to say, the number of cases that involved supraclavicular lymph nodes must be exceedingly rare, if they exist at all, unless they are thymic carcinoma. If the latter is correct, then once again, it proves that the TNM system may work better for thymic carcinoma and not very well for thymoma. In 2004, Asamura and associates [26], with the thought in mind that thymoma needs a new staging system, launched a different spin of a modified Masaoka's schema and provided a staging system in which tumor size appears to be a conspicuous feature, namely, a tumor size of 10 cm. In addition, the authors [26] provided a breakdown of the stages into two different schemas. This proposal is as follows:

- Stage I – tumors without any invasion into other structures/organs regardless of capsular involvement
- Stage II:
  - Tumors smaller than 10 cm in diameter and involving only one neighboring structure/organ (Schema 1)
  - Tumors of all combinations of diameter and number of involved structures/organs other than those in stage III (Schema 2)
- Stage III:
  - Tumors of all combinations of diameter and number of involved structures/organs other than those in stage II (Schema 1)
  - Tumors 10 cm or more in diameter and involving two or more neighboring structures/organs
- Stage IV – tumors with pleural or pericardial dissemination (IVa) or lymphatic/vascular metastasis (IVb)

Several concerns can be raised about the approach of this Masaoka-modified system. Although according to conventional wisdom one can assume that a larger tumor is likely to become invasive, how is that the size of 10 cm became the "magic size?" The author correctly observed that stages I and II of Masaoka's schema provide similar clinical follow-up; thus, the authors cleverly merge those stages into one. Interestingly, their stage I includes encapsulated tumors and the minimally invasive neoplasm. Stage IV of Masaoka's schema is essentially untouched, while stages II and III include two different schemas based on tumor size and involvement of structures/organs. However, it is here where the "play" of staging and schemas becomes a puzzle. For instance, it is well known that tumor size and invasiveness do not correlate, and tumors of less than 10 cm can show the so-called drop metastasis (invasion into the diaphragm), thus following the Asamura-modified Masaoka's system; such a tumor can easily be staged II – schema 1. More important is the fact that, in this system, the authors mention structure/organs for stage II schema 2 and structure/organs for stage III schema 1 but do not specify what structures they mean. It is one thing to have invasion into the great vessels and quite another to have invasion into the pericardium. Also, the authors interject another "magic number" for structures involved: two or more. The number of variables included in this system interestingly has not been found statistically significant in any other series of cases. One important feature to highlight in this study is the fact that, out of the 152 cases presented, the authors did not find evidence of metastatic disease in lymph nodes in any of the cases.

More recently, the ITMIG has published a series of review manuscripts without the actual review of cases and has made several proposals regarding the use of a universal system for thymic epithelial tumors (thymoma and thymic carcinoma) following the TNM system. Interestingly, one of those proposals is incorporated in the 8th edition of the TNM classification of malignant tumors. One has to wonder how is that a system is applied that consistently by different series of cases has shown not to be appropriate to be staged. And yet the ITMIG is proposing to include it as the standard staging system for thymoma; this is clearly not the most scientific manner of adopting a system for any pathological condition [27–30]. Perhaps this is a similar story to the one about the subtyping of thymomas by the WHO, which was never conceived as a classification but merely as a "translator" of two different proposed schemas. One can easily identify two glaring problems with the ITMIG approach: (1) proposing a TNM system for thymoma which clearly has shown to be ineffective for these

tumors and (2) attempting to use a TNM system for thymoma and thymic carcinoma, which even those who have published series of cases of thymic epithelial neoplasm have concluded as a system better suited for thymic carcinoma than thymoma. The most important conclusion that one can draw regarding the ITMIG proposal is that it is based on "some literature review" and not on actual comprehensive review of cases. It is important to highlight in this context an observation made by Wick [31] in a review of prognostic factors for thymic epithelial neoplasm, in which the author stated "the TNM substrata were created intuitively rather than being tied to a rigorous statistical modeling procedure… one must be skeptical of their soundness unless and until TNM systems for thymic tumors are tested systematically."

In a different study, Gamondes and associates [32] evaluated 65 patients with thymoma over a period of 17 years. The patients were 28 men and 37 women between the ages of 20 and 73 years. Fifty-four patients had a history of MG. However, contrary to previous studies using the Masaoka schema [11], this particular study focused on the French schema for thymic tumors, also known for its acronym GETT (Groupe d'Etudes des Tumeurs Thymiques), which is as follows:

- Stage I
  - A. Encapsulated, noninvasive. Total excision
  - B. Localized growth into the surrounding structures. Total excision
- Stage II
  - A. Invasive growth into the surrounding organs. Total excision
- Stage III
  - A. Invasive growth into surrounding organs. Incomplete excision
  - B. Invasive growth into the surrounding organs. Biopsy of the tumor
- Stage IV
  - A. Largely invading tumor cells with clavicular lymph nodes or pleural or pulmonary grafts
  - B. Hematogenous metastasis

From the description of the different stages, it is evident that this system is essentially based on "complete surgical resection of the tumor," which essentially could be used in a more abbreviated form and that is (A) complete surgical resection and (B) incomplete surgical resection or unresectable. For instance, that is exactly the difference between stage IB and stage IIA. On the other hand, for stage IVA, as it has been the experience of others, lymphogenous metastasis is rare, and also the presence of "pleural or pulmonary grafts" is rather ambiguous as it was in the Masaoka schema with pleural invasion and pleural dissemination, for two different stages. However, one essentially can shorten this staging system into complete resection and incomplete resection or unresectable, regardless of the anatomic structures involved. Based on this GETT system, the 65 cases evaluated [14] broke down as follows: 38 cases were in stage I, 6 in stage II, 13 in stage III, and 8 in stage IV. The mean survival for all patients was 70 months. Thus, the authors concluded that the prognosis of thymoma relates to total surgical resection and stage of the tumor, and it is not influenced by age, sex, tumor cell type, or the presence or absence of MG.

One of the most recent proposals exclusively for the staging of thymomas was a collaborative effort of a group of pathologists and surgeons based on a study of 250 thymomas [33]. The authors essentially separated patients into those with limited disease (limited to the mediastinal compartment without invasion into any adjacent structure) and patients with tumors with invasion. The goals of this staging system are not only to stratify patients who need only surgical resection as opposed to those who may need additional medical treatment but also to clearly determine which structures are involved so that the staging is more reproducible by anyone involved in the treatment of these patients. The study included only surgical resections in 120 men and 130 women between the ages of 13 and 92 years. The sizes of these tumors vary from 2 to 20 cm in diameter: 80% of the tumors were larger than 5 cm with an average size of 7 cm; however, tumor size did not correlate with invasiveness of the tumor. The staging system is as follows:

- Stage 0 – Encapsulated tumor. No evidence of tumor invasion into adjacent structures (Fig. 6.1a, b)
- Stage I – Invasive tumor that has breached the capsule of the tumor. The tumor is into the perithymic fat (Fig. 6.2a–c), but it is not compromising adjacent structures (pleura, pericardium, etc.).
- Stage II – Direct invasion
  - IIA
    - Innominate vein
    - Mediastinal pleura
    - Lung (Fig. 6.3a, b)
  - IIB
    - Pericardium (Fig. 6.4a, b)
  - IIC
    - Great vessels (aorta, superior vena cava) (Fig. 6.5a, b)
    - Heart
- Stage III – Metastatic disease
  - IIIA – Intrathoracic structures
    - Diaphragm (so-called drop metastases) (Fig. 6.6a, b)
    - Lymph nodes
  - IIIB – Extrathoracic (Fig. 6.6c, d)

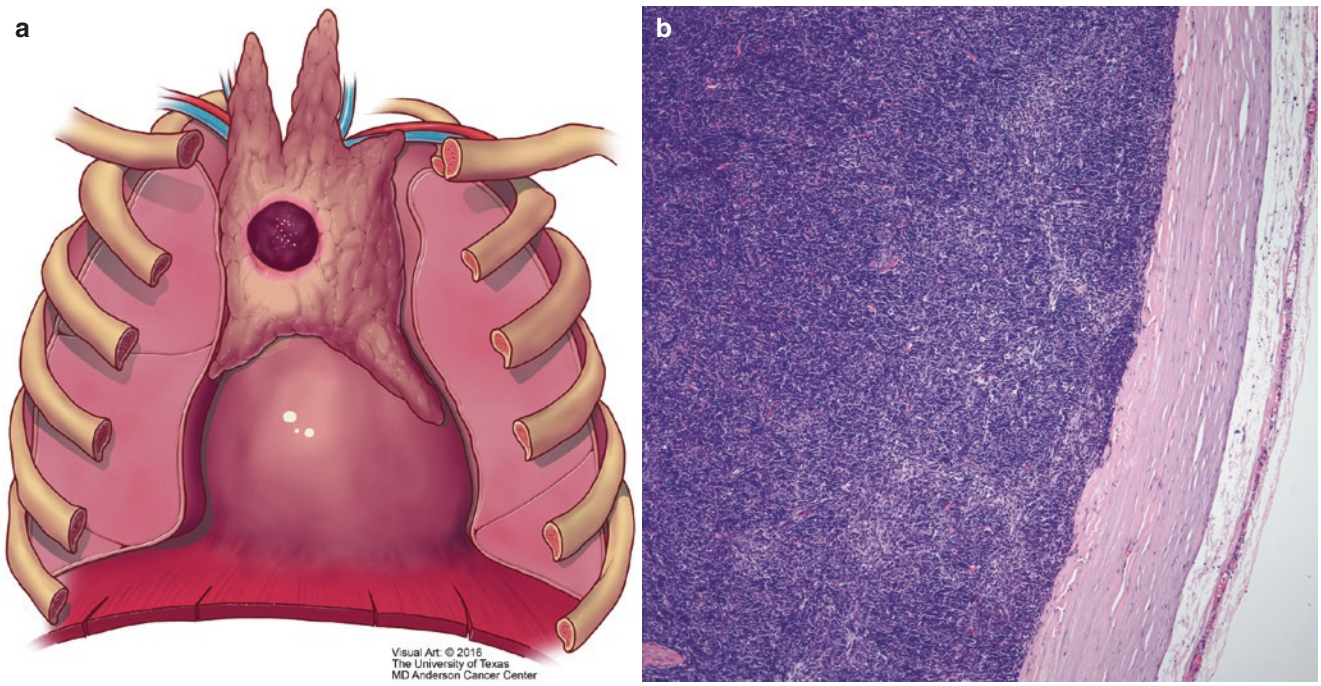

Fig. 6.1 (**a**, **b**) Stage 0. (**a**) Graphical illustration of an encapsulated thymoma. (**b**) Histological section of an encapsulated thymoma. (**a**: Copyright © 2016 with permission from Dr. Kalhor and Moran)

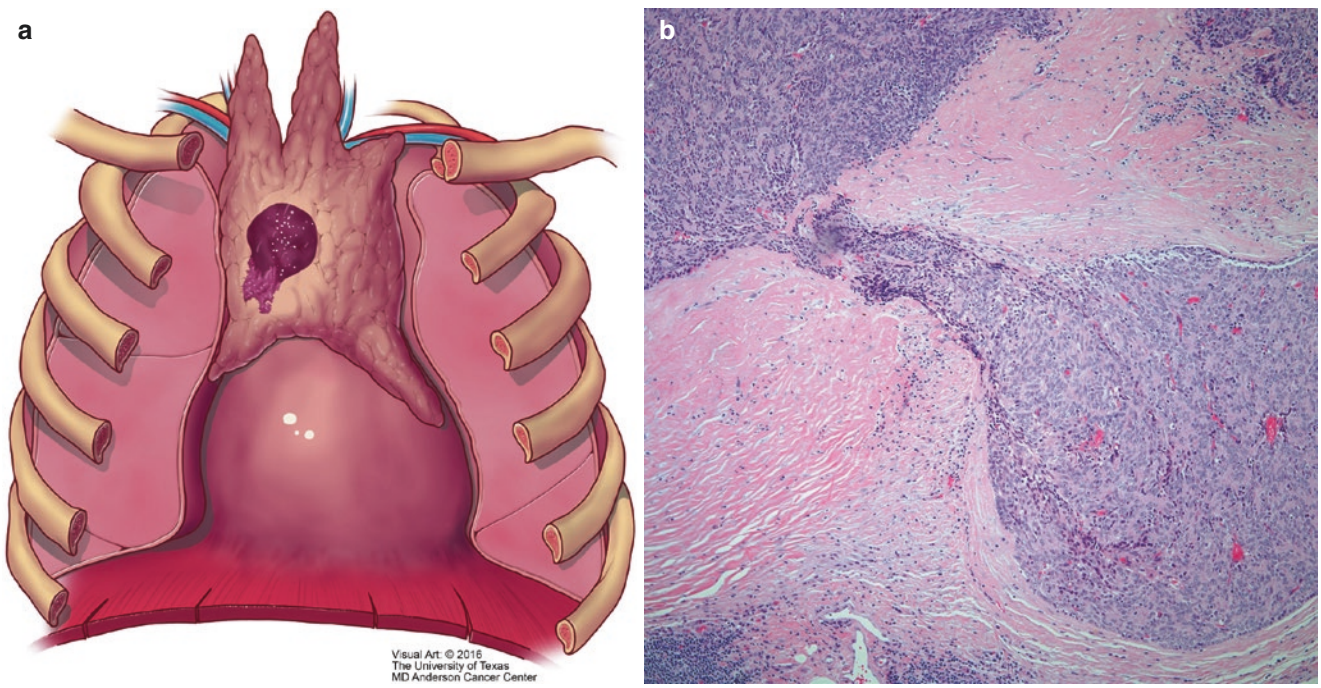

Fig. 6.2 (**a**–**c**) Stage I. (**a**) Graphical illustration of a minimally invasive thymoma. (**b**) Thymoma has breached the capsule. (**a**: Copyright © 2016 with permission from Dr. Kalhor and Moran)

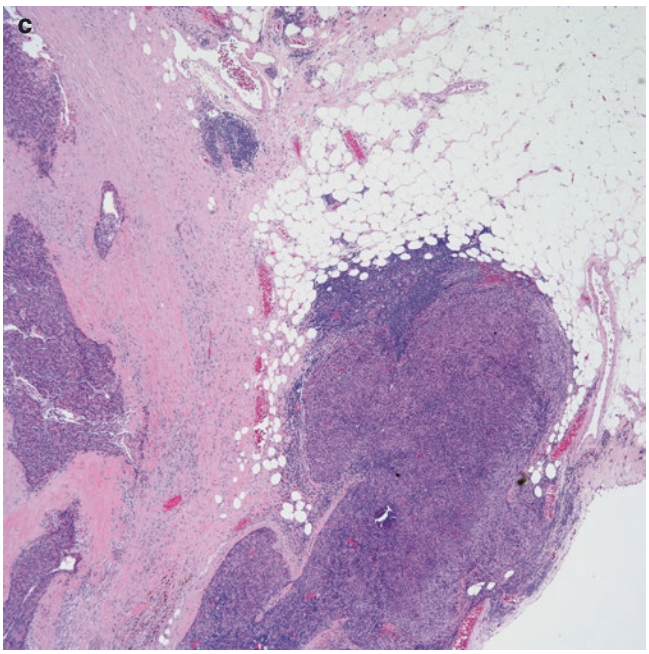

Fig. 6.2 (continued) (**c**) Thymoma is invading the perithymic adipose tissue

In this study, of 250 cases, the authors observed statistically significant overall survival curves with a *p*-value of 0.044, while the recurrence-free survival *p*-value was 0.015. The important message of this staging system is to lower down the number of patients who by the fact that they have invasive disease will be inevitably treated as such with possible radiation therapy. The staging system's goal is to make the determination that, in some cases, even though the tumor is invasive (limited disease), the patients may be treated with surgical resection alone. In addition, this staging system places the pathologist in more direct control of proper staging by documenting the structures involved. Needless to say, the schema provides histological definitions of what is to be diagnosed as pleural or pericardial invasion. More recently, in a multi-institutional effort to clarify not only histological classification but also staging for thymomas, Weissferdt and associates [34] reported 1470 thymoma cases in which the authors found statistically significant correlation using this particular schema.

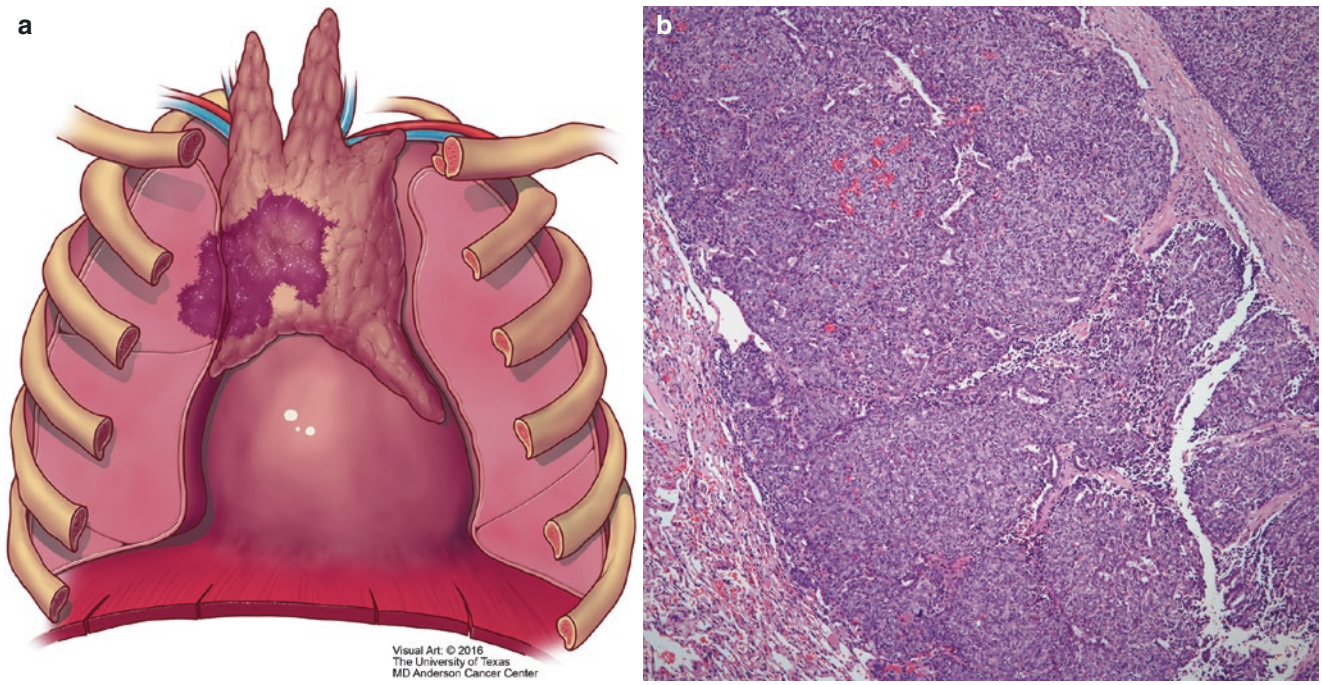

Fig. 6.3 (**a**, **b**) Stage IIA. (**a**) Graphical illustration of a thymoma with direct invasion of the pleura and lung. (**b**) Histological section of an invasive thymoma going through the visceral pleura into the lung parenchyma (**a**: Copyright © 2016 with permission from Dr. Kalhor and Moran)

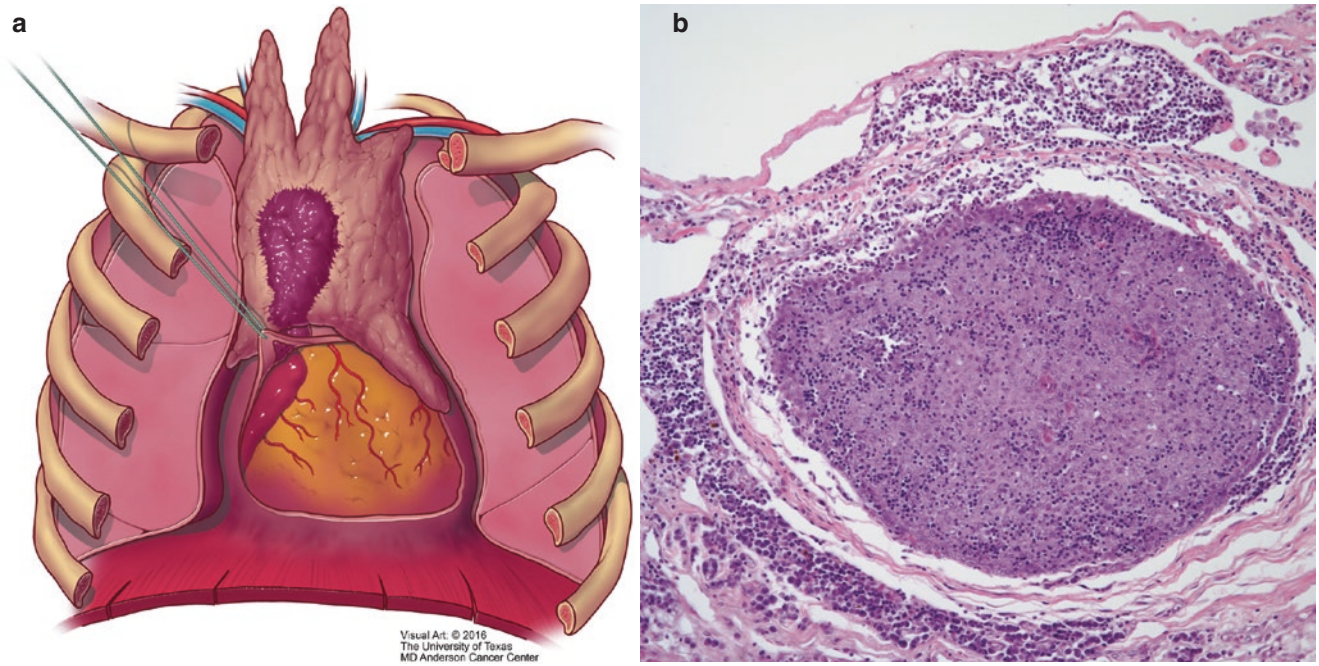

Fig. 6.4 (**a**, **b**) Stage IIB. (**a**) Graphical illustration of a pericardial invasion of a thymoma. (**b**) Histological section of a thymoma invading the pericardium (**a**: Copyright © 2016 with permission from Dr. Kalhor and Moran)

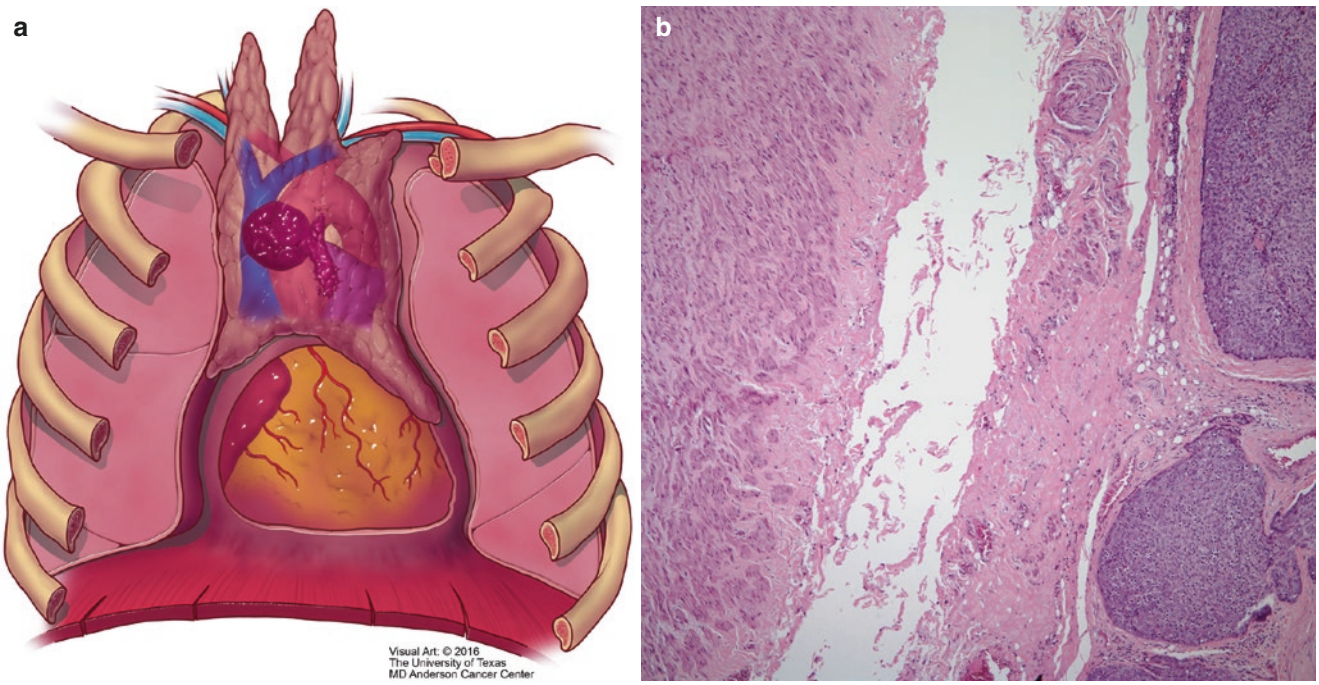

Fig. 6.5 (**a**, **b**) Stage IIC. (**a**) Graphical illustration of a thymoma invading the great vessels. (**b**) Histological section of a thymoma adjacent to the wall of a great vessel. (**a**: Copyright © 2016 with permission from Dr. Kalhor and Moran)

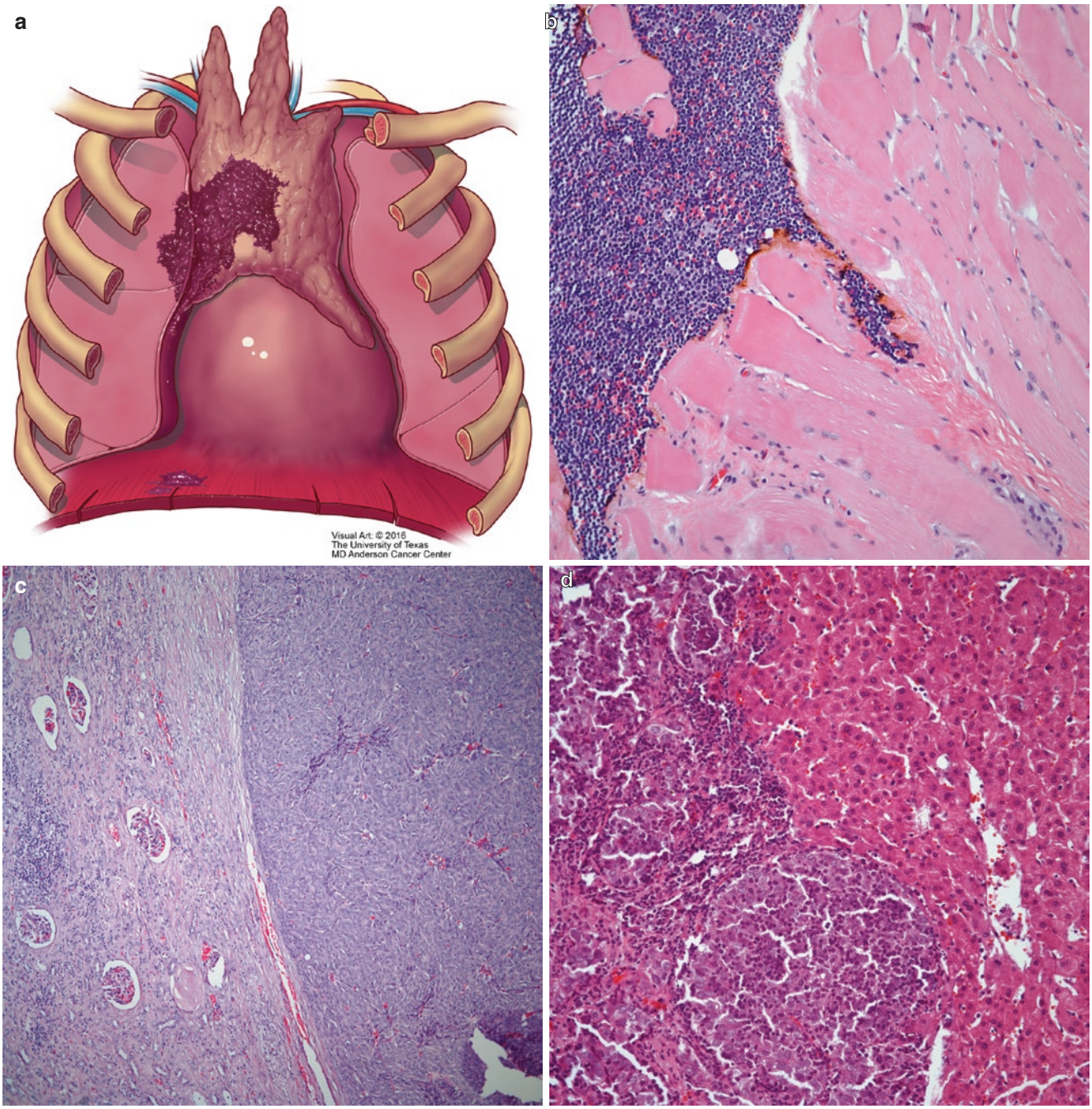

Fig. 6.6 (**a**–**d**) Stages IIIA (**a** and **b**) and IIIB (**c** and **d**). (**a**) Graphical illustration of a thymoma showing diaphragmatic invasion, so-called drop metastasis. (**b**) Histological section of a thymoma infiltrating the skeletal muscle of the diaphragm. (**c**) Metastatic spindle cell thymoma to the kidney. (**d**) Metastatic thymoma to the liver (**a**: Copyright © 2016 with permission from Dr. Kalhor and Moran)

Staging of Thymic Carcinoma

Contrary to the several publications on the staging of thymomas, a specific staging system for thymic carcinoma has been essentially nonexistent. Part of this problem is that the approach taken for thymic epithelial neoplasms (thymoma and thymic carcinoma) has been that of "one size fits all," and little attention has been placed to addressing different problems with the diagnosis, treatment, and staging of thymic carcinoma. In addition, one important fact to recognize is that thymic carcinoma is not a common neoplasm, and it is an entity that requires unequivocal pathological-radiological correlation. Regarding thymic carcinoma, it has been stated that it corresponds to a poorly defined group of lesions that have as a common denominator a primary location in the anterior mediastinum without evidence of a similar tumor elsewhere [35]. Therefore, even though the histology may not represent a problem in diagnosis, it is the specific anatomic location that cannot be determined by histological evaluation alone in the great majority of cases. As stated above, even in the larger series of thymic carcinomas presented [2], the issue of staging has been for the most part not properly addressed or staged-based on the staging system designed for thymomas.

Using the TNM approach for thymomas, Yamakawa and associates [23] stated that such an approach appears to be more useful for thymic carcinoma and thymic carcinoids than for thymoma. The most important issue with this study is that not only was it designed for thymomas (207 cases) but also that the number of cases of thymic carcinoma and thymic carcinoid was limited to 19 cases in total. In 1999, Blumberg and associates [36] evaluated 43 cases of thymic carcinoma and observed that the overall survival was 65% at 5 years and 35% at 10 years, while the overall recurrence was 65% at 5 years and 75% at 10 years. In addition, the authors did not observe any correlation with age, gender, tumor size, or Masaoka staging. One important feature that the authors correlated with survival was innominate vein invasion. The authors concluded, based on their analysis of the 43 cases, that Masaoka's staging system does not appear to predict outcome for patients with thymic carcinoma. Tseng and associates [37] presented a similar experience in a study of 38 cases of thymic carcinoma over a period from 1988 to 2002. The authors observed a median survival of 81 months and a median recurrence of 52 months after a follow-up ranging from 15 months to 10 years. Based on this experience, the authors concluded that the prognosis of thymic carcinoma appears to be mainly dependent on tumor invasion of the great vessels and also added that Masaoka's staging could not predict prognosis. Interestingly, the authors also stated that nodal metastasis (perithymic or paratracheal) was relatively rare and that nodal status did not influence prognosis.

Tsuchiya and associates [38] presented a more formal TNM staging for thymic carcinoma, recognizing the need to separate thymoma from thymic carcinoma, which essentially modified or readapted the previously presented TNM staging proposal of Yamakawa [23] (see the previous description of this system). Basically, the proposal of Tsuchiya and associates [38] defines groups as follows:

- Stage I – T1 or T2 N0 M0
- Stage II – T1 or T2 N1 M0
- Stage III – T3 N0 or N1 M0
- Stage IV – (a) T4 N0 or N1 M0, (b) any T N2 M0, or (c) any T, any N M1

Although this proposal addresses important issues such as the presence of lymph node metastasis, there are several shortcomings with this study: (1) the number of cases presented (19 cases) is hardly a large enough study, even with uncommon tumors, to propose a rather cumbersome staging system when it comes to lymph node sampling, (2) there is no statistically significant difference presented by the authors to support their proposal, (3) the T descriptions are at best ambiguous and not clearly stated, and (4) the requirement of extensive lymph node sampling is not only clinically unsupported but also statistically not proven to be significant.

Lee and associates [39], in a report of 60 patients (42 men and 18 women over a period of 20 years from 1986 to 2005) with thymic carcinoma, staged all the patients following Masaoka's schema of thymoma. Based on that schema, they identified that the 5-year survival rate after complete resection was 85% and that those patients did significantly better than those with incomplete surgical resection or nonsurgical treatment. This finding led the authors to conclude that the most important factor for disease control and long-term survival of patients with thymic carcinoma is complete surgical resection of early Masaoka stage. A few issues are worth mentioning regarding this particular study: (1) the authors decided to include in this study what appears to be bona fide thymic carcinoma and also cases of neuroendocrine carcinoma (possibly carcinoid and atypical carcinoid); (2) despite the fact that the authors mention that anterior mediastinal lymph nodes were obtained, there is no mention whether those were positive or negative; in either case, such findings should have been correlated with the outcome; and (3) the authors provide their own definition of "complete resection" as follows:

- R0 resection – macroscopically and microscopically total resection of the tumor
- R1 resection – microscopically incomplete resection (pleural seeding, completely resected is considered R1)
- R2 resection – macroscopically incomplete resection

This type of redefinition of complete surgical resections raised a different issue regarding the Masaoka staging system. For instance, pleural seeding, which likely represents what Masaoka defined as pleural "dissemination," is a late stage in Masaoka's schema, which, if viewed in a different way, can lead to a different interpretation of this R0, R1, and R2 resection: R0 for encapsulated tumors or minimally invasive neoplasms and R1/R2 for everything else. However, as it has been the experience of others, the lymph node issue is not defined and clearly not addressed in this schema. Essentially, the findings of Lee and associates [38] are in agreement with the majority of views regarding thymic epithelial neoplasms (thymoma/thymic carcinoma) and that complete surgical resection of the tumor is the most important predictor of prognosis. Also in support of the Masaoka staging system, Hosaka and associates [40] presented a series of 21 patients (15 men and 6 women) with thymic carcinoma. The spin of this study is to highlight that histologic grade and Masaoka stage predict prognosis in patients with thymic carcinoma. The authors presented 14 cases of squamous cell carcinoma, 2 of adenocarcinoma, 2 of atypical carcinoid, and 2 of undifferentiated carcinoma. Fourteen patients had complete surgical resection, and the 5-year survival rate in those patients was 66.8%. Based on those findings, the authors concluded that patients with early Masaoka stage and low or intermediate histologic grade had favorable prognoses. Important to highlight in this study are the following: (1) the authors state that "systematic lymph node dissection was not routine," thus leaving the unknown factor of possible nodal invasion, despite the fact that the authors documented a case of "recurrence" in a mediastinal lymph node; (2) even though the authors raised the valid issue of histological grade, it is also known that the occurrence of thymic adenocarcinoma is very uncommon; (3) just like other series of cases, this study also includes neuroendocrine neoplasms; and (4) the number of cases of higher-grade histology are too few to properly assess the impact of histology and outcome in a more comprehensive statistical manner. It is possible that the suggestion in this manuscript is that higher-grade tumors have increased tendencies to be in late stages; however, if that is the hypothesis, then the total number of cases – whether low-, intermediate-, or high-grade histology – is definitely not adequate to make such an assessment. It is very possible that only cases of intermediate histology are represented by the cases of neuroendocrine neoplasms, which have been shown to have a different survival rate (see the Chap. 9), rather than by the conventional cases of thymic carcinoma, which traditionally have been divided into low- and high-grade neoplasms.

Park and associates [41], raising the issue of the importance of lymph node dissection in cases of thymic carcinoma, presented a series of 37 patients who had complete surgical resection of thymic carcinoma. The patients were divided into four groups: (1) no lymph node dissection Nx = 8 cases, (2) limited dissection N0 = 13 cases, (3) extensive dissection N0b = 10 cases, and (4) node metastasis N1 = 6 cases. In those six patients with lymph node metastasis, the lymph nodes were either anterior mediastinal or intrathoracic. Based on this experience, the authors concluded that extensive lymph node dissection of more than ten lymph nodes is required to predict prognosis accurately and added that anterior mediastinal and paratracheal lymph nodes should be dissected in thymic carcinoma. Interestingly, despite the fact that the authors acknowledge the role of lymph nodes as predictor of survival in patients with thymic carcinoma, the actual staging of the patients presented in this study was the Masaoka staging system of thymomas with the caveat of lymph node sampling, once more raising concerns whether the best staging system is the one presented for thymoma or a TNM approach. In that regard, Viti and associates [42] reviewed the extensive literature on the topic of lymph node metastasis and lymphadenectomy in thymic carcinoma and carcinoids and concluded that the surgical approach for thymic carcinoma should include a form of lymphadenectomy to allow nodal staging.

Based on the existing literature, in 2012 we presented a series of 65 thymic carcinomas [43], of which in 33 cases, lymph node sampling was available [44]. The proposed staging system for thymic carcinoma, contrary to the one for thymoma, clearly states the need for the use of a TNM system and suggests abandoning the Masaoka schema for this particular tumor. Our schema is a three-tier system as follows:

- T1 – tumor limited to thymic gland (Fig. 6.7a–c)
- T2 – tumor invading the visceral pleura, lung, pericardium, great vessels, chest wall, or diaphragm (Fig. 6.8a–c)
- T3 – direct extrathoracic tumor extension, beyond the thoracic inlet (consisting of the manubrium, the first thoracic vertebra, and the first ribs and their cartilages) or diaphragm
- N0 – no lymph node metastasis
- N1 – lymph node to intrathoracic lymph nodes
- M0 – no distant metastasis
- M1 – distant metastasis (indirect tumor spread, including metastasis to extrathoracic lymph nodes) (Fig. 6.9a, b)

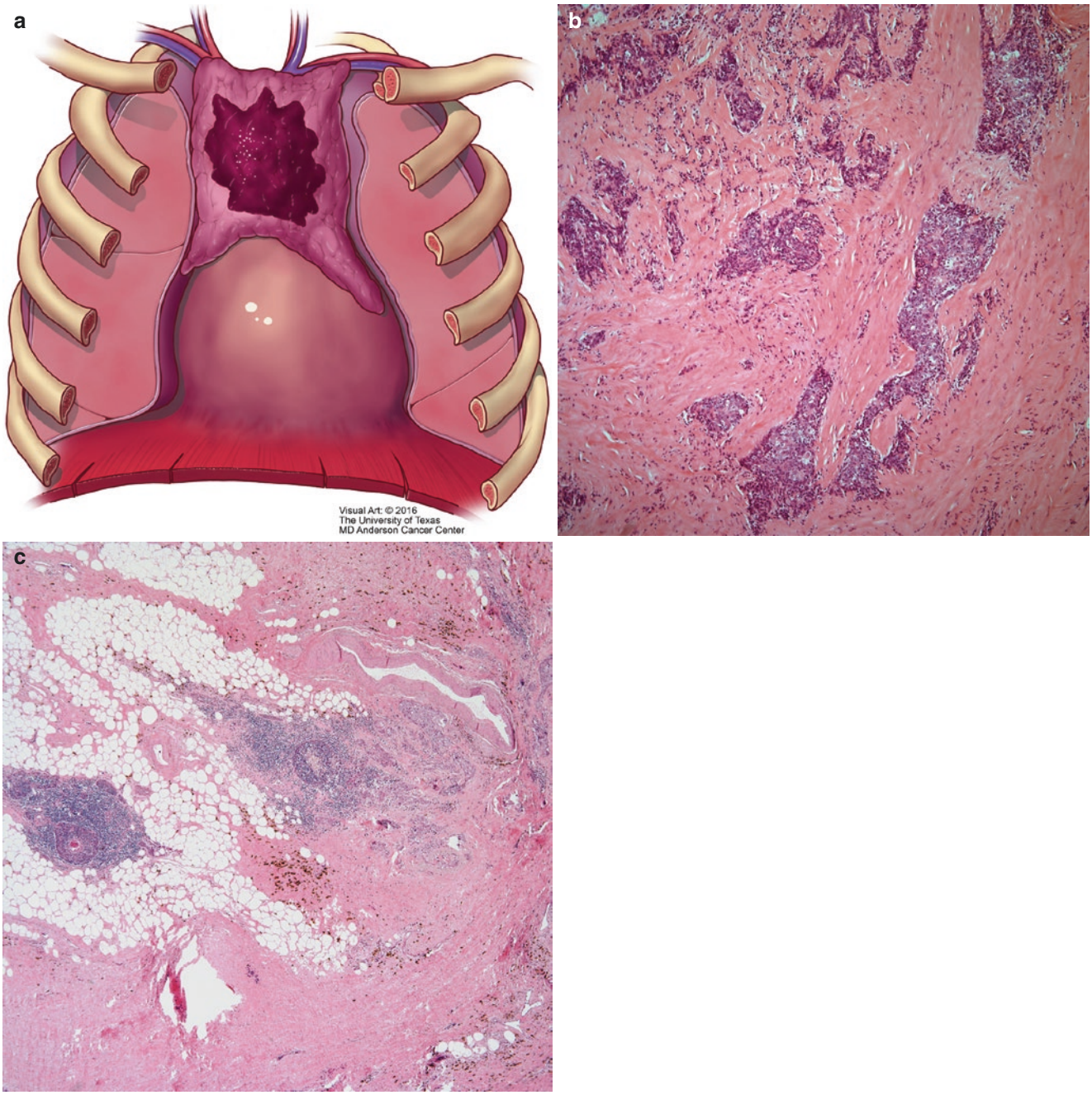

Fig. 6.7 (**a**–**c**) T1 thymic carcinoma. (**a**) Graphical illustration of the tumor is limited to the thymus gland in the anterior mediastinum. (**b**) Histological illustration of a thymic carcinoma; note the loss of organotypical features. (**c**) Tumor is limited to the thymic gland; note small remnants of the thymic tissue (**a**: Copyright © 2016 with permission from Dr. Kalhor and Moran)

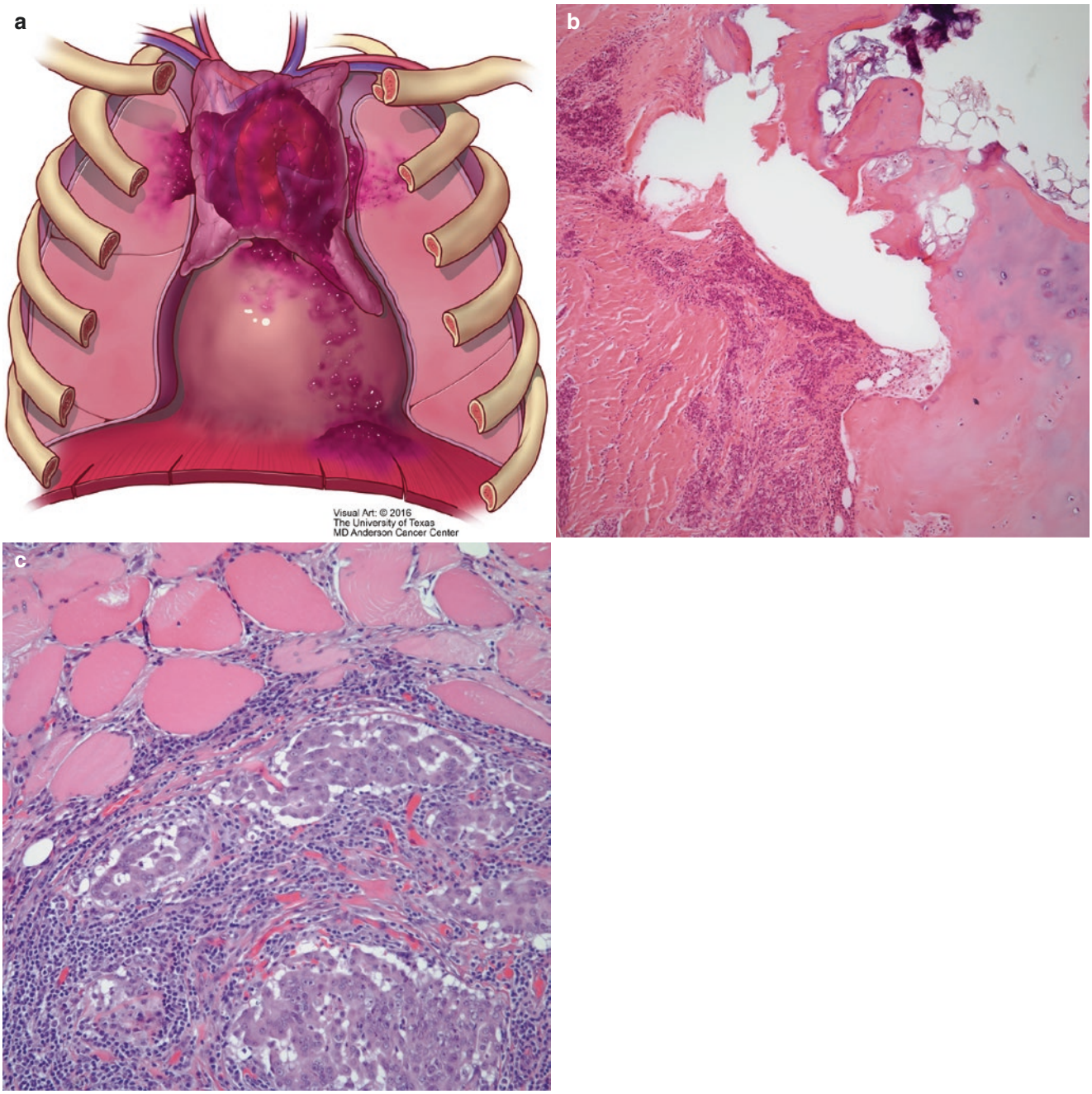

Fig. 6.8 (**a**–**c**) T2 thymic carcinoma. (**a**) Graphical illustration of the different routes that thymic carcinoma may invade. (**b**) Thymic carcinoma invading the cartilage of a rib. (**c**) Thymic carcinoma infiltrating the diaphragm (**a**: Copyright © 2016 with permission from Dr. Kalhor and Moran)

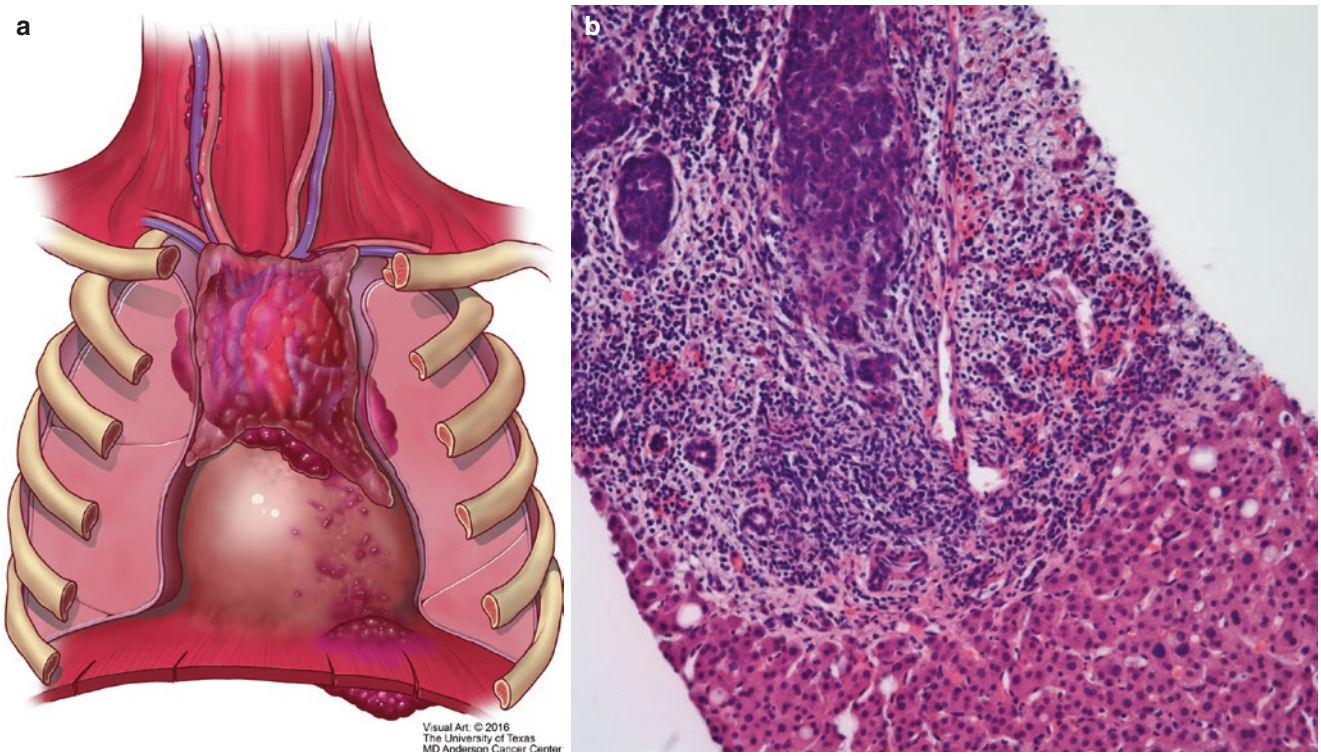

Fig. 6.9 (**a**, **b**) M1 thymic carcinoma. (**a**) Graphical illustration of M disease in thymic carcinoma either beyond the thoracic inlet or below the diaphragm. (**b**) Liver biopsy with metastatic thymic carcinoma (**a**: Copyright © 2016 with permission from Dr. Kalhor and Moran)

Based on this TNM system, the staging groups are as follows:

- Stage I – T1N0M0
- Stage II – T2N0M0
- Stage III – T3N0M0
  - Any T, N1, M0
  - Any T, any N, M1

Based on this study, we encountered 7 patients in stage I, 11 patients in stage II, and 15 patients in stage III. In addition, it was documented that 27 of the 33 patients had received additional therapy besides the surgical resection, while two patients were documented to have received no additional therapy besides the surgical resection. The clinical follow-up information ranged from 1 to 128 months, identifying 19 patients alive over a period of 3 to 126 months after diagnosis, while 14 patients had died of the tumor. Of the 19 patients who were found to be alived, 6 were in stage I, 7 were in stage II, and 6 were in stage III. On the other hand, of the 14 patients who had died, 1 was in stage I, 4 were in stage II, and 9 were in stage III. This information was correlated using the Masaoka and Tsuchiya proposal, and we encountered no statistically significant correlation by those two proposals when used as proposed. Correlations can be observed by combining different proposed staging categories, which essentially make those proposals unworkable. On the contrary, when analyzed using our proposed staging system, we obtained clear and significant correlation. One important difference in our opinion is the lymph node involvement by tumor, which in our opinion should be regarded as stage III regardless of the location of the lymph node.

Summary

It is highly advisable that the staging of thymoma and the staging for thymic carcinoma be separated as the two tumors represent two different clinicopathological entities. In one tumor, thymoma, the tumor should be staged according to the extent of tumor invasion, while in thymic carcinoma, a TNM approach should be followed to properly predict prognosis in these patients. Based on our experience, the two systems proposed by us [33, 44] are the ones that we suggest for staging thymoma and thymic carcinoma.

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