Lung Cancer 83 (2014) 126–132

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review

Historical perspectives: The evolution of the thymic epithelial tumors staging system

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ARTICLE INFO

Article history:
Received 12 June 2013
Received in revised form
16 September 2013
Accepted 23 September 2013

Keywords:
Thymoma
Thymic carcinoma
Staging system
TNM classification
History
Thymus
Masaoka staging system

ABSTRACT

Thymic epithelial tumors (thymomas, thymic carcinomas and neuroendocrine tumors – NETs) are rare primary mediastinal neoplasms, recently classified as orphan diseases. Their rarity might explain the fact that currently, no official staging system has been defined by the Union Internationale Contre le Cancer (UICC) and the American Joint Commission on Cancer (AJCC). However, the appropriate staging of these tumors has been matter of debate and several proposals have been published over the years, but very few have received a clinical validation.

Recently an international database for thymic malignancies has been provided by the International Thymic Malignancy Interest Group (ITMIG); one of its aims is to accomplish a new and evidence based staging system, to allow progress in clinical management in thymic tumors.

This paper will review the history of proposed staging systems, comparing resemblances and differences, being a sort of starting point for the development of a new widely accepted clinical staging system.

1. Introduction

Thymic epithelial tumors (TETs) are rare neoplasms which include thymomas, thymic carcinomas and neuroendocrine tumors (NETs), accounting for less than 1% of all tumors. The etiology of these tumors is largely unclear. The available data comes primarily from retrospective single-institutional studies highlighting aspects such as an association with paraneoplastic disorders (e.g. Myasthenia Gravis [MG]), a frequently indolent clinical course, a predilection to develop pleural and pericardial metastases, and histologic variability and heterogeneity. Surgery is the mainstay of treatment, but chemotherapy and radiotherapy are also useful. Several papers [1–4] demonstrate that complete tumor resection, histology and tumor stage statistically correlate with prognosis.

Many different staging systems have been proposed. Ruffini et al. [5] recently underlined that several different systems (Masaoka, Masaoka-Koga, TNM, Groupe d'Etude des Tumeurs Thymique [GETT]) are used, and no official stage classification system for thymic malignancies has been defined by the Union Internationale Contre le Cancer (UICC) and the American Joint Commission on Cancer (AJCC).

The aim of this paper is to review the history of proposed staging systems, to compare similarities and differences, and thus provide a springboard for development of a formal UICC/AJCC stage classification system.

2. History of thymic epithelial tumors staging systems

2.1. Non-TNM staging systems

In the 1960s, thymomas were classified as non-invasive and invasive [6,7], and four histologic subtypes were recognized Bernatz et al. [8]. The first staging system was proposed by Bergh et al. [9], based on 43 thymoma patients treated at Sahlgren's Hospital in Gothenburg (Sweden) from 1954 to 1975. Bergh differentiated thymomas according to the presence of symptoms, the tumor extent and histology, and designed a three-stage classification system (Table 1). A complete tumor resection (R0), (commonly observed in stages I and II), was associated with a longer survival. Postoperative radiotherapy was offered to incompletely resected patients and to most stage II and III ones. Survival rates differed considerably for stages II and III, leading the authors to conclude that

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http://dx.doi.org/10.1016/j.lungcan.2013.09.013

Table 1
The Bergh staging system.

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

Table 2
The Wilkins–Castleman staging system.

Stage	Description
I	Encapsulated tumor
II	Pericapsular growth into the mediastinal fat tissue or adjacent pleura or pericardium infiltration
III	Invasive tumor with invasion of mediastinal structures, intrathoracic metastases, or both

Table 3
The Masaoka staging system.

Stage		Description
I		Macroscopically encapsulated tumor without microscopic invasion of capsule
II	a	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
	b	Microscopic invasion into capsule
III		Macroscopic invasion into neighboring organs, i.e. pericardium, great vessels or lung
IV	a	Pleural or pericardial dissemination
	b	Lymphogenous or hematogenous metastasis

these should be separated. Recurrences were also more frequent in higher stage and incompletely resected patients.

Wilkins and Castleman [10] published an update in 1979 of their previous series of patients treated at the Massachusetts General Hospital [11]. These authors made minor modifications to the Bergh staging system, including mediastinal pleura or pericardial invasion in stage II (Table 2). They demonstrated that tumor invasiveness was an adverse prognostic factor, and it may guide postoperative radiotherapy, and that completeness of resection was the strongest prognostic factor (10-year cumulative survival: 68%).

Masaoka first highlighted that the clinical course of thymoma, usually indolent, may be characterized by local invasion, infiltration and finally by distant spread with lymphogenous/hematogenous metastases. He demonstrated the clinical importance of tumor local invasiveness compared to lymphogenous/hematogenous metastasis, with a step-wise decrease in survival. The Masaoka 4-stage system, published in 1981, was based on the 1954–1979 Osaka University experience with 93 thymoma patients (Table 3) [12]. They suggested that establishing a correct stage at the beginning of the treatment would help select the appropriate therapy and improve survival. R0 resections were performed in stage I and II patients; subtotal resections (debulking procedures) were done in 8/11 stage IV thymomas. After R0 resections the 3- and 10-year survival rates were 89% and 75%, respectively. Invasiveness was recognized as one of the main prognostic factors, along with the completeness of surgical resection.

The Masaoka staging system differed from that of Berg and Wilkins primarily in the description of stage II: (1) macroscopic invasion into thymic surrounding fatty tissue or mediastinal pleura, and (2) microscopic capsule invasion. However, as Rosai and Levine observed [13], it is difficult to distinguish tumor tissue infiltration from fibrous adhesion to the mediastinal pleura, and different rates of invasive tumors reported in the literature may reflect this.

In 1985, Verley and Hollmann published the 1955–1982 Marie Lannelongue Hospital (Paris, France) experience on surgical management of 200 thymoma [14]. Their staging system (Table 4) was based on the gross tumor invasion observed at surgery and the degree of excision. Survival rates decreased progressively with the degree of tumor invasion. Statistical models highlighted the importance of invasion, but not the degree of tumor invasion as a prognostic factor (despite a statistical difference between encapsulated stage I and invasive stage IIIa thymomas, there was no difference between stages Ia vs Ib, Ib vs IIa, IIa vs IIb and IIb vs IIIa). Overall 5- and 10-year survival rates of non-invasive and invasive thymomas were 85% and 80% and 50% and 35%, respectively.

Table 4
The Verley–Hollmann staging system.

Stage		Description
I		Encapsulated, noninvasive tumor; total excision
	a	Without adhesion to the environment
	b	With fibrous adhesion to mediastinal structures
II		Localized invasiveness (e.g. pericapsular growth into mediastinal fat tissue or adjacent pleura or pericardium
	a	Complete excision
	b	Incomplete excision with local remnants of tumor
III		Largely invasive tumor
	a	Invasive growth into the surrounding organs and/or intrathoracic tumorous grafts (pleura/pericardium)
	b	Lymphogenous or hematogenous metastasis

The authors also designated stage I as noninvasive, stage II as moderately invasive and stage III as largely invasive thymomas.

Table 5
The Groupe d'Etude des Tumeurs Thymiques (GETT) staging system.

Stage		Description
I	a	Encapsulated, non-invasive. Total excision
	b	Macroscopically encapsulated, but localized mediastinal invasion. Total excision or suspected microscopic capsular invasion. Total excision
II		Invasive growth into surrounding organs. Total excision
III	a	Invasive growth into surrounding organs. Incomplete excision
	b	Invasive growth into surrounding organs. Biopsy of the tumor only
IV	a	Grossly invasive tumor with supraclavicular lymph nodes or pleural or pulmonary nodules
	b	Hematogenous metastasis (1 or more)

Gamondes et al. reported the 1970–1987 experience of the Lyon (France) Thoracic Surgery Unit on 67 patients with thymoma [15]. The GETT, a consortium of 11 hospitals in the Paris region, validated the proposed clinical staging system. The GETT staging system combined the Masaoka scheme with the macroscopic assessment and completeness of resection (Table 5). The 5- and 10-year survival rates ranged from 96% to 88% for stage I, 84% and 56% for stage III and 73% and 18% for stage IV, respectively. The tumor stage and the completeness of surgical resection were the major prognostic factors. The GETT system is still used in some French Institutions [5].

Koga et al. proposed a revised Masaoka staging system in 1994 (Table 6) [16]. Masaoka stage IIb patients were included in a new stage I, since microscopic capsule invasion was not considered a real invasion unless the tumor breaks through the capsule itself. Microscopic transcapsular invasion was classified as IIa and macroscopic invasion into surrounding fat is stage IIb (flipping around how IIa and IIb are classified by Masaoka). Survival curves according to the Masaoka-Koga system demonstrated no significant difference between stages I and II and between stages III and IV. Tumor-related death and recurrences were more frequent in advanced stages. The authors concluded that a four-staged staging system could be simplified to only differentiating between invasive (stage III/IV) and non-invasive (stage I/II) thymomas. The