



Pathological features of thymoma and thymic carcinoma with therapeutic implications

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Abstract: The prognosis of patients with thymomas (TMs) and thymic carcinomas (TCs) is currently mainly determined by tumor stage, resectability, resection status and, to some extent, by histotype, while molecular tumor markers play a minor role. However, meticulous clinical, imaging and serological studies, eventual followed by needle biopsy (e.g., to exclude lymphoma or germ cell tumors) are indispensable prior to the establishment of any therapeutic concept. Once surgery has been performed, classical pathological features of the resection specimen are the major determinants for subsequent therapeutic decision in almost all TMs and TCs. Predictive molecular markers will play an increasingly important role in the future, as exemplified by the rare TCs with KIT and NUT mutations and those thymic cancers that are susceptible to immune checkpoint inhibitors.

Keywords: Resection; close margin; KIT mutation; sunitinib; PD-L1

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Introduction

Primary R0 surgical resection is the key therapeutic aim to eradicate thymomas (TMs) and thymic carcinomas (TCs). If this is impossible, resection or debulking after neoadjuvant chemo-therapy or somatostatin/prednisone ‘induction’; postoperative radiotherapy (PORT); ‘definite chemotherapy’ in disseminated and recurrent, unresectable disease; and various “targeted” approaches alone or in combination with chemotherapy have been strategies to combat these cancers. Immune check-point inhibitors are currently in early phase clinical testing, revealing efficacy but also a high risk of dangerous autoimmune adverse effects, particularly in TM, i.e., the tumor with the highest frequency of paraneoplastic autoimmune phenomena (1). Since predictive biomarkers are largely missing (2), pathological features of TMs and TCs—(immuno-)

histological properties, stage and resection status—continue to play the most relevant roles in guiding treatment decisions, as detailed next.

Pathological features with treatment implications

Histotype is usually the first feature recognized on needle biopsy of a mediastinal mass of unknown differentiation [a clinical diagnosis of thymoma is almost certain only in patients with Myasthenia gravis, while positive tumor markers like AFP, HCG and neuroendocrine markers hint to subsets of germ cell tumors and neuroendocrine tumors, respectively, entailing therapeutic consequences very different from those of TMs and TCs (3)]. If a histological diagnosis of TM or TCs is made, imaging studies become

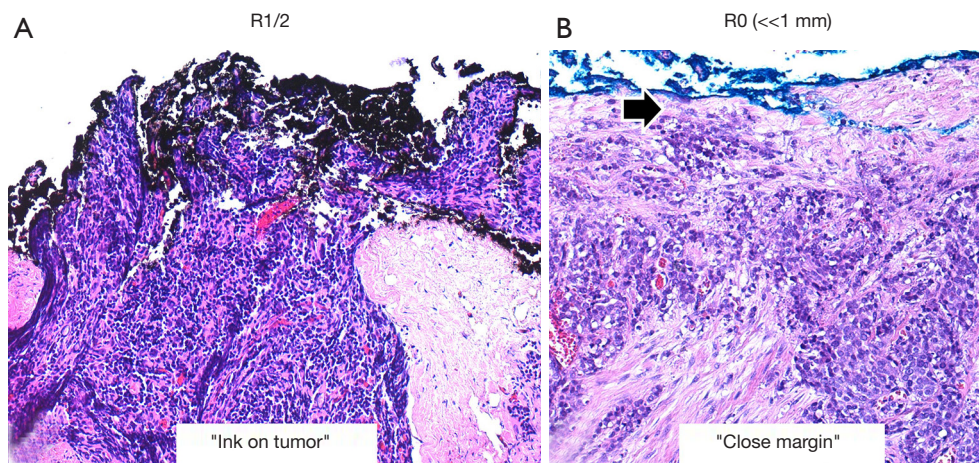


Figure 1 Surface inking of resection specimens is relevant to recognize (A) incomplete resection (R1 or R2) and (B) a close margin. However, close margins have not yet been evaluated as prognostic marker in terms of recurrence and survival in thymomas and thymic carcinomas (H&E stain, $\times 200$). The arrow shows the region of the invasion front that is closest (<1 mm) to the inked resection margin.

key to make a decision either for primary resection or neoadjuvant approaches. While neoadjuvant chemotherapy is the standard approach in unresectable TMs and TCs alike (4), a histological diagnosis of lymphocyte-rich AB, B1 or B2 thymoma in conjunction with a positive 'octreoscan' may, alternatively, argue for a (chemotherapy-sparing) neoadjuvant octreotide/prednisone intervention to achieve secondary resectability (5). Histology may also affect the decision for PORT: there is some evidence that patients with type B2 and B3 TMs and TCs at low Masaoka-Koga stages (MKS) I or II but not patients with A or AB TMs profit from PORT after R0 resection (4). Also in the adjuvant setting, the distinction between B3 thymoma and TC appears to be important, since only TCs responded to the TKI, sunitinib in a recent phase II clinical trial (6). Immunohistochemistry (IHC) for NUT or neuroendocrine markers, respectively is key to distinguish NUT carcinomas and Large cell neuroendocrine carcinomas from poorly differentiated squamous cell carcinomas, small cell carcinomas or undifferentiated carcinomas, to draw better therapeutic conclusions (7). Whether quantifying PD-L1 expression by IHC in TMs and TCs is a valid predictive marker for therapies with immune checkpoint inhibitors is currently unclear (8,9). Tumor stage is one of the strongest independent prognostic features of TMs and TCs. MKS I/II TMs are usually cured by surgery alone and may not need adjuvant therapy (4), although recent studies suggest that PORT may also improve the control of some stage IIA tumors (10,11). In any case, advanced tumor stages irrespective of TM and TC histotype or resection

status entail PORT (MKS III), pleurectomy with or without hyperthermic intrathoracic chemotherapy (HITOC) (stage IVa) (12) and/or chemotherapy (MKS IVb) (4). Resection status is not only an important prognostic factor (13,14), but the histological diagnosis of incomplete resection (R1 or R2)—defined as "ink on tumor"—typically is an indication for PORT irrespective of histotype, as PORT significantly improves survival in TMs and TCs (4,10,11). By contrast, the role of 'close margins' (distance of tumor to the surface of the given resection specimen) has not been evaluated in terms of recurrence and survival (*Figure 1*).

Conclusions

Taking into account that tumor stage, resection status and histotype are currently the most important factors in terms of prognosis, histopathological tumor features remain the basis of therapeutic decisions in almost all TMs and TCs. Molecular markers hopefully will play an increasingly important role in the futures, as exemplified by the rare TCs with KIT and NUT mutations (7,15).

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