Extended Abstract

Tumor-node-metastasis (TNM) update (pathological)—extended abstract

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Background

The 9th tumor-node-metastasis (TNM) staging classification is based on the analysis, performed by the Cancer Research and Biostatistics (CRAB) organization, of over 9,000 cases of thymic epithelial tumors (TETs) collected in the new International Association for the Study of Lung Cancer (IASLC) database, and on the extensive discussion among members of IASLC Staging and Prognostic Factors Committee (SPFC)-Thymic Domain (TD). Some choices of the SPFC-TD were determined by the peculiar TET biology: a single TNM stage classification for all TET types [thymoma, thymic carcinoma (TC), thymic neuroendocrine neoplasms] was maintained (for simplicity and for the existence of "combined" carcinoma-thymoma cases); moreover, thymomas are frequently locally invasive rather than metastatic and the spread is observed in advanced stages. Therefore, the precise definition of the anatomical T extension, in a region so complex such as the mediastinum, cannot be overemphasized. A "T" subcommittee, in the SPFC-TD, was specifically encharged to propose solutions for the "T"-related problems. The T indicator in the TNM system provides important information on tumor size (Tsize) and on surrounding tissues/organs invasion. Clinical (c) and pathological (p)T are strictly interrelated. However, some problems in the discussion concerned more the pathological workup than the clinical side of patient evaluation.

Statistical methodology

To assess the impact of Tsize on survival indicators, "T" analysis was performed separately for TC and thymoma, both for c and p Tsize, and cases were allocated in a training and in a validation set. The allocation in the 2 sets was stratified by geographical region, age (<65 *vs.* ≥65 years), sex, Eastern Cooperative Oncology Group (ECOG) performance status (0/1 *vs.* ≥2), resection status (R), and T category, to ensure that invaded anatomical structures were similarly distributed among datasets. The complete list of methods and results were reported in the original paper (1).

Results

As a general rule, microscopic confirmation of invasion is required for the "p" staging; therefore, the pT is determined after primary tumor removal, completely (R0) or incompletely (R1R2).

- Tsize: the impact of Tsize on survival was among the main unresolved issues of the TET 8th TNM (2), investigated in order to determine if size could be relevant for prognostic evaluation. Among TET, Tsize ranged from less than 1 cm to over 20 cm, and the median p Tsize was 5.4 cm in thymomas and 6 cm in TC. Although a single definite cut point was not determined, 5 cm was found within the range of optimal cut points, approximated the median Tsize for both thymomas and TC, seemed to have the broadest application in both thymoma and TC, and allowed a prognostic stratification of T1 patients in 2 groups, having Tsize of 5 cm or less *vs.* more than 5 cm. Both overall survival (OS) and freedom from recurrence (FFR) were statistically significantly different in the 2 groups.

Therefore, T1 was changed in T1a and T1b in relation to Tsize (T1a: 5 cm or less) (T1b: >5 cm).

- Mediastinal pleura (MP) invasion: the SPFC-TD acknowledged the difficulty in recognizing and reporting MP invasion both preoperatively (by imaging) and by pathological examination. Moreover, in patients with tumors classified as pT1 according to the 9th TNM proposals, different models were tested including contemporarily Tsize and MP invasion, however the results were not statistically significant. Therefore, for the 9th TNM, MP was dropped from relevant to the T1 indicator; however, MP was recommended as "additional histologic descriptor", to be recorded when available.
- Re-assessment of T3 level structures: FFR and cumulative incidence of recurrence (CIR) in T3N0M0 patients with TC and with thymoma—undergoing R0 resection with involvement of the lung or phrenic nerve—appeared to be similar to that of T2N0M0 R0 cases. Therefore, the proposal of the SPFC-TD was to downstage T3-lung and T3-phrenic nerve invasion to T2 in the 9th TNM. Concerning phrenic nerve invasion, it was proposed to include either pretreatment diaphragm elevation or pathological invasion of the perineurium without nerve function loss. The Committee is aware that the new IASLC database does not contain detailed information allowing a precise definition of pathological/clinical lung invasion with prognostic relevance.

Therefore, for the T component, the SPFC-TD proposals were as it follows: T1 category is divided into T1a (≤5 cm) and T1b (>5 cm Tsize) irrespective of MP invasion; T2 includes direct invasion of pericardium, lung or phrenic nerve, at variance with the 8th TNM; T3 includes direct invasion of the brachiocephalic vein, superior vena cava, chest wall, or extrapericardial pulmonary arteries and veins; and T4 category remained the same as in the 8th TNM.

No changes have been made to the N and M categories (3), nor to the International Thymic Malignancy Interest Group (ITMIG) nodal map, other than some added clarifications (4).

Discussion

Tsize, one of the most important prognostic indicators in most tumor systems, was now introduced as staging criterium in the 9th TNM. It should be noted that there are several recent papers dealing with the impact of TET's Tsize on survival, e.g., Cangir *et al.* (5) found better OS in thymomas <5 cm in Tsize measured both in the longest and mean diameters. For the 8th TNM, the Japanese Association for Research on the Thymus (JART) data included systematically the MP invasion, which showed a prognostic relevance. In the new IASLC database Tsize >5 cm was more frequent in T1 cases with MP invasion compared to those without MP involvement. In TC, most patients with T1 tumors with MP invasion had a pathological Tsize >5 cm, whereas less than half of T1 cases without MP involvement had a p Tsize >5 cm. Also, in thymomas, >5 cm Tsize was seen in 57% of T1 cases with MP invasion versus 44% of T1 cases with no MP involvement. Thus, MP, although recorded when available, was dropped from the TNM system and replaced by Tsize.

Unresolved issues that remain for the next 10th TNM edition (6,7), in particular for the "T" indicator include:

- More "granular" data should be collected for the next 10th TNM, in order to better define invasion criteria of anatomical structures. In particular a precise definition—both clinical and pathological—of lung invasion should be reached.
- More details for the cT in nonsurgical (more advanced) cases are needed.

Beside this, we need standardized specimen work up and reporting of relevant pathologic details such as Tsize, characteristics of the specific organ invasion, and uniform and accepted definitions of invasion. It should be pointed out that the recent 3rd edition of expert consensus of the International Collaboration on Cancer Reporting (ICCR) dataset defined and proposed most of the essential data to be investigated and reported for TET (8). The joint collaboration of radiologists, surgeons and pathologist is required to achieve an improved level of TET knowledge for the next 10th TNM.

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Extended Abstract

Pathologic responses to neoadjuvant therapy in thymic epithelial tumors: extended abstract

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The goal of neoadjuvant therapy in thymic epithelial tumors (TETs) is to decrease tumor stage and therefore to increase resectability of the tumor (1). In TET complete resection and stage are the most important prognostic parameter (2-4). Neoadjuvant therapy should also prevent systemic disease progression (1). While pathologic response to neoadjuvant therapy is reported in resection specimens of TET as percentage of viable tumor, it is not clear whether percentage of viable tumor in post-neoadjuvant therapy specimens is of prognostic value. Large studies are lacking, mainly because of the paucity of these tumors.

In TET complete pathologic response has been reported in 0% to 31% of thymomas and 0% to 14% of thymic carcinomas (1,5-8). Near complete response rate was defined as less than 10% of viable tumor and was reported in 20% to 40% of TET following chemotherapy or chemoradiation (7,9,10). There is a suggestion that the pathologic response is larger in thymic carcinoma than thymoma (5), however, that finding has not been validated.

Pathologic response to neoadjuvant treatment has been used as a surrogate endpoint for overall survival in clinical trials in other tumors such as melanoma, breast carcinoma, colorectal carcinoma, and non-small cell lung carcinoma (NSCLC). Major pathologic response, as defined as less or equal to 10% of viable tumor has been utilized as surrogate of long-term survival after neoadjuvant chemotherapy and immunotherapy in clinical trials in NSCLC. In addition, there are recommendations for standardized practices for the pathologic assessment of response to neoadjuvant therapies in other organs such as breast and lung (11-13). For instance, recommendations for a standardized approach to evaluation of the pathologic response to treatment in NSCLC in the setting of clinical trials includes mapping of the tumor on the gross specimen. Percentage of viable tumor, percentage of necrosis, and percentage of stroma (encompassing fibrosis and inflammation) should sum up to 100% of the tumor bed. Staging of the tumor should be performed according to the size of viable tumor calculated as percentage of viable tumor multiplied by the size of the tumor bed (11,14).

In TET the International Collaboration on Cancer Reporting (ICCR) recommends to report the percentage of viable tumor in relation to the tumor bed including metastases and implants, to sample at least one block/cm of maximum tumor diameter or, in case of complete pathologic response, the entire tumor if feasible (15,16). National accreditation institutions such as the College of American Pathologists also recommend to report the percentage of viable tumor. Only a few studies evaluated the pathologic response to neoadjuvant therapy in TET. In a study of 28 thymomas stages I through III that were treated with neoadjuvant chemotherapy followed by resection the authors found necrosis in 75% of tumors, histiocytic proliferation (75%), hemorrhage (54%), calcifications (29%), cholesterol granulomas (25%), and cystic changes (21%) in the treated tumors (17). However, none of these findings are specific to post-neoadjuvant TETs as they can also be seen in TETs without neoadjuvant therapy. In this study, tumor viability ranged between 100% for type A thymomas, 10% to 100% for B1 and B2 thymomas, and 80% to 100% for B3 thymomas. Another study including 28 unresectable thymomas and 21 thymic carcinomas that were resected after chemotherapy, radiation, or chemoradiation revealed that thymic carcinomas had a significantly higher response to treatment with lower percentage of viable tumor and more necrosis than thymomas (5). That study

used a 5-tiered tumor response grading with grade 1 representing complete pathologic response and grade 5 showing no obvious pathologic tumor response. In that study, 14% of thymic carcinomas had a complete pathologic response and 19% a tumor response grade 2 while none of the thymomas had a complete pathologic response and only a single type B3 thymoma had a tumor response grade of 2. However, there was no significant difference in the post-neoadjuvant therapy resection rate between thymomas and thymic carcinomas.

There are many opportunities for future studies. For instance, what is the effect of neoadjuvant therapy on thymoma *vs.* carcinoma? What should encompass standardized reporting of pathologic treatment response in TET beyond percentage of viable tumor? Should post-neoadjuvant therapy staging be based on percentage of viable tumor or size of tumor bed? To obtain sufficient power, these and other questions need to be investigated in multi-institutional and global studies.

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Extended Abstract

Autoimmune phenomena: extended abstract for thymoma and clinical neurology

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Background

Although relatively rare, thymomas are associated with a variety of autoimmune and paraneoplastic phenomena, with the neuromuscular transmission disorder myasthenia gravis (MG) being the most common. However, a variety of other peripheral and central nervous system disorders have been described in the context of thymoma (1). It is believed that aberrant T cell activity mediated by thymic neoplasia generates dysfunctional autoreactive mechanisms that lead to this wide variety of neurologic disorders.

Methods

Case series literature was reviewed based on a PubMed search that merged autoimmune and paraneoplastic neurologic disorders with thymoma. Autoantibody associations and therapeutic approaches beyond thymoma resection and systemic tumor management were also reviewed for the various peripheral and central nervous system disorders.

Results

From the standpoint of neurologic disorders linked to thymoma, MG predominates, representing one-third to one-half of all associations. B2 thymomas are the most common histologic type, and autoantibodies to the acetylcholine receptor are present in nearly all these MG cases. The second most common association is most likely the central nervous system disorder of limbic encephalitis/encephalomyelitis, associated with autoantibodies to ANNA-1 and Ma2. Cognitive, neuropsychiatric, spinal cord and even peripheral nerve involvement can occur with this syndrome, with immunosuppressive therapy (IST), plasma exchange (PE), intravenous immunoglobulin (IVIg), and B-cell depletion representing the avenues of therapy. Other central nervous system disorders include brainstem encephalitis (ANNA-2 and Ma2 autoantibodies), opsoclonus-myoclonus (ANNA-1 or 2, Ma1 or 2, or Yo autoantibodies), cerebellar degeneration (Yo or ANNA-1 autoantibodies), and neuromyelitis optica (NMO; AQPR, MOG, or ANNA-1 autoantibodies). Management of these disorders is similar to the approach for limbic encephalitis with the exception that C5 complement inhibitors, and anti-IL6 receptor and anti-CD19 agents are approved for NMO (2).

The spectrum of peripheral nervous system disorders associated with thymoma is wide. In addition, to MG, Lambert Eaton myasthenic syndrome (LEMS) associated with the typical autoantibodies to the P/Q voltage-gated calcium channel has been reported with thymoma. Other conditions include cranial and polyneuropathies (GAD, amphiphysin, glycine receptor autoantibodies), autonomic neuropathy (neuronal acetylcholine receptor and CRMP5 autoantibodies), rippling muscle disease (neuronal acetylcholine receptor autoantibodies if thymomatous MG also present), neuromyotonia in the form of either Isaacs' or Morvan's syndrome (LGI1/CASPR2 autoantibodies), and inflammatory myopathies including granulomatous myositis (3). Of note, rippling muscle disease can also be inherited, with caveolin-3 gene mutations (4), and both stiff person and Morvan's syndromes do cross over to involve the central nervous system. Beyond the specialized

symptomatic and immunotherapy used for MG and LEMS, management of these other disorders typically involves IST, PE and IVIg. Stiff person syndrome can respond to benzodiazepines and anti-spasticity agents such as baclofen, while acetylcholinesterase inhibitors and agents used for orthostatic hypotension such as midodrine can help with autonomic neuropathies (5). Anti-epileptic agents such as phenytoin and carbamazepine have been used for many years to ameliorate symptoms of muscle stiffness in neuromyotonia.

Conclusions

Although thymomas are an uncommon form of neoplasia, they are frequently associated with a wide variety of autoimmune disorders and paraneoplastic syndromes, with the peripheral and central nervous systems often involved. Although the association with MG is well recognized, it is important for clinicians from a variety of specialty backgrounds to be aware of these disorders so that appropriate chest imaging can be ordered. For instance, some studies suggest that when autoimmune or paraneoplastic phenomena herald the presence of an underlying thymoma, the risk of tumor recurrence following therapy is lowered and clinical outcomes improve. Although the data on prognosis remains mixed, earlier diagnosis and management of thymoma in general can positively influence survival and minimize adverse events. Meanwhile, immunotherapy and other treatment modalities can favorably impact most autoimmune and paraneoplastic neurologic manifestations.

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Extended Abstract

Adoptive cell therapy and cytokine release syndrome

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Standard of care systemic therapy for recurrent thymic epithelial tumors (TETs) is generally limited to single agent cytotoxic chemotherapy or the use of targeted biologic agents until disease progression or development of intolerable adverse events (1). Immune checkpoint inhibition with anti-programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy is now routinely used in various settings across most tumor types, but its application for patients with TETs is limited to treatment of recurrent thymic carcinoma due to a high risk for development of immune-mediated toxicity (2-4). While "immunotherapy" is often used interchangeably with immune checkpoint inhibitors (ICIs), this umbrella terminology extends well beyond ICIs and encompasses a broad array of anti-cancer therapeutic approaches with a common strategy that aims to harness various aspects of the immune system to enhance its ability to recognize and eradicate malignant cells (5,6). Immunotherapeutic strategies to date include ICIs, cancer vaccines, cytokine-based therapies, oncolytic virotherapies, and adoptive cell therapies (ACT) (5-9). The use of ACTs for treatment of advanced solid tumors is an area of active investigation, and these interventions could potentially have a role for treatment of TETs in the future. In our presentation, we briefly review ACTs and describe cytokine release syndrome (CRS), which is one of the most common post-infusion complications of ACT.

ACT

The ultimate aim of ACT is to generate a robust immune-mediated antitumor response via manipulated immune cells. ACTs, specifically chimeric antigen receptor (CAR)-T cells, were first investigated in patients with hematologic malignancies and have demonstrated unprecedented success leading to Food and Drug Administration (FDA) approvals for six CAR-T cell therapy products to date for patients with relapsed/refractory B-cell malignancies including B-cell acute lymphocytic leukemia, non-Hodgkin lymphoma, and multiple myeloma (10,11). While the development of ACTs for solid tumors is still largely in preclinical stages or in early phase trials, there are more than 150 actively enrolling ACT clinical trials for various solid tumors (12). ACT involves identification, isolation, and autologous collection of the selected immune cell subset, most commonly T cells. These cells then undergo *ex vivo* manipulation to improve antitumor activity, either through activation and expansion of existing autologous immune cells, such as seen with tumor-infiltrating lymphocytes, or genetic modification of cells to express receptors that recognize tumor-associated antigens and can induce cell death, as seen with CAR-T cells (7-9). Following manipulation, cells undergo *in vitro* expansion to achieve the desired cell dose and then are given via simple infusion. Prior to cell infusion, patients are treated with a conditioning regimen, commonly with cyclophosphamide and fludarabine, causing transient host lymphodepletion to maximize further cell expansion and activity (7-10,13). As with other investigational agents in development, ACTs must demonstrate an acceptable toxicity profile while maintaining clinical activity. When evaluating safety for a given cellular product, it is critical to understand the sequential steps by which this treatment modality is delivered as each aspect of the platform can contribute to both toxicity and efficacy. While the cellular product infusion is straightforward and generally tolerated well, the post-infusion inflammatory responses can result in

significant toxicities, most commonly in the form of CRS.

CRS

CRS is characterized by a proinflammatory milieu of immune cell activation, primarily T and myeloid cells, and secretion of immune proteins, such as soluble factors and interleukins (7,8,14-17). The American Society for Transplantation and Cellular Therapy (ASTCT) 2019 Consensus Guidelines defined CRS as a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells and published a standardized grading system for broad applicability across institutions and cellular immunotherapies (17). Risk factors for CRS include a high tumor burden, rapidly progressing disease, specific CAR construct proteins, lack of lymphodepletion, high doses of cellular product, and *in vivo* cell product expansion (14,15,18).

Clinically, CRS presents as fever and can be accompanied by non-specific constitutional symptoms (grade 1) progressing in severity to hypoxia and/or hypotension (grade 2), capillary leak, end organ dysfunction, and/or cardiopulmonary decompensation; CRS requiring one vasopressor and/or high flow nasal cannula is considered grade 3, while grade 4 CRS is when multiple vasopressors and/or positive pressure oxygen support are required (17). The onset and duration of CRS varies based on patient and disease characteristics in addition to the cellular product/platform and use of any prophylactic, pre-emptive, or therapeutic interventions for CRS and is not limited to a specific timeframe. Per ASTCT Consensus Guidelines, there should be a reasonable temporal relationship to the cellular therapy infusion. Generally, the median onset of any grade CRS is within 1–3 days of infusion, rarely presenting beyond 14 days, with a duration of about 7 days (14,15,17).

CRS left untreated can be rapidly fatal and requires prompt assessment and early intervention to decrease the overwhelming, systemic inflammatory response with immunosuppressive strategies including tocilizumab (IL-6 receptor binding antibody), corticosteroids, and/or inhibition of inflammatory cytokine signaling (7,10,15). Tocilizumab with supportive care is the frontline treatment for CAR-induced CRS and is FDA approved for this indication (15,16). In tocilizumab-refractory cases, corticosteroids are routinely used as second line therapy while adjunct immunosuppressive interventions such as anakinra (IL-1 receptor antibody), siltuximab (IL-6 binding antibody), emapalumab (IFN-γ binding antibody), anti-thymocyte globulin, alemtuzumab, and cyclophosphamide have been used off label in cases of severe or life-threatening CRS (15). Of note, it is imperative to rule out concomitant immune effector cell-associated neurotoxicity syndrome (ICANS) as tocilizumab does not cross the blood-brain barrier, therefore rendering it ineffective, and treatment with corticosteroids as front-line therapy is indicated (7,14,15). Ongoing clinical trials evaluating the role of CRS prophylaxis with tocilizumab or alternative immunosuppressive agents are underway and may change the current paradigm of CRS management.

In conclusion, ACTs hold immunotherapeutic potential when a tumor-specific antigen or target can be identified. If successful, the ACT platform can potentially be utilized to develop newer treatments for TETs. However, ACTs can invoke robust inflammatory responses, resulting in toxicities such as CRS and ICANS, which must be treated promptly and aggressively with anti-cytokine-directed treatments and corticosteroids. Translating ACTs to TETs requires careful consideration of treatment components, including the potential for development of excessive, unchecked inflammation, which is especially relevant due to defective immune tolerance associated with TETs.

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Extended Abstract

Uncommon manifestations of paraneoplastic autoimmunity associated with thymic epithelial tumors

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Thymic epithelial tumors (TETs) are rare cancers that arise from the epithelial compartment of the thymus and exhibit a spectrum of histological, genomic, and clinical features (1,2). Due to the role of the thymus in development of immunological tolerance, a complex process that is mediated by the interactions between thymic epithelial cells and developing thymocytes (3), TETs, especially thymomas, are often associated with paraneoplastic autoimmune diseases (ADs) (Figure S1) (4-7).

The development of autoimmunity affects the quality-of-life of patients and can substantially increase morbidity (8,9). The presence of paraneoplastic AD in patients with TETs has prognostic implications and influences treatment selection in the era of immunotherapy. ADs are associated with favorable prognostic factors such as younger age, favorable histology (World Health Organization types A, AB, B1 and B2 thymoma), earlier stage, and increased rate of complete resection, but are not an independent prognostic factor in patients with TETs (10). AD is also a contraindication for immunotherapy in most cases due to a high risk for development of immune-related adverse events (11). This issue is especially relevant for patients with TETs since defective immunological tolerance increases the risk for severe or life-threatening immune-mediated toxicity (12).

Given the clinical implications of paraneoplastic ADs in patients with TETs, early recognition of uncommon ADs is crucial in facilitating adequate management and improving quality-of-life. In this review, we describe four rare and often under-recognized TET-associated ADs that affect widely disparate organ systems, which if undiagnosed and inadequately managed, can lead to poor clinical outcomes.

Lymphocytic pneumonitis

Lymphocytic pneumonitis, or lymphoid interstitial pneumonia (LIP), is characterized by lymphocyte infiltration of the interstitial and alveolar spaces of the lungs (13). LIP can occur due to impaired central immune tolerance. Central immune tolerance mechanisms ensure that lymphocytes with self-antigen receptors are deleted at the early stages of development of lymphocyte precursors within the thymus (3). The autoimmune regulator (AIRE) gene regulates the processes of positive and negative selection of T cells in the thymus (14).

Patients with TETs and other AIRE deficient states can develop lymphocytic pneumonitis and present with chronic respiratory symptoms in addition to radiographic and pulmonary function abnormalities (15). These symptoms, if left untreated, can lead to hypoxemic respiratory failure and death. CT findings of lymphocytic pneumonitis include nodular opacities and bronchiectasis (15). Endobronchial biopsies show a submucosal lymphocytic infiltrate and serology can detect autoantibodies to lung-specific bactericidal and permeability-increase fold-containing B1 (BPIFB1) and/or the potassium channel regulator (KCNRG) in approximately 75% of affected patients (15). These clinical, radiological, histologic and serological features are shared with other AIRE deficiency conditions such as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) and RAG deficiency (15).

T and B cell-directed immunosuppressive strategies, such as T cell modulation with azathioprine in combination with B cell-targeting rituximab, can decrease lung inflammation and improve pulmonary function in patients with AIRE deficiency-associated lymphocytic pneumonitis (15).

Large granular lymphocytic (LGL) leukemia

LGL leukemia is a rare clonal lymphoproliferative disease that is T or NK cell-derived and can be associated with neutropenia and ADs (16). T-LGL is often chronic and indolent in nature. Bone marrow biopsies in patients with LGL leukemia show a hypercellular marrow with frequent small lymphoid cells, compact chromatin, and negligible to moderately abundant cytoplasm with azurophilic granules (17).

The pathogenesis of LGL leukemia involves chronic antigenic stimulation that causes polyclonal expansion of T-cells, which evolves into monoclonal expansion that can cause inhibition of erythroid or myeloid precursors and lead to pure red cell aplasia (PRCA) and neutropenia, respectively (18). LGL leukemia has been described in AIRE deficiency states, including both APECED and thymoma, with or without other blood dyscrasias and ADs (19-21). In a series of 327 patients with thymoma, LGL leukemia was diagnosed in 3 (0.9%) cases, with or without concurrent PRCA (20). Methotrexate is often used for treatment of LGL leukemia and can restore bone marrow function in patients with concurrent cytopenias (17).

Anti-PIT-1 antibody syndrome

Pituitary-specific transcription factor-1 (PIT-1) regulates the expression of growth hormone (GH), prolactin (PRL), and thyroid-stimulating hormone (TSH) (22). Anti-PIT-1 antibody syndrome occurs when there is an acquired and combined deficiency of GH, PRL and TSH in the presence of circulating anti-PIT-1 antibodies and PIT-1-reactive cytotoxic T cells (CTLs) (23,24). In patients with thymoma, anti-PIT-1 antibody syndrome was first described in three patients, who were first diagnosed with endocrinopathies and found to have circulating anti-PIT-1 antibodies (24). During follow-up, all patients developed a mediastinal mass, with histological confirmation of thymoma in two out of three cases. Thymectomy resulted in a decrease in anti-PIT-1 antibody titers and diminished reactivity of CTLs toward PIT-1 protein (24). However, at 2 years post-thymectomy, there was no improvement in anterior pituitary function, possibly indicating irreversible immune-mediated damage to pituitary cells (24).

Anticytokine autoantibody-mediated acquired immunodeficiency

Good syndrome is a well-recognized, albeit poorly understood cause of adult-onset immunodeficiency in patients with thymoma that is characterized by hypogammaglobulinemia and an increased risk for developing opportunistic infections (25). However, patients with thymoma can be at increased risk for recurrent infections even in the absence of hypogammaglobulinemia. A less well recognized cause of thymoma-associated acquired immunodeficiency is the presence of circulating anti-cytokine autoantibodies (ACAAs) (26,27). In patients with thymoma, ACAAs are most often directed against interferon-α (IFN-α) and IFNω, and a subset of patients develop chronic mucocutaneous candidiasis, chronic viral infections, recurrent bacterial sinopulmonary disease, including *Mycobacterium avium* infection, and severe infections, such as disseminated cryptococcosis and severe cytomegalovirus or varicella zoster virus (VZV) infections (26,27). Treatment directed at ACAAs is an area of active research and includes T and B cell-directed immunosuppressive therapies and interventions to deplete ACAAs, such as plasma exchange or the use of high-dose intravenous immunoglobulins (27).

In conclusion, a wide variety of paraneoplastic ADs can occur in patients with TETs due to defects in immunological tolerance. Although predominantly associated with thymoma, ADs can also occur in patients with thymic carcinoma. Early recognition and aggressive treatment of ADs is essential to decrease morbidity and improve quality-of-life. Further research is required to understand the pathophysiology of TET-associated ADs and to develop better immunosuppressive therapies to treat these conditions.

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Extended Abstract

Molecular pathology/genetics of thymic tumors: extended abstract

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Genetics of thymic epithelial tumors (TETs)

Comprehensive profiling of genetic or chromosomal abnormalities and gene expression has significantly advanced our molecular understanding of TETs. The most valuable discovery in TET genetics was made by Petrini *et al.* (1), who found that TETs can harbor the general transcription factor IIi (*GTF2I*) L424H variant: GTF2I(NM_032999.4):c.1271T>A p.(Leu424His). The significance of this finding is highlighted by two observations. First, this variant is common to TETs. The original study reported that the frequency in type A, AB, B1, B2, and B3 thymomas, and thymic carcinoma is 82%, 74%, 32%, 22%, 21%, and 8%, respectively (1). This high frequency contrasts with the fact that TETs have the fewest variants among cancers in humans (2-4). The study conducted as part of The Cancer Genome Atlas (TCGA) project confirmed the subtype dependency because the variant was observed in 100% and 72% of type A and type AB thymomas, respectively, but in 0% to 10% of type B thymomas and thymic carcinomas (2). Second, *GTF2I* L424H is virtually specific to TETs. Among 10,844 tumors from 31 TCGA studies for non-TETs, only 2 tumors harbored *GTF2I* L424H (3,4). These findings suggest that *GTF2I* L424H is biologically relevant in a thymus-specific manner.

Two recent *in vivo* mouse studies successfully addressed this hypothesis. Giorgetti *et al.* induced *Gtf2i* L384H with the *Foxn1* promoter into thymic epithelial cells (TECs) and demonstrated that this caused developmental abnormalities of the thymus, such that the border between the cortex and medulla became obscured (5). He *et al.*, the group that first reported *GTF2I* variant in TETs, established a *Foxn1*-dependent *GTF2I* L424H knock-in model and demonstrated that this caused tumor-like expansion of the thymus through proliferation of keratin-positive epithelial cells (6). These *in vivo* studies have demonstrated the biological significance of the *GTF2I* variant, and future studies may address the possibility that this variant could be a treatment target. Alternatively, these models could be improved by inducing the transgenes not congenitally but conditionally in adult mice.

Radovich *et al.* conducted the most comprehensive genomic profiling of TETs to date, as part of the TCGA study cited above (2). According to the study, *HRAS*, *NRAS*, and *TP53* can be recurrently mutated in TETs, although in minor proportions. One drawback of the TCGA study is that the number of cases may not be sufficient, especially for minor thymoma subtypes and thymic carcinoma. On the other hand, some recent studies enrolled many cases for genetic studies by utilizing gene panel testing, a method that is gaining popularity. Girard *et al.* genetically analyzed 274 advanced-stage TETs (7). As found with the TCGA dataset, they reported few genomic alterations in thymomas. That study included many thymic carcinomas (n=144) with detailed histological subtypes and noted that even thymic carcinoma generally harbors few variants. A new

* The affiliation 2: from February 1st, 2024.

finding was that *CDKN2A* and *CDKN2B* were relatively frequently mutated. A recent study from Japan enrolled the largest number of cases (n=794) (8) and reported results that overlapped substantially with that of Girard *et al.* (7). Collectively, we can summarize representative TET genetics as follows: (I) *GTF2I* L424H occurs often in type A and AB thymomas; (II) *HRAS* variants might be expected in type A thymoma, but the frequency is unconvincing; (III) *TP53*, *CDKN2A*, and *CDKN2B* variants are seen in about 30% of thymic carcinomas; (IV) druggable *KIT* variants can be detected in around 10% of thymic carcinomas (9); and (V) tumor mutation burden-high and microsatellite instability-high statuses are observed in less than 10% of thymic carcinomas, and these may be useful biomarkers for applying immune checkpoint inhibitors. Thus, it is true that TETs generally lack druggable variants; however, because TETs are rare and establishing treatment strategies based on big data is challenging, each case can be treated based on its unique features, which can be identified through genomic profiling. One example is a thymic carcinoma case that harbored a *PI3KCA* variant and substantially responded to everolimus (7). Another important finding about TET genetics is that thymomas rarely harbor gene fusions relevant to prognosis or diagnosis. *KMT2A-MAML2* fusion in rare type B2 and B3 thymomas and *YAP1-MAML2* fusion in metaplastic thymoma should be mentioned here (10,11).

Molecular pathology of TETs

The TCGA project (2) has played a fundamental role in this topic. By combining five omics platforms, it showed that TETs can be divided into four molecular subtypes: A (type A thymoma)-like, AB-like, B-like, and C (thymic carcinoma)-like, which are correlated with histotypes. Of note, the B-like and C-like clusters are entirely separate. A recent review indicated almost no histogenetic link between type B3 thymoma and thymic carcinoma (12). In contrast, recent studies, with the help of the TCGA dataset, have suggested that thymic carcinoma may have a phenotype related to medullary TECs. Our group proposed that thymic carcinoma often exhibits an expression profile similar to that of tuft cells, a unique subset of mTECs (13,14), and another group showed that thymic carcinoma can express *AIRE*, the representative mTEC gene (15). The functional and therapeutic relevance of this medullary characteristic has not been addressed, and future studies should answer these questions to advance our understanding of TET histogenesis.

Potential role of epigenetics linking genetics and molecular pathology in TETs: closing remarks

The relevance of epigenetic signatures in cancer has been appreciated (16). Indeed, the TCGA study of TETs demonstrated that methylation status alone is highly correlated with histological subtype (2,17). In addition, studies by Wang *et al.* (18) have indicated that epigenetic regulatory genes, such as *BAP1*, *SETD2*, and *ASXL1*, are recurrently mutated in thymic carcinomas, which was confirmed by a large Japanese study (8). Therefore, future in-depth epigenetic studies might contribute to a more comprehensive understanding of TETs. Accordingly, the significance of loss of 16q, the most common chromosomal abnormality in thymic carcinoma, should be investigated not only because the locus may contain functionally relevant genes for carcinogenesis, but because chromosomal abnormalities can cause global epigenetic alterations (19).

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Extended Abstract

Management of stage IVA (M1a) thymoma: observation versus chemotherapy versus surgery versus radiation therapy? —extended abstract

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The treatment of tumor, node, metastasis (TNM) stage IVA thymoma due to M1a disease (pleural/pericardial metastases) is challenging mainly due to several factors which preclude establishing high-level recommendations. Stage IVA thymoma is a rare stage of a rare tumor. It is estimated that only 7% of thymoma patients present with *de novo* stage IVA disease and 15% of patients develop pleural/pericardial metastases after previously treated early-stage disease (1). Additionally, it has been suggested that *de novo* disease is associated with a worse prognosis as compared to patients who relapse with pleural/pericardial metastases after initial therapy consequentially may require a more aggressive treatment approach (2). The current 8th edition staging system does not account for the number of pleural/pericardial metastases, the size of metastases, or invasion into any local organ therefore lacks granularity. Most deaths following treatment of other solid neoplasms are due to recurrent disease which is not necessarily the case with thymoma. Due to mainly indolent biology, thymoma patients with recurrent pleural/pericardial disease typically experience extended survival. In addition, late deaths are not infrequently due to other conditions such as secondary malignancies. Finally, thymoma patients present with wide range of ages and comorbidities which can contribute to non-thymoma mortality. When critically analyzing outcomes of any treatment approach to stage IVA thymoma, disease-free and disease-specific survival analyses thus become important, however these variables are not uniformly available. Collectively, these factors not only make randomized trials very difficult to conduct but also may confound individual treatment approaches.

Several treatment options for stage IVA thymoma, either alone or in combination, are currently worthy of consideration. First, given the typically indolent biology and absence of a randomized study demonstrating that any treatment improves overall survival as compared to "doing nothing", observation, at least initially, becomes not unreasonable particularly for patients with high comorbidities. Initial observation could also be considered for patients with relapsed pleural/pericardial disease after remote surgery for early-stage thymoma.

There are a growing number of systemic options available including combination and single-agent chemotherapy. Immunotherapy and targeted agents are emerging and may hold promise. Platinum-based chemotherapy regimens typically result in a moderate response although a wide range of responses from none to complete are observed. Induction chemotherapy followed by surgery appears to be most productive of R0 resections therefore constitutes National Comprehensive Cancer Network/European Society for Medical Oncology (NCCN/ESMO) guidelines for potentially operable patients (3). A review of published series treating stage IVA thymoma patients with induction therapy followed by surgery, found an 81% average response rate to therapy and an impressive 59% average 10-year survival (4). Studies included in this review were however small and mainly retrospective involving select patients. Additionally, as disease-free survival was not provided for

most of these reports, it is reasonable to speculate that many patients in these series relapsed and were "alive with disease" at last follow-up. There is currently no randomized study demonstrating that induction chemotherapy provides an overall survival benefit, therefore upfront surgery is also a reasonable option in select cases and constitutes an alternative treatment per NCCN/ESMO guidelines (2).

From a surgical standpoint, there are three general approaches, all with distinct advantages and disadvantages. A discrete pleural metastatectomy is probably reasonable for a limited number of pleural/pericardial metastases and associated with low morbidity. Total pleurectomy/decortication (with or without intrathoracic heated chemotherapy) has been proposed as a more aggressive approach while sparing lung parenchyma for stage IVA disease although an improvement in disease-free survival as compared to discrete metastatectomy has not been demonstrated to date. Extrapleural pneumonectomy has traditionally been reserved as a "last ditch" procedure for patients with bulky pleural disease. Arguably however of all the surgical approaches, extrapleural pneumonectomy has the best potential to remove all microscopic pleural disease with the obvious downside of significantly higher morbidity and mortality. A literature review identified six published series reporting on outcomes of patients undergoing either pleural metastatectomy or extrapleural pneumonectomy for stage IVA disease (5-10). Not surprisingly, most patients in these series underwent pleural metastatectomy but on average, 70% to 80% of these patients had relapsed at last follow-up. There was a distinct trend of patients undergoing extrapleural pneumonectomy in these series having improved disease-free survival which is noteworthy as extrapleural pneumonectomy is usually reserved for patients with a larger burden of pleural disease.

Finally, radiation therapy is typically used in the adjuvant setting after R1 and R2 resections. To date, no benefit of adjuvant radiation therapy has been demonstrated after R0 resections. For therapeutic purposes standard external beam radiation therapy to large areas of pleural disease is believed to present prohibitive lung toxicity, therefore intensity modulated radiation therapy is currently being evaluated for non-surgical patients in conjunction with chemotherapy. For treatment of isolated areas of pleural disease, focused radiation therapy utilizing stereotactic body radiation therapy or proton beam radiation appear to be reasonable considerations.

In summary, stage IV thymoma is heterogeneous from disease severity and patient demographic standpoints. For most patients, an individualized multidisciplinary approach is therefore needed keeping all options in mind. Neoadjuvant chemotherapy followed by surgery or surgery alone as per NCCN/ESMO guidelines, is reasonable for select patients but doesn't rise to a high evidence level. There are a wide range of surgical approaches which can be utilized however the optimal approach is unknow and needs further study. Unfortunately, for most stage IVA thymoma patients, this will ultimately become a chronic disease to greater or lesser extents regardless of treatment approach and future intervention may be required. Accordingly at Indiana University, we have trended to use a "one bullet at a time" approach with the aim of minimizing morbidity, particularly for patients with preexisting comorbidities or minimal symptomology. This approach involves beginning with first line platinum-based chemotherapy. If a good response is achieved, then the patient is observed. When there is disease progression, this process is repeated with second and even third line systemic therapy keeping surgery as a salvage option. This approach also needs further study. Given the poor ability to conduct randomized studies, mining large databases and performing single-arm clinical trials will hopefully refine staging and improve treatment recommendations for stage IVA thymoma patients.

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Extended Abstract

Extended abstract: radiomics and artificial intelligence in thymic tumors

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Radiomics has arisen as a burgeoning field of translational research predicated on the acquisition of high-dimensional data from radiological images, with the objective of discerning distinctive imaging patterns that may not be readily perceptible to the human observer.

The utility of radiomics extends across several critical applications. It can serve as a diagnostic tool capable of ascertaining the overall normalcy or abnormality of an imaging study under scrutiny, rendering it an invaluable asset for screening purposes. Furthermore, radiomics can pinpoint the precise location of pathological conditions within a study and exclude the presence of specific diseases. Additionally, among other applications, it can contribute to the enhancement of image quality, such as through contrast optimization.

Radiomics features are derived via a meticulous and structured process. The initial step involves segmenting the area of interest, typically a lesion, by delineating its boundaries on each image slice. This segmentation process can be accomplished either manually, although this method is time-intensive, or automatically or semi-automatically through algorithmic approaches, often necessitating subsequent manual refinement for precision.

While it is feasible to extract radiomics features from individual slices, it is commonplace to derive these features across all image slices, thus yielding a comprehensive dataset representing the entire volume of interest. Various methodologies exist for feature extraction, which can be categorized into statistical, model-based, and transform-based methods, each providing distinct types of variables. Python is the predominant software platform employed for radiomics feature extraction and subsequent analysis.

First-order statistical radiomics features encapsulate the distribution of grayscale values in a histogram, encompassing metrics like entropy, skewness, and kurtosis. Entropy quantifies the stochasticity or randomness within the pixel intensity distribution, while skewness characterizes its asymmetry, and kurtosis gauges the shape of the histogram.

Second-order statistical radiomics features establish mathematical relationships between neighboring pixels and are expressed in terms of neighborhood matrices, including entities like gray level cooccurrence matrix (GLCM), gray level run length matrix (GLRLM), and gray level size zone matrix (GLSZM).

Third-order radiomics features, such as harmonization and wavelet transformations, contribute to capturing texture and spatial information, while fourth-order features, associated with convolutional neural networks (CNNs), enable the extraction of high-level representations for more advanced and nuanced analysis of medical images.

Upon the extraction of radiomics features, a plethora of variables is generated. Feature selection is a pivotal step in the process, involving the curation of the most pertinent attributes to enhance analytical precision and the development of efficient predictive models. This task may encompass traditional statistical methodologies, chiefly logistic regression models, as well as advanced artificial intelligence (AI) analysis.

Machine learning, a subset of AI, demonstrates superior proficiency in handling extensive datasets and exhibits improved diagnostic performance compared to traditional statistical approaches. For AI analysis, the dataset is divided into training and validation subsets, which encompass

60–70% of the data, and a distinct test subset with the remaining 30–40%. Machine learning algorithms are employed during the training phase to construct models tailored to the study's objectives, and these models are subsequently evaluated for performance. Adjustments to hyperparameters are made if the obtained area under the curve (AUC) falls short of expectations. The final assessment of model performance occurs when tested against an independent, previously unseen dataset, which provides a reliable estimate of the diagnostic accuracy of the model.

In the context of thymic tumors, radiomics with AI analysis hold substantial promise across various domains. Our recent published study, conducted by the chest radiology team at Memorial Sloan Kettering Cancer Center, aimed to develop radiomics and AI models for distinguishing between benign and malignant prevascular mediastinal lesions, as well as differentiating between thymomas and thymic carcinomas in preoperative computed tomography (CT) studies (1). When relying solely on conventional CT features, the diagnostic performance of these models proved suboptimal. However, the inclusion of radiomics features in the models significantly enhanced their AUC, with the highest performance achieved when both conventional and radiomics features were combined. Specifically, this integration resulted in an AUC value of 0.72 for distinguishing between benign and malignant anterior mediastinal lesions, and an AUC of 0.81 for differentiation between thymomas and thymic carcinomas.

In a previously published study, we examined the utility of radiomics in predicting the resectability and stage of thymic tumors (2). Our findings indicated a robust diagnostic performance for resectability prediction, with an AUC of 0.80, and a moderate discriminative ability for stage prediction, with an AUC of 0.71. These results align with a recent meta-analysis that included our study (3). In this meta-analysis, the evaluation of combined diagnostic performance for stage prediction of thymic tumors yielded a pooled AUC of 0.83 (for distinguishing between early and advanced disease) and a combined AUC of 0.86 for predicting histologic subtypes (for discriminating between low and high-risk tumors).

In conclusion, radiomics, coupled with AI analysis, represents a reliable and potent tool for predicting risk stratification, stage, and resectability of thymic tumors, offering the potential to enhance the preoperative evaluation of these conditions and advancing the goal of personalized medicine.

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Extended Abstract

Extended abstract: pathologic considerations concerning mediastinal germ cell tumors

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Mediastinal germ cell tumors (GCTs) have diverse features, and time does not allow for anything other than coverage of some key considerations in this brief talk. What I would like to emphasize is the importance of understanding that there are two pathogenetically different types of mediastinal GCT, and that the clinical and pathologic features of these two types are dissimilar. These differences become most evident in teratomas; hence, the talk will concentrate on those neoplasms, with some consideration of a few key properties of mediastinal yolk sac tumor (YST).

Primary anterior mediastinal GCTs are felt to originate within the thymus, with possible sources being a mismigrated primordial germ cell or a thymic stem cell. Isolated anterior mediastinal involvement by a GCT indicates a primary neoplasm (1); when it is accompanied by middle or posterior mediastinal or retroperitoneal disease, the anterior mediastinal tumor is likely a metastasis. In adults, GCTs represent about 15% of anterior mediastinal tumors, trailing in frequency thymic neoplasms and cysts (46%), lymphomas (23%), and endocrine tumors (16%) (2). In children, they are a greater proportion of anterior mediastinal tumors (24%) (2), although the overall number of cases is much less than in adults.

Oosterhuis and Looijenga (3,4) consider that there are two basic forms of anterior mediastinal GCT; type I, originating from a benign precursor cell and initially forming teratoma with the possible subsequent development of YST via dedifferentiation of teratoma; and type II, developing from a malignantly transformed precursor cell that subsequently gives rise to the familiar spectrum of GCT types (seminoma/germinoma, embryonal carcinoma, YST, choriocarcinoma, and teratoma). Malignant transformation, therefore, occurs after teratoma is formed in type I GCTs, and before any invasive GCT, including teratoma, is formed in the type II pathway.

Type I GCTs consist only of teratoma and YST, are the type children exclusively develop, also occur in adults, and lack the chromosome 12p overrepresentation of the type II GCTs. In children 58% are pure teratomas, and the remainder have a YST component, with or without teratoma (2). The hypothesis is that YST develops in type I teratomas from embryonic-type neuroectoderm, which is supported by the juxtaposition of these elements in type I mixed GCTs. Pure teratomas of the anterior mediastinum in women and a subset of those in men show similar features to those in children, and, like the pediatric teratomas, are benign (5). On histological examination, the teratomas lack cytological atypia and are often organoid, the latter often reflected by bronchus-like structures, pancreatic tissue containing lobules of acinar cells with associated ducts and embedded islets, or skin formation.

The type II GCTs occur almost exclusively in young, post-pubertal males, show a very high frequency in Klinefelter syndrome (estimated at 19-fold higher, with 22% of cases having Klinefelter syndrome), include the entire spectrum of GCT types, have consistent chromosome 12p overrepresentation, may progress to a somatic-type malignancy (i.e., sarcoma or carcinoma), and have a unique association with vascular neoplasia and hematopoietic malignancies of GCT origin (5-13). About 50% are pure seminomas followed by mixed GCTs and YST (14). The type II teratomas, unlike the type I, show cytological atypia, with mitotic figures, and are less frequently organoid (5). They may induce cystic change of thymic epithelium,

causing a confusing radiographic picture because teratomas also form cysts.

A virtually uniform property of mediastinal YSTs is epithelial-mesenchymal transition. This may be manifest as blastema-like aggregates of tumor cells adjacent to epithelial YST, followed by their transition to dispersed spindle cells in a myxoid stroma. The resulting loose meshwork represents the neoplastic homology of the extraembryonic mesoderm of the early blastocyst. Overgrowth of such foci to greater than 5 mm in diameter results in sarcomatoid YST (SYST) (15). Histologically, SYST shows spindled to epithelioid cells of varying cell density in a myxoid to fibrous stroma with curvilinear blood vessels. The spindled cells in such foci may progress to vasoformative cells, a not totally unexpected occurrence given that the homologous extra-embryonic mesoderm is both a vasculogenic and hematopoietic site. Thus, neoplastic blood vessels, with both atypical endothelial and smooth muscle components, are found admixed with non-differentiated spindle cells, a lesion designated as either vasculogenic mesenchymal stroma or vasculogenic mesenchymal tumor (VMT), depending on whether there is overgrowth in excess of a 5-mm diameter field (9). VMT in a post-chemotherapy resection has been shown to increase the risk for subsequent sarcoma, either angiosarcoma or other sarcomas (9). Furthermore, the presence of vasculogenic lesions in mediastinal GCTs is associated with an increased risk of death (11% *vs.* 1%; P=0.001) due to leukemia or myelodysplasia of GCT origin (9). This is because neoplastic hematopoiesis of germ cell origin occurs within vasculogenic lesions, either within the blood vessels or the intervening stroma (9,13). Type II GCTs of the mediastinum are prone to progress to sarcomas or carcinomas ("somatic-type" malignancies). While most observers attribute this phenomenon to "dedifferentiation" of teratoma, it seems probable that many cases of sarcoma develop from SYST. Furthermore, many apparent "adenocarcinomas" in this context have morphological and immunohistochemical evidence of glandular YST.

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Extended Abstract

Extended abstract: cutting edge developments and new therapeutics in myasthenia gravis

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Over the past fifteen years, there have been remarkable strides in our comprehension of myasthenia gravis and the development of therapeutic approaches. This progress has evolved from a single Phase 3 trial to an impressive array of over 25 trials encompassing various early phases and the approval of new medications by the FDA. This substantial therapeutic advancement has been propelled by a deeper understanding of the immune system, coupled with technological advancements in immune system analysis (1).

Within this context, myasthenia gravis is stratified based on several key metrics that significantly influence the choice of treatment. From an autoantibody perspective, individuals with acetylcholine receptor antibodies can be classified into early-onset and late-onset categories, with symptom onset occurring either before age 45 to 50 years or later in life. Early-onset patients, who are predominantly women and often exhibit thymic hyperplasia, tend to benefit from thymectomy (2-4). On the other hand, late-onset patients, who are more frequently men and typically associated with thymic atrophy, do not typically show improvement following thymus removal. Moreover, late-onset and early-onset patients exhibit genetic distinctions (5,6).

Approximately 10% of myasthenia gravis patients are diagnosed with a thymoma, which is more prevalent in cases with AB and B2 thymomas. Interestingly, transcription profiling has revealed variations in the mechanisms underlying myasthenia gravis induction for each thymoma subtype (7). Thymoma patients almost invariably present with acetylcholine receptor antibodies, although there have been rare reports of muscle-specific kinase antibodies. The pathogenesis of myasthenia gravis induced by acetylcholine receptor antibodies involves complement activation, receptor cross-linking, rapid muscle surface removal, and receptor function blockade. The recognition of complement-mediated injury has spurred the development of inhibitors for myasthenia gravis treatment over the course of two decades (8). Eculizumab, ravulizumab, and zilucoplan are approved treatments (9). Clinical trials of these agents have yielded positive results, albeit with some variability, underscoring the significance of other mechanisms contributing to neuromuscular junction injury.

Immunoglobulins undergo a robust recycling process in which antibodies attach to Fc receptors on endothelial cells and are subsequently internalized, with a portion undergoing proteolysis and the majority returning to circulation (10). This physiological process has been targeted by inhibitors that enhance antibody removal, resulting in a concurrent reduction in circulating antibodies. Neonatal Fc receptor (FcRn) inhibitors, such as rozanolixizumab and efgartigimod, have received approval for myasthenia gravis. Rozanolixizumab is approved for both muscle-specific kinase and acetylcholine receptor antibody myasthenia gravis, while efgartigimod is specifically indicated for acetylcholine receptor antibody myasthenia. These FcRn inhibitors, although currently approved only for myasthenia gravis, hold promise for the treatment of other antibody-mediated diseases. It is worth noting that these novel treatments come with a significant cost, ranging from $225,000 to $700,000 per year.

Despite these encouraging advancements, it is important to acknowledge that the new treatments do not directly impact the production of underlying antibodies. Rituximab, an antibody targeting CD20, has shown efficacy in muscle-specific kinase myasthenia, but its effectiveness is somewhat limited in cases of acetylcholine receptor antibody myasthenia gravis (11). This distinction suggests

that CD20-expressing short-lived plasma cells drive the pathology in muscle-specific kinase myasthenia, whereas long-lived plasma cells lacking CD20 contribute to the pathology in acetylcholine receptor myasthenia gravis (12).

Within the context of new treatment options and appreciation of biomarkers that guide therapy, conventional treatment, in particular prednisone, are highly effective and offer patients the potential for long-term remission (13-15). As a neurologist and scientist, I am excited to be living during the most exciting time in myasthenia gravis therapeutic development and I look forward to a bright future in the field.

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Extended Abstract

Extended abstract: cancer and autoimmunity: survivin as a driver of sustaining autoreactive cells and its role in neoplasia

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Myasthenia gravis (MG), an autoimmune disease, involves autoreactive T cells that support the maturation of B cells, leading to the production of autoantibodies. These autoantibodies predominantly target nicotinic acetylcholine receptors (AChRs) on the post synaptic membrane of the neuromuscular junction (NMJ) (1). The self-recognition of these lymphocytes demonstrates the dysregulation of the adaptive immune response and the breakdown in tolerance. While the mechanism causing the breakdown in tolerance is unknown, evidence suggests that the anti-apoptotic pathway may have a role (2).

The recognition of specific antigens by B and T lymphocytes begins at the site of central tolerance. Antigen-specific receptors on these cells enable immune activation, with T cells generating T cell receptors (TCRs) and B cells producing surface-bound immunoglobulins to recognize the antigen (3). As the repertoire pool expands, the immune system protects self-antigens by directing self-reactive lymphocytes to undergo apoptosis. The failure in this highly regulated process of self-tolerance leads to autoimmunity (2). The active immune process initiates with the presentation of the antigen, proceeds by the proliferation of lymphocytes, and terminates as the lymphocytes undergo apoptotic removal. In various autoimmune disorders, including MG, the inability to eliminate or control autoreactive lymphocytes and autoantibodies results in the main pathology (2).

The thymus serves as the selection and maturation site for T cells. The migration of precursor double-negative ($CD4^-$ $CD8^-$) T cells from the bone marrow to the thymus initiates a shift to double-positive (DP) ($CD4^+CD8^+$) expression. Selection is critical for tolerance, allowing DP cells to shift further to single-positive $CD4^+$ or $CD8^+$ T cells (3). This process generates a pool of T follicular helper cells and T cytotoxic T cells for the adaptive immune response.

In MG, negative selection is impaired, leading to the generation of autoreactive T cells (1). Additionally, the thymus transforms into a site of hyperplasia, forming germinal centers that recruit B cells. B cells undergo multiple rounds of interaction with T follicular helper cells to fine-tune the antibody repertoire and class switch (4). As the B cell population expands, the selection of autoreactive plasma cells and memory B cells generates autoantibodies to AChR and a persistent population of sensitized B cells.

The ability of autoreactive cells to escape apoptosis may involve the action of survivin, a member of the inhibitor of apoptosis proteins (IAPs). Survivin (BIRC5) contains one baculovirus IAP repeat (BIR) domain which is characteristic of the family proteins, making it one of the smallest members. The BIR domain regulates the inhibition of apoptosis as well as directing proliferation. The protein is highly regulated by modifications, containing phosphorylation sites on serine and threonine residues, as well as, several lysine residues that can be modified by ubiquination and acetylation (5).

During proliferation, survivin identifies phosphorylated histone H3, recruits proteins to the chromosomal passenger complex, and binds DNA to mitotic spindles for proper chromosome orientation. The function of survivin in proliferation is demonstrated by an increased expression during embryonic and fetal development but is absent in differentiated tissue. Survivin's proliferative role is also evident in increased expression in most cancers, leading to drug resistance (6).

With localization to the mitochondria, survivin functions in the inhibition of apoptosis through the association with other IAPs. Although survivin contains only one BIR

domain, the protein will form complexes with other IAPs to stabilize their expression. The complex will inhibit caspase activity, specifically caspase 3 and 7 (7).

The immune system incorporates survivin in various immune cells. T cells in the thymus require survivin for the transition from double-negative to DP cells and the formation of memory T cells. B cells also use survivin for proliferative functions, immunoglobulin isotype switching, somatic hypermutation, and differentiation into plasma cells (8,9). Due to its diverse roles in immune cells, survivin's involvement in autoimmunity has been investigated in diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS) (10,11).

To investigate the role of survivin expression in MG, studies on circulating lymphocytes were assessed along with non-autoimmune controls. The results revealed increased survivin expression in $CD20^+$ B cells from MG patients compared to non-autoimmune controls (12,13). This expression was also observed on the outer membrane of B cells exposed to the extracellular space (13). Taking information from the cancer field which found secreted survivin in vescicles that promoted the tumor microenvironment (14,15) we propose that the expression of survivin on the outer membrane comes from this pool due to the known secretion of vesicles from lymphocytes (16). Survivin expression in autoreactive cells may contribute to the evasion of tolerance mechanisms. The capacity of survivin to transfer to other cells in an autoimmune context could enable additional autoreactive cells to bypass checkpoints and evade elimination. The expression of survivin on the outer surface of $CD20^+$ B cells suggests a potential role for survivin in cell-cell signaling.

To assess survivin's potential role in driving autoimmunity in the thymus, thymus sections from early-onset MG patients were analyzed for survivin through immunostaining. Survivin expression was detected in germinal centers in hyperplastic thymus samples (12). As seen as survivin's role in B cell development, the high level of expression may be suggestive of an active germinal center that is expanding the autoreactive B cell population, generating immunoglobulin G (IgG) class switching and producing plasma cells.

The expression of survivin in lymphocytes from MG patients suggests a role in the continued expansion of autoreactive cells and the potential to target the protein for elimination. Survivin has been implicated in other autoimmune conditions such as RA and MS, therefore survivin may play a key role in the dysregulation of the immune system. Ongoing investigations are required to determine the divergent roles it may play and the potential as a therapeutic target.

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Extended Abstract

Perspective on thymectomy in adults

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Kooshesh and colleagues, in their recent study (1), as well as a supporting editorial (2), have put forth the notion that surgical removal of the thymus from adults may increase overall mortality, the risk of cancer, and autoimmune diseases. They argue against total thymectomy whenever possible. My presentation during International Thymic Malignancy Interest Group (ITMIG) 2023 provided a counterargument to this sweeping conclusion. I believe that such a bold statement does a disservice to patients, surgeons, and physicians who may be considering procedures that involve thymus removal.

During fetal development and the first year of life, the thymus plays a pivotal role as the site where T cells mature and learn to distinguish between self-antigens and foreign invaders, such as bacteria and cancer cells. The thymus is highly metabolically active during this period, but over its natural lifespan, it begins to involute, having fulfilled its primary function by the first year of life (3). As Kooshesh *et al.* point out, for decades it was believed that thymic atrophy had no significant consequences. However, it has become increasingly clear that thymic atrophy may be linked to the broader phenomenon of immune senescence, which likely contributes to the age-related increase in susceptibility to infection, cancer, and possibly autoimmunity. Nevertheless, the crucial question remains: how significant is the impact of surgical thymus removal, especially in the context of therapeutic thymectomy?

The study in question is a retrospective, single-center evaluation, which inherently comes with certain limitations. Among the 1,146 subjects with matched controls who had undergone non-laparoscopic cardiac surgery, 871 had a cancerous or suspected thymic mass as the indication for surgery. This immediately raises questions about potential underlying genetic predispositions to future cancers, which cannot be adjusted for in the control population. Approximately 100 patients underwent therapeutic thymectomy for myasthenia gravis, a population known to have higher rates of autoimmune diseases and be treated with immunosuppressives, which increase the risk of infection and neoplasia (4). Consequently, they might exhibit biased results, not necessarily because of thymus removal. The indications for thymectomy included 183 cases of parathyroidectomy and 63 indeterminate cases. Notably, there is no assessment of the extent of thymectomy. Even when a surgeon aims for a "complete" thymectomy, this is seldom achieved due to the diffuse nature of the thymus, which extends across the mediastinum and up into the neck (5). Another methodological limitation is the reliance on the Mass General Brigham Research Registry (rc.partners.org), an excellent resource, but one that relies on electronic health record entries, thus inherently having limitations in data quality (6).

One significant concern is that the conclusions drawn from this study may discourage physicians and myasthenia gravis patients from considering thymectomy. Thymectomy for acetylcholine receptor antibody-positive myasthenia gravis has been shown to reduce disease severity (7). Previous studies of myasthenia gravis patients who underwent thymectomy did not reveal an increased risk of cancer (8-10). It is undeniable that patients with a thymoma, regardless of whether they have myasthenia gravis, should have the tumor removed. Furthermore, the removal of the surrounding thymic tissue may reduce the risk of tumor recurrence. Additionally, since the immune reaction to the tumor is triggered by the immune response and does not originate in the tumor itself, thymectomy has the potential to limit the development or reduce the severity of autoimmune diseases.

In conclusion, Kooshesh *et al.* conducted an intriguing study, but its findings do not warrant a recommendation to change current surgical practice. It is prudent to acknowledge that if one does not need to remove the thymus or any organ, then it should not be removed without due consideration of the potential risks and benefits.

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Extended Abstract

Extended abstract: clinical diagnosis and workup of prevascular mediastinal tumors

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The most frequent prevascular mediastinal masses are thymic tumors, lymphomas, teratomas, and intrathoracic thyroid. Most of the prevascular mediastinal masses are incidental findings. Due to the location, it is difficult to obtain a tissue diagnosis and clinical diagnosis is crucial before deciding the best treatment options.

Thymic tumors are rare, the incidence is 0.13–0.32/100,000/year and they represent 0.2–1.5% of all malignancies. The incidence reaches the peak at the age of 30s and 70s with similar distribution between male and female (1).

It is always important to evaluate the clinical presentation in patients with mediastinal mass. Thirty percent to 50% of patients are asymptomatic. Cough, chest pain, fever/chills and dyspnea are the most frequent symptoms at diagnosis. Lymphoma clinical signs such as fever or night sweats (B symptoms) have to be investigated and excluded. In case of large mediastinal mass direct tumor invasion or compression of airways, vascular structures or nerves can cause respiratory compromise, diaphragmatic elevation, vocal cords paralysis with hoarseness, Horner syndrome, superior vena cava syndrome and dysphagia (2).

In a series of 47 patients with thymic epithelial tumors, 42.5% of patients with thymoma were asymptomatic (n=17), 19.1% presented with chest pain (n=7), and 40% presented with autoimmune manifestations mainly myasthenia gravis (MG) (n=11). In thymic carcinoma patients, only 14% were asymptomatic and there were no case of MG (3).

The release of excess hormones, antibodies, or cytokines releases are responsible for systemic symptoms. Associations with MG, Graves' disease, and hematological disorders have been reported in the literature. Thirty percent to 50% of patients with thymoma present MG, but only 10–15% MG patients are diagnosed with thymoma. Pure red cell aplasia is rare, only 2% to 5%, and it is more common in women. Also, hypogammaglobulinemia has been reported in 2% to 5% of patients with thymic tumors (1,2).

The typical presentation of MG includes exertional voluntary muscle weakness and fatigability. In 15% of patients, ocular symptoms could represent the only symptoms (4). Typically, patients complain of diplopia and ptosis. In more severe forms of MG, patients may present with slurred speech, arms and legs weakness, difficulty chewing or swallowing with progression to generalize weakness and to respiratory insufficiency. In these patients, clinical examination and neurological evaluation are important to make a correct diagnosis.

Antibodies against the acetylcholine receptor, abnormal results of electrolytes, renal, and liver function tests can be associated with thymoma. As part of the differential diagnosis serum parathyroid hormone (PTH), α-fetoprotein, and β-human chorionic gonadotropin (β-hCG) levels have to be checked. If the germ cell tumor markers are elevated, malignant, non-seminomatous germ cell tumor should be considered as main diagnosis. Chemotherapy should be considered in malignant germ cell tumors and radical surgery for teratoma. The markers provide crucial information for diagnosis, prognosis, and response to treatment. A tissue biopsy is recommended considering the different treatment options available, usually in non-operable patients. The exact diagnosis has crucial clinical implications for selecting the most appropriate chemotherapy regimens.

As part of the preoperative work up lung function test

and echocardiogram are mandatory tests to optimize the perioperative management. The clinical staging is usually completed with a chest computed tomography (CT) scan, and a positron emission tomography (PET) scan. A transesophageal echocardiogram and cardiac magnetic resonance imaging (MRI) are considered when there is concern regarding possible cardiac involvement in order to establish resectability. The MRI can also be used to better characterized the content of the mediastinal lesion and exclude a possible benign cyst.

In conclusion, clinical presentation with radiological imaging is crucial when no tissue biopsy is feasible to make a diagnosis. The radiological findings play a pivotal role but clinical symptoms and signs are equally important. The blood tests have to be considered to make differential diagnosis with teratoma, thyroid mass, and lymphoma when biopsy is not available.

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Extended Abstract

Extended abstract: imaging workup of prevascular mediastinal tumors

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Anterior (prevascular) mediastinal tumors can present with diverse characteristics on imaging that allow them to be differentiated and classified, subsequently benefitting therapy planning (1-3). When anterior mediastinal tumors present as diffuse enlargements, they can be benign, as seen in cases of thymic hyperplasia, or malignant, as often seen in cases of lymphoma. When anterior mediastinal tumors present as discrete masses, they can also be benign, as seen in cases of thymic cyst and thymolipoma, or malignant, as seen in cases of thymoma, thymic carcinoma, and thymic carcinoid. In this context, various aspects of imaging have been explored for the differentiation and classification of anterior mediastinal tumors. Moreover, the need for improved differentiation and classification sets the stage for novel imaging assessment methods like radiomics.

Currently, chest X-rays (CXR) and contrast-enhanced computed tomography (CT) are considered essential for identifying and evaluating anterior mediastinal tumors. CXR can identify 45–80% of mediastinal tumors, which usually present as a well-defined lobulated soft tissue density in the prevascular space, towards one side of the mediastinum. For the evaluation and characterization of anterior mediastinal tumors, contrast-enhanced CT is considered the best initial imaging modality. Magnetic resonance (MR) may be preferred if iodinated contrast is contraindicated, for differentiating cystic from solid masses, and for detecting intralesional fat. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) is not typically used for routine evaluation due to its lack of specificity but can be valuable for staging and assessing disease extent.

We review the presentation of several different anterior mediastinal tumors on imaging below:

(I) Thymic hyperplasia, which can develop in response to stress or autoimmune conditions, can present as diffuse thymic enlargement with an arrowhead like morphology on CT and sometimes with intralesional fat. The differentiation of thymic hyperplasia, which is benign, from thymic tumors can be achieved using chemical shift sequences on magnetic resonance imaging (MRI), as the former is characterized by the loss of signal intensity on out-of-phase imaging stemming from the presence of microscopic fat (4).

(II) Thymic cysts are characterized by low density lesions on CT. However, a significant number of cysts do not present as hypodense, and MR provides a certain diagnosis by exhibiting T2-hyperintensity, sometimes with a fluid-fluid level suggesting a hemorrhagic or mucinous component.

(III) Thymomas appear as well-defined, rounded, or lobular masses with heterogeneous or cystic areas due to hemorrhage and necrosis, sometimes outlined by fat and containing punctate or coarse curvilinear calcifications.

(IV) In contrast to thymomas, thymic carcinomas usually lack a well-defined capsule; can present as necrotic, cystic, or calcified lesions; and exhibit irregular contours. Distinguishing between these entities is not possible on imaging alone.

(V) Thymic neuroendocrine tumors may be large, invasive masses within the anterior mediastinum and are difficult to differentiate from other invasive thymic epithelial tumors. The use of gallium-68

DOTATATE (^{68}Ga-DOTATATE) PET/CT is valuable for imaging neuroendocrine tumors that express somatostatin receptors, aiding in tumor localization, detection of metastatic disease, monitoring of treatment effects, and the selection of patients for specific therapies.

(IV) Thymic lymphomas may involve the thymus as part of disseminated disease or manifest as an isolated mass, with the majority representing Hodgkin lymphoma.

For presurgical planning, differentiating benign thymic tumors from early-stage thymic malignancies on imaging is particularly crucial to avoid unnecessary invasive diagnostic procedures (5). CT is the imaging modality of choice for the initial evaluation of anterior mediastinal tumors. Features such as intralesional fat, midline location, and a triangular thymic shape can suggest a benign etiology. In contrast, the infiltration of mediastinal fat, especially in older patients or those with large masses, increases the likelihood of malignancy.

Additionally, predicting the invasiveness and the completeness of resection is crucial. Preoperative CT characteristics, such as a lobulated tumor contour, extensive vessel abutment, thoracic lymphadenopathy, adjacent lung changes, and pleural nodularity, can help determine the likelihood of successful surgical resection and identify patients who may benefit from neoadjuvant chemotherapy (6).

Radiomics, an evolving field, involves the computerized extraction of quantitative features from radiologic images, subsequently allowing for the analysis of various extracted quantitative features, including tumor size, tumor location, tumor shape, tumor vascularity, necrosis, and more. Several radiomic features have been associated with malignancy and have shown promise for the prediction of prognosis and response to therapy.

We recently published an article on the value of CT radiomic features to predict the pathologic classification of anterior mediastinal lesions (7). For the differentiation of benign from malignant lesions, the predictive model based on radiomic features slightly outperformed the predictive model based on conventional imaging features [area under the curve (AUC) of 0.678 and 0.605, respectively]; the predictive model that combined the best-performing conventional imaging and radiomic features demonstrated the best accuracy, with a moderate AUC of 0.715. For the differentiation between thymoma and thymic carcinoma, the predictive model based on conventional imaging features had a limited AUC of 0.558. On the other hand, the predictive model based on radiomic features demonstrated a moderate AUC of 0.774, and the predictive model based on the combination of both radiomics and conventional imaging features demonstrated a good AUC of 0.810.

In summary, this presentation covered various aspects of imaging for the differentiation and classification of anterior mediastinal tumors, emphasizing the importance of differentiating benign thymic tumors from early-stage thymic malignancies on imaging, in particular for presurgical planning, with CT as the imaging modality of choice for the initial evaluation of anterior mediastinal tumors. It also highlighted the potential of radiomics for improved tumor characterization and prognostication, offering a promising avenue for future research in the field of thoracic oncology.

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Extended Abstract

State of the art in radiation therapy for thymic malignancies: extended abstract

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For patients with thymic malignancies, radiation therapy has an established role as an adjuvant treatment following surgical resection to improve local tumor control and, in select patients, overall survival (OS). Among patients with thymomas, in a National Cancer Database of over 4,000 patients who underwent thymic resections, post-operative radiation therapy (PORT) was associated with longer OS, with the greatest relative benefits for Masaoka stage IIB–III disease and positive margins (1). Similarly, in an International Thymic Malignancy Interest Group (ITMIG) Database analysis of 1,263 patients who underwent R0 resection for stage II–III thymoma, there was an OS benefit from PORT for both stage II (P=0.021) and stage III (P=0.0005) patients (2). With randomized data lacking, these analyses are the most comprehensive reports assessing PORT for thymoma and provide support for its use, particularly in patients at higher risk of recurrence, which has historically included Masaoka stage II patients with R1/R2 resections or with unfavorable histology and larger tumor size (>5 cm) (3), as well as Masaoka stage III and IVA patients. As the American Joint Committee on Cancer (AJCC) staging stage I thymic malignancies include a subset of patients Masaoka stage I, II, and III patients, additional data are needed to better characterize which AJCC stage I patients can benefit from PORT, along with AJCC stage II and III patients (4).

When radiation therapy is being considered, radiation oncologists should communicate closely with surgeons and pathologists to review operative findings to inform target volumes. Target volumes should include the preoperative tumor bed, surgical clips and potential sites of residual disease with margin, whereas prophylactic treatment of the entire mediastinum or supraclavicular region should not be performed. Doses of 45–50.4 Gy should be delivered for R0 patients, whereas doses of 54 and ≥60 Gy should be delivered for R1/R2 patients, respectively.

Adjuvant radiation therapy similarly plays an important role for thymic carcinoma (5,6). A recent analysis of the ITMIG/European Society of Thoracic Surgeons Database found that PORT was associated with an OS benefit (P=0.002), with this benefit statistically significant for advanced stage patients and for those early-stage disease following R1/R2 resections, but not for early-stage patients with R0 resections (7). Recent Appropriate Use Criteria guidelines from the American Radium Society (ARS) recommend adjuvant radiotherapy across disease stages delivered to doses of 45–60 Gy (8).

In patients with unresectable locally-advanced thymic malignancies, radiotherapy to doses of ≥60 Gy to gross disease with margin without elective nodal irradiation should be considered, often in combination with chemotherapy (8-10).

The aforementioned ARS guidelines recommend intensity-modulated radiation therapy (IMRT) or proton therapy as more appropriate than 3D-conformal radiation therapy (3D-CRT) for adjuvant and definitive radiotherapy for thymic tumors (8). These modalities can better protect normal tissues from excess irradiation, thus allowing for a potential reduction in acute and late toxicities. This is particularly important for patients with thymomas, who typically present at a younger age and with a more favorable cancer-specific survival relative to patients with lung cancer and pleural mesothelioma, and are thus at greater risk of late complications like pulmonary fibrosis, major cardiac events, and radiation-induced secondary malignancies. Advanced modalities like IMRT and proton therapy can

be particularly advantageous when delivering high doses of definitive radiotherapy for inoperable cases or those with gross residual or recurrent disease, as well as those with a local recurrence after prior radiation therapy.

In a report of 65 patients treated for stage III thymoma who underwent R0 resection, adjuvant 3D-CRT/IMRT improved median OS compared to surgery alone, but adjuvant conventional radiotherapy did not, likely due to higher rates of pneumonitis and cardiac complications reported in patients receiving conventional radiotherapy (11).

Proton therapy can further improve the risk:benefit ratio and reduce dose to critical thoracic normal tissues relative to IMRT (12,13). The 2024 National Comprehensive Cancer Network guidelines for thymic malignancies states, "*Compared to IMRT, proton therapy has been shown to improve dosimetry, thus allowing for better sparing of normal organs (lungs, heart, and esophagus) with favorable local control and toxicity*" (14). Numerous dosimetric studies have demonstrated that proton therapy can significantly reduce doses to thoracic normal tissues (15,16). Such reductions in dose to the heart can lead to fewer expected major cardiac events with proton therapy relative to IMRT (17). Additionally, by reducing the integral dose to adjacent normal tissues, proton therapy can reduce the risk of developing radiation-induced secondary malignancies (18). The first prospective report of proton therapy in a cohort of 27 patients with high-risk thymic tumors—including patients with thymic carcinomas, gross residual or inoperable disease, and recurrent disease—showed 100% local control at 3 years with no grade ≥3 toxicities, and only 1 grade 2 pneumonitis (4%) (19). Similarly, investigators assessing 30 patients prospectively enrolled in the Proton Collaborative Group or University of Florida Prospective Registries found very low toxicity rates, with the only grade ≥3 toxicity occurring in a patient receiving reirradiation (20). Notably, the lack of exit irradiation dose with proton therapy is particularly favorable in reducing toxicities in the reirradiation setting (21,22).

Advanced radiation modalities are increasingly being employed in the treatment of pleural dissemination or recurrences of thymic malignancies (8). Radiotherapy delivered in ultra-high doses per fraction, termed stereotactic body radiation therapy (SBRT), can provide durable local control of pleural disease and/or metastases, with several institutions reporting excellent local control following SBRT for recurrent pleural mesothelioma (23,24). Such a treatment approach is increasingly being considered for patients with thymic malignancies with pleural metastases, especially those with oligometastatic or oligoprogressive disease (25). Furthermore, intensity-modulated pleural radiation therapy (IMPRINT) delivered to the hemithorax is currently being trialed to treat or prevent pleural dissemination of thymic malignancies (NCT05354570).

Notably, however, there are additional challenges to consider when delivering radiotherapy with advanced modalities, including a need to account for and potentially mitigate respiratory motion and to monitor for anatomical changes during radiotherapy that could affect the radiation dose distribution (26,27), especially for next-generation pencil beam scanning proton therapy (28), underscoring the importance of care being delivered by radiation oncologists with experience managing thymic tumors.

In summary, radiotherapy can improve outcomes in the adjuvant setting for completely resected locally advanced thymic tumors and for early-stage and locally advanced thymic tumors following R1/R2 resections, as well as in the definitive setting for inoperable cases. Radiotherapy has emerging roles for reirradiation and for pleural recurrences or dissemination. To reduce the risks of late complications in patients with thymic malignancies, many of whom have excellent cancer-specific survival, advanced modalities like IMRT and proton therapy should preferentially be utilized for adjuvant and definitive therapy.

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Letter to the Editor

The valuable role of extended pleurectomy decortication and HITHOC for disseminated pleural thymoma

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Treatment for advanced-stage thymoma with pleural dissemination [Masaoka Stage IVa–TNM stage IVA (TNM 8th edition)] (TPD) is rapidly evolving and remains a topic of debate within the surgical/medical community. Due to the low incidence of TPD, and heterogeneous literature with a wide variety of therapeutic protocols, no clear consensus is reached on its treatment (1,2).

Foremost, when assessing and managing TPD it is crucial to recognize a stage IVA thymoma as locally advanced disease and treat it accordingly. Therefore, proper oncological staging is required. We propose that every patient would be staged by whole-body positron emission tomography-computed tomography (PET-CT) and chest magnetic resonance imaging (MRI), to rule out distant metastasis and assess local invasion (e.g., ingrowth in the thoracic wall or mediastinal vessels). We believe PET-CT should become standard practice for thymomas/thymic carcinomas as it helps with the differentiation between the two (3), helps with the detection of distant metastasis, and decreased fluorodeoxyglucose (FDG) uptake might even be associated with superior outcomes (4). Additionally, a functional assessment (e.g., ergospirometry, ventilation/perfusion scintigraphy, cardiac ultrasound, myocardial scintigraphy), should be performed to ensure the patient's fitness and estimate the operative risk.

Although thymomas are highly chemo-and radiosensitive, the cornerstone for treating TPD, in patients with good functionality, should be obtaining complete cytoreduction (R0-resection), as this is directly associated with favorable oncological outcomes (1,2,5-7). The value of surgery in TPD was prominently emphasized in the 2017 European Society of Thoracic Surgeons (ESTS) working group paper by Moser *et al.* (6). In two recent reviews, Ruffini *et al.* and Aprile *et al.* highlight that complete surgical resection is an important predictor for good oncological outcome (2,6,7).

However, since debulking surgery can vary from partial pleurectomy to extra-pleural pneumonectomy, and the type of procedure is not always well-defined in literature, it is challenging to determine the preferred surgical approach for TPD (2,6,7).

Based on our experience with mesothelioma-surgery, the optimal surgical approach to achieve complete resection of the thymoma and all pleural implants (macro- and microscopically) is extended pleurectomy decortication (ePD) in combination with hyperthermic intra-thoracic chemotherapy (HITHOC) (1,2). Our ePD procedures follow a standardized technique involving a complete parietal pleurectomy, visceral decortication, and lymph node resection, followed by hemo-and aërostasis, and finally the construction of a neopleura, as described in malignant pleural mesothelioma surgery (8). Regarding the visceral decortication, we create a plane between the visceral pleura and the lung parenchyma, then peel/strip the visceral pleura outwards without damaging underlying lung parenchyma.

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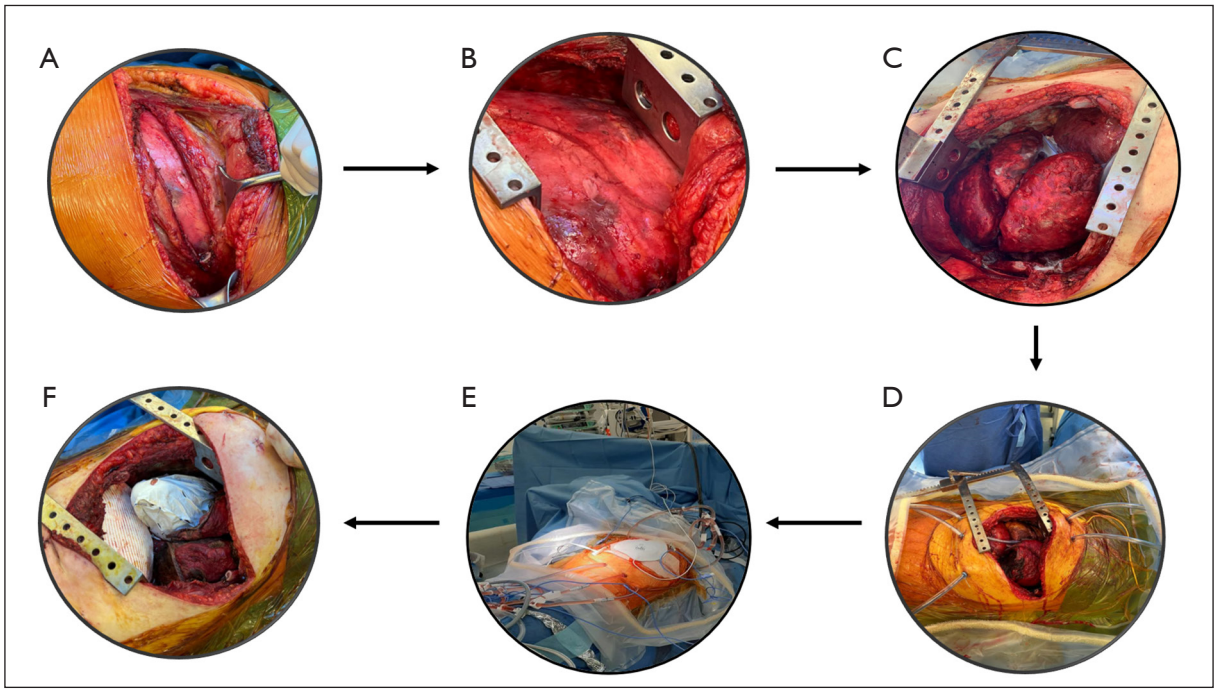

Figure 1 Visualization of our extended pleurectomy decortication with hyperthermic intrathoracic chemotherapy procedure. (A,B) Thoracotomy with resection of the 6th rib to achieve proper exposure; (C) status after parietal pleurectomy and visceral decortication; (D) installation of the HITHOC setup; (E) during HITHOC perfusion; (F) after reconstruction of the diaphragm and pericardium. HITHOC, hyperthermic intra-thoracic chemotherapy.

Thereafter, aërostasis is achieved by suturing major air leaks and constructing a neopleura using an absorbable polyglycolic acid sheet (Neoveil) and polymeric hydrogel sealant (Progel) (*Figure 1*).

Despite meticulous surgery and maximal resection, microscopic residual disease may be inadvertently left in the thoracic cavity (2). HITHOC has emerged as a novel intra-operative treatment modality, drawing inspiration from its abdominal counterpart, hyperthermic intraperitoneal chemotherapy (1,2,7). During HITHOC, the thoracic cavity is irrigated with heated chemotherapy to enhance local disease control by targeting residual microscopic disease. The mechanism of HITHOC is based upon two main principles: (I) hyperthermia increases the penetration depth of the chemotherapeutic agents and enhances the permeability of tumoral cells to these drugs; (II) during HITHOC high concentrations of cytotoxic agents can be presented to the target tissue (1). The main oncological benefit of HITHOC is seen in improving local disease-free survival, as highlighted in a review by Aprile *et al.* (2). According to Ruffini *et al.*, the use of HITHOC in the treatment of stage IVA thymomas can achieve long-term overall survival rates ranging from 67% to 89% (7).

It is crucial that the treatment approach is tailored to the patient, and disease (6). The most suitable indication for ePD + HITHOC would be a patient meeting the following criteria: (I) unilateral disease confined to the pleural cavity, (II) a tumor sensitive to chemotherapy, and (III) a functionally fit patient. Nevertheless, in case of stage IVA disease with a limited number of well-localized pleural droplet metastases (≤3), an ePD may be deemed excessive, and a local resection of the pleural implants might be sufficient as a first stage (6,7). This aligns with previous findings, indicating that the number of pleural implants was inversely correlated with positive oncological outcomes (7). Furthermore, it is essential to distinguish between *de novo* stage IVA thymoma (DNT) and thymoma with pleural relapse (TPR), because the outcomes might differ between both groups (6).

There is also no consensus on the preferred HITHOC protocol for TPD (1). Many protocols incorporate a platinum derivative, typically cisplatin, as their primary agent (1,2). Some protocols also include a secondary agent, usually anthracycline or mitomycin C (1,2). In

our institutional HITHOC protocol the patient typically receives 400 mg/m^2 5-FU and 20 mg/m^2 leucovorin intravenously one hour before HITHOC. During HITHOC the thoracic cavity is rinsed with 460 mg/m^2 of oxaliplatin at a temperature of <43 ℃ for 45 minutes (1). Our preference for oxaliplatin as primary agent is justified by its favorable systemic safety profile, improved renal tolerance compared to cisplatin, and the synergetic effect of hyperthermia and oxaliplatin. Despite the heterogeneity in HITHOC protocols, our systematic review on the topic (capturing 171 cases) concluded that HITHOC is a safe and feasible procedure with very low complication rates, irrespective of the choice of chemotherapeutic agents, temperature, and duration of perfusion (1).

In three of our recent cases—a DNT in a 60-year-old male, a TPR in a 23-year-old female, and a TPR in a 33-year-old male—our ePD/extrapleural pneumonectomy (EPP) + HITHOC protocol was used, resulting in favorable short-term oncological outcomes. All patients remained disease-free with the longest follow-up being three years. Similar findings from recent studies looking at ePD/EPP + HITHOC for TPD underscore the efficacy of this approach, with local recurrence rates of 30% and disease-free intervals ranging from 6 to >88 months (1). Beyond thymoma cases, the application of ePD + HITHOC is expanding to other rare thoracic malignancies such as thoracic pseudomyxoma (9), pleural yolk sac tumor (10), Ewing sarcoma, etc.

In conclusion, we would like to propose an International Thymic Malignancy Interest Group (ITMIG) working group to formulate a consensus statement on the work-up and treatment of stage IVA thymomas. This consensus statement should encompass a thorough oncological and functional work-up for every patient, offer guidance on the choice of debulking surgery, and outline a detailed HITHOC-protocol including the choice-and dosage of chemotherapeutic agents.

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