

Locally advanced thymic epithelial tumors: a foreword to the special series

This special series contributes to improved management and better understanding of locally advanced thymic epithelial tumors (TETs), although definitions of locally advanced TETs vary. Locally advanced TETs have several radiological characteristics, such as tumors >8 cm in the greatest axial diameter and tumors with obvious great vessel and/or adjacent organ invasion or encirclement (1). Current guidelines recommended multidisciplinary management including induction therapy and adjuvant therapy (2,3).

Herein, the authors (*Figure 1*) in this series provided a comprehensive review of each topic.

Dr. So Takata focuses on its genetic profile to aid targeted therapy development. Analyses reveal *TP53*, *CDKN2A*, and other genes as frequently mutated, with *TP53* and *CDKN2A* linked to poor prognosis. *CYLD* mutations may predict immunotherapy response, while *KIT* mutations suggest targeted therapy potential. Thymic carcinoma's distinct genomic landscape, characterized by higher tumor mutation burden (TMB) and 16q loss, emphasizes the need for tailored treatments. Sharing molecular data could advance understanding and treatment options for this rare cancer.

Dr. Yoshihisa Shimada and his colleagues examined induction therapy followed by surgery for stage III or IV cases, revealing primarily retrospective studies and limited prospective trials. While randomized phase III studies are lacking, anthracycline-based chemotherapies are common. Reported rates of complete resection and 5-year overall survival (OS) suggest promise, supporting multimodal treatment for selected patients. Further research is needed to fully assess induction therapy's benefits.

Dr. Yoshito Yamada and his colleagues emphasized the re-evaluation process and surgical indications post-induction therapy for TETs. Induction therapy, comprising chemotherapy and/or radiation, aims to downstage advanced or unresectable tumors.



Figure 1 First authors of the included manuscripts. Dr. Yosuke Yamada, Dr. Hitomi Ajimizu, Dr. Yoshihisa Shimada, and Dr. Masaru Takenaka (top row left to right). Dr. So Takata, Dr. Sho Koyasu, Dr. Noriko Kishi, and Dr. Yoshito Yamada (bottom row left to right).

Re-evaluation is vital for gauging treatment response and deciding on surgical intervention. It explores concepts, methodologies, challenges, and future perspectives of re-evaluation, along with criteria for surgical decision-making in such patients.

Dr. Hitomi Ajimizu and Dr. Yuichi Sakamori focused on induction therapy, typically chemotherapy, aimed to downstage tumors for successful resection. Anthracycline-based regimens are common for thymomas, while alternatives like cisplatin and etoposide are considered for thymic carcinomas. Emerging immunotherapy and targeted therapies offer additional options. While induction radiotherapy alone is uncommon due to concerns of tissue damage, combining it with surgery shows promise. Concurrent chemoradiation is often preferred, particularly for thymic carcinoma patients. However, optimal treatment strategies for locally advanced TETs remain uncertain, necessitating further research and well-designed studies.

Dr. Yosuke Yamada and Dr. Hironori Haga offered pathological insights into tumors invading neighboring structures, crucial for understanding locally advanced TETs. Tumor subtype, whether thymoma or thymic carcinoma, also influences treatment decisions, with distinct biological features identified through studies like The Cancer Genome Atlas project. New features, particularly in epithelial-rich thymomas and thymic squamous cell carcinoma, are highlighted. Sharing these insights aids clinicians in daily practice and prepares them for the forthcoming 9th edition of the TNM classification.

Dr. Noriko Kishi and Dr. Yukinori Matsuo analyzed literature on postoperative radiotherapy (PORT) for TETs, considering Masaoka-Koga staging, histological subtypes, and resection status. While PORT's efficacy varies across stages, further research is needed to determine its optimal use, particularly for stage IIB–III TETs. Advanced radiotherapy techniques and emerging therapies offer promising avenues for improving outcomes, although their efficacy requires further investigation.

Dr. Sho Koyasu's review underscored the significance of precise diagnostic approaches for TETs, encompassing thymomas, thymic carcinomas, and thymic neuroendocrine tumors. Imaging plays a crucial role, particularly in differentiating solid and cystic lesions via contrast-enhanced computed tomography (CT). Thymomas exhibit distinct imaging characteristics, emphasizing the importance of histological classification. Case studies underscore diagnostic complexities and underscore the value of imaging modalities such as CT, magnetic resonance imaging (MRI), and fluorodeoxyglucose-positron emission tomography (FDG-PET). The review extends to rare mediastinal lesions, emphasizing the necessity of comprehensive evaluation for accurate identification and management.

Dr. Masaru Takenaka explored perioperative management and postoperative outcomes in patients with locally advanced TETs, frequently diagnosed at advanced stages. Surgical intervention following chemotherapy or chemoradiotherapy poses specific challenges, emphasizing the importance of perioperative care. Analysis of 18 references from 2000 to 2022 (n=646) reveals induction therapy aims for complete tumor resection, with systemic chemotherapy and chemoradiation commonly used. Surgical intervention may involve resection of surrounding organs and vascular structures, with varying rates of postoperative complications but low mortality. Careful patient evaluation and treatment response assessment are crucial for optimal surgical decision-making.

As described above, all the articles in this series should be read in detail and understood carefully. All the above contributions are seminal work that provides excellent learning opportunities for readers to overcome challenges of locally advanced TETs.

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