Re-evaluation and operative indications after induction therapy for thymic epithelial tumors

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Abstract: Thymic epithelial tumors (TETs), encompassing thymoma and thymic carcinoma, represent a rare and heterogeneous group of thoracic malignancies with varying prognoses and treatment strategies. Surgical resection is the cornerstone of therapy for localized stages, but the management of locally advanced or unresectable TETs often involves induction therapy, including chemotherapy and/or radiation therapy, as a neoadjuvant approach aimed at downstaging the tumor to facilitate subsequent resection. This review synthesizes current knowledge on the re-evaluation process and operative indications following induction therapy for TETs, highlighting the pivotal role of accurate assessment in guiding surgical decisions and optimizing patient outcomes. Induction therapy's efficacy is contingent upon precise re-evaluation methods to accurately gauge treatment response and assess resectability post-therapy. This review discusses the various modalities employed in re-evaluation, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography-CT (PET-CT), and the significance of tumor markers, underlining their strengths and limitations. The adoption of modified RECIST criteria for TETs by the International Thymic Malignancy Interest Group (ITMIG) underscores the necessity for standardized assessment guidelines to ensure consistency and reliability across studies and clinical practices. Furthermore, we explore the implications of induction therapy on surgical decision-making, emphasizing the criteria for determining the suitability of patients for surgical intervention post-therapy. The review addresses the challenges and future perspectives associated with the re-evaluation process, including the potential for advanced imaging techniques and the integration of molecular and genetic markers to enhance the precision of treatment response assessment. In conclusion, the re-evaluation of TETs post-induction therapy is a complex but critical component of the multidisciplinary management approach for these patients. Standardizing re-evaluation methodologies and incorporating novel diagnostic tools could significantly improve the prognostication and treatment stratification, ultimately enhancing the therapeutic outcomes for patients with advanced TETs.

Keywords: Thymic epithelial tumors (TETs); re-evaluation; re-staging; induction therapy

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Introduction

Thymic epithelial tumors (TETs), including thymoma and thymic carcinoma, are rare, with an incidence rate of approximately 1.3–3.2 cases per million (1). Surgical resection is the primary treatment approach for stage I–III TETs; however, complete resection can be challenging in cases of locally advanced TETs. In such cases, preoperative induction therapies have been explored to achieve complete resection. Various chemotherapeutic regimens have been utilized, including adriamycin and/or platinum-based multiagent combinations (2). If remarkable tumor shrinkage occurs, extensive surgery should be offered, and postoperative radiotherapy might be considered. Conversely, in patients with unresectable tumor after systemic induction treatment, concomitant chemoradiotherapy may be considered (3,4). The latest National Comprehensive Cancer Network guidelines recommend induction chemotherapy for patients with potentially resectable locally advanced TETs (5). A significant clinical challenge lies in assessing potential resectability at two critical time points: before induction therapy (or any treatment) and after induction therapy but before surgery. Re-evaluation is important because it is related with the decision for an invasive surgery after burdensome systemic therapy. This review specifically focuses on the re-evaluation process and operative indications following induction therapy for TETs.

While recognizing the distinct oncological and clinical behaviors of thymoma and thymic carcinoma, the limited evidence in this field necessitates a discussion of these issues under the broader category of TETs, including both thymoma and thymic carcinoma. Where possible, we have endeavored to discuss them separately, acknowledging the nuances between the two.

This review focuses on the re-evaluation process and operative indications following induction therapy for TETs.

Re-evaluation methods

Computed tomography (CT) scan

In the re-evaluation of TETs after induction therapy as well as in the primary evaluation (6), CT is the reference standard for radiological evaluation (7). CT is primarily used to evaluate therapeutic effects of induction therapy. Measuring the tumor response to induction therapy is important for both clinical decision-making and in the setting of multi-institutional studies (8). Among various methods, the Response Evaluation Criteria In Solid Tumors

(RECIST) version 1.1 is most commonly used, and the International Thymic Malignancy Interest Group (ITMIG) has suggested using a practical guide for standard outcome measures of TETs (8,9). The RECIST criteria for TETs will be described below.

CT is also performed to assess resectability. Locally advanced TETs extend into the mediastinum and thoracic cavity and can encompass nearby structures (10). Although CT results cannot reveal a tumor cell-free border, it can still provide hints that might support performing complete resection. Particularly in contrast-enhanced CT scans, there is a potential to somewhat delineate the boundaries between the tumor and surrounding structures due to the contrast. According to a prospective study for thymoma conducted by Shen et al., lobulated or irregular tumor shape, unsmooth contour, heterogeneous nature, heterogeneous enhancement pattern, and invasion of adjacent structures were found to be related to incomplete resection in univariable analysis (11). Subsequent multivariable logistic regression showed that only absence of arterial system invasion was a significant factor supportive of complete resection. Similarly, in a study by Hayes et al., the factors related with incomplete resection of thymoma included a lobulated tumor contour, ≥50% abutment of the circumference of an adjacent vessel, thoracic lymphadenopathy, adjacent lung changes, and pleural nodularity (12). Tumor size was larger in the incompletely resected group than in the completely resected group. The multivariable analysis performed by Hayes et al. revealed that ≥50% abutment of the circumference of an adjacent vessel and pleural nodularity were independent predictors of incomplete resection. In the case of thymic carcinoma, Hayes et al. also found that incomplete resection was associated with tumors contacting >25% of an adjacent mediastinal structure and a tumor size of >7.5 cm (13). Furthermore, other radiographic characteristics associated with advanced stages of TETs consist of tumor sizes of ≥7 cm, a lobulated tumor contour, mediastinal fat infiltration, and an elevated hemidiaphragm (14,15). In recent years, evidence has emerged suggesting that the size of TETs plays a role in patient prognosis with several papers published assessing the impact of tumor size on survival (16). Additionally, the International Association for the Study of Lung Cancer Thymic Epithelial Tumor Staging Project recently proposed the ninth edition of the Tumor-Node-Metastasis (TNM) Classification of Malignant Tumors. This new classification includes the division of the T1 category into T1a (≤5 cm) and T1b (>5 cm) (17). However, there has been a debate regarding

the size threshold for predicting incomplete resection status or advanced stage because some larger thymomas can be noninvasive and fully resected upfront in asymptomatic patients (18). Furthermore, the necessity for phrenic nerve resection is challenging to predict solely based on imaging in the absence of an elevated hemidiaphragm, presenting an ongoing challenge for surgeons (19).

Magnetic resonance imaging (MRI)

MRI can be used in addition to CT for better evaluation of the tumor composition and in patients with suspicious tumor infiltration of adjacent structures (6,20). Particularly, cystic or necrotic parts combined with inhomogeneous contrast-enhancement strongly suggest invasiveness (21,22). However, MRI is incapable of precisely detecting low-level invasiveness. To overcome this problem, MRI with cine sequences may show sliding motions between the tumor and cardiovascular structures and might provide more reliable tumor invasion detection (23).

Positron emission tomography-CT (PET-CT)

Encouraging results showing the prognostic ability of PET-CT after induction therapy have been published, although the reports were from studies with a small number of patients (24). In a study with fourteen patients, Fukumoto *et al.* have documented a noteworthy decline in the standardized uptake value $(SUV)_{max}$ in six patients exhibiting an Ef2 response. Conversely, in 5 out of 8 patients with an Ef0–Ef1 response, there was a decrease in SUV_{max}, although it did not reach statistical significance (25). Korst *et al.* also suggested the effectiveness of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET-CT for tumor response assessment after induction therapy (26). Similarly, Matsumoto *et al.* reported the effectiveness of ^{18}F-FDG PET-CT for assessing the therapeutic efficacy in five patients with increased pathological responses associated with larger decreases in SUV_{max} (27).

Tumor markers

Although there are no specific tumor markers for thymoma, some are practically available for thymic carcinoma. A recent multi-institutional retrospective study on advanced thymic carcinoma has revealed significant insights into these markers. According to the NEJ 023 study (28), serum neuron-specific enolase (NSE) was identified as a potential prognostic tumor marker for advanced thymic carcinoma across various histological subtypes. Additionally, squamous cell carcinoma (SCC) antigen levels have shown promise as prognostic indicators in patients with thymic SCC. In fact, a case report involving a patient with thymic small cell carcinoma who underwent multimodal therapy revealed that NSE levels partly reflected tumor progression and treatment responsiveness (29). Another study highlighted the diagnostic potential of the cytokeratin 19 fragment (CYFRA 21-1) in thymic SCC (30). However, this marker was not found to be associated with overall survival or progression-free survival in a separate study (28). This discrepancy underscores the need for further investigation into the prognostic value of CYFRA 21-1. Therefore, for cases of advanced thymic carcinomas, it can be reasonably inferred that during the re-evaluation phase, measuring tumor markers has the potential to offer valuable insights for evaluating the therapeutic efficacy of initial treatment and making well-informed decisions regarding subsequent interventions.

Pathological examination

In the context of the re-evaluation, the role played by pathological examination may not be extensive. In fact, re-biopsy for TETs is infrequently performed. This procedure is typically considered when induction treatment proves ineffective in achieving the desired outcomes, and tumor regrowth is observed. A possible purpose of re-biopsy is to modify the treatment for the next therapeutic session (31,32).

On the other hand, pathological findings after the primary treatment provide valuable treatment-related information and insights into prognosis. Johnson *et al.* introduced a concept of tumor response grade (TRG), proposed by Mandard *et al.*, into TETs (33,34). Pathological tumor response after induction therapy is graded from 1 to 5 based on necrosis and viable tumor cells (33-35). Johnson *et al.* reported that TRG for TETs appeared reproducible and correlated with the radiologic response of tumor size. Moreover, Wang *et al.* identified TRG as one of the independent prognostic factors, alongside ypTNM, ypMasaoka, and complete resection, through multivariable analysis in a cohort of 81 patients with TETs undergoing induction therapy (35). Of note, clinical downstaging (c > yc) of TNM or Masaoka classifications did not change the pooled hazard ratio for survival in their study. This implies an interesting notion that pathological evaluation with TRG might be more accurate in predicting prognosis than

other radiological evaluations in the re-assessment phase.

Therefore, while re-biopsy might be considered important in cases requiring careful evaluation for surgery after neoadjuvant treatment in TETs, its effectiveness in guiding surgical decisions remains unproven. Similarly to TETs, although biopsy-guided pathological response assessment in cancers such as breast cancer and melanoma has shown promise, it has not been widely adopted in clinical practice due to a lack of conclusive evidence. This underscores the universal challenge in establishing the clinical utility of biopsy-based prognostic evaluations across different types of cancers.

Assessment of treatment response

The timing for the assessment

Surgical resection is typically considered 4 to 8 weeks after induction therapy, assuming patients are deemed to have sufficiently recovered (36,37). If delayed further, the efficacy of the induction therapy may diminish. Therefore, although there are no specific guidelines on the timing for reassessing the initial treatment's effectiveness, some literature suggests a window of 2 to 4 weeks after completing preoperative therapy (36).

Evaluation based on RECIST criteria

To evaluate the change in tumor burden after treatment, the ITMIG suggests using the modified RECIST criteria to perform a standardized assessment of the treatment response of TETs (8). Currently, the most commonly used method is RECIST version 1.1, which is basically a unidimensional tumor measurement. ITMIG recommends RECIST version 1.1 for response assessment, but with certain caveats and modifications (38). First, pretreatment and post-treatment imaging should be interpreted by the same individual. Second, because TETs tend to spread along the pleura, the RECIST version 1.1 criteria may not be ideal. Therefore, ITMIG recommends adhering to the criteria previously established for pleural measurements in mesothelioma, measuring the short axis of the tumor.

According to a meta-analysis, four studies have reported analyses correlating the completeness of resection with responses to induction therapy measured by RECIST criteria. (26,39-42). Collectively, these studies included a total of 105 patients. One study employed induction chemoradiotherapy with a radiation dose of 45 Gy,

whereas the remaining studies focused solely on induction chemotherapy. All studies utilized cisplatin-based regimens. The pooled odds ratio assessed in the meta-analysis favored a response to induction therapy predicting complete resection, with a value of 1.4 (95% confidence interval: 0.49 to 4.0; P=0.53). Although the result did not reach statistical significance, the assessment by the RECIST criteria remains an essential tool to evaluate the therapeutic efficacy of induction therapy for TETs.

Re-staging

Theoretically, benefits of induction therapy lie in the downstaging of advanced TETs. However, according to Wang et al.'s retrospective study, clinical Masaoka downstaging was only observed in 24.7% of patients, while 46.9% experienced clinical TNM downstaging (35). They also noted that clinical outcomes were similar between patients who underwent clinical downstaging post induction therapy and those who did not. Whether it was the clinical downstaging of Masaoka, TNM, T, N, or M classifications, these factors didn't stand as independent prognostic variables. The authors suggested that assessing clinical re-staging was challenging due to other biases. Therefore, a possibility of underestimating clinical downstaging might be considered.

Evaluation beyond oncological aspects

Induction therapy, such as chemotherapy and radiation, may lead to a decline in the patient's overall health, potentially affecting their physical fitness for surgery. The treatment can also result in the impairment of specific organ functions, such as the heart, liver, kidneys, and lungs, which can impact the patient's ability to undergo surgical procedures. Thus, some patients may become ineligible for the intended surgical procedures after undergoing induction therapy, which raises the challenge of determining alternative treatment options. Therefore, assessing a patient's surgical tolerance after induction therapy is crucial to ensure that they can withstand the rigors of surgery (43).

When there is infiltration into the cardiovascular system, a more meticulous evaluation is required to assess the need for cardiopulmonary bypass and to determine the feasibility of surgical intervention (44). Close collaboration with cardiothoracic surgeons, anesthesiologists, and the cardiopulmonary bypass team is indispensable in such cases. In situations where patients have concomitant neurological

disorders like severe myasthenia gravis, it is necessary to coordinate with the neurology department for an evaluation of the specific condition. Even if no crisis is evident at the time of evaluation, it is imperative to anticipate the possibility of post-operative crises and engage in discussions involving anesthesiologists, neurologists, and intensive care unit physicians (45).

Surgical indication after induction therapy

Complete resection

The primary goal of induction therapy in TETs, as reiterated, is to achieve complete resection by reducing the tumor, inducing pathological changes in the tumor, downstaging, and other alterations, following the primary treatment. This is because achieving a complete resection after induction therapy may represent a significant prognostic factor or indicate a tendency for improved overall survival (39,41,46-48).

The final decision is typically entrusted to the surgeon's judgment regarding the invasiveness of TETs and the possibility of complete resection (19). However, determining the feasibility of complete resection is not a straightforward task. Hence, objective assessments using imaging studies, as mentioned earlier, become crucial. An analysis of the Japanese Association for Research on the Thymus database revealed that in patients with TETs infiltrating major vessels, the rate of complete resection was lower than that in patients with TET infiltration into the pericardium or lungs (49). In fact, resection of small wedge-shaped portions of the lung adjacent to the pericardium essentially does not increase morbidity associated with thymectomy and almost always achieves negative margins in these areas. Contrarily, vascular resections are far more complex and are associated with higher morbidity; therefore, surgeons outside high-volume centers may hesitate to perform such resections (19).

Considering the surgical approach is crucial. To achieve optimal exposure, the standard sternotomy is generally employed, with the addition of more extensive approaches such as the hemiclamshell, clamshell, or even the transmanubrial osteomuscular-sparing approach (50,51). Furthermore, video-assisted procedures can complement open thoracotomy to ensure an adequate surgical view (51). Recent reports have highlighted the successful application of minimally invasive approaches exclusively for the surgery of advanced TETs. Taken together, the choice of surgical approach should be individually tailored based on the tumor's location, degree of infiltration, response to initial treatment, patient-specific factors, and the surgeon's expertise (52,53).

Debulking surgery

Even if achieving complete resection is not feasible, debulking surgery or volume reduction surgery yields certain therapeutic effects. A meta-analysis demonstrated improved overall survival in patients undergoing debulking surgery for unresectable thymoma with radical intent compared to those undergoing surgical biopsy (54). Similarly, in cases of thymic cancer, maximal debulking surgery might be beneficial and warrant evaluation for advanced diseases where complete resection is challenging, as indicated by a nationwide database in Japan (55). Other researchers have suggested that combining debulking surgery with radiation could be a treatment option for unresectable TETs (56,57). Recently, Mastromarino *et al.* presented an intriguing study on unradical surgery for locally-advanced thymoma (58). In their research, patients who underwent incomplete resection followed by adjuvant treatments exhibited similar cancer-specific survival and overall survival rates to those who underwent complete resection in stage III–IVa thymomas. Certainly, the utility of debulking surgery requires further validation through prospective studies or similar research. Nevertheless, in scenarios where complete surgical removal of the tumor is not possible following initial treatments, debulking surgery could be considered as a viable treatment strategy.

Cessation of surgery after induction therapy

In certain cases, due to the morbidity associated with induction therapy and the potential for treatment-related complications or disease progression, secondary resection is not performed. The rate of surgery cessation after induction therapy varies widely, ranging from 4.8% to 38.1% (41,59-61). In these instances, induction therapy might unnecessarily delay or hinder curative resection, potentially allowing disease progression (60). Hence, when there exists a high level of confidence in the potential for achieving complete resection, opting for upfront surgical resection can be considered. Additionally, patients with a compromised performance status or comorbidities that might worsen due to chemotherapy or similar treatments might also be candidates for a surgical approach. As noted in a previous section, debulking surgery yields certain therapeutic effects.

In any case, the indication for induction therapy remains a significant issue to consider. Understanding such high-risk features that may hinder complete resection should help healthcare providers appropriately select patients for induction therapy. Candidate selection for induction therapy should be performed by a multidisciplinary oncology committee that includes oncologists, diagnostic radiologists, surgeons, therapeutic radiologists, and pathologists with experience in managing advanced thymic malignancies (62).

Future perspective in re-evaluation of induction therapy for TETs

Advancements in imaging techniques for accurate re-evaluation

In recent years, the field of radiology has witnessed remarkable advancements in imaging techniques, and their application in the re-evaluation of TETs has been particularly promising. High-resolution CT and PET-CT have become indispensable tools for precise disease evaluation after induction therapy. The integration of artificial intelligence and machine-learning algorithms into image interpretation has further improved the accuracy of identifying resectability of TETs (63-65). The development of more specific radiotracers and functional imaging modalities has offered enhanced sensitivity for detecting small residual lesions and assessing their metabolic activity. These advancements provide a foundation for more informed clinical decision-making, which enables selecting tailored therapeutic strategies based on the extent and characteristics of any remaining disease.

Incorporation of molecular and genetic markers for personalized treatment strategies

Recent advancements in precision medicine can now be applied to TETs (66). The programmed cell death ligand-1 (PD-L1) expression and the tumor mutational burden, biomarkers for response to immunotherapy, are studied well in this field (67). Although promising response rates and survival outcomes have been observed, the application of immunotherapy in TETs is complicated by the occurrence of severe autoimmune-related adverse events, highlighting the need for careful patient selection and management. Further research is essential to identify reliable predictive markers and to optimize the balance between efficacy and toxicity. Moreover, recent research has led to the identification of specific molecular alterations associated with TETs, such as GFT2I, HRAS, NRAS, TP53, c-KIT, EGFR and IGFR (68-70).

Then, the integration of molecular and genetic markers into re-evaluation is a promising approach. The identification of specific genetic alterations and biomarkers associated with TETs can guide tailored therapeutic approaches with the emergence of next-generation sequencing technologies, we can now delve into a tumor's genomic landscape, identifying mutations and alterations that might influence the treatment response. For instance, research into activating mutations in the *KIT* oncogene, found in approximately 5% of thymic carcinomas, has been pursued as a potential therapeutic target. Tyrosine kinase inhibitors such as imatinib and sunitinib, which target these mutations, have shown promising results in certain patients, according to studies (71,72).

Incorporation of these markers into re-evaluation enables assessment of treatment effectiveness and development of personalized treatment strategies. This molecular insight not only aids in the identification of targetable alterations but also offers valuable prognostic information that will help clinicians optimize the management of TETs.

Prospects of targeted therapies in the neoadjuvant setting

Targeted therapies have revolutionized cancer treatment, and their potential application in the neoadjuvant setting for TETs is an exciting new area (66). By understanding the genetic and molecular profiles of a patient's tumor through re-evaluation, clinicians can tailor neoadjuvant therapies to target specific pathways or mutations. Targeted agents, such as tyrosine kinase inhibitors and immune checkpoint inhibitors, hold promise in improving treatment responses and minimizing surgical complications. Early-phase clinical trials investigating the neoadjuvant use of these agents are underway with the aim of assessing their effect on disease downstaging, treatment tolerability, and long-term outcomes. As we gain a deeper understanding of the biological underpinnings of TETs, the integration of targeted therapies in the neoadjuvant context potentially can reshape the landscape of treatment strategies for these rare malignancies.

Discussion

One of the key limitations of this review article is the relatively limited number of published studies and clinical
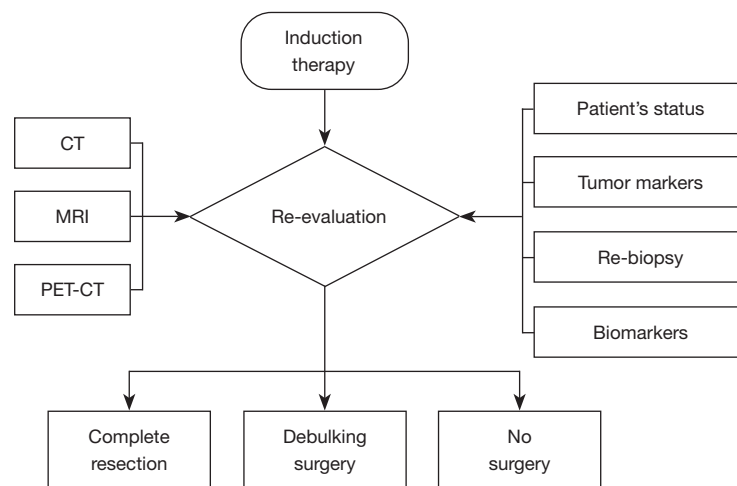
Figure 1 A flow chart of re-evaluation after induction therapy for thymic epithelial tumors. CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

trials in the field of TETs induction therapy and re-evaluation. The scarcity of high-quality, comprehensive data has made it challenging to draw robust conclusions. Our perspective, to a certain extent, was derived from the existing body of knowledge on TETs. Additionally, the heterogeneity in TETs' subtypes, treatment approaches, and evaluation systems across different institutions and regions has hindered our ability to perform a meta-analysis or provide a uniform, evidence-based guideline for re-evaluation protocols. Nevertheless, this review primarily explores current practices through the lens of available literature. We believe that by accumulating and discussing current clinical experiences and practices, this review can pave the way for future recommendations on how to proceed in the face of such evidence gaps.

Furthermore, another significant issue was our consolidation of discussions on thymoma and thymic carcinoma under the single umbrella of TETs, despite their distinct oncological and clinical profiles. This amalgamation was driven by the extreme scarcity of re-evaluation literature specific to each type, compelling us to address them as a collective entity. However, it is important to acknowledge that there are many commonalities between these two histological types, allowing for a degree of discussion from a comprehensive perspective. Where possible, we endeavored to discuss them separately, acknowledging the nuances between the two.

On the other hand, a notable strength of this review is its pioneering approach to the topic of TETs induction therapy and re-evaluation. To the best of our knowledge, no previous review has comprehensively addressed the specific challenges and opportunities related to re-evaluation in the context of TETs management. We consolidated existing knowledge and provided insights into this crucial aspect of TETs' treatment demonstrates. While the limitations mentioned earlier exist, our review incorporates the available evidence and provides a synthesis of the current state of knowledge. By doing so, we aim to guide clinicians in their decision-making processes and inspire additional research efforts that may eventually enhance our understanding of the re-evaluation and its implications for patient care.

Conclusions

We have conducted a review of induction therapy and re-evaluation for TETs. *Figure 1* shows a flow chart of re-evaluation after induction therapy for TETs. In practical terms, the decision-making process for surgery following induction therapy relies heavily on the empirical judgment of practicing surgeons. Consequently, our conclusion underscores the need for further data accumulation on this subject. If any guidance can be derived from existing retrospective case series, the next logical step should involve conducting randomized prospective trials across multiple institutions. Another critical aspect to address is the attempt to reduce the instances of failure to progress to surgery despite undergoing induction therapy. To this end, it is imperative to prioritize careful patient selection for initial treatment. The candidate selection for the treatment should

be performed by a multidisciplinary oncology committee that includes oncologists, surgeons, and radiation oncologists with experience in managing advanced TETs.

Acknowledgments

Footnote

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