Editorial

Pretreatment biopsy for thymic epithelial tumors—does histology subtype matter for treatment strategy?

Sukhmani K. Padda[1*], Marlies Keijzers[2*], Heather A. Wakelee[1]

[1]Department of Medicine (Oncology), Stanford University/Stanford Cancer Institute, Stanford, CA, USA; [2]Department of Cardiothoracic Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

*These authors contributed equally to this work.

Correspondence to: Dr. Heather A. Wakelee. Department of Medicine (Oncology), Stanford University/Stanford Cancer Institute, 875 Blake Wilbur Drive, Stanford, CA 94304, USA. Email: hwakelee@stanford.edu.

Submitted May 18, 2016. Accepted for publication Jun 10, 2016.
doi: 10.21037/jtd.2016.06.77
View this article at: http://dx.doi.org/10.21037/jtd.2016.06.77

Thymic epithelial tumors (TETs) originate from thymic epithelial cells and represent a heterogeneous group of malignancies including thymomas and thymic carcinomas. Thymomas are relatively rare tumors, with an estimated incidence of 0.13 per 100,000 person-years in the United States (US) (1). Thymomas are the most frequently encountered masses in the anterior mediastinum. However, differentiating thymomas from more malignant considerations such as thymic carcinomas, lymphomas, neuroendocrine tumors, malignant germ cell tumors and metastasis is important as the treatment approach can differ drastically (2). However, it is unclear if further defining the World Health Organization (WHO) histologic subtype of TET adds to the importance of clinical staging in deciding the treatment approach.

Brief summary of Chinese Alliance for Research in Thymomas (ChART) results

In this issue of the *Journal of Thoracic Disease*, Yue *et al*. report the value of pretreatment biopsy for TETs for histologic diagnosis and induction therapy (3). The ChART database was retrospectively reviewed, and included 1,902 patients treated from 1994 to 2012. Three hundred thirty-six patients (17.1%) had a pretreatment biopsy in this cohort. An increase in pretreatment biopsies was observed in the most recent time period reported [2004–2012]. Patients who underwent a pretreatment biopsy had significantly higher stage lesions and higher grade histology (P=0.000). When all patients who underwent preoperative biopsy were included, those who received induction therapy had a worse overall survival (OS) compared to those who had upfront surgical resection (5-year OS 53.5% *vs*. 93.1%, respectively; P=0.000). However, patients who were downstaged after induction therapy did not have a statistically significant different OS than those who received upfront surgical resection (5-year OS 92.3% *vs*. 84.2%, respectively; P=0.51). Patients who were not downstaged after induction therapy had a significantly worse 5-year OS than those who received upfront surgical resection (37.2% *vs*. 84.2%; P=0.004), and also had a trend for worse 5-year OS than those who received definitive chemoradiation (37.2% *vs*. 62.4%; P=0.216). These data suggest the potential importance of downstaging of an initially "unresectable" tumor prior to attempted surgery. The authors conclude "it is crucial to get histological diagnosis for advanced stage TETs before treatment decision is decided."

Review of current guidelines on preoperative biopsy for thymic malignancies

The National Comprehensive Cancer Network (NCCN) guidelines recommend that TETs are managed by an experienced multidisciplinary team. Tissue diagnosis is recommended for clinically and radiographically suspected locally advanced unresectable TETs, with either a core needle biopsy or an open biopsy (with avoidance of a transpleural approach to prevent tumor seeding) (4). The NCCN also states that a surgical biopsy should be avoided if the diagnosis of thymoma is strongly suspected and it

is resectable. These recommendations are in agreement with the European Society of Medical Oncology (ESMO) guidelines, which recommend either percutaneous core needle biopsy or surgical biopsy via mediastinotomy or mini-thoracotomy approach for suspected unresectable TETs (5). The International Thymic Malignancy Interest Group (ITMIG) has previously reviewed that biopsy can be obtained by multiple approaches including fine-needle aspirations (FNA), needle core biopsies, minimally invasive surgical techniques such as video-assisted thoracoscopic surgery (VATS) and mediastinoscopy, or more invasive surgical techniques such as a thoracotomy. The sensitivity for needle biopsies ranges between 43–93% and the sensitivity is higher for surgical biopsies (6). Yue *et al*. did not address the factors that were associated with the performance of pretreatment biopsy for patients with TETs but focused on the factors that were associated with receipt of induction therapy *vs*. upfront surgical resection in patients who underwent preoperative biopsy. We would hypothesize there would be differences in patients who receive pretreatment biopsies compared to those who do not, including a higher proportion of advanced stage disease (III-IV) and thymic carcinoma. Since pretreatment biopsy is generally performed in more advanced disease, observing a difference in stage distribution could have relieved concerns of potential misclassification of this variable and any bias related to missing information. We do know that the patients who underwent preoperative biopsy had worse prognostic features indirectly since it was reported that patients who underwent upfront surgical resection with preoperative biopsy had a statistically significant worse OS than those who underwent upfront surgical resection without preoperative biopsy (5-year OS 79.4% *vs*. 89.5%; P=0.000). Interestingly, of the patients who underwent upfront surgical resection and had a preoperative biopsy, 56% were early stage. These early stage biopsies were potentially performed to rule out other competing diagnoses.

Increased use of biopsies in most recent time period in ChART database

Yue *et al*. reported that the percentage of pretreatment biopsies increased significantly in the most recent time period (2004–2012, 18.6% *vs*. 1994–2003, 11.8%; P=0.008). It should be noted that fewer patients were included in the database between 1994–2003 compared with the time period 2004–2012 (254 *vs*. 1,645 patients). The authors also observed that minimally invasive biopsies [thoracoscopy/mediastinoscopy/endobronchial ultrasound (EBUS) biopsy] were increasingly performed in the time period 2004–2012 (16.3% *vs*. 0%, respectively P=0.029) and there was a slight decrease in the performance of needle biopsies (45.8% *vs*. 56.7%, respectively.) When performing a pretreatment biopsy, disrupting the capsule of an early stage thymoma and inducing tumor seeding of the biopsy tract remains a concern (7). In the available literature, tumor seeding is reported at exceedingly low rates (7-9). However, biopsies violating the pleural space, such as VATS biopsy of an anterior mediastinal mass, should be avoided due to potential pleural seeding which has been reported (10,11). Thoracoscopic approaches were reported in ChART but it is unclear how many were performed since they were analyzed in conjunction with mediastinoscopy and EBUS.

The reason for increasing pretreatment biopsies is likely two-fold: (I) improved radiologic techniques for detection of invasion of tumor and evaluation of resectability with computed tomography (CT) (12,13), magnetic resonance imaging (14), and even positron emission tomography (PET) modalities (15) and (II) increasing use of minimally invasive surgical techniques (6). The use of these imaging techniques in the most recent time period may have identified more invasive disease and increased the use of biopsy. CT imaging with intravenous (iv) contrast is recommended by both the NCCN and ESMO guidelines for the diagnostic workup of a mediastinal mass suspicious for thymoma (4,5). CT use has spiked in the last decade due to its improvement in resolution and its ease of use for both physicians and patients. As a reflection of CT's widespread use, many publications warning of its radiation exposure were published in the mid-late 2000s (16,17). There have been several reports examining specific preoperative CT characteristics that predict for higher stage and/or resection status for TETs (18). This is critical since the mainstay of thymoma treatment is achievement of a complete (R0) resection as this has been the strongest independent prognostic factor for survival (19). MRI can also help with assessment of invasion and resectability when CT is equivocal (20). PET is not recommended by ESMO guidelines but is optional per NCCN guidelines (4,5). Although some reports have shown CT characteristics to be associated with histology (18), PET is being increasingly used to assist with determination of histology, with thymic carcinomas having higher standard uptake value (SUV) than thymomas (21,22). There is no discussion of what imaging modalities were used prior to diagnosis in this study, but we expect it would be variable in such a large

multicenter retrospective database. Imaging plays an integral role in whether or not to proceed with biopsy and other treatment decisions for TETs because of its ability to evaluate clinical Masaoka-Koga staging and potential resectability. However, the authors report there was no stage or histologic migration in these time periods, and therefore, the increased use of pretreatment biopsy may have been performed increasingly to rule out competing diagnoses.

Histologic findings in ChART cohort

A histologic diagnosis based on WHO classification could be achieved in 89% of patients' biopsy samples. Forty-seven percent only had a needle biopsy. TETs can be quite heterogeneous with 30–50% having several histologies found in a single tumor after extensive sampling (23,24). ITMIG generally recommends caution in classifying WHO subtype on a FNA or biopsy specimen since it is usually not possible due to the heterogeneity. Also, the highest proportion of tumors in this cohort were thymic carcinomas (~30%), the rarest subtype of TETs, but this is expected as the majority of thymic carcinomas are advanced stage and unresectable at diagnosis (25).

Biopsy for patients with an anterior mediastinal mass and myasthenia gravis (MG)

A different approach could be taken for MG patients who have an anterior mediastinal mass. MG is an antibody-mediated disease of the neuromuscular junction in which a thymoma is found in 15% of patients (26,27), most commonly type B1, B2 and B3 thymoma. Approximately 30% of thymoma patients have concomitant MG. Because of this high correlation, performing a biopsy may not always be necessary for MG patients, even when a locally advanced suspected TET is seen on imaging (28). Yue *et al.* reported that only 11% of patients with pretreatment biopsy had concomitant MG upon presentation, which is much less than the expected 30% of patients.

Worse survival in patients with induction therapy—an issue of selection bias in a retrospective database study

Yue *et al.* reported that of the patients who had a pretreatment biopsy, 56.5% underwent upfront surgical resection, 17.3% induction therapy, and 26.2% definitive chemoradiation. In patients who had a surgical resection, the induction therapy group had worse OS compared to the upfront surgical resection group (5-year OS 53.5% *vs.* 93.1%, P=0.000). This is most likely because of selection bias as the authors acknowledge, with higher risk tumors more likely to receive induction therapy. In their discussion, the authors acknowledge examples in the literature with opposite findings of the induction therapy group either doing better or equivalent to the upfront surgical group (29-32). In the ChART cohort, patients who received induction therapy had a statistically significant higher stage and grade of tumors along with a lower complete resection rate, which are all poor prognostic features and could explain the worse OS. To address these biases, the authors examined 5-year OS stratified by resection status (R0 or R1/R2), histology (thymoma or thymic carcinoma), and stage (III or IV), with all strata favoring upfront surgical treatment numerically. The upfront surgical treatment group had a statistically significant improved 5-year OS in the stage III disease strata (85% *vs.* 32.5%; P=0.003). The improved outcomes of upfront surgical treatment in stage III disease could also be attributed to selection bias since stage III disease is heterogeneous, encompassing a spectrum of involved organs or vessels, some of which are more amenable to upfront surgical resection (i.e., pericardium or lung). When examining only pathologic stage III-IV disease in the upfront surgical resection group, there was higher stage and more incomplete resections but a lower proportion of thymic carcinomas compared to the induction therapy group. Despite this, the outcomes were still worse for those who received induction therapy *vs.* upfront surgical resection (5-year OS 53.5% *vs.* 84.2%; P=0.03). It is plausible that the higher proportion of thymic carcinomas could be driving the worse outcomes for the patients who received induction treatment. However, this is not definitive as the patients with thymoma also had a trend for worse outcome with induction therapy (5-year OS 57% *vs.* 87%; P=0.084). These subgroup analyses involving stratification of specific factors don't account for all potential confounding factors, since there is a strong correlation between Masaoka-Koga stage and histologic subtype of TETs (33). A multivariate model adjusted for these factors may have assisted in estimating the true effect of induction therapy.

Induction therapy for stage III-IV TETs

In addition, the authors did not specify which kind of induction therapy patients received. However, another analysis of the ChART database in this issue of the

Journal of Thoracic Disease describes the varied induction therapies in 68 patients, including 30 with preoperative chemotherapy, 9 with radiotherapy alone, and 29 with chemoradiation. Induction chemotherapy is currently recommended by ITMIG, NCCN, and ESMO (4,5,34) for the treatment of locally advanced TETs (35). The role of induction chemoradiotherapy has been demonstrated in pilot studies as it may enhance the response rate, however, it is currently not routinely recommended (36). Despite the recommendation from guidelines for induction therapy for locally advanced TETs, in ChART, 44.2% with stage III/IV disease underwent upfront surgical resection without induction therapy (4,5). Upfront surgery could be considered for the treatment of stage III TETs where there is macroscopic invasion of neighboring structures (i.e., lung, pericardium) if a complete resection is feasible (37). These patients can be treated with adjuvant radiotherapy to reduce the risk of local recurrences (29). This highlights that outcome data needs to be reported in relation to the use of adjuvant treatment, especially since 9% had R1 resection and 19% had R2 resection in the ChART cohort.

The importance of 'downstaging'

Of all the patients in the induction therapy group (all clinical stage III and higher), only 25% of patients were downstaged and the R0 resection rate was 65.5%. The complete resection rate is in line with other reports. Kim *et al*. reported that after cisplatin-based induction therapy in patients with stage III-IV TETs, 17 out of 22 patients had a major response and a R0 resection rate of 76% (38). Kunitoh *et al*. reported that after induction therapy in patients with stage III TETs, 13 of 21 patients achieved a partial response, and of those, 9 had a R0 resection (39).

Patients in the ChART cohort who were downstaged after induction therapy had a similar 5-year OS as upfront surgery patients. However, those who were not downstaged had worse outcomes than those who received upfront surgical resection and also a trend for worse outcomes than those who received definitive chemoradiation. The authors did not specify how downstaging related to resection status. Based on this data, however, if a clinical stage III or higher tumor is not downstaged, the benefit of surgery is questionable.

Does TET WHO subtype help us tailor therapy in preoperative setting?

Although we agree with the authors that TETs, particularly thymomas *vs*. thymic carcinomas, have different biologic behavior, other WHO subtypes are less important in the initial management of TETs. The first line therapies for induction treatment (and also in the palliative-intent setting) are platinum-based ± the addition of an anthracycline, irrespective of the TET WHO subtype. In our opinion, the authors could more strongly conclude the importance of stage and "downstaging" since it was the only factor that had a clear impact on outcome. WHO histology may be a surrogate for stage and analyses adjusting for stage may eliminate the importance of WHO histology as a prognostic factor (33).

Currently there are no biomarkers that allow for selection of therapy in the neoadjuvant or palliative setting, except for positive octreotide scan for use of octreotide (40), and the rare c-KIT mutation in thymic carcinomas for use of imatinib (41). Even targeted therapies like sunitinib and everolimus are in use in the palliative setting without a corresponding biomarker (42). The search for biologic agents in thymoma and thymic carcinoma has been challenging (43). However, when data becomes available from ongoing systematic genomic analyses of TETs (i.e., The Cancer Genome Atlas), targeted therapies could be a more effective induction therapy in the right subset of TETs, although the 70–80% response rate achieved with chemotherapy will be difficult to surpass. In addition, with the recent detection of programmed-death receptor-ligand-1 in TETs (44), there may be a role for immune-based therapies, though development of this approach must be made with extreme caution given the high rates of autoimmune disease in patients with thymoma. We see the most important role for histological biopsies in advanced TETs for the exclusion of other malignancies rather than the identification of TET WHO subtype.

The authors should be commended on this work, which adds significantly to our understanding of the preoperative treatment of TETs. As the authors addressed, this study suffers from its retrospective design and thus well-known limitations. There was no uniform standard for the chemotherapy regimen and incorporation of radiation therapy in the induction setting was not elucidated. Adjuvant radiotherapy after incomplete R1/R2 resection is important in eradicating residual disease and this was not addressed (5). It is unclear if patients underwent a thymectomy or a thymomectomy, which in some reports may affect clinical outcomes (45). The ChART database is of great value for better understanding TETs. It is only with the collaboration of multiple institutions internationally that

we will be able to solve questions around the management of TETs. Prospective studies of an individualized neoadjuvant approach for TETs will be necessary when more molecular information becomes available.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Guest Editor Wentao Fang (Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Yue J, Gu Z, Yu Z, *et al*. Pretreatment biopsy for histological diagnosis and induction therapy in thymic tumors. J Thorac Dis 2016;8:656-64.

References

1. Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol 2010;5:S260-5.
2. Strollo DC, Rosado de Christenson ML, Jett JR. Primary mediastinal tumors. Part 1: tumors of the anterior mediastinum. Chest 1997;112:511-22.
3. Yue J, Gu Z, Yu Z, et al. Pretreatment biopsy for histological diagnosis and induction therapy in thymic tumors. J Thorac Dis 2016;8:656-64.
4. National Comprehensive Cancer Network. Thymomas and Thymic Carcinomas 2016; (version 1. 2016).
5. Girard N, Ruffini E, Marx A, et al. Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v40-55.
6. Marchevsky A, Marx A, Ströbel P, et al. Policies and reporting guidelines for small biopsy specimens of mediastinal masses. J Thorac Oncol 2011;6:S1724-9.
7. Detterbeck FC. Does an anecdote substantiate dogma? Ann Thorac Surg 2006;81:1182; author reply 1182-3.
8. Kattach H, Hasan S, Clelland C, et al. Seeding of stage I thymoma into the chest wall 12 years after needle biopsy. Ann Thorac Surg 2005;79:323-4.
9. Nagasaka T, Nakashima N, Nunome H. Needle tract implantation of thymoma after transthoracic needle biopsy. J Clin Pathol 1993;46:278-9.
10. Vannucci J, Pecoriello R, Ragusa M, et al. Multiple pleuropericardial implants of thymoma after videothoracoscopic resection. Interact Cardiovasc Thorac Surg 2010;11:696-7.
11. Xie A, Tjahjono R, Phan K, et al. Video-assisted thoracoscopic surgery versus open thymectomy for thymoma: a systematic review. Ann Cardiothorac Surg 2015;4:495-508.
12. Marom EM, Milito MA, Moran CA, et al. Computed tomography findings predicting invasiveness of thymoma. J Thorac Oncol 2011;6:1274-81.
13. Marom EM, Rosado-de-Christenson ML, Bruzzi JF, et al. Standard report terms for chest computed tomography reports of anterior mediastinal masses suspicious for thymoma. J Thorac Oncol 2011;6:S1717-23.
14. Carter BW, Benveniste MF, Truong MT, et al. State of the Art: MR Imaging of Thymoma. Magn Reson Imaging Clin N Am 2015;23:165-77.
15. Benveniste MF, Moran CA, Mawlawi O, et al. FDG PET-CT aids in the preoperative assessment of patients with newly diagnosed thymic epithelial malignancies. J Thorac Oncol 2013;8:502-10.
16. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med 2007;357:2277-84.
17. Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. Arch Intern Med 2009;169:2078-86.
18. Zhao Y, Chen H, Shi J, et al. The correlation of morphological features of chest computed tomographic scans with clinical characteristics of thymoma. Eur J Cardiothorac Surg 2015;48:698-704.
19. Detterbeck FC, Parsons AM. Thymic tumors. Ann Thorac Surg 2004;77:1860-9.
20. Marom EM. Advances in thymoma imaging. J Thorac Imaging 2013;28:69-80; quiz 81-3.
21. Viti A, Terzi A, Bianchi A, et al. Is a positron emission tomography-computed tomography scan useful in the staging of thymic epithelial neoplasms? Interact Cardiovasc Thorac Surg 2014;19:129-34.
22. Treglia G, Sadeghi R, Giovanella L, et al. Is (18)F-FDG PET useful in predicting the WHO grade of malignancy in thymic epithelial tumors? A meta-analysis. Lung Cancer 2014;86:5-13.
23. Marx A, Chan JK, Coindre JM, et al. The 2015 World Health Organization Classification of Tumors of the

Thymus: Continuity and Changes. J Thorac Oncol 2015;10:1383-95.
24. Moran CA, Walsh G, Suster S, et al. Thymomas II: a clinicopathologic correlation of 250 cases with a proposed staging system with emphasis on pathologic assessment. Am J Clin Pathol 2012;137:451-61.
25. Ahmad U, Yao X, Detterbeck F, et al. Thymic carcinoma outcomes and prognosis: results of an international analysis. J Thorac Cardiovasc Surg 2015;149:95-100, 101.e1-2.
26. Marx A, Pfister F, Schalke B, et al. The different roles of the thymus in the pathogenesis of the various myasthenia gravis subtypes. Autoimmun Rev 2013;12:875-84.
27. Huang J, Ahmad U, Antonicelli A, et al. Development of the international thymic malignancy interest group international database: an unprecedented resource for the study of a rare group of tumors. J Thorac Oncol 2014;9:1573-8.
28. Hoerbelt R, Keunecke L, Grimm H, et al. The value of a noninvasive diagnostic approach to mediastinal masses. Ann Thorac Surg 2003;75:1086-90.
29. Cardillo G, Carleo F, Giunti R, et al. Predictors of survival in patients with locally advanced thymoma and thymic carcinoma (Masaoka stages III and IVa). Eur J Cardiothorac Surg 2010;37:819-23.
30. Lucchi M, Melfi F, Dini P, et al. Neoadjuvant chemotherapy for stage III and IVA thymomas: a single-institution experience with a long follow-up. J Thorac Oncol 2006;1:308-13.
31. Modh A, Rimner A, Allen PK, et al. Treatment Modalities and Outcomes in Patients With Advanced Invasive Thymoma or Thymic Carcinoma: A Retrospective Multicenter Study. Am J Clin Oncol 2016;39:120-5.
32. Rea F, Marulli G, Di Chiara F, et al. Multidisciplinary approach for advanced stage thymic tumors: long-term outcome. Lung Cancer 2011;72:68-72.
33. Ruffini E, Filosso PL, Mossetti C, et al. Thymoma: inter-relationships among World Health Organization histology, Masaoka staging and myasthenia gravis and their independent prognostic significance: a single-centre experience. Eur J Cardiothorac Surg 2011;40:146-53.
34. Girard N, Lal R, Wakelee H, et al. Chemotherapy definitions and policies for thymic malignancies. J Thorac Oncol 2011;6:S1749-55.
35. Wei Y, Gu Z, Shen Y, et al. Preoperative induction therapy for locally advanced thymic tumors: a retrospective analysis using the ChART database. J Thorac Dis 2016;8:665-72.
36. Korst RJ, Bezjak A, Blackmon S, et al. Neoadjuvant chemoradiotherapy for locally advanced thymic tumors: a phase II, multi-institutional clinical trial. J Thorac Cardiovasc Surg 2014;147:36-44, 46.e1.
37. Yamada Y, Yoshino I, Nakajima J, et al. Surgical Outcomes of Patients With Stage III Thymoma in the Japanese Nationwide Database. Ann Thorac Surg 2015;100:961-7.
38. Kim ES, Putnam JB, Komaki R, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. Lung Cancer 2004;44:369-79.
39. Kunitoh H, Tamura T, Shibata T, et al. A phase II trial of dose-dense chemotherapy, followed by surgical resection and/or thoracic radiotherapy, in locally advanced thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9606). Br J Cancer 2010;103:6-11.
40. Loehrer PJ Sr, Wang W, Johnson DH, et al. Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: an Eastern Cooperative Oncology Group Phase II Trial. J Clin Oncol 2004;22:293-9. Erratum in: J Clin Oncol 2004;22:2261.
41. Hagemann IS, Govindan R, Javidan-Nejad C, et al. Stabilization of disease after targeted therapy in a thymic carcinoma with KIT mutation detected by clinical next-generation sequencing. J Thorac Oncol 2014;9:e12-6.
42. Simonelli M, Zucali PA, Suter MB, et al. Targeted therapy for thymic epithelial tumors: a new horizon? Review of the literature and two cases reports. Future Oncol 2015;11:1223-32.
43. Rajan A, Giaccone G. Targeted therapy for advanced thymic tumors. J Thorac Oncol 2010;5:S361-4.
44. Padda SK, Riess JW, Schwartz EJ, et al. Diffuse high intensity PD-L1 staining in thymic epithelial tumors. J Thorac Oncol 2015;10:500-8.
45. Tseng YC, Hsieh CC, Huang HY, et al. Is thymectomy necessary in nonmyasthenic patients with early thymoma? J Thorac Oncol 2013;8:952-8.

Cite this article as: Padda SK, Keijzers M, Wakelee HA. Pretreatment biopsy for thymic epithelial tumors—does histology subtype matter for treatment strategy? J Thorac Dis 2016;8(8):1895-1900. doi: 10.21037/jtd.2016.06.77

