GRAND ROUND SESSIONS

GR01.01
Pathology

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The pathologist is an integral member of the thymic malignancies tumor board team as he/she provides information on diagnosis, tumor stage, completeness of resection, and potential performance of biomarkers which is necessary for the team to decide on the optimal treatment for each individual patient. Information that will be expected from the pathologist differs dependent on whether a preoperative biopsy, a resection specimen or a specimen from a recurrence/metastasis is discussed (Table 1). For preoperative biopsies it is important to establish a histologic diagnosis including thymoma, thymic carcinoma, thymic neuroendocrine tumor, or benign thymic gland. Morphologic mimickers of thymic epithelial tumors (TET) such as lymphoma or germ cell tumors also need to be considered. Thymoma are not further subtyped on biopsies given the potential heterogeneity of these tumors. Moreover, the subtype of a thymoma in general does not play a role for treatment decisions. In contrast, the subtype of a thymic carcinoma might be of value at the time of biopsy as some subtypes behave in a very aggressive manner and might be treated differently from a squamous cell carcinoma, the most common subtype of thymic carcinomas. For instance NUT carcinoma commonly have already metastasized at time of diagnosis(1). Similarly, *SMARCA4*-deficient tumors (even though not included in the current WHO) are highly aggressive tumors(2). Lymphoepithelioma-like carcinoma can also behave more aggressively(3). Although these subtypes of thymic carcinoma are quite rare, they should be kept in mind and the threshold of ordering ancillary tests such as immunohistochemical stains for NUT and/or BRG1 or an EBV in situ hybridization should be low. As some TET are unresectable, suggestions for biomarker testing might also be expected from the pathologist. If a resection specimen of a TET is discussed stage and resection status are critical as they are the most important prognostic parameters and guide additional treatment decisions. To stage TET the recently introduced 8th edition of the UICC/AJCC TNM should be used. Currently, in many centers, both, Masaoka-Koga stage(4) and TNM stage(5) are reported simultaneously as some treatment protocols are still based on the Masaoka-Koga stage. The histologic classification also plays a role especially if the TET was not previously biopsied (which is the most common scenario in thymoma). In resection specimens the histologic classification should include the distinction between thymoma, thymic carcinoma and thymic neuroendocrine tumor vs benign thymic gland (i.e., thymic follicular hyperplasia, true thymic hyperplasia) vs mimickers of TET. In resection specimens the thymoma should be further subtyped, which is usually performed according to the 2015 WHO classification.(6) If the patient underwent neoadjuvant therapy, a comment on treatment effect of the resection specimen might be made(7). Although uncommon, biopsies or resections of recurrences or metastases of TET are performed and are discussed during tumor board. Based on the type of specimen (biopsy vs resection specimen) similar issues as described above will be discussed. In addition, especially in resection specimens, the WHO subtype of the TET should be mentioned as it might differ from the original specimen. In conclusion, the pathologist will contribute important information in regards to histologic diagnosis, stage, completeness of resection and biomarker testing of TET to the tumor board discussion which will be crucial for further treatment decision.

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Table 1. Pathology discussion points at thymic malignancies tumor boards

Time / type of specimen	Important information from pathology
Presurgical / initial biopsy	Histologic subtype of thymic epithelial tumor Subtype of thymic carcinoma Mimicker of thymic epithelial tumor Biomarker testing
Resection specimen	Stage Resection status Thymic epithelial tumor histologic subtype including thymoma subtype Treatment effect Biomarker testing
Recurrence / metastasis	Histologic subtype of thymic epithelial tumor including thymoma subtype (especially if resection) Resection status if excision Biomarker testing

GR01.02
Surgical Oncology

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The treatment strategy for Thymic Epithelial Tumors (TETs) is based first on the tumour resectability. If complete resection is deemed feasible upfront, as it is the case in Masaoka-Koga stage I/II as well as for some stage III tumours, surgery represents the first step of the treatment, sometimes followed by postoperative radiotherapy and, less frequently, chemotherapy. Pretreatment biopsy is not always required, if the diagnosis of thymic tumour is highly probable and upfront surgical resection is achievable. Biopsy is therefore required in all other clinical situations: approaches may consist of percutaneous core-needle biopsy or incisional surgical biopsy through mediastinotomy or mini-thoracotomy. Pleural spaces should be respected to avoid tumour cell seeding. Fine-needle aspiration is generally not recommended. The standard approach is median sternotomy, which allows the complete opening of the mediastinum and both pleural cavities, and the evaluation of tumour macroscopic capsular invasion, infiltration of peri-thymic and mediastinal fat, peritumoural and pleural adherences and

possible involvement of surrounding anatomical structures. Generally, complete thymectomy including the tumour, the residual thymus gland and perithymic fat is preferred because local recurrences have been sometimes observed after partial thymectomy, when a part of the thymus gland is left behind. However, thymomectomy alone is an option in stage I tumours and in non-myasthenic patients. If the tumour is widely invasive (stage III/IV), en bloc removal of all affected structures, including lung parenchyma (usually through limited resection), pericardium, great vessels, nerves and pleural implants, should be carried out. Resection of venous vascular structures (innominate vein(s) and superior vena cava) includes partial resection with suturing or complete resection and vessel reconstruction using vascular prosthesis. Areas of uncertain resection margins are marked with clips to allow a precise postoperative radiotherapy delivery.. Phrenic nerve preservation does not affect survival, but increases the risk of local recurrence, and should be balanced with the achievement of a complete resection, especially in patients with severe and uncompensated myasthenia gravis. Frozen sections to assess tumour involvement of resection margins are not always recommended, since the risk of false-negative results is high. Minimally invasive surgery is an option for presumed stage I and possibly stage II tumours in the hands of appropriately trained thoracic surgeons. This includes transcervical, extended transcervical, video-assisted thoracoscopy (VATS) and robotic approaches (right or left, right and left, right and cervical, left and cervical, subxiphoid and right and left, cervical and subxiphoid); furthermore, robotic surgery may allow a better visualisation of the tumour when compared with VATS. The choice for minimally invasive resection should not jeopardise or change the principles that are deemed appropriate for an open approach, especially the achievement of complete resection that may ultimately require switching to an open procedure. Minimally invasive surgery is not recommended for stage III tumours, because the lack of long-term follow-up. Lymphadenectomy has historically rarely performed after resection of thymic tumours. The new IASLC/ITMIG TNM staging system of thymic tumours, however, leads to the recommendation that locoregional lymphoadenectomy should be carried out during resection of all types of thymic tumours. A proposed nodal map is available from ITMIG. Routine removal of anterior mediastinal nodes and anterior cervical nodes is also recommended. Systematic sampling of other intrathoracic sites is encouraged (i.e. paratracheal, aortopulmonary window and subcarinal areas, depending on tumour location) in stage III/IV tumours. Systematic lymphadenectomy (N1 + N2) is strongly recommended in case of thymic carcinoma due to the high rate of lymphatic spread (20% versus 3% in thymomas) If complete resection is deemed not to be achievable upfront on the basis of imaging studies, as it is frequently the case in Masaoka-Koga stage III/IVA tumours, a biopsy should be carried out, followed by primary/induction chemotherapy as part of a curative-intent sequential strategy that integrates subsequent surgery or radiotherapy. Patients not eligible for local treatment should receive palliative chemotherapy only. Recurrences of thymic epithelial tumours are not uncommon (10%—15% of all-stage resected tumours) and should be managed according to the same strategy as newly diagnosed tumours. Complete resection of recurrent lesions represents a major predictor of favourable outcome, and surgery is then recommended in case of resectable lesions. **Keywords:** Thymus, Tumour, Surgery

GR01.03
Surgical Oncology

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In this section we will address the controversial areas of surgical management in the more advanced stages of thymoma. Using case-based discussion we will debate the following clinical scenarios: Stage III Thymic tumours (with invasion of great vessels) **Is there a role for primary surgical debulking leaving an intentional R2 resection?** There is little survival evidence to support intentional debulking but such procedures may reduce the dose and extent of radiotherapy subsequently required and therefore the associated morbidity [1]. However, there is a lack of supportive evidence for debulking surgery in thymic carcinoma. [2,3] **Should primary treatment be chemo-radiotherapy followed by consolidation surgery?** Induction therapy is feasible in locally advanced thymic tumours and has been reported to achieve around a 50% partial response. A complete pathological response has not been seen but such treatment can facilitate a high rate (over75%) of R0 resection.[4] Stage IVa Thymic tumours — pleural/pericardial deposits **Is there a role for radical surgery?** The International Thymic Malignancies Interest Group have recommended that in locally-advanced Stage IVa patients with pleural involvement, major pleural resections, including pleurectomy/decortication or extrapleural pneumonectomy are indicated, provided a complete resection of the pleural deposits is anticipated, usually in a multidisciplinary setting [5] **Should this be extrapleural pneumonectomy or thymectomy and extended pleurectomy/decortication?** As in other disease, extrapleural pneumonectomy (EPP) is associated with a high 30 day mortality of up to 17% (6). Providing a complete resection can be achieved there is no difference between EPP and extended pleurectomy decortication (EPD) (7) and median survival may exceed 4 years. The contribution of occult nodal metastases must be recognized and radical resection must include lymph node dissection. Stage migration due to lymph node metastases, WHO-classification type C, and T3/4-status are associated with inferior survival but extended surgery has been found to be the only independent significant prognosticator in multivariate analysis [8,9]. **Which surgical incision is best?** Radical resections can be facilitated by extended approaches which are well tolerated and adequate exposure is necessary to ensure a complete resection Recurrent thymic tumour — after previous resection **Is there evidence that extending local control prolongs overall survival over systemic therapy alone?** Survival is acceptable and superior to non surgical treatment if complete resection of recurrence is achieved. There is no evidence to support debulking of recurrent thymoma [10] A significant poorer prognosis is associated with multiple versus single relapses, Masaoka stage III primary tumour versus Masaoka stage I-II primary tumour, distant versus loco-regional relapses and B3 histotype versus other. On multivariate analysis, completeness of resection, number of metastases, Masaoka stage of primary tumour and site of relapse were identified as the only independent predictors of prognosis [10] **Conclusions:** The relative rarity of thymic neoplasms has contributed to the lack of high grade evidence from randomized controlled trials of large numbers of patients. Most supportive evidence for radical surgery in advanced thymic malignancies has therefore been provided by relatively small selected case series. However, the formation of larger collaborative groups with cumulative databases has provided more robust support for extended surgical procedures that many have avoided previously. The superiority of resection as part of multimodality treatment over non-surgical treatment alone seems to be justified provided high quality surgical standards are maintained. **References:** 1. Ried M et al. Extended surgical resections of advanced thymoma Masaoka stages III and IVa facilitate outcome. Thorac Cardiovasc Surg. (2014) 2. Hamaji M et al A meta-analysis of debulking surgery versus surgical biopsy for unresectable thymoma.. Eur J Cardiothorac Surg. (2015) 3. Attaran S et al , Does surgical debulking for advanced stages of thymoma improve survival? Interact Cardiovasc Thorac Surg. 2012 Sep;15(3):494-7 4. Korst RJ, et a. lNeoadjuvant chemoradiotherapy for locally advanced thymic tumours: a phase II, multi-institutional clinical trial. J Thorac Cardiovasc Surg. 2014 Jan;147(1):36- 44 5. Ruffini E et al, Optimal surgical approach to thymic malignancies: New trends challenging old dogmas. Lung Cancer. 2018 Apr;118:161-170. 6. Fabre Det al.Long-term outcome of pleuro-pneumonectomy for Masaoka stage IVa thymoma. Eur J Cardiothorac Surg. 2011 ;39:e133-8 7. Moser B et al, Surgical therapy of thymic tumours with pleural involvement: an ESTS Thymic Working Group Project. Eur J Cardiothorac Surg. 2017 Aug 1;52(2):346-355 8. Kaba E