Thymic Epithelial Tumours
Histopathology Reporting Guide

Family/Last name

Given name(s)

Gender ☐ Male ☐ Female

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are REQUIRED. Elements in **grey text** are RECOMMENDED.

CLINICAL INFORMATION (Note 1)

◯ Not provided

☐ Myasthenia gravis
☐ Pure Red Cell Aplasia (PRCA)
☐ Rheumatoid arthritis
☐ Hypogammaglobulinemia (Good's syndrome)
☐ Lupus
☐ Addison's disease
☐ Cushing's disease
☐ Previous neoplasm *(specify)*

☐ Preoperative therapy *(specify)*

☐ Other disorders *(specify)*

OPERATIVE PROCEDURE (Note 2)

◯ Extended thymectomy
◯ Radical thymectomy
◯ Other *(specify)*
◯ Partial thymectomy
◯ Total thymectomy
◯ Not specified

SPECIMEN(S) SUBMITTED (select all that apply) (Note 3)

☐ Partial thymus
☐ Complete thymus
☐ Thymus plus surrounding tissue (radical thymectomy)
☐ Mediastinal pleura
☐ Pericardium
☐ Lung ⇒ ☐ Right ☐ Wedge ☐ Lobe ☐ Entire lung ☐ Left ☐ Wedge ☐ Lobe ☐ Entire lung
☐ Phrenic nerve ⇒ ☐ Right ☐ Left
☐ Great vessels ⇒ ☐ Brachiocephalic (innominate) vein ☐ Superior vena cava ☐ Extrapericardial pulmonary artery/veins ☐ Aorta (ascending, arch or descending) ☐ Arch vessels ☐ Intrapericardial pulmonary artery
☐ Myocardium
☐ Diaphragm
☐ Separate extrathymic tumour nodules
☐ Lymph nodes
☐ Other *(specify)*
◯ Not specified

SPECIMEN INTEGRITY (Note 4)

◯ Intact specimen
◯ Surface disrupted
◯ Fragmented specimen

MACROSCOPIC SITE OF PRIMARY TUMOUR (Note 5)

◯ Thymic
◯ Single tumour
◯ >1 tumour
◯ Not specified
◯ Ectopic *(specify site(s))*

MAXIMUM DIMENSION OF PRIMARY TUMOUR (Note 6)

mm

◯ Cannot be assessed

BLOCK IDENTIFICATION KEY (Note 7)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (Note 8)

(Use the 2015 WHO classification. Where relevant, if more than one subtype, list in 10% increments)

Thymoma ◯ Present ◯ Not identified

Predominant subtype ⇒ %

Other thymoma types ⇒ %

⇒ %

⇒ %

Thymic carcinoma ◯ Present ◯ Not identified

Predominant subtype ⇒ %

Other thymic carcinoma patterns ⇒ %

⇒ %

⇒ %

Thymic neuroendocrine tumours

○ Present ○ Not identified

⇩

Typical carcinoid tumour ⇨ %

Atypical carcinoid tumour ⇨ %

Large cell neuroendocrine carcinoma ⇨ %

Small cell carcinoma ⇨ %

Final histological diagnosis

(Use 2015 WHO classification for combined tumours)

EXTENT OF DIRECT INVASION (Note 9)

Tumour capsule

- ○ No invasion beyond capsule or limit of the thymus
- ○ Transcapsular invasion less than or equal to 3mm*
- ○ Invasion more than 3mm, limited to the mediastinum*
- ○ Invasion beyond the mediastinum

(**refer to Note 17 Staging, Table 2 for definitions)*

Mediastinal pleura

○ Not involved ○ Cannot be assessed
○ Involved ○ Not applicable

Pericardium

○ Not involved ○ Cannot be assessed
○ Involved ○ Not applicable

Lung (pulmonary parenchyma, visceral pleura, or both)

○ Not involved ○ Cannot be assessed
○ Involved ○ Not applicable

⇩

Specify lobe(s) of the lung

GREAT VESSELS

Brachiocephalic (innominate) vein

○ Not involved ○ Cannot be assessed
○ Involved ○ Not applicable

Superior vena cava

○ Not involved ○ Cannot be assessed
○ Involved ○ Not applicable

Extrapericardial pulmonary artery or veins

○ Not involved ○ Cannot be assessed
○ Involved ○ Not applicable

Aorta (ascending, arch or descending)

○ Not involved ○ Cannot be assessed
○ Involved ○ Not applicable

Arch vessels

○ Not involved ○ Cannot be assessed
○ Involved ○ Not applicable

Intrapericardial pulmonary artery

○ Not involved ○ Cannot be assessed
○ Involved ○ Not applicable

Phrenic nerve

○ Not involved ○ Cannot be assessed
○ Involved ○ Not applicable

Other involved organ(s)/site(s) by direct spread

SEPARATE EXTRATHYMIC TUMOUR NODULES/METASTASES (Note 10)

Pleural and/or pericardial

○ Present ○ Not identified

⇩

Specify location(s) — Specify number/location

⇨

Pulmonary intraparenchymal

○ Present ○ Not identified

Distant organ

○ Present ○ Not identified

⇩

Specify site(s)

RESPONSE TO NEOADJUVANT THERAPY (Note 11)

- ○ Cannot be assessed
- ○ Prior treatment not known
- ○ No prior treatment
- ○ No response
- ○ Positive response ⇨ Specify % residual viable tumour on cross-section %

COEXISTENT PATHOLOGY (Note 12)

☐ Thymic hyperplasia
- ○ Follicular
- ○ Epithelial
- ○ True

☐ Cystic changes
- ☐ In tumour
- ☐ In adjacent thymus

☐ Other *(specify)*

MARGIN STATUS (Note 13)

- ○ Cannot be assessed
- ○ Not involved
- ○ Involved

⇩

○ Macroscopic

⇩

Specify margin(s), if possible

○ Microscopic

⇩

Specify margin(s), if possible

LYMPH NODE STATUS (Note 14)

- ◯ No nodes submitted or found
- ◯ Not involved
- ◯ Involved

⇩

☐ **Anterior (perithymic) nodes (zone 1)**

Number of lymph nodes examined

Number of positive lymph nodes

◯ Number cannot be determined

☐ **Deep intrathoracic or cervical nodes (zone 2)**

Number of lymph nodes examined

Number of positive lymph nodes

◯ Number cannot be determined

☐ **Unspecified location within zones 1 or 2**

Number of lymph nodes examined

Number of positive lymph nodes

◯ Number cannot be determined

☐ **Location(s) outside zones 1 or 2 (M1 disease)**

Number of lymph nodes examined

Number of positive lymph nodes

◯ Number cannot be determined

ANCILLARY STUDIES

IMMUNOHISTOCHEMICAL MARKERS (Note 15)

◯ Performed ◯ Not performed

⇩

Positive markers	
Negative markers	
Equivocal markers	

Interpretation and conclusions

MOLECULAR STUDIES (Note 16)

◯ Performed ◯ Not performed

⇩

Specify tests and results

PATHOLOGIC STAGING FOR THYMOMAS AND THYMIC CARCINOMAS - MODIFIED MASAOKA (*with updated ITMIG definitions)* (Note 17)

- ◯ Not applicable
- ◯ Cannot be determined
- ◯ I Grossly and microscopically completely encapsulated tumour
- ◯ IIa Microscopic transcapsular invasion
- ◯ IIb Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium
- ◯ III Macroscopic invasion into neighbouring organ (i.e. pericardium, great vessel or lung)
- ◯ IVa Pleural or pericardial metastases
- ◯ IVb Lymphogenous or haematogenous metastases

PROPOSED TNM PATHOLOGIC STAGING FOR THYMIC EPITHELIAL TUMOURS (Note 17)

☐ m - multiple primary tumors ☐ r - recurrent
☐ y - post treatment

Primary tumour (pT)

- ◯ TX Primary tumour can not be assessed.
- ◯ T0 No evidence of primary tumour
- ◯ T1 A tumour that either is limited to the thymus with or without encapsulation, directly invades into the mediastinum only or directly invades the mediastinal pleura but does not involve any other mediastinal structure
- ◯ T1a no mediastinal pleural involvement
- ◯ T1b direct invasion of the mediastinal pleura
- ◯ T2 A tumour with direct invasion of the pericardium (either partial or full-thickness)
- ◯ T3 A tumour with direct invasion into any of the following: Lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins
- ◯ T4 A tumour with invasion into any of the following: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, or oesophagus

Regional lymph nodes(pN)

- ◯ No nodes submitted or found
- ◯ N0 No nodal involvement
- ◯ N1 Anterior (perithymic) nodes
- ◯ N2 Deep intrathoracic or cervical nodes

Distant metastases (pM)

- ◯ Not applicable
- ◯ pM1a Separate pleural or pericardial nodule(s)
- ◯ pM1b Pulmonary intraparenchymal nodule or distant organ metastasis

Note 1 - Clinical information (Recommended)

Reason/Evidentiary Support

It is helpful to know whether the patient has myasthenia gravis or other conditions including neoplasms that can be associated with thymomas. Knowledge of any neoadjuvant treatment is also important as it may explain necrosis and scarring seen macroscopically and microscopically, and allows the pathologist to comment on histologic treatment response.

If clinical conditions other than those listed are provided, then these should be noted under 'Other disorders'.

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Note 2 - Operative procedure (Recommended)

Reason/Evidentiary Support

Documentation of the operative procedure is useful, as correlation of the type of procedure with the material received can be important for both pathological diagnosis and patient safety. Further, the type of surgical procedure is important in determining the assessment of surgical margins.[1]

The surgeon should inform the pathologist of the type of operation/procedure.

A thymectomy is an operation to remove the thymus. A partial thymectomy is the removal of less than the whole thymus. A total (standard) thymectomy is the removal of the thymus gland without surrounding fatty tissue. An extended thymectomy is the removal of the thymus gland including the fatty tissue of the mediastinum and neck. A radical (maximal) thymectomy is the removal of the thymus gland and wide resection of fatty tissue of the middle and anterior mediastinum and neck from the diaphragm to the thyroid gland and between both phrenic nerves; the technique includes visualization of recurrent laryngeal and phrenic nerves and wide opening of both pleural spaces.

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Note 3 – Specimen(s)s submitted (Required)

Reason/Evidentiary Support

Specimen type should indicate what was submitted.[1] Specimen type varies according to the type of operation. If the specimen was obtained by a radical thymectomy, the specimen type is indicated as "Thymus plus surrounding tissue."

Specimens obtained by combined resection with other organs or parts thereof, should be itemised, such as lung, pleura, pericardium, great vessels and myocardium. Other organs or tissues are reported as "Other" and details should be recorded.[1-3]

Separate extrathymic tumour nodules submitted should be recorded; these include pleural and pericardial seedings, pulmonary intraparenchymal nodules and distant organ metastases. The location, number and size of extrathymic nodules are described later in the dataset (see **Note 10 - SEPARATE EXTRATHYMIC TUMOUR NODULES/METASTASES**).

Submitted lymph nodes should also be recorded.[4,5] These may be submitted separately or within a combined mediastinal specimen, so labelling or discussion with the surgeon may be required. Further details on lymph nodes are captured later in the dataset (see **Note 14 – LYMPH NODE STATUS**).

Orientation of the specimen is crucial given the prognostic importance of margin status and pathologic tumour stage in resected thymic epithelial tumours (TETs). Once the tumour is removed from the tumour bed, orientation becomes difficult. Furthermore, the fatty tissue can become easily disrupted. Therefore, orientation of the specimen ideally should be started in situ by the surgeon and areas of concern need to be clearly communicated to the pathologist. Orientating the specimen on a mediastinal board is encouraged

(Figure 1).[1] Anterior, posterior, right and left surfaces should be clearly distinguished (e.g. inked with different colours or with a detailed block key). Furthermore, the surgeon should mark areas of concern and also representative areas adjacent to the pericardium, the innominate (brachiocephalic) vein and superior vena cava (or mark these structures if resected) and right/left mediastinal pleural surfaces (if resected).

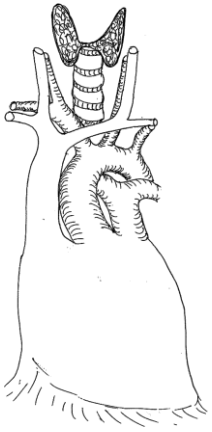

Figure 1: Mediastinal board that could be used to orient the specimen[1] [Plastic laminated sheets can be obtained from ITMIG upon request] (Reprinted from Detterbeck FC, Moran C, Huang J, Suster S, Walsh G, Kaiser L and Wick M (2011). Which way is up? Policies and procedures for surgeons and pathologists regarding resection specimens of thymic malignancy. J Thorac Oncol 6:S1730-1738 with permission from Elsevier)

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Note 4 - Specimen integrity[1,3] (Recommended)

Reason/Evidentiary Support

Although there are no studies specifically evaluating the prognosis of patients who underwent thymectomy where the capsule was disrupted intraoperatively or the lesion was resected in fragments, it is important to record these features because in these circumstances the pathologist cannot properly evaluate the presence of capsular invasion or completeness of resection. The latter are important prognostic features.

- 'Intact specimen' means that a TET is either completely surrounded by a fibrous capsule or is present in its entirety within the submitted specimen, without rupture of the tumour into surrounding tissues or on to the external surface of the specimen.
- 'Surface disrupted' means that a TET remains in one piece but shows rupture of the tumour onto the external surface of the specimen.
- A fragmented specimen is when a TET is submitted in piecemeal form that precludes satisfactory identification of margins.

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Note 5 - Macroscopic site of primary tumour (Recommended)

Reason/Evidentiary Support

TETs usually arise as a single nodule or mass in the thymus in the anterior mediastinum. However, cases of multiple, synchronous TETs have been described.[6-8] Although synchronous TETs generally occur in the thymus in the anterior mediastinum, these tumours can also occur at ectopic sites. Although rare, ectopic TETs have been described in the neck, posterior mediastinum, pretracheal fat, deep to phrenic nerves, posterior to innominate (brachiocephalic) vein, aortopulmonary window, aortocaval groove, anterior mediastinal fat, cardiophrenic fat and base of skull. Importantly, ectopic TETs should be distinguished from pleural or pericardial implants and metastases because the latter will up-stage the tumour. Many reported synchronous TETs differ in tumour subtype and stage. In addition, a case of synchronous thymoma and thymic carcinoid tumour has been reported in a patient with multiple neuroendocrine neoplasia type I.[9] Therefore, when synchronous TETs are identified, each tumour should be recorded, microscopically reviewed and staged.

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Note 6 - Maximum dimension of primary tumour (Recommended)

Reason/Evidentiary Support

A retrospective analysis of 5845 cases showed that size was not useful in predicting survival in relation to staging of TETs, so this is viewed as a recommended rather than as a required parameter.[3]

Identification of the primary tumour may be uncertain in cases with multiple foci and therefore the maximum dimension of the largest tumour should be recorded.

The maximum tumour size should still be recorded as the number of blocks sampled in a resected tumour is recommended to be 1 per centimetre of the maximum diameter. Inadequate sampling may lead to incorrect tumour classification.[10]

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Note 7 - Block identification key (Recommended)

Reason/Evidentiary Support

In general it is considered good practice to record the origin of tissue blocks from any surgical specimen. Specifically, the block identification key, together with the description of the macroscopic specimen and possibly photographic images of the gross specimen and/or the specimen in-situ, help the pathologist to determine margin status and extent of invasion of the tumour into adjacent structures such as great vessels, pleura, pericardium and lung. The macroscopic findings should be documented in the pathology report. Completeness of tumour resection and extent of tumour spread determine the pathological tumour stage and thereby prognosis, and also influence decisions about potential adjuvant therapy.

Therefore, a block identification key should be provided with a full description of the origin of each block. If the block is taken from a resection margin, the specific margin should be clearly indicated. The key should reflect whether the specimen was taken from the tumour near a specific structure or area (i.e., close to superior vena cava) and whether the tissue comes from the tumour itself, the surrounding thymic parenchyma or other sites such as mediastinal pleura, pericardium etc. Lymph nodes should be defined in the key based on location as this is potentially important for staging purposes.

If the block identification key is not recorded in the final report for logistical reasons, then it must be recorded somewhere within the specimen records to ensure the information is available if/when needed.

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Note 8 - Histological tumour type (Required and recommended)

Reason/Evidentiary Support

Tumours should be classified according to the WHO 2015 classification system for thymic tumours (see below).[11,12]

In cases of TETs showing more than one morphological subtype the following should be applied:

1) TETs showing more than one histological thymoma subtype: The diagnosis in such tumours should list all the histological WHO types, starting with the predominant component and then minor components. All should be quantified in 10% increments. This rule does not apply to AB thymoma which is a distinct entity (this should be documented as type AB 100%).[13,14]

2) TETs consisting of a thymic carcinoma component together with one or more thymoma component: Irrespective of the size/percentage of the thymic carcinoma component the diagnosis in such tumours should begin with the label "thymic carcinoma" (specifying the histological type and percentage) followed by the thymoma component(s) (quantified in 10% increments).[11,12]

3) TETs consisting of more than one thymic carcinoma component (with or without a thymoma component, and excluding thymic small cell carcinoma and thymic large cell neuroendocrine carcinoma, see below): the diagnosis in such tumours should begin with the predominant carcinoma; minor carcinoma components should be quantified next in 10% increments, eventually followed by the thymoma components.[11,12]

4) Heterogeneous thymic tumours with a small cell or large cell neuroendocrine carcinoma component: These tumours are labelled 'combined small cell carcinoma' or 'combined large cell neuroendocrine carcinoma'; the various components should be given and quantified in 10% increments.

WHO classification of tumours of the thymus[a,b]

Descriptor	ICD0 codes
Epithelial tumours	
Thymoma	
Type A thymoma, including atypical variant	8581/3*
Type AB thymoma	8582/3*
Type B1 thymoma	8583/3*
Type B2 thymoma	8584/3*
Type B3 thymoma	8585/3*
Micronodular thymoma with lymphoid stroma	8580/1*
Metaplastic thymoma	8580/3
Other rare thymomas	
Microscopic thymoma	8580/0
Sclerosing thymoma	8580/3
Lipofibroadenoma	9010/0*
Thymic carcinoma	
Squamous cell carcinoma	8070/3
Basaloid carcinoma	8123/3
Mucoepidermoid carcinoma	8430/3
Lymphoepithelioma-like carcinoma	8082/3
Clear cell carcinoma	8310/3
Sarcomatoid carcinoma	8033/3
Adenocarcinomas	
Papillary adenocarcinoma	8260/3
Thymic carcinoma with adenoid cystic carcinoma-like features	8200/3
Mucinous adenocarcinoma	8480/3
Adenocarcinoma, NOS	8140/3
NUT carcinoma	8023/3*
Undifferentiated carcinoma	8020/3
Other rare thymic carcinomas	
Adenosquamous carcinoma	8560/3
Hepatoid carcinoma	8576/3
Thymic carcinoma, NOS	8586/3
Thymic neuroendocrine tumours	
Carcinoid tumours	
Typical carcinoid	8240/3
Atypical carcinoid	8249/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Combined thymic carcinomas	

a The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. b The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions. * These new codes were approved by the IARC/WHO Committee for ICD-O.

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Note 9 - Extent of direct invasion (Required)

Reason/Evidentiary Support

The Masaoka-Koga staging system has been the most frequently used for staging,[13,14] with refinement of definitions for anatomic staging parameters proposed in 2011,[15] but this staging system will likely be superseded in the near future by proposals for a TNM-based classification by an International Association for the Study of Lung Cancer (IASLC), thymic domain, committee, based on data from the ITMIG retrospective database of over 8000 patients.[3,5] Both these systems are dependent on extent of direct local invasion. Use of an elastic stain is strongly recommended in assessing involvement of mediastinal structures in relation to elastic layers within mediastinal and visceral pleura, fibrous layer of the pericardium and the adventitia and media of the great vessels.

In relation to the proposed TNM-based staging system, the presence of capsular invasion was not prognostically significant in the ITMIG retrospective database study and tumours would therefore be staged as pT1, independent of whether the capsule is breached. Similar data were found in separate meta-analyses.[3,16] However, it remains part of Masaoka-Koga staging so pathologists need to record this parameter until/if the TNM staging system proposed by ITMIG & IASLC is approved, along with the extent of any capsular invasion in the context of Masaoka-Koga stages IIa and IIb. Invasion through the mediastinal pleura was also not found to be of prognostic significance although evidence from Japanese patients demonstrated that invasion of the mediastinal pleura was associated with the cumulative incidence of recurrence (CIR)[17] so this parameter remains part of the dataset, to be collected (a) for further review, although it is recognised that this anatomic margin may not be easily identifiable on histology,[3] and (b) in the context of the Masaoka-Koga staging system. Discussion with the surgeon may facilitate its identification in specimens.[1]

In order to maintain consistency in data collection, the following definitions, agreed by expert consensus, were proposed by an ITMIG-based group:

- Pericardial invasion - microscopic involvement of the pericardium (either partial in the fibrous layer or penetrating through the serosal layer);
- Visceral pleura/lung - microscopically confirmed direct penetration through the outer elastin layer of the visceral pleura with or without invasion into the lung parenchyma.

In relation to the great vessels, opinions differed between involvement being defined as tumour cells being present within the adventitia, media or lumen. The consensus opinion, in the context of great vessels, was that tumour cells present within the media is the preferred histological compartment through which to define involvement, as it is easily seen compared to the adventitia on an elastic stain, and its involvement is likely relevant to surgical management in terms of need for partial resection and repair. In a similar fashion, involvement of the phrenic nerve is defined as tumour cells being present within the perineurium. 'Other' should be used if tumours infiltrate structures such as myocardium, trachea, oesophagus or chest wall. Involvement of muscle layers is viewed as the most reproducible parameter through which to collect data on positive involvement.

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Note 10 - Separate extrathymic tumour nodules/metastases (Required)

Reason/Evidentiary Support

Separate extrathymic tumour nodules must be recorded as they form part of both the Masaoka-Koga and the ITMIG & IASLC-proposed TNM staging systems. These are divided into two groups: first, those nodules that are limited to the pericardium and/or pleura (sometimes referred to as pericardial and pleural seeding), which constitute stage IVa disease in Masaoka-Staging and pM1a in ITMIG & IASLC TNM staging, second, nodules that are either within the lung parenchyma or distant organs, which constitute stage IVb disease in Masaoka-Staging and pM1b in ITMIG & IASLC TNM staging.[1,4] The number of nodules in the pleura/pericardium should be recorded as there is some evidence that greater numbers portend an adverse prognosis.[18]

These synchronous metastatic foci will usually have the same morphology as the primary thymic neoplasm and need to be distinguished from the far rarer synchronous primary thymic epithelial tumours (see **Note 5 - MACROSCOPIC SITE OF PRIMARY TUMOUR**).[7,8]

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Note 11 - Response to neoadjuvant therapy (Recommended)

Reason/Evidentiary Support

There is no recommended or agreed system for tumour regression grading (TRG) in TETs. There are sparse reports documenting the effects of neoadjuvant chemotherapy on TETs[19] but there are no systematic studies on this subject. In other organ systems including carcinomas of the breast, stomach, oesophagus and colorectum, there is evidence that the response to neoadjuvant therapy provides prognostic information. Schemes for TRG for several of these organ systems have been published.[20] Steroid therapy may also affect morphology by eliminating lymphocytes although this is not viewed as part of neoadjuvant therapy.

In TETs, RECIST (Response Evaluation Criteria In Solid Tumours) parameters have been recorded as indicators of TRG. Histological features which have been assessed as TRG factors include decrease in number of viable cells,[21,22] fibrosis,[23] necrosis[24,25] and cystic change. Biological cell cycle markers (e.g. p53) were used in one study combined with viability according lung cancer parameters (25% increments).[22] However, few studies have systematically recorded TRG elements in a methodical fashion[19] and there are no studies which have correlated TRG with disease outcome. A scoring system for the degree of fibrosis, adapted from lung cancer TRG, has been applied to TETs[23] and it has been suggested that macroscopic evaluation with microscopic confirmation of the extent of necrosis should be recorded and that the viable tumour cell proportion should be recorded in 10% increments.[1,26] It should be noted that similar changes to those documented in neoadjuvant-treated TETs may be observed in non-treated thymomas (necrosis, cystic change) as degenerative features.[19]

It is recommended that the response to neoadjuvant treatment in TET be recorded with the following provisos:

1. TRG is performed on resection specimens
2. Resected specimens should be adequately sampled (at least 1 block per centimetre of maximum tumour diameter)
3. The amount of viable tissue should be assessed as a percentage of the tumour
4. TRG should be scored using a 3-tier system – refer to Table 4.

Table 1: Proposed 3-tiered TRG system

Score	Criterion	TRG
1	Mainly viable tumour with no or minimal regression-associated fibro-inflammatory and cystic change* limited to a few foci	No or minimal tumour response
2	Multifocal or diffuse regression associated fibro-inflammatory changes and cystic change*, with viable tumour ranging from diffuse sheets, streaks or nodules, to extensive regression with multifocal but easily identifiable residual tumour.	Partial tumour response
3	Mainly regression, with few irregularly scattered individual tumour cells or cell groups (all measuring less than 2 mm), or no residual tumour identified.	Complete or near-complete response

* Regression associated fibro-inflammatory changes: fibrosis associated with macrophages, including foam cells, mixed inflammatory cells and calcification.

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Note 12 - Coexistent pathology (Recommended)

Reason/Evidentiary Support

Thymectomy specimens from myasthenia gravis patients commonly demonstrate pathologic findings in the non-neoplastic thymus and the most common feature is thymic follicular hyperplasia. Thymic hyperplasia can be classified into three types: follicular, epithelial and true hyperplasia. Follicular hyperplasia is defined by the presence of B-cell follicles irrespective of the size or weight of the thymus. The standardised macroscopic and histopathological work-up of thymectomy specimens including the grading of thymic follicular hyperplasia has been reported by MGTX[a].[27,28] Epithelial hyperplasia (nodular epithelial hyperplasia, also called 'microscopic thymoma') is a thymic epithelial cell proliferation forming discrete microscopic islands and it is not infrequently observed in thymic tissue from myasthenia gravis patients.[29,30] It should be differentiated from 'microthymoma' which represents microscopic-sized true thymoma.[31] True thymic hyperplasia is an increase in volume of the thymus which maintains normal histology.[32] Because of wide variations of sizes and weights of the thymus in the normal population, true thymic hyperplasia is difficult to define except for extreme cases. The presence of thymic hyperplasia adjacent to a thymoma, irrespective of the type, has no known clinical significance.

Cystic changes can involve both thymic epithelial tumours and adjacent thymus.[33-37] The description of cystic changes, although not of prognostic significance, may be important for clinicopathological correlation.

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Note 13 - Margin status (Required)

Reason/Evidentiary Support

Complete resection has been repeatedly shown to be a prognostic parameter in thymomas and thymic carcinomas.[38-40] Therefore, the evaluation and recording of the margin status is important. To be able to assess the margins, orientation of the specimen is crucial. As discussed earlier (see **Note 5 MACROSCOPIC SITE OF PRIMARY TUMOUR**), once the tumour is removed from the tumour bed, orientation becomes difficult. Furthermore, the fatty tissue can become easily disrupted. Therefore, orientation of the specimen should ideally be started in situ by the surgeon and areas of concern need to be clearly communicated to the pathologist. Anterior, posterior, right and left surfaces should be clearly distinguished (e.g. inked with different colours or with a detailed block key). Furthermore, the surgeon should mark areas of concern and also representative areas adjacent to the pericardium, the large vessels (or mark these structures if resected) and right/left mediastinal pleural surfaces (if resected). If the resection specimen includes neighbouring organs such as lung, or large vessels, margins need to be evaluated on those organs as well.

R0 resection is defined as complete resection without macroscopic or microscopic involvement of the margin by the tumour. R1 (incomplete) resection indicates microscopic tumour at the resection margin. R2 (incomplete) resection is defined as macroscopic tumour present at the resection margin. If the specimen is disrupted at the time of gross evaluation and cannot be reconstructed, then the assessment of margins might not be possible.

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[a] Thymectomy and Myasthenia gravis multicentre, international clinical trial (MGTX)

Note 14 - Lymph node status (Required and recommended)

Reason/Evidentiary Support

Involvement of lymph nodes by TETs is an adverse prognostic factor.[4,41] Lymph node status should be recorded according to the recommended anatomic map in relation to the ITMIG & IASLC TNM system,[4,5] namely anterior (perithymic) nodes (zone 1) and deep intrathoracic or cervical nodes (zone 2), whilst any positive lymph node is viewed as stage IVb within the Masaoka-Koga system. As the location of lymph nodes found during the gross inspection of a thymectomy specimen may be problematic, either the specimen needs to be properly oriented by the surgeon, or labelled specifically within separate pots. Lymph nodes outside N1 and N2 are regarded as distant metastasis.[4]

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Note 15 - Immunohistochemical markers (Recommended)

Reason/Evidentiary Support

Immunohistochemical analysis of thymic resection specimens may be performed for several reasons:

1. To exclude or confirm the presence of a tumour of thymic epithelial origin[42]
2. To aid in subtyping of thymomas[43]
3. To establish the origin of a thymic carcinoma as either a primary thymic carcinoma or a metastasis

The differential diagnostic spectrum of thymoma is related to either its epithelial component or to the lymphoid component. The lymphoid component of "B-type" thymoma and of thymic follicular hyperplasia may raise the suspicion of non-Hodgkin lymphoma. Immunohistochemistry may be applied to type the lymphoid population [normally composed of immature, CD3/terminal deoxynucleotidyl transferase (TdT/CD1a/CD99+) lymphocytes], or to confirm the presence of an epithelial component, which may be highlighted by pan-cytokeratin and/or p63 stains. The epithelial component in thymic epithelial tumours with a sparse lymphoid component may raise the possibility of either a germ cell tumour or metastatic carcinoma.[42,44] Germ cell tumours may be diagnosed by appropriate immunohistochemical stains including SALL4, OCT4, CD117, CD30, D2-40, human chorionic gonadotropin (hCG), placental alkaline phosphatase (PLAP), carcinoembryonic antigen (CEA) and α-fetoprotein (AFP).[42]

Subtyping of thymomas is primarily based on histology; immunohistochemical stains (cytokeratin and/or p63) may be helpful in the evaluation of the density of the epithelial cells in B-type thymoma thus aiding the diagnosis of B1/2/3 thymoma. Similarly, cytokeratin stains may be used to confirm the epithelial nature of the spindle cells in type A, type AB and in metaplastic thymoma. Epithelial expression of CD20 is reported to be more frequent among type A and AB thymomas.[45] Neuroendocrine markers may be useful to rule out neuroendocrine tumours.[43]

Distinguishing thymoma (in particular type B3 thymoma) and thymic carcinoma may occasionally be problematic; there are no immunohistochemical markers that can reliably segregate these entities. However, CD5, CD117 and the recently described markers GLUT1 and MUC1 show a higher incidence of staining in thymic carcinoma (in particular, thymic squamous cell carcinoma) compared to thymoma.[46,47] Ki-67 labelling index in epithelial tumour cells of ≥13.5% has been suggestive of thymic carcinoma.[48]

The diagnosis of thymic carcinoma essentially involves the exclusion of metastasis; immunohistochemical analysis may support a diagnosis of thymic carcinoma but cannot establish the diagnosis with certainty. Expression of CD5, particularly in combination with CD117 positivity, lends some support to a diagnosis of thymic carcinoma. Several new markers (FoxN1 and CD205) may further support a diagnosis of thymic carcinoma. Other markers may be applied to rule out thymic carcinoma by confirming a non-thymic origin, such as TTF-1. However, given the great diversity in histological subtypes of thymic carcinoma, the specificity of markers routinely used to diagnose carcinoma of a particular origin may be considerably lower in this situation.[12]

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Note 16 – Molecular studies (Recommended)

Reason/Evidentiary Support

Molecular studies have not been applied routinely for the diagnosis of thymic epithelial tumours. A diagnosis of NUT carcinoma needs immunohistochemical confirmation[49,50] or molecular studies if immunohistochemistry is not available, and exploration of tumour-specific molecular markers is expected in the future. There have been a few reports of primary mediastinal synovial sarcoma confirmed by FISH.

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Note 17 – Staging for thymomas and thymic carcinomas – modified Masaoka (Required) and proposed TNM Pathologic Staging for Thymic Epithelial Tumours (Recommended)

Reason/Evidentiary Support

At least 15 different stage classification systems have been proposed, beginning as far back as 1978,[51] with most widely known being the Masaoka system,[13] modified and refined in 1994,[14] with refinement of definitions for anatomic staging parameters proposed in 2011.[15]

Although this remains the required staging system, it is highly likely that this system will be superseded by a TNM-based classification based on data from the ITMIG retrospective database of over 8000 patients.[5] In the newly-proposed system, T stage is based on the extent of direct invasion of mediastinal structures (see above section),[3] nodal disease is based on involvement of lymph nodes in anterior (perithymic) (N1) and deep/cervical (N2) compartments, and M stage based on the presence of separate pleural and pericardial nodules (M1a) and pulmonary intraparenchymal nodule or distant organ metastasis (M1b).[4] This system is currently viewed as recommended, although will likely become the recognized system in the near future.

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Table 2: ITMIG Definition of Details of the Masaoka-Koga Staging System

Stage Definition *(the ITMIG interpretation of details is in italics)*

I Grossly and microscopically completely encapsulated tumour
This includes tumours with invasion into but not through the capsule, or …
Tumours in which the capsule is missing but without invasion into surrounding tissues

II a Microscopic transcapsular invasion
M*icroscopic transcapsular invasion (not grossly appreciated)*

b Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium
Gross visual tumour extension into normal thymus or perithymic fat surrounding the thymoma (microscopically confirmed), or …
Adherence to pleura or pericardium making removal of these structures necessary during resection, with microscopic confirmation of perithymic invasion (but without microscopic extension into or through the mediastinal pleura or into the fibrous layer of the pericardium)

III Macroscopic invasion into neighbouring organ (i.e. pericardium, great vessel or lung)
This includes extension of the primary tumour to any of the following tissues:
Microscopic involvement of mediastinal pleura (either partial or penetrating the elastin layer); or …
Microscopic involvement of the pericardium (either partial in the fibrous layer or penetrating through to the serosal layer); or …
Microscopically confirmed direct penetration into the outer elastin layer of the visceral pleura or into the lung parenchyma; or …
Invasion into the phrenic or vagus nerves (microscopically confirmed, adherence alone is not sufficient); or …
Invasion into or penetration through major vascular structures (microscopically confirmed);
Adherence (i.e. fibrous attachment) of lung or adjacent organs only if there is mediastinal pleural or pericardial invasion (microscopically confirmed)

IV a Pleural or pericardial metastases
Microscopically confirmed nodules, separate from the primary tumour, involving the visceral or parietal pleural surfaces, or the pericardial or epicardial surfaces,

b Lymphogenous or hematogenous metastasis
Any nodal involvement (e.g. anterior mediastinal, intrathoracic, low/anterior cervical lymph nodes, any other extrathoracic lymph nodes)
Distant metastases (i.e. extrathoracic and outside the cervical perithymic region) or pulmonary parenchymal nodules (not a pleural implant)

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