Les tumeurs du thymus

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Liens d’intérêt

Je suis coordonateur adjoint du réseau RYTHMIC.

Je ne suis pas membre du comité de staging de l’IASLC.

Je ne suis pas membre du comité de publication de l’ITMIG.

Je suis consultant pour les laboratoires BMS, MSD, Novartis, Pfizer.
Tumeurs thymiques

2016
Tumeurs thymiques

- Incidence: 0,15-0,30/100 000 people
- 250 cases in France / year
BACKGROUND AND OBJECTIVE

TETs are rare malignancies with an overall incidence of 0.13 per 100,000 person-years. Given this, most of our knowledge is largely derived from small single-institution series.

RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a French network for TET created by INCa (French National Cancer Institute) with the objective of territorial coverage by regional expert centers, systematic discussion of patients at national tumor board and collection of nationwide data within a centralized database. OBJECTIVE: We reviewed our activity in 2016 to describe the epidemiology and main characteristics at diagnosis of Tumours thymiques in France.

PATIENTS AND METHODS

We prospectively collected all patients (pts) with new diagnosis of primary TET in France discussed at national or regional RYTHMIC tumor board from January to December 2016. Epidemiologic, clinical, pathologic and surgical data were prospectively collected within a centralized database.

Histologic sub-type was centrally reviewed according to the WHO classification and stage by modified Masaoka-Koga classification.

Fisher exact test was used for correlations.

RESULTS

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Patient's characteristics and treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=226 (%)</td>
<td></td>
</tr>
</tbody>
</table>

- **Age**
  - Median (range): 62 (25 – 86)
- **Gender**
  - Male: 129 (57)
  - Female: 97 (43)
- **Auto-immune disorder**
  - Myasthenia: 35
  - Thyroiditis: 2
  - Hypergammaglobulinemia: 2
  - Others: 4
- **Previous cancer**
  - Prostate: 34 (15)
  - Breast: 9
  - Melanoma: 7
  - Hematologic: 4
  - Other: 11
- **Mode of diagnosis**
  - Resection: 158 (70)
  - Surgical biopsy: 35 (15)
  - Imaging guided biopsy: 33 (15)

**Distribution of stage (Masaoka-Koga ITMIG modified) and histology (WHO 2004 classification).**

Significant correlations were found between histologic sub-type (Thymoma vs. Thymic carcinoma) and presence of an autoimmune disorder (p=0.01) and stage (II-I vs. III-IV; p=0.004); no significant correlations were seen with gender (p=0.27).

**Frequencies (%)**

- **Primary treatment**
  - Uptown Surgery: 170 (75)
  - Neo-adjuvant chemotherapy: 8 (3)
  - Chemotherapy: 40 (18)
  - Adjuvant radiotherapy: 55 (24)
  - Surgery Approach: 178 (100)
  - Sternotomy: 108 (61)
  - Videothoracoscopy: 37 (21)
  - Robot assisted: 15 (8)
  - Thoracotomy: 9 (4)
  - Other: 9 (4)
- **Chemotherapy**
  - CAP: 33 (63)
  - Carboplatin-paclitaxel: 16 (31)
  - Carboplatin-etoposide: 3 (6)

**A. Observed incidence of TET in France**

- *Based on INSEE (Institut National de la Statistique et des Etudes Économiques) population data registries according to gender for France 2016. B. Age-specific incidence of thymoma: observed values for thymoma incidence (per 100,000 person-years) plotted in function of age.

CONCLUSION

- The estimated incidence of TETs in France in 2016 is 0.34 per 100,000 persons, based on our activity. The inclusion in the RYTHMIC network is mandatory but is still based on physician's request. Although we might underestimate the incidence, it seems to be higher compared to other countries' registries. The high occurrence of previous cancer might underlie variations in environmental or genetic risk factors.
A. Observed incidence of TET in France (per 100,000-person-year) according to gender. *Based on INSEE (Institut National de la Statistique et des Etudes Economiques) population data registries according to gender for France 2015. B. Age-specific incidence of thymoma: observed values for thymoma incidence (per 100,000 person-years) plotted in function of age.
Tumeurs thymiques

Specificities

2016
Tumeurs thymiques

Specificities

- Thymic origin

2016
The thymus
Thymus

Cellule épithéliale médullaire

Cellule dendritique

Apoptose

Tolérance immunitaire

Aux antigènes du soi

Délétion clonale

Lymphocyte immature
Thymus

Lymphocyte immature
Thymus

Lymphocyte immature
Sélection positive des lymphocytes

Cellule épithéliale thymique

CORTEX

Lymphocyte immature

Tolérance immunitaire aux antigènes du soi
Sélection négative des lymphocytes

Cellule épithéliale thymique

MEDULLA

Lymphocyte immature

Sélection négative des lymphocytes

Lymphocyte immature

Apoptose

Cellule épithéliale thymique

Sélection négative des lymphocytes

Lymphocyte immature

Tolérance immunitaire aux antigènes du soi

Apoptose

Cellule épithéliale thymique

Sélection négative des lymphocytes

Lymphocyte immature

Apoptose

Cellule épithéliale thymique

Tolérance immunitaire Aux antigènes du soi

Sélection négative des lymphocytes

- Tolérance immunitaire
  - Aux antigènes du soi

Tumeurs thymiques

Specificities

- Thymic origin
- Complex histology
Histo-pathologic classification

- World Health Organization 2016

<table>
<thead>
<tr>
<th></th>
<th>Thymoma</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>“Médullary”</td>
<td>SCC</td>
</tr>
<tr>
<td>AB</td>
<td>Mixed</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>“Cortical”</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reproductibilité de la classification ?

• Reproductibilité imparfaite
  - Variabilité de la proportion de chaque type
  - Etude de reproductibilité inter-observateur: $k=0.45-0.49$

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Marchevsky et al. Cancer 2008; 112:2780
Reproductibilité de la classification ?

- Reproductibilité imparfaite

  - Hétérogénéité tumorale des thymomes de type A
Reproductibilité de la classification ?

• Reproductibilité imparfaite:
  - Formes combinées : 25% des cas?
  - Formes frontières
Genomic profiling of thymic epithelial tumors

- MSKCC, 45 patients
The 2016 WHO classification

ITMIG Consensus Statement on the Use of the WHO Histological Classification of Thymoma and Thymic Carcinoma: Refined Definitions, Histological Criteria, and Reporting

Alexander Marx, MD,* Philipp Ströbel, MD,*† Sunil S. Badve, MD,‡ Lara Chalabreysse, MD, John K.C. Chan, MD,∥ Gang Chen, MD, PhD,¶ Laurence de Leval, MD, PhD,# Frank Detterbeck, MD, Nicolas Girard, MD, PhD,†+ Jim Huang, MD,‡+ Michael O. Kurrer, MD,§§ Libero Lauriola, MD, Mirella Marino, MD,¶¶ Yoshihiro Matsuno, MD,### Thierry Jo Molina, MD, PhD,**** Kiyoshi Mukai, MD,††† Andrew G. Nicholson, MD,‡‡‡ Datsuke Nonaka, MD,§§§ Ralf Rieker, MD, Juan Rosai, MD,¶¶¶ Enrico Ruffini, MD,### and William D. Travis, MD****

(J Thorac Oncol. 2014;9: 596-112)
Actualisation de la classification histo-pathologique

### TABLE 1. Major and Minor Criteria of “Conventional” Type A Thymomas

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Type A Thymoma</th>
<th>Type AB Thymoma</th>
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<tbody>
<tr>
<td>Occurrence of rosettes and/or subcapsular cysts (to be distinguished from PVS)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Presence of focal glandular formations</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pericytomatous vascular pattern</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Paucity or absence of PVS contrasting with presence of abundant capillaries</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lack of Hassall’s corpuscles</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Complete or major encapsulation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Expression of CD20 in epithelial cells; absence of cortex-specific markers</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Paucity implies no (immature) lymphocyte-rich regions with dense, “impossible-to-count” TdT(+) lymphocytes; or at most 10% tumor regions with moderate (see text) immature lymphocyte counts (Fig. 2).

### TABLE 2. Major and Minor Histological Features Encountered in Type A and AB Thymomas

<table>
<thead>
<tr>
<th>Major criteria</th>
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<tr>
<td>Biphasic pattern at low magnification due to variable lymphocyte content</td>
<td>No</td>
<td>Common*</td>
</tr>
<tr>
<td>High epithelial cell content</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Spindled or oval epithelial cells</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Paucity or absence of TdT+ T cells</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Medullary islands</td>
<td>No</td>
<td>Rarely present*</td>
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<th>Minor criteria</th>
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<tr>
<td>Small lobular growth pattern</td>
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<td>Rare</td>
</tr>
<tr>
<td>Large lobular growth pattern</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Perivascular spaces</td>
<td>Rarely present</td>
<td>Rarely present</td>
</tr>
<tr>
<td>CD20 expression in epithelial cells</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Cortical marker expression</td>
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<td>Yes</td>
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*These features are minor criteria in type AB thymoma.

*Atypia in type AB thymoma has not been addressed so far.

*As defined in Table 1.

*Detection of medullary islands is usually clear-cut on hematoxylin–eosin staining but may require immunohistochemistry (IHC), particularly when Hassall’s corpuscles are missing.

*In lymphocyte-rich areas, usually with lack of Hassall’s corpuscles.

*Beta5t, PRSS16, and cathepsin V (detectable by IHC in epithelial cells within lymphocyte-rich areas).

(J Thorac Oncol. 2014;9: 596–611)
Actualisation de la classification histo-pathologique

### TABLE 1. Major and Minor Criteria of “Conventional” Type A Thymomas

**Major criteria**
- Spindled and/or oval-shaped tumor cells lacking nuclear atypia (see text)
- Paucity or absence of immature, TdT(+) thymocytes throughout the tumor

**Minor criteria**
- Occurrence of rosettes and/or subcapsular cysts (to be distinguished from PVS)
- Presence of focal glandular formations
- Pericytomaous vascular pattern
- Paucity or absence of PVS contrasting with presence of abundant capillaries
- Lack of Hassall’s corpuscles
- Complete or major encapsulation
- Expression of CD20 in epithelial cells; absence of cortex-specific markers

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*a These features are minor criteria in type AB thymoma.
*b Atypia in type AB thymoma has not been addressed so far.
*c As defined in Table 1.
*d Detection of medullary islands is usually clear-cut on hematoxylin-cosin staining but may require immunohistochemistry (IHC), particularly when Hassall’s corpuscles are missing.
*Beta5, PRSS16, and cathepsin V (detectable by IHC in epithelial cells within lymphocyte-rich areas).

(J Thorac Oncol. 2014;9: 596–611)
Actualisation de la classification histo-pathologique

<table>
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<tr>
<th>Major (indispensable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear-cut atypia of tumor epithelial cells with the severity typical of carcinoma</td>
</tr>
<tr>
<td>Exclusion of “thymoma with atypia and/or anaplasia” and of typical or atypical carcinoids</td>
</tr>
<tr>
<td>Exclusion of metastasis to the thymus and germ cell and mesenchymal tumors with epithelial features</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor (typical)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrative growth pattern</td>
</tr>
<tr>
<td>Small tumor cell nests within desmoplastic stroma</td>
</tr>
<tr>
<td>Absence of immature, TdT+ T cells (with rare exceptions)</td>
</tr>
<tr>
<td>Immunohistochemistry: epithelial expression of CD5, CD117; extensive expression of GLUT1, MUC1*</td>
</tr>
</tbody>
</table>

Features compatible* with the diagnosis of TC

- Invasion with pushing borders
- Occurrence of perivascular spaces
- Occurrence of “Hassall-like” epidermoid whorls and/or of myoid cells
- Occurrence of (usually rare) immature, TdT+ T cells

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*CD5, CD117, GLUT1, and MUC1 are expressed by many nonthymic cancers.

*Although most of these features are “organotypic,” that is, characteristic of thymoma, their presence does not exclude a diagnosis of TC if major diagnostic criteria of TC are fulfilled.

TC, thymic carcinoma.

(J Thorac Oncol. 2014;9: 596–611)
Intérêt de la double lecture anatomopathologique

Pathological Central Review of 290 Thymic Epithelial Tumors (TET): The French National Network RYTHMIC Experience

Molina T1, Bludgen ME2, Chaisbreyesse L3, De Montpréville V1, De Muret A1, Hofman V4, Lantuejoul S5, Parrens M6, Rouquette P2, Secq V3, Girard N7, Marx A1, Bassa B2
1Service d’anatomo-pathologie, AP-HP, Hôpital Universitaire Necker-Enfants-Malades, Université Paris Diderot, Sorbonne Paris Cité, France; 2Département de cancer médine, Gustave Roussy, Villejuif, France; 3Département de pathologie, Hôpital Louis-Pasteur, hôpital civil de Lyon, France; 4Service d’anatomo-pathologie, institut Francilien thoracique, Centre hospitalier Marcel-Lemesle, La Fleche-Robinson, France; 5Département de pathologie, CHU de Tours, France; 6Laboratoire de pathologie cellulaire et moléculaire, Hôpital Paul-Brousse, CHU de Nice, France; 7Département d’anatomo-病理ologie, CHU de Daxence, France; 8Département de pathologie, CHU de Bordeaux, France; 9Service d’anatomo-pathologie, CHU Pitié-Salpétrière, Paris, France; 10Département d’anatomo-pathologie, Hôpital Louis-Pasteur, hôpital civil de Lyon, Lyon, France; 11Institut de Pathologie, Université de Montpellier, Université de Montpellier, France; 12Cell and Molecular Pathology Laboratory, Virginia, USA.  

BACKGROUND

- RYTHMIC (Réseau tumours THYMiques et Cancer) is a nationwide network for TET appointed in 2012 by the French National Cancer Institute (INCa).
- The objective of the network are territorial covers by regional expert centers with systematic discussion of patients management at national tumor board and central pathologic review of all cases.
- RYTHMIC Tumor Board is based on initial histopathological diagnosis.

OBJECTIVE

- To evaluate the clinical impact of central pathological review of the cases discussed at clinical tumor board

PATIENTS AND METHODS

- Pathological central review of patients diagnosed with Thymoma (T) or Thymic carcinoma (TC) from January 2012 to December 2015 was made by a panel of 10 expert pathologist from the working group.
- Assessment of agreement or disagreement between the initial institutions and the panel review was made according the WHO 2004/2015 and new ITMIG proposals for histologic typing and staging.
- Discrepancies were classified as "minor" when they would have changed the therapy or management of patients according to the RYTHMIC guidelines.
- RYTHMIC Guidelines post-operative recommendations are based on histopathological subtype, Masatoa-Koga stage and resection status.

RESULTS

- Spectra from a total of 290 patients were reviewed: discrepancies were identified in 37.6% of the patients (n=109). Among them, 60% concerned histological diagnosis / subtype (n=65), 32% staging (n=35) and 8% both (n=23). The most frequent disagreement was the sub-diagnosis of stage III reflecting the underlying difficulty in particular / mediastinal pleura histological involvement recognition. (Figure 1)

CONCLUSION

The RYTHMIC experience confirms the relevance of an expert histopathological panel diagnosis of thymic malignancies for better decision-making, in particular concerning post-operative radiotherapy to avoid over- or under-treatment of the patients.
Intérêt de la double lecture anatomopathologique
Intérêt de la double lecture anatomopathologique
Tumeurs thymiques

Specificities

- Thymic origin
- Complex histology
- Auto-immunity
Sélection négative des lymphocytes

Cellule épithéliale thymique

Lymphocyte immature

Apoptose

Tolérance immunitaire Aux antigènes du soi

Les thymomes n’expriment pas AIRE

Expression de AIRE (ARNm) dans 20 thymomes (controle : thymus sain).

Ströbel et al. J Pathol 2007;211:563
Manifestations auto-immunes

Cellule épithéliale thymique tumorale

Lymphocyte immature

Auto-immunité

Pas d’apoptose

Apoptose

Délétion clonale


Cellule dendritique

Auto-immunité

Pas de délétion clonale

Pas d’apoptose
Auto-immune disorders

**Neuromuscular**
- Myasthenia gravis
- Peripheral neuropathy
- Polymyositis
- Dermatomyositis
- Encephalitis
- Optical myelitis

**Haematologic disorders**
- Red cell aplasia
- Pernicious anaemia
- Erythrocytosis
- Pancytopoenia
- Haemolytic anaemia
- Leukaemia
- Multiple myeloma

**Auto-immune disorders**
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Sjogren’s syndrome
- Scleroderma

**Endocrine disorders**
- Multiple endocrine neoplasia
- Cushing’s syndrome
- Thyrotoxicosis
- Pneumonitis

**Dermatologic disorders**
- Pemphigus
- Lichen planus
- Chronic mucosal candidiasis
- Alopecia areata

**Miscellaneous**
- Giant cell myocarditis
- Nephrotic syndrome
- Ulcerative colitis
- Hypertrophic osteoarthropathy
- Interstitial pneumonitis

**Immune deficiency disorders**
- Hypogammaglobulinaemia
- T-cell deficiency syndrome
Syndromes para-thymiques

- Bilan minimal recommandé en cas de suspicion de manifestations auto-immunes associées aux tumeurs thymiques

- Hémogramme avec taux de réticulocytes
- Electrophorèse des protéines sériques, avec dosage pondéral des immunoglobulines
- Dosage des anticorps anti-nucléaires
- Dosage des anticorps anti-récepteurs à l’acétylcholine (si positif, pas d’indication d’EMG)
- Dosage de la TSH

Prognosis of thymoma

• Causes of death:
Tumeurs thymiques

- Thymic origin
- Complex histology
- Auto-immunity
- Staging

2016
# Masaoka-Koga staging system

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Grossly and microscopically completely encapsulated tumor</td>
</tr>
<tr>
<td>IIa</td>
<td>Microscopic transcapsular invasion</td>
</tr>
<tr>
<td>b</td>
<td>Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium</td>
</tr>
<tr>
<td>III</td>
<td>Macroscopic invasion into neighboring organ (i.e., pericardium, great vessel, or lung)</td>
</tr>
<tr>
<td>IVa</td>
<td>Pleural or pericardial metastases</td>
</tr>
<tr>
<td>b</td>
<td>Lymphogenous or hematogenous metastasis</td>
</tr>
</tbody>
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Classification Masaoka-Koga-ITMIG

- Classification anatomo-clinique: pTNM
- Evaluabile après résection chirurgicale

**TABLE 1. Masaoka-Koga Staging System**

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**TABLE 2. ITMIG Definition of Details of the Masaoka-Koga Staging System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition (the ITMIG Interpretation of Details Is in Italic)</th>
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<tbody>
<tr>
<td>IIa</td>
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</tr>
<tr>
<td></td>
<td>Gross visual tumor extension into normal thymus or perithymic fat surrounding the thymoma (microscopically confirmed), or ...</td>
</tr>
</tbody>
</table>

This includes tumors with invasion into but not through the capsule, or ...

Tumors in which the capsule is missing but without invasion into surrounding tissues.

Stade I

Stage I

- Vessels
- Mediastinal fat
- Capsule absent but no invasion
- Separate nodule within capsule
- Direct intracapsular spread
- Tumor
- Lung
- Visceral pleura
- Mediastinal pleura
- Pericardium

Stade IIA

Stage IIA

Limited microscopic transcapsular invasion

Vessels

Mediastinal fat

Lung

Visceral pleura

Mediastinal pleura

Pericardium

Stade IIB

Localized gross invasion, limited to mediastinum

Stade IIB

More extensive invasion, but limited to mediastinal fat

Stage IIb

Tumor

Vessels

Mediastinal fat

Lung

Visceral pleura

Mediastinal pleura

Fibrous layer

Serosal layer

Pericardium

Stade III

Stage III

Direct mediastinal pleural involvement or partial pericardial or vessel invasion

Lung

Visceral pleura

Mediastinal pleura

Mediastinal fat

Tumor

Fibrous layer

Serosal layer

Pericardium

Stade III

Direct penetration through visceral pleura, pericardium, or vessels

Stage III

Vessels

Mediastinal fat

Tumor

Fibrous layer

Serosal layer

Pericardium

Lung

Visceral pleura

Mediastinal pleura

Stade IVA

Stage IVa

- Tumor of any size/infiltration
- Pleural nodules
- Vessels
- Mediastinal fat
- Pericardial nodules
- Fibrous layer
- Serosal layer
- Pericardium

Stade IVB

Stage IVb

Lymph node involvement

Nodules within lung parenchyma

Distant organ involvement

Tumor of any size/infiltration

Masaoka-Koga staging system

Surgical pathology staging

No clinical staging
Thymic epithelial tumors: stage and histology

WHO, 2016
Prognostic value of the Masaoka staging system

Regnard et al. J Thorac Cardiovasc Surg 1996; 112: 376
Tumeurs thymiques

Specificities
- Thymic origin
- Complex histology
- Auto-immunity
- Staging

2016
The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposal for an Evidence-Based Stage Classification System for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors

Frank C. Detterbeck, MD
John Crowley, PhD,†
Giuseppe Giaccone, MD
Marco Lucchi, MD,‡‡, M
Meinoshin Okumura, MD,||||

Masaoka-Koga: I, IIA, IIB, III

O. Asamura, MD,‡
S. A. Frazier, MD,||||
H. Kondo, MD,††
S. G. Nicholson, MD,||||

On behalf of the Staging Standards,‡‡‡
The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposal for an Evidence-Based Stage Classification System for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors

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Marco Lucchi, MD, ‡
Mino Meinoshin Okumura, MD
and Progno.

Masaoka-Koga: III
The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposal for an Evidence-Based Stage Classification System for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors

Masaoka-Koga: III
The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposal for an Evidence-Based Stage Classification System for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors.

Masaoka-Koga: IVA, IVB

Masaoka-Koga: IVB
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**Figure e1: Outcomes of all Patients by Proposed Stage Groups**

**Recurrence, R0**

**Overall Survival, R0**

**Overall Survival, any R**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Events/N</th>
<th>5-Year Estimate (CI)</th>
<th>10-Year Estimate (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>206258</td>
<td>91% (89.1, 92.3)</td>
<td>95% (93.5, 96.2)</td>
</tr>
<tr>
<td>II</td>
<td>22124</td>
<td>92% (90.3, 93.3)</td>
<td>94% (93, 95.4)</td>
</tr>
<tr>
<td>IIIa</td>
<td>142455</td>
<td>88% (86.3, 90.2)</td>
<td>92% (89.3, 95.1)</td>
</tr>
<tr>
<td>IIIb</td>
<td>3983</td>
<td>85% (83, 87.2)</td>
<td>90% (88, 92.7)</td>
</tr>
<tr>
<td>IVa</td>
<td>1169201</td>
<td>85% (83.3, 86.7)</td>
<td>90% (88.3, 92.3)</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

(J Thorac Oncol. 2014;9: S65–S72)
Prognosis of thymoma

• Causes of death:

A

- Post-Operative
- Autoimmune
- Myasthenia Gravis
- Unrelated
- Unknown

B

% of all Deaths

Masaoka Stage

I
II
III
IVa

Other
Thymoma

Huang et al. J Thorac Oncol 2010;5:2017
Stage, Histology, Other?

- The most significant prognostic factor in Tumeurs thymiques is the completion of surgical resection, whatever classification is used.
Treatment of Tumeurs thymiques

- First question is: resectable or not?

Thymic malignancy likely: All patients should be managed by a multidisciplinary team with experience in the management of thymoma

- Surgically resectable
  - Surgical resection (total thymectomy and complete excision of tumor)

- Locally advanced, unresectable
  - Tissue diagnosis with core needle biopsy or open biopsy (Biopsy should not violate the pleural space)

National Comprehensive Cancer Network Guidelines
Treatment of Tumeurs thymiques

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National Comprehensive Cancer Network Guidelines
Tumeurs thymiques

Specificities
- Thymic origin
- Complex histology
- Auto-immunity
- Staging

Resectable tumors

2016
Diagnostic différentiel

- Les tumeurs primitives du médiastin antérieur ont un aspect radiologique souvent similaire

  - Tératome
  - Maladie de Hodgkin
  - Tumeur germinale non séminomateuse
  - Thymome
Tumeurs médiastinales: signes cliniques

- **Absence de tabagisme:** 80% des tumeurs médiastinales
- **Age < 40 ans:** 50% des tumeurs médiastinales

<table>
<thead>
<tr>
<th>Suspected Tumor</th>
<th>Clinical Features at Presentation</th>
<th>Confirmatory Test(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Onset of Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NSGCT</strong></td>
<td>Pulmonary metastases common</td>
<td>↑↑ α-FP, ↑ β-HCG</td>
</tr>
<tr>
<td><strong>LB-NHL</strong></td>
<td>Pleural effusion, “B” symptoms, ↑↑ LDH</td>
<td>Needle biopsy of mass, bone marrow, pleural fluid cytology</td>
</tr>
<tr>
<td>Intermediate Onset of Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lymphoma (HD/MLC)</strong></td>
<td>Multiple enlarged nodes typical, “B” symptoms; ↑WBC, ↑ Alk φ</td>
<td>Multiple core biopsies or surgical biopsy</td>
</tr>
<tr>
<td><strong>Seminoma</strong></td>
<td>Homogeneous mass, pulmonary metastases common</td>
<td>FNAB</td>
</tr>
<tr>
<td>Asymptomatic or Prolonged Onset of Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thymoma</strong></td>
<td>Age &gt;30 years, paraneoplastic syndromes (myasthenia gravis)</td>
<td>Typically no biopsy needed</td>
</tr>
<tr>
<td><strong>Teratoma</strong></td>
<td>Various tissue components of mass; fat density, fat-fluid level</td>
<td>No biopsy needed</td>
</tr>
</tbody>
</table>

J Thorac Oncol 2014;9:S102
Tumeurs thymiques

Specificities
- Thymic origin
- Complex histology
- Auto-immunity
- Staging

Resectable tumors

2016
Nécessité d’une biopsie pré-thérapeutique

• La chirurgie est recommandée d’emblée pour certaines tumeurs du médiastin:
  - Tumeurs bénignes: tératomes
  - Tumeurs kystiques
  - Thymomes non invasifs/encapsulés/avec envahissement limité

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  - Tumeurs kystiques
  - Thymomes non invasifs/encapsulés/avec envahissement limité

• La chimiothérapie est une urgence en cas de tumeur germinale maligne:
  - si les marqueurs sont élevés: 14-35% of cases
    - α-foeto-protéine > 1000kUI/L
      - tumeur germinale non séminomateuse (sac vitellin)
    - β-human chorionic gonadotrophin >5000kUI/L
      - tumeur germinale non séminomateuse (choriocarcinome)
    - rare en cas de séminome

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  - tumeur germinale non séminomateuse (sac vitellin)
  - β-human chorionic gonadotrophin >5000kU/L (tumeur germinale non séminomateuse) (choriocarcinome)
  - rare en cas de séminome

Dans tous les autres cas
biopsie

Policies and Reporting Guidelines for Small Biopsy Specimens of Mediastinal Masses

Alberto Marchevsky, MD,* Alex Marx, MD,† Philipp Ströbel, MD,† Saul Suster, MD,‡ Federico Venuta, MD,§ Mirella Marino, MD,‖ Samuel Yousem, MD,¶ and Maureen Zakowski, MI

TABLE 6. Policies Regarding Surgical Incisional Biopsies of Mediastinal Lesions

Technical aspects when obtaining incisional biopsies
- Frozen section is useful to assess whether the tissue is representative
- Frozen section diagnoses should be interpreted cautiously
- Additional tissue not processed for frozen section should be obtained

Multiple biopsies are recommended because of frequent heterogeneity of mediastinal tumors

Biopsies that are deep rather than wide are suggested

Policies in interpretation and reporting of surgical incisional biopsies
- Interpretation should be correlated with clinical and radiologic findings
- Consultation with an experienced second pathologist is recommended whenever there is any diagnostic difficulty
- Immunostains may be helpful in addressing issues related to subtyping of thymic malignancies and differentiation from other mediastinal malignancies

(J Thorac Oncol. 2011;6: S1724–S1729)
Specificities

- Thymic origin
- Complex histology
- Auto-immunity
- Staging

Resectable tumors

Tumeurs thymiques

2016
Thymome ou hyperplasie thymique?

- **CT scan**: low-attenuation, symmetric and fatty pattern, maintaining the bi-pyramidal shape of the thymus

- **“Rebound” hyperplasia**:
  - stress: pneumonia, surgery, burns, corticoid treatment
  - chemotherapy:
    - 10-25% of cases, young adults, intensive treatment

- **Lymphoid hyperplasia**
  - autoimmune and inflammatory disorders
  - connective tissue diseases and vasculitis
  - myasthenia

Thymome ou hyperplasie thymique?

- ELCAP lung cancer screening study:
  - forme ovoïde et taille <3cm : hyperplasie

<table>
<thead>
<tr>
<th>Shape</th>
<th>Width (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.7–1.0</td>
</tr>
<tr>
<td>Ovoid</td>
<td>6</td>
</tr>
<tr>
<td>Arrowhead</td>
<td>0</td>
</tr>
<tr>
<td>Bi-lobed</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size Change</th>
<th>Width (cm)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0.7–1.0</td>
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<tr>
<td>Decreased</td>
<td>0</td>
</tr>
<tr>
<td>No change</td>
<td>1</td>
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<tr>
<td>Increased</td>
<td>2</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>3</strong></td>
</tr>
</tbody>
</table>

Henschke et al. Radiology 2006; 23:239:586
- Utilisation du PET-scan : corrélation avec classifications
Imagerie pré-thérapeutique

- Utilisation du PET-scan : hyperplasie vs. thymome vs. carcinome thymique

Hyperplasie thymique
Tumeurs thymiques

Specificities
- Thymic origin
- Complex histology
- Auto-immunity
- Staging

Resectable tumors

2016
Imagerie pré-thérapeutique

- Prédiction de l’invasivité par la tomodensitométrie: MD Anderson, 99 patients

**Preoperative Computed Tomography Findings Predict Surgical Resectability of Thymoma**

Sara A. Hayes, MD,† James Huang, MD,‡ Andrew J. Plodkowski,* Janine Katzen, MD,‡ Jinhong Zheng, MS,§ Chaya S. Moskowitz, PhD,§ and Michelle S. Ginsberg, MD*

**TABLE 5. Association of Preoperative Computed Tomography Features and Other Factors with Risk of Incomplete Surgical Resection**

<table>
<thead>
<tr>
<th></th>
<th>Complete Resection (n = 116)</th>
<th>Incomplete Resection (n = 23)</th>
<th>Univariate Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X(%)</td>
<td>X(%)</td>
<td>Fisher's Exact Test</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Degree of abutment of adjacent vessel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>97 (88%)</td>
<td>12 (52%)</td>
<td>&lt;0.001</td>
<td>1.002</td>
</tr>
<tr>
<td>50%</td>
<td>13 (12%)</td>
<td>11 (48%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of necrosis</td>
<td></td>
<td></td>
<td>0.001</td>
<td>1.012</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (10%)</td>
<td>9 (39%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>99 (90%)</td>
<td>14 (61%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contour</td>
<td></td>
<td></td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>66 (60%)</td>
<td>20 (87%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Round</td>
<td>44 (40%)</td>
<td>3 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of mediastinal vessels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37 (34%)</td>
<td>3 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>79 (72%)</td>
<td>20 (87%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltration of pretracheal fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31 (28%)</td>
<td>12 (52%)</td>
<td></td>
<td>0.048</td>
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<tr>
<td>No</td>
<td>79 (72%)</td>
<td>11 (48%)</td>
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Définition de la résécabilité

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Masaoka-Koga : I, IIA, IIB, III
Tumeurs thymiques

Specificities
- Thymic origin
- Complex histology
- Auto-immunity
- Staging

Resectable tumors
- Surgery
Surgery recommendations

- **Median sternotomy** is the standard approach
- Complete exploration of the pleural cavities

- **Complete thymectomy**, including tumor, normal thymus, and mediastinal fat
- *en bloc* resection of involved structures:
  - lung, vessels, pleural implants, phrenic nerves
  - surgical clips in areas of concern

- Mediastinal notes sampling/resection (stage III tumor/thymic carcinoma)
- Frozen section not recommended for margins assessment
Orientation and marking in the operative room

• Use of a mediastinal board
Minimally-invasive surgery?

Standard Terms, Definitions, and Policies for Minimally Invasive Resection of Thymoma

Alper Toker, MD,* Joshua Sonett, MD,† Marcin Zielinski, MD,‡ Federico Rea, MD,§ Victor Tomulescu, MD,‖ and Frank C. Detterbeck, MD¶

1. A minimally invasive resection of a thymic malignancy should involve no rib spreading or sternal cutting. The intent should be to perform a complete resection, and a significant portion should be done with visualization on a video monitor.

2. Resection should involve the thymoma, thymus, and mediastinal fat.

3. Dissection and visualization of innominate vein and both phrenic nerves should be done.

4. Conversion to open is required if oncologic principles are being compromised or violated: e.g., perforation of the capsule, incomplete resection, risk of a discontinuous (not en bloc) resection, or disruption of the tissues exposing the tumor.

5. The access incision for retrieval of the thymoma should be large enough to prevent specimen disruption.

6. Exploration of pleura should be done if the thymoma invades the mediastinal pleura.

7. Retrieval in the bag.

8. Examination of the removed specimen to assess for completeness of the resection is required.

9. Communication with pathologist about suspicious areas is essential. The issues are orientation of the specimen, marking of several routine areas both on the specimen and in the patient, and identification of areas of tissue disruption that were not “close” during the dissection.

Overall, the planned and or completed resection should not be diminished or compromised in any way to accomplish the resection in a minimally invasive manner. Opening should be considered standard expectation, and not a complication, if variation from the planned resection is encountered.
Tumeurs thymiques

Specificities

- Thymic origin
- Complex histology
- Auto-immunity
- Staging

Resectable tumors

- Surgery
- Postoperative radiotherapy

2016
Postoperative radiotherapy: SEER database

- Population: thymomas and thymic carcinomas
  - 1973-2005, 901 patients: 275 stage I, 626 stage II-III

...but no benefit after complete resection ($p=0.12$)

Postoperative radiotherapy: “meta-analysis”

• Inclusion criteria:
  - studies published from 1981 to 2008
  - surgery vs. surgery + radiotherapy
  - thymoma and thymic carcinoma
  - complete resection
  - stage II and III

• Results:
  - 13 studies, 542 patients
    - radiotherapy: 250 patients
    - no radiotherapy: 342 patients
  - OR=1.05 (0.63; 1.75-0.84) on recurrence rate

Postoperative radiotherapy: ITMIG database

Postoperative Radiation Therapy is Associated with Longer Overall Survival in Completely Resected Stage II and III Thymoma – An Analysis of the International Thymic Malignancies Interest Group (ITMIG) Retrospective Database

Andreas Rimner, MD*; Xiaopan Yao†, PhD; James Huang‡, MD; Alberto Antonicelli‡, MD; Usman Ahmad‡.
Tumeurs thymiques

Specificities
- Thymic origin
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- Staging

2016

Resectable tumors
- Surgery
- Postoperative radiotherapy
Recurrence rates

**ITMIG retrospective database**

Cumulative incidence of recurrences in Masaoka-Koga groups

<table>
<thead>
<tr>
<th></th>
<th>Events/n</th>
<th>10-year recurrence % (IC95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymomas (n = 7 005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I/II</td>
<td>121/3 097</td>
<td>8 (7-8)</td>
</tr>
<tr>
<td>Stage III</td>
<td>140/654</td>
<td>29 (27-31)</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>64/109</td>
<td>71 (34-100)</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>17/38</td>
<td>57 (24-90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thymic carcinomas (n = 977)</th>
<th>Events/n</th>
<th>10-year recurrence % (IC95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I/II</td>
<td>28/112</td>
<td>25 (22-29)</td>
</tr>
<tr>
<td>Stage III</td>
<td>68/143</td>
<td>59 (44-76)</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>19/26</td>
<td>76 (58-100)</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>20/37</td>
<td>54 (37-67)</td>
</tr>
</tbody>
</table>

Detterbeck et al. WCLC 2013, abstr. MS16.2
**Recurrence by WHO Histology, R0, stage I,II**

Population: All R0 stage I,II pts with recurrence outcome and WHO subtype information

Weiss et al. ITMIG 2014

Recurrence by WHO Histology, R0, stage I,II

- TC (N=78)
- A (N=191)
- AB (N=475)
- B1 (N=286)
- B2 (N=328)
- B3 (N=193)

P < 0.006 for TC vs any WHO type

P = NS

P < 0.01
Failure Patterns Relative to Radiation Treatment Fields for Stage II–IV Thymoma

Andreas Rimner, MD,* Daniel R. Gomez, MD,# Abraham J. Wu, MD,* Weiji Shi, MS,¶ Ellen D. Yorke, PhD,‖ Andre L. Moreira, MD,§ David Rice, MD,** Ritsuko Komaki, MD,# Kenneth E. Rosenzweig, MD,†† Gregory J. Riely, MD,‡ and James Huang, MD,†

(J Thorac Oncol. 2014;9: 403–409)
Tumeurs thymiques

Specificities
- Thymic origin
- Complex histology
- Auto-immunity
- Staging

Resectable tumors
- Surgery
- Postoperative radiotherapy

2016
Recommandations RYTHMIC
ESMO Clinical Practice Guidelines

Recommandations RYTHMIC
ESMO Clinical Practice Guidelines

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ESMO Clinical Practice Guidelines

Recommandations RYTHMIC ESMO Clinical Practice Guidelines
Postoperative radiotherapy (PORT) in thymic epithelial tumors (TET): Consistency with guidelines, implementation of multi-disciplinary tumor board decisions, and assessment of quality criteria

Insights from the RYTHMIC prospective cohort

Clémence BASSE1, Sébastien THUREAU1, Suzanna BOTA1, Eric DANSIN2, Pascal-Alexandre THOMAS3, Eric PICHON3, Hervé LENA4, Carole MASSABEAU4, Christelle CLEMENT-DUCHENE4, Gilbert MASSARD4, Virginie WESTEEL4, François THILLAYS5, Xavier QUANTIN6, Youssef OULXHOUIR7, Serge DANHIER8, Delphine LEROUGE9, Luc THIBERVILLE2, Benjamin BESSE10, Nicolas GIRARD16

1 Centre Henri Becquerel, Rouen; 2 University Hospital, Rouen; 3 Centre Oscar Lambret, Lille; 4 University Hospital, Marseille; 5 University Hospital, Tours; 6 University Hospital, Aix-en-Provence; 7 University Cancer Institute, Toulouse; 8 Centre Alexis Vautrin, Nancy; 9 University Hospital, Strasbourg; 10 University Hospital, Besançon; 11 Cancer Center, Nantes; 12 University Hospital, Montpellier; 13 University Hospital, Caen; 14 Centre François Baclesse, Caen; 15 Institut Gustave Roussy, Villejuif; 16 Hôpitaux Civils de Lyon, Lyon, France

INTRODUCTION
- TET are rare intrathoracic malignancies.
- Surgery is central in the management of TET.
- Current practice for PORT is highly variable, and there is paucity of prospective, multicentre evidence.

- RYTHMIC is the nationwide network for TET in France, established in 2012. A database prospectively collects data for all patients discussed at a national multidisciplinary tumor board (MTB).
- Decision-making is based on guidelines that are similar to the European Society for Medical Oncology Clinical Practice Guidelines (Girard et al. Ann Oncol 2015;26:v40).
- Whether PORT should be delivered was the most frequent question raised at the RYTHMIC MTB.

OBJECTIVES
- To assess whether decisions of PORT made at the MTB were consistent with RYTHMIC guidelines.
- To assess whether decisions of PORT made at the MTB were actually implemented.
- To assess whether ITMIG standard quality criteria for PORT were ultimately fulfilled.

METHODS
- All consecutive patients for whom PORT was discussed at the RYTHMIC MTB from 2012 to 2015 were identified from the RYTHMIC prospective database.
- Analysis of patients medical records and follow-up was conducted.

RESULTS

Population demographics
- 274 patients were included.
- 243 (89%) patients had thymomas, and 31 (11%) had thymic carcinomas; 81% of cases had a complete resection.
- 78 (28%) cases were stage I, 115 (42%) stage II, 48 (18%) stage III, and 33 (12%) stage IV, according to the Masaoka-Koga system.

Were decisions of PORT made at the RYTHMIC MTB consistent with guidelines?
- PORT was recommended by the RYTHMIC MTB for 117 (43%) patients, and not recommended for 157 (57%) patients.

- Excluding stage IV cases, decisions of PORT were consistent with guidelines for 92% of patients (Table 1, Figure 1).

- Most inconsistencies consisted of abstention related to poor general condition (10 patients); 5 patients - 2 patients with type B2, stage IIA thymomas, and 3 patients with type AB, stage IIB thymomas - were recommended for PORT in the setting of "grey zones" of guidelines.

Table 1: Consistency of MTB decisions with RYTHMIC guidelines

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<tr>
<th></th>
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<tr>
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<td></td>
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<tr>
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<td>241</td>
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Figure 1: Histology, stage, and resection status of 84 patients for whom PORT was recommended by the RYTHMIC MTB in accordance with guidelines.

Were decisions of PORT made at the MTB actually implemented? Were ITMIG standard quality criteria ultimately fulfilled?
- The decision of delivering PORT which was made the MTB, was actually implemented in 86% of cases.
- The non delivery of PORT despite the MTB decision was mostly due to delays related to prolonged recovery time after surgery.
- ITMIG quality criteria for PORT were ultimately fulfilled in 96% of patients.

CONCLUSIONS
- Our data provide a unique insight into the decision-making process for PORT in TET, highlighting the need for a systematic discussion at an expert MTB, while stressing the value of currently available guidelines, and the relevance of ITMIG quality criteria.
Tumeurs thymiques

Specificities
- Thymic origin
- Complex histology
- Auto-immunity
- Staging

Resectable tumors
- Surgery
- Postoperative radiotherapy

Unresectable tumors

2016
Tumeur thymiques localement avancée

• Critères d’inclusion dans les essais en cours

- Diamètre supérieur à **8 cm**

- Diamètre compris entre 5 et 8 cm, avec l’un des critères suivants:
  - calcification multifocale
  - apparence hétérogène
  - bords irréguliers
  - invasion ou engainement vasculaire

- Diamètre inférieur à 5 cm et invasion ou engainement vasculaire

NCT00387868 (PI: R. Korst)
Définition de la non-résécabilité?

The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposal for an Evidence-Based Stage Classification System for the Forthcoming (8th) Edition of the TNM Classification

Frank C. Detterbeck, MD
John Crowley, PhD,† Conrad
Giuseppe Giaccone, MD,
Marco Lucchi, MD,‡‡, Mirella
Meinoshin Okumura, MD,#
and Prognostic
and/or

Masaoka-Koga : III

(J Thorac Oncol. 2014;9: S65–S72)
Tumeurs thymiques

Specificités
- Origine thymique
- Histologie complexe
- Auto-immunité
- Staging

2016

Tumeurs thymiques résécables
- Chirurgie
- Radiothérapie postopératoire

Tumeurs thymiques non résécables
- Chemothérapie primaire
Locally-advanced tumors: multimodal treatment

Localized tumor → Chemotherapy → Re-evaluate for surgery

- Resectable → Surgical resection of primary tumor and isolated metastases
- Unresectable → RT ± chemotherapy

National Comprehensive Cancer Network Guidelines
## Pre-operative chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Chemotherapy Regimen</th>
<th>No. of Patients</th>
<th>Tumor Type</th>
<th>Tumor Stage</th>
<th>Design</th>
<th>Response Rate (%)</th>
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Response rate 80%
### Chimiothérapie pré-opératoire

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<th>Stage</th>
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</tr>
</tbody>
</table>

*En pratique:* CAP

2 + 2 cycles

Girard N. ASCO 2012 Educational Book
Park et al. J Thorac Oncol 2013;8:959
RYTHMIC: Chimiothérapie d’induction

Proposed regimens
- CAP: 65%
- Carboplatin, Paclitaxel: 16%
- Etoposide: 3%
- Other/Unknown: 9%
- VIP, PE: 3%, 4%

n=149

Administered regimens
- CAP: 76%
- Etoposide +/- Platin: 8%
- Others: 6%

n=91

RYTHMIC: Chimiothérapie d’induction

Administered regimens
n=91

- CAP 76%
- Etoposide +/- Platin 8%
- Paclitaxel +/-... 6%
- Others 6%

RYTHMIC: Chimoiothérapie d’induction

Administered regimens
n=91

- CAP 76%
- Paclitaxel 8%
- Etoposide +/- Platin 6%
- Others 6%

Tumor response

- Progression 2%
- Stable 17%
- Partial response 42%
- Complete response 77%
Administered regimens
n=91

Etoposide +/- Platin 8%

Paclitaxel 76%

Others 6%

Primary Exclusive Recurrence 1
Recurrence 2
Recurrence 3
Recurrence 4

Tumor response

Median: 20.7 months

Recurrence-free survival

RYTHMIC: Chimiothérapie d’induction

Tumeurs thymiques

Specificités
- Origine thymique
- Histologie complexe
- Auto-immunité
- Staging

2016

Tumeurs thymiques réséctables
- Chirurgie
- Radiothérapie postopératoire

Tumeurs thymiques non réséctables
- Chimiothérapie primaire
- Chirurgie
Treatment of thymic tumors

- Locally advanced tumors: primary chemotherapy

National Comprehensive Cancer Network Guidelines
### Pre-operative chemotherapy

#### Complete resection rate (14-78%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Chemotherapy Regimen</th>
<th>No. of Patients</th>
<th>Tumor Type</th>
<th>Tumor Stage</th>
<th>Any Surgery</th>
<th>Complete Resection</th>
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<td>Girard N. Eur Respir Rev 2013;22:75</td>
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Pleuropneumonectomy for the Treatment of Masaoka Stage IVA Thymoma

Cameron D. Wright, MD
Division of Thoracic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Background. The treatment of locally advanced Masaoka stage IVA thymoma is not standardized and is problematic.

Methods. A single-institution retrospective study was made of 5 patients with World Health Organization B3 thymomas who underwent pleuropneumonectomy for locally advanced thymoma. Two patients had recurrent thymoma and 3 presented de novo with stage IVA disease. Patients had a variety of induction and adjuvant treatments.

Results. There was no operative mortality, and only 1 patient had a major complication. Several patients had relatively prolonged disease-free survival. The median survival was 86 months, and the Kaplan-Meier survival was 75% (95% confidence interval: 53% to 97%) at 5 years and 50% (95% confidence interval: 25% to 75%) at 10 years.

Conclusions. Pleuropneumonectomy can be performed safely in patients with advanced thymomas and may improve survival. Highly selected patients might be cured with this approach if a complete resection is performed. While the optimal multimodality strategy for these patients is unknown, induction chemotherapy followed by resection then chemoradiotherapy seems promising.

(Ann Thorac Surg 2006;82:1234–9) © 2006 by The Society of Thoracic Surgeons
Pleural chemo-hyperthermia

Resection and heated pleural chemoperfusion in patients with thymic epithelial malignant disease and pleural spread: A single-institution experience

Alon Yellin, MD, David A. Simansky, MD, Ronny Ben-Avi, MD, Marina Perelman, MD, Nona Zeitlin, MD, Yael Refaely, MD, and Alon Ben-Nun, MD

Objective: Our objective was to evaluate whether resection and heated pleural chemoperfusion (HPCP) is an effective treatment for de novo stage IVa thymoma (DNT) and thymic carcinoma (TC) and for thymoma with pleural relapse (TPR).

<table>
<thead>
<tr>
<th>TABLE 2. Surgical and perfusion data (n = 41)</th>
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<tr>
<td>DNT (n = 17)</td>
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<tr>
<td>Maximum procedure</td>
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<tr>
<td>Local resection</td>
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<tr>
<td>Pleurectomy</td>
</tr>
<tr>
<td>Wedge/lobectomy</td>
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<tr>
<td>Chest wall</td>
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<tr>
<td>Diaphragm</td>
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<tr>
<td>Pleuropneumonectomy</td>
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<td>Atrium</td>
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<td>Perfusion volume</td>
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<td>Cisplatinum 100 mg/m²</td>
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<td>Doxorubicin</td>
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<td>Perfusion temperature</td>
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<td>≤41.8°C</td>
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<tr>
<td>&gt;41.8°C</td>
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DNT: De novo stage IVa thymoma; TPR, thymoma with pleural relapse; TC, thymic carcinoma.
Tumeurs thymiques

**Specificités**
- Origine thymique
- Histologie complexe
- Auto-immunité
- Staging

**Tumeurs thymiques resectables**
- Chirurgie
- Radiothérapie postopératoire

**Tumeurs thymiques unresectables**
- Chimiothérapie primaire
- Chirurgie
- Traitement postopératoire
Tumeurs thymiques

Specificités
- Origine thymique
- Histologie complexe
- Auto-immunité
- Staging

2016

Tumeurs thymiques resectables
- Chirurgie
- Radiothérapie postopératoire

Tumeurs thymiques non resectables
- Chimiothérapie en première intention
- Chirurgie
- Radiothérapie définitive
Treatment of thymic tumors

• Locally advanced tumors: primary chemotherapy
Chimio-radiothérapie exclusive

<table>
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<th>No. of Patients</th>
<th>Tumor Type</th>
<th>Stage</th>
<th>Any Surgery</th>
<th>Complete Resection</th>
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<td>Rea et al 1993</td>
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</table>

Girard N. Eur Respir Rev 2013;22:75

20-30% of patients
Definitive chemo-radiotherapy for thymomas

- Limited data in the literature...no consensus

- **Sequential approach:**
  - 23 patients, stage III-IV unresectable thymoma
  - induction with CAP (4 cycles), then radiotherapy
  - 5-year PFS: 54%
  - 5-year OS: 53%

- **Concurrent approach:**

Stades localement avancés: chimio-radiothérapie

En pratique:

Réponse partielle: radiothérapie séquentielle

Progression/stabilisation (B2-B3): radio-chimiothérapie concomitante
Tumeurs thymiques

Specificités
- Thymic origin
- Complex histology
- Auto-immunity
- Staging

2016

Resectable tumors
- Surgery
- Postoperative radiotherapy

Unresectable tumors
- Primary chemotherapy
- Surgery
  - postoperative treatment
  - Definitive radiotherapy

Metastatic tumors
- First-line chemotherapy
Palliative-intent chemotherapy

Thymoma or thymic carcinoma:
All patients should be managed by a multidisciplinary team with experience in the management of thymoma and thymic carcinoma.

Locally advanced

- Chemotherapy
- Re-evaluate for surgery

Resectablea,b
- Surgical resection of primary tumor and isolated metastases

Unresectablea
- RTd ± chemotherapy e

Isolated solitary metastasis
- Chemotherapy e or Surgeryb
- Consider chemotherapy e or RTd

Evidence of distant metastases
- Chemotherapy e
Palliative-intent chemotherapy regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Period of Accrual (years)</th>
<th>Tumor Type</th>
<th>Design</th>
<th>Regimen</th>
<th>Agents</th>
<th>Doses</th>
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<td>Cisplatin</td>
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<td>Etoposide</td>
<td>120 mg/m² × 3/3 weeks</td>
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<td>Etoposide</td>
<td>75 mg/m² × 4 days/3 weeks</td>
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<td>Ifosfamide</td>
<td>1.2 g/m² × 4 days/3 weeks</td>
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<td>Cisplatin</td>
<td>20 mg/m² × 4 days/3 weeks</td>
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<td>16</td>
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<td>PE</td>
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<td>Cisplatin-Irinotecan</td>
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<td>80 mg/m²/4 weeks</td>
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Girard N. ASCO 2012 Educational Book
### Palliative-intent chemotherapy regimens

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<tr>
<th>Study</th>
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<td>Cisplatin</td>
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<td>46</td>
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<td>27</td>
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<td>T/TC</td>
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<td>Pemetrexed</td>
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</table>

**Anthracyclin-based**  
- Response: 70-80%

**Non-anthracyclin-based**  
- Response: 30-50%

---

Girard N. ASCO 2012 Educational Book
Carboplatine-Paclitaxel

- Reproducible results
- A new standard for thymic carcinomas?
- Do we need a trial of platine-paclitaxel vs. CAP?
### Stades avancés ou métastatiques

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Period of Accrual (years)</th>
<th>Tumor Type</th>
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<td>T/TC</td>
<td>Phase II</td>
<td>Cisplatin</td>
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<td>12 &amp;</td>
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</tr>
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</table>

#### En pratique

**Première ligne: CAP**

**Carboplatine-Paclitaxel**

**4-6 cycles**
Corticosteroids and thymomas

• Depletion of the lymphocytic population
  - “thymolytic effect”

• Steroid receptors in 83% of thymomas

• Tumor responses reported in type B thymomas
  - 18 cases, mixed thymoma: 10 partial responses, 4 complete responses
    - response may be prolonged > 12 months
    - re-response may be prolonged

• Specificities:
  - opportunistic infections
  - increased risk of myasthenic crisis

Mimae et al. Cancer 2011;117:4396
RYTHMIC: Exclusive (first-line) chemotherapy

Proposed regimens
- CAP: 35%
- Carboplatin: 32%
- Paclitaxel: 11%
- Other/Unknown: 11%
- PE: 19%
- VIP: 3%

Administered regimens
- CAP: 66%
- Etoposide +/- Platin: 12%
- Paclitaxel + Carboplatin: 20%
- Others: 2%

n=37
n=41
Administered regimens
n=41

RYTHMIC: Exclusive (first-line) chemotherapy
RYTHMIC: Exclusive (first-line) chemotherapy

Administered regimens
n=41

- CAP 66%
- Paclitaxel + Carboplatin 20%
- Etoposide +/- Platin 12%
- Others 2%

Tumor response

- Progression: 36%
- Stable: 36%
- Partial response: 28%
- Complete response: 7%

Exclusive
RYTHMIC: Exclusive (first-line) chemotherapy

Administered regimens
- CAP: 66%
- Paclitaxel + Carboplatin: 20%
- Etoposide +/- Platin: 12%
- Others: 2%

n=41

Tumor response:
- Complete response: 36%
- Partial response: 28%
- Stable: 28%
- Progression: 31%

Progression-free survival:
Median: 6.2 months
Tumeurs thymiques

Specificités
- Origine thymique
- Histologie complexe
- Auto-immunité
- Staging

2016

Resectable tumeurs
- Chirurgie
- Radiothérapie postopératoire

Unresectable tumeurs
- Chimiothérapie première ligne
- Chirurgie
- Traitement postopératoire
- Radiothérapie définitive

Metastatic tumeurs
- Chimiothérapie première ligne
- Récurrences :
  - Chimiothérapie deuxième ligne
Failure Patterns Relative to Radiation Treatment Fields for Stage II–IV Thymoma

Andreas Rimner, MD, * Daniel R. Gomez, MD, # Abraham J. Wu, MD, * Weiji Shi, MS, † Ellen D. Yorke, PhD, ‡ Andre L. Moreira, MD, § David Rice, MD, ** Ritsuko Komaki, MD, # Kenneth E. Rosenzweig, MD, † † Gregory J. Riely, MD, † † and James Huang, MD, †

(J Thorac Oncol. 2014;9: 403–409)
### Surgery for recurrences

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Total</th>
<th>Recurrence (%)</th>
<th>Site</th>
<th>Surgery</th>
<th>Complete Res.</th>
<th>Mean Time to Recurrence</th>
<th>Survival (Years)</th>
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<tr>
<td>Haniuda (2001)</td>
<td>126</td>
<td>24 (19%)</td>
<td>22 PI, 6 Loc, 5 Dis</td>
<td>15/24</td>
<td>4/15 (27%)</td>
<td>68</td>
<td>47% (5 y), 35% (10 y)</td>
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<tr>
<td>Ruffini (1997)</td>
<td>266</td>
<td>30 (11%)</td>
<td>13 PI, 11 Loc, 4 Dis</td>
<td>16/30</td>
<td>10/16 (62%)</td>
<td>86</td>
<td>48% (5 y), 24% (10 y)</td>
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<tr>
<td>Regnard (1997)</td>
<td>285</td>
<td>28 (10%)</td>
<td>15 PI, 8 Loc, 5 Dis</td>
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<td>19/28 (68%)</td>
<td>88</td>
<td>51% (5 y), 43% (10 y)</td>
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<td>Ciccone (2005)</td>
<td>211</td>
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<td>8 PI, 2 Loc, 6 Dis</td>
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<td>N.S.</td>
<td>64% (5 y), 44% (10 y)</td>
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<td>Wright (2005)</td>
<td>179</td>
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<td>N.S.</td>
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<td>Blumberg (1995)</td>
<td>86</td>
<td>25 (29%)</td>
<td>1 PI, 17 Loc, 7 Dis</td>
<td>13/25</td>
<td>N.S.</td>
<td>48</td>
<td>65% (5 y)</td>
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Surgical Management of Recurrent Thymic Epithelial Tumors

A Retrospective Analysis Based on the Japanese Nationwide Database

Tetsuya Mizuno, MD,* Meinoshin Okumura, MD,† Hisao Asamura, MD,‡ Kazuo Yoshida, MD,§ Hiroshi Niwa, MD,¶ Kazuya Kondo, MD,‖ Hirotsoshi Horio, MD,¶ Akihide Matsumura, MD,∗∗ and Kohei Yokoi, MD,* for the Japanese Association for Research on the Thymus

FIGURE 2.  A, Overall survival after recurrence among the patients with recurrent thymic epithelial tumors, (B) thymic epithelial tumors treated with complete resection of the primary tumor, and (C) thymic epithelial tumors treated with incomplete resection of the primary tumor according to the treatment for recurrence. Pts, patients.
Surgery for recurrences

\[ p = 0.014 \]
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<td>Retrospec</td>
<td>Ifosfamide</td>
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<td>Fornasiero et al 1990(^{30})</td>
<td>32</td>
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<td>T</td>
<td>Retrospec</td>
<td>ADOC</td>
<td>Doxorubicin, Cisplatin, Vincristin, Cyclophosphamide</td>
<td>40 mg/m(^2)/3 weeks, 50 mg/m(^2)/3 weeks, 0.6 mg/m(^2)/3 weeks</td>
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<td>T/TC</td>
<td>Phase II</td>
<td>CAP</td>
<td>Cisplatin, Doxorubicin, Cyclophosphamide</td>
<td>50 mg/m(^2)/3 weeks, 50 mg/m(^2)/3 weeks, 700 mg/m(^2)/3 weeks</td>
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<tr>
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<td>T</td>
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<td>Phase II</td>
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<td>Carboplatin</td>
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<td>CAP-GEM</td>
<td>Capecitabine, Gemcitabine</td>
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<td>TC</td>
<td>Retrospec</td>
<td>Cisplatin-Irinotecan</td>
<td>Cisplatin, Irinotecan</td>
<td>80 mg/m(^2)/4 weeks, 60 mg/m(^2)/3 days/4 weeks</td>
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</table>
Second-line treatment of Tumeurs thymiques

Thymoma

Thymic carcinoma

PFS (months)

Thymoma

Thymic carcinoma

Pemetrexed
CAP-GEM
Sunitinib
Octreotide
Everolimus
Amrubicine

Pemetrexed
CAP-GEM
SUNITINIB
Octreotide
Everolimus
Amrubicine

Progression
Stable disease
Objective response
Seconde ligne et plus

En pratique:

Carbo-Px, PE, Pemetrexed

re-administration du CAP

(PS=0/1, réponse antérieure, rechute tardive; max. 8 cycles)
RYTHMIC: Systemic treatments for recurrence

Chemotherapy
- Carboplatin: 38%
- Paclitaxel: 6%
- Etoposide: 16%
- CAP: 12%
- PE: 11%
- Other: 7%
- Iriamycin: 2%
- Capecitabine: 4%
- Gemcitabine: 4%
- Pemetrexed: 4%
- Adriamycin: 2%
- Capecitabine: 4%
- Gemcitabine: 4%
- Pemetrexed: 4%
- Other: 7%

n=114

Proposed regimens
- Sunitinib: 47%
- Sorafenib: 3%
- Bevacizumab: 15%
- Everolimus: 11%
- Milciclib*: 8%
- Lucitanib*: 4%
- Somatostatine: 12%

n=67
**RYTHMIC: Systemic treatments for recurrence**

Administered regimens

- **First recurrence**
  - Paclitaxel +/- Carboplatin in 44%
  - Etoposide 12%
  - Etoposide +/- Platinum 16%
  - Sunitinib/Lu etc 13%
  - CAP 4%
  - Milciclib 3%
  - Others 6%

  - **n=79**

- **Recurrence 2**
  - Paclitaxel +/- Carboplatin
  - Sunitinib/other...
  - Etoposide
  - Everolimus
  - Pemetrexed
  - Others

  - **n=54**

- **Recurrence 3**
  - Paclitaxel +/- Platinum
  - Sunitinib/other...
  - Everolimus
  - Pemetrexed
  - Etoposide

  - **n=29**

- **Recurrence 4**
  - Paclitaxel +/- Platinum
  - Sunitinib/other...
  - Etoposide
  - Everolimus

  - **n=13**
RYTHMIC: Systemic treatments for recurrence
Tumeurs thymiques

Specificités
- Origine thymique
- Histologie complexe
- Auto-immunité
- Staging

2016

Tumeurs thymiques

Tumeurs thymiques

- Biopsie
- Chemotherapy primaire
- Chirurgie
- Traitement postopératoire
- Radiothérapie définitive

Tumeurs thymiques

- Tumeurs résécables
- Chirurgie
- Radiothérapie postopératoire

Tumeurs thymiques

- Tumeurs non résécables
- Biopsie
- Chemotherapy primaire
- Chirurgie
- Radiothérapie définitive

Tumeurs thymiques

- Tumeurs métastatiques
- Chemotherapy de ligne première
- Recurrences:
  - Chemotherapy de ligne deuxième
  - Agents ciblés
• About 50% of thymomas do express high levels of somatostatin receptors at 111In-DTPA-octreotide (OctreoScan®)

• Response rates are higher in thymoma vs. thymic carcinoma:

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<th></th>
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<td>n</td>
<td>CR+PR</td>
<td>SD</td>
<td>n</td>
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<td>4</td>
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<td>+/-</td>
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<td>11</td>
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<td>Schalke, ASCO 2012</td>
<td>+</td>
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</table>

Specificités
- Origine thymique
- Histologie complexe
- Auto-immunité
- Staging

Tumeurs thymiques

2016

Tumeurs resectables
- Chirurgie
- Radiothérapie postopératoire

Tumeurs non-resectables
- Biopsie
- Chimiothérapie de premier choix
- Chirurgie
- Traitements postopératoires
- Radiothérapie définitive

Tumeurs métastatiques
- Chimiothérapie de premier choix
- Recurrences :
  - Chimiothérapie de deuxième choix
  - Agents ciblés
**KIT and thymic tumors**

- **Overexpression:**
  - collectively 20% of 501 tumors
  - correlation with histologic type:
    - 2% of thymomas
    - *vs.* 87% of carcinomas (*p*=0.003)
  - diagnostic biomarker for thymic carcinoma

- **Mutations:**
  - 11% of thymic carcinomas
    (14/129 tested)

### Sensitivity to KIT inhibitors
- Imatinib
- Sunitinib
- Sorafenib

### KIT Overexpression

<table>
<thead>
<tr>
<th>References</th>
<th>Thymoma</th>
<th>KIT Overexpression, n (%)</th>
<th>Thymic Carcinoma</th>
<th>KIT Overexpression, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan et al.(^{31})</td>
<td>110</td>
<td>0 (0%)</td>
<td>22</td>
<td>19 (86%)</td>
</tr>
<tr>
<td>Henley et al.(^{32})</td>
<td>20</td>
<td>1 (5%)</td>
<td>15</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>Nakagawa et al.(^{33})</td>
<td>50</td>
<td>2 (1%)</td>
<td>20</td>
<td>16 (80%)</td>
</tr>
<tr>
<td>Yoh et al.(^{20})</td>
<td>24</td>
<td>0 (0%)</td>
<td>17</td>
<td>15 (88%)</td>
</tr>
<tr>
<td>Tsuchida et al.(^{34})</td>
<td>20</td>
<td>0 (0%)</td>
<td>12</td>
<td>11 (92%)</td>
</tr>
<tr>
<td>Girard et al.(^{7})</td>
<td>33</td>
<td>0 (0%)</td>
<td>6</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Aisner et al.(^{21})</td>
<td>34</td>
<td>2 (6%)</td>
<td>5</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Zucali et al.</td>
<td>107</td>
<td>4 (3%)</td>
<td>6</td>
<td>13 (46%)</td>
</tr>
</tbody>
</table>

### Mutation

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Exon</th>
</tr>
</thead>
<tbody>
<tr>
<td>E490K</td>
<td>9</td>
</tr>
<tr>
<td>Y553N</td>
<td>11</td>
</tr>
<tr>
<td>W557R</td>
<td>11</td>
</tr>
<tr>
<td>V559A</td>
<td>11</td>
</tr>
<tr>
<td>V560del</td>
<td>11</td>
</tr>
<tr>
<td>L576P</td>
<td>11</td>
</tr>
<tr>
<td>P577-D579del</td>
<td>11</td>
</tr>
<tr>
<td>D579del</td>
<td>11</td>
</tr>
<tr>
<td>H697Y</td>
<td>14</td>
</tr>
<tr>
<td>D820E</td>
<td>17</td>
</tr>
</tbody>
</table>
Neoangiogenesis

• **Expression of angiogenesis-related biomarkers**
  - increased number of cells expressing VEGF-A, -C, -D, and VEGFR-1, -2
  - increased serum levels of VEGF in thymic carcinomas

Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial


**Kit wild-type tumors**

<table>
<thead>
<tr>
<th></th>
<th>Thymic carcinoma (n=23)</th>
<th>95% CI</th>
<th>Thymoma (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response*</td>
<td>6 (26%)</td>
<td>10.2-48.4†</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>15 (65%)</td>
<td>42.7-83.6</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (9%)</td>
<td>1.1-28.0</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Disease control</td>
<td>21 (91%)</td>
<td>72.0-98.9</td>
<td>13 (81%)</td>
</tr>
</tbody>
</table>

**Figure 1: Waterfall plots of tumour responses to sunitinib**

Thymic carcinoma
SSP : 7.6 mois

Thymoma
SSP : 6.7 mois
Tumeurs thymiques

Specificités
- Thymic origin
- Complex histology
- Auto-immunity
- Staging

2016

Resectable tumors
- Surgery
- Postoperative radiotherapy

Unresectable tumors
- Biopsy
- Primary chemotherapy
- Surgery
  - postoperative treatment
  - Definitive radiotherapy

Metastatic tumors
- First-line chemotherapy
- Recurrences:
  - second-line treatment
  - Targeted agents
Phase I trials

Thymoma Patients Treated in a Phase I Clinic at MD Anderson Cancer Center: Responses to mTOR Inhibitors and Molecular Analyses

Jennifer Wheler¹, David Hong¹, Stephen G. Swisher², Gerald Falchook¹, Apostolia M. Tsimberidou¹, Thorunn Helgason¹, Aung Naing¹, Bettzy Stephen¹, Filip Janku¹, Philip J. Stephens³, Roman Yelensky³, Razelle Kurzrock⁴

¹ Department of Investigational Cancer Therapeutics – a Phase I Clinical Trials Program, The University of Texas MD Anderson Cancer Center

21 patients

DCR=60% with mTOR inhibitors

Oncotarget 2013;4:890
Phase I trials

Thymoma Patients Treated in a Phase I Clinic at MD Anderson Cancer Center: Responses to mTOR Inhibitors and Molecular Analyses

Jennifer Wheler¹, David Hong¹, Stephen G. Swisher², Gerald Falchook¹, Apostolia M. Tsimberidou¹, Thorunn Helgason¹, Aung Naing¹, Bettzy Stephen¹, Filip Janku¹, Philip J. Stephens³, Roman Yelensky³, Razelle Kurzrock⁴

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Figure 2: Kaplan-Meier curve to compare TTF in patients with advanced/metastatic thymoma or thymic carcinoma on their best phase I clinical trial versus TTF on their last conventional therapy before referral to the phase I clinic.

Median: 11.6 months
Median: 2.3 months
PHASE II STUDY OF EVEROLIMUS IN PATIENTS WITH THYMOMA AND THYMIC CARCINOMA PREVIOUSLY TREATED WITH CISPLATIN-BASED CHEMOTHERAPY


1-Humanitas Cancer Center, Rozzano, Italy; 2-European Institute of Oncology, Milan, Italy; 3-Univ. Federico II, Naples, Italy; 4-Institute Oncology Veneto, Padua, Italy; 5-University Hospital, Padua, Italy; 6-Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; 7-Humanitas Centro Catanese di Oncologia, Cattolica, Italy

BACKGROUND

- New studies for treatment are necessary in patients with advanced thymic epithelial tumors (TET) that have progressed on cisplatin-containing regimens.
- The activation of PI3K and AKT proteins results in increased levels of FOXO transcription factors, which promotes cell survival. TETs express high levels of PI3K/AKT signaling. TETs are sensitive to mTOR inhibitors, which are activated by AKT activity in cisplatin-resistant tumors.

STUDY DESIGN

- The treated TET pts were prospectively enrolled in single arm, open label, multicenter, phase II trial.

EVALUATION

- Tumor assessment was done every six weeks.
- Everolimus 10 mg once daily was given until disease progression, death of patient, or patient refusal.
- Safety was assessed every three weeks.

RESULTS

- Overall response rate 28% R+R+PR (7/26).

TOXICITY

- Grade 3/4 adverse events: diarrhea 10(38.5), stomatitis 2(7.7), nausea 2(7.7), vomiting 2(7.7), infection 1(3.8), fatigue 1(3.8), anorexia 1(3.8), pyrexia 1(3.8), hand-foot syndrome 1(3.8), elevated creatinine kinase 1(3.8), cardiovascular 1(3.8), elevated transaminases 1(3.8).

CONCLUSIONS

- The primary endpoint of the study was achieved.
- These results suggest that Everolimus is able to achieve a satisfactory number of CR in this setting of phase II studies.
- These exploratory analyses are evaluating clinical characteristics of responders and non-responders.
- The efficacy should be better evaluated in subsequent larger studies.

REFERENCES


ACKNOWLEDGMENTS

The study was partially supported by the patients and their families. A manuscript prepared by Advanced Medical Information Services. For additional information, visit www.humanitas.it or call 800.335.338.
Survie Globale sous everolimus

SG à 1 an, tous : 75,5%, Thymome : 82,3%, Carcinome thymique : 62,3%

Survie Globale sous everolimus
Tumeurs thymiques

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Initiatives & Opportunities
- ITMIG: databases
ITMIG Databases: website is ccehub.org
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Initiatives & Opportunities
- ITMIG: databases
- ETOP/EORTC: translational medicine
Targeting immune checkpoints?

![Diagram showing T cell interaction with cancer cell](image)

**Table: PD-L1 expression (tumor cells)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Antibody</th>
<th>Definition of Positive</th>
<th>Positive thymomas</th>
<th>Positive thymic carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown 2003</td>
<td>Ab 29E.5A9 or 29E.2A3</td>
<td>Not stated</td>
<td>81% (21/26)</td>
<td>88% (7/8)</td>
</tr>
<tr>
<td>Padda 2015</td>
<td>Rabbit MoAb clone 15</td>
<td>High intensity</td>
<td>68% (44/65)</td>
<td>75% (3/4)</td>
</tr>
<tr>
<td>Naidoo ASCO 2015</td>
<td>Rabbit MoAb E1L3N</td>
<td>&gt; 25% tumor cells positive</td>
<td>94% (11/12)</td>
<td>34% (4/12)</td>
</tr>
<tr>
<td>Katsuya ASCO 2015</td>
<td>Rabbit MoAb E1L3N</td>
<td>H-score ≥ 3</td>
<td>67% (6/9)</td>
<td>41% (7/17)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td>73% (82/112)</td>
<td>51% (21/41)</td>
</tr>
</tbody>
</table>

Giaconne. ASCO 2014
Pembrolizumab phase II trial (NCI, G Giaccone)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>24</td>
</tr>
<tr>
<td>PS: 0, 1, 2</td>
<td>12, 10, 2</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>57 (35-75)</td>
</tr>
<tr>
<td>Gender: M, F</td>
<td>16, 8</td>
</tr>
<tr>
<td>Race: Caucasian, Black, Latino, Asian</td>
<td>20, 2, 1, 1</td>
</tr>
<tr>
<td>Stage (Masaoka): III, IVA, IVB</td>
<td>1, 1, 22</td>
</tr>
<tr>
<td>Metastatic sites: 1, 2, 3, 4, 5, 6</td>
<td>2, 5, 8, 7, 1, 1 (median 3)</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>13</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>5</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>8</td>
</tr>
<tr>
<td>Histology: squamous, undifferentiated, neuroendocrine</td>
<td>11, 11, 2</td>
</tr>
<tr>
<td>Prior lines of systemic therapy: 1, 2, 3, 4, 6</td>
<td>7, 8, 5, 3, 1 (median 2)</td>
</tr>
<tr>
<td>Prior surgery (thymectomy)</td>
<td>11</td>
</tr>
<tr>
<td>Prior radiation (chest)</td>
<td>12</td>
</tr>
</tbody>
</table>

**Best Response (target lesions)**

- Green = CR
- Orange = PR

**Side effects of special interest**

- Polymyositis/myocarditis
  - Developed after 2 cycles with severe asthenia, dyspnea and muscle aches. Required hospitalization, complete A-V block, pace-maker placement and steroids. Patient recovered completely.
- Diabetes mellitus type 1
  - Developed hyperglycemia grade 4, after 4 cycles. Associated with severe increase of lipase (grade 3) and amylase (grade 1) and grade 3 transaminitis. Required insulin. Did not reverse. Patient on insulin, doing well.
- Bullous pemphigus
  - Started with severe itching after 10 cycles. Histologically diagnosed after 12 cycles. Recovering on oral steroids.
EORTC-ETOP NIVOTHYM: B3 and carcinomas

**Primary objective:**
To detect activity of nivolumab as single agent

50 patients

**Eligible patients**
Second-line

**Stratification factors**
- Histology (squamous vs non-sq vs small cell)
- Previous RT (yes versus no)
- Best response to first line treatment (PR vs SD vs PD)
- Center

**Primary endpoint:** PFS at 6 months

**Secondary endpoints:** TTP, Response, Duration of response, OS, QOL, Safety

**Nivolumab 3 mg/kg IV q2 weeks**

**Biomarkers**
- PD-L1 at baseline and PD
- Others: immune patterns, molecular profile

Courtesy J Menis
Tumeurs thymiques

Specificités
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- Complex histology
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- Staging

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Initiatives & Opportunities
- ITMIG: databases
- ETOP/EORTC: translational medicine
- RYTHMIC: Tumor board and network
RYTHMIC: a regional network of expert centers

Coordinator:
B. Besse
Gustave Roussy
RYTHMIC: Infrastructure of the network

Guidelines
CME activities
Prospective database and trials

National Pathology Panel
National expert tumor board

Treating Physician
Regional expert center

Patients
Online virtual tumor board

Regional expert teams

Thoracic surgeons
Medical oncologists
Radiation oncologists
Pathologists
Radiologists
Pneumonologists
Neurologists
RYTHMIC: Multidisciplinary tumor board

- 1000 patients: 1401 questions raised at the multi-disciplinary tumor board

**Diagnosis / Imaging**
- Upfront Surgery? 
  - n=182 (13%)
- Surgery? 
  - n=28 (2%)
- Definitive Radiotherapy? 
  - n=45 (3%)
- Exclusive Chemotherapy? 
  - n=37 (3%)
- Follow-up? 
  - n=104 (7%)

**Initial management**
- Primary Chemo therapy? 
  - n=149 (11%)
  - Surgery? 
    - n=28 (2%)
  - Post-operative Radio therapy? 
    - n=494 (35%)
  - Post-operative Chemo therapy? 
    - n=5 (0%)

**Recurrences**
- Diagnosis? 
  - n=47 (3%)
- Surgery? 
  - n=30 (2%)
- Radiotherapy? 
  - n=17 (1%)
- Chemotherapy? 
  - n=114 (8%)
- Targeted agent? 
  - n=67 (5%)
Tumeurs thymiques

Specificities
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- Origine thymique
- Histologie complexe
- Auto-immunité
- Staging

Résécutables
- Chirurgie
- Radiothérapie postopératoire

Unrécductables
- Biopsie
- Chirurgie primaire
- Radiothérapie définitive

Métastatiques
- Chimiothérapie de première ligne
- Récidives : traitement de deuxième ligne
- Agents ciblés

Initiatives & Opportunités
- ITMIG : bases de données
- ETOP/EORTC : médecine de traduction
- RYTHMIC : conseil tumoral et réseau

Thank you!
nicolas.girard@chu-lyon.fr
www.rythmic.org