Les tumeurs du thymus

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Liens d’intérêt

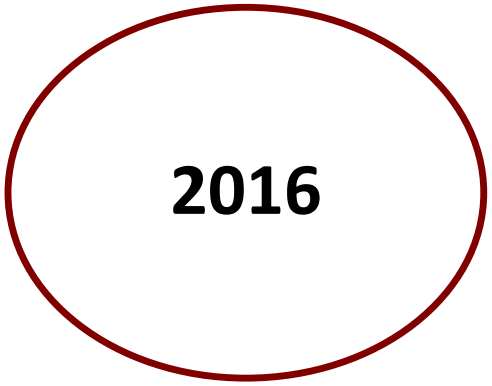
Je suis coordonateur adjoint du réseau RYTHMIC.

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

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

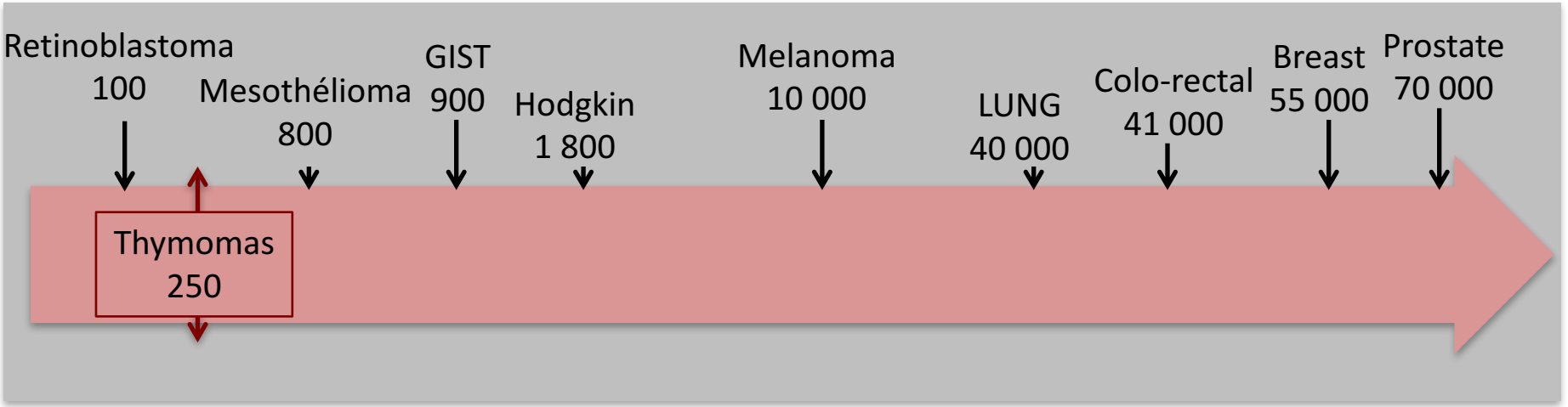
Je suis consultant pour les laboratoires BMS, MSD, Novartis, Pfizer.

Tumeurs thymiques



Tumeurs thymiques

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



Engels et al. Int J Cancer 2003;105:546
Institut National du Cancer, e-cancer.fr

Updated incidence of Thymic Epithelial Tumors (TET) in France and clinical presentation at diagnosis

Bluthgen MV[1], Dansin E[2], Kerjouan M[3], Mazieres J[4], Pichon E[5], Thillays F[6], Massard G[7], Quantin X[8], Oulkhouir Y[9], Westeel V[10], Thiberville L[11], Clement-Duchene C[12], Thomas P[13], Girard N[14], Besse B[1]

[1] Gustave Roussy, Villejuif, France; [2]Oscar Lambret, Lille, France; [3]Centre Hospitalier Universitaire de Rennes, Rennes, France; [4]Centre Hospitalier Universitaire de Tolouse, Tolouse, France; [5]Hôpital Bretonneau, Tours, France; [6]Institut de Cancérologie de l'ouest, Rouen, France; [7]Centre Hospitalier Universitaire de Strasbourg, Strasbourg, France; [8]Centre Hospitalier Universitaire de Montpellier, Montpellier, France; [9]Centre Hospitalier Universitaire de Caen, Caen, France; [10]Centre Hospitalier Universitaire de Besancon, Besancon, France; [11]Centre Hospitalier Universitaire de Rouen, Rouen, France; [12]Centre Hospitalier Universitaire de Nancy, Nancy, France; [13]Hôpital Nord, Marseille, France; [14]Hôpital Louis Pradel, Lyon, France

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 14 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 in order to describe the epidemiology and main characteristics at diagnosis of Tumeurs thymiquesin 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

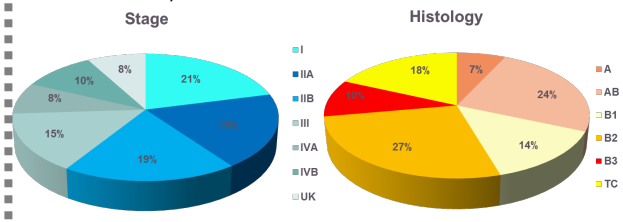
	Frequency n=226 (%)
Age	
Median [range]	62 [25 – 86]
Gender	
Male	129(57)
Female	97(43)
Auto-inmune disorder	46 (20)
Myasthenia	35
Anemia	3
Thyroiditis	2
Hypogammaglobulinemia	2
Others	4
Previous cancer	34 (15)
Prostate	9
Breast	7
Melanoma	4
Hematologic	2
Other	11
Mode of diagnosis	
Resection	158 (70)
Surgical biopsy	35 (15)
Imaging guided biopsy	33 (15)

Patient's characteristics and treatment

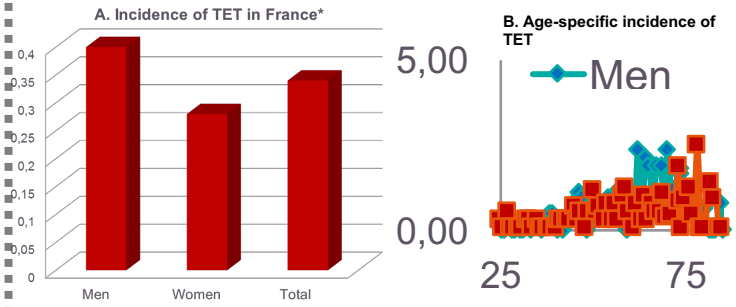
	Frequency n=226 (%)
Primary treatment	
Upfront Surgery	170 (75)
Neo-adjuvant chemotherapy	8 (3)
Chemotherapy	40 (18)
Adjuvant radiotherapy	55 (24)
Surgery Approach	178 (100)
Sternotomy	108 (61)
Videothoracoscopy	37 (21)
Robot assisted	15 (8)
Thoracotomy	9 (5)
Other	9 (5)
Chemotherapy	
CAP	33 (63)
Carboplatin-paclitaxel	16 (31)
Carboplatin-etoposide	3 (6)

UK: unknown; CAP: cisplatin, doxorubicin, cyclophosphamide; VIP: cisplatin, etoposide, ifosfamide.

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 (I-II *vs.* III-IV, p=0.004); no significant correlations were seen with gender (p=0.27).



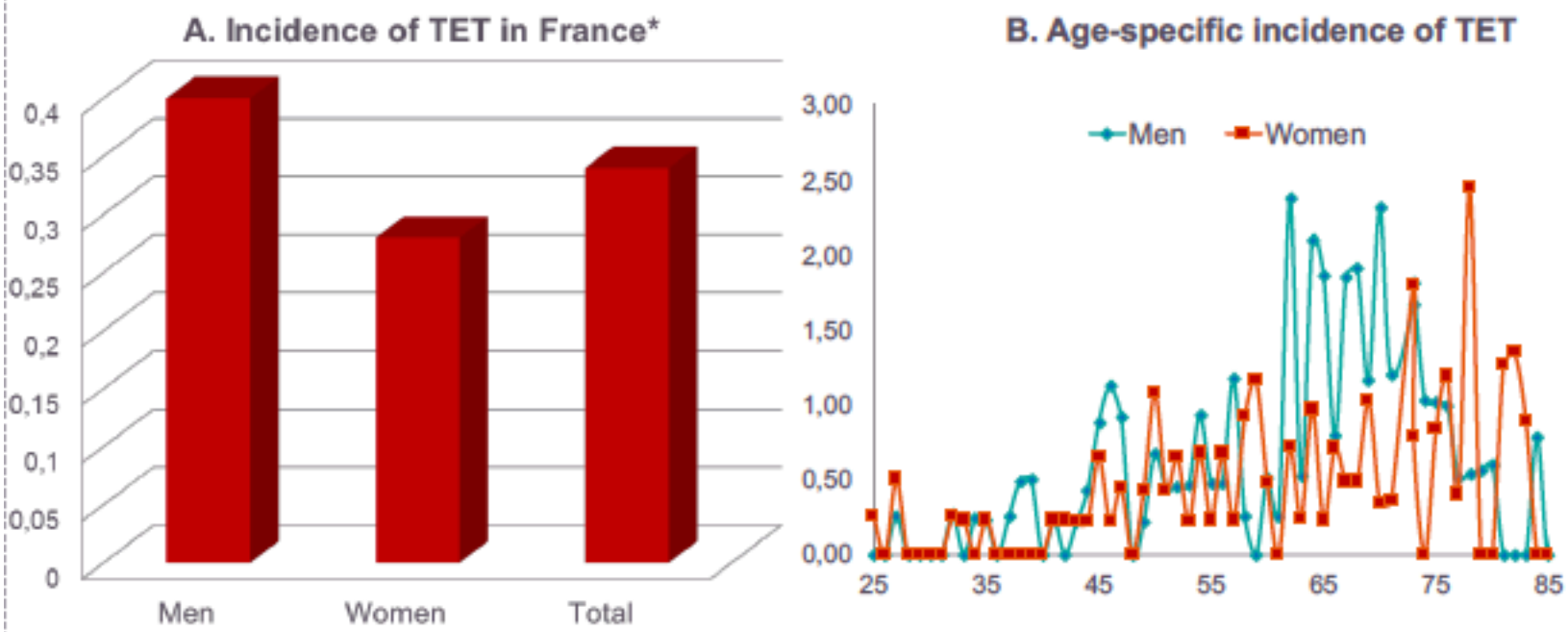
A. Observed incidence of TET in France (per 100.000-person-year) according to gender. *Based on INSEE (Institut National de la Statistique et des Etudes Economiques) population data registries according to gender for France 2016. B. Age-specific incidence of thymoma: observed values for thymoma incidence (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.

Updated incidence of Thymic Epithelial Tumors (TET) in France and clinical presentation at diagnosis

Bluthgen MV[1], Dansin E[2], Kerjouan M[3], Mazieres J[4], Pichon E[5], Thillays F[6], Massard G[7], Quantin X[8], Oulkhouir Y[9], Westeel V[10], Thibaudeau L[11], Clement-Duchene C[12], Thomas P[13], Girard N[14], Besse B[1]



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

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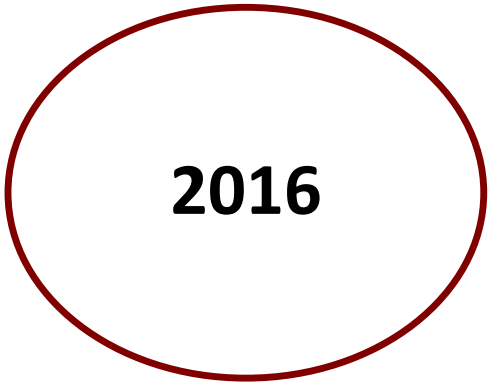
Tumeurs thymiques

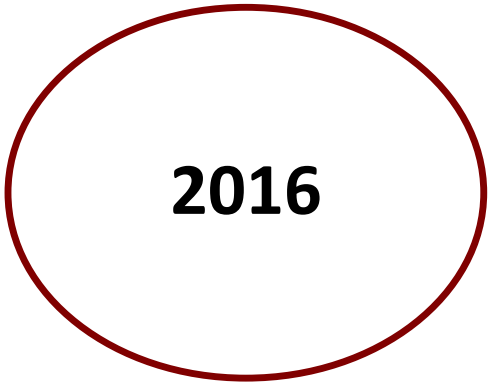
Specificities



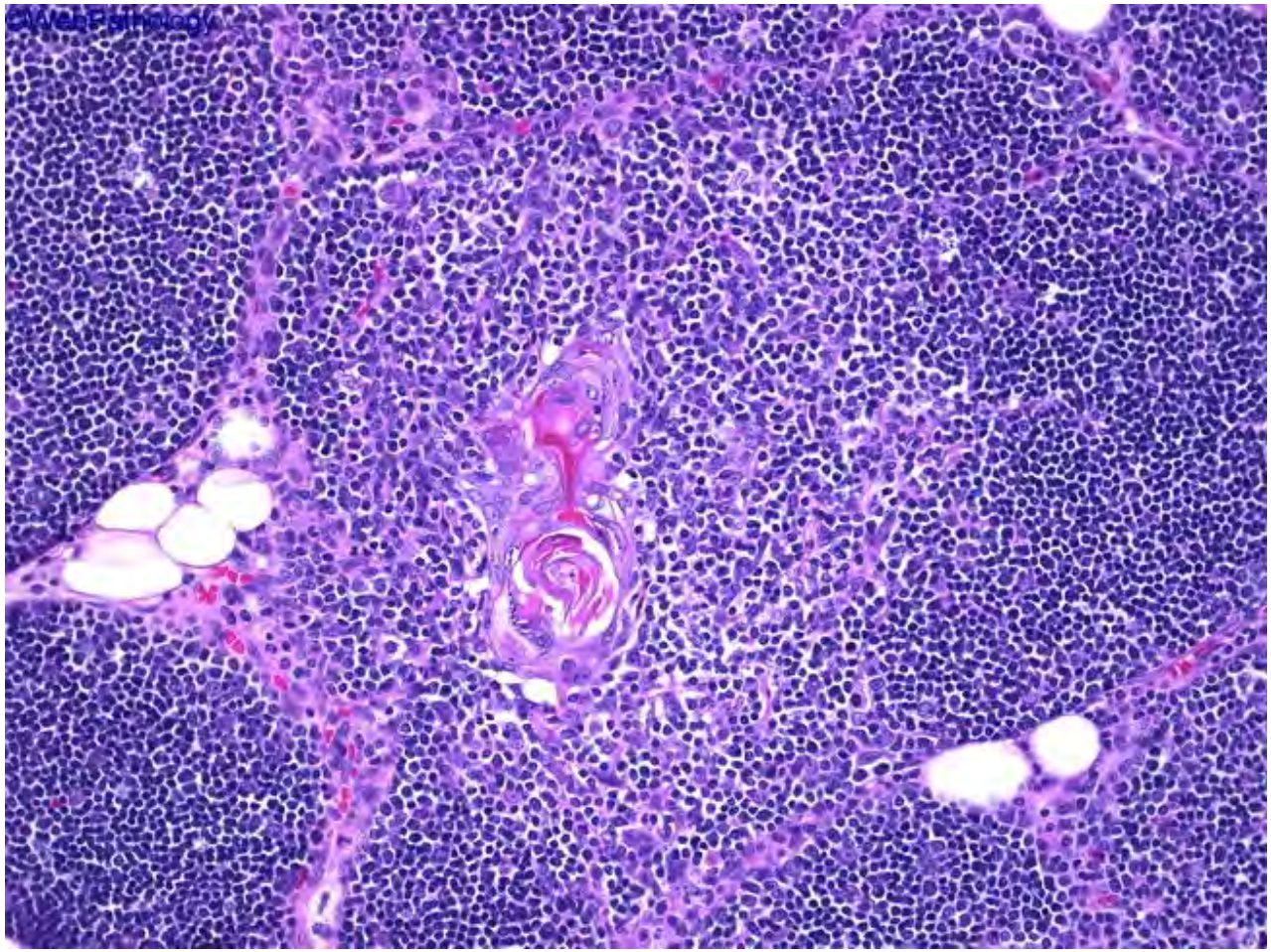
Tumeurs thymiques

Specificities

- **Thymic origin**



The thymus

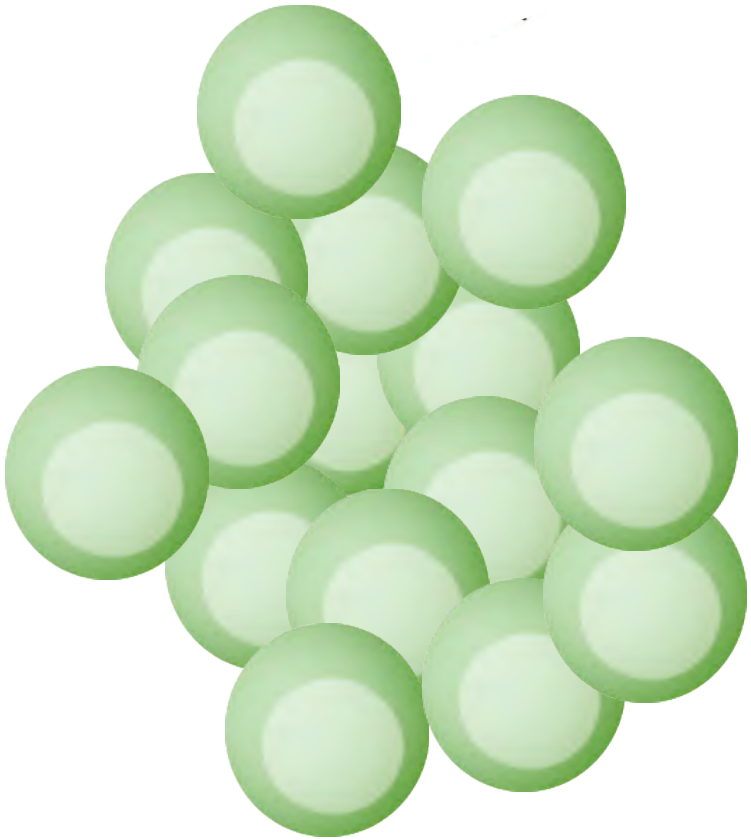


Thymus

Lymphocyte immature

Thymus

Lymphocyte
immature



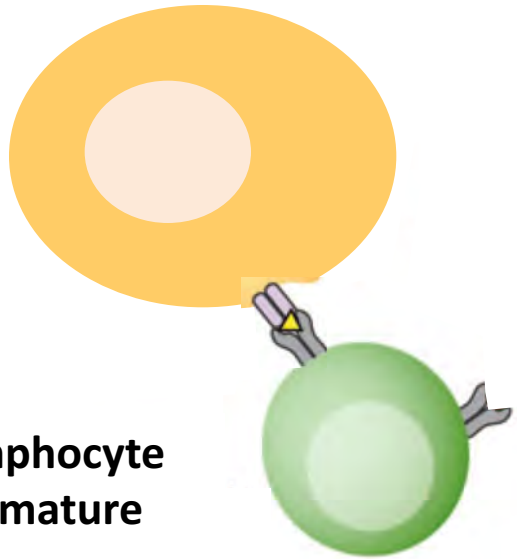
Thymus

Lymphocyte immature

Sélection positive des lymphocytes

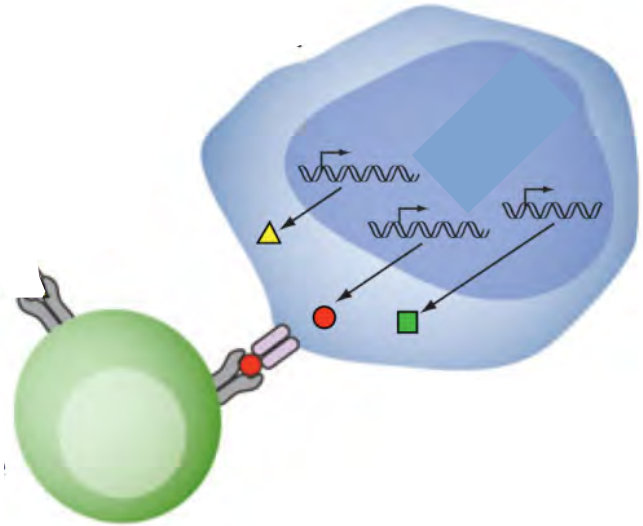
Cellule épithéliale thymique

CORTEX



Lymphocyte immature

Sélection négative des lymphocytes



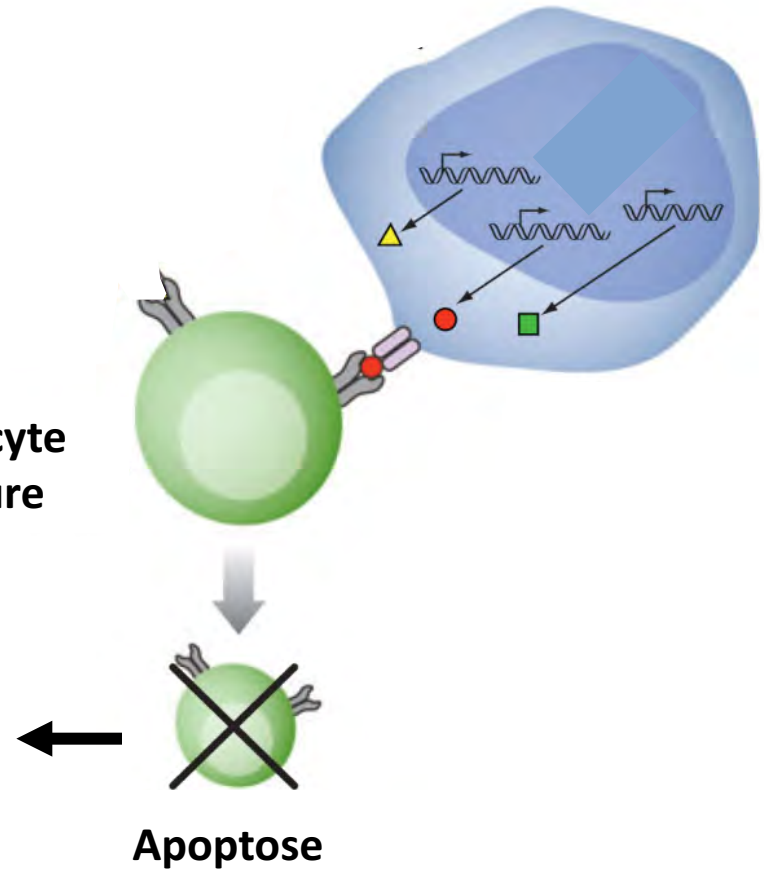
Lymphocyte immature

Cellule épithéliale thymique

MEDULLA

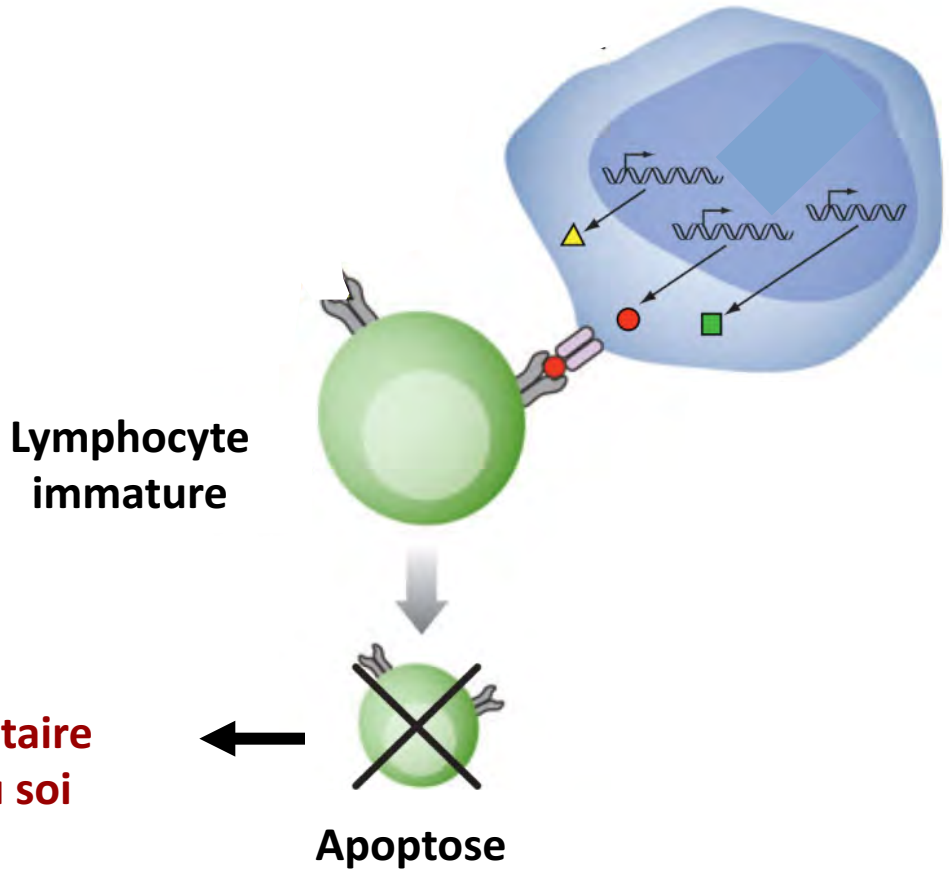
Mathis et al. Annu Rev Immunol 2009;27:287

Sélection négative des lymphocytes



Mathis et al. Annu Rev Immunol 2009;27:287

Sélection négative des lymphocytes



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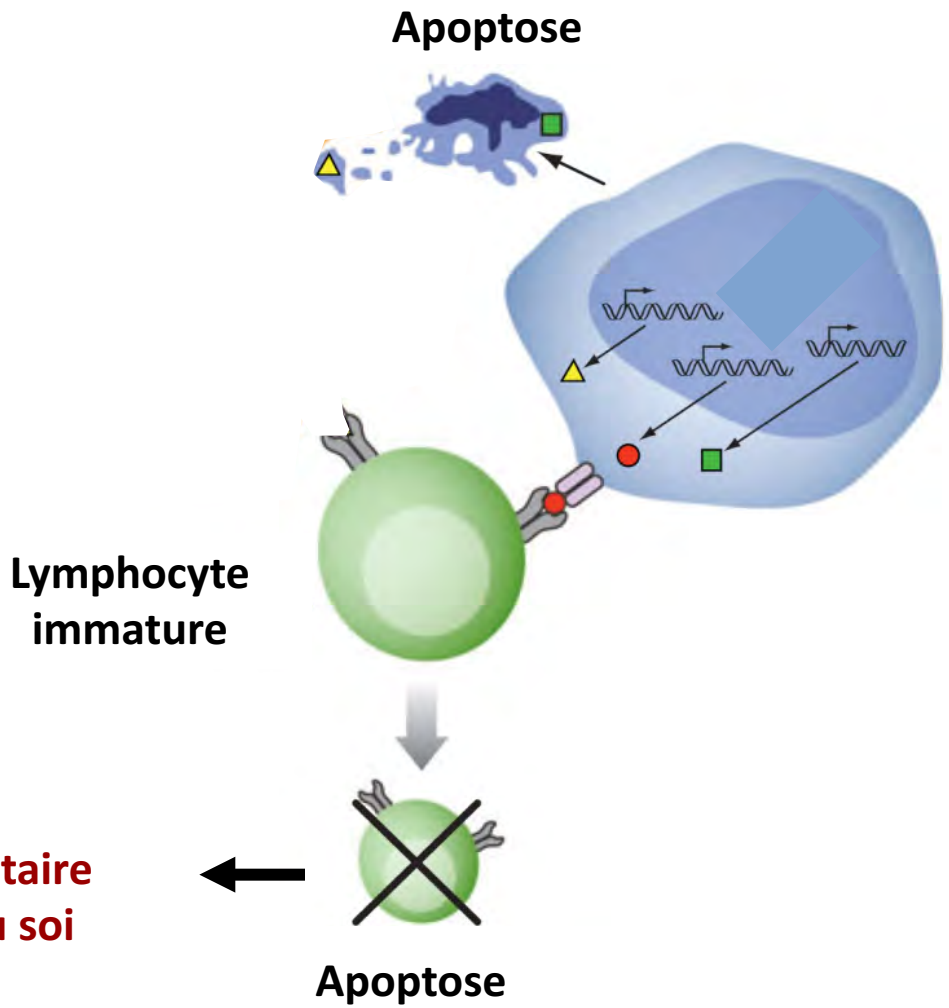

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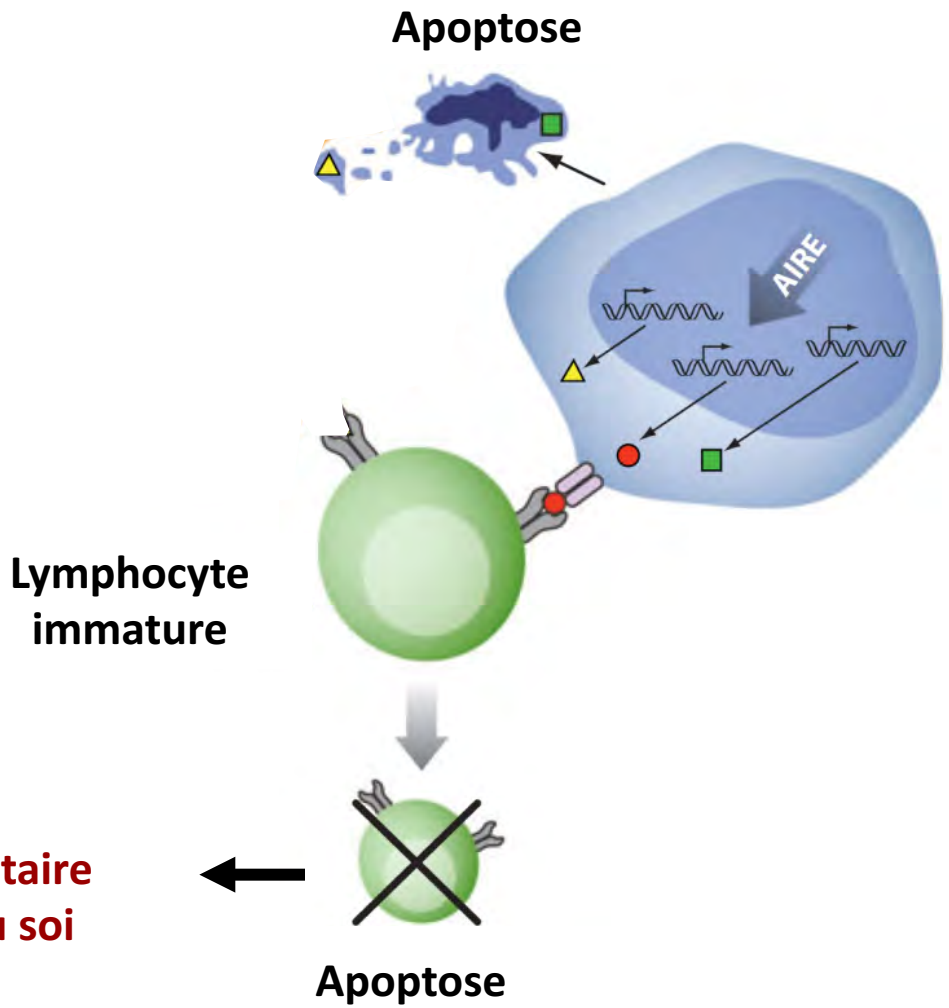
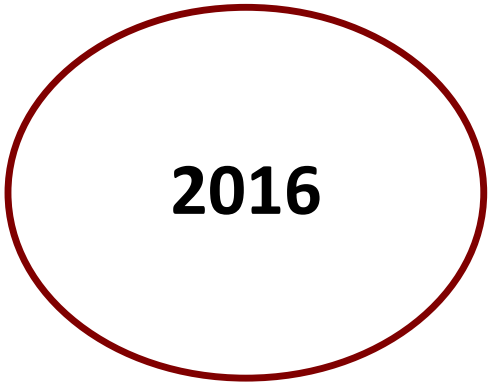


Mathis et al. Annu Rev Immunol 2009;27:287

Tumeurs thymiques

Specificities

- Thymic origin
- **Complex histology**

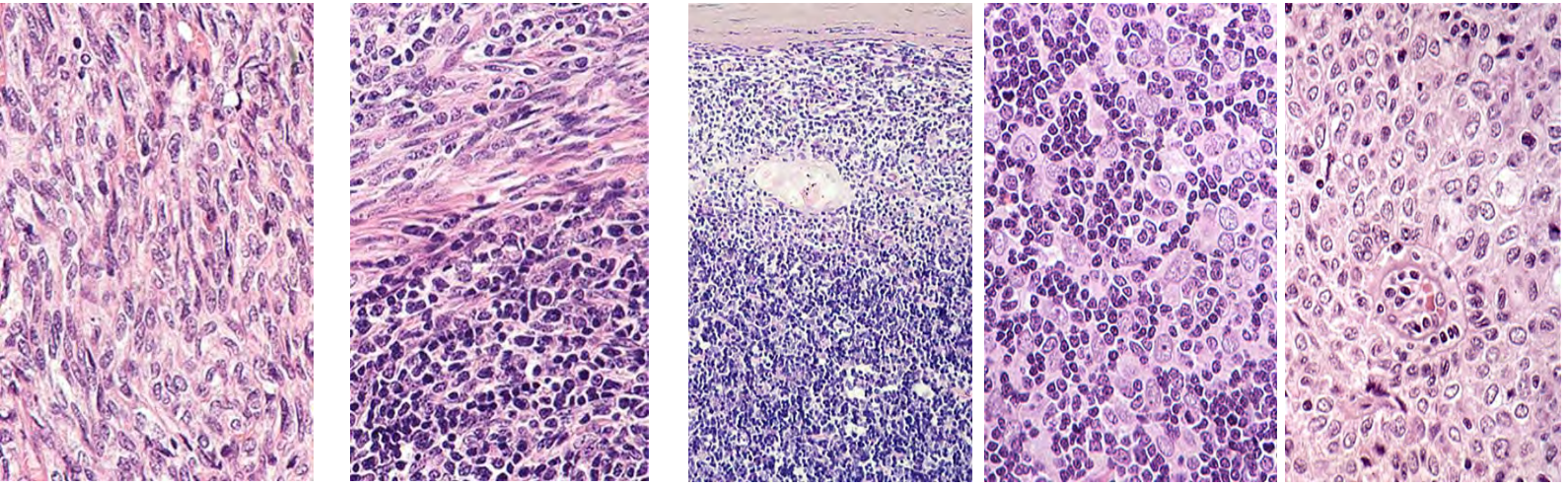


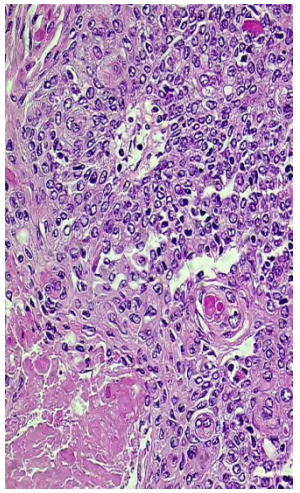
Histo-pathologic classification

- World Health Organization 2016

Thymoma | **Carcinoma**

A | **AB** | **B1** | **B2** | **B3**





“Médullary” | **Mixed** | **“Cortical”** | **SCC**

Reproductibilité de la classification ?

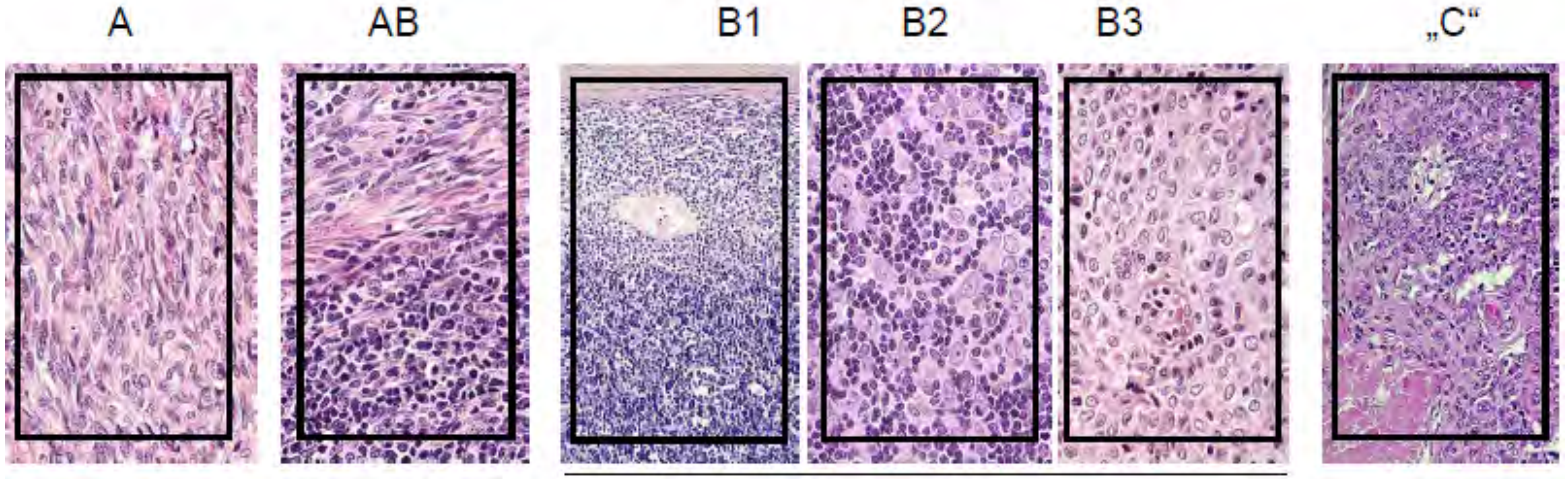
- **Reproductibilité imparfaite**

  - Variabilité de la proportion de chaque type

  - Etude de reproductibilité inter-observateur: *k*=0,45-0,49

Numbers of Cases and Proportions of Thymomas by WHO Type in Different Studies

	Percentage of cases by histology				
Study	A	AB	B1	B2	B3
Range of %	5–24%	11–43%	8–38%	4–46%	6–34%



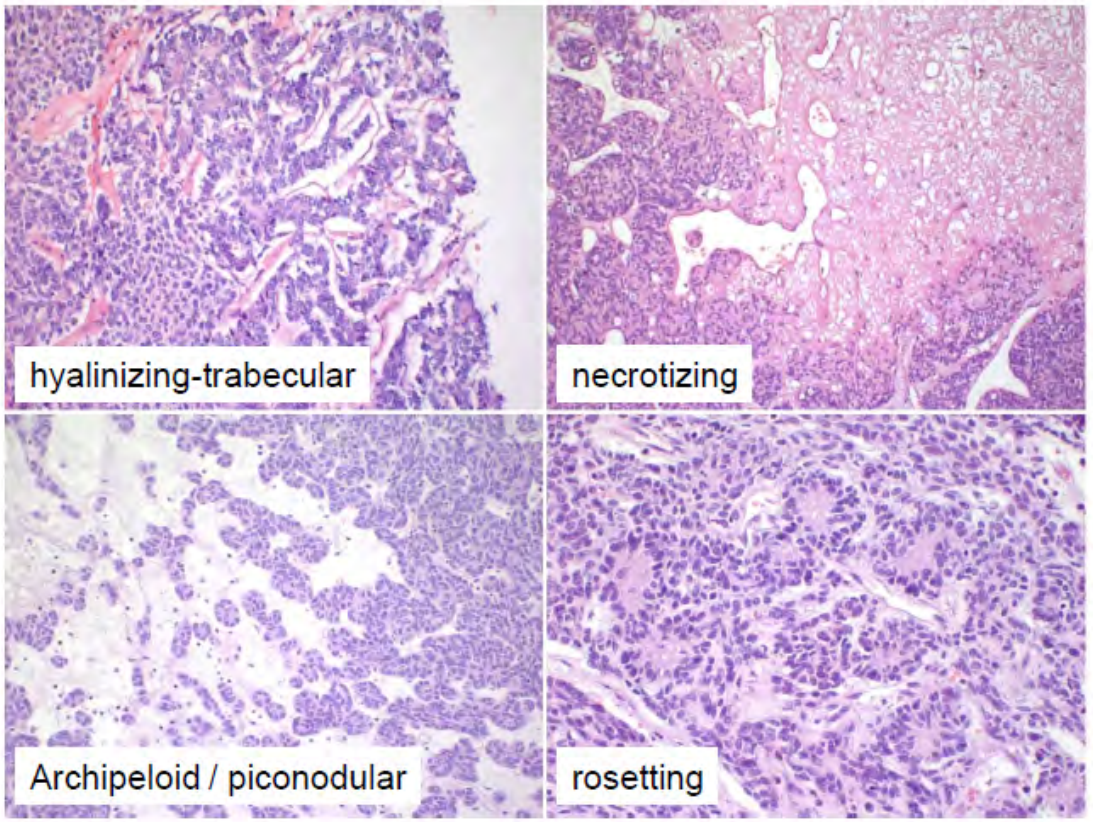
Marchevsky et al. Cancer 2008; 112:2780

Rieker et al. Int J Cancer 2002;98:900; Verghese et al. Histopathology 2008;53:218

Reproductibilité de la classification ?

- **Reproductibilité imparfaite**

  - Hétérogénéité tumorale des thymomes de type A

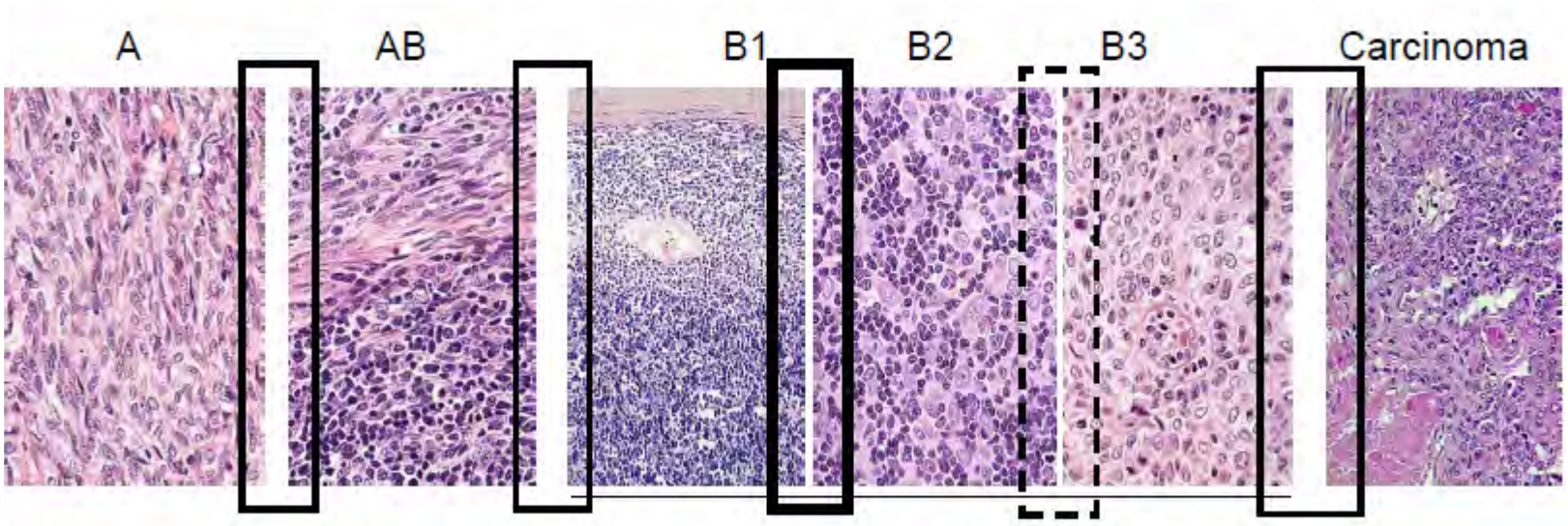


International Thymic Malignancy Interest Group 2011

Reproductibilité de la classification ?

- **Reproductibilité imparfaite:**

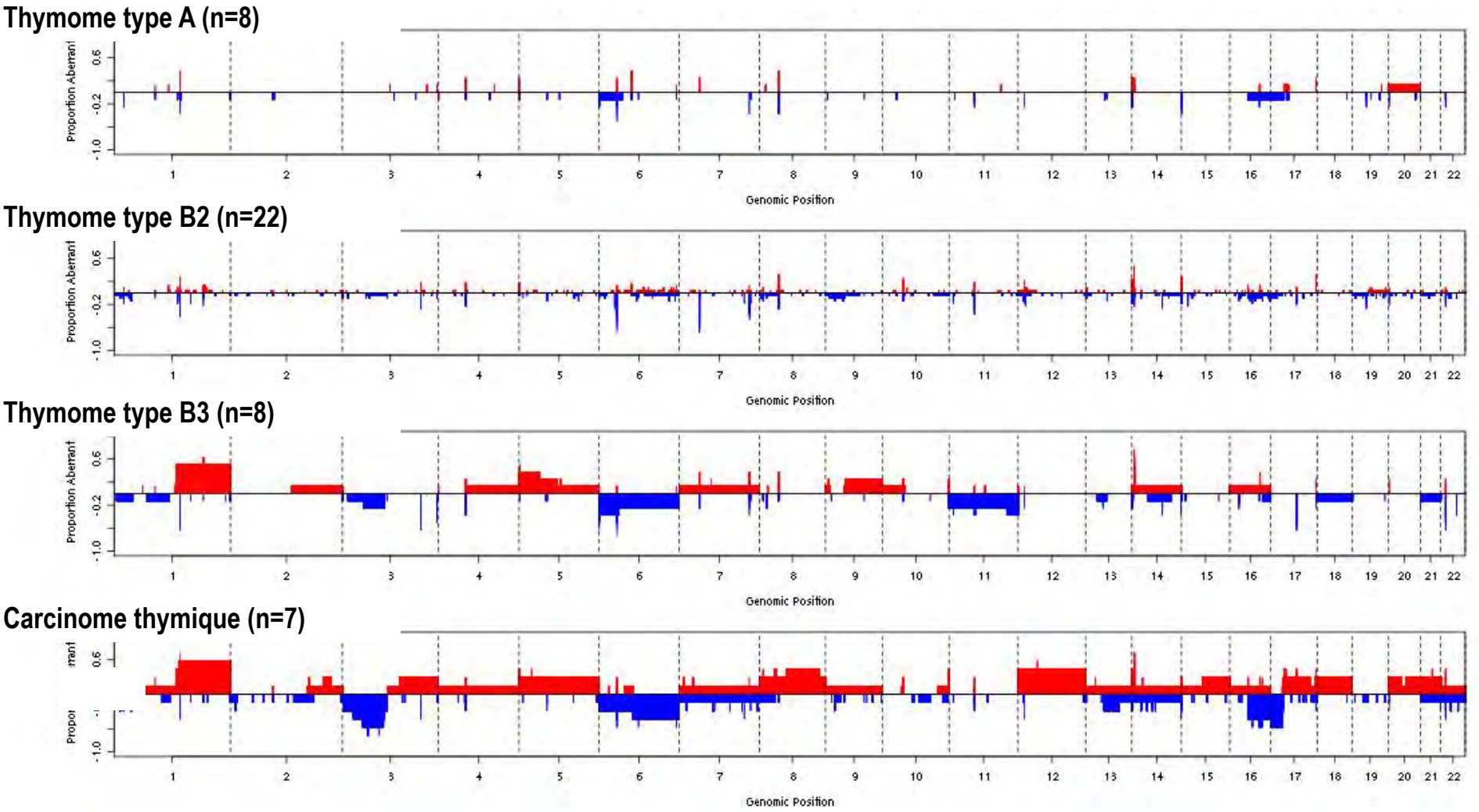
  - Formes combinées : 25% des cas?
  - Formes frontières



International Thymic Malignancy Interest Group 2011

Genomic profiling of thymic epithelial tumors

- MSKCC, 45 patients



Girard et al. Clin Cancer Res 2009; 15:6790

The 2016 WHO classification

SPECIAL ARTICLE

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, M*
John K.C. Chan, MD,|| Gang Chen, MD, PhD,¶ Laurence de Leval, MD, PhD,# Frank Detterbe
Nicolas Girard, MD, PhD,†† Jim Huang, MD,‡‡ Michael O. Kurrer, MD,§§ Libero Lauriola,
*Mirella Marino, MD,¶¶ Yoshihiro Matsuno, MD,## Thierry Jo Molina, MD, PhD,****
Kiyoshi Mukai, MD,††† Andrew G. Nicholson, MD,‡‡‡ Daisuke Nonaka, MD,§§§ Ralf Rieker,
*Juan Rosai, MD,¶¶¶ Enrico Ruffini, MD,### and William D. Travis, MD*****

(*J Thorac Oncol.* 2014;9: 596

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[a] 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
Pericytomatous 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[b]

[a]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).
[b]Beta5t, PRSS16, and cathepsin V by immunohistochemistry (IHC).
PVS, perivascular space.

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

	Type A Thymoma	Type AB Thymoma
Major criteria		
Biphasic pattern at low magnification due to variable lymphocyte content	No	Common[a]
High epithelial cell content	Yes	Yes
Spindled or oval epithelial cells[b]	Yes	Yes
Paucity[c] or absence of TdT+ T cells	Yes	No
Medullary islands[d]	No	Rarely present[a,c]
Minor criteria		
Small lobular growth pattern	No	Rare
Large lobular growth pattern	Common	Common
Perivascular spaces	Rarely present	Rarely present
CD20 expression in epithelial cells	Common	Common
Cortical marker expression[f]	No	Yes

[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-eosin staining but may require immunohistochemistry (IHC), particularly when Hassall's corpuscles are missing.
[e]In lymphocyte-rich areas, usually with lack of Hassall's corpuscles.
[f]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

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(*J Thorac Oncol.* 2014;9: 596–611)

Actualisation de la classification histo-pathologique

TABLE 4. Criteria for the Histological Diagnosis of TC

Major (indispensible)
Clear-cut atypia of tumor epithelial cells with the severity typical of carcinoma
Exclusion of "thymoma with atypia and/or anaplasia" and of typical or atypical carcinoids
Exclusion of metastasis to the thymus and germ cell and mesenchymal tumors with epithelial features
Minor (typical)
Infiltrative growth pattern
Small tumor cell nests within desmoplastic stroma
Absence of immature, TdT+ T cells (with rare exceptions)
Immunohistochemistry: epithelial expression of CD5, CD117; extensive expression of GLUT1, MUC1[a]
Features compatible[b] 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

[a]CD5, CD117, GLUT1, and MUC1 are expressed by many nonthymic cancers.

[b]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 TJ[1], Bluthgen MV[2]*, Chalabreysse L[3], De Montpréville VT[4], De Muret A[5], Hofman V[6], Lantuejoul S[7], Parrens M[8], Rouquette I[9], Secq V[10], Girard N[11], Marx A[12], Besse B[2]

[1]Service d'anatomie pathologique, AP-HP, Hôpital Universitaire Necker-Enfants-Malades, Université Paris Descartes, Sorbonne Paris Cité, France; [2]Department of cancer medicine, Gustave Roussy, Villejuif, France; [3]Département de pathologie, Hôpital Louis-Pradel, hospices civils de Lyon, France; [4]Service d'anatomie pathologique, Institut d'oncologie thoracique, Centre chirurgical Marie-Lannelongue, Le Plessis-Robinson, France; [5]Département de pathologie, CHU de Tours, France; [6]Laboratoire de pathologie cellulaire et expérimentale, Hôpital Pasteur, CHU de Nice, France; [7]Département d'anatomie et de cytologie pathologiques, CHU de Grenoble, France; [8]Département de pathologie, CHU de Bordeaux, France; [9]Service d'anatomie pathologique, CHU Rangueil, Toulouse, France; [10]Laboratoire d'anatomie pathologique, Hôpital Nord, AP-HM, Marseille, France; [11]Département des maladies respiratoires, Hôpital Louis-Pradel, hospices civils de Lyon, Lyon, France; Institut de Pathologie; [12]Université médicale de Mannheim, Université de Heidelberg, Mannheim, Germany. *Marie-Virginie.BLUTHGEN@gustaveroussy.fr

BACKGROUND

- RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a nationwide network for TET appointed in 2012 by the French National Cancer institute (INCa).
- The objectives of the network are territorial coverage 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 pathologists from the working group.
- Assessment of agreement or disagreement between the initial institution and the panel review was made according the WHO 2004/2015 and new ITMIG proposals for histologic typing and staging.
- Discordances were classified as "major" 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, Masaoka-Koga stage and resection status.

RESULTS

-Specimens from a total of 290 patients were reviewed: discordances 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=8). The most frequent disagreement was the sub-diagnosis of stage III reflecting the underlying difficulty in pericardial / mediastinal pleura histological involvement recognition. (Figure 1)

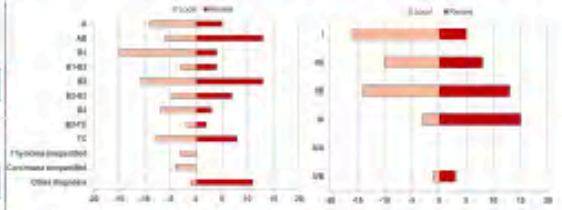


Figure 1. Description of discordances over 109 patients according to histology (left) and stage (right) before and after pathological central review

Discordances were classified as minor in 31% of the patients (n=90) and as major discordances in 6.6 % (n=19) of them. (Figure 2)

Figure 2. Description of pathological central review classified according to type of discordances.

Figure 3.Description of major discordances identified in 19 patients (6.6%).
7 patients for whom management of disease should have been modified and 12 patients for whom post-surgical treatment recommendation concerning adjuvant radiotherapy would have been changed.
Additionally, major disagreement between the initial / panel pathology's stage and subsequent interpretation by the working group at national tumor board (RCP) was found in 3 patients.

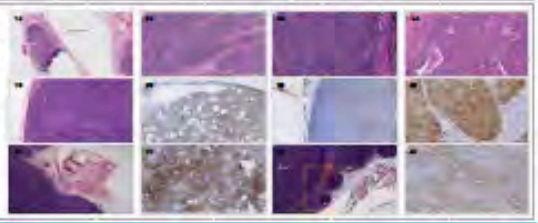


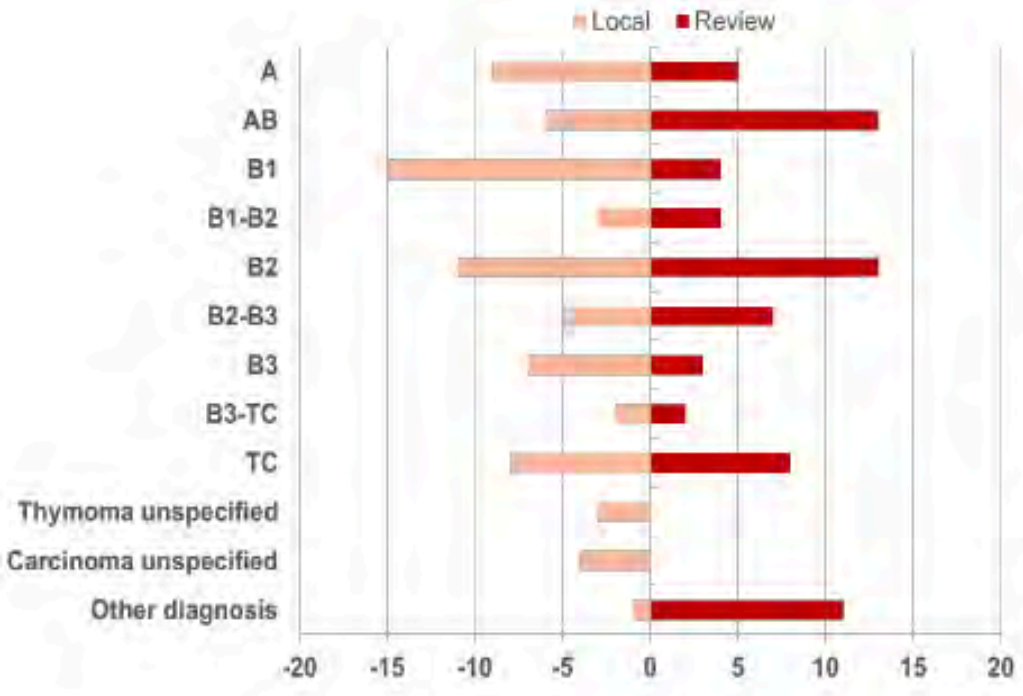
Figure 4. Sub-diagnosis of stage III TETs and AB histology sub-type were the discordances most frequently observed. 1. Stage III with pericardial (A) or mediastinal pleural invasion (B, C). 2. Thymoma AB with biphasic pattern (AE1/AE3 + thymocytes (B) and CD20 expression in epithelial cells (C). 3. Thymoma AB with biphasic pattern (A), CD20+ (B), with minimal mediastinal fat invasion (C). 4. Thymic carcinoma (A) with epithelial expression of CD5 (B), and CD117 / C-KIT (C).

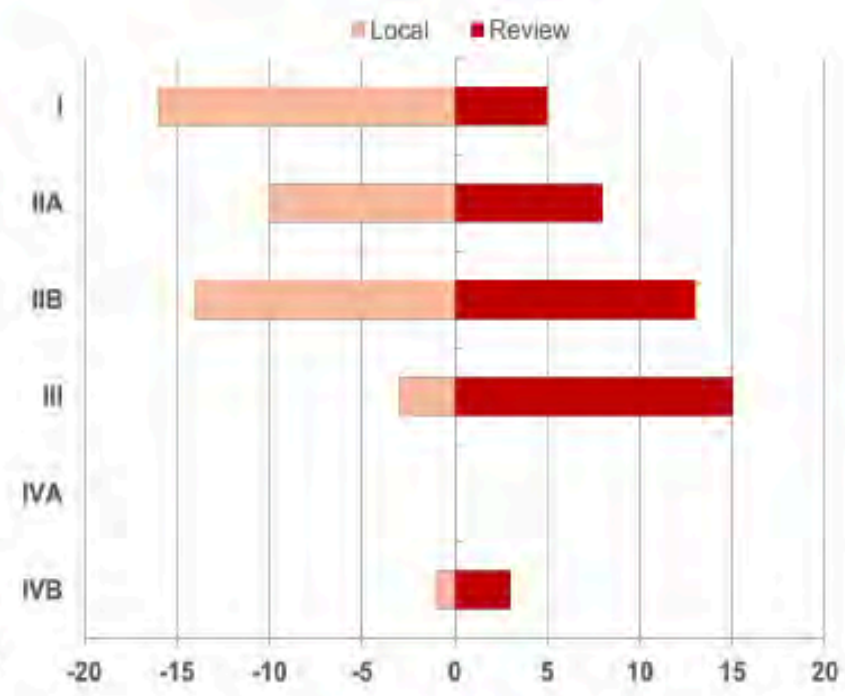
CONCLUSION

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

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





- RYTHMIC Guidelines post-operative recommendations are based on histopathological subtype, Masaoka-Koga stage and resection status.

n =290

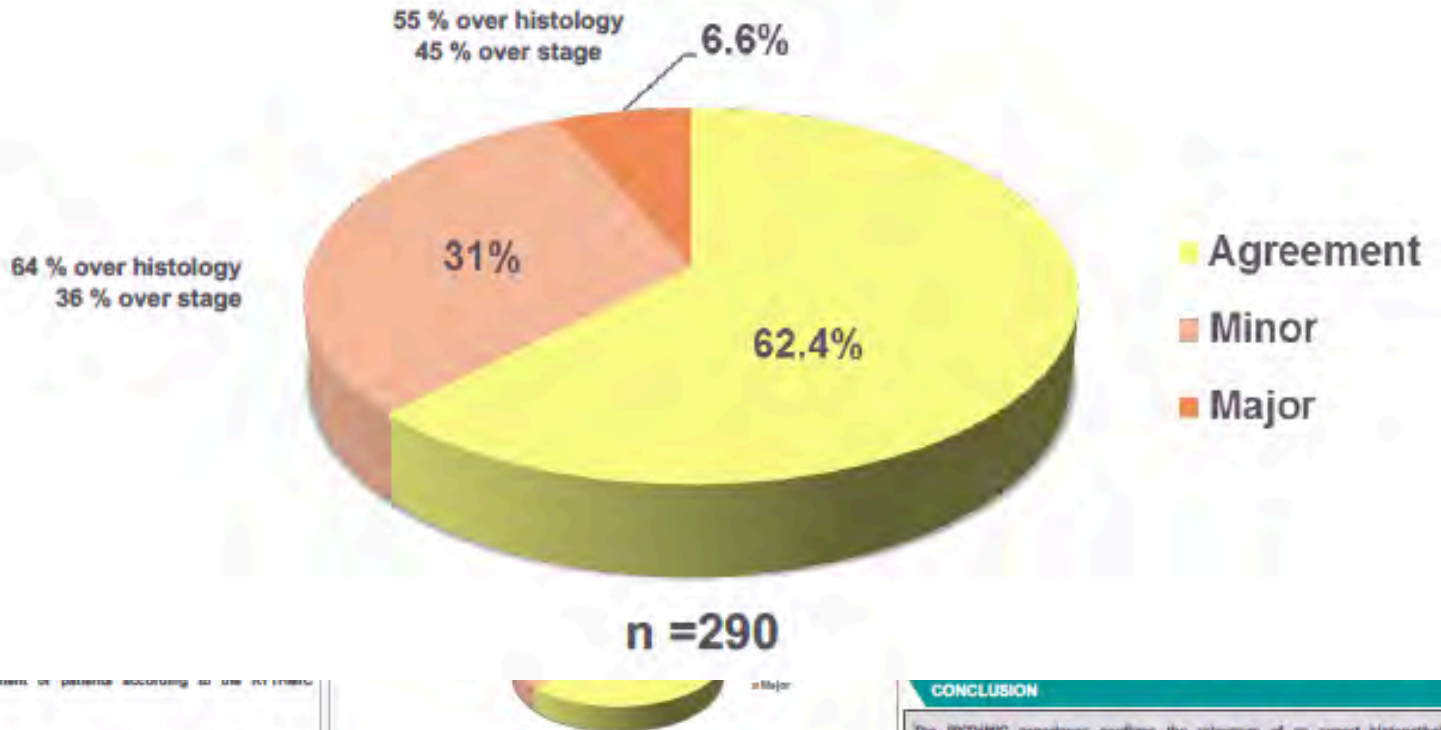
Figure 2: Description of pathological central review classified according to type of discordances.

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

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

Molina TJ[1], Bluthgen MV[2]*, Chalabreysse L[3], De Montpréville VT[4], De Muret A[5], Hofman V[6], Lantuejoul S[7], Parrens M[8], Rouquette I[9], Secq V[10], Girard N[11], Marx A[12], Besse B[2]



guidelines.

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Figure 2. Description of pathological central review classified according to type of discordances.

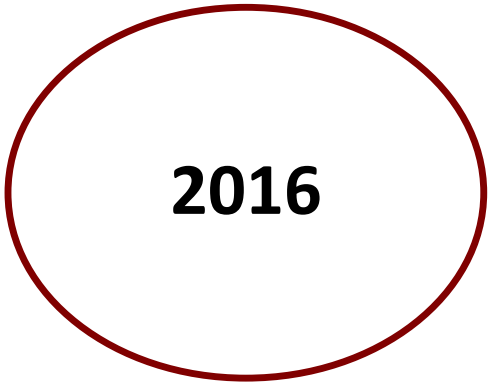
CONCLUSION

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.

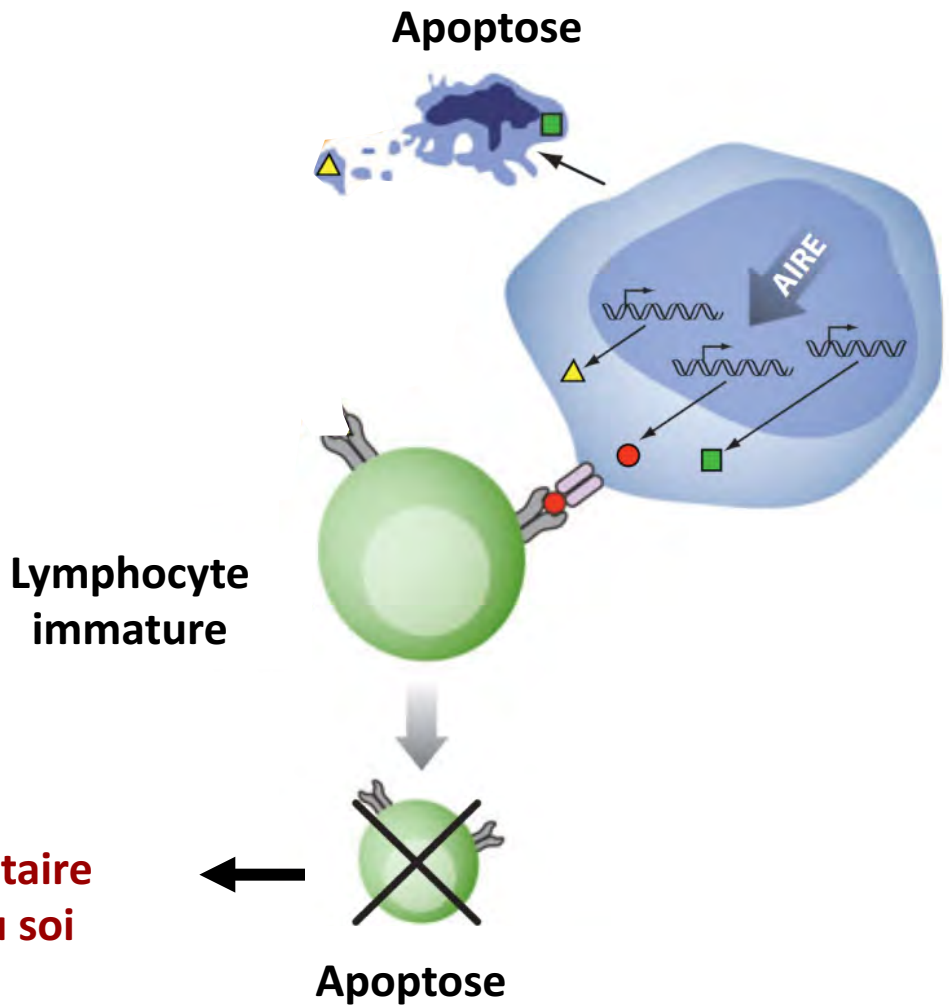
Tumeurs thymiques

Specificities

- Thymic origin
- Complex histology
- **Auto-immunity**

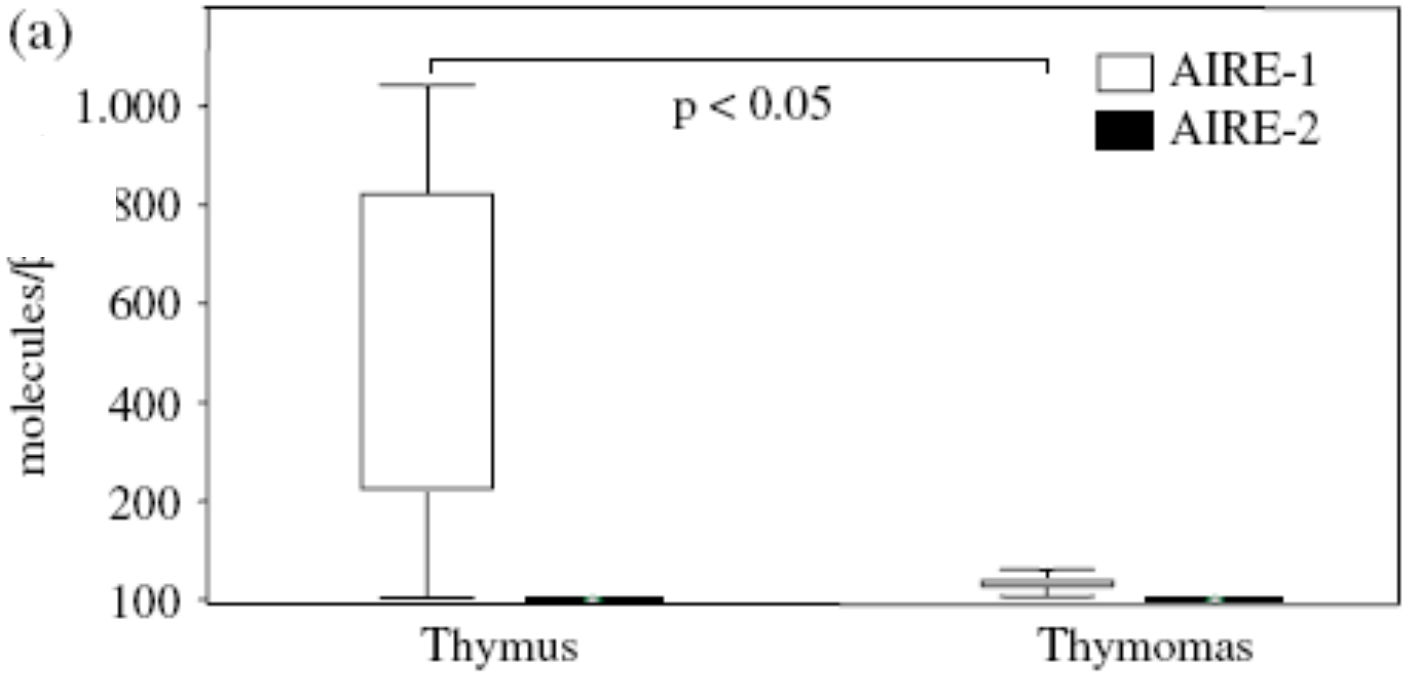


Sélection négative des lymphocytes



Mathis et al. Annu Rev Immunol 2009;27:287

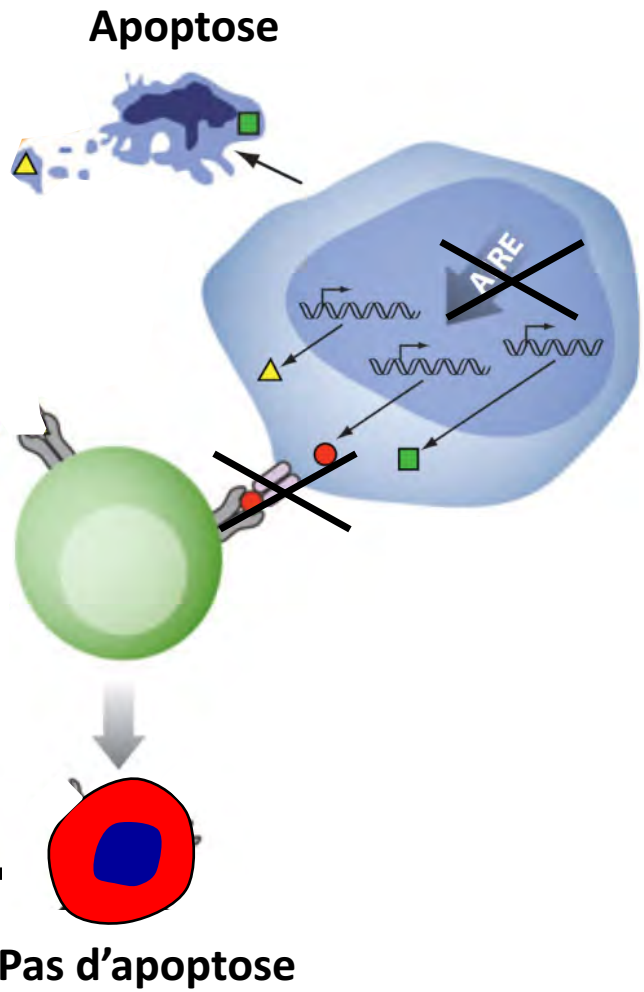
Les thymomes n'expriment pas AIRE



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

Ströbel et al. J Pathol 2007;211:563

Manifestations auto-immunes



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 collitis
Hypertrophic osteoarthropathy
Interstitial pneumonitis

Immune deficiency disorders
Hypogammaglobulinaemia
T-cell deficiency syndrome

Syndromes para-thymiques

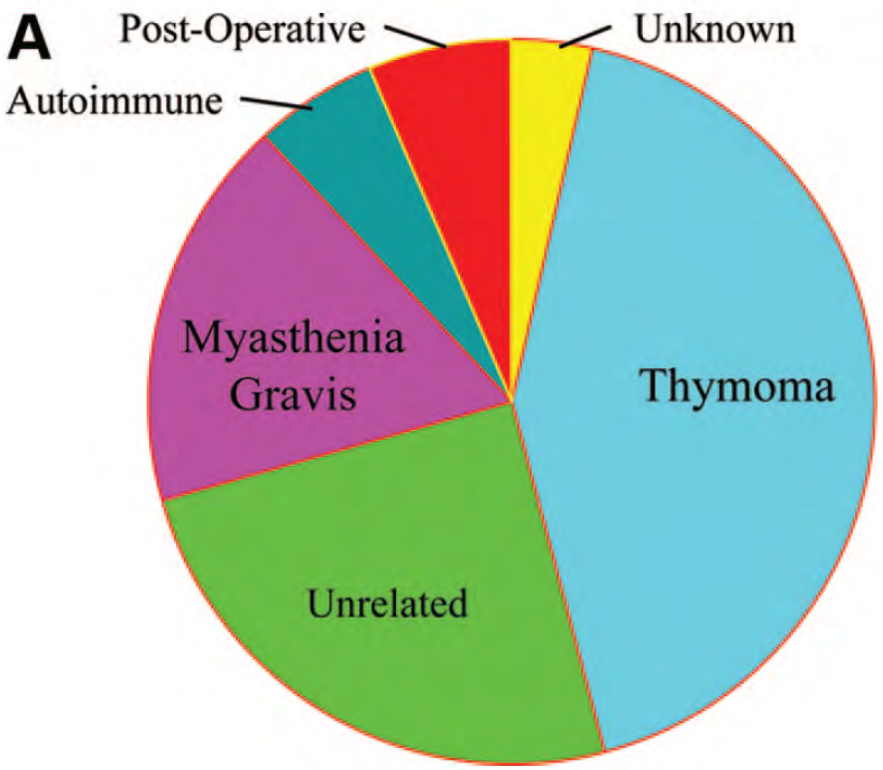
- Bilan minimal recommandé en cas de suspicion de manifestations auto-immunes associées aux tumeurs thymiques

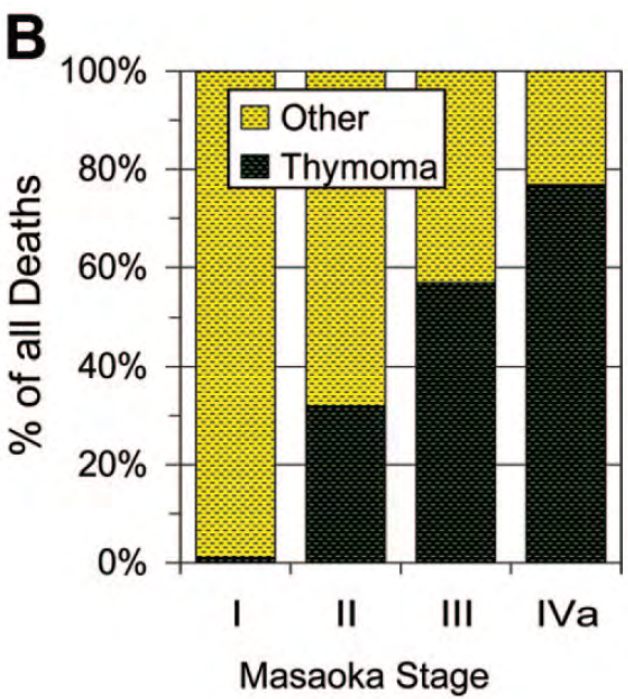
- Hémogramme avec taux de réticulocytes
- Electrophorèse des protéines sériques, avec dosage pondéral des immunoglobulines
- Dosage des anticorps anti-nucléaires
- Dosage des anticorps anti-récepteurs à l'acétylcholine (si positif, pas d'indication d'EMG)
- Dosage de la TSH

Rinaldi et al. Neurol Sci 2009;30:237

Prognosis of thymoma

- **Causes of death :**



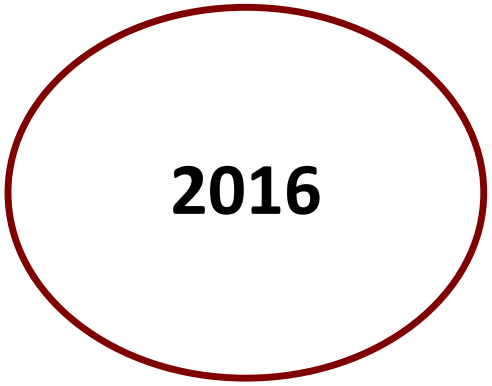


Huang et al. J Thorac Oncol 2010;5:2017

Tumeurs thymiques

Specificities

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



Masaoka-Koga staging system

TABLE 1. Masaoka-Koga Staging System

Stage	Definition
I	Grossly and microscopically completely encapsulated tumor
IIa	Microscopic transcapsular invasion
b	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organ (i.e., pericardium, great vessel, or lung)
IVa	Pleural or pericardial metastases
b	Lymphogenous or hematogenous metastasis

Adapted from *Pathol Int* 1994;44:359–367.

Classification Masaoka-Koga-ITMIG

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

TABLE 1. Masaoka-Koga Staging System

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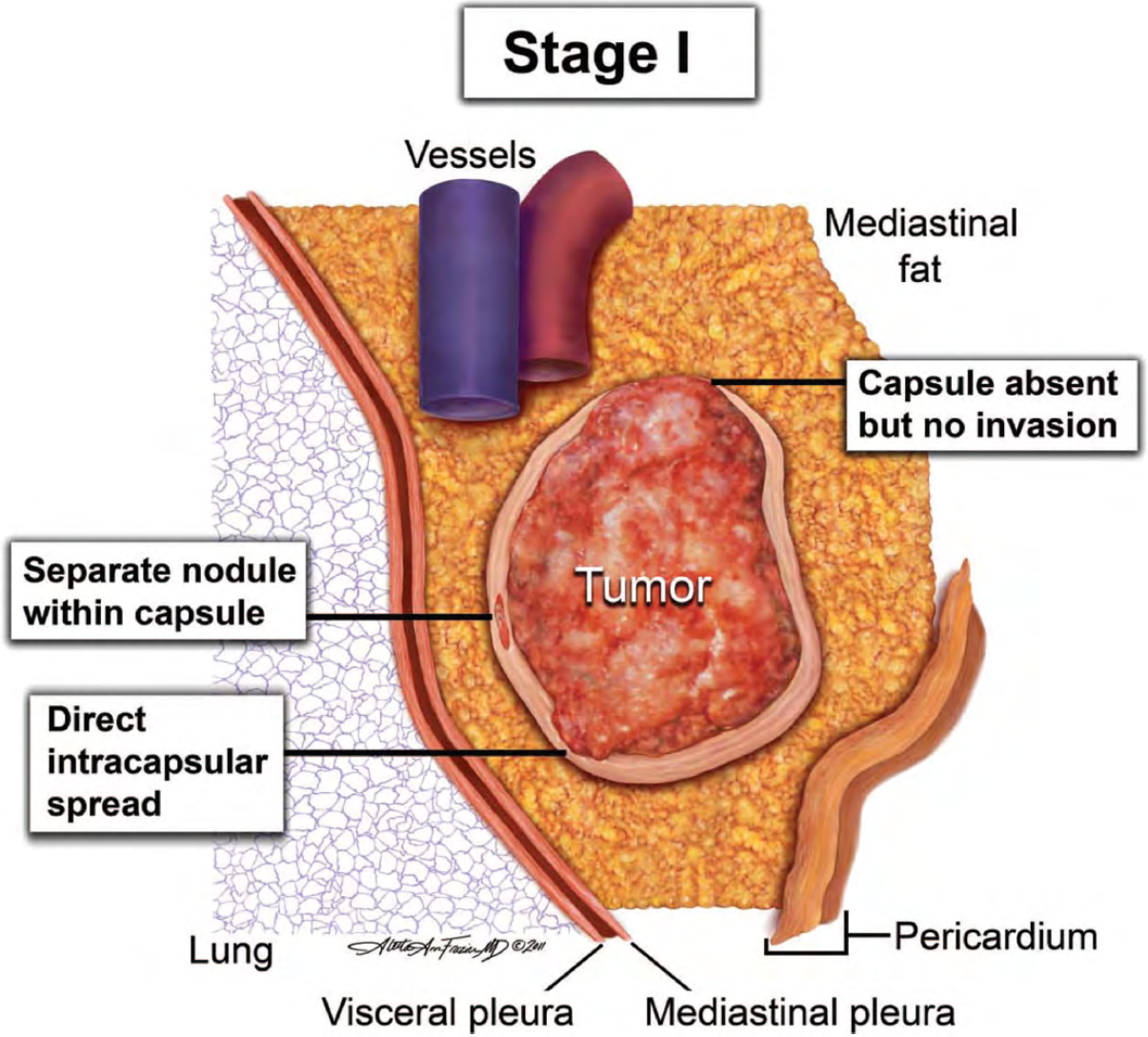
Adapted from *Pathol Int* 1994;44:359–367.

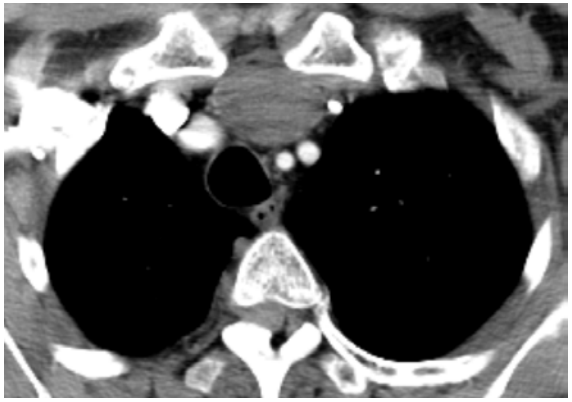
TABLE 2. ITMIG Definition of Details of the Masaoka-Koga Staging System

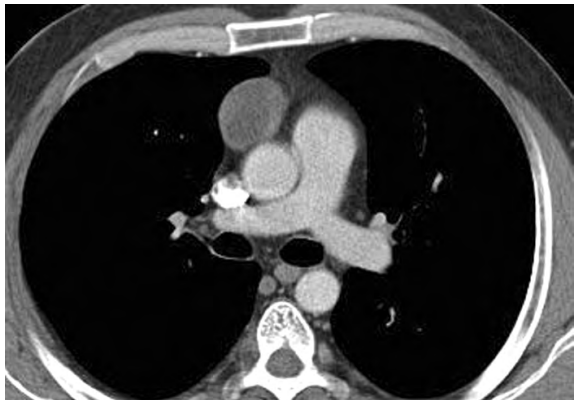
Stage	Definition (the ITMIG Interpretation of Details Is in Italics)
	Grossly and microscopically completely encapsulated tumor *This includes tumors with invasion into but not through the capsule, or …* *Tumors in which the capsule is missing but without invasion into surrounding tissues*
IIa	Microscopic transcapsular invasion *Microscopic 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 tumor extension into normal thymus or perithymic fat surrounding the thymoma (microscopically confirmed), or …*

Detterbeck et al. J Thorac Oncol 2011;6:S1710

Stade I

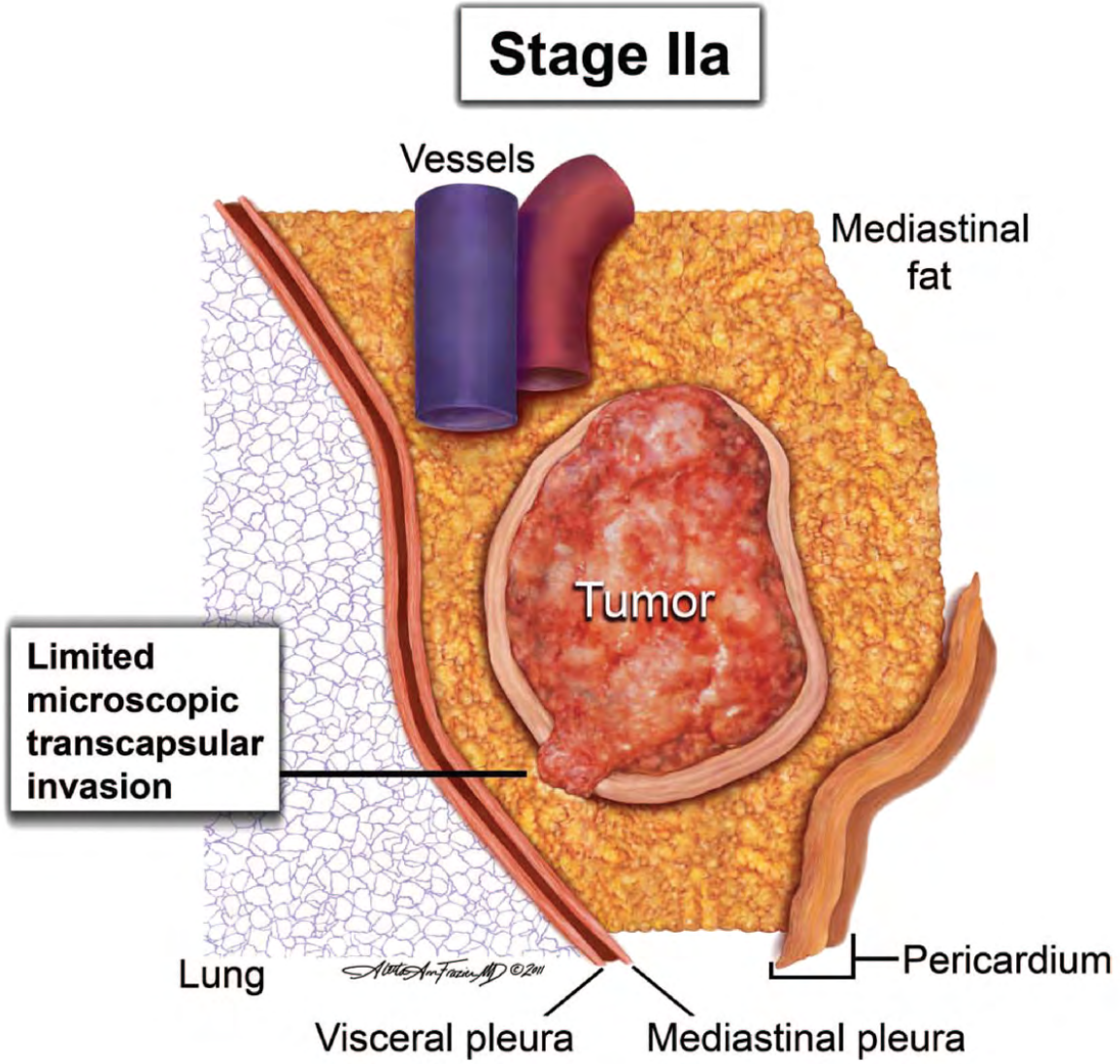


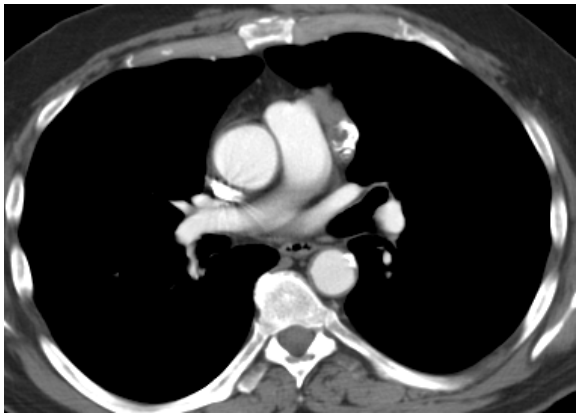


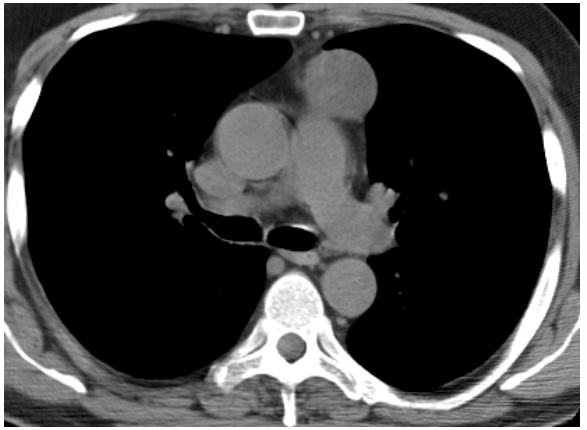


Detterbeck et al. J Thorac Oncol 2011;6:S1710

Stade IIA

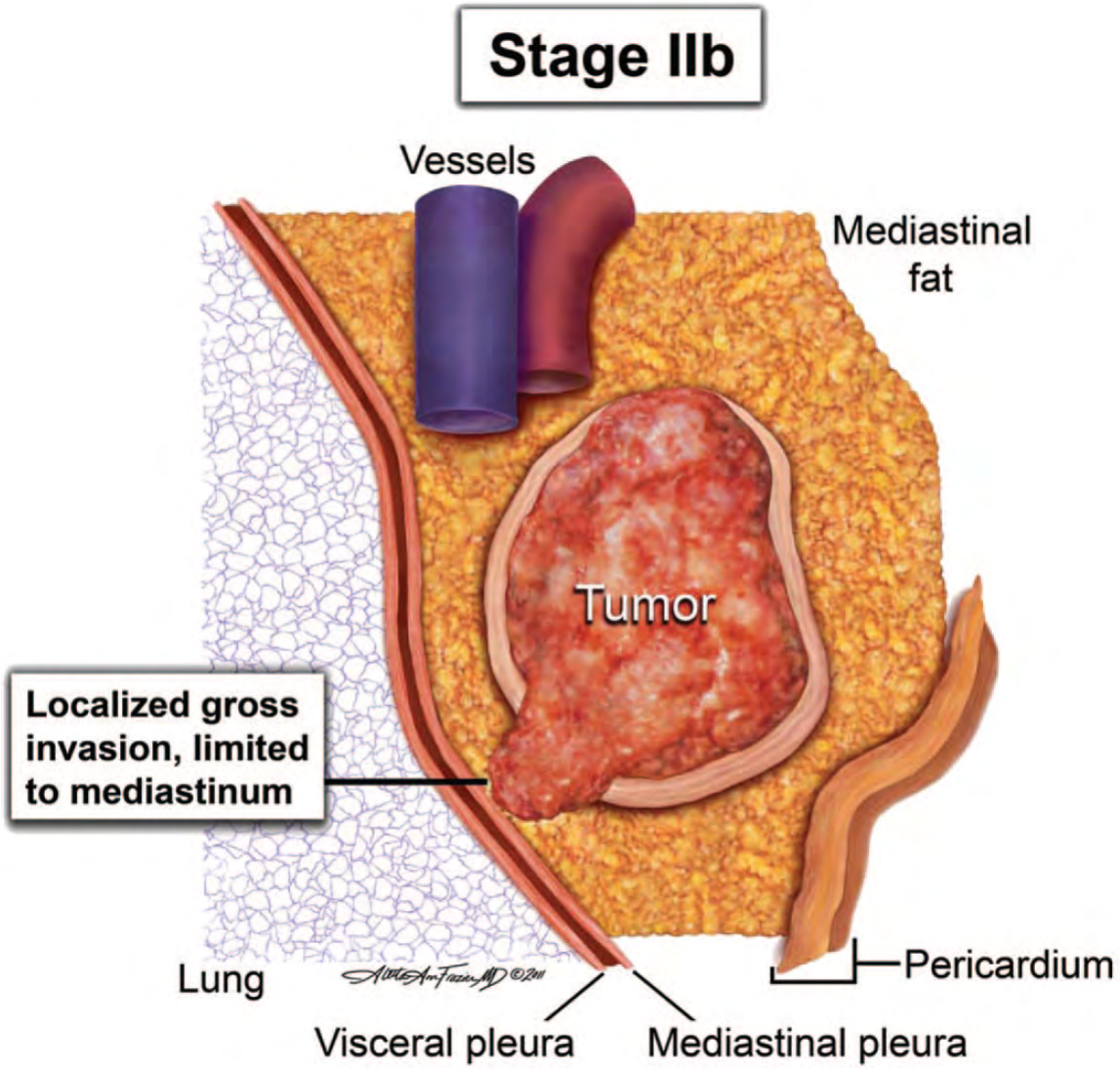


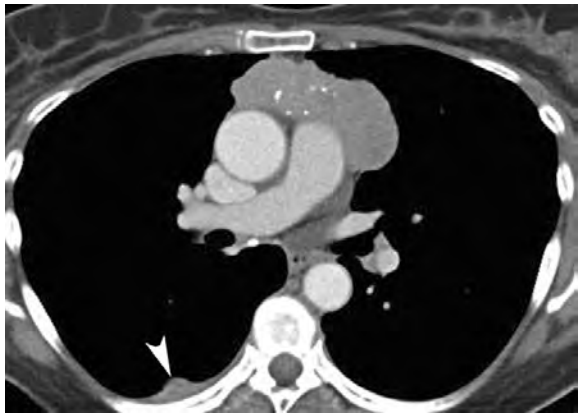




Detterbeck et al. J Thorac Oncol 2011;6:S1710

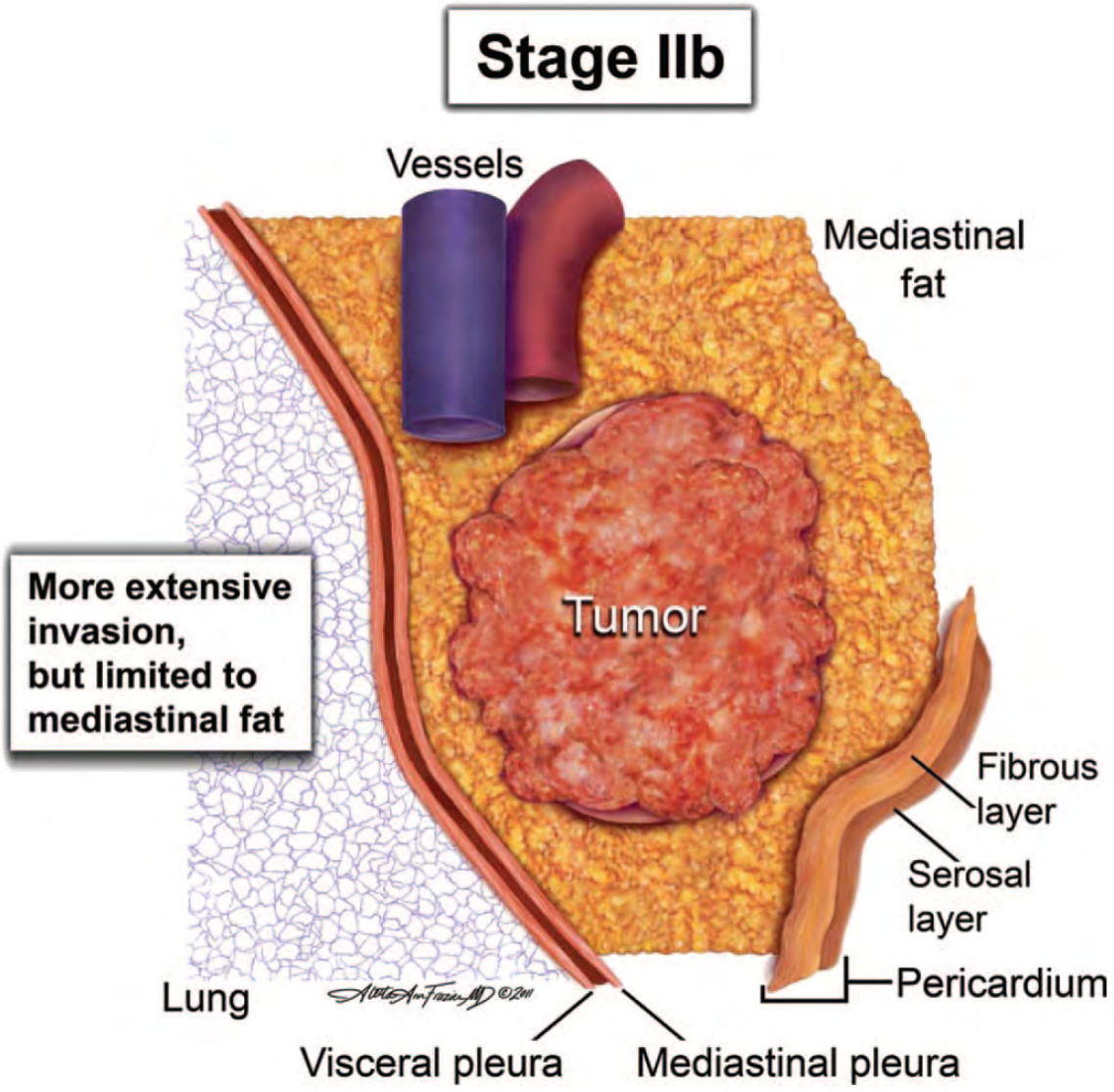
Stade IIB

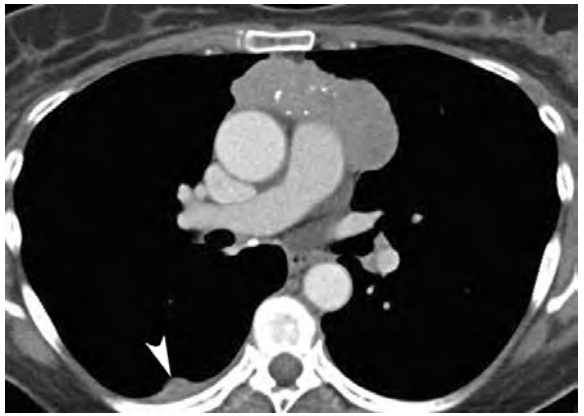


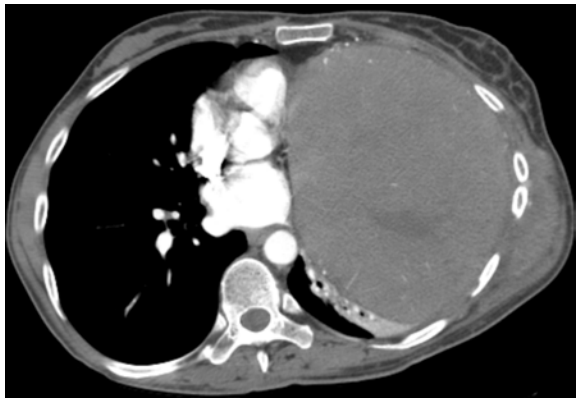


Detterbeck et al. J Thorac Oncol 2011;6:S1710

Stade IIB

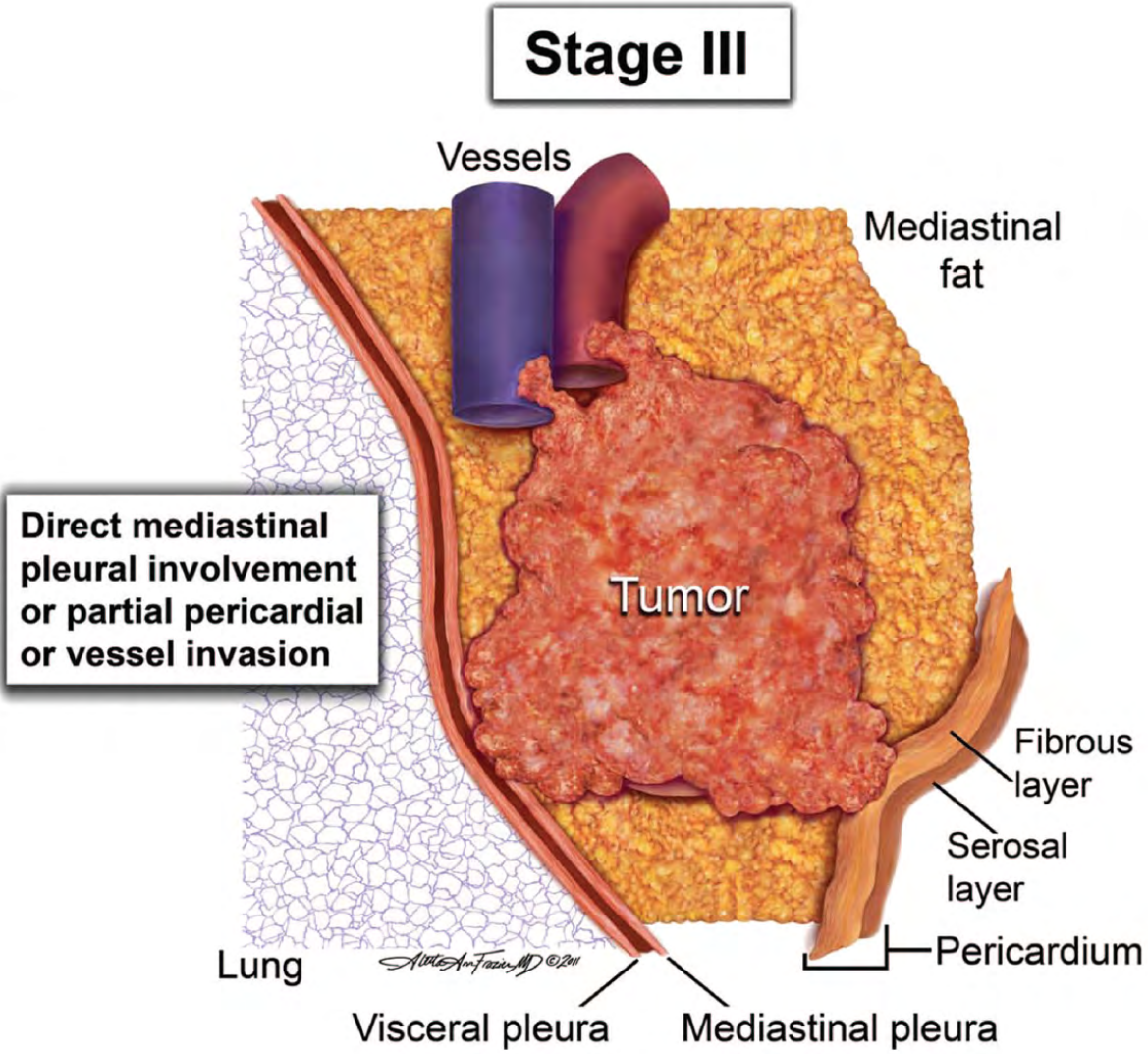


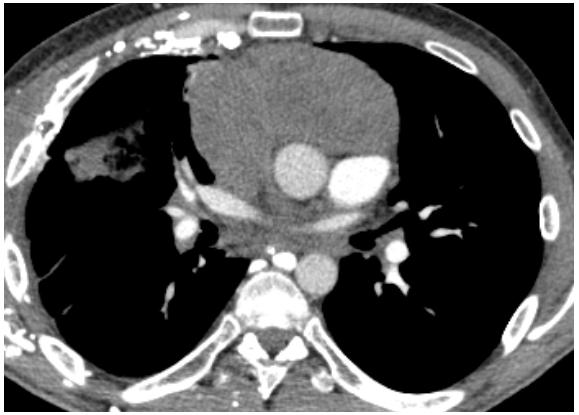




Detterbeck et al. J Thorac Oncol 2011;6:S1710

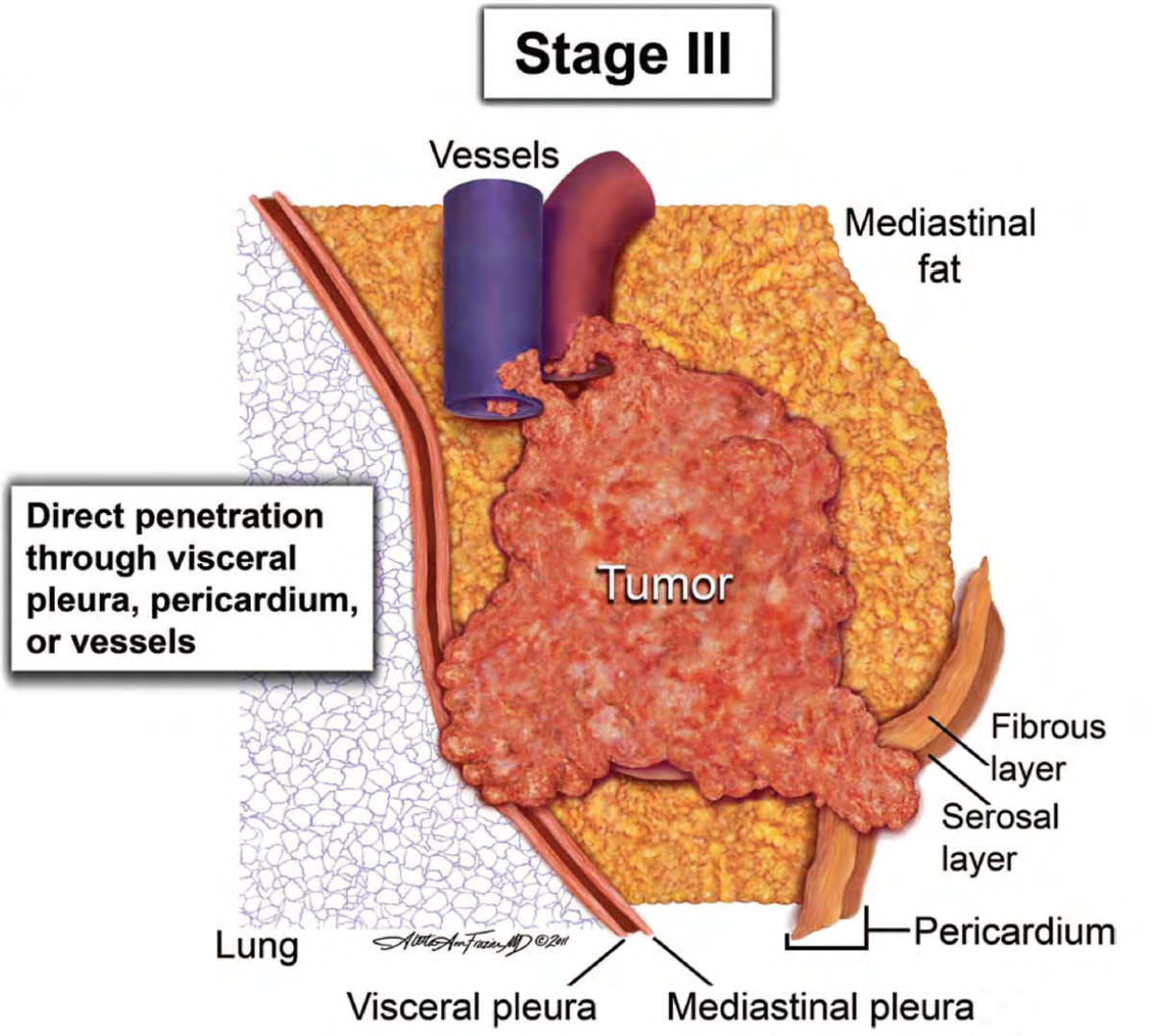
Stade III

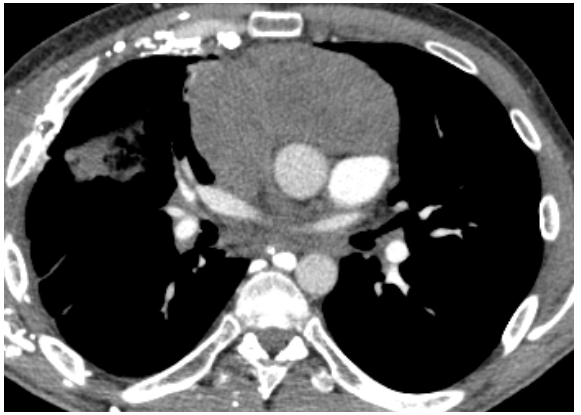




Detterbeck et al. J Thorac Oncol 2011;6:S1710

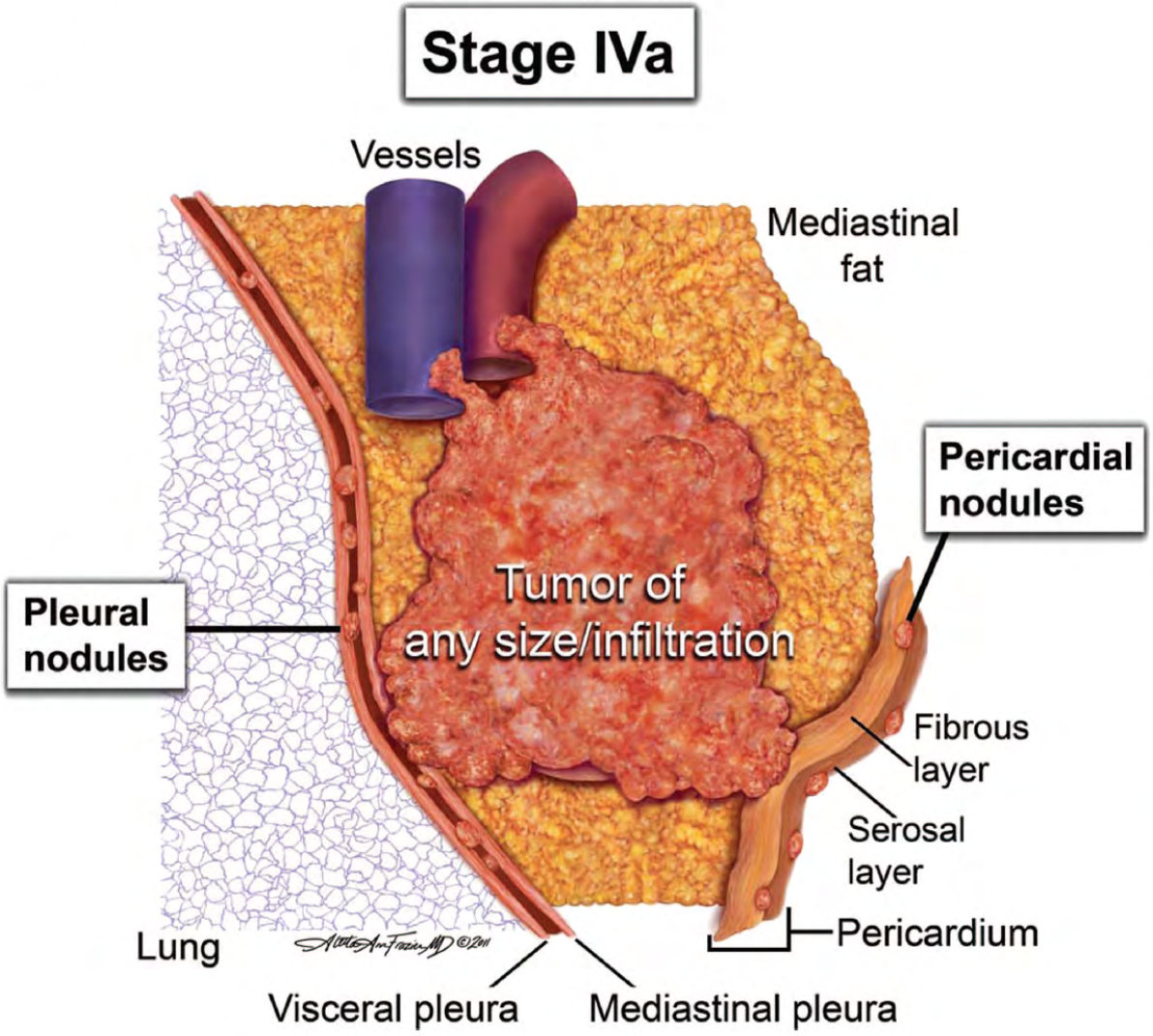
Stade III

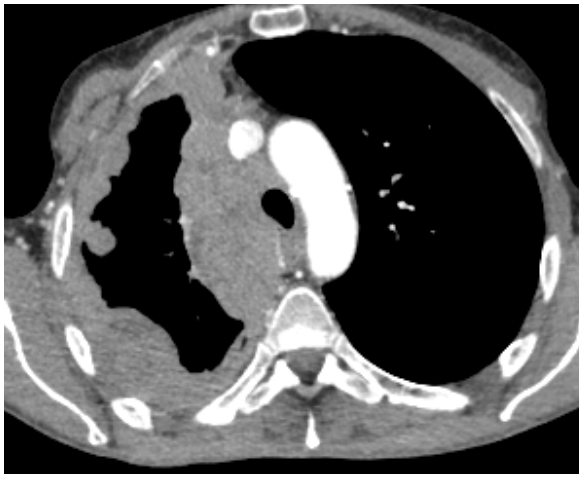




Detterbeck et al. J Thorac Oncol 2011;6:S1710

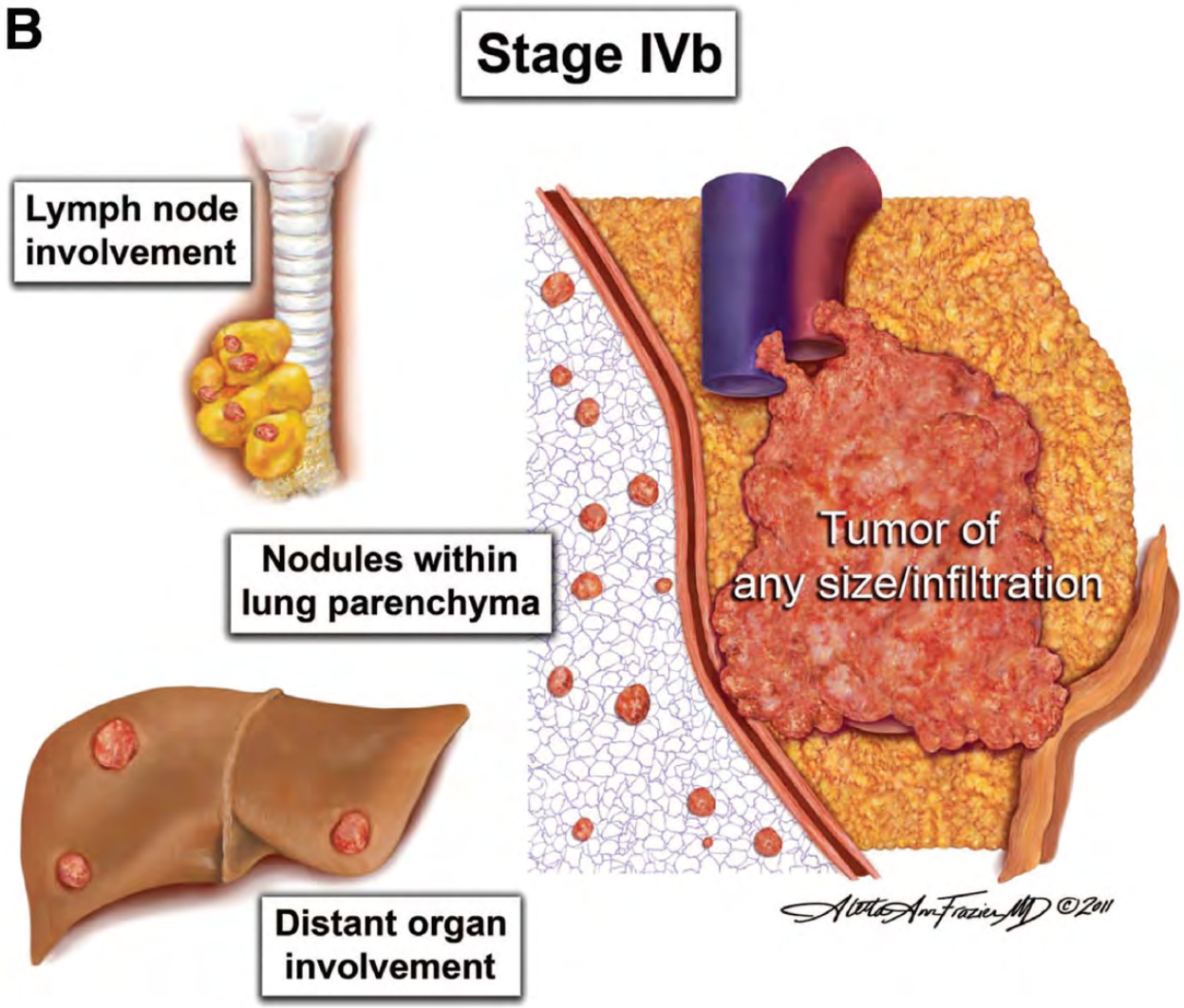
Stade IVA





Detterbeck et al. J Thorac Oncol 2011;6:S1710

Stade IVB

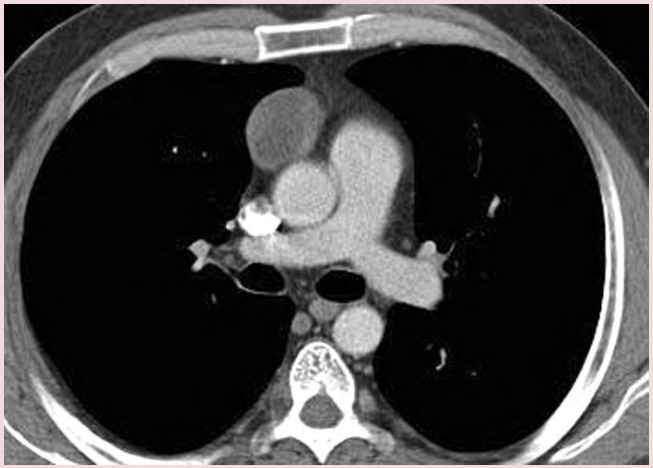


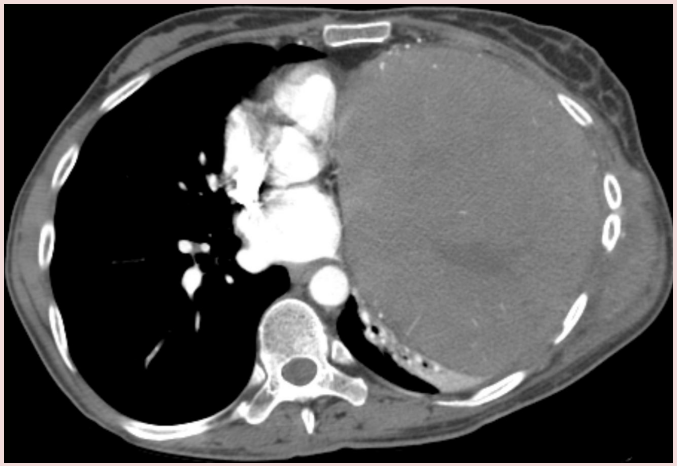
Detterbeck et al. J Thorac Oncol 2011;6:S1710

Masaoka-Koga staging system

Surgical pathology staging

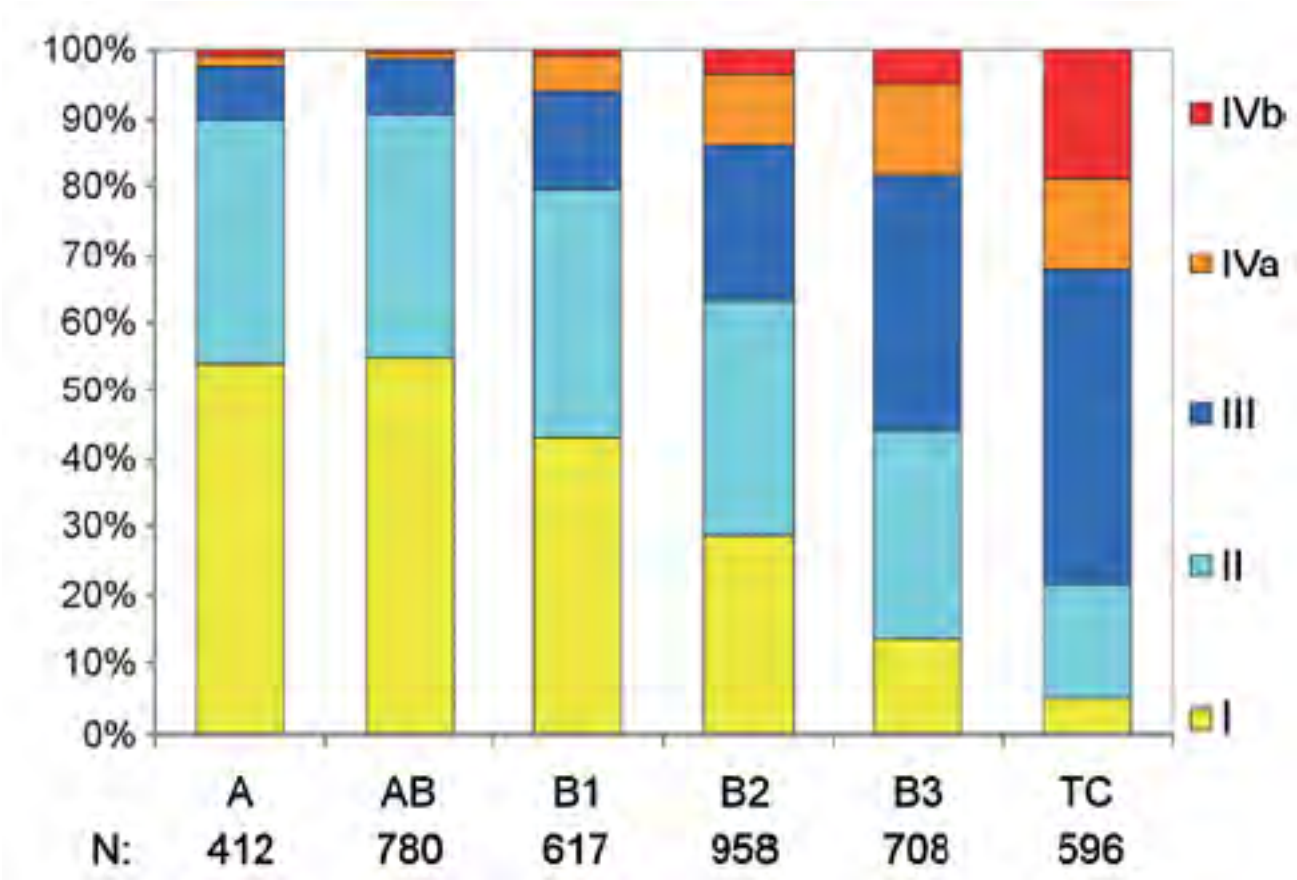
No clinical staging



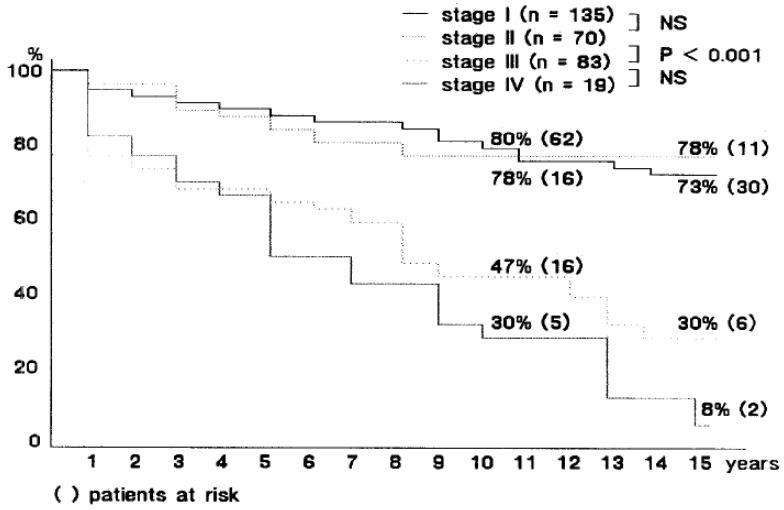


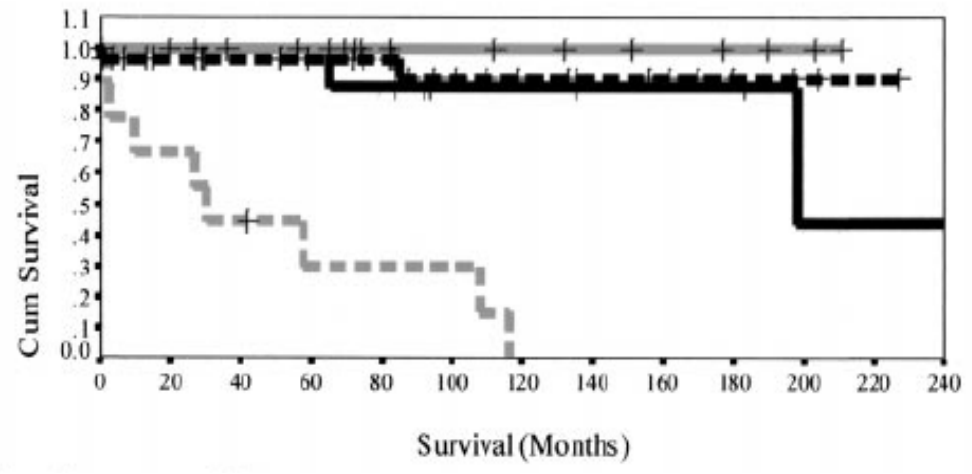
Thymic epithelial tumors: stage and histology

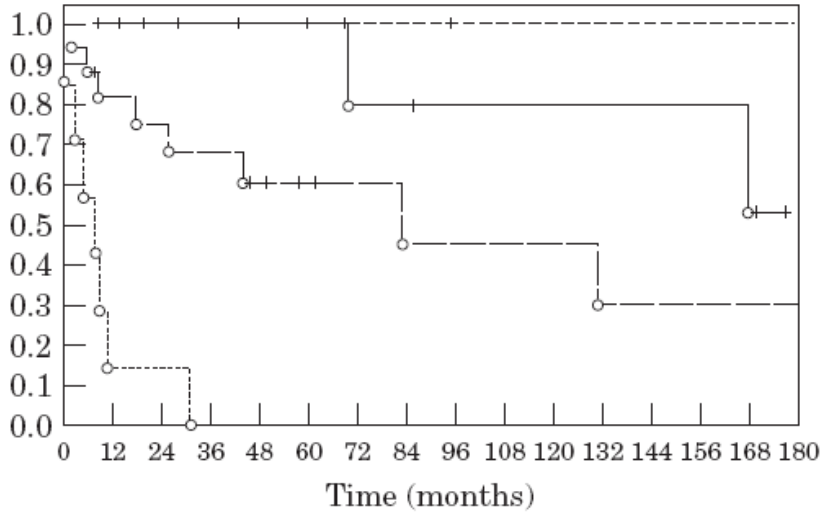
WHO, 2016



Prognostic value of the Masaoka staging system







Regnard et al. J Thorac Cardiovasc Surg 1996; 112: 376
Moore et al. Ann Thorac Surg 2001; 72: 203
Gawrychowski et al, EurJ Surg Oncol 2000; 26: 203-8

Tumeurs thymiques

Specificities

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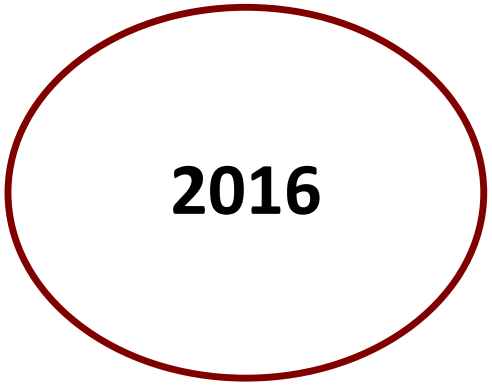
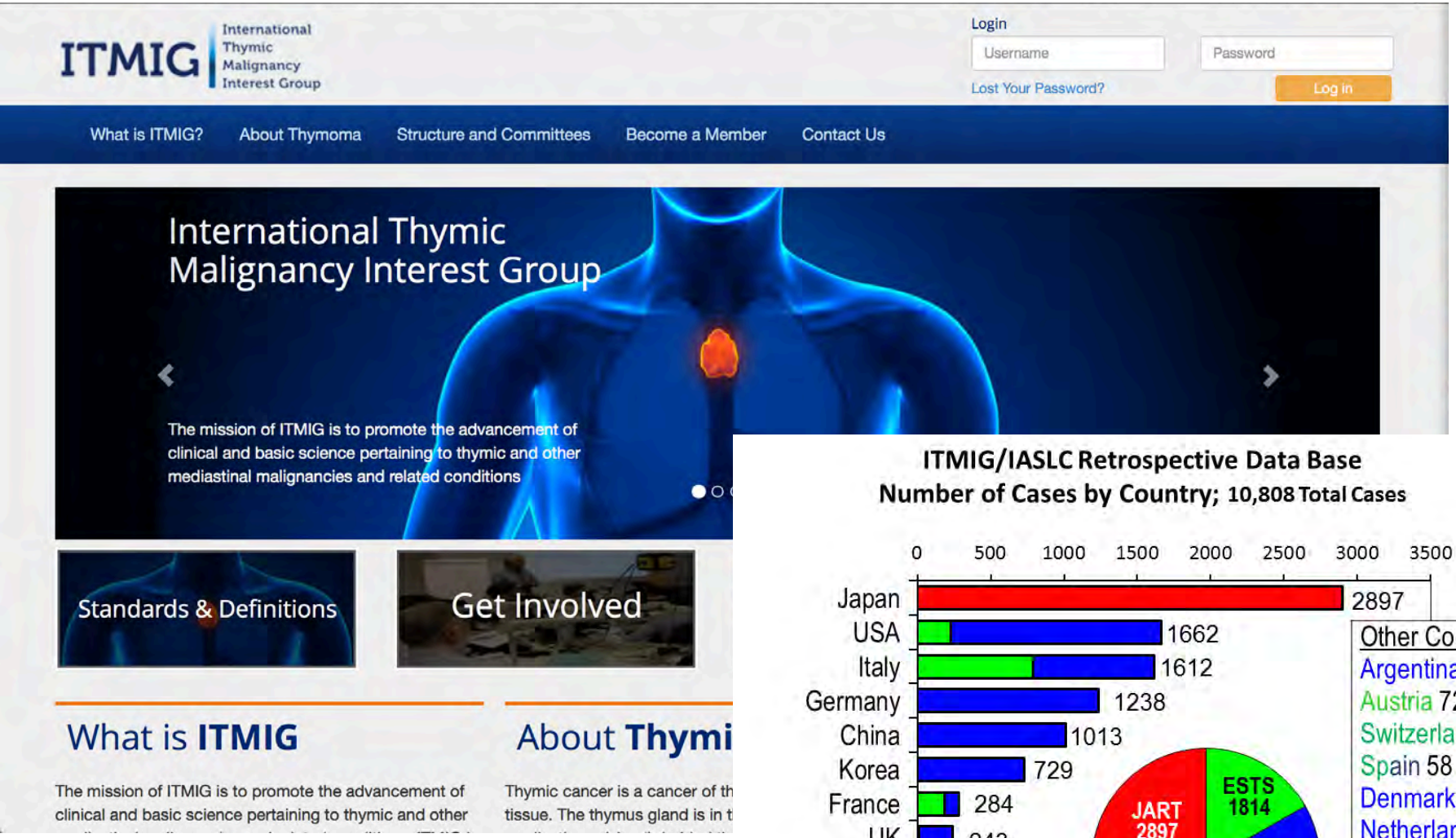
- Complex histology
- Auto-immunity
- **Staging**

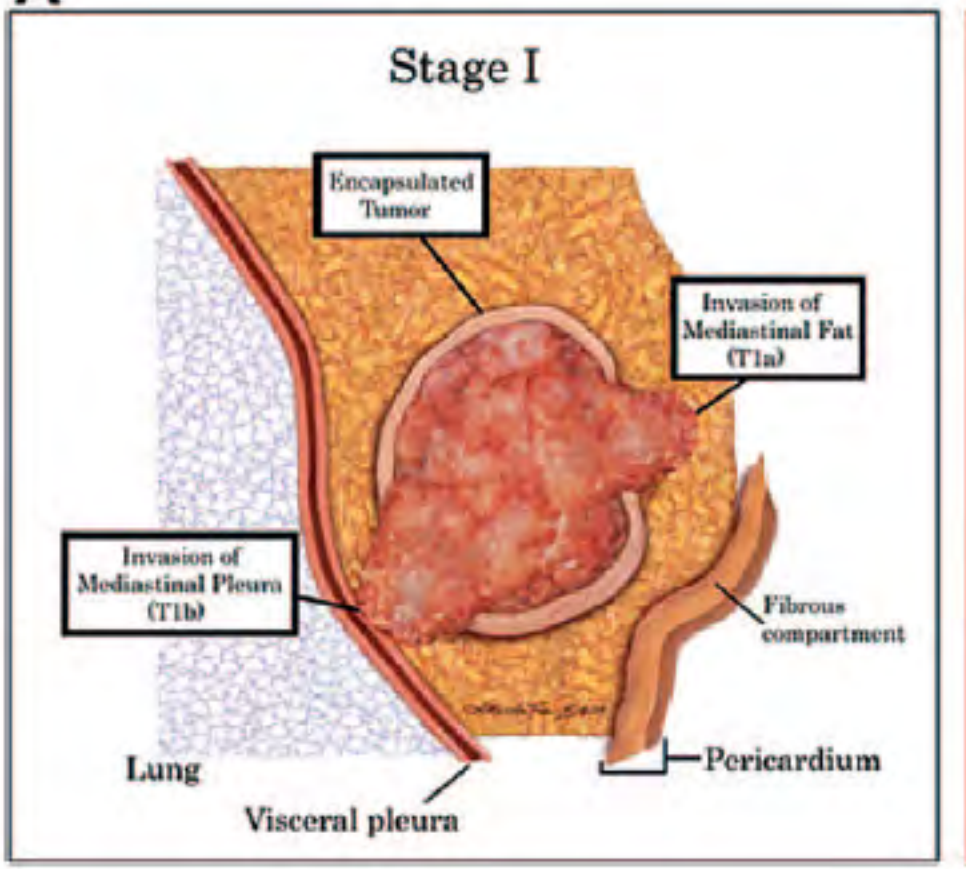


International Thymic Malignancy Interest Group



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. Detterbec… o Asamura, MD,‡ John Crowley, PhD,† C… ta A. Frazier, MD,‖‖‖ Giuseppe Giaccone, …ya Kondo, MD,††, Marco Lucchi, MD,‡‡, M… G. Nicholson, MD,¶¶, Meinoshin Okumura, M… behalf of the Staging and Progn… …ards,‡‡‡



Masaoka-Koga : I, IIA, IIB, III

(*J Thorac Oncol.* 2014;9: S65–S72

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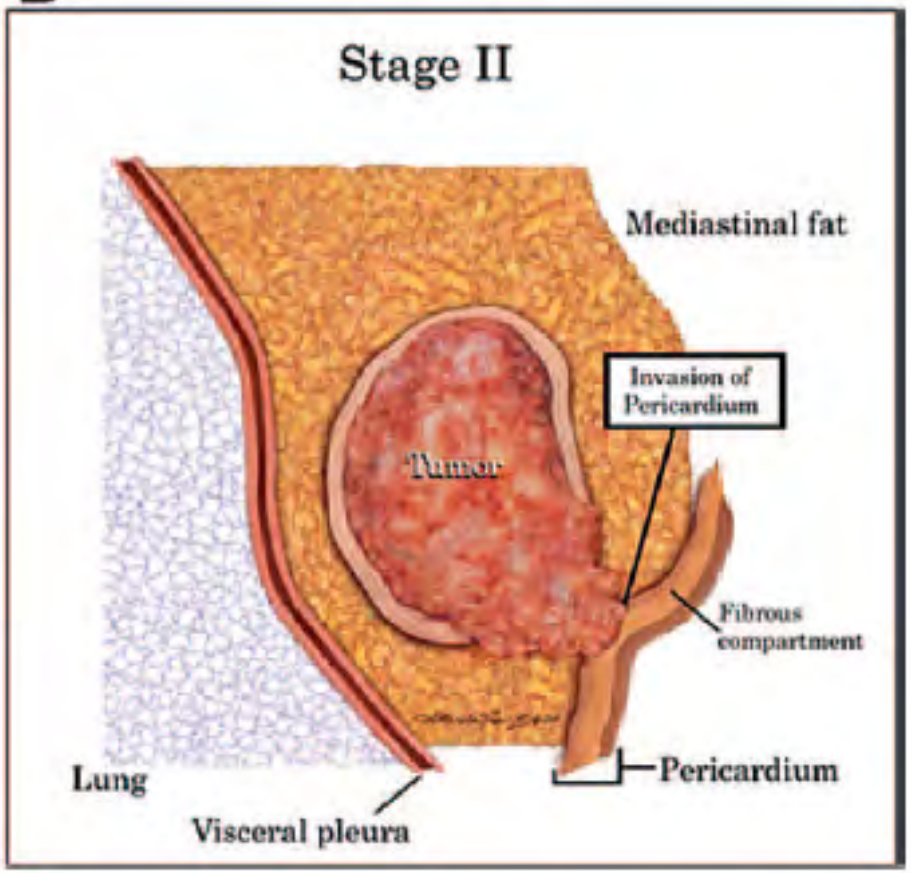
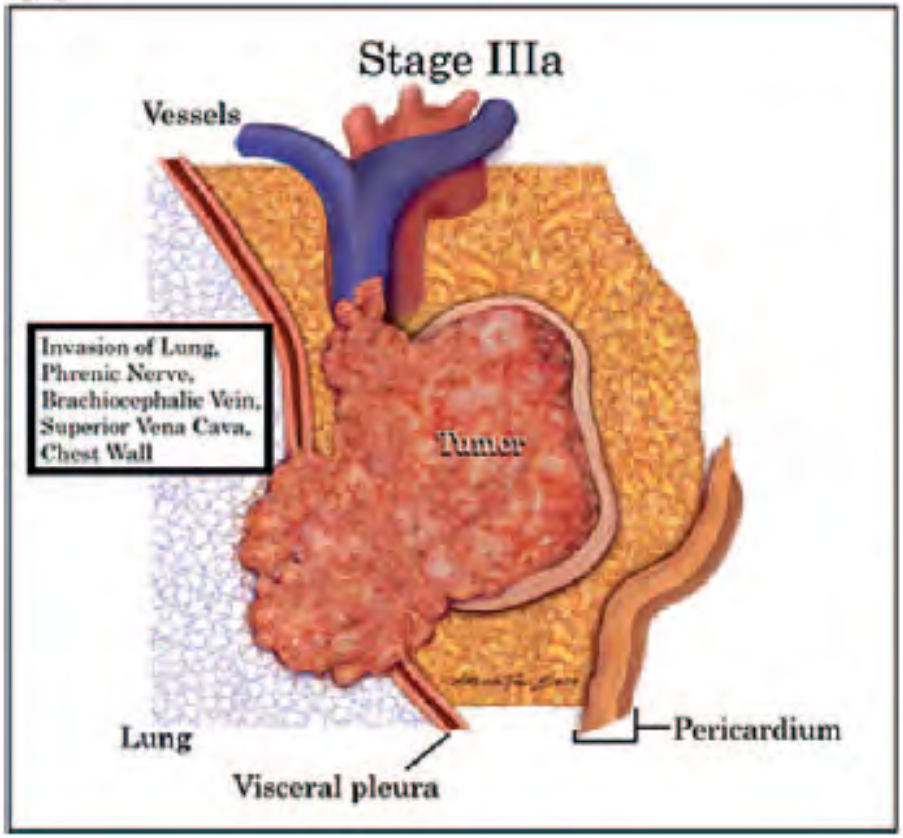
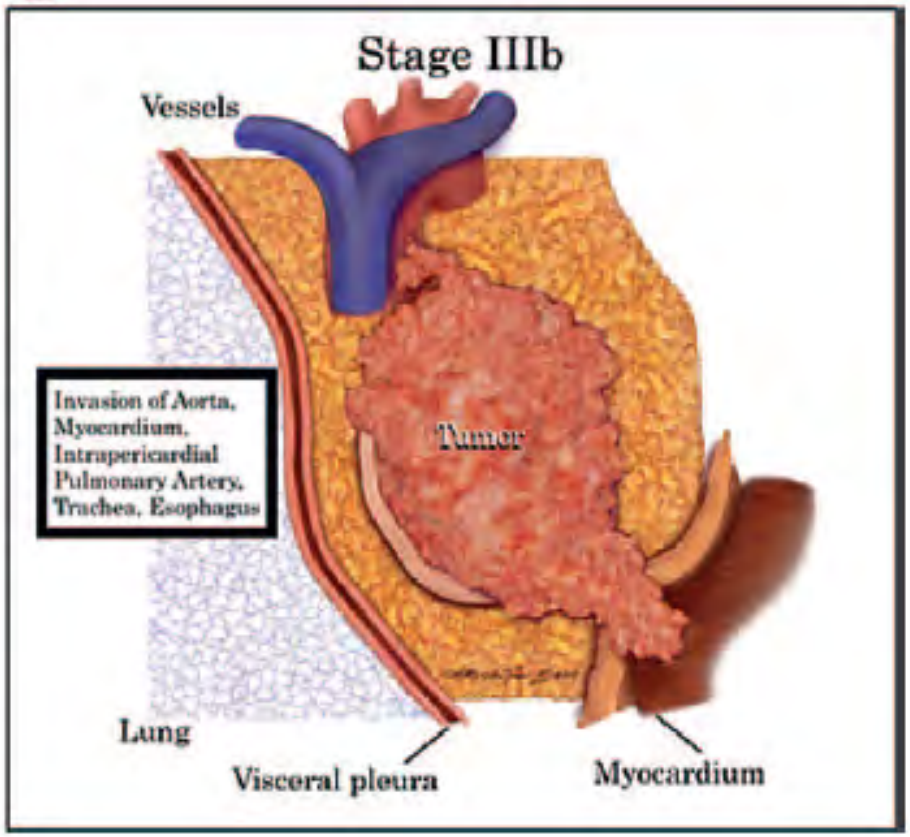


Masaoka-Koga : III

(*J Thorac Oncol.* 2014;9: S65–S72

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

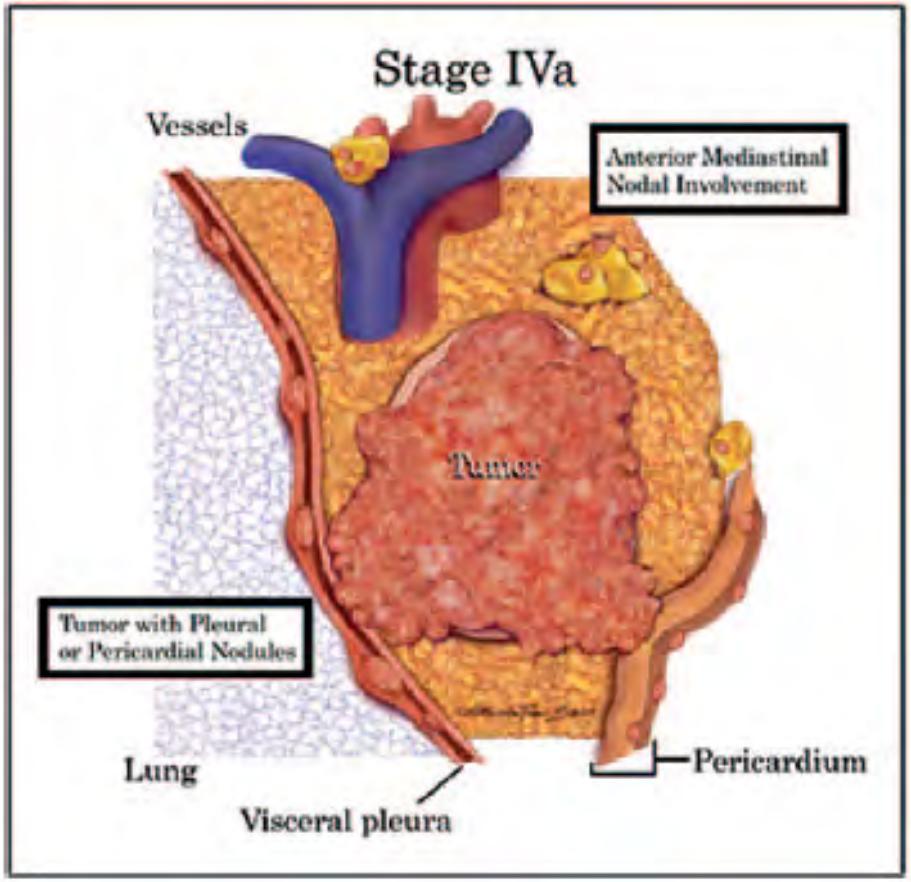


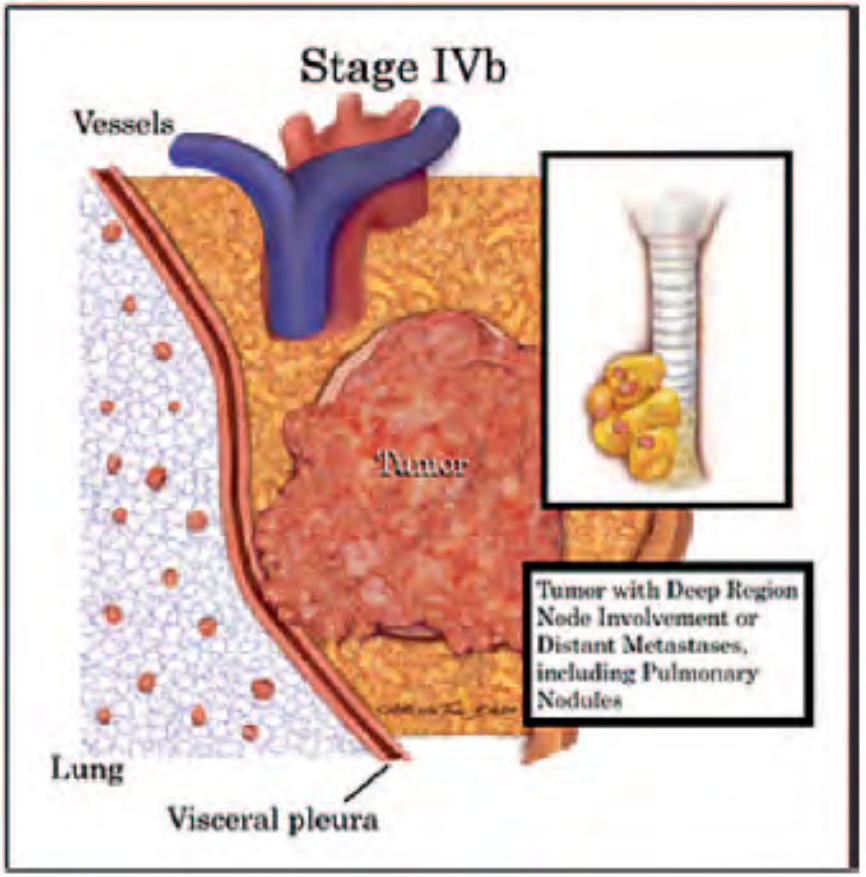


Masaoka-Koga : III

(*J Thorac Oncol.* 2014;9: S65–S72

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

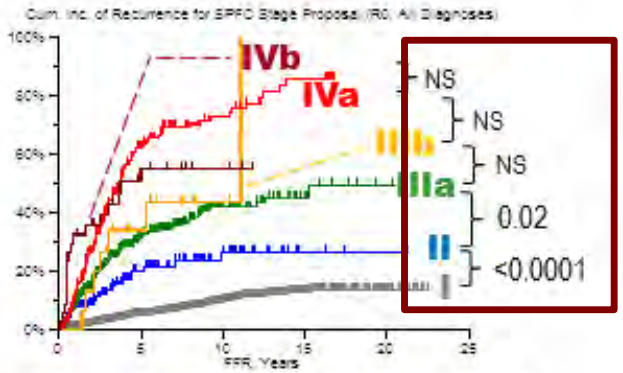
Masaoka-Koga : IVB

(*J Thorac Oncol.* 2014;9: S65–S72

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

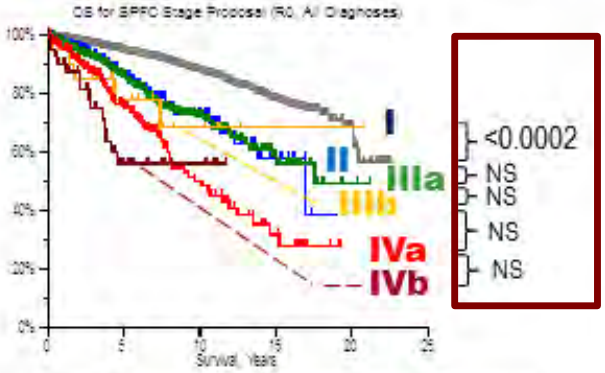
Figure e1: Outcomes of all Patients by Proposed Stage Groups

Recurrence, R0



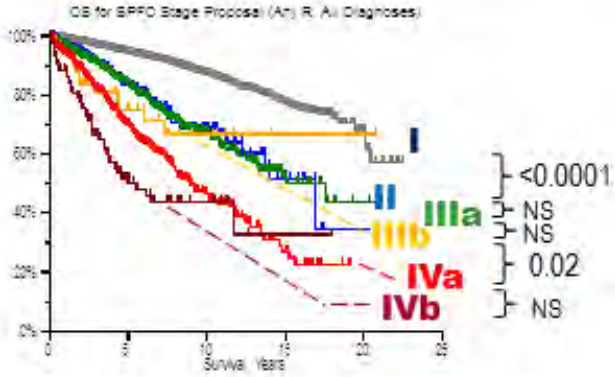
Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
I	192/3659	5.1% (5.1, 5.2)	5.7% (5.6, 5.9)
II	22/124	20% (17.6, 22.8)	27% (22.1, 31.1)
IIIa	142/455	32% (29.6, 34.4)	42% (37.0, 45.9)
IIIb	[illegible]	[illegible]	[illegible]
IVa	119/201	62% (47.4, 77.3)	73% (43.3, 100)
IVb	17/35	51% (23.5, 78.0)	55% (27.8, 82.4)

Overall Survival, R0



Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
I	363/5134	94% (93.6, 95.2)	88% (86.2, 89.2)
II	30/187	87% (80.3, 93.3)	73% (63.5, 83.1)
IIIa	108/588	85% (82.6, 89.2)	73% (67.3, 77.7)
IIIb	[illegible]	[illegible]	[illegible]
IVa	75/251	75% (68.5, 81.7)	59% (39.9, 60.2)
IVb	14/43	56% (38, 74)	56% (38, 74)

Overall Survival, any R

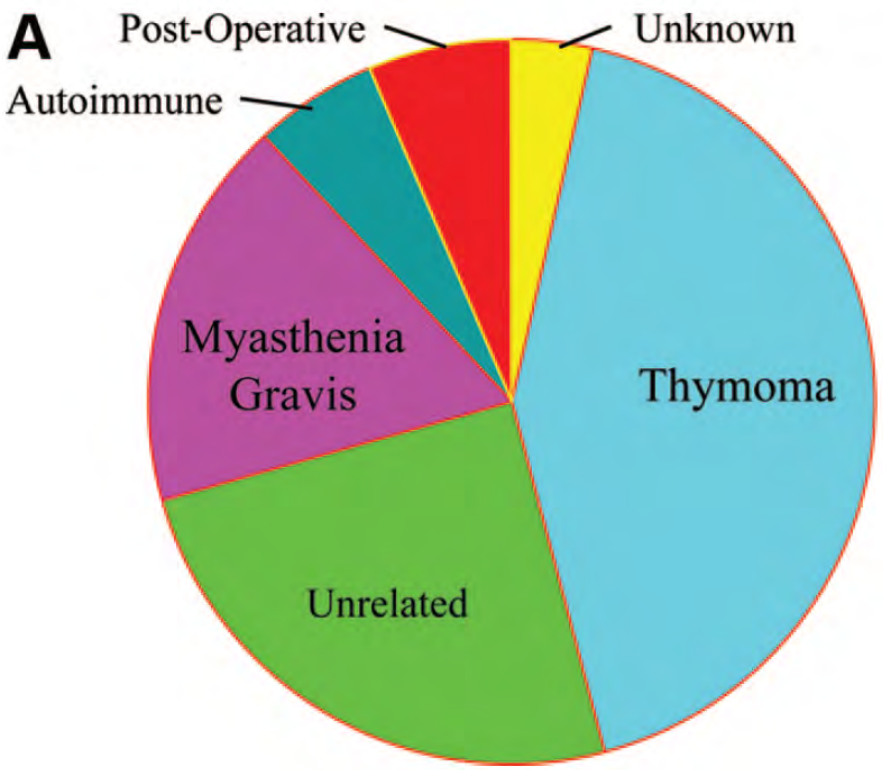


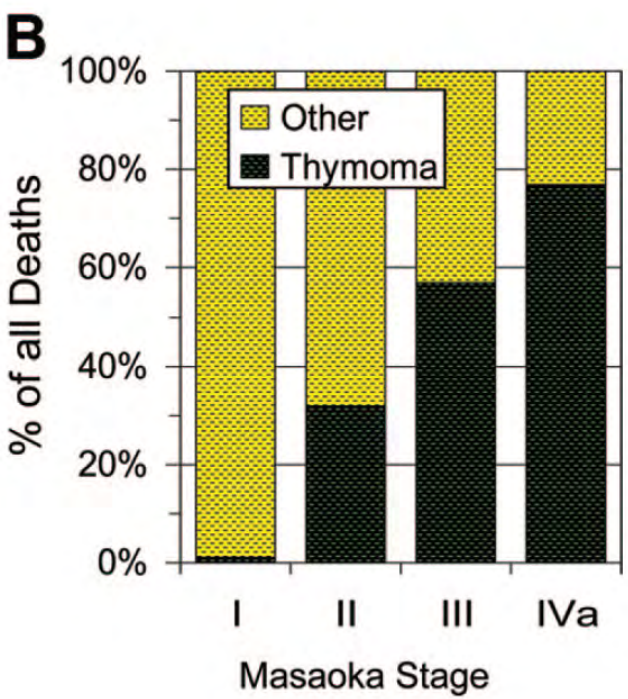
Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
I	405/8487	94% (93.5, 95)	87% (86.5, 88.5)
II	43/239	84% (77.6, 90)	69% (59.7, 78.1)
IIIa	163/778	83% (80.3, 86.5)	67% (62.4, 72.2)
IIIb	[illegible]	[illegible]	[illegible]
IVa	209/654	70% (65.7, 74.4)	46% (40.1, 52.6)
IVb	43/99	52% (40.2, 63.6)	44% (31.5, 55.9)

(*J Thorac Oncol.* 2014;9: S65–S72

Prognosis of thymoma

- **Causes of death :**

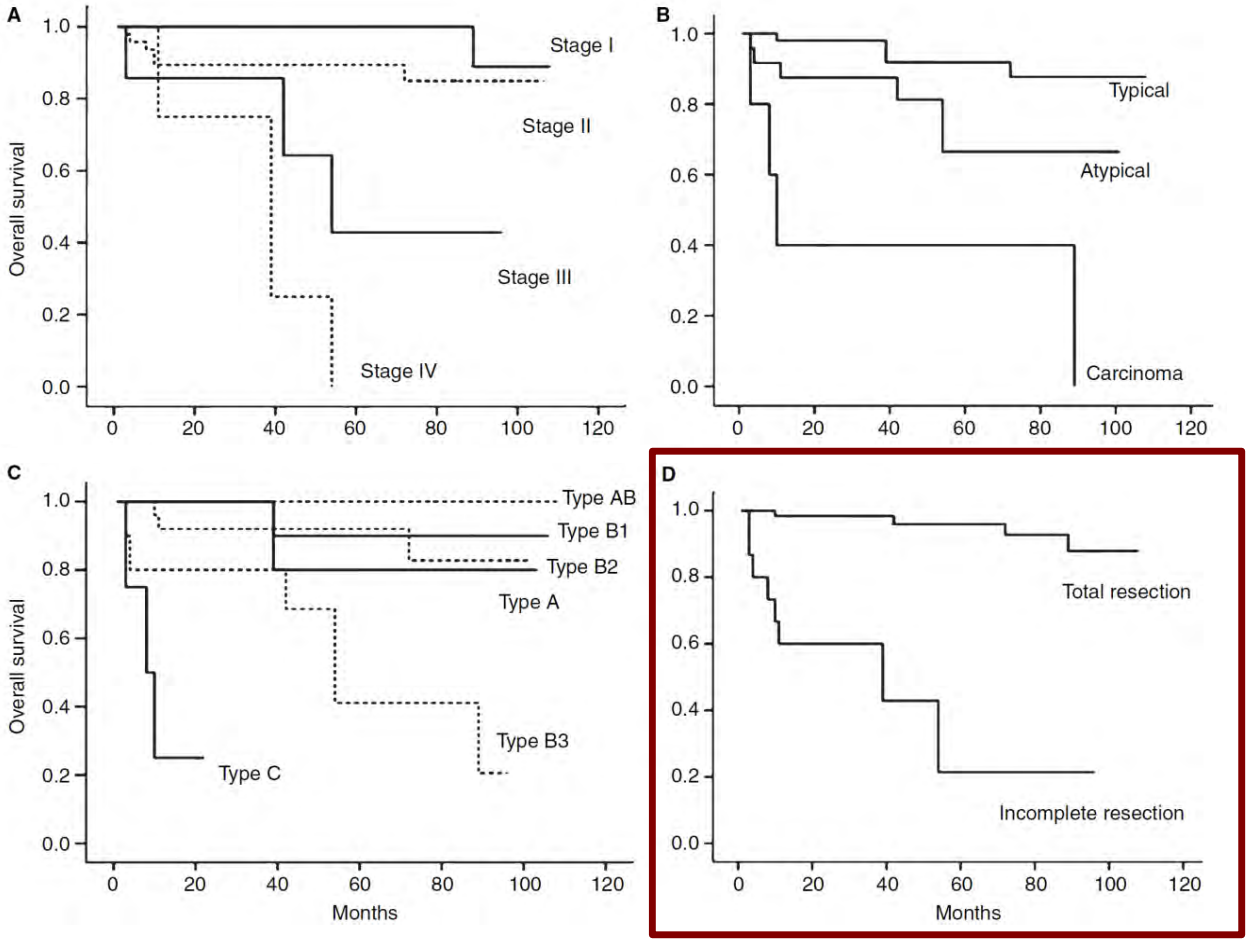




Huang et al. J Thorac Oncol 2010;5:2017

Stage, Histology, Other?

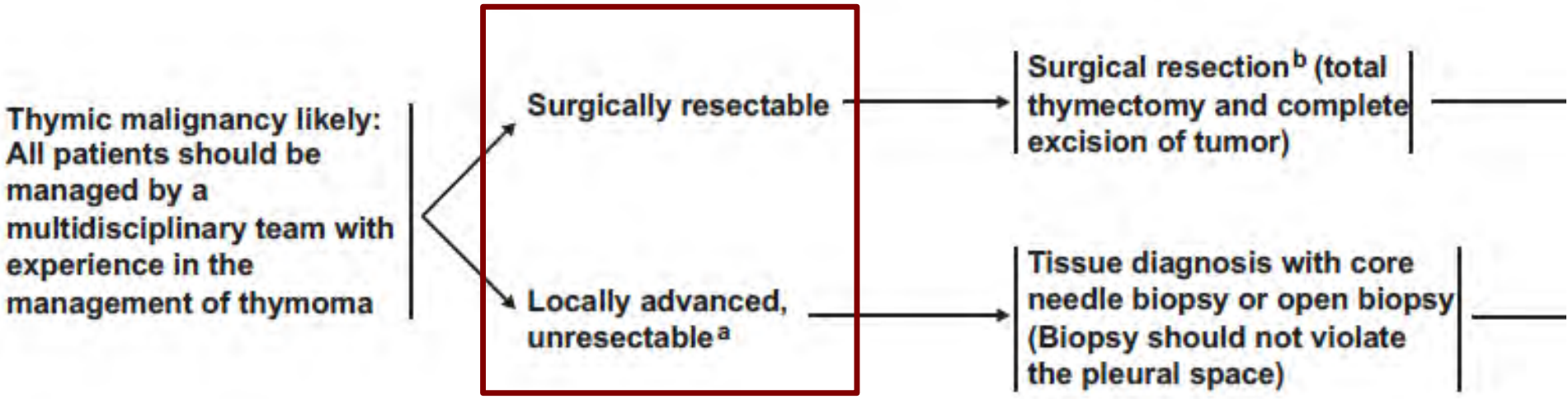
- The most significant prognostic factor in Tumeurs thymiquesis **the completion of surgical resection**, whatever classification is used.



Rossi et al. Histopathology 2008;53:483

Treatment of Tumeurs thymiques

- **First question is : resectable or not?**



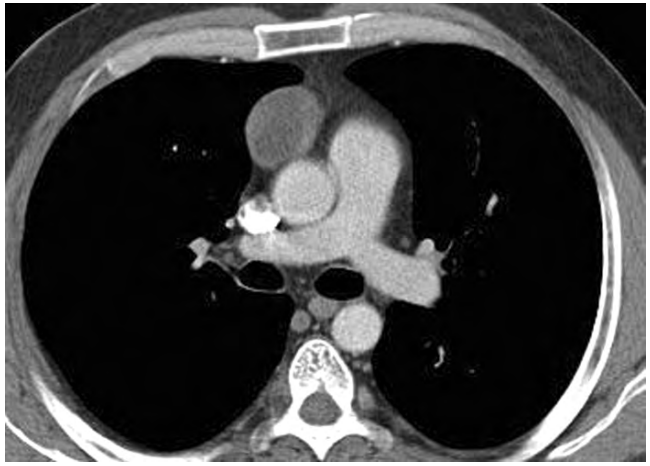
National Comprehensive Cancer Network Guidelines

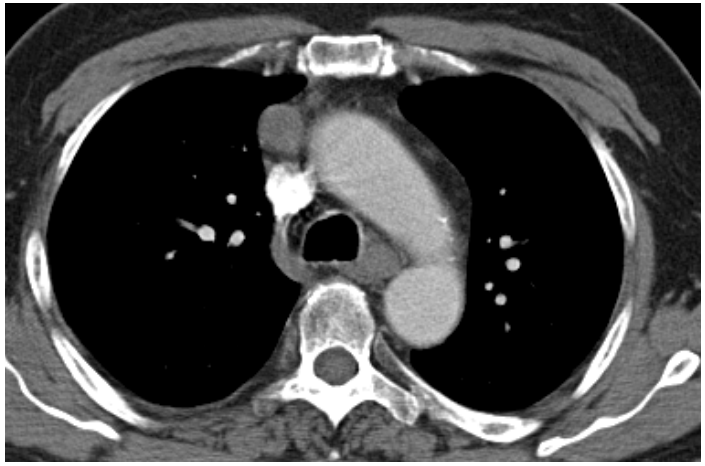
Treatment of Tumeurs thymiques

- **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[b] (total thymectomy and complete excision of tumor)**
- **Locally advanced, unresectable[a]** → **Tissue diagnosis with core needle biopsy or open biopsy (Biopsy should not violate the pleural space)**





National Comprehensive Cancer Network Guidelines

Tumeurs thymiques

Specificities

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

2016

Resectable tumors

Diagnostic différentiel

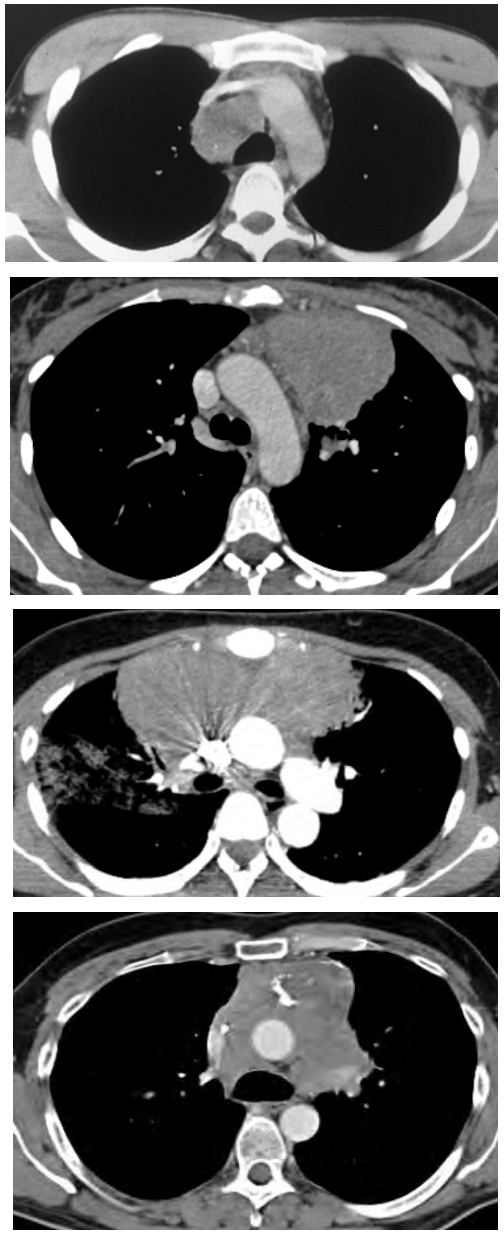
- **Les tumeurs primitives du médiastin antérieur ont un aspect radiologique souvent similaire**

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

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

J Thorac Oncol 2014;9:S102

Tumeurs thymiques

Specificities

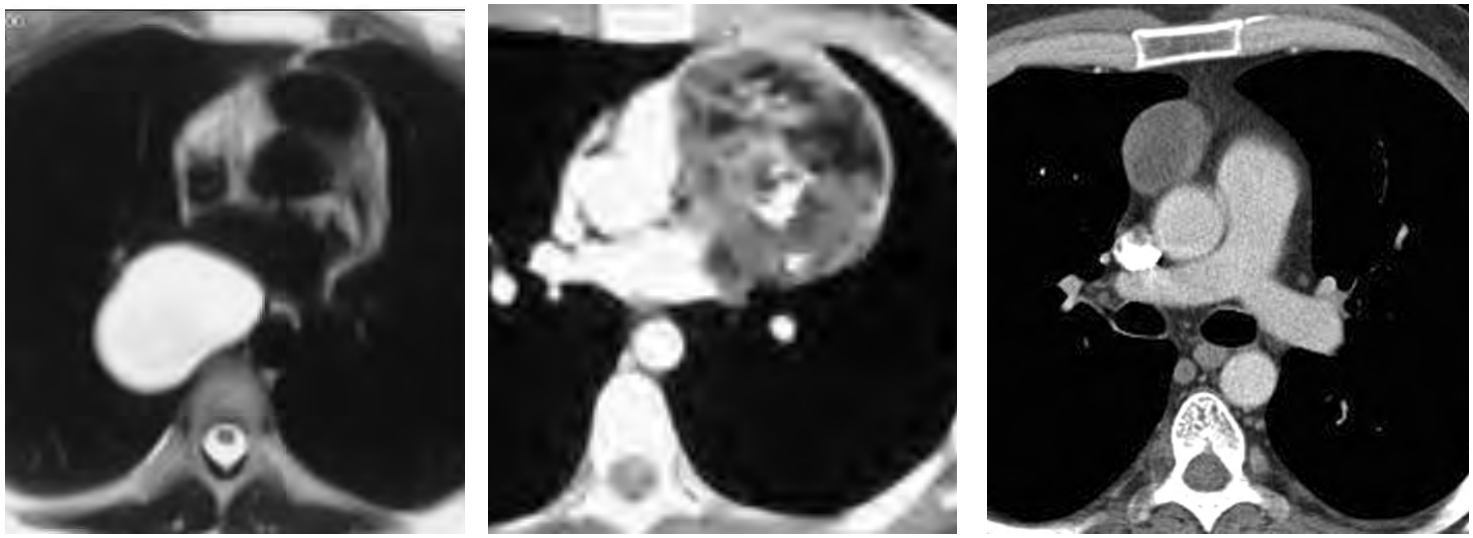
- Thymic origin
- Complex histology
- Auto-immunity
- Staging

2016

Resectable tumors

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**



Kesler et al. Ann Thorac Surg 2008;85:371
Kesler et al. Thor Surg Clin 2009;19:63
Lemarié et al. Chest 1992;102:1477

Nécessité d'une biopsie pré-thérapeutique

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  - Tumeurs bénignes: tératomes
  - 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

Kesler et al. Ann Thorac Surg 2008;85:371
Kesler et al. Thor Surg Clin 2009;19:63
Lemarié et al. Chest 1992;102:1477

Nécessité d'une biopsie pré-thérapeutique

- **La chirurgie est recommandée d'emblée pour certaines tumeurs du médiastin:**
  - Tumeurs bénignes: tératomes
  - Tumeurs kystiques
  - Thymom

- **La chimiothe** **maligne:**
  - si les mar
    - α-foe
    - β-hu
      - tumeur germinale non séminomateuse (choriocarcinome)
      - rare en cas de séminome

Dans tous les autres cas

biopsie

Kesler et al. Ann Thorac Surg 2008;85:371
Kesler et al. Thor Surg Clin 2009;19:63
Lemarié et al. Chest 1992;102:1477

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)

ITMIG International Thymic Malignancy Interest Group

Tumeurs thymiques

Specificities

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

2016

Resectable tumors

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

Hendrick et al. Rofo 1989:150:268;
Miniero R. Bone Marrow Transplant.1993;11:67
Gerhardt et al. Dtsch Med Wochenschr 2004;129:1916

Thymome ou hyperplasie thymique?

- **ELCAP lung cancer screening study:**

  - forme ovoïde et taille <3cm : hyperplasie

Shape and Width of Thymic Masses at Baseline CT

Shape	Width (cm) 0.7–1.0	1.0–3.0	>3.0	Total
Ovoid	6	28	5	39
Arrowhead	0	1	0	1
Bi-lobed	0	1	0	1
Total	6	30	5	41

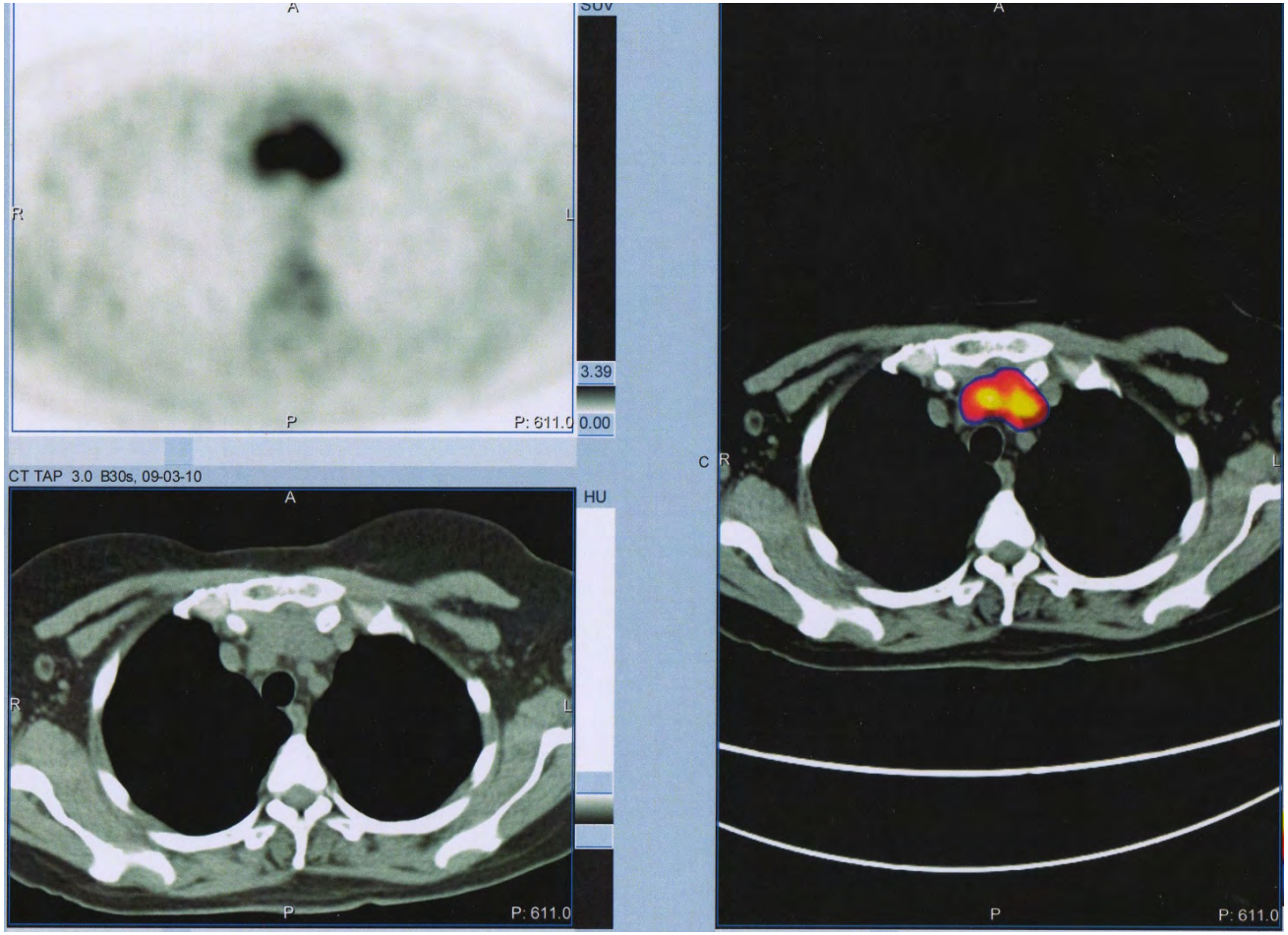
Change in Size of Ovoid Thymic Masses at 1-year Follow-up CT

Size Change	Width (cm) 0.7–1.0	1.0–3.0	Total
Decreased	0	2	2
No change	1	17	18
Increased	2	3	5
Total	3	22	25

Henschke et al. Radiology 2006; 23:239:586

Imagerie pré-thérapeutique

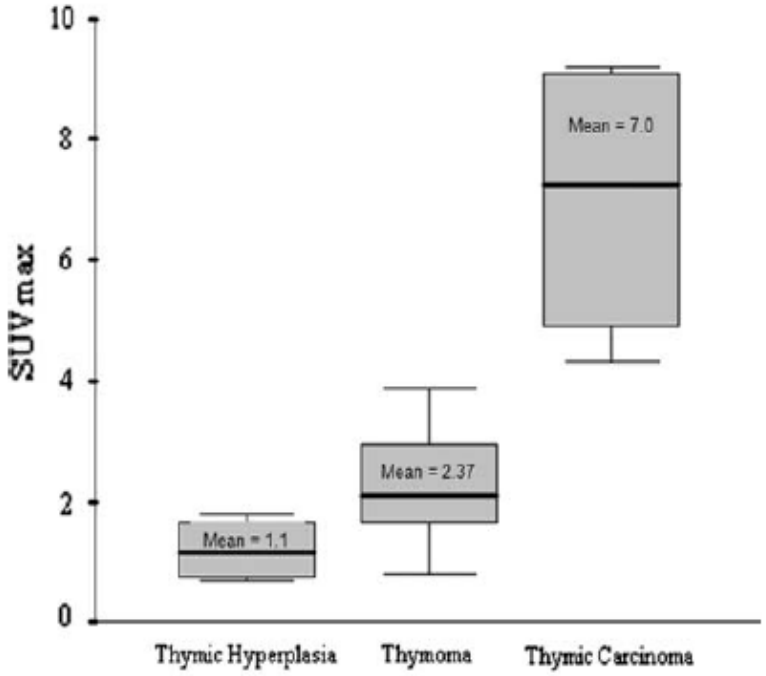
- **Utilisation du PET-scan : corrélation avec classifications**

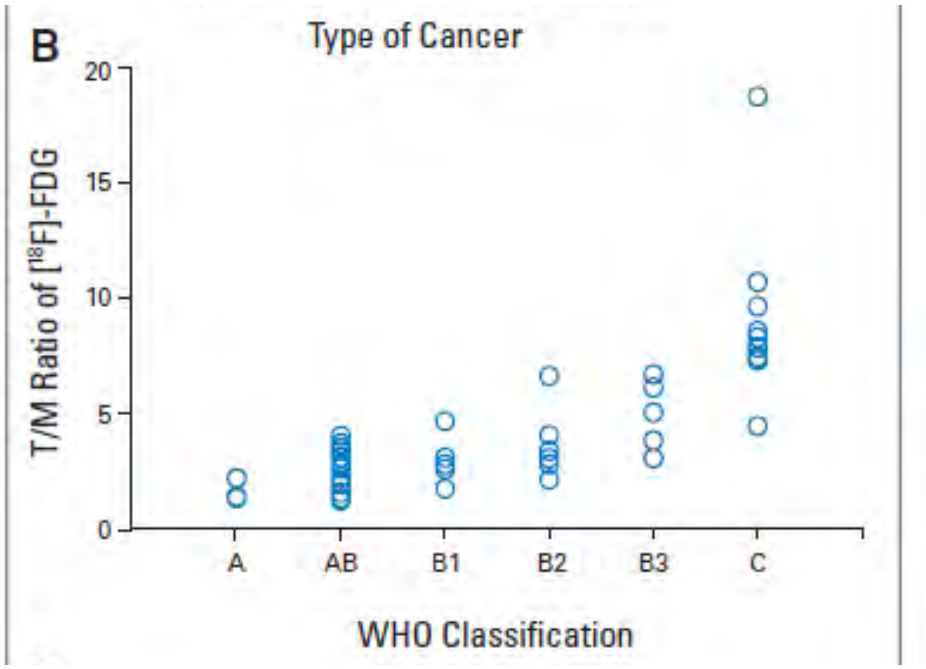


Kimar et al. Ann Nucl Med 2009; 23:569
Endo et al. Lung Cancer 2008; 61:350

Imagerie pré-thérapeutique

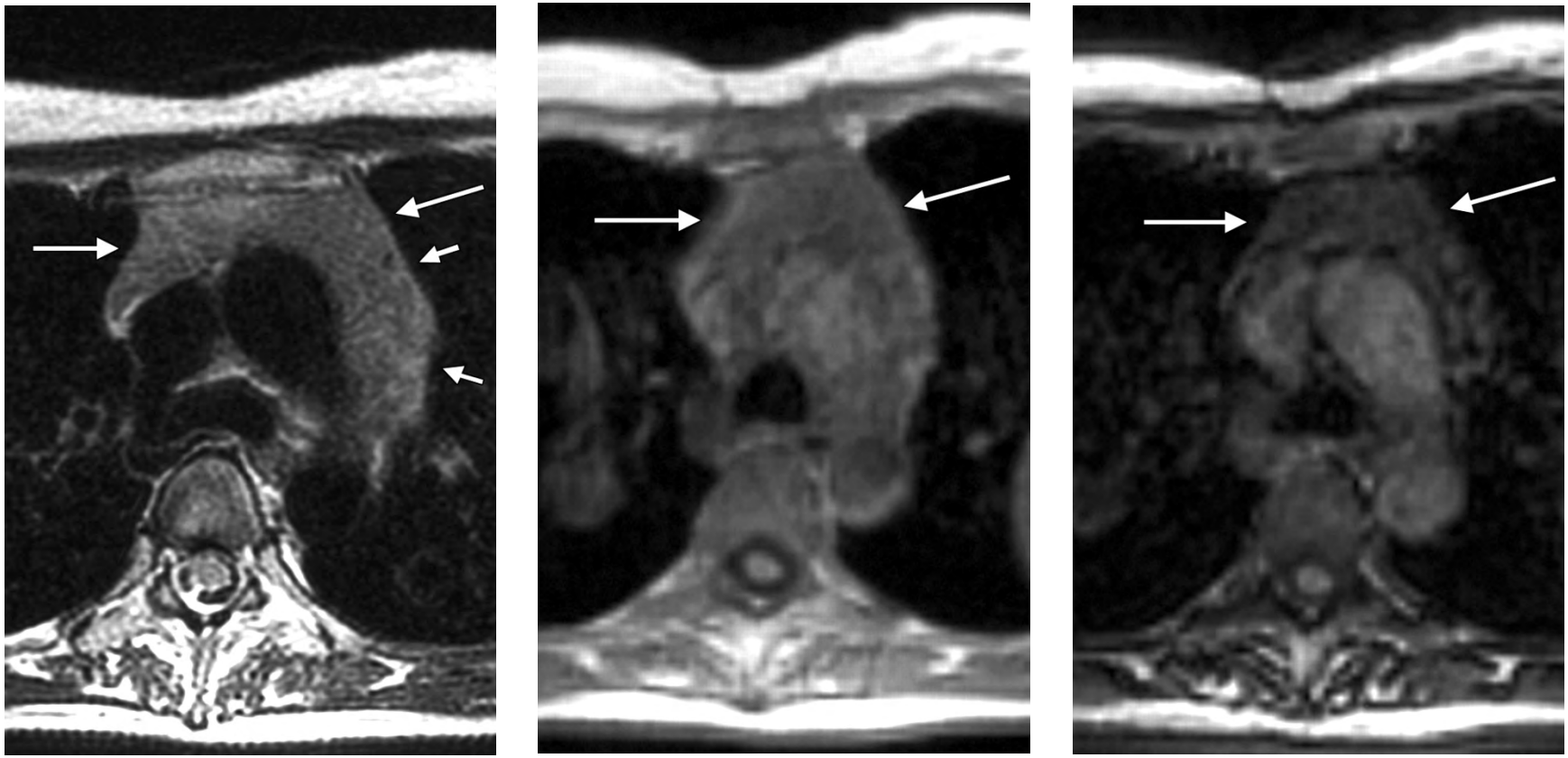
- Utilisation du PET-scan : hyperplasie vs. thymome vs. carcinome thymique





Igai et al .Eur J Cardiothor Surg 2011;40: 143
Kimar et al. Ann Nucl Med 2009; 23:569; Endo et al. Lung Cancer 2008;61:350
Kaira et al. J Clin Oncol 2011;28:3746; Shibata et al. Cancer 2009;115:2531

Hyperplasie thymique



Tumeurs thymiques

Specificities

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

2016

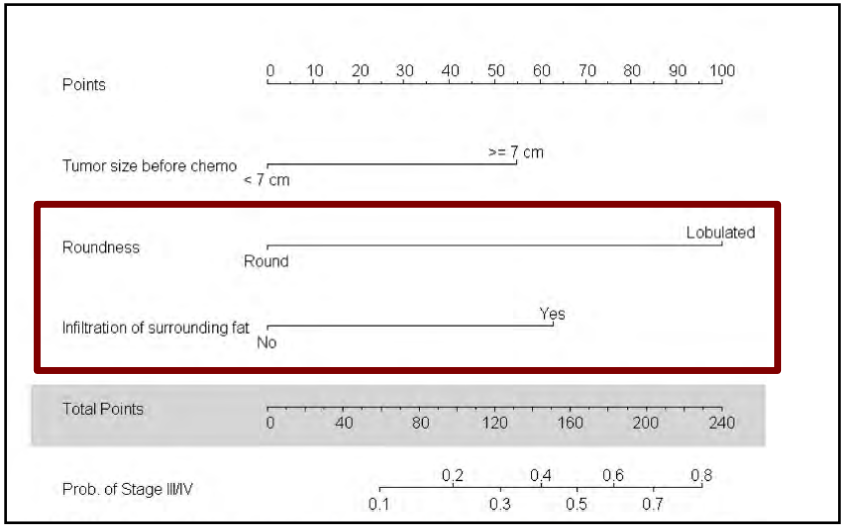
Resectable tumors

Imagerie pré-thérapeutique

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

Computed Tomography Findings Predicting Invasiveness of Thymoma

Edith M. Marom, MD, Miguel A. Milito, MD,* Cesar A. Moran, MD,† Ping Liu, MS,‡ Arlene M. Correa, PhD,§ Edward S. Kim, MD,‖ Ritsuko Komaki, MD,¶ Jeremy J. Erasmus, MD,* Wayne L. Hofstetter, MD,§ David C. Rice, MD,§ and Stephen G. Swisher, MD§*



J Thorac Oncol 2011;6:1274

Preoperative Computed Tomography Findings Predict Surgical Resectability of Thymoma

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

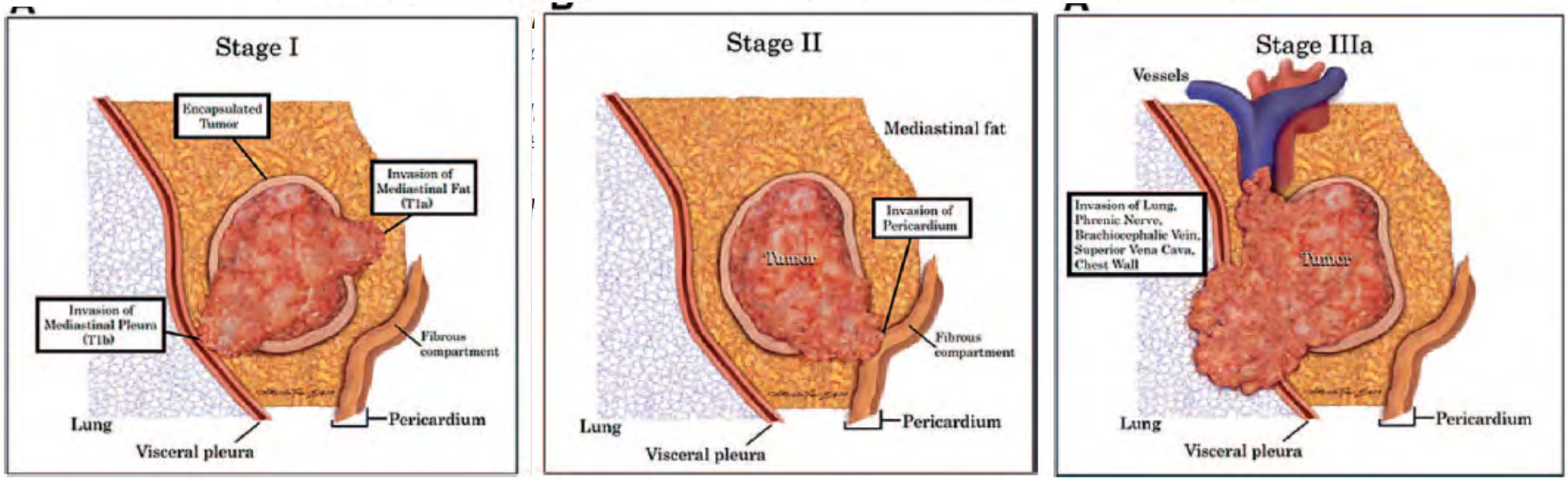
TABLE 5. Association of Preoperative Computed Thomography Features and Other Factors with Risk of Incomplete Surgical Resection

	Complete Resection (n = 110)	Incomplete Resection (n = 23)	Univariate Analysis	Multivariable Analysis[a]	
	N (%)	N (%)	Fishers Exact Test p Value	Odds Ratio (95% Confidence Interval) of Incomplete Resection	p Value
Degree of abutment of adjacent vessel circumference			<0.001		0.002
<50%	97 (88%)	12 (52%)		1	
≥50%	13 (12%)	11 (48%)		5.4 (1.9–15.5)	
Pleural nodularity			0.001		0.012
Yes	11 (10%)	9 (39%)		1	
No	99 (90%)	14 (61%)		4.3 (1.4–13.1)	
Contour			0.016		
Lobular	66 (60%)	20 (87%)			
Round	44 (40%)	3 (13%)			
Fat plane separating tumor from mediastinal vessels			0.078		
Yes	37 (34%)	3 (13%)			
No	73 (66 %)	20 (87%)			
Infiltration of peritumoral fat			0.048		
Yes	31 (28%)	12 (52%)			
No	79 (72%)	11 (48%)			

J Thorac Oncol. 2014;9: 1023

Définition de la 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 of Malignant Tumors



Masaoka-Koga : I, IIA, IIB, III

(*J Thorac Oncol.* 2014;9: S65–S72

Tumeurs thymiques

Specificities

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

2016

Resectable tumors

- **Surgery**

Surgery recommendations

Which Way is Up? Policies and Procedures for Surgeons and Pathologists Regarding Resection Specimens of Thymic Malignancy

Frank C. Detterbeck, MD, Cesar Moran, MD,† James Huang, MD,‡ Saul Suster, MD,§ Garrett Walsh, MD,# Lawrence Kaiser, MD,‖ and Mark Wick, MD¶*

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

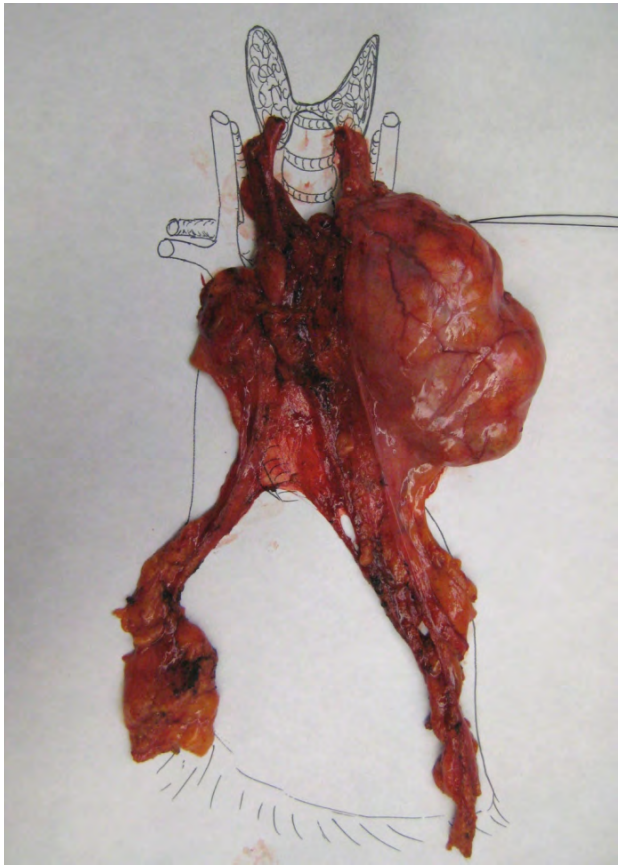
- **Complete thymectomy**, including tumor, normal thymus, and mediastinal fat
- *en bloc* resection of involved structures:
  - lung, vessels, pleural implants, phrenic nerves
  - surgical clips in areas of concern

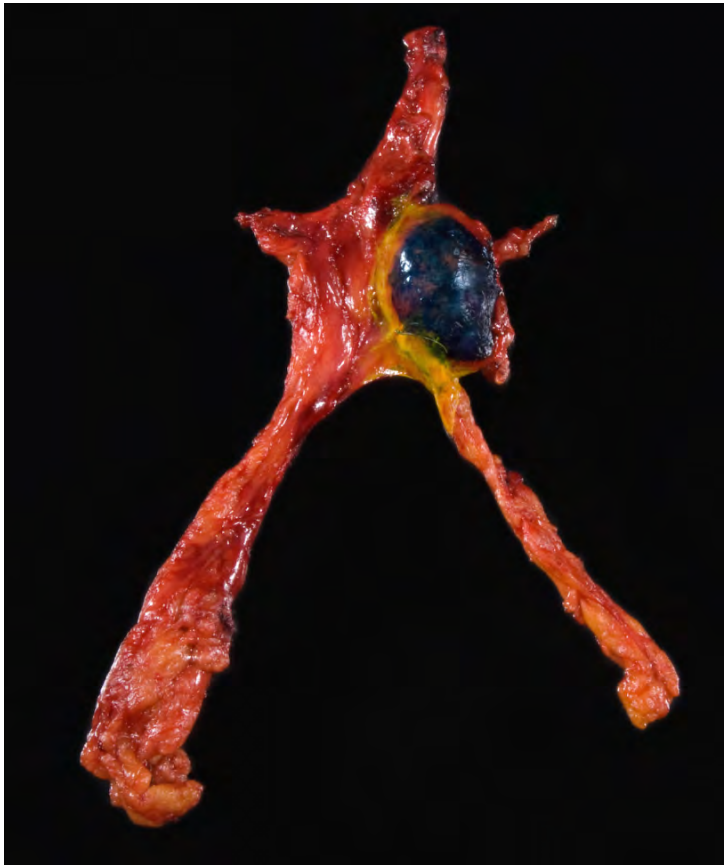
- Mediastinal notes sampling/resection (stage III tumor/thymic carcinoma)

- Frozen section not recommended for margins assessment

Orientation and marking in the operative room

- **Use of a mediastinal board**





ITMIG International Thymic Malignancy Interest Group

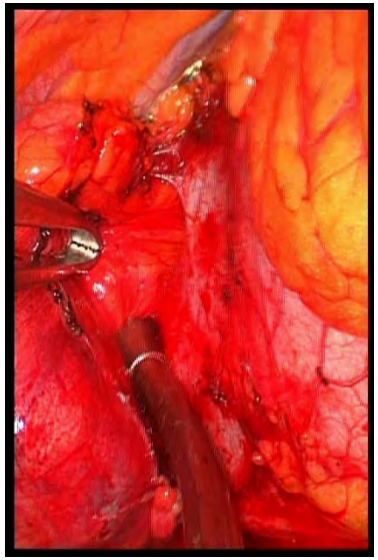
Minimally-invasive surgery?

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

2016

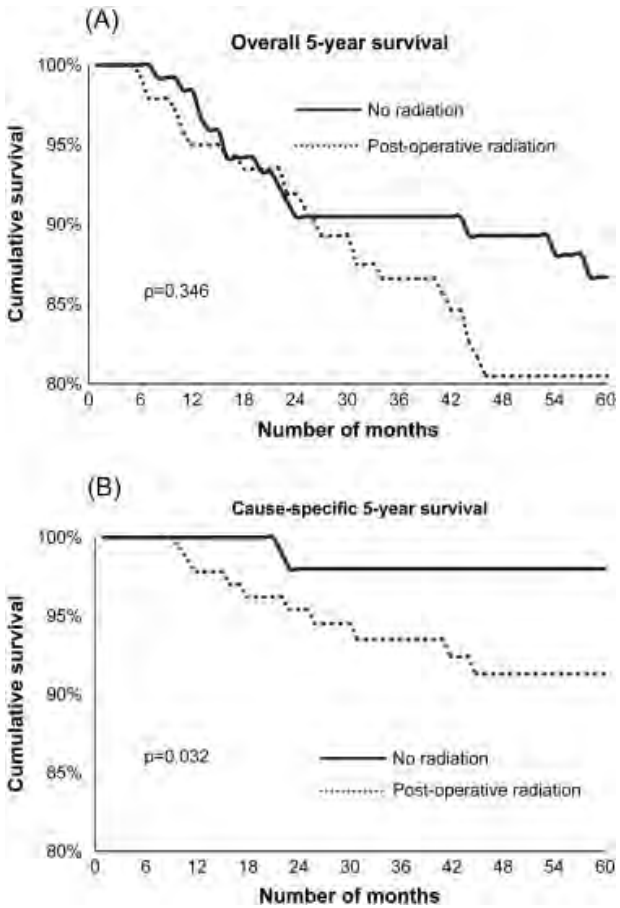
Resectable tumors

- Surgery
- **Postoperative radiotherapy**

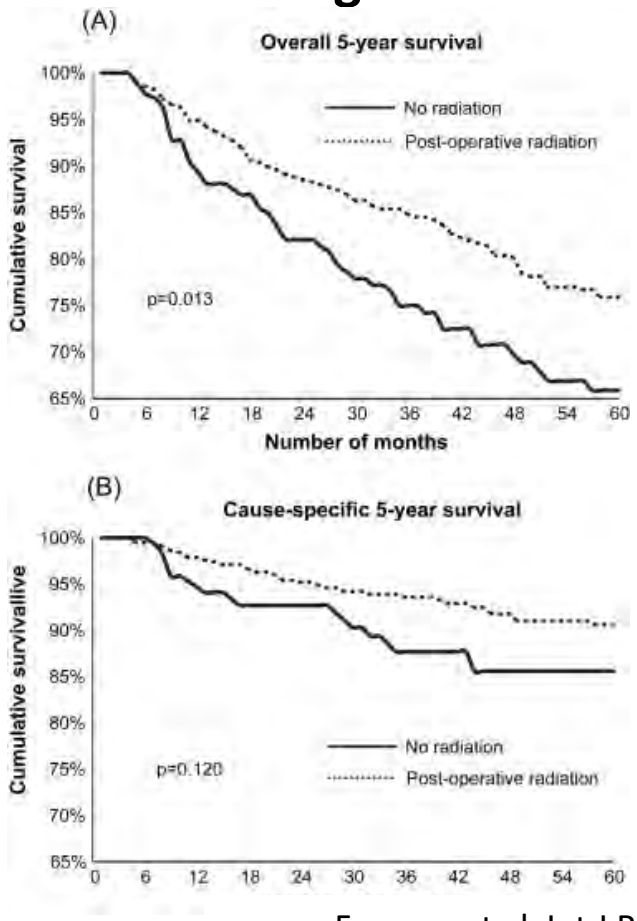
Postoperative radiotherapy: SEER database

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

Stage I



Stage II-III



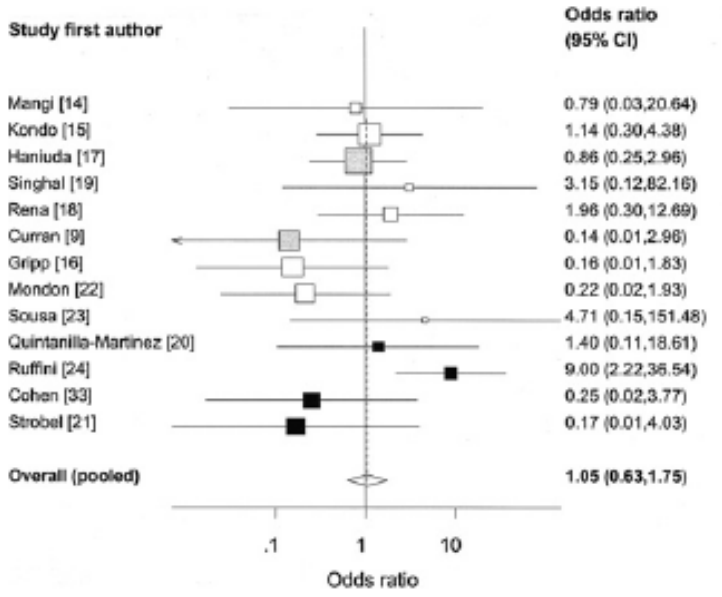
…but no benefit after complete resection (p=0.12)

Forquer et al. Int J RadiatOncol Biol Phys 2008;76:440

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**

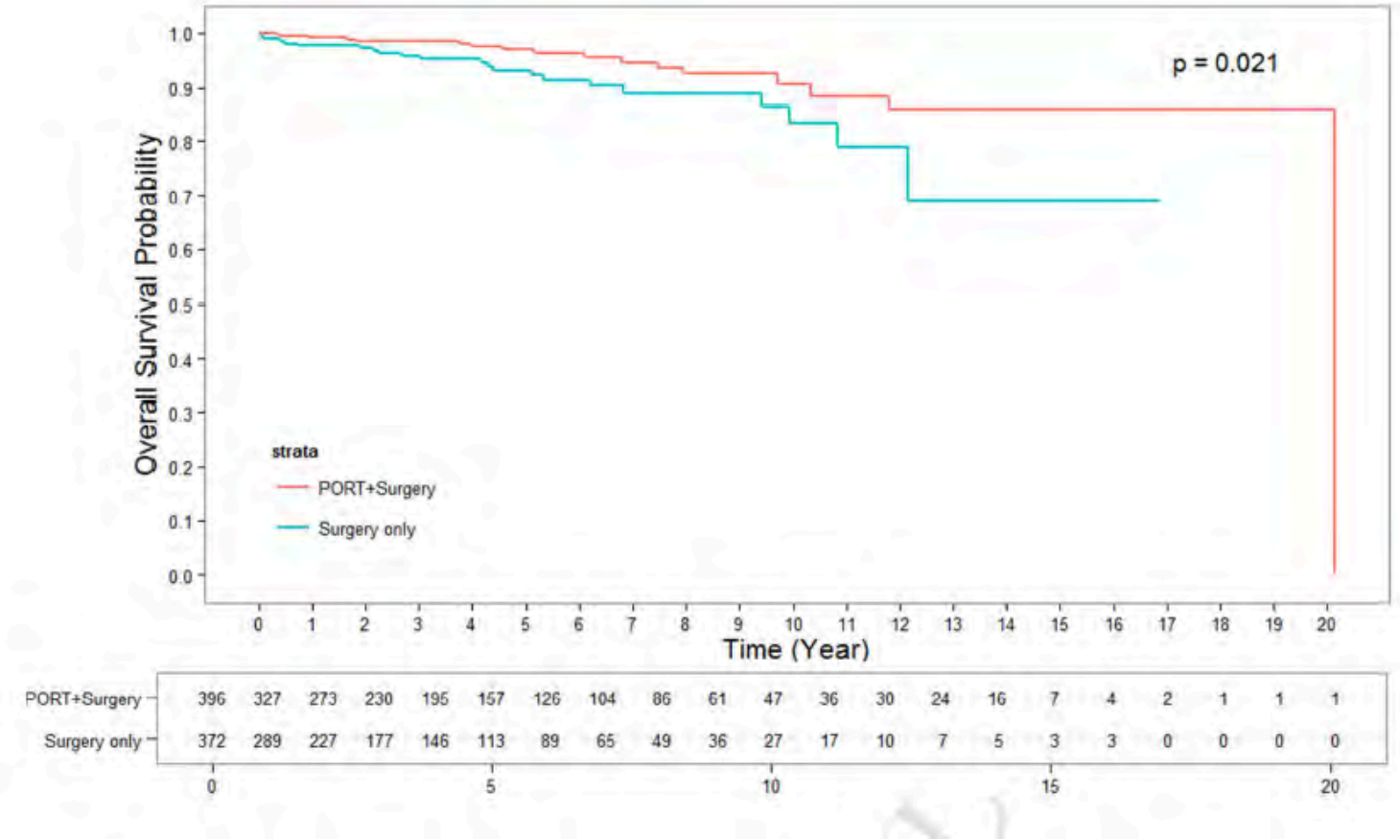


Korst et al. Ann Thorac Surg 2009;87:1641

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
- Complex histology
- Auto-immunity
- Staging

2016

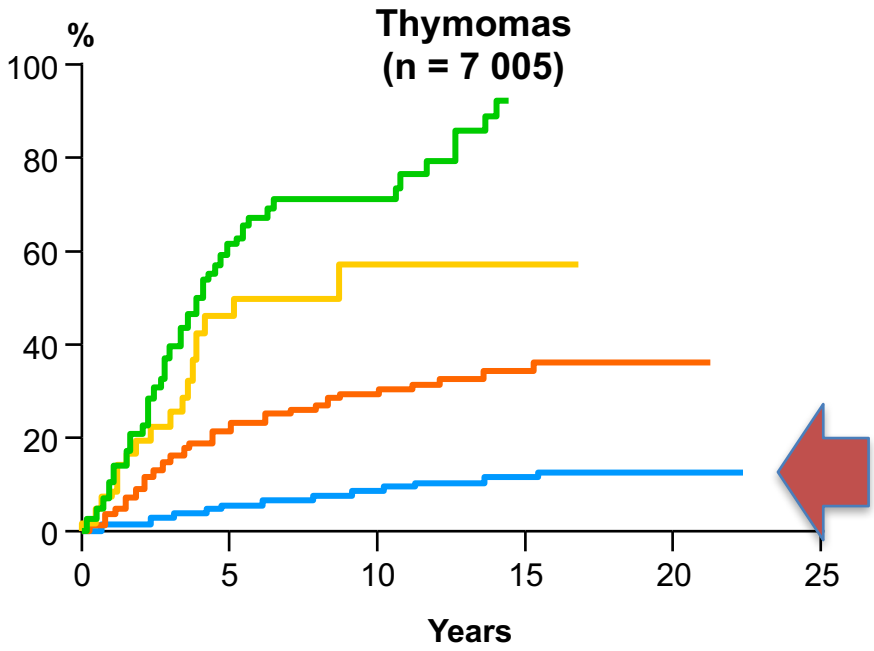
Resectable tumors

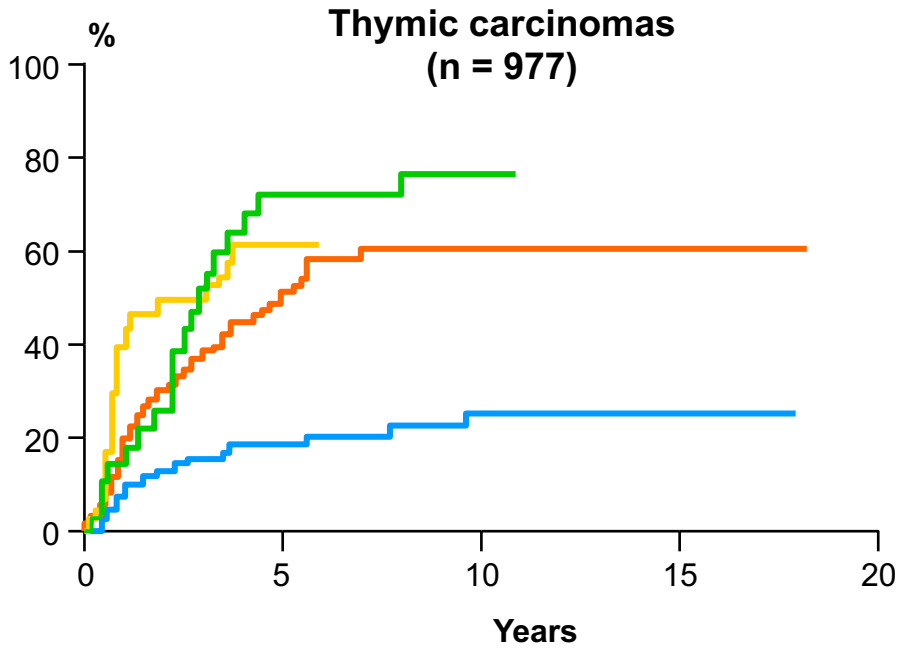
- Surgery
- **Postoperative radiotherapy**

Recurrence rates

ITMIG retrospective database

Cumulative incidence of recurrences in Masaoka-Koga groups



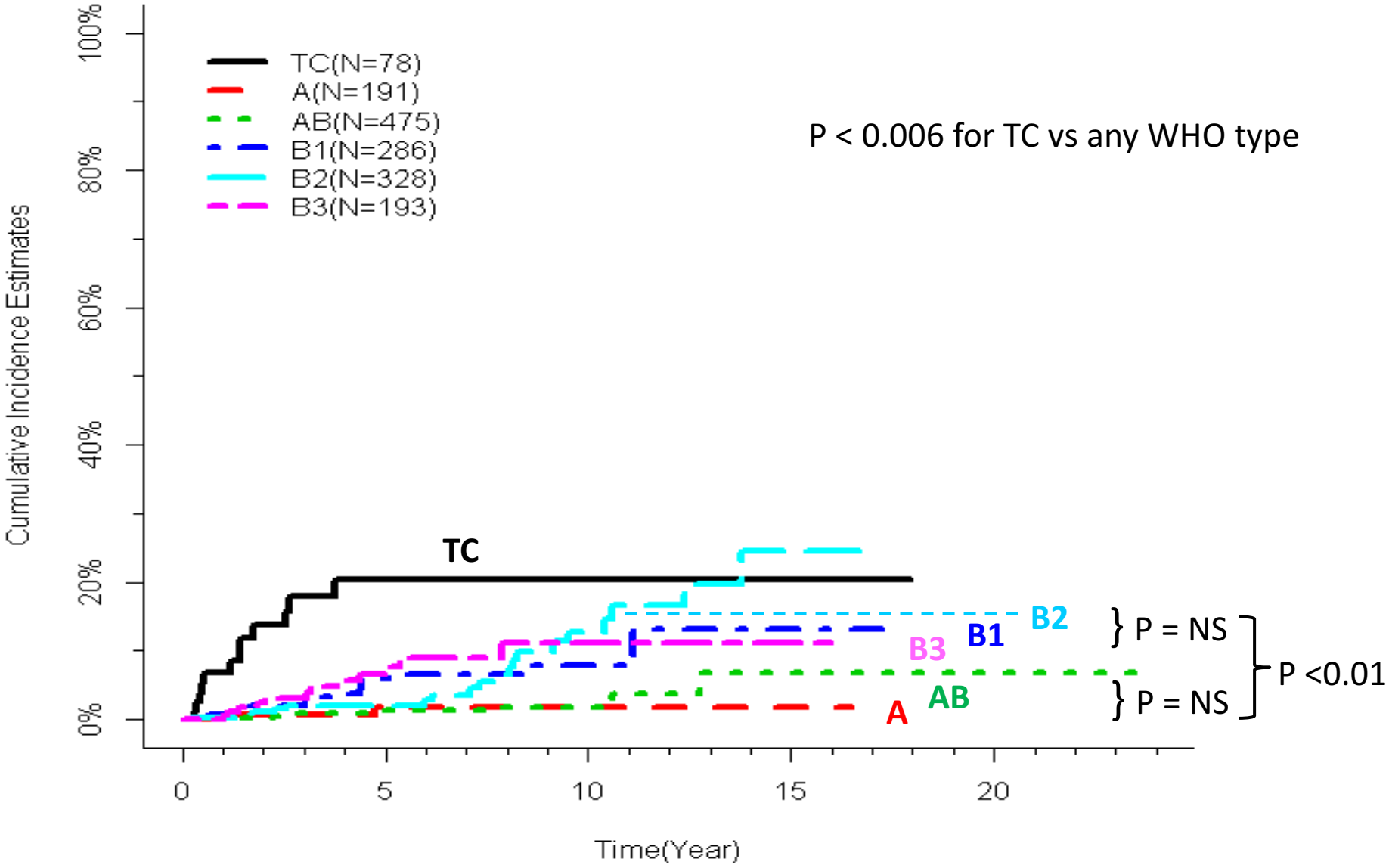


	Events/n	10-year recurrence % (IC_{95})
Stage I/II	121/3 097	8 (7-8)
Stage III	140/654	29 (27-31)
Stage IVA	64/109	71 (34-100)
Stage IVB	17/38	57 (24-90)

	Events/n	10-year recurrence % (IC_{95})
Stage I/II	28/112	25 (22-29)
Stage III	68/143	59 (44-76)
Stage IVA	19/26	76 (58-100)
Stage IVB	20/37	54 (37-67)

Detterbeck et al. WCLC 2013, abstr. MS16.2

Recurrence by WHO Histology, R0, stage I,II



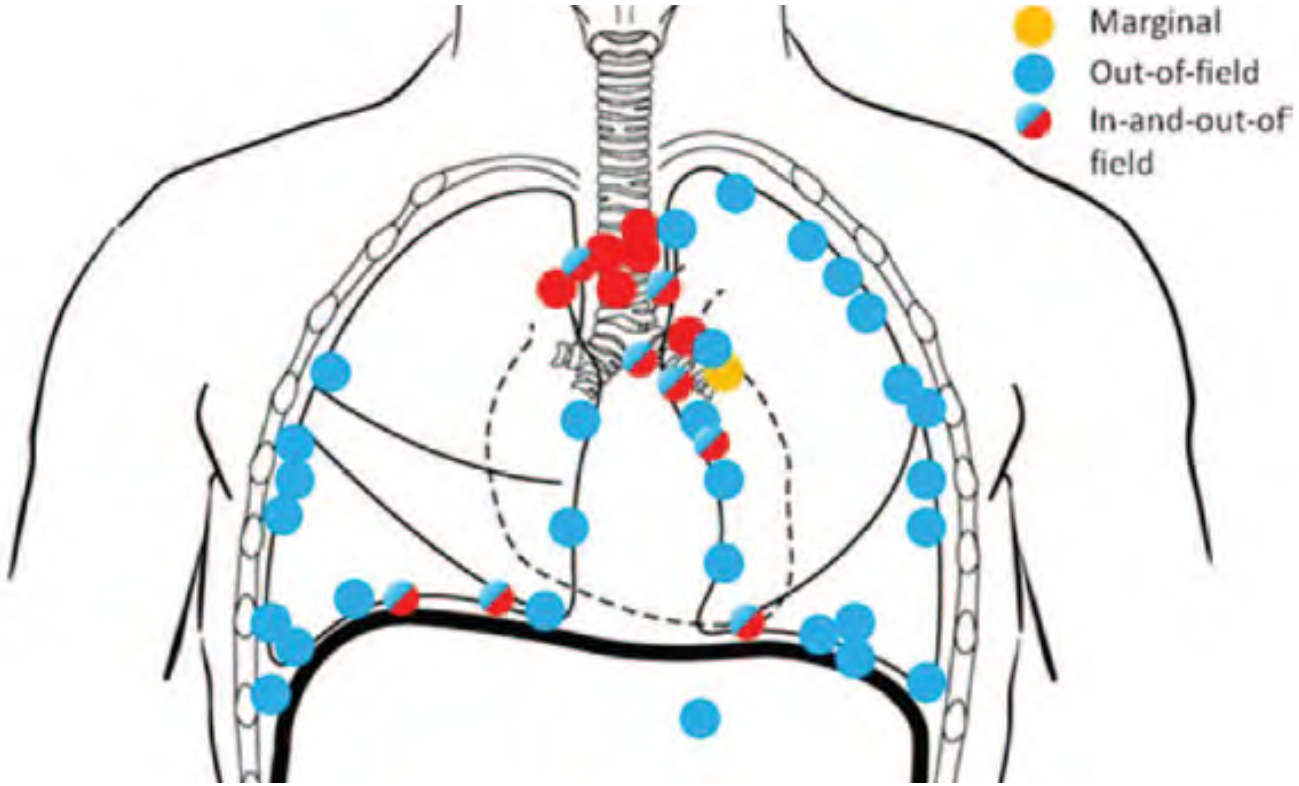
P < 0.006 for TC vs any WHO type

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

Weiss et al. ITMIG 2014

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

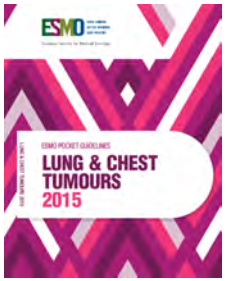
- Thymic origin
- Complex histology
- Auto-immunity
- Staging

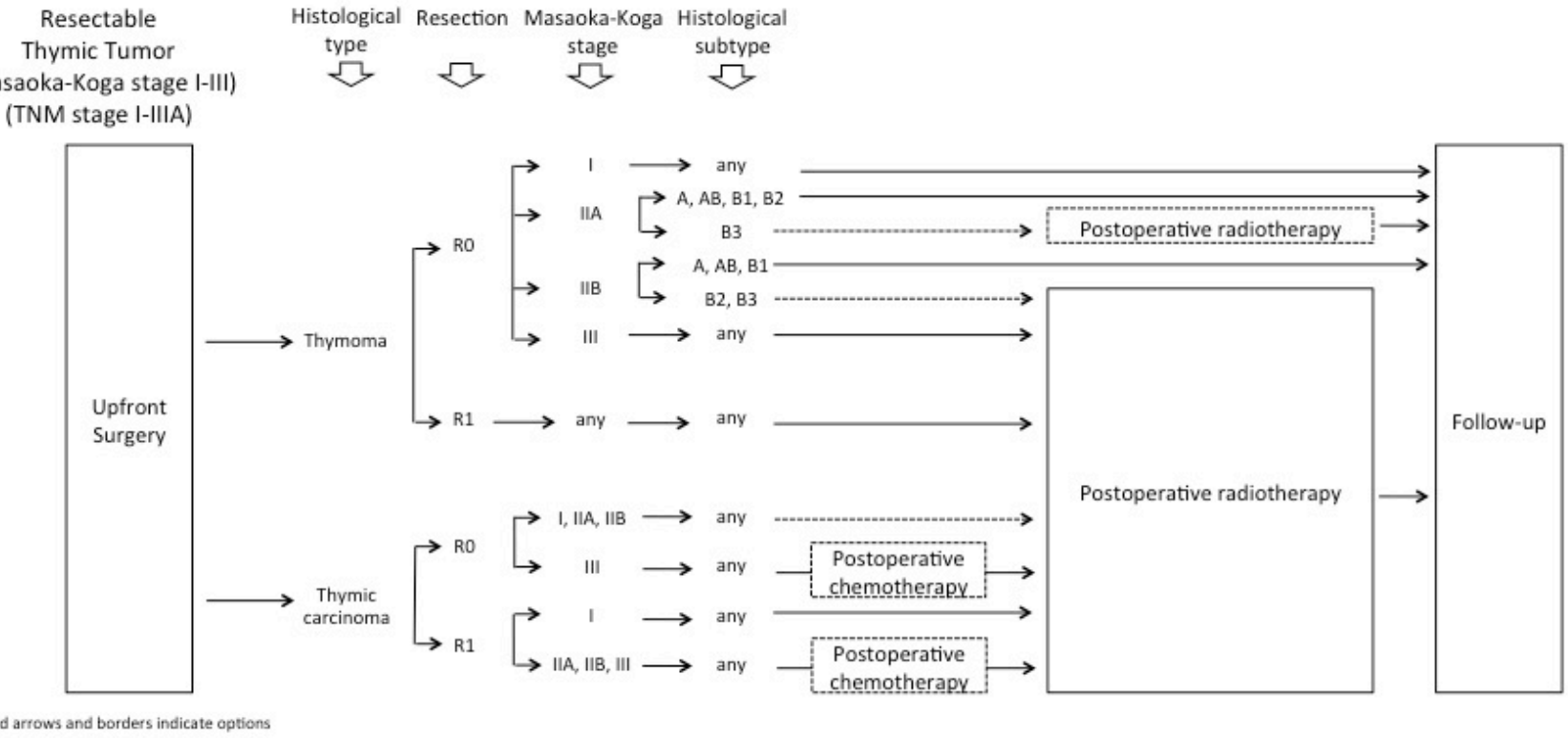
2016

Resectable tumors

- Surgery
- **Postoperative radiotherapy**

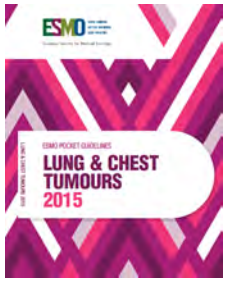
Recommandations RYTHMIC
ESMO Clinical Practice Guidelines

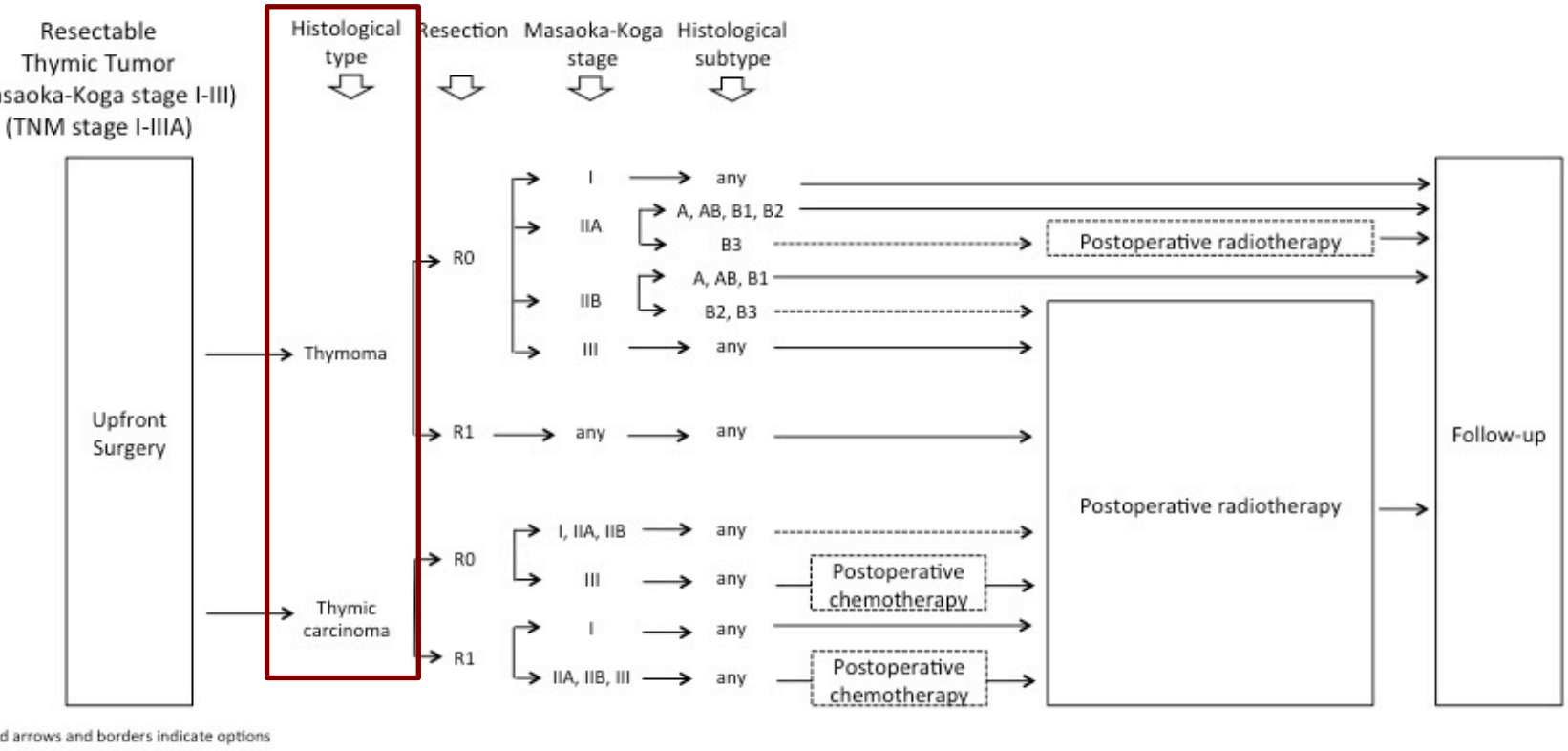




Girard et al. Ann Oncol 2016;26: v40

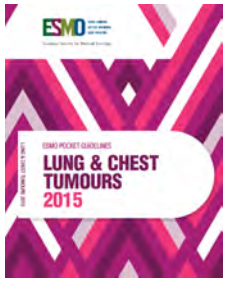
Recommandations RYTHMIC
ESMO Clinical Practice Guidelines

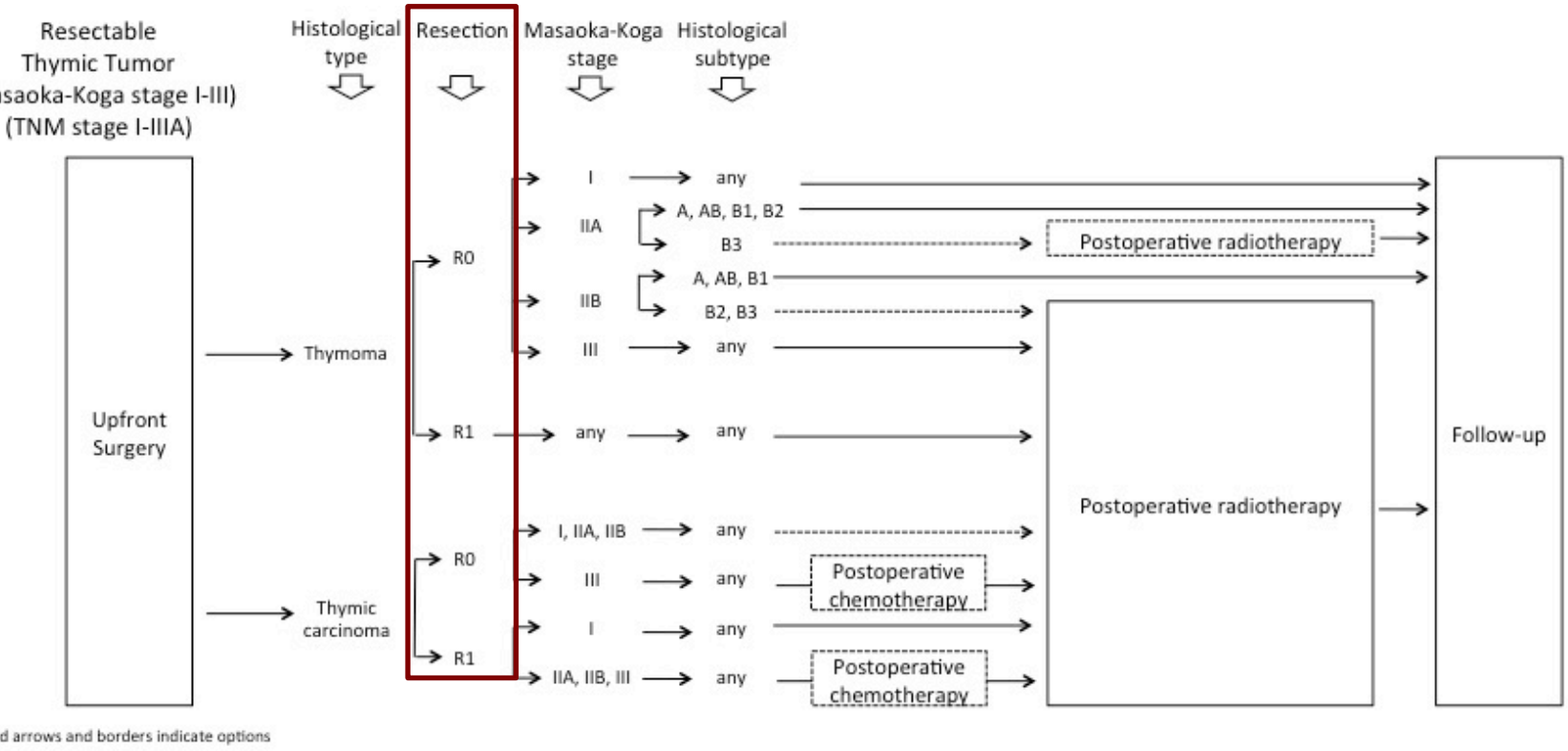




Girard et al. Ann Oncol 2016;26: v40

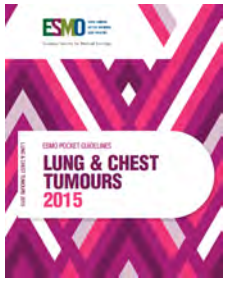
Recommandations RYTHMIC
ESMO Clinical Practice Guidelines

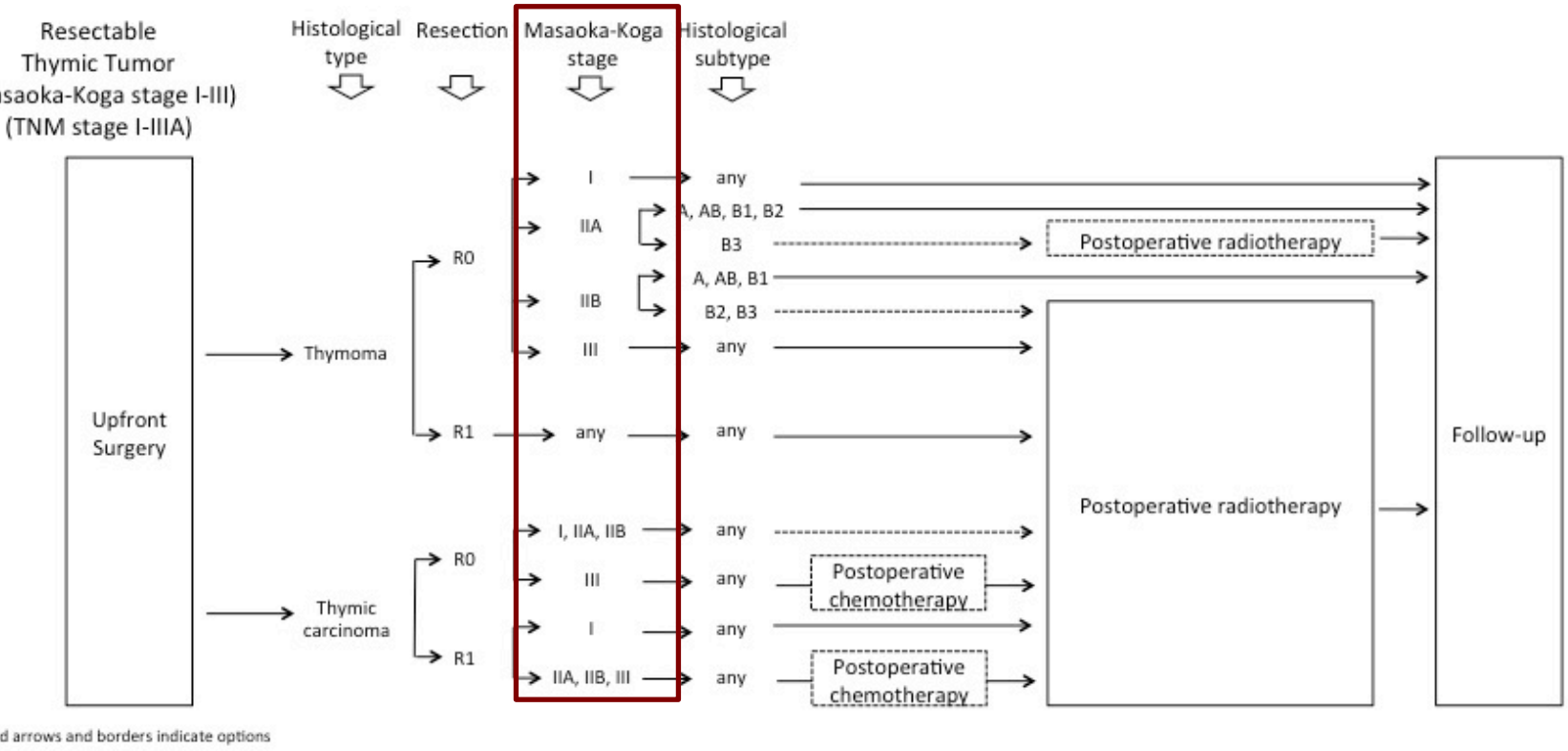




Girard et al. Ann Oncol 2016;26: v40

Recommandations RYTHMIC
ESMO Clinical Practice Guidelines





Girard et al. Ann Oncol 2016;26: v40

Recommandations RYTHMIC
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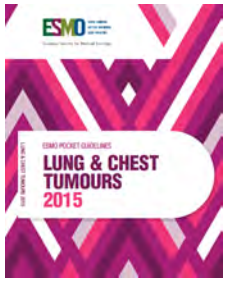

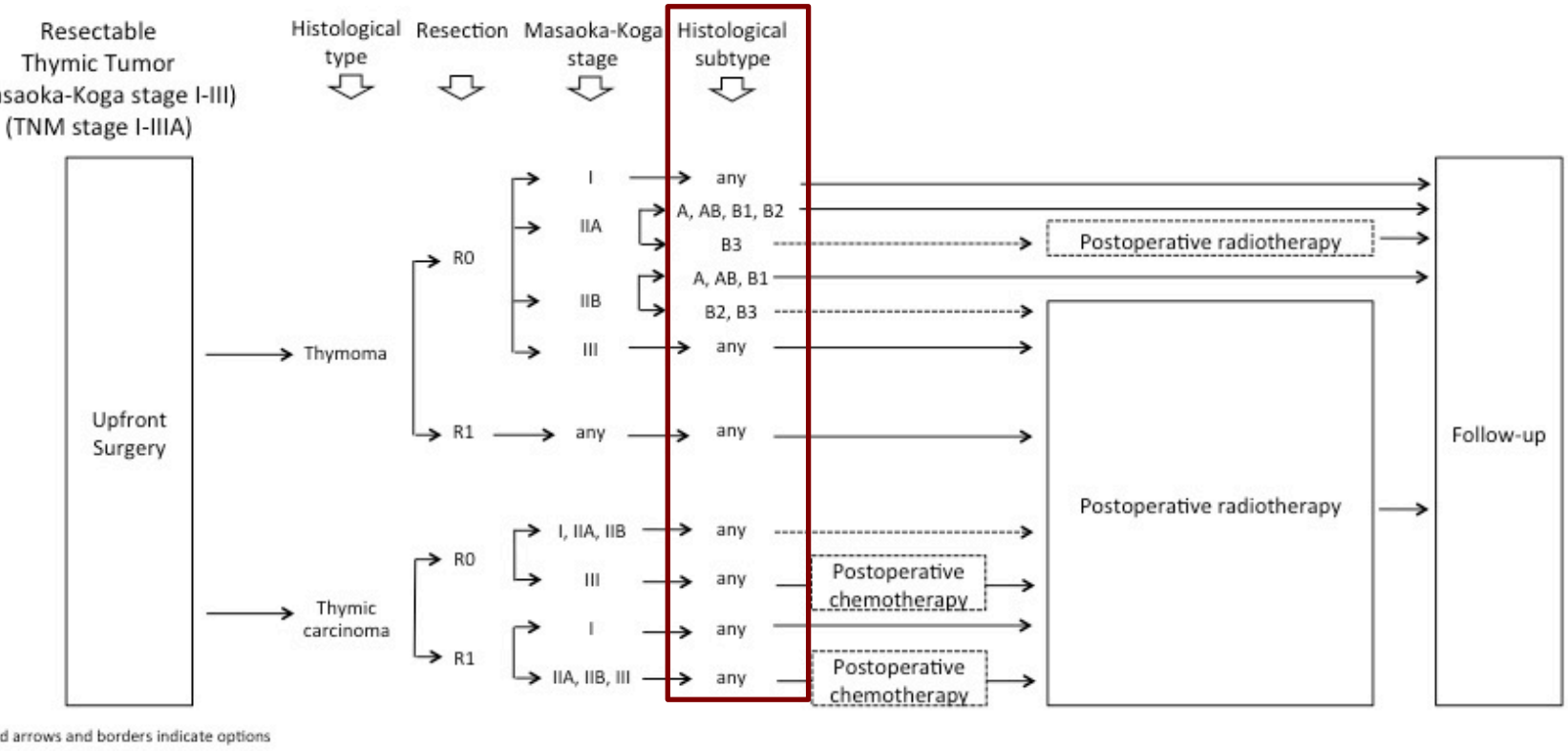

Girard et al. Ann Oncol 2016;26: v40

Recommandations RYTHMIC
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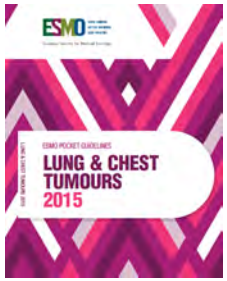
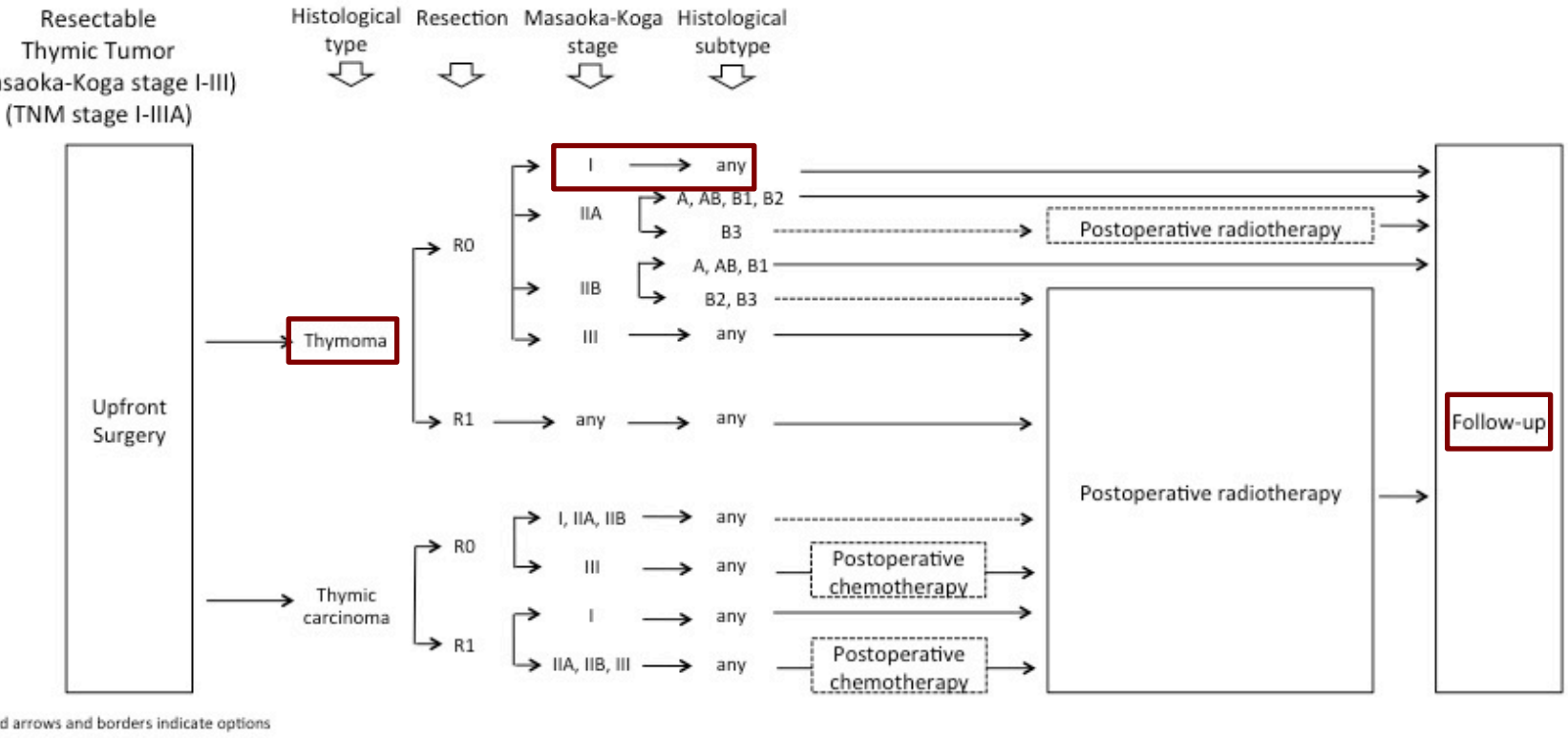
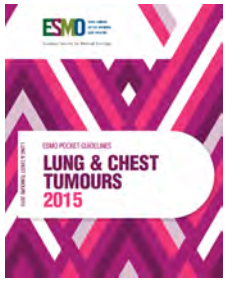
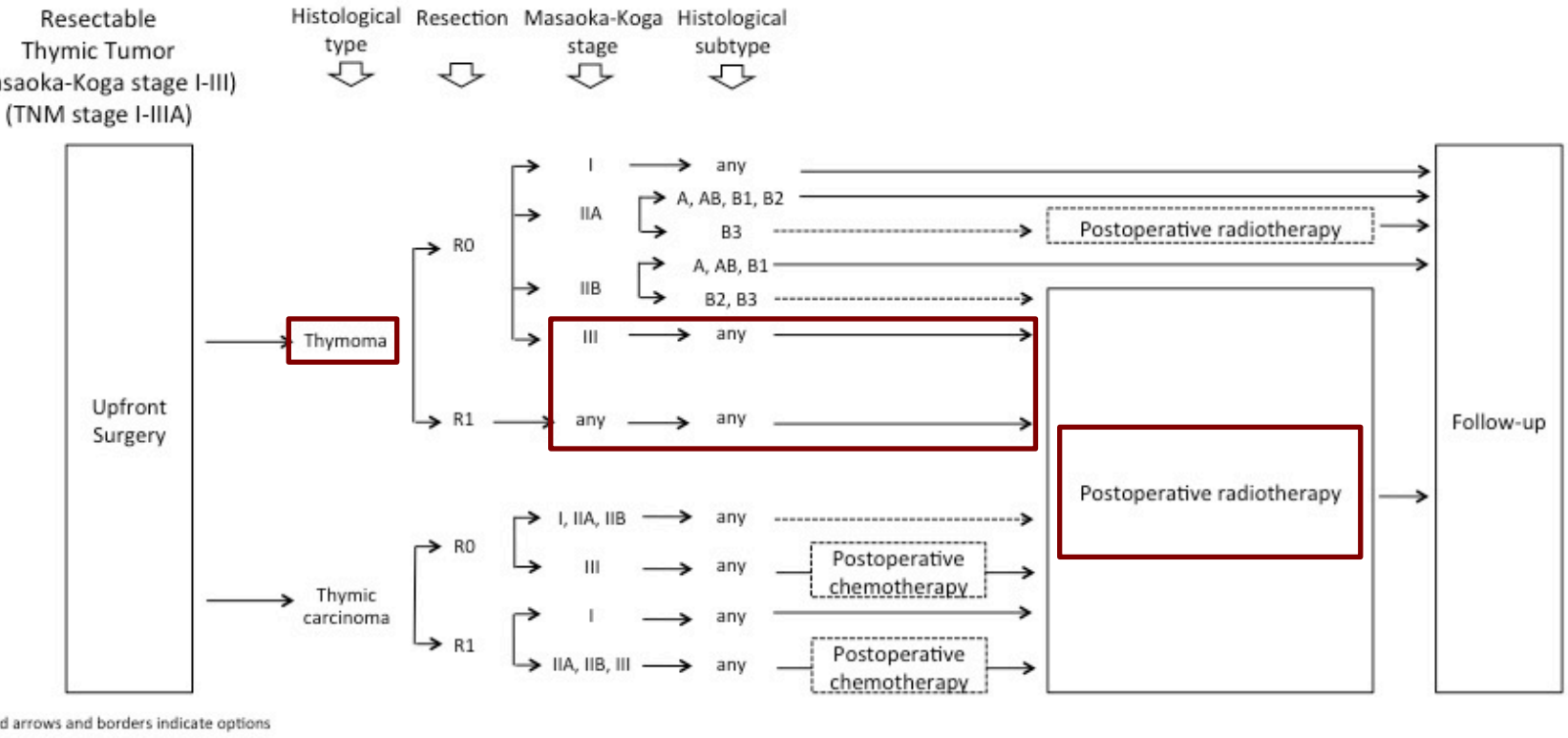




Girard et al. Ann Oncol 2016;26: v40

Recommandations RYTHMIC
ESMO Clinical Practice Guidelines





Girard et al. Ann Oncol 2016;26: v40

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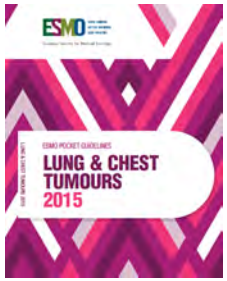
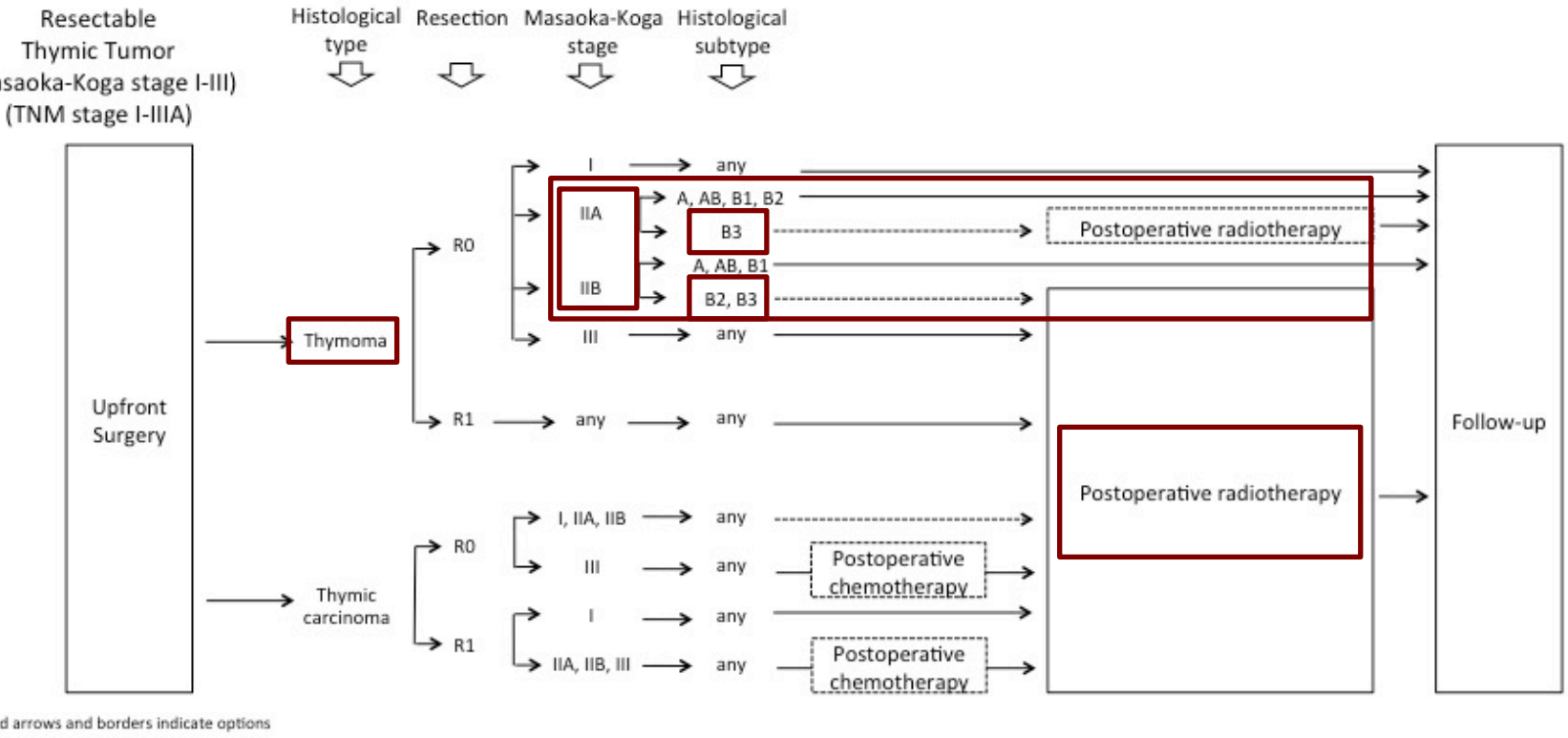
ESMO Clinical Practice Guidelines





Girard et al. Ann Oncol 2016;26: v40

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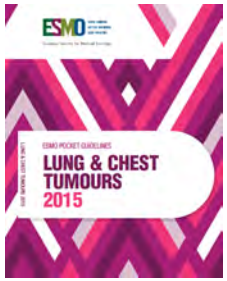
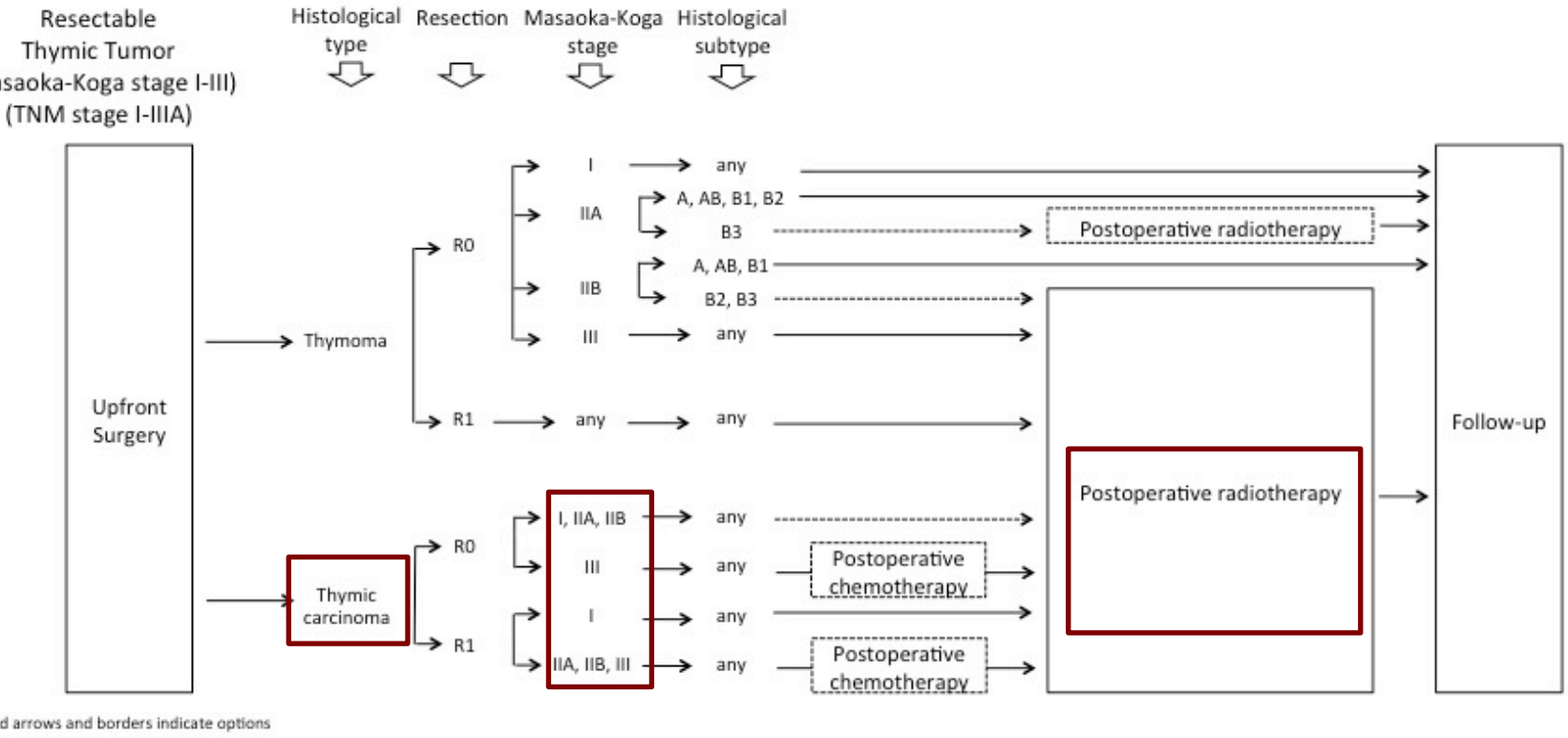




Girard et al. Ann Oncol 2016;26: v40

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

rythmic.org
Réseau tumeurs THYMiques et Cancer

Clémence BASSE[1], Sébastien THUREAU[1], Suzanna BOTA[2], Eric DANSIN[3], Pascal-Alexandre THOMAS[4], Eric PICHON[5], Hervé LENA[6], Carole MASSABEAU[7], Christelle CLEMENT-DUCHENE[8], Gilbert MASSARD[9], Virginie WESTEEL[10], François THILLAYS[11], Xavier QUANTIN[12], Youssef OULKHOUIR[13], Serge DANHIER[14], Delphine LEROUGE[14], Luc THIBERVILLE[2], Benjamin BESSE[15], Nicolas GIRARD[16]

[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, Rennes; [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; [14] University Hospital, Caen; [14] Centre François Baclesse, Caen; [15] Institut Gustave Roussy, Villejuif; [16] Hospices 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

		RYTHMIC guidelines		TOTAL
		PORT recommended	PORT not recommended	
MTB decisions	PORT	84	13	97
	No PORT	7	137	144
TOTAL		91	150	241

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 with 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.**

SUPPORT

IFCT

Tumeurs thymiques

Specificities

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

2016

Resectable tumors

- Surgery
- Postoperative radiotherapy

Unresectable tumors

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

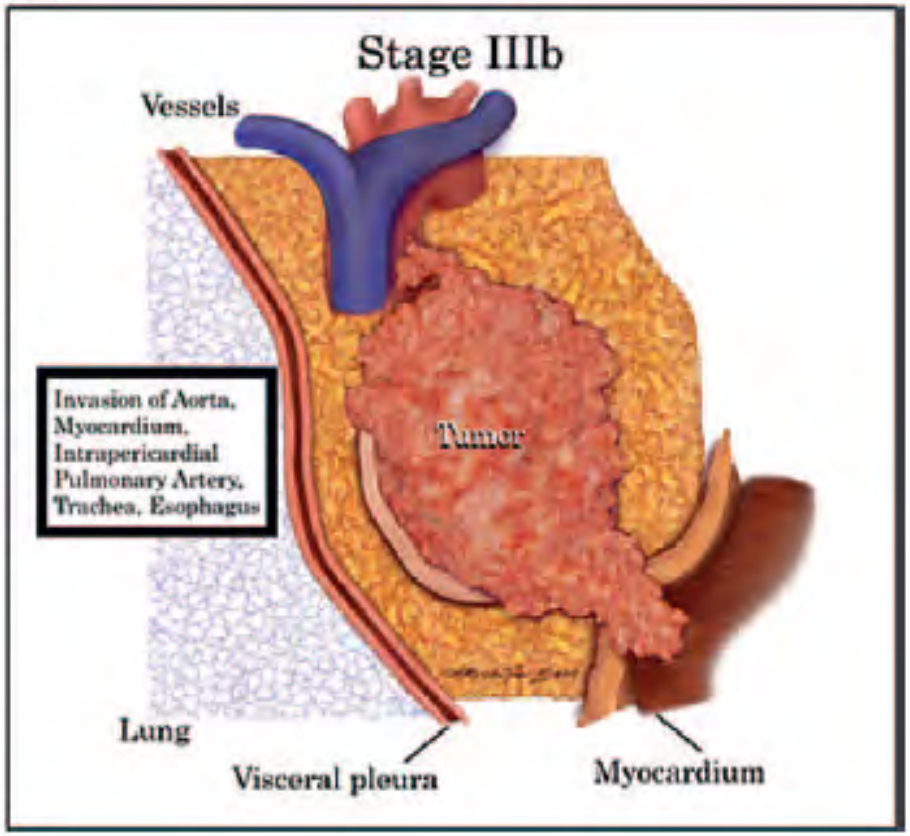
NCT00387868 (PI: R. Korst)

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, MI
John Crowley, PhD,† Conrad
Giuseppe Giaccone, MD,
Marco Lucchi, MD,‡‡, Mirella
Meinoshin Okumura, MD,#
and Prognostic
and I

ID,‡
MD,‖‖‖
D,††,
ı, MD,¶¶,
Staging



Masaoka-Koga : III

(*J Thorac Oncol.* 2014;9: S65–S72

Tumeurs thymiques

Specificities

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

2016

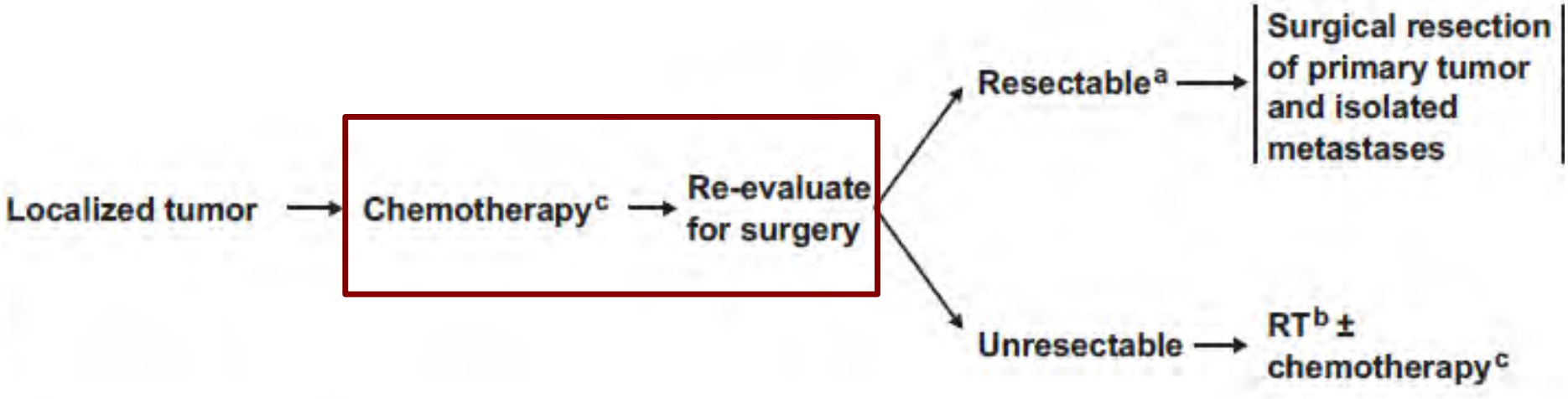
Unresectable tumors

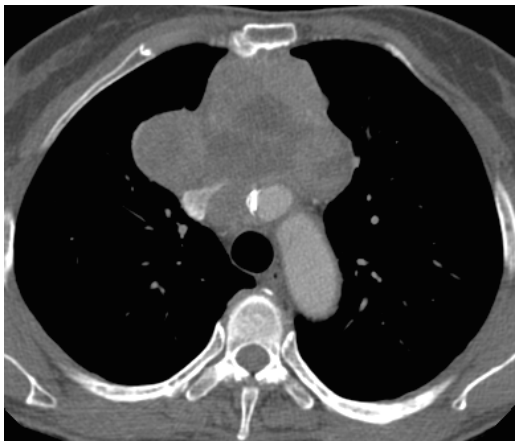
- **Primary chemotherapy**

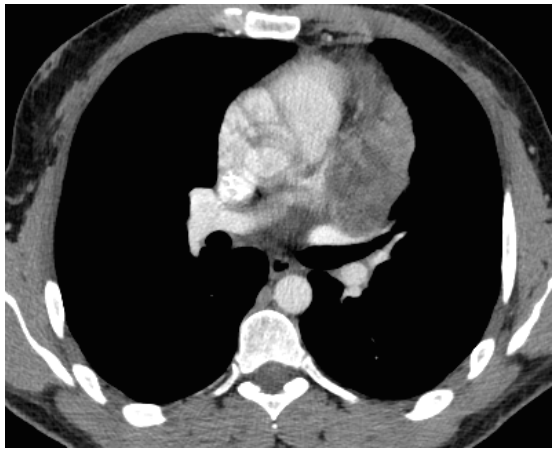
Resectable tumors

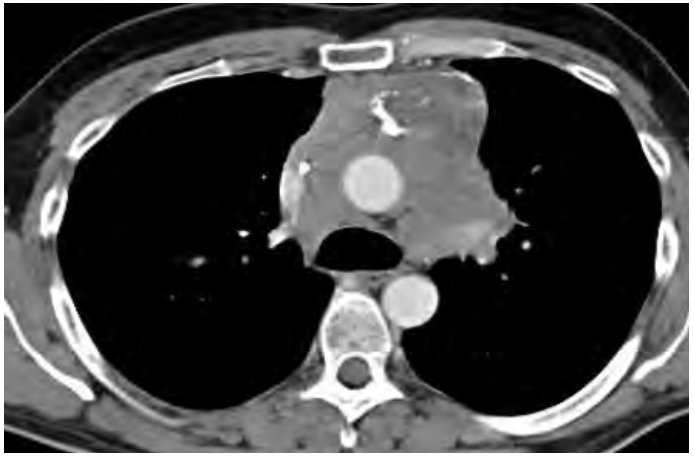
- Surgery
- Postoperative radiotherapy

Locally-advanced tumors: multimodal treatment









National Comprehensive Cancer Network Guidelines

Pre-operative chemotherapy

Study	Primary Chemotherapy Regimen	No. of Patients	Tumor		Design	Response Rate (%)
			Type	Stage		
Chemotherapy						
Macchiarini et al 1991[14]	CEE	7	T/TC	III	Phase II	100
Berruti et al 1993[15]	ADOC	6	T	III-IVA	Phase II	83
Rea et al 1993[16]	ADOC	16	T	III-IVA	Retrosp	100
Berruti et al 1999[17]	ADOC	16	T	III-IVA	Phase II	
Venuta et al 2003[18]	CEE	15	T/TC	III	Retrosp	
Bretti et al 2004[19]	ADOC/PE	25	T/TC	III-IVA	Retrosp	
Kim et al 2004[20]	CAPP	22	T		Phase II	
Lucchi et al 2005[21]	CEE	36	T/TC	III-IVA	Retrosp	67
Jacot et al 2005[22]	CAP	5	T/TC	III-IVA	Retrosp	75
Yokoi et al 2007[23]	CAMP	14	T/TC	III, IV	Retrosp	93
Kunitoh et al 2009[24]	CODE	21	T	III	Phase II	62
Park et al, 2013	CDDP-Doc	27	T/TC	III/IV	Phase I I	63

Response rate **80%**

Girard N. Eur Respir Rev 2013;22:75

Chimiothérapie pré-opératoire

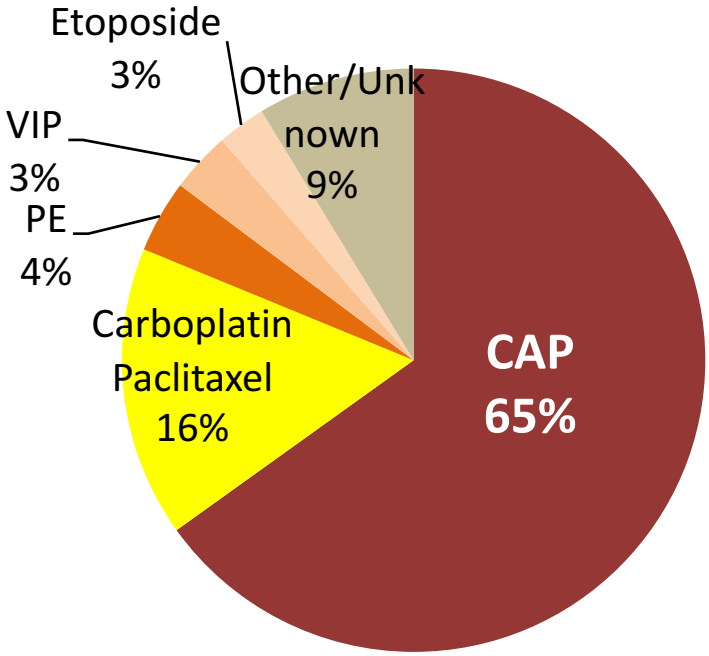
Study	Primary Chemotherapy Regimen	No. of Patients	Tumor		Design	Response Rate (%)
			Type	Stage		
Chemotherapy						
Macchiarini et al 1						
Berruti et al 1993[1]						
Rea et al 1993[16]						
Berruti et al 1999[1]						
Venuta et al 2003						
Bretti et al 2004[19]						
Kim et al 2004[20]						
Lucchi et al 2005[2]						
Jacot et al 2005[22]						
Yokoi et al 2007[23]						
Kunitoh et al 2009						
Park et al, 2013						

En pratique:

CAP
2 + 2 cycles

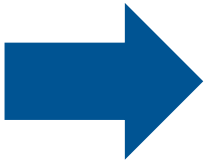
Girard N. ASCO 2012 Educational Book
Park et al. J Thorac Oncol 2013;8:959

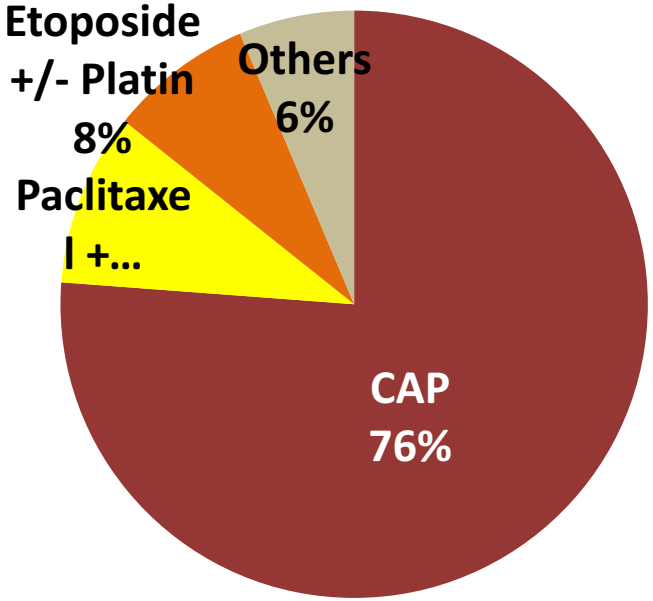
RYTHMIC: Chimiothérapie d'induction



Proposed regimens

n=149



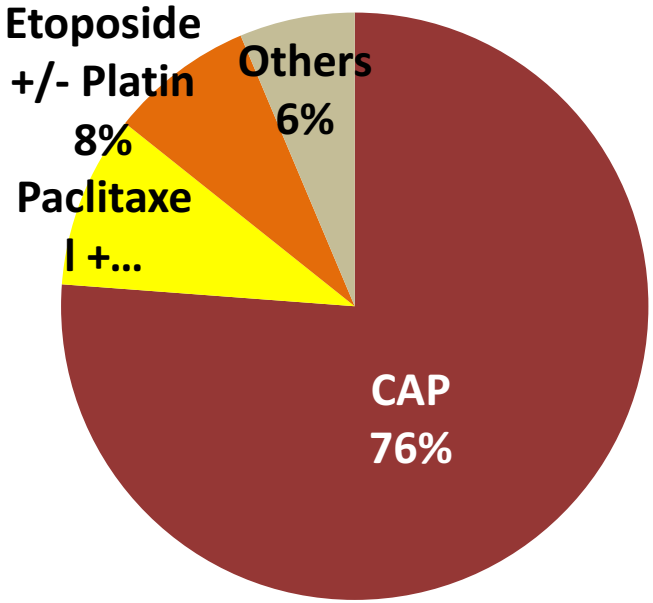


Administered regimens

n=91

Merveilleux du Vignaux, et al. ITMIG 2016

RYTHMIC: Chimiothérapie d'induction

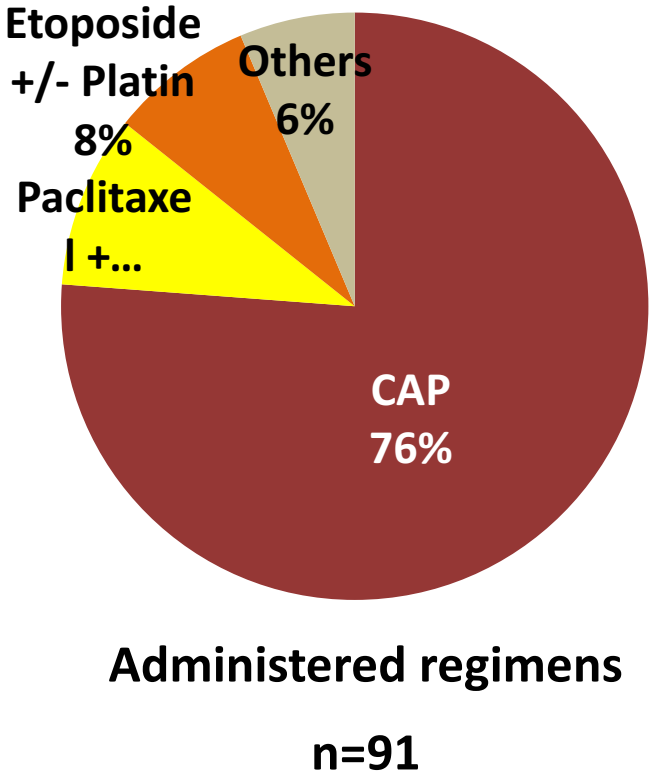


Administered regimens

n=91

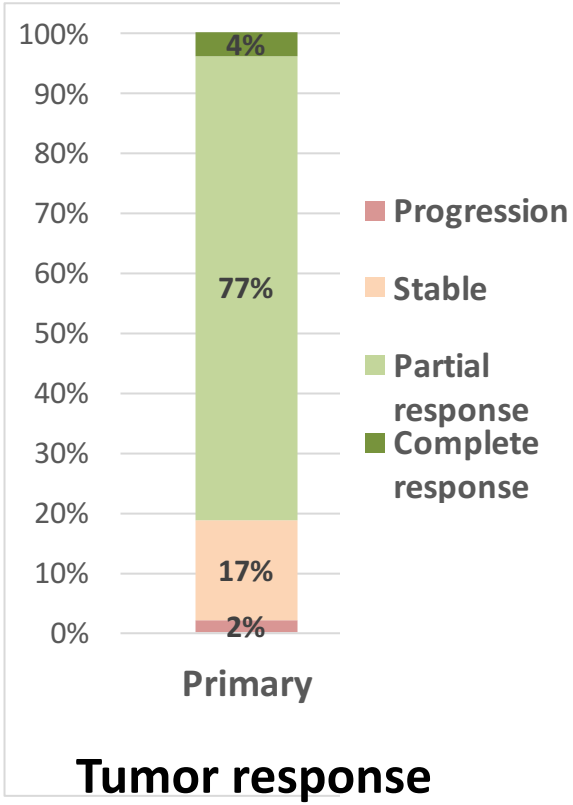
Merveilleux du Vignaux, et al. ITMIG 2016

RYTHMIC: Chimiothérapie d'induction



Administered regimens

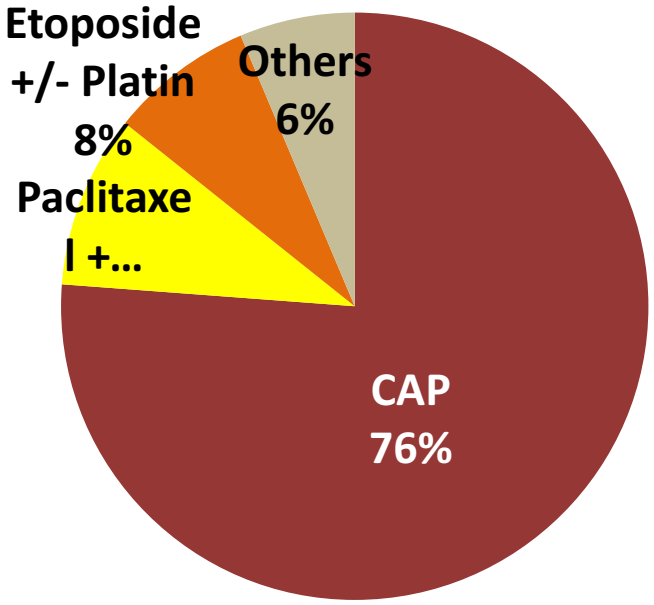
n=91



Tumor response

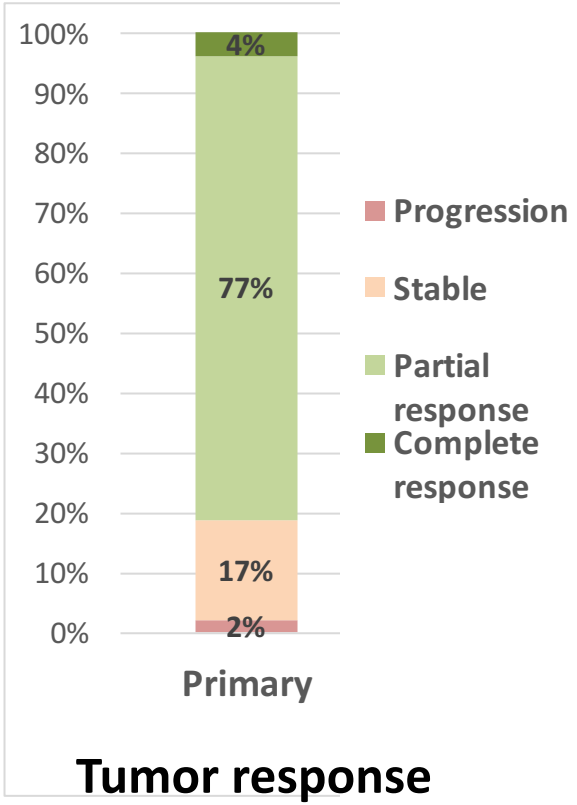
Merveilleux du Vignaux, et al. ITMIG 2016

RYTHMIC: Chimiothérapie d'induction



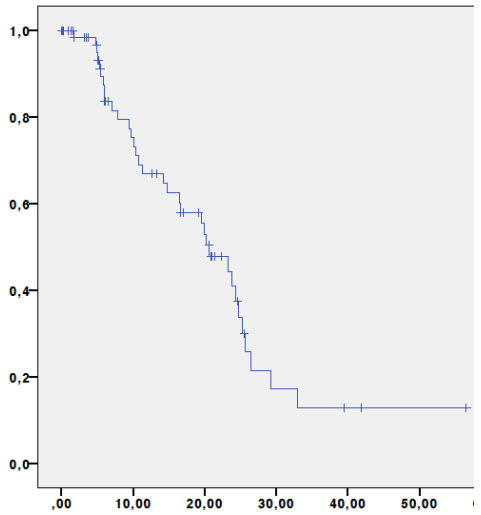
Administered regimens

n=91



Tumor response

Median: 20.7 months



Recurrence-free survival

Merveilleux du Vignaux, et al. ITMIG 2016

Tumeurs thymiques

Specificities

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

2016

Unresectable tumors

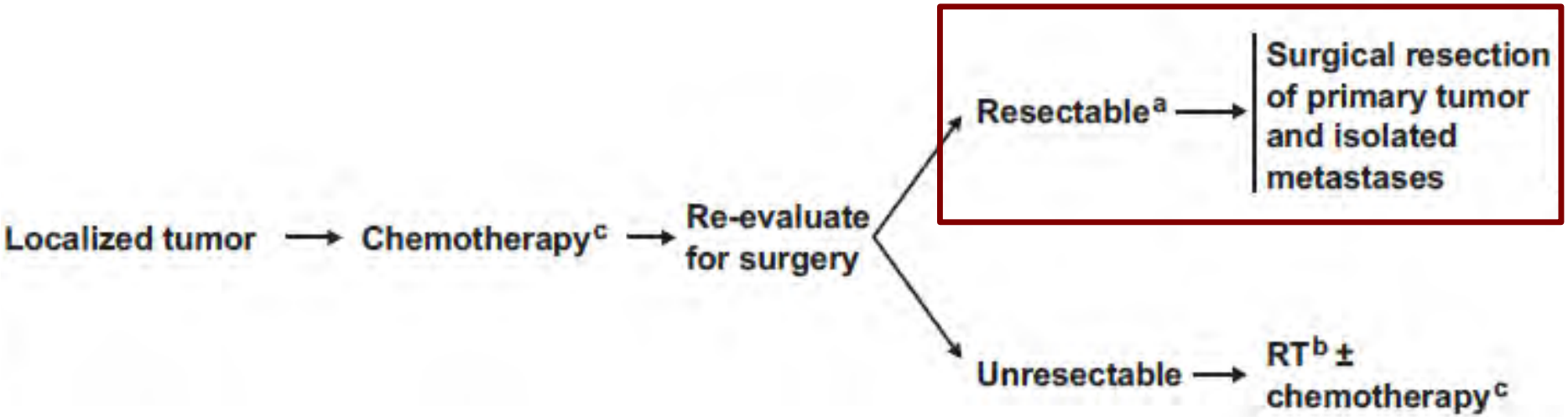
- Primary chemotherapy
- **Surgery**

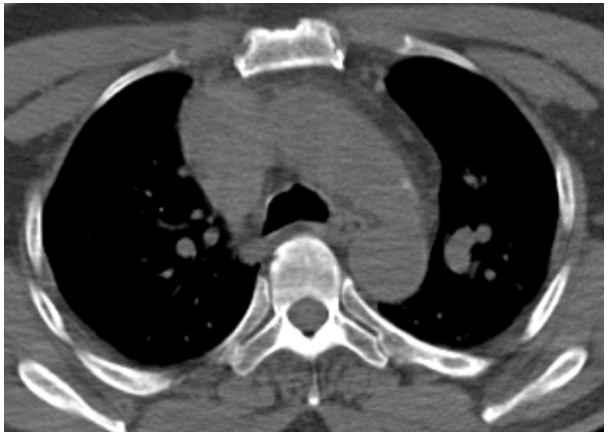
Resectable tumors

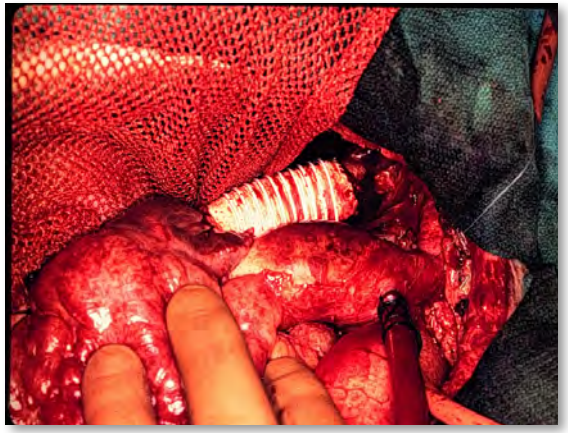
- Surgery
- Postoperative radiotherapy

Treatment of thymic tumors

- **Locally advanced tumors: primary chemotherapy**







National Comprehensive Cancer Network Guidelines

Pre-operative chemotherapy

Study	Primary Chemotherapy Regimen	No. of Patients	Tumor		Subsequent Treatment (%)			
					Surgery			
			Type	Stage	Any Surgery	Complete Resection	Radiotherapy	None
Chemotherapy								
Macchiarini et al 1991[14]	CEE	7	T/TC	III	100	57	0	0
Berruti et al 1993[15]	ADOC	6	T	III-IVA	NA	17	NA	NA
Rea et al 1993[16]	ADOC	16	T	III-IVA			0	0
Berruti et al 1999[17]	ADOC	16	T	III-IVA			31	13
Venuta et al 2003[18]	CEE	15	T/TC	III			NA	NS
Bretti et al 2004[19]	ADOC/PE	25	T/TC	III-IVA			NA	NA
Kim et al 2004[20]	CAPP	22	T				0	0
Lucchi et al 2005[21]	CEE	36	T/TC	III-IVA			19	3
Jacot et al 2005[22]	CAP	5	T/TC	III-IVA			50	12
Yokoi et al 2007[23]	CAMP	14	T/TC	III, IV			14	21
Kunitoh et al 2009[24]	CODE	21	T	III	62	43	24	14
Park et al, ASCO 2012	CDDP-Doc	27	T/TC	III/IV	70	63	4	25

Complete resection **50%** **(14-78%)**

Girard N. Eur Respir Rev 2013;22:75

Chirurgie des tumeurs de stade IVA

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

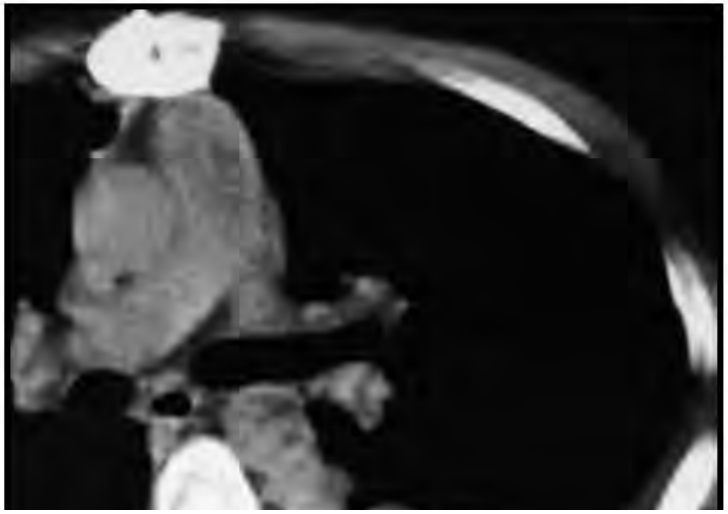
Background. The treatment of locally advanced Masaoka stage IVA thymoma is not standardized and is problematic.

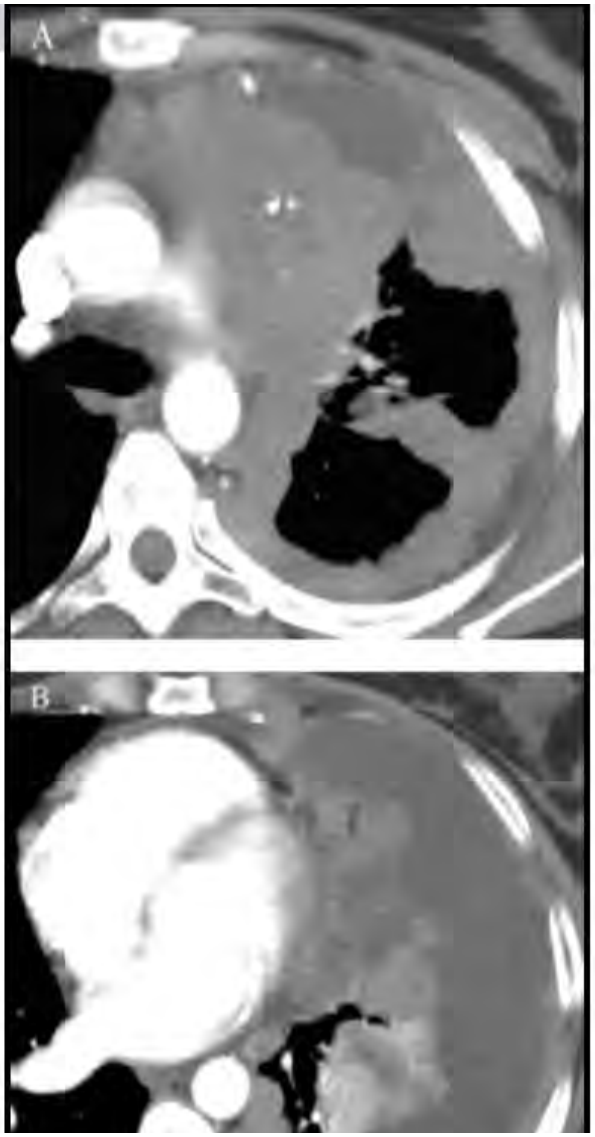
Methods. A single-institution retrospective study was made of 5 patients with World Health Organization B3 thymomas who underwent pleuropneumonectomy for locally advanced thymoma. Two patients had recurrent thymoma and 3 presented de novo with stage IVA disease. Patients had a variety of induction and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





Pleural chemo-hyperthermia

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

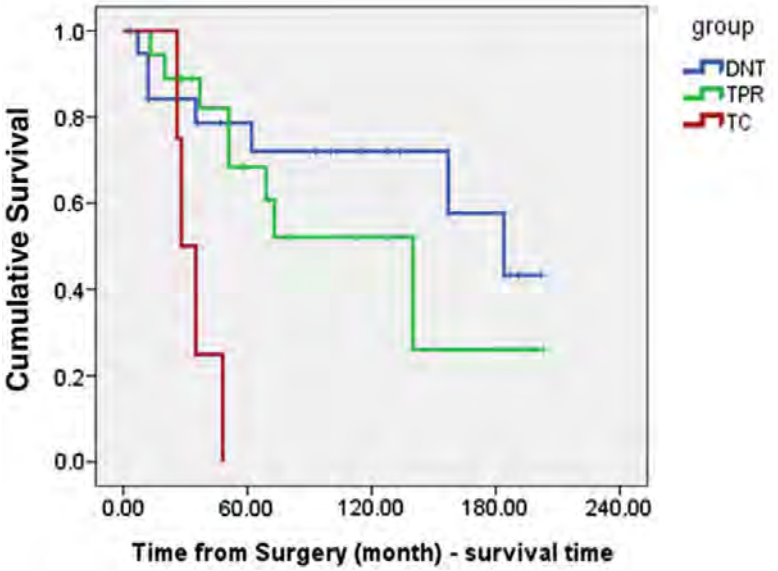
Alon Yellin, MD,[a] David A. Simansky, MD,[a] Ronny Ben-Avi, MD,[a] Marina Perelman, MD,[b] Nona Zeitlin, MD,[a] Yael Refaely, MD,[a] and Alon Ben-Nun, MD[a]

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 2. Surgical and perfusion data (n = 41)

	DNT (n = 17)	TPR (n = 14)	Redo (n = 7)	TC (n = 4)
Maximum procedure				
Local resection	4	5	3	1
Pleurectomy	2	6		1
Wedge/lobectomy	3/1	1	2	
Chest wall	3	2	2	2
Diaphragm	1			
Vena cava	2			
Pleuropneumonectomy	1			
Atrium				
Resection R0:R1:R2	7:9:1	6:6:2	4:1:2	1:1:2
Chemotherapeutic agents				
Cisplatinum 100 mg/m^2	16	14	7	4
Doxorubicin	8	10	5	0
Perfusion temperature				
≤41.8°C	6	6		2
>41.8°C	11	8	7	2

DNT, De novo stage IVa thymoma; *TPR*, thymoma with pleural relapse; *TC*, thymic carcinoma.



(J Thorac Cardiovasc Surg 2013;145:83-9)

Tumeurs thymiques

Specificities

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

Resectable tumors

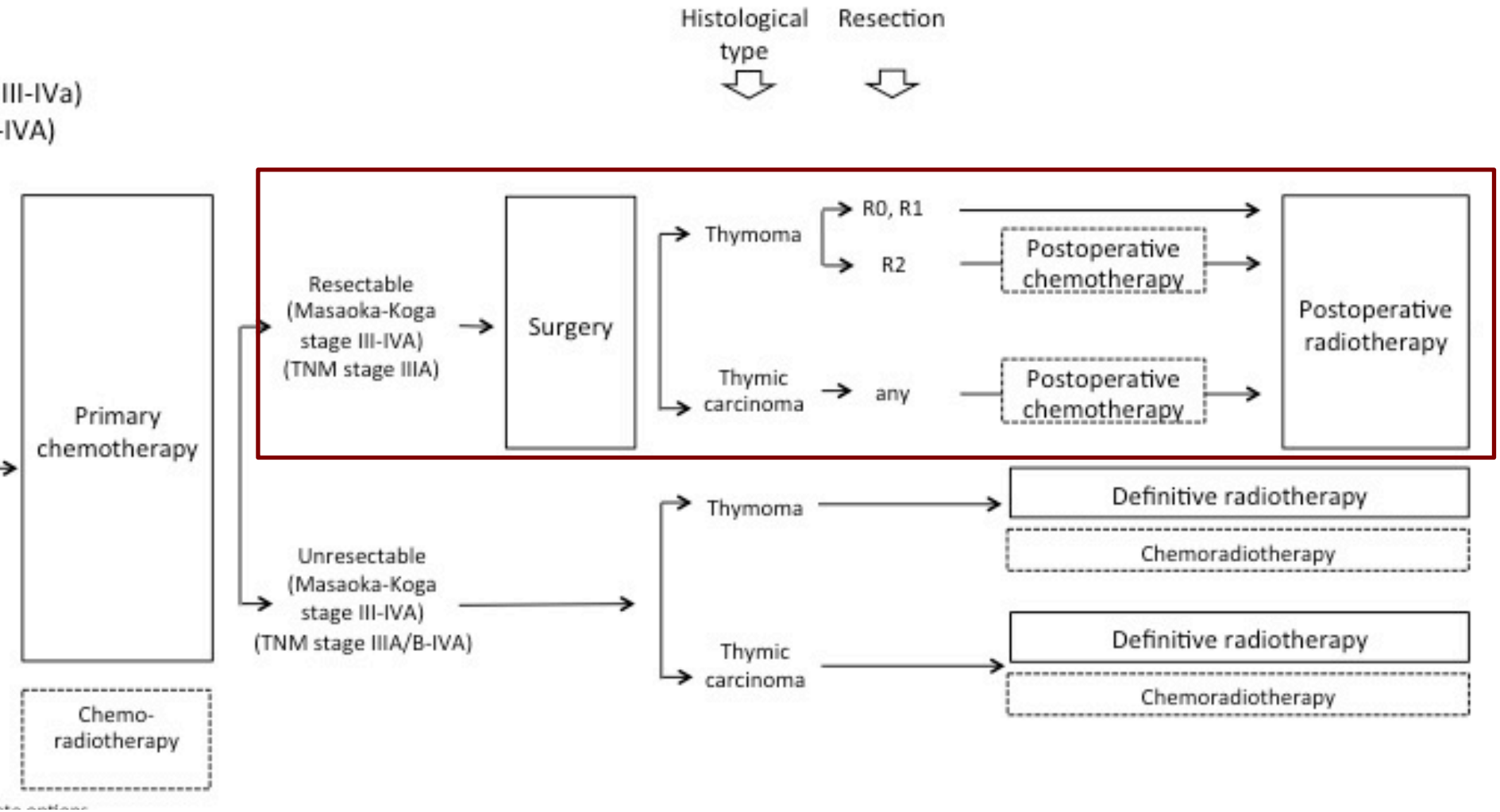
- Surgery
- Postoperative radiotherapy

2016

Unresectable tumors

- Primary chemotherapy
- **Surgery**
  - **postoperative treatment**

Recommandations RYTHMIC
ESMO Clinical Practice Guidelines



Tumeurs thymiques

Specificities

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

2016

Resectable tumors

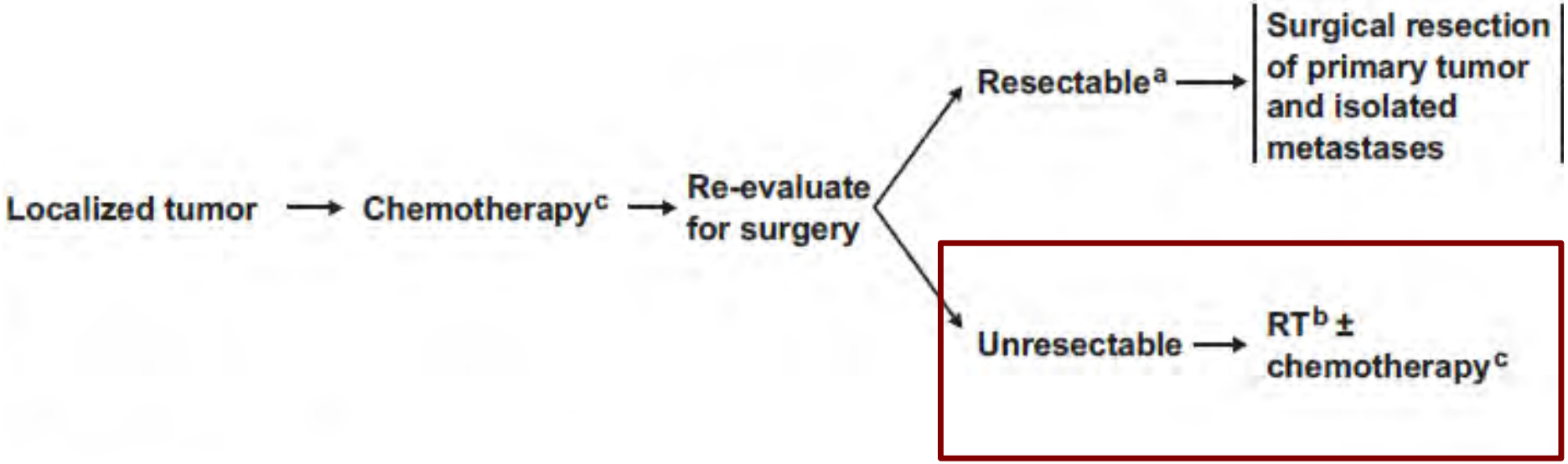
- Surgery
- Postoperative radiotherapy

Unresectable tumors

- Primary chemotherapy
- Surgery
  - postoperative treatment
- **Definitive radiotherapy**

Treatment of thymic tumors

- **Locally advanced tumors: primary chemotherapy**



National Comprehensive Cancer Network Guidelines

Chimio-radiothérapie exclusive

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					Surgery			
			Type	Stage	Any Surgery	Complete Resection	Radiotherapy	None
Chemotherapy								
Macchiarini et al 1991[14]	CEE	7	T/TC	III	100	57	0	0
Berruti et al 1993[15]	ADOC	6	T	III-IVA	NA	17	NA	NA
Rea et al 1993[16]	ADOC	16	T	III-IVA	100	69		0
Berruti et al 1999[17]	ADOC	16	T	III-IVA	56	56		13
Venuta et al 2003[18]	CEE	15	T/TC	III	100	NA		NS
Bretti et al 2004[19]	ADOC/PE	25	T/TC	III-IVA	68	44		NA
Kim et al 2004[20]	CAPP	22	T		100	72		0
Lucchi et al 2005[21]	CEE	36	T/TC	III-IVA	69	78	19	3
Jacot et al 2005[22]	CAP	5	T/TC	III-IVA	38	25	50	12
Yokoi et al 2007[23]	CAMP	14	T/TC	III, IV	64	14	14	21
Kunitoh et al 2009[24]	CODE	21	T	III	62	43	24	14
Park et al, ASCO 2012	CDDP-Doc	27	T/TC	III/IV	70	63	4	25

20-30% of patients

Girard N. Eur Respir Rev 2013;22:75

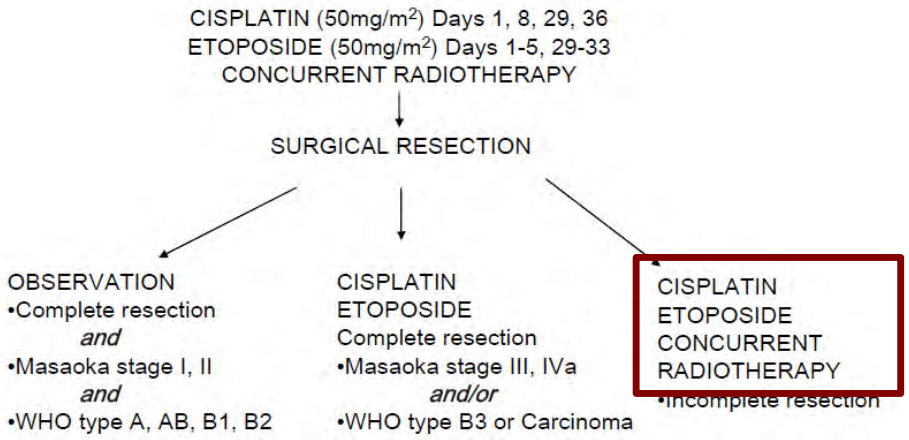
Definitive chemo-radiotherapy for thymomas

- **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%

Loehrer et al. J Clin Oncol 1997;15:3093

  - **Concurrent approach:**



Korst et al. J Thorac Cardiovasc Surg 2014;147:36

Stades localement avancés: chimio-radiothérapie

En pratique:

Réponse partielle:
radiothérapie séquentielle

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

Tumeurs thymiques

Specificities

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

2016

Resectable tumors

- Surgery
- Postoperative radiotherapy

Unresectable tumors

- Primary chemotherapy
- Surgery
  - postoperative treatment
- Definitive radiotherapy

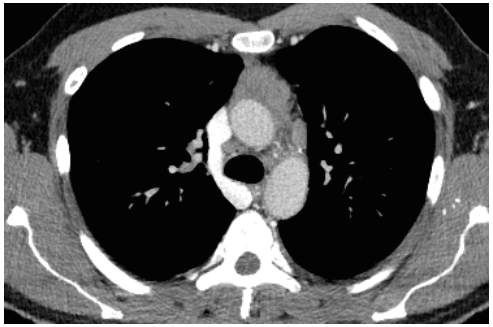
Metastatic tumors

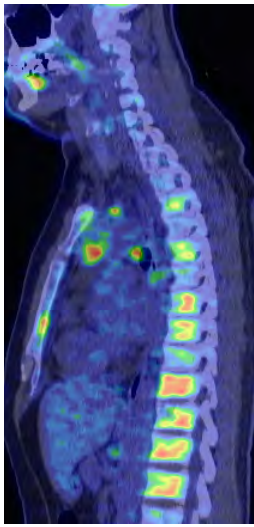
- **First-line chemotherapy**

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[e] → Re-evaluate for surgery
  - Resectable[a,b] → Surgical resection of primary tumor and isolated metastases
  - Unresectable[a] → RT[d] ± chemotherapy[e]
- Isolated solitary metastasis → Chemotherapy[e] or Surgery[b]
  - → Consider chemotherapy[e] or RT[d]
- Evidence of distant metastases → Chemotherapy[e]





National Comprehensive Cancer Network Guidelines

Palliative-intent chemotherapy regimens

Study	No. of Patients	Period of Accrual (years)	Tumor Type	Design	Regimen	Agents	Doses	Response Rate (%)
Single-agent chemotherapy								
Bonomi et al 1993[27]	21	4	T/TC	Phase II	Cisplatin		50 mg/m^2/3 weeks	10
Highley et al 1999[28]	15	12	T/TC	Retrosp	Ifosfamide		1.5g/m^2 × 5 days/3 weeks	46
Loehrer et al 2006[29]	27	1	T/TC	Phase II	Pemetrexed		500 mg/m^2/3 weeks	17
Combination chemotherapy								
Fornasiero et al 1990[30]	32	11	T	Retrosp	ADOC	Doxorubicin	40 mg/m^2/3 weeks	91
						Cisplatin	50 mg/m^2/3 weeks	
						Vincristin	0.6 mg/m^2/3 weeks	
						Cyclophosphamide	700 mg/m^2/3 weeks	
Loehrer et al 1994[31]	30	9	T/TC	Phase II	CAP	Cisplatin	50 mg/m^2/3 weeks	51
						Doxorubicin	50 mg/m^2/3 weeks	
						Cyclophosphamide	500 mg/m^2/3 weeks	
Giaccone et al 1996[32]	16	6	T	Phase II	PE	Cisplatin	60 mg/m^2/3 weeks	56
						Etoposide	120 mg/m^2 × 3/3 weeks	
Loehrer et al 2001[33]	34	2	T/TC	Phase II	VIP	Etoposide	75 mg/m^2 × 4 days/3 weeks	32
						Ifosfamide	1.2 g/m^2 × 4 days/3 weeks	
						Cisplatin	20 mg/m^2 × 4 days/3 weeks	
Lemma et al 2011[34]	46	7	T/TC	Phase II	Carbo-Px	Carboplatin	AUC 5/3 weeks	43
						Paclitaxel	225 mg/m^2/3 weeks	
Palmieri et al 2011[35]	15	3	T/TC	Phase II	CAP-GEM	Capecitabine	650 mg/m^2 bid × 14 days/3 weeks	40
						Gemcitabine	1000 mg/m^2 × 2 days/3 weeks	
Okuma et al 2011[36]	9	8	TC	Retrosp	Cisplatin-Irinotecan	Cisplatin	80 mg/m^2/4 weeks	56
						Irinotecan	60 mg/m^2 × 3 days/4 weeks	

Girard N. ASCO 2012 Educational Book

Palliative-intent chemotherapy regimens

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						Irinotecan	60 mg/m^2 × 3 days/4 weeks	

Anthracyclin-based
Response: 70-80%

Non-anthracyclin-based
Response: 30-50%

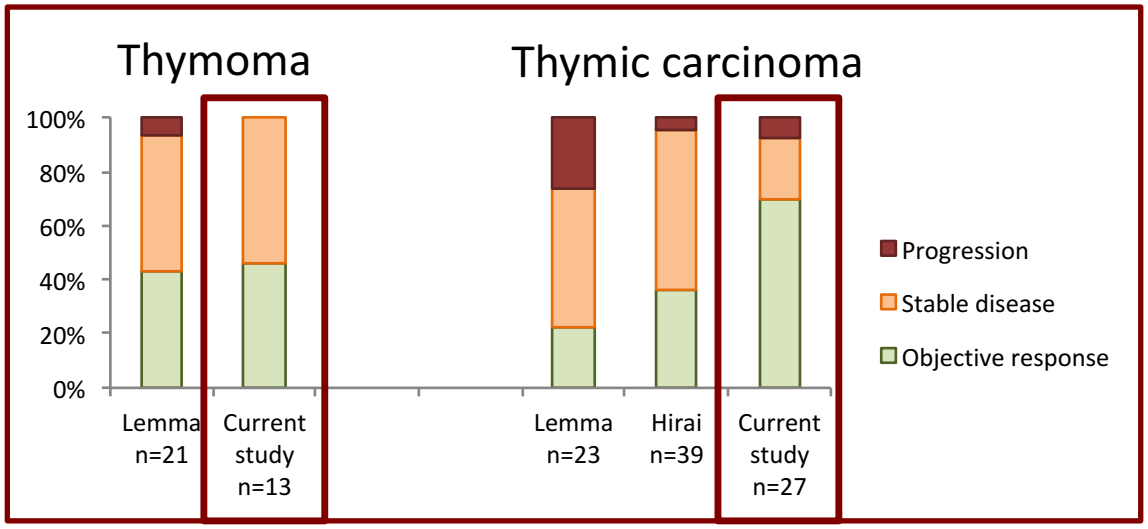
Girard N. ASCO 2012 Educational Book

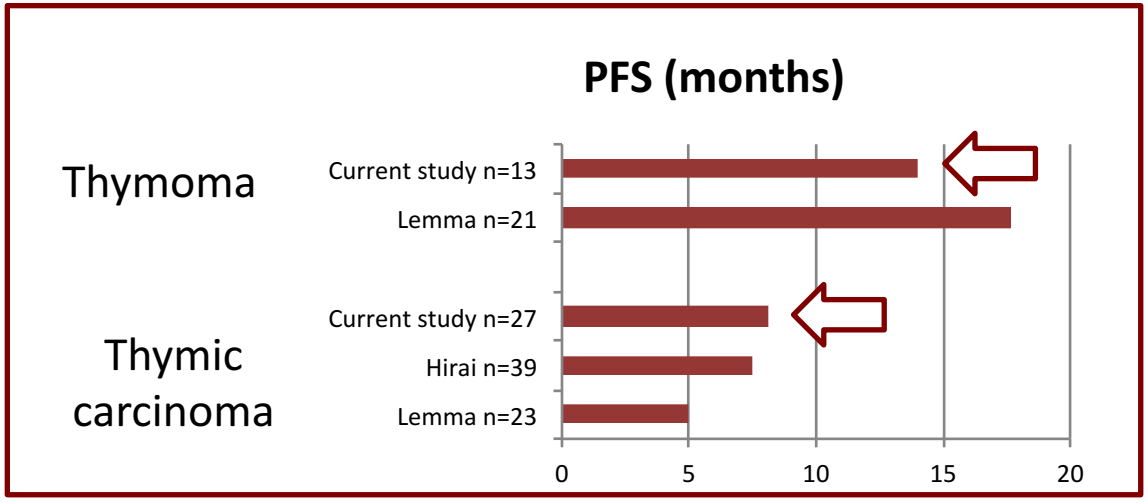
Carboplatine-Paclitaxel

- Reproductible results

- A new standard for thymic carcinomas?

- Do we need a trial of platine-paclitaxel vs. CAP?





Stades avancés ou métastatiques

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Lemma et al 2011[34]								43
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Okuma et al 2011[36]						Irinotecan	60 mg/m^2 × 3 days/4 weeks	56

En pratique

Première ligne: CAP

Carboplatine-Paclitaxel

4-6 cycles

Girard N. ASCO 2012 Educational Book

Corticosteroids and thymomas

- Depletion of the lymphocytic population
  - "thymolytic effect"

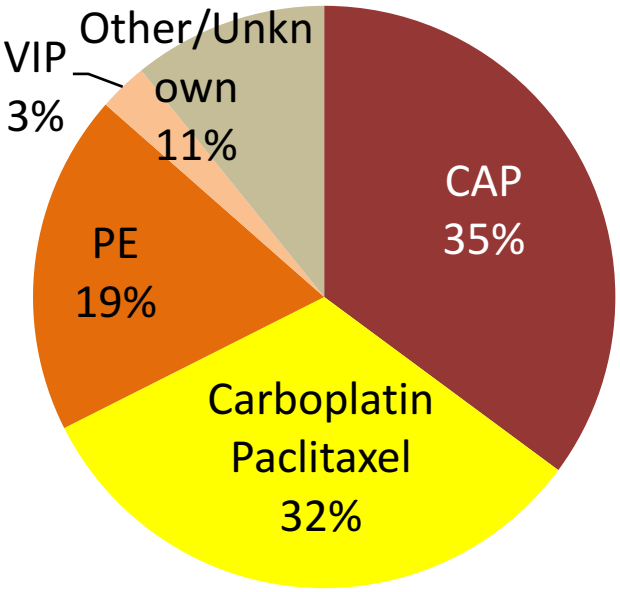
- Steroid receptors in 83% of thymomas

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

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

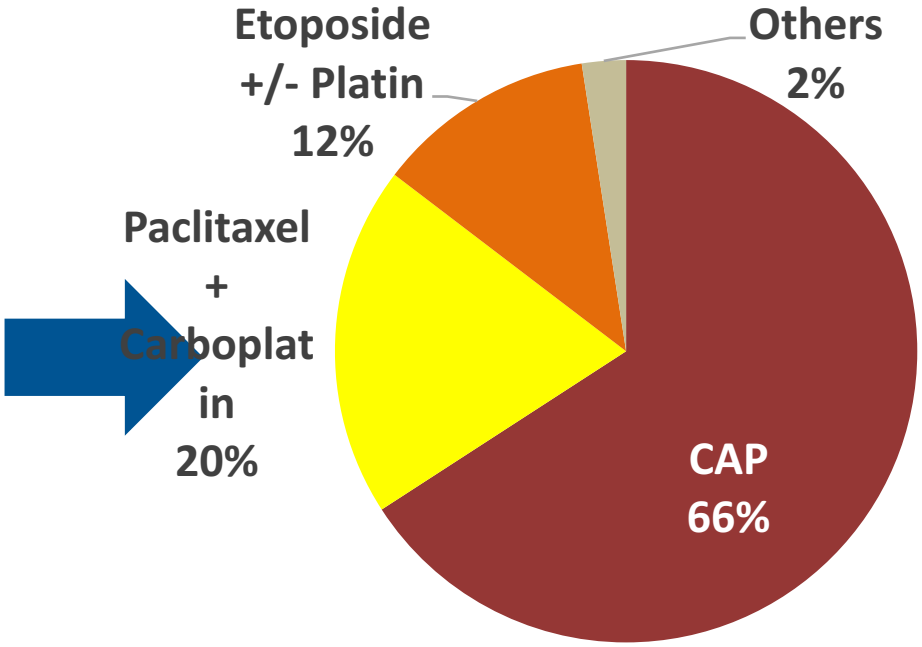
Craven et al. Muscle Nerve 1981;4:425
Mimae et al. Cancer 2011;117:4396
Kirkove C et al. Clin Oncol 1992;4:64

RYTHMIC: Exclusive (first-line) chemotherapy



Proposed regimens

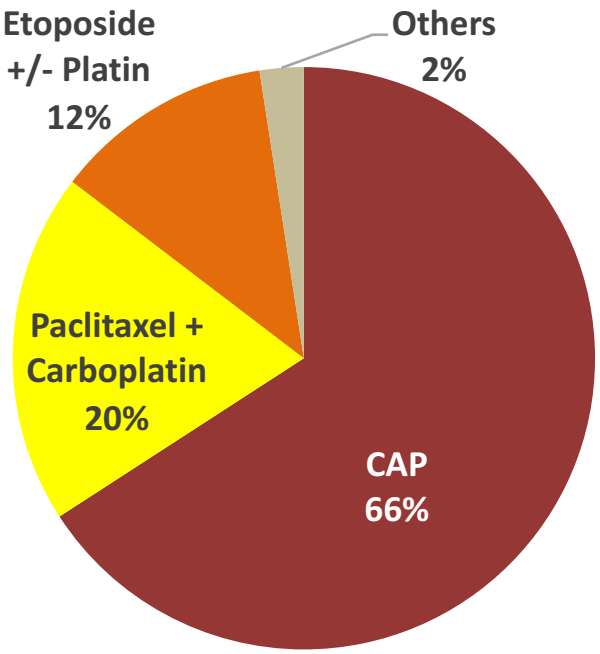
n=37



Administered regimens

n=41

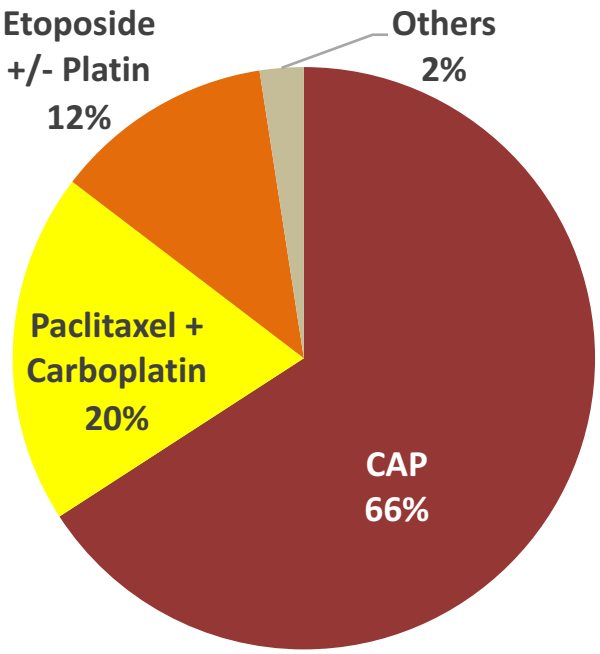
RYTHMIC: Exclusive (first-line) chemotherapy



Administered regimens

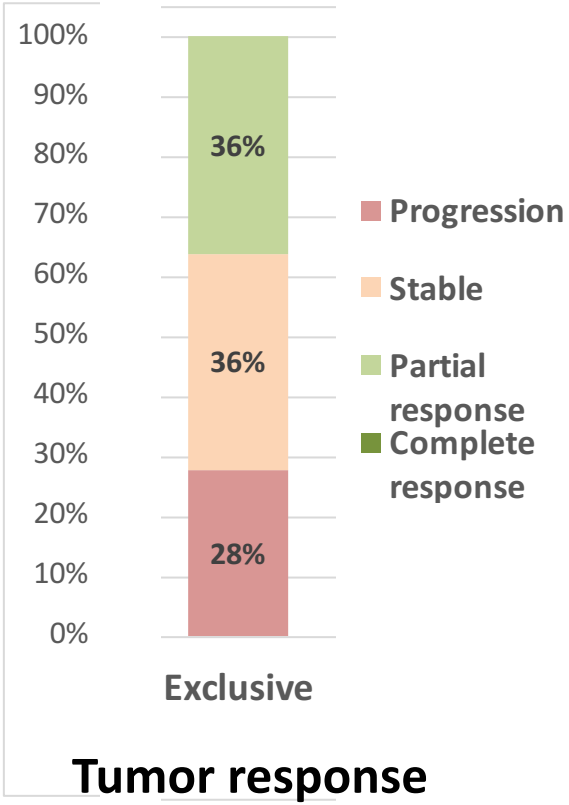
n=41

RYTHMIC: Exclusive (first-line) chemotherapy



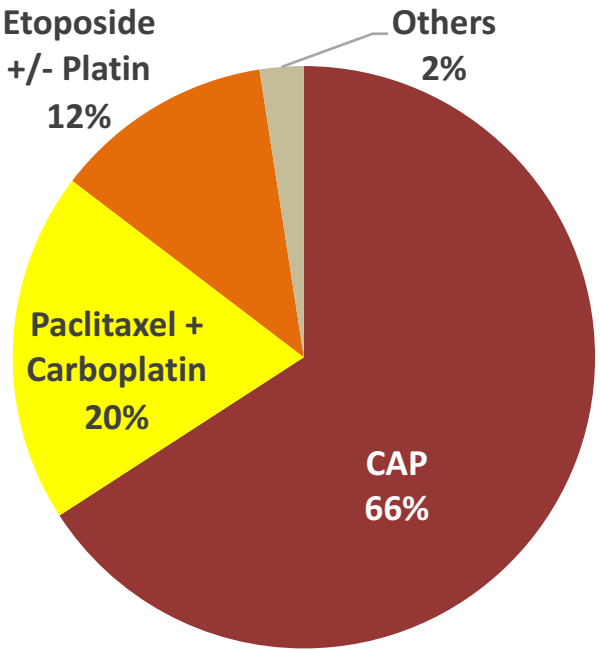
Administered regimens

n=41



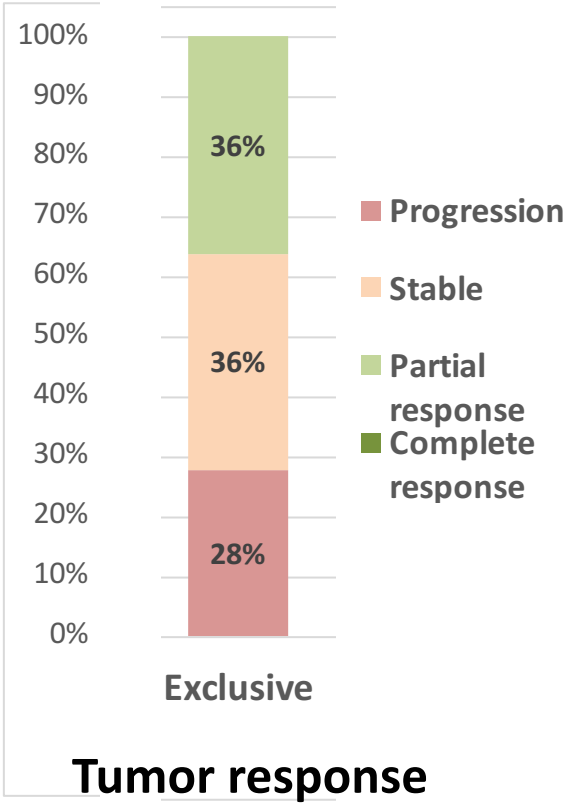
Tumor response

RYTHMIC: Exclusive (first-line) chemotherapy



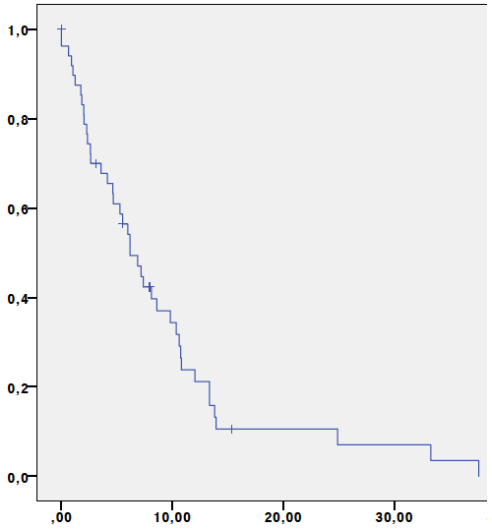
Administered regimens

n=41



Tumor response

Median: 6.2 months



Progression-free survival

Tumeurs thymiques

Specificities

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

2016

Resectable tumors

- Surgery
- Postoperative radiotherapy

Unresectable tumors

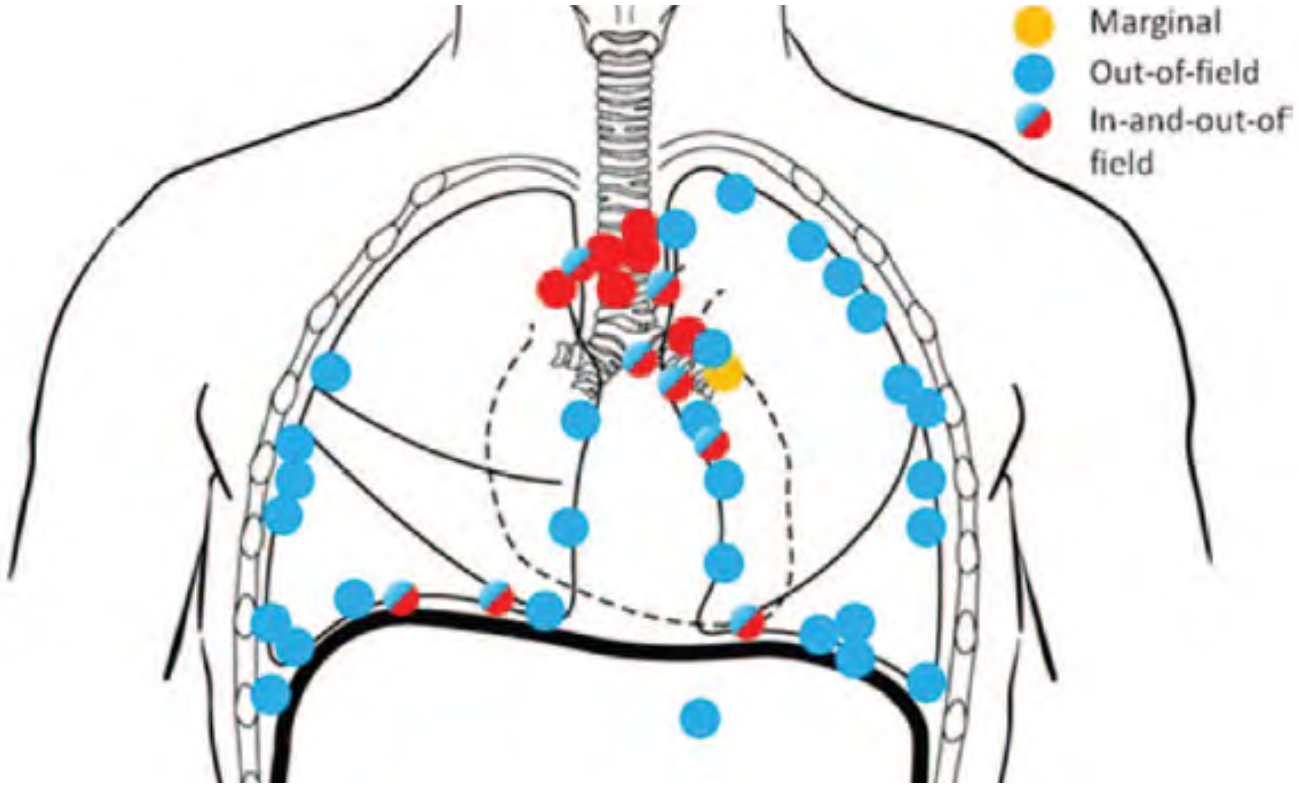
- Primary chemotherapy
- Surgery
  - postoperative treatment
- Definitive radiotherapy

Metastatic tumors

- First-line chemotherapy
- **Recurrences:**
  - **second-line treatment**

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 4
Results of surgical treatment of recurrent thymomas among the largest series published in the last 20 years

Author (Year)	Total	Recurrence (%)	Site	Surgery	Complete Res.	MeanTime to Recurrence	Survival (Years)
Haniuda (2001)	126	24 (19%)	22 Pl 6Loc 5 Dis	15/24	4/15 (27%)	68	47% (5 y) 35% (10 y)
Ruffini (1997)	266	30 (11%)	13 Pl 11 Loc 4 Dis	16/30	10/16 (62%)	86	48% (5 y) 24% (10 y)
Regnard (1997)	285	28 (10%)	15 Pl 8 Loc 5 Dis	28/28	19/28 (68%)	88	51% (5 y) 43% (10 y)
Ciccone (2005)	211	16 (7.5%)	8 Pl 2 Loc 6 Dis	16/16	N.S.	N.S.	64% (5 y) 44% (10 y)
Wright (2005)	179	20 (11%)	16 Pl 2 Loc 2 Dis	N.S.	N.S.	N.S.	N.S.
Blumberg (1995)	86	25 (29%)	1 Pl 17 Loc 7 Dis	13/25	N.S.	48	65% (5 y)

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,¶ Hirotoshi Horio, MD,# Akihide Matsumura, MD,** and Kohei Yokoi, MD,* for the Japanese Association for Research on the Thymus*

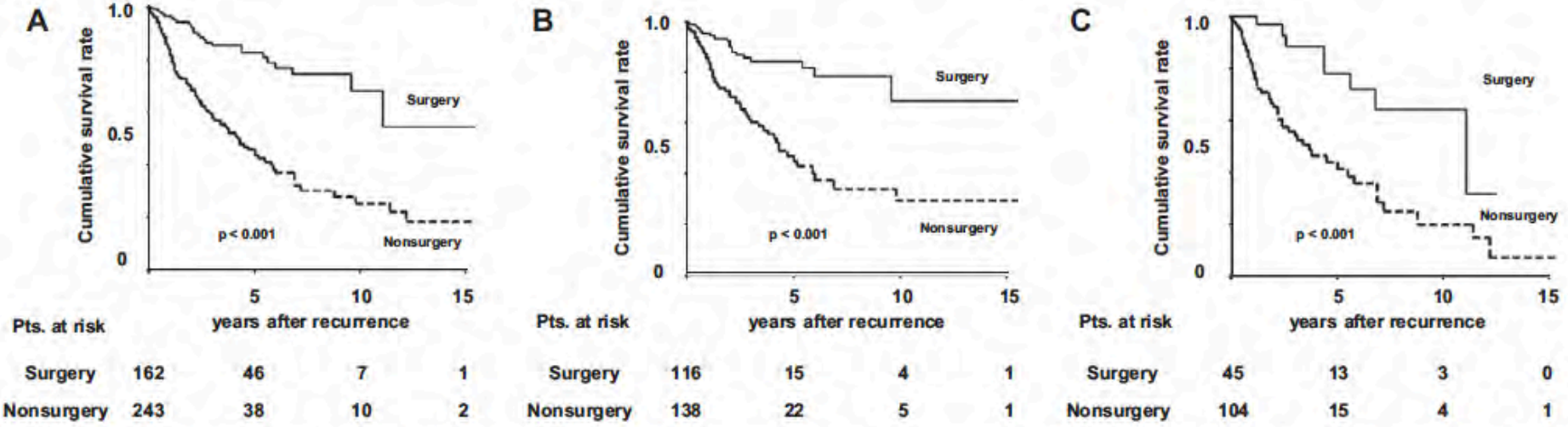
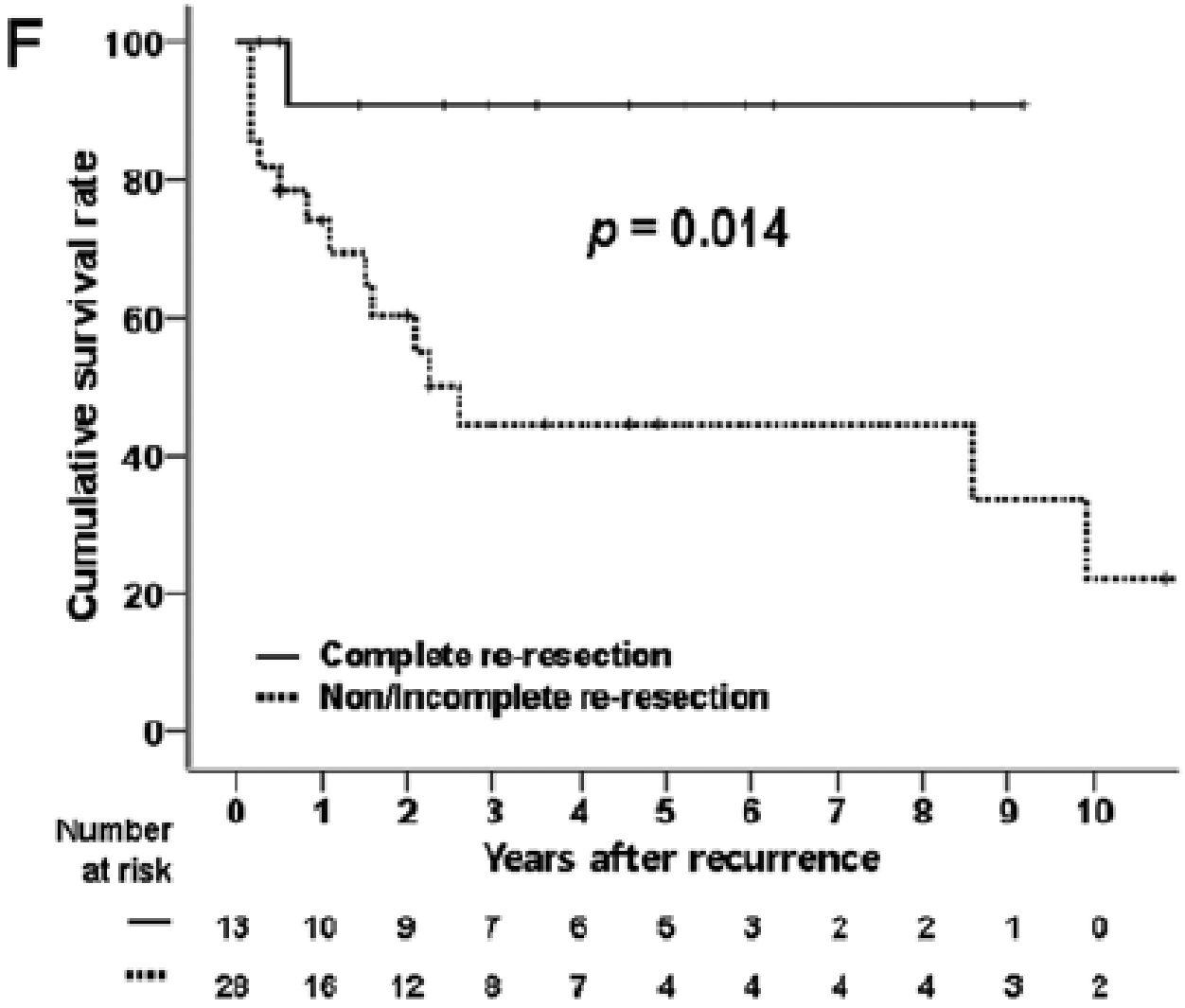


FIGURE 2. *A*, Overall survival after recurrence among the patients with recurrent thymic epithelial tumors, (*B*) thymic epithelial tumors treated with complete resection of the primary tumor, and (*C*) thymic epithelial tumors treated with incomplete resection of the primary tumor according to the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

Surgery for recurrences



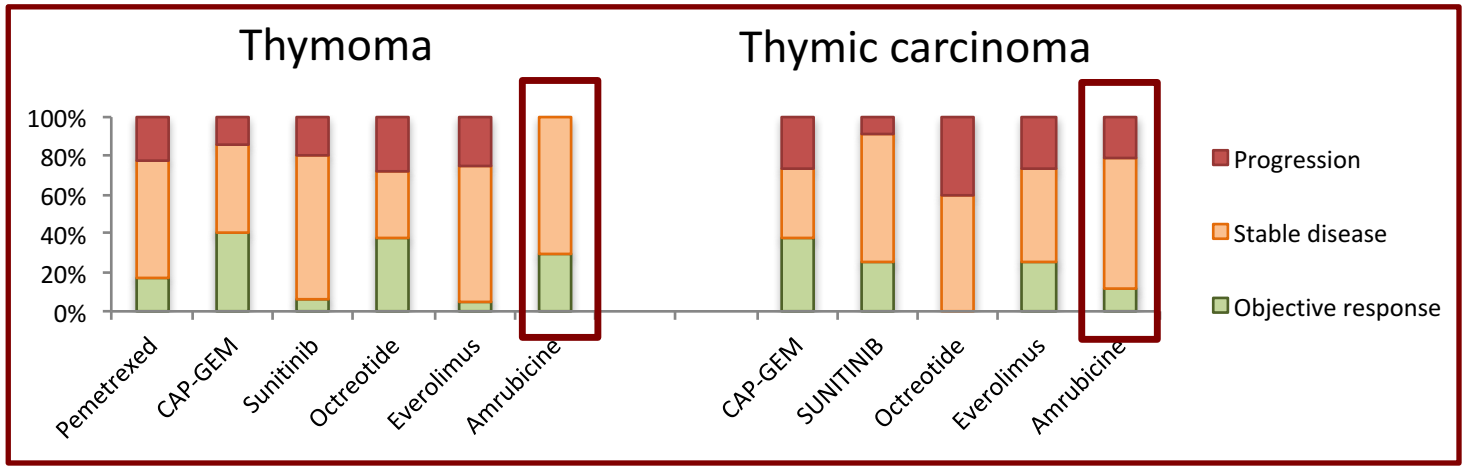
Bae et al. J Thorac Oncol 2012;7:1304

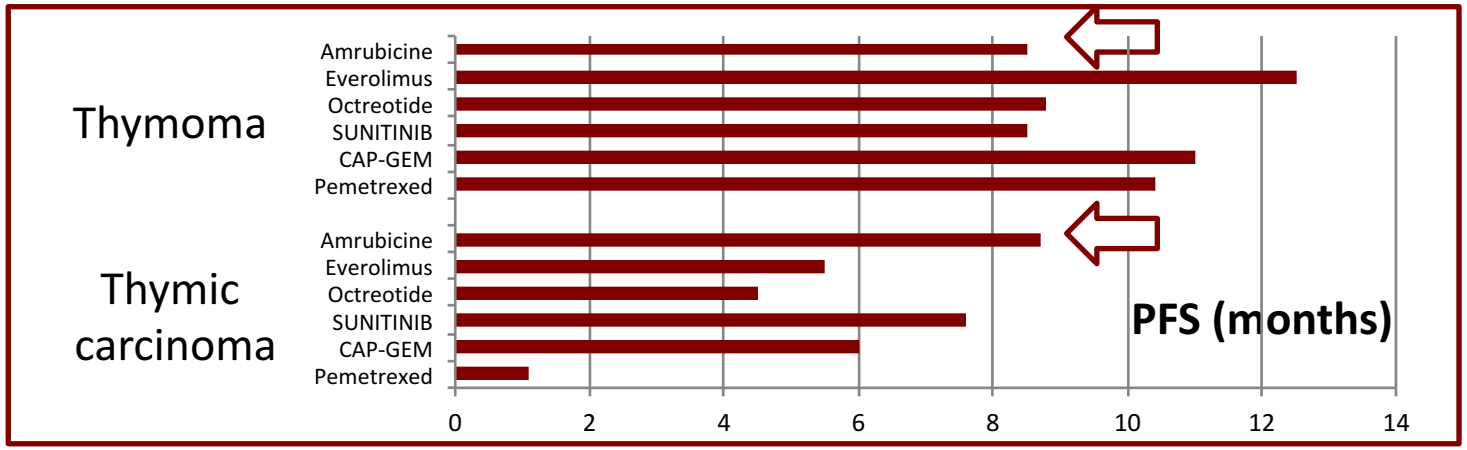
Second-line chemotherapy and beyond

Study	No. of Patients	Period of Accrual (years)	Tumor Type	Design	Regimen	Agents	Doses	Response Rate (%)
Single-agent chemotherapy								
Bonomi et al 1993[27]	21	4	T/TC	Phase II	Cisplatin		50 mg/m^2/3 weeks	10
Highley et al 1999[28]	15	12	T/TC	Retrosp	Ifosfamide		1.5g/m^2 × 5 days/3 weeks	46
Loehrer et al 2006[29]	27	1	T/TC	Phase II	Pemetrexed		500 mg/m^2/3 weeks	17
Combination chemotherapy								
Fornasiero et al 1990[30]	32	11	T	Retrosp	ADOC	Doxorubicin	40 mg/m^2/3 weeks	91
						Cisplatin	50 mg/m^2/3 weeks	
						Vincristin	0.6 mg/m^2/3 weeks	
						Cyclophosphamide	700 mg/m^2/3 weeks	
Loehrer et al 1994[31]	30	9	T/TC	Phase II	CAP	Cisplatin	50 mg/m^2/3 weeks	51
						Doxorubicin	50 mg/m^2/3 weeks	
						Cyclophosphamide	500 mg/m^2/3 weeks	
Giaccone et al 1996[32]	16	6	T	Phase II	PE	Cisplatin	60 mg/m^2/3 weeks	56
						Etoposide	120 mg/m^2 × 3/3 weeks	
Loehrer et al 2001[33]	34	2	T/TC	Phase II	VIP	Etoposide	75 mg/m^2 × 4 days/3 weeks	32
						Ifosfamide	1.2 g/m^2 × 4 days/3 weeks	
						Cisplatin	20 mg/m^2 × 4 days/3 weeks	
Lemma et al 2011[34]	46	7	T/TC	Phase II	Carbo-Px	Carboplatin	AUC 5/3 weeks	43
						Paclitaxel	225 mg/m^2/3 weeks	
Palmieri et al 2011[35]	15	3	T/TC	Phase II	CAP-GEM	Capecitabine	650 mg/m^2 bid × 14 days/3 weeks	40
						Gemcitabine	1000 mg/m^2 × 2 days/3 weeks	
Okuma et al 2011[36]	9	8	TC	Retrosp	Cisplatin-Irinotecan	Cisplatin	80 mg/m^2/4 weeks	56
						Irinotecan	60 mg/m^2 × 3 days/4 weeks	

Girard N. ASCO 2012 Educational Book

Second-line treatment of Tumeurs thymiques





Seconde ligne et plus

Study	No. of Patients	Period of Accrual (years)	Tumor Type	Design	Regimen	Agents	Doses	Response Rate (%)
Single-agent chemotherapy								
Bonomi et al 1993[27]	21	4	T/TC	Phase II	Cisplatin		50 mg/m^2/3 weeks	10

En pratique:

Carbo-Px, PE, Pemetrexed

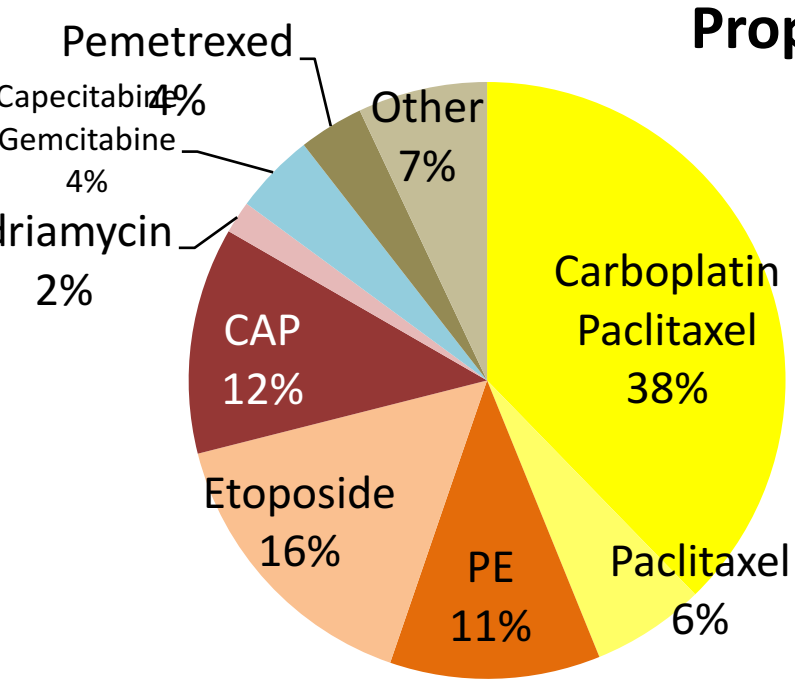
re-administration du CAP

(PS=0/1, réponse antérieure, rechute tardive; max. 8 cycles)

Girard N. ASCO 2012 Educational Book

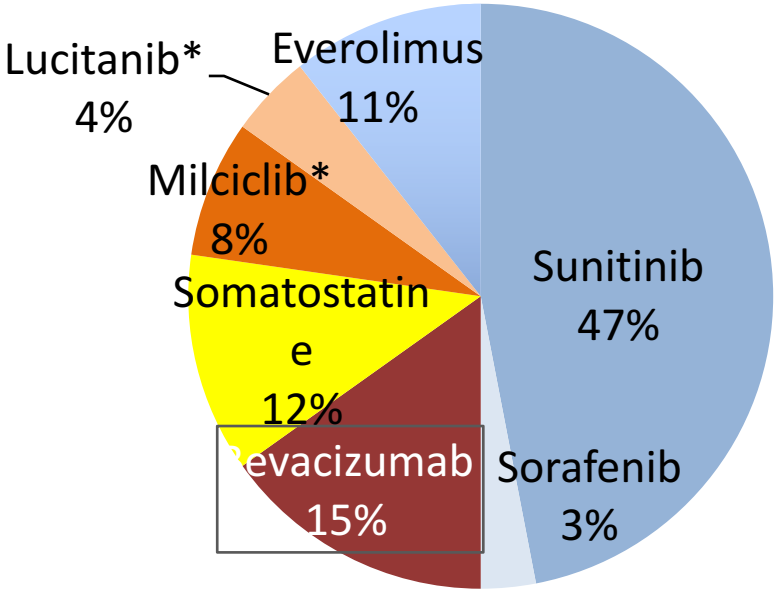
RYTHMIC: Systemic treatments for recurrence

Proposed regimens



Chemotherapy

n=114

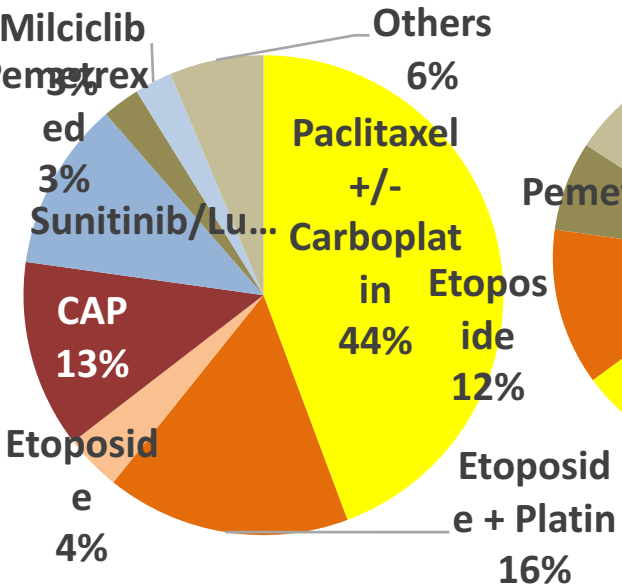


Targeted agents

n=67

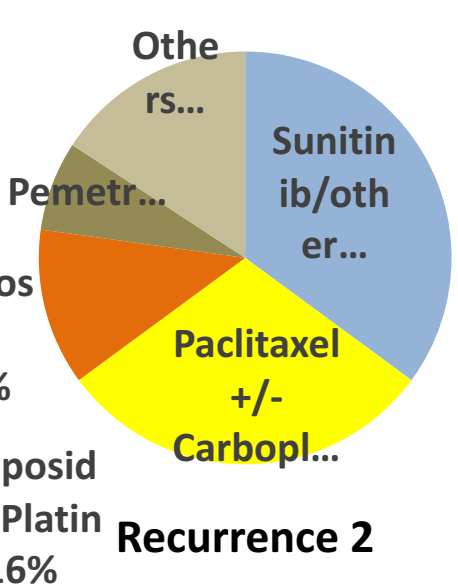
RYTHMIC: Systemic treatments for recurrence

Administered regimens



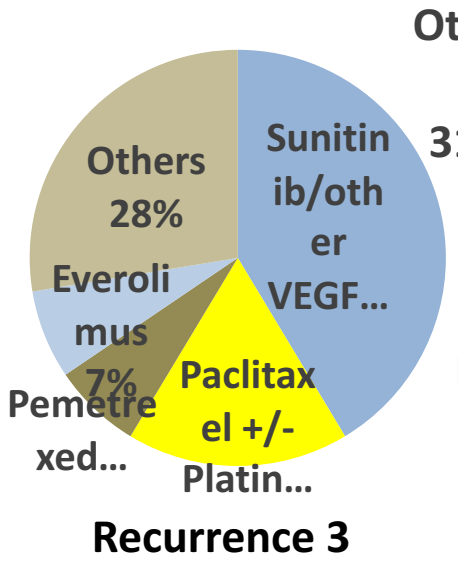
First recurrence

n=79



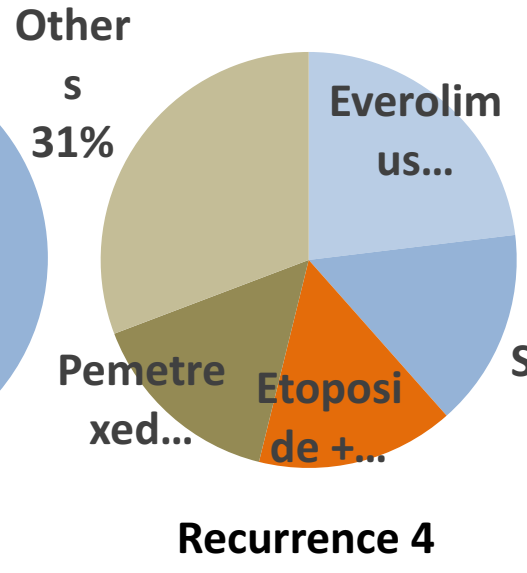
Recurrence 2

n=54



Recurrence 3

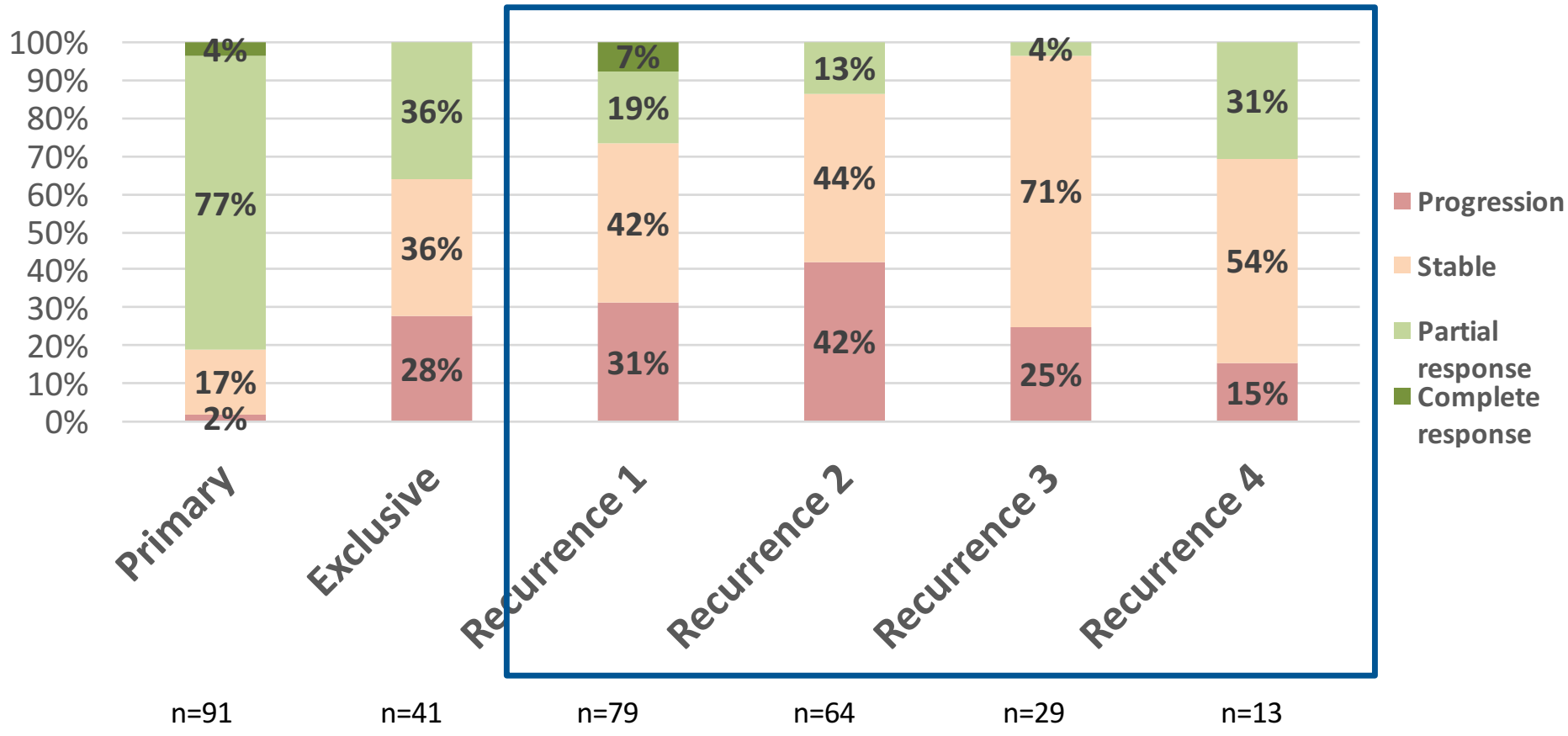
n=29



Recurrence 4

n=13

RYTHMIC: Systemic treatments for recurrence



Tumeurs thymiques

Specificities

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

2016

Resectable tumors

- Surgery
- Postoperative radiotherapy

Unresectable tumors

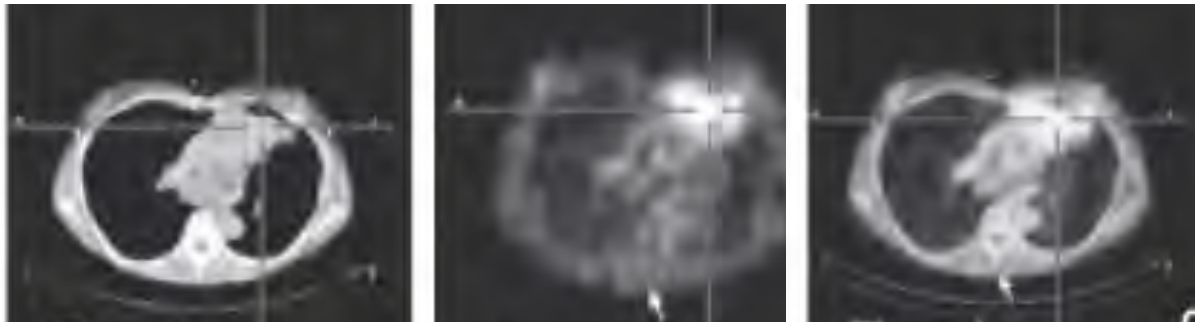
- Biopsy
- Primary chemotherapy
- Surgery
  - postoperative treatment
- Definitive radiotherapy

Metastatic tumors

- First-line chemotherapy
- Recurrences:
  - second-line treatment
- **Targeted agents**

Octreotide

- **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:**

	Corticoids	Thymoma			Thymic carcinoma		
		n	**CR+PR**	**SD**	**n**	**CR+PR**	**SD**
Palmieri, 2002	+	10	4	4	3	1	1
Loehrer, 2004	+/-	32	12	11	5	0	3
Schalke, ASCO 2012	+	17	15	0	0	0	0

Palmieri et al. Cancer 2002;94:1414; Loehrer et al. J Clin Oncol 2004;22:293
Schalke B, et al. J Clin Oncol 2012;30 (suppl; abstr 7105)

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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

	Thymoma		Thymic Carcinoma	
References	*n*	KIT Overexpression, *n* (%)	*N*	KIT Overexpression, *n* (%)
Pan et al.[31]	110	0 (0%)	22	19 (86%)
Henley et al.[32]	20	1 (5%)	15	12 (80%)
Nakagawa et al.[33]	50	2 (1%)	20	16 (80%)
Yoh et al.[20]	24	0 (0%)	17	15 (88%)
Tsuchida et al.[34]	20	0 (0%)	12	11 (92%)
Girard et al.[7]	33	0 (0%)	6	3 (50%)
Aisner et al.[21]	34	2 (6%)	5	1 (20%)
Zucali et al.	107	4 (3%)	6	13 (46%)

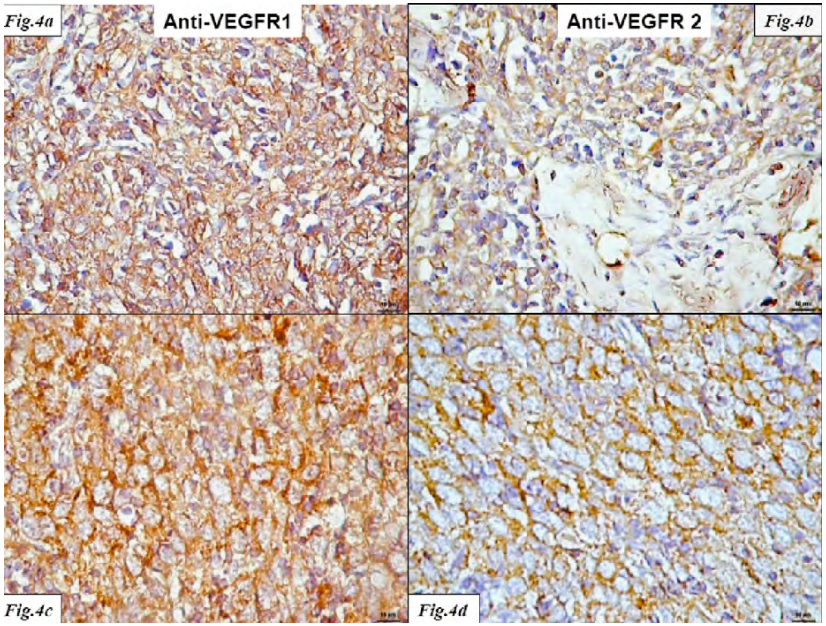
- **Mutations**: - 11% of thymic carcinomas (14/129 tested)

Mutation	Exon
E490K	9
Y553N	11
W557R	11
V559A	11
V560del	11
L576P	11
P577-D579del	11
D579del	11
H697Y	14
D820E	17

Sensitivity to KIT inhibitors
Imatinib
Sunitinib
Sorafenib

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



Cimpean et al. Ann Anat 2008;190:238;
Sasaki et al. Surg Today 2001;31:1038; Marino et Piantelli. Thor Surg Clin 2011;21:33

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

Anish Thomas, Arun Rajan, Arlene Berman, Yusuke Tomita, Christina Brzezniak, Min-Jung Lee, Sunmin Lee, Alexander Ling, Aaron J Spittler, Corey A Carter, Udayan Guha, Yisong Wang, Eva Szabo, Paul Meltzer, Seth M Steinberg, Jane B Trepel, Patrick J Loehrer, Giuseppe Giaccone

KIT wild-type tumors

	Thymic carcinoma (n=23)		Thymoma (n=16)	
	Patients (%)	95% CI	Patients (%)	95% CI
Objective response*	6 (26%)	10·2–48·4†	1 (6%)	0·2–30·2
Stable disease	15 (65%)	42·7–83·6	12 (75%)	47·6–92·7
Progressive disease	2 (9%)	1·1–28·0	3 (19%)	4·1–45·7
Disease control	21 (91%)	72·0–98·9	13 (81%)	54·4–96·0

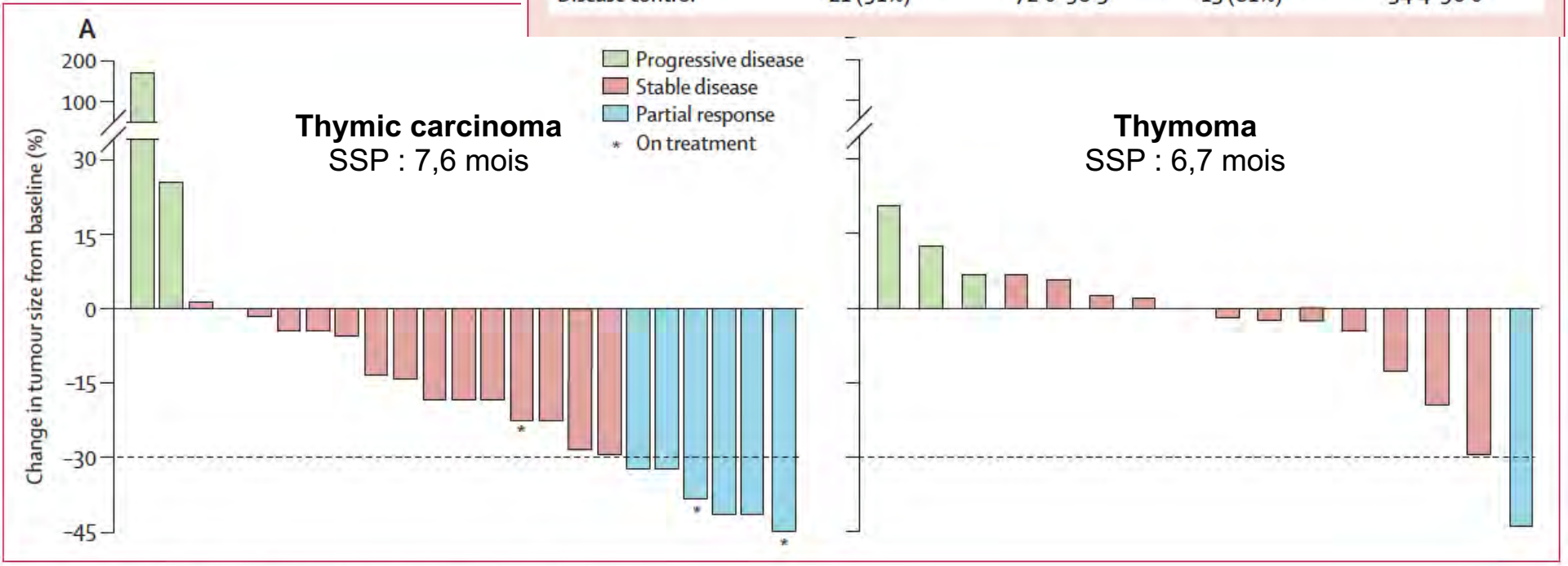


Figure 1: Waterfall plots of tumour responses to sunitinib

Lancet Oncol 2016; 16: 177

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2016

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- **Targeted agents**

Phase I trials

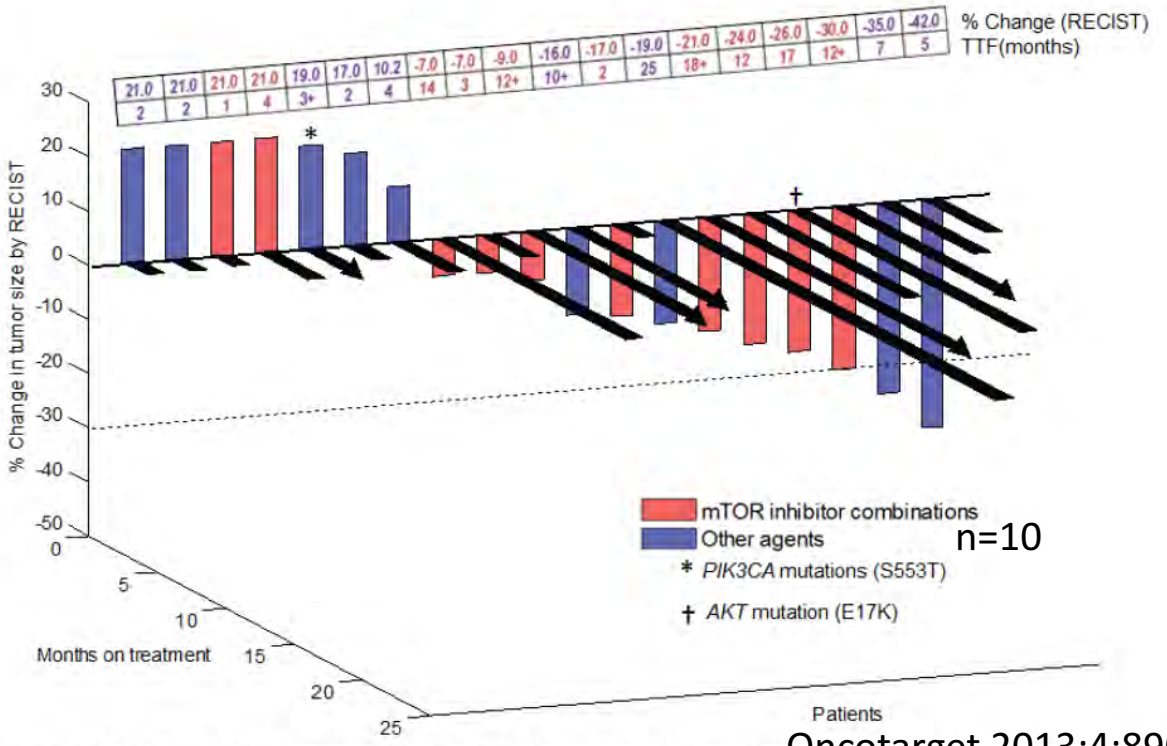
Thymoma Patients Treated in a Phase I Clinic at MD Anderson Cancer Center: Responses to mTOR Inhibitors and Molecular Analyses

Jennifer Wheler[1], David Hong[1], Stephen G. Swisher[2], Gerald Falchook[1], Apostolia M. Tsimberidou[1], Thorunn Helgason[1], Aung Naing[1], Bettzy Stephen[1], Filip Janku[1], Philip J. Stephens[3], Roman Yelensky[3], Razelle Kurzrock[4]

[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

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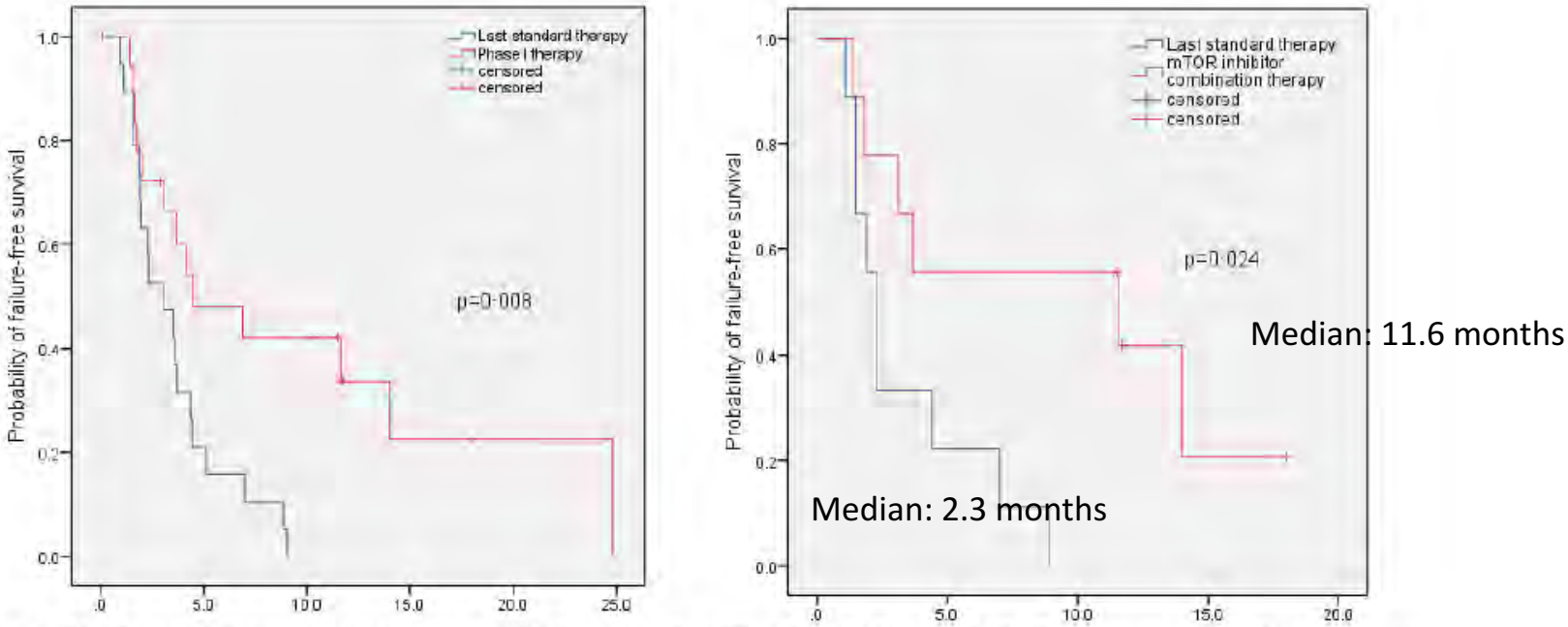


Figure 2: Kaplan - Meier curve to compare TTF in patients with advanced/metastatic thymoma or thymic carcinoma on their best phase I clinical trial versus TTF on their last conventional therapy before referral to the phase I clinic.

ASCO 2014: everolimus

HUMANITAS CANCER CENTER

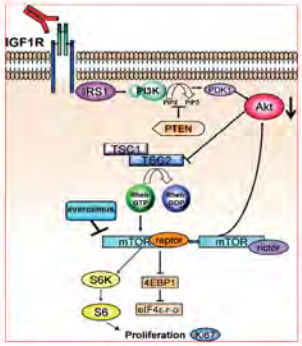
PHASE II STUDY OF EVEROLIMUS IN PATIENTS WITH THYMOMA AND THYMIC CARCINOMA PREVIOUSLY TREATED WITH CISPLATIN-BASED CHEMOTHERAPY

P.A. Zucali[1], T. De Pas[2], G. Palmieri[3], A.G. Favaretto[4], A. Chella[5], M. Tiseo[6], M. Caruso[7], M. Perrino[1], F. De Vincenzo[1], M. Simonelli[1], F. Toffalorio[2], P. Federico[3], G. Pasello[4], M. Ali[5], L. Giordano[1], M. Bertossi[1], A. Santoro[1]

1)Humanitas Cancer Center, Rozzano, Italy; 2)European Institute of Oncology, Milan, Italy; 3)Università Federico II, Naples, Italy; 4)Istituto Oncologico Veneto, Padua, Italy; 5)University Hospita, Pisa, Italy; 6)Azienda Ospedaliero-Universitaria of Parma, Parma, Italy; 7)Humanitas Centro Catanese di Oncologia, Catania, Italy

BACKGROUND

- New options for treatment are necessary in patients with advanced thymic epithelial tumors (TET) that have progressed on cisplatin-containing therapy.
- The IGF-1R and pAKT proteins resulted expressed in all WHO-defined subtypes of TET and their expression were significantly associated with aggressive subtypes [1,2].
- The activation of PI3K signalling may sensitize tumors to serine-threonine kinase mammalian target of rapamycin (mTOR) inhibition. Tumor growth conferred by AKT activation is also reversed by mTOR inhibitors [3].
- Recently, mTOR is emerging as a potential target in patients with advanced TET, following tumor responses observed in phase I trials, with recent data from several groups [4].
- The aim of this study is to determine the activity of Everolimus monotherapy in patients with advanced or recurrent TET previously treated with cisplatin-containing chemotherapy.

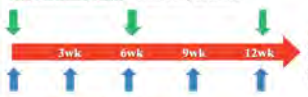


IGF1-R and mTOR pathways.
José Baselga, *The Oncologist 2011, 16:12-19.*

METHODS

STUDY DESIGN: Pre-treated TET pts were prospectively enrolled in single arm, single-stage, open label, multicentre, phase II trial.

TUMOUR ASSESSMENT was done every six weeks.



EVEROLIMUS 10 mg once daily was done continuously until documented disease progression, unacceptable toxicity, or patient refusal.

SAFETY was assessed every three weeks.

PRIMARY ENDPOINT:
- Disease control rate (DCR), considered as complete response (CR) plus partial response (PR) plus stable disease (SD).

SECONDARY ENDPOINTS:
- Progression free survival (PFS), duration of response, and overall survival (OS).
- Safety
- To correlate response to therapy with changes in FDG-PET imaging at baseline and first restaging.
- To evaluate the predictive role of the expression of several biomarkers by immunoistochemistry (IGF-1R, pAKT, mTOR, p-S6K, p-S6, p4E-BP1, and pTEN) on tumor samples.

STATISTICAL ANALYSIS: A Fleming phase II trial was designed considering a DCR of 40% or lower as clinically unworthy, whereas a rate of 60% or higher was considered of potential interest, $\alpha = \beta = 0.10$. It was calculated that 21 pts with DC would be observed in the first 41 evaluable pts.

RESULTS

PATIENT CHARACTERISTICS

	50	50 pts / studies	% range
Age (years)		55	36-80
Sex			
• Male		28	56
• Female		22	44
Histotype			
• Tymoma		30	60
• Timic Carcinoma		19	38
• Missing		1	2
Disease			
• Locally advanced		8	16
• Metastatic		40	80
• Missing		2	4

In order to have 41 evaluable pts, 50 pts have been enrolled and treated.

RESULTS

EFFICACY

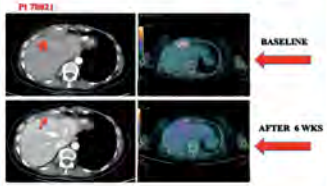
First 41 pts	N	%
CR	1	2.4
PR	8	19.5
SD	29	70.7
PD	3	7.3

DCR: 92.7% (N=38)*
Thymomas (26): 100%
Thym. Carc. (11): 78.5%
*1 pt without histotype

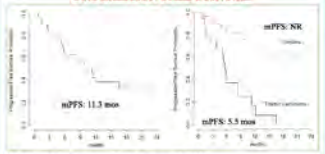
All 50 treated pts	N	%
CR	1	2.0
PR	10	20.0
SD	32	64.0
PD	4	8.0
Missing	3	6.0

DCR: 86.0% (N= 43)*
Thymomas (28): 93.3%
Thym. Carc. (14): 73.7%
*1 pt without histotype

Pt 78821

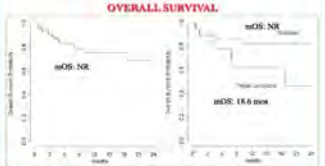


PROGRESSION FREE SURVIVAL



Median Follow up (mos): 12.4, range: 0.7-36.9
1 year PFS , ALL: 42.7%, Thymoma: 70.2%, thymic carcinoma: 16.6%

OVERALL SURVIVAL



1 year OS , ALL: 75.5%, Thymoma: 82.3%, Thymic carcinoma: 62.3%

TOXICITY:

Toxicities N= 50 pts	All Grade N (%)	G3-G4 N (%)
Neutropenia	4 (8)	2 (4)
Thrombocytopenia	4 (8)	1 (2)
Anemia	3 (6)	1 (2)
Asthenia	20 (40)	3 (6)
Stomatitis	16 (32)	-
Dyspnea	13 (26)	3 (6)
Diarrhea	12 (24)	-
Nausea and vomiting	6 (12)	-
Hypercholestorolemia	5 (10)	-
Hyperglycemia	2 (4)	1 (2)

Adverse events (AE)	n (%)
Total AE	536 (100)
AE ≥ G3	56 (10.4)
Serious AE	21 (4)
AE leading to permanent treatment discontinuation	10 (2)
AE leading to death (same patient)	2 (0.4)

CONCLUSIONS

- The primary end-point of this study was reached.
- These results suggest that Everolimus is able to achieve a satisfactory number of DC in this setting of pts.
- Ongoing exploratory analyses are evaluating biologic determinants of activity and mechanisms of resistance.
- The efficacy should be better evaluated in subsequent larger study phases.

REFERENCES

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2. Girard N, Teruya-Feldstein J, Payabyab EC, et al. Insulin-like growth factor-1 receptor expression in thymic malignancies. J Thorac Oncol 2010; 5: 1439–1446.
3. Bjornsti MA and Houghton PJ. The TOR pathway: A target for cancer chemotherapy. Nature Reviews Cancer, 2004;4:335-338.
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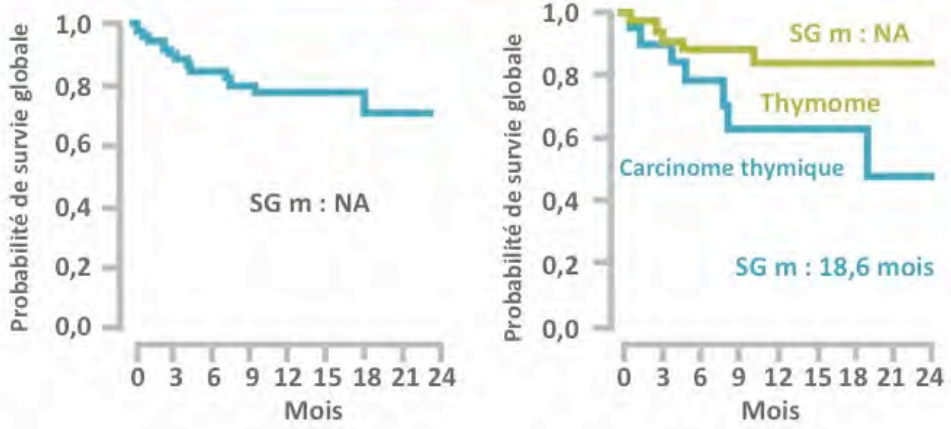
ACKNOWLEDGMENTS

The study team is particularly grateful to the patients and their families, and to personnel from Novartis for advice and support.

Additional information are on www.clinicaltrials.gov (NCT01017458)

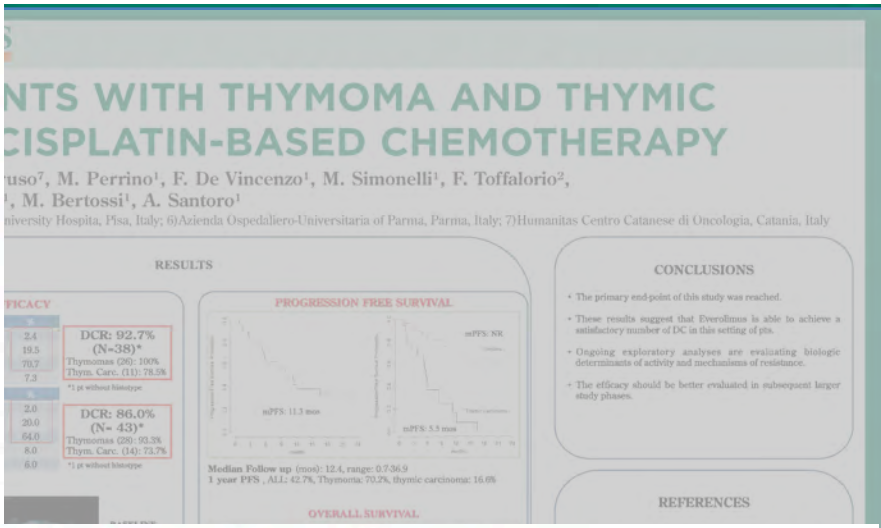
ASCO 2014: everolimus

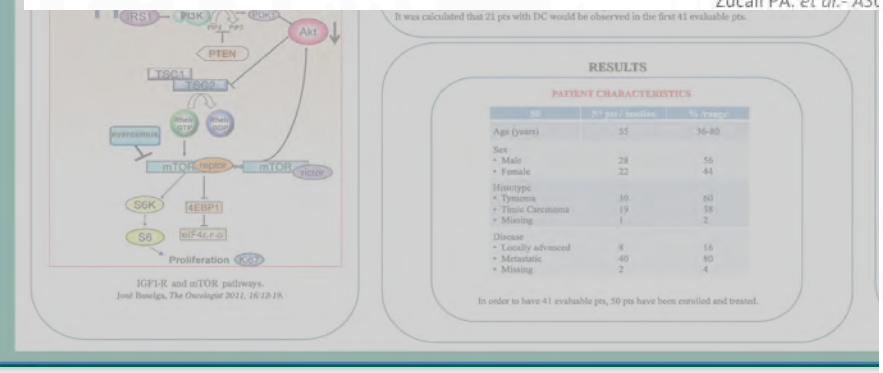
Survie Globale sous everolimus



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

Zucali PA. *et al.- ASC*





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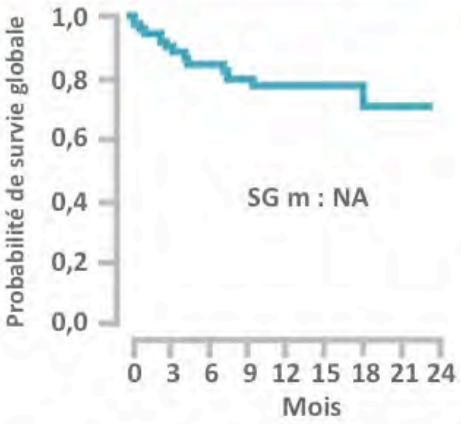

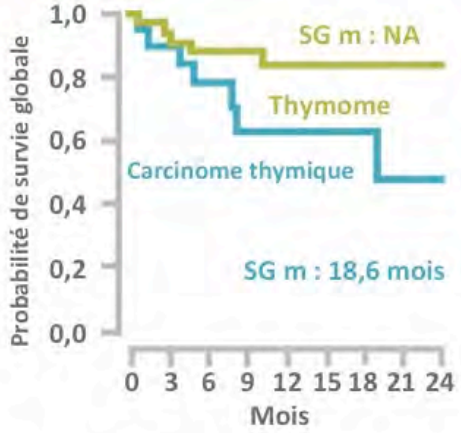

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Zucali PA. *et al.- ASCO®2014* - Abs 7527

Tumeurs thymiques

Specificities

- 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

Initiatives & Opportunities

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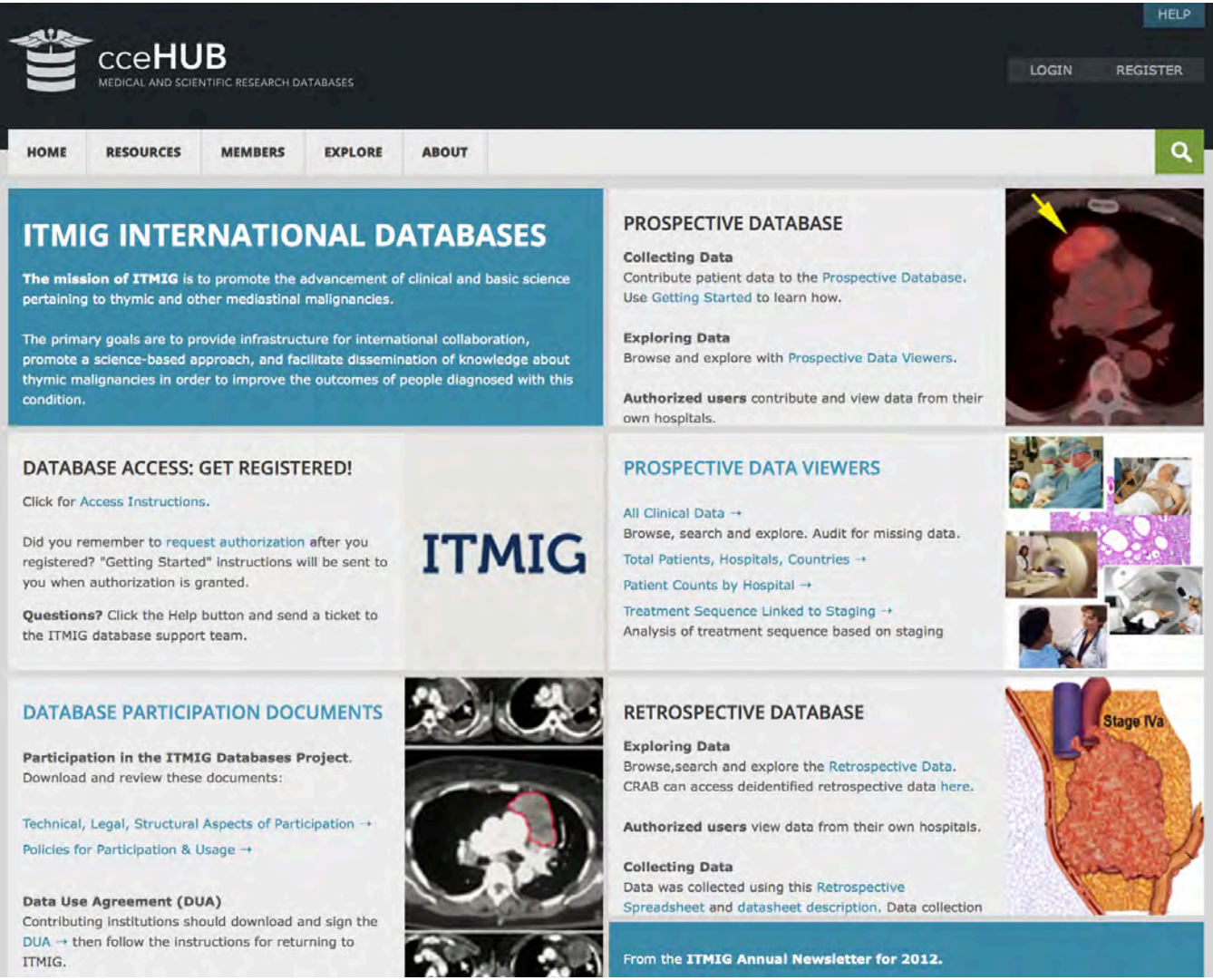
Initiatives & Opportunities

- **ITMIG: databases**

ITMIG Databases: website is ccehub.org



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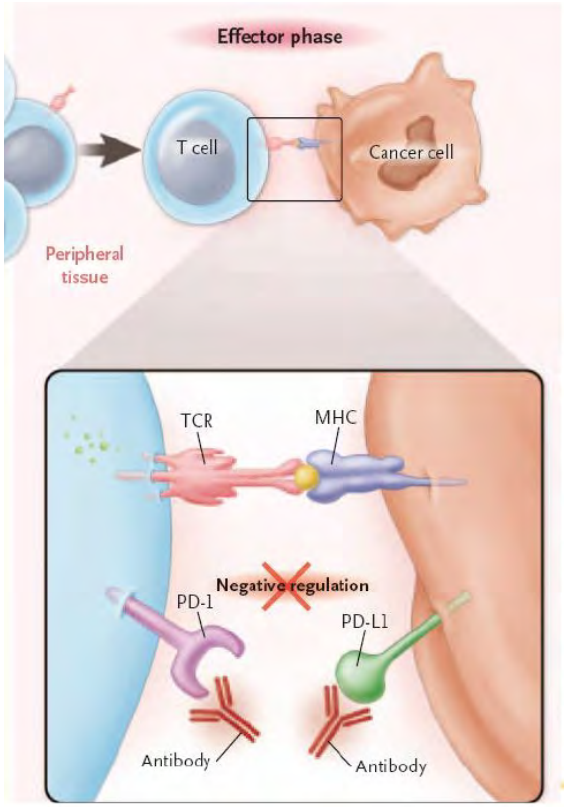
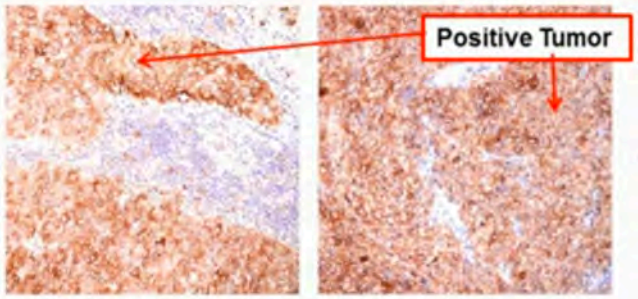
- **ETOP/EORTC: translational medicine**

Targeting immune checkpoints?





- 11/12 (94%) Thymomas PD-L1+
- 4/12 (34%) Thymic carcinomas PD-L1+

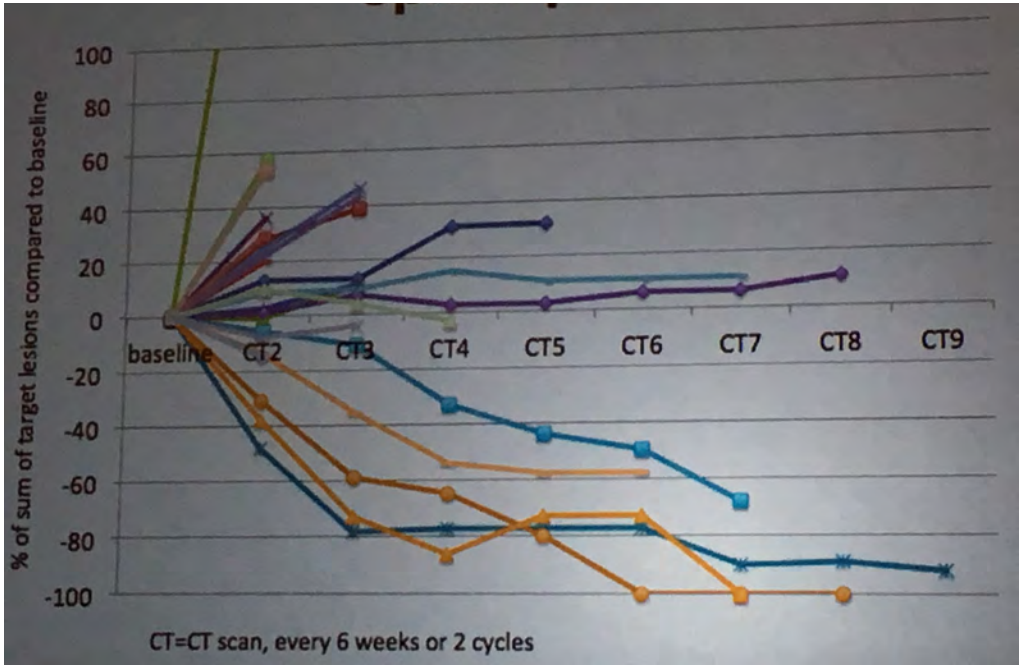
p<0.01

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

Giaconne. ASCO 2014

Pembrolizumab phase II trial (NCI, G Giaccone)

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



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

→

Nivolumab 3 mg/kg IV q2 weeks

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

Biomarkers

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

Primary endpoint: PFS at 6 months

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

Courtesy J Menis

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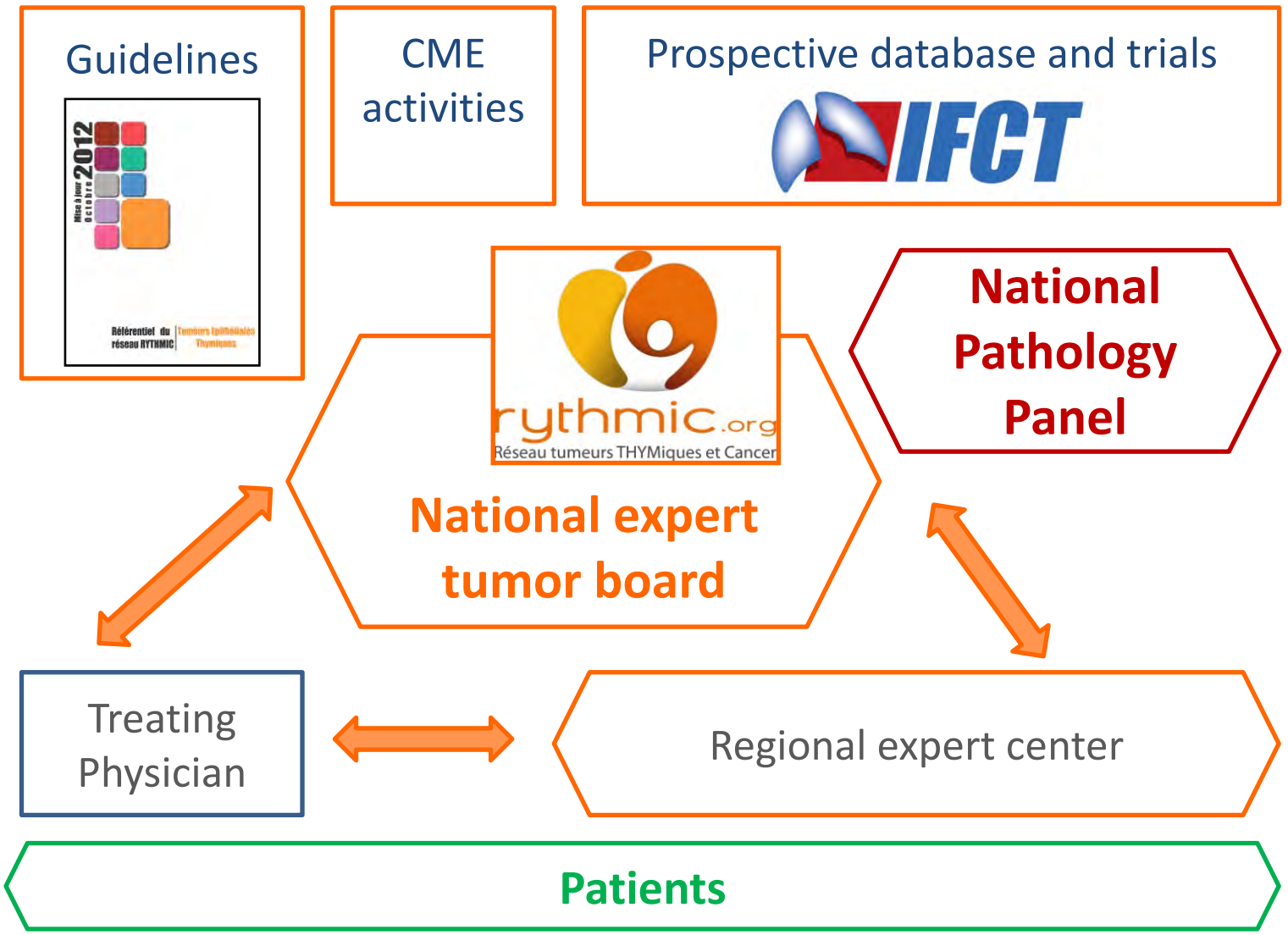
- ETOP/EORTC: translational medicine
- **RYTHMIC: Tumor board and network**

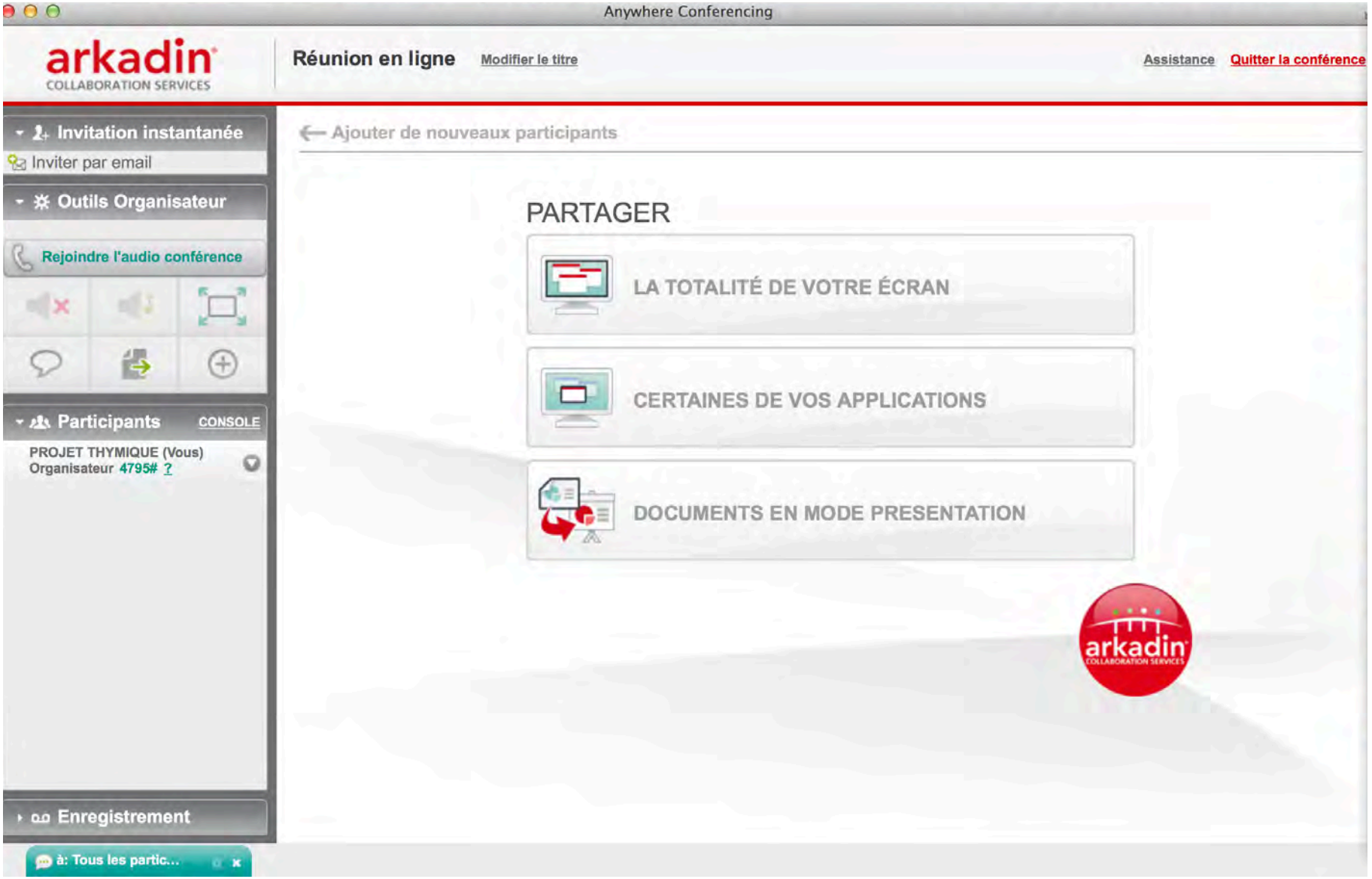
RYTHMIC: a regional network of expert centers

Coordinator:
B. Besse
Gustave Roussy

RYTHMIC: Infrastructure of the network



RCP RYTHMIC


Anywhere Conferencing
arkadin
COLLABORATION SERVICES
Réunion en ligne
Modifier le titre
Assistance
Quitter la conférence
Invitation instantanée
Inviter par email
Outils Organisateur
Rejoindre l'audio conférence
Participants
CONSOLE
PROJET THYMIQUE (Vous)
Organisateur 4795# ?
Enregistrement
à: Tous les partic...
Ajouter de nouveaux participants
PARTAGER
LA TOTALITÉ DE VOTRE ÉCRAN
CERTAINES DE VOS APPLICATIONS
DOCUMENTS EN MODE PRESENTATION
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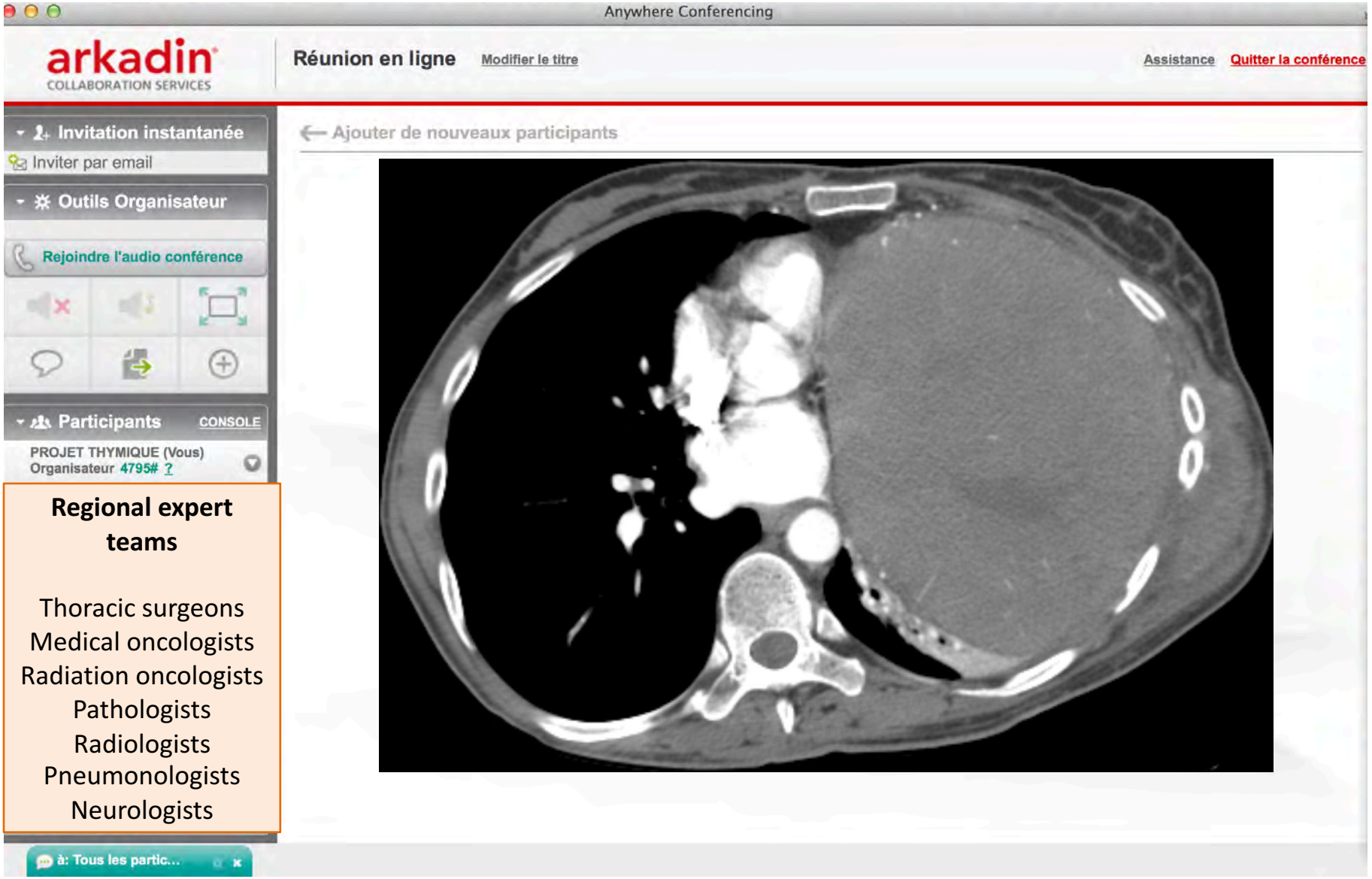
COLLABORATION SERVICES

Online virtual tumor board

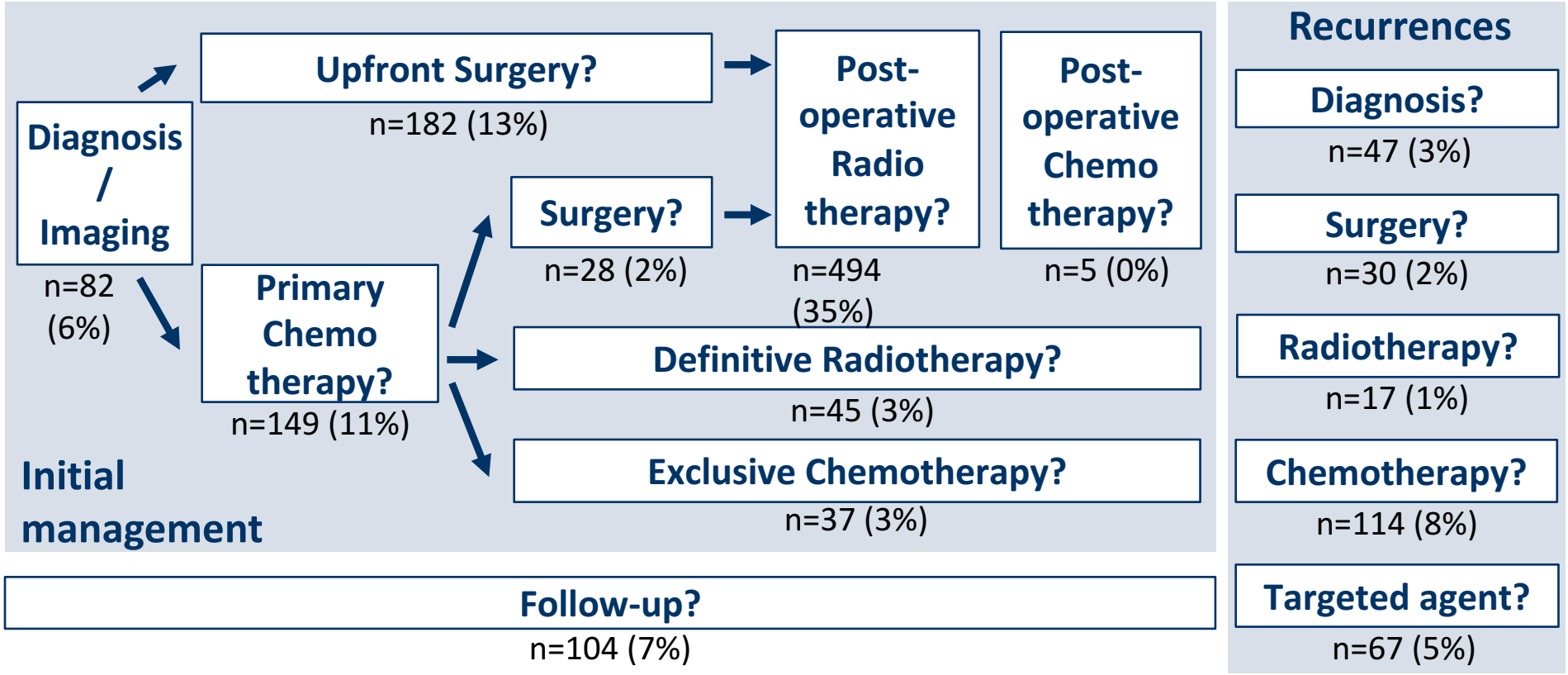


Regional expert teams

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



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Unresectable tumors

Thank you !

nicolas.girard@chu-lyon.fr

www.rythmic.org

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