Société de Pneumologie d'Île-de-France

TUMEURS EPITHELIALES THYMIQUES

Benjamin Besse
Nicolas Girard

21 mars 2015

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

rythmic.org
Réseau tumeurs THYMiques et Cancer

Disclosures

- **No personal financial disclosures**
- **Institutional grants for clinical and translational research**
  - Abbott, Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Clovis, GSK, Servier, EOS

Pathology

- **2 components**
- **Epithelial cells :** consideration of morphology (spindle, polygonal, mixed tumourcells)
- **Lymphocyte content**

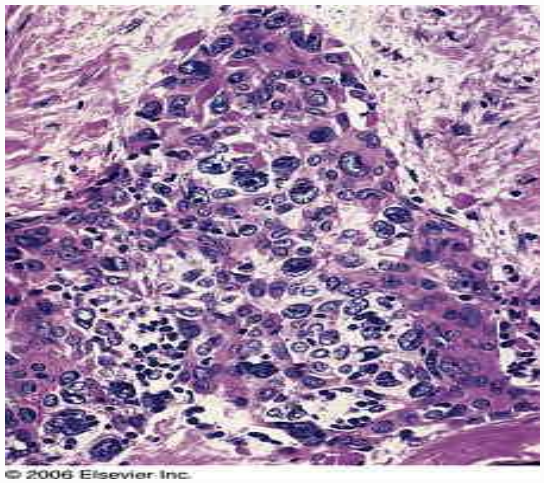
- **« Thymic epithelial tumors»**
  - Include thymomas
  - And thymic carcinomas

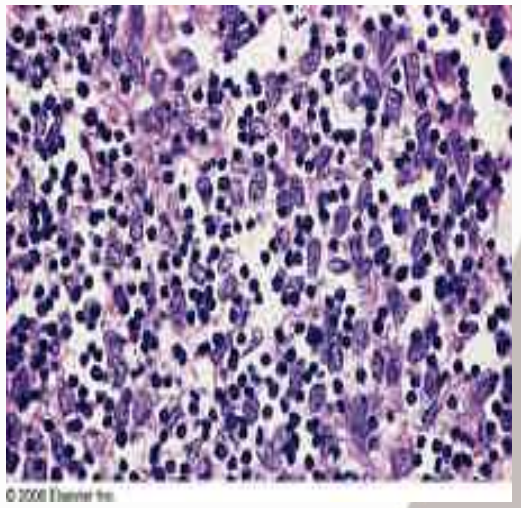
WHO classification - 2006

Based on:

1. Ratio lymphocytes/epithelial cells
2. Morphology of epithelial cells
3. Atypia / number of mytosis

Type C





Type B2

Upcoming WHO 2015

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

(*J Thorac Oncol.* 2014;9: 596–611)

Upcoming WHO 2015

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,e]
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)

Upcoming WHO 2015

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]

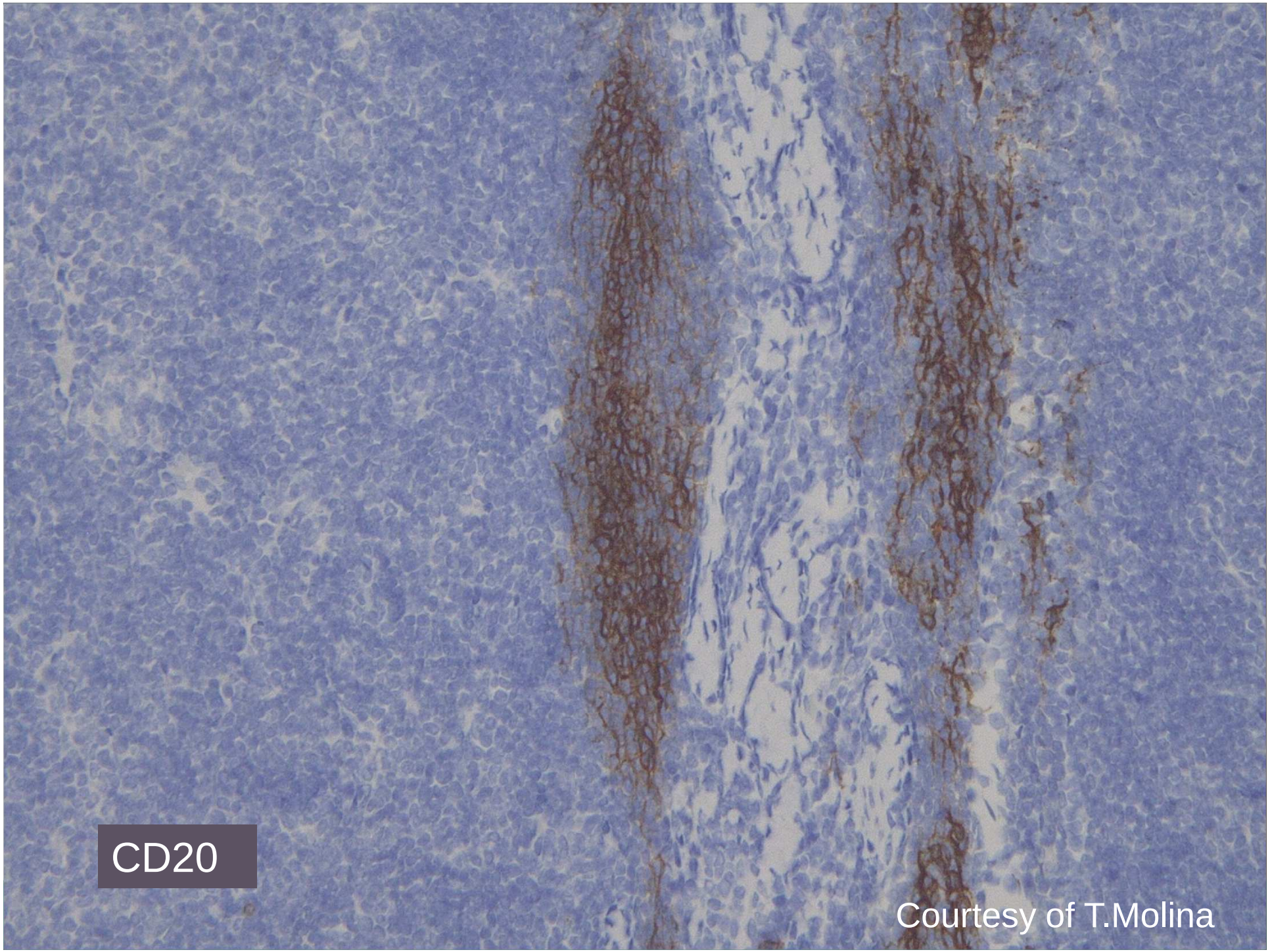
[a]Paucity implies no (immature) lymphocyte-rich regions with dense, "impossible-to-count" TdT(+) lymphocytes; or at most 10% tumor regions with moderate (see text) immature lymphocyte counts (Fig. 2).
[b]Beta5t, PRSS16, and cathepsin V by immunohistochemistry (IHC).
PVS, perivascular space.

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,e]
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)


CD20
Courtesy of T.Molina

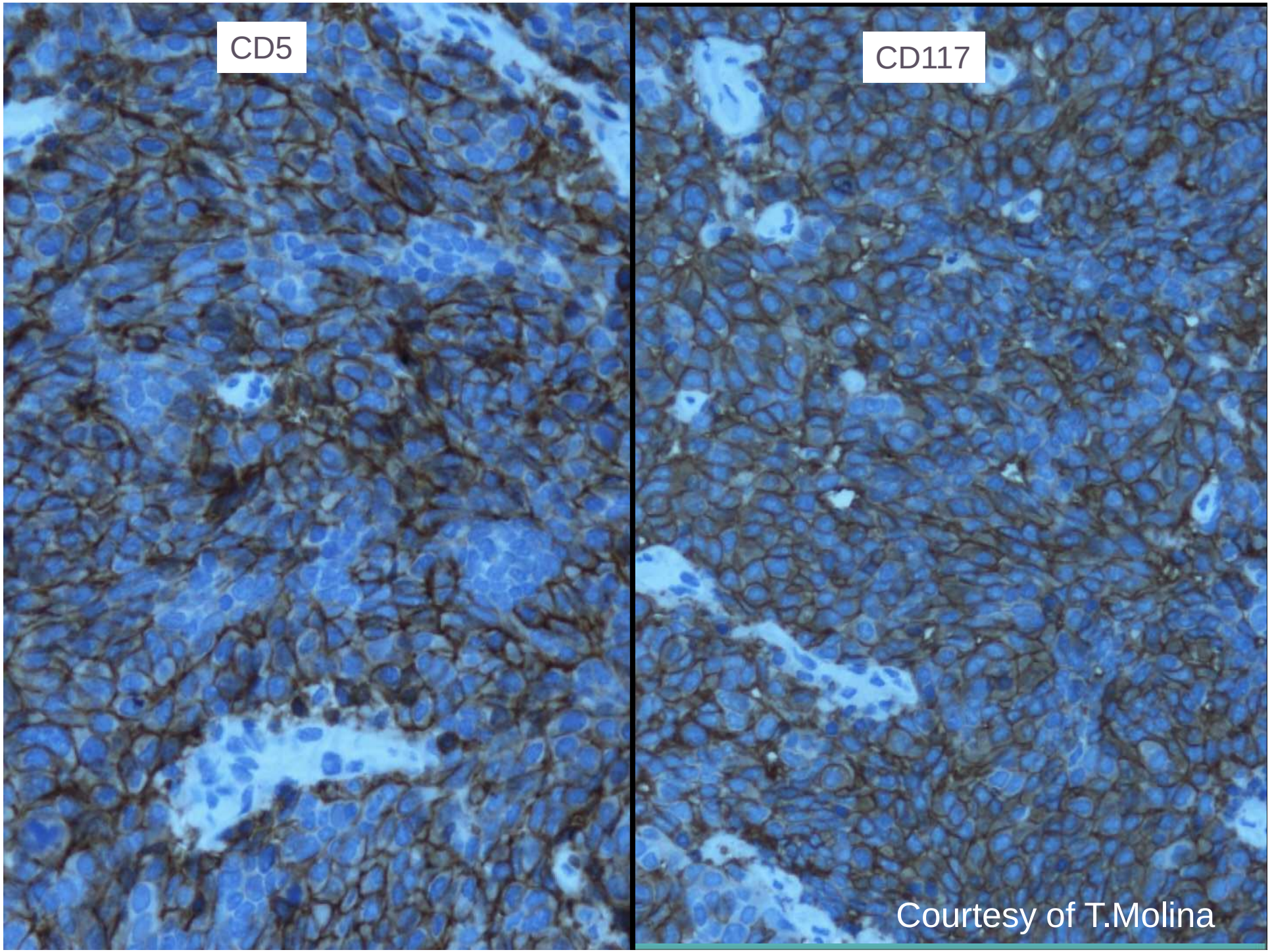
Upcoming WHO 2015

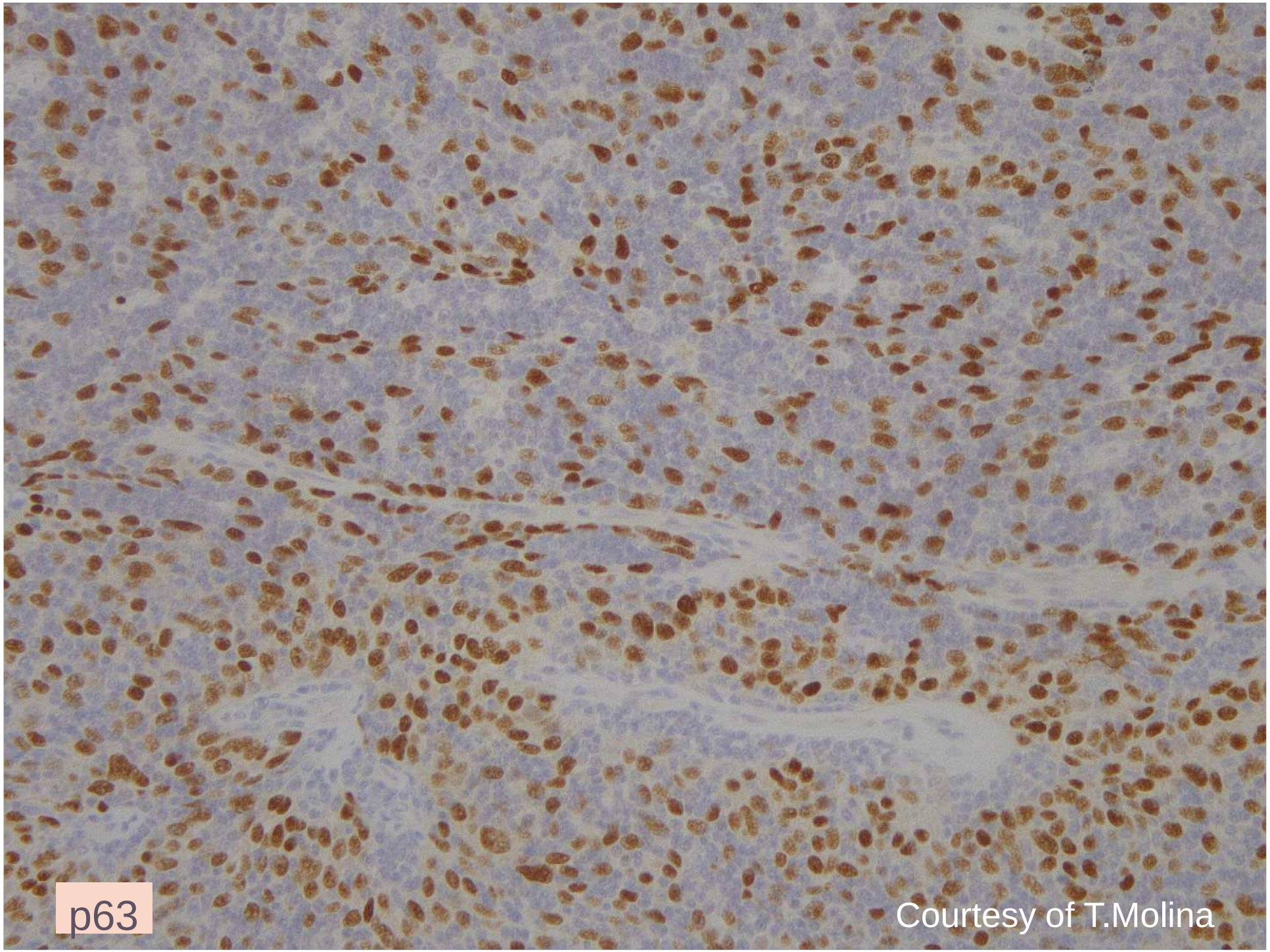
TABLE 4. Criteria for the Histological Diagnosis of TC

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)


CD5
CD117
Courtesy of T.Molina


p63
Courtesy of T.Molina

Masaoka-Koga-ITMIG

- Classification based on clinical and pathological items
- After resection

TABLE 1. Masaoka-Koga Staging System

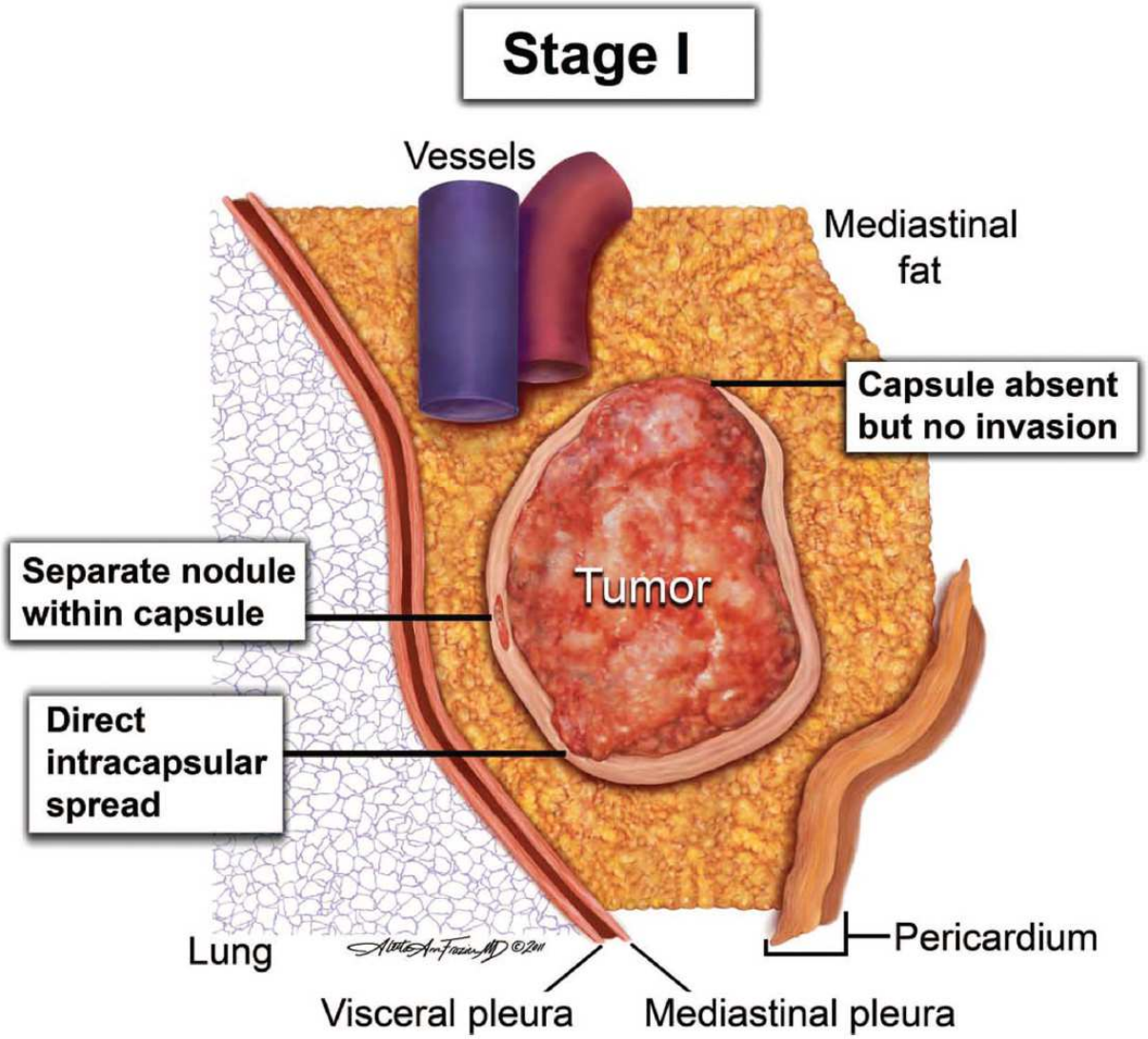
Stage	Definition
I	Grossly and microscopically completely encapsulated tumor
IIa	Microscopic transcapsular invasion
b	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring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

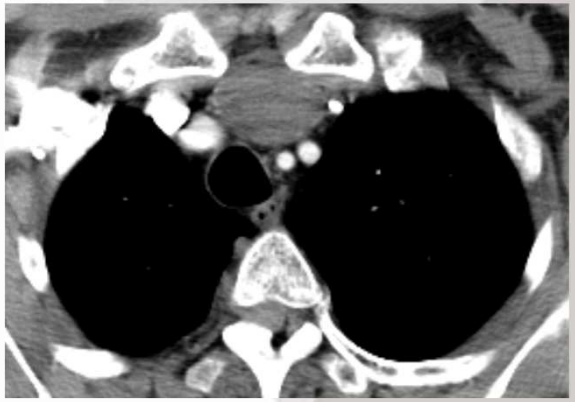
Adapted from *Pathol Int* 1994;44:359–367.

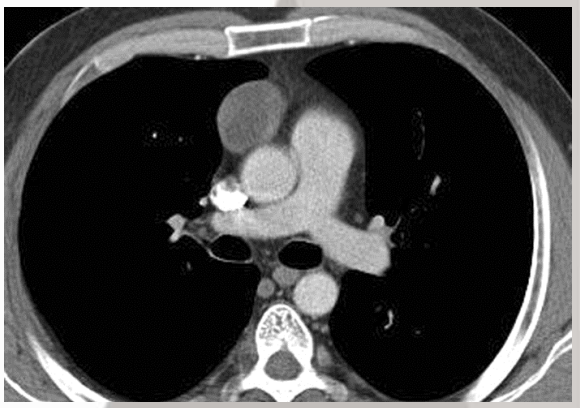
TABLE 2. ITMIG Definition of Details of the Masaoka-Koga Staging System

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 …*

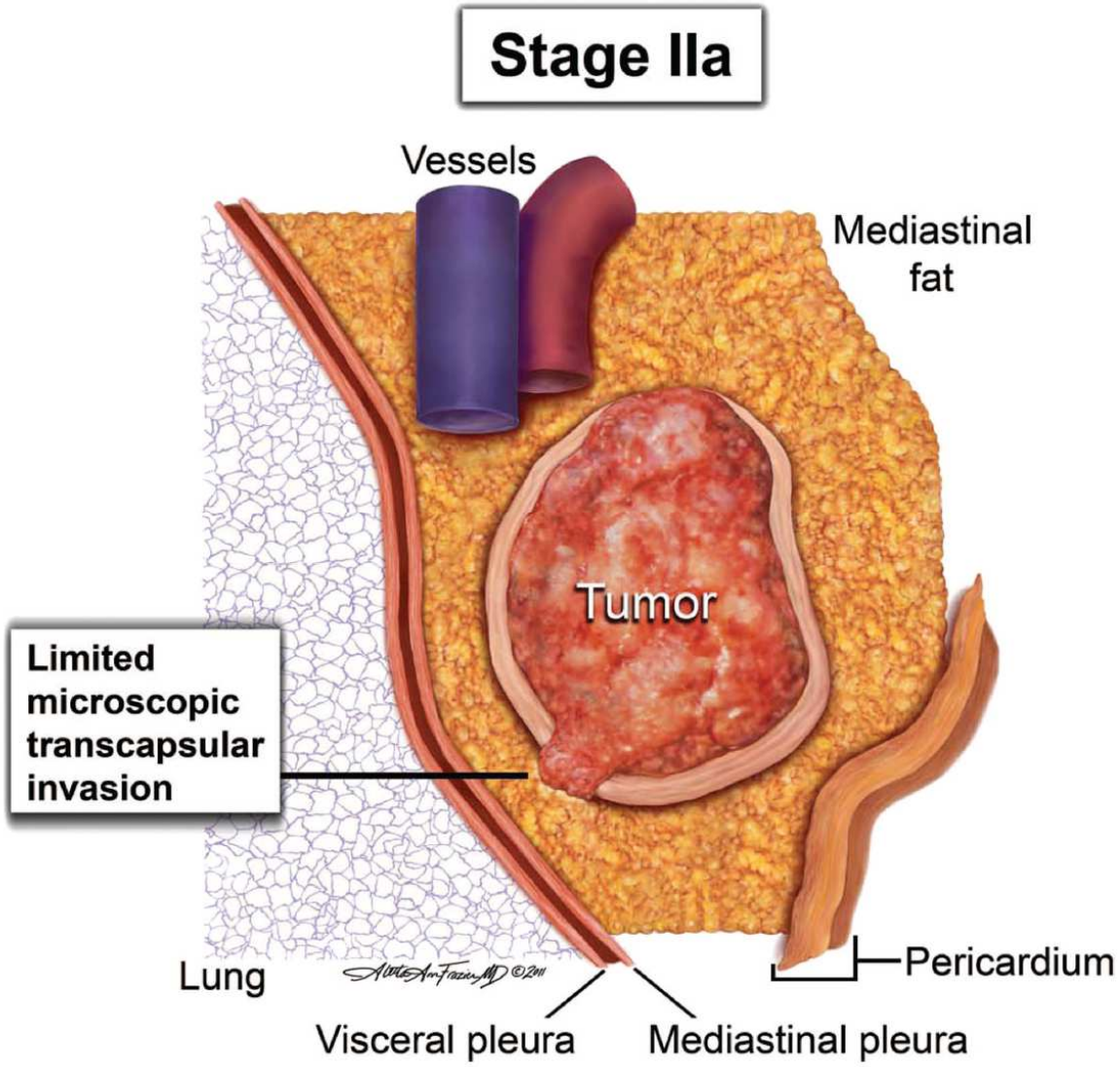
Detterbeck et al. J Thorac Oncol 2011;6:S1710

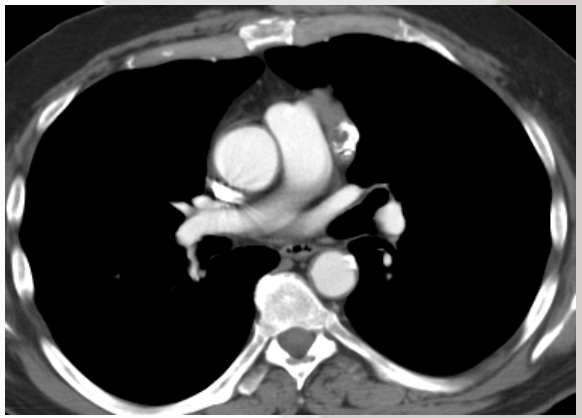


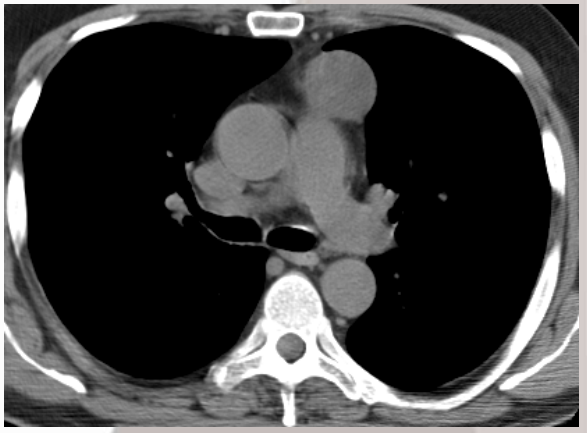




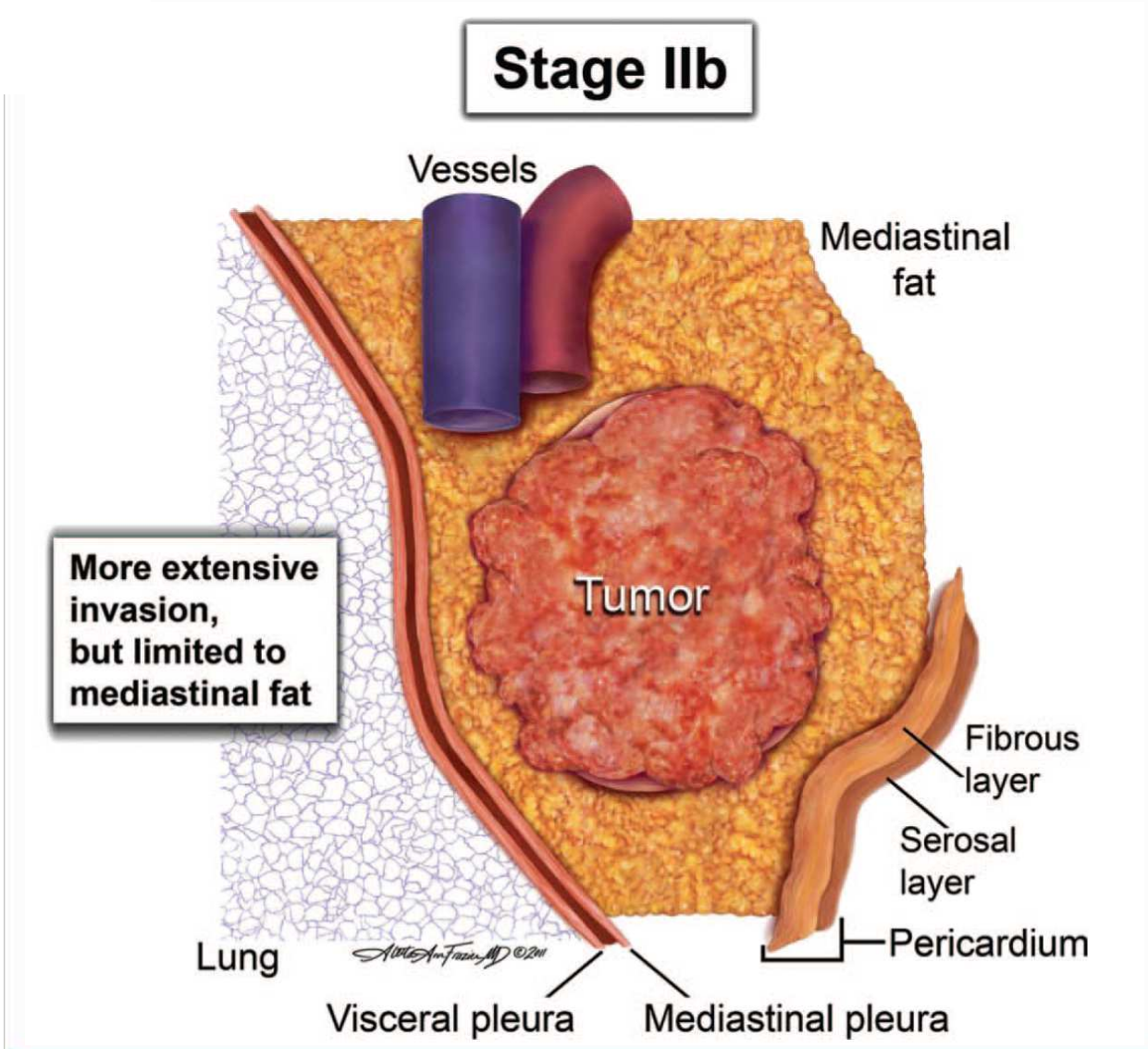
Detterbeck et al. J Thorac Oncol 2011;6:S1710

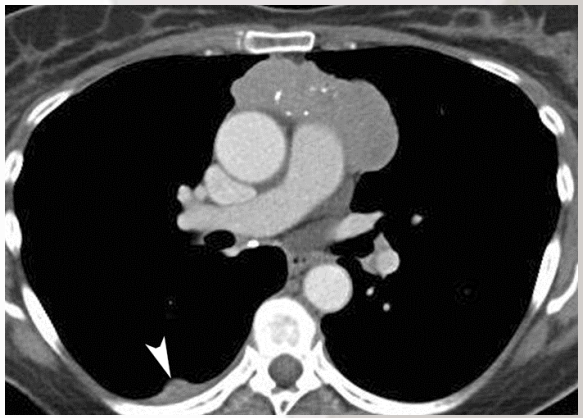


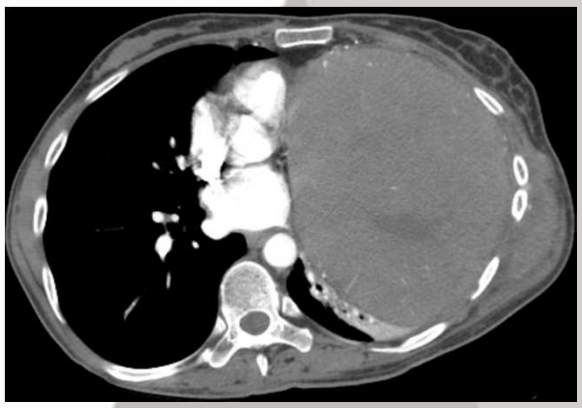




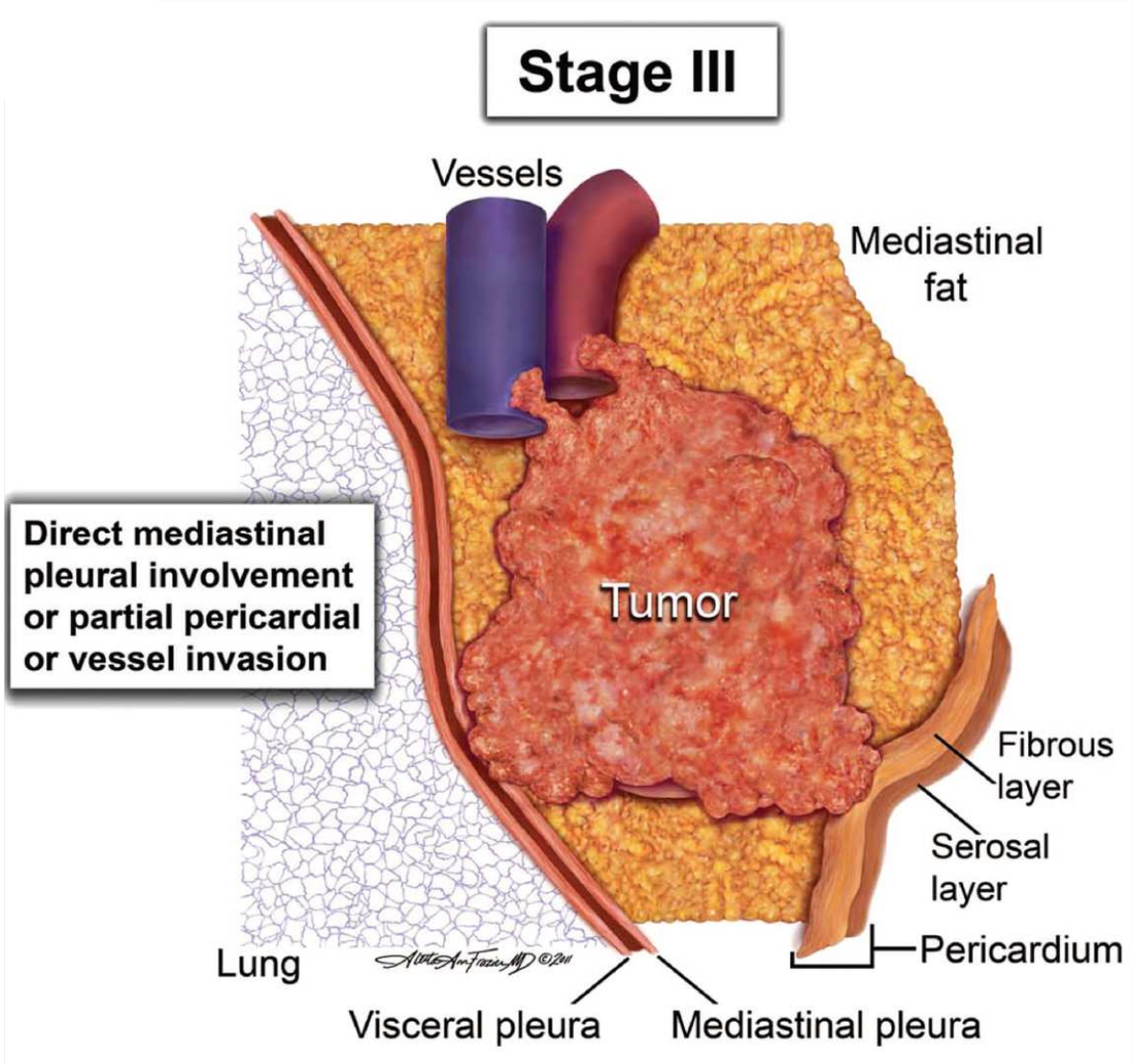
Detterbeck et al. J Thorac Oncol 2011;6:S1710

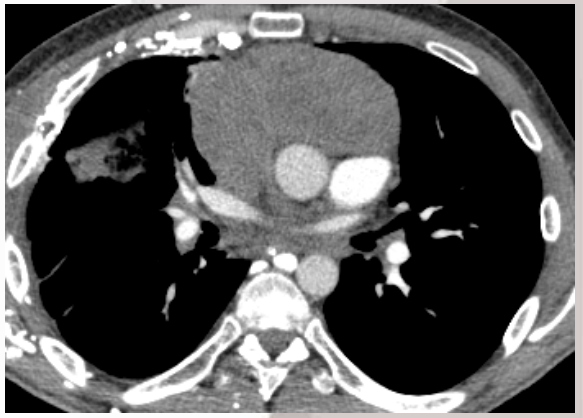




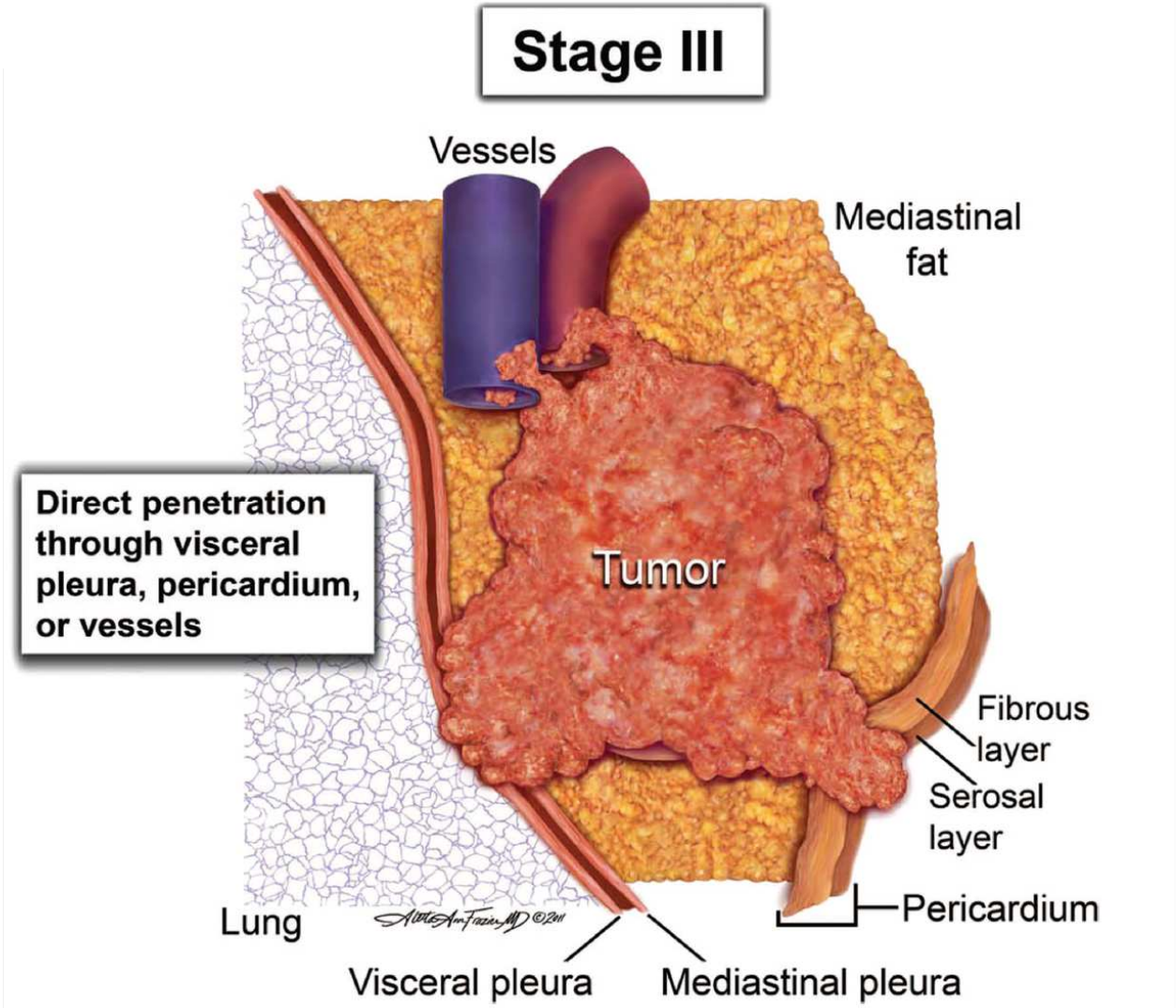


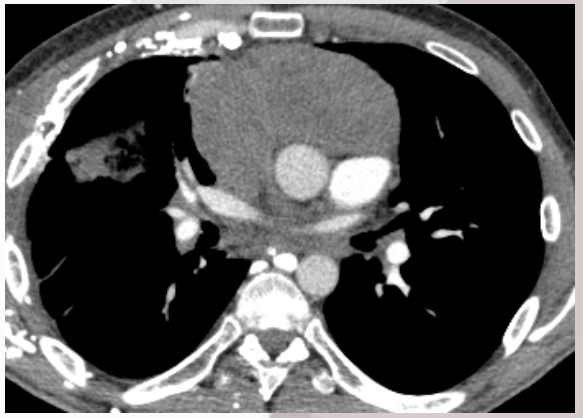
Detterbeck et al. J Thorac Oncol 2011;6:S1710



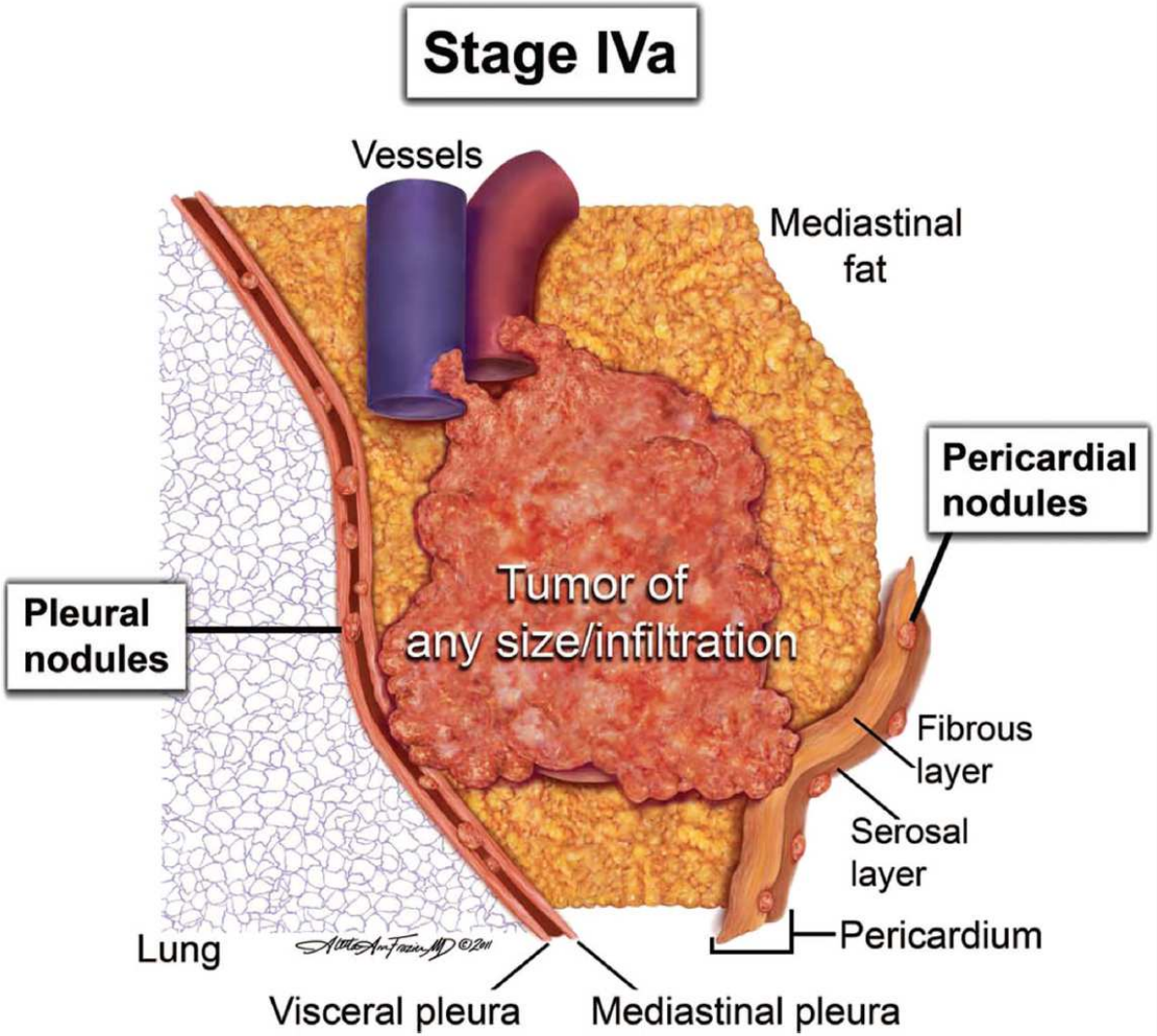


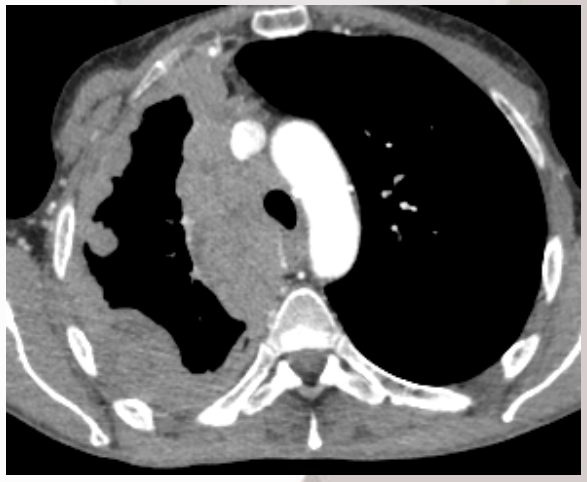
Detterbeck et al. J Thorac Oncol 2011;6:S1710



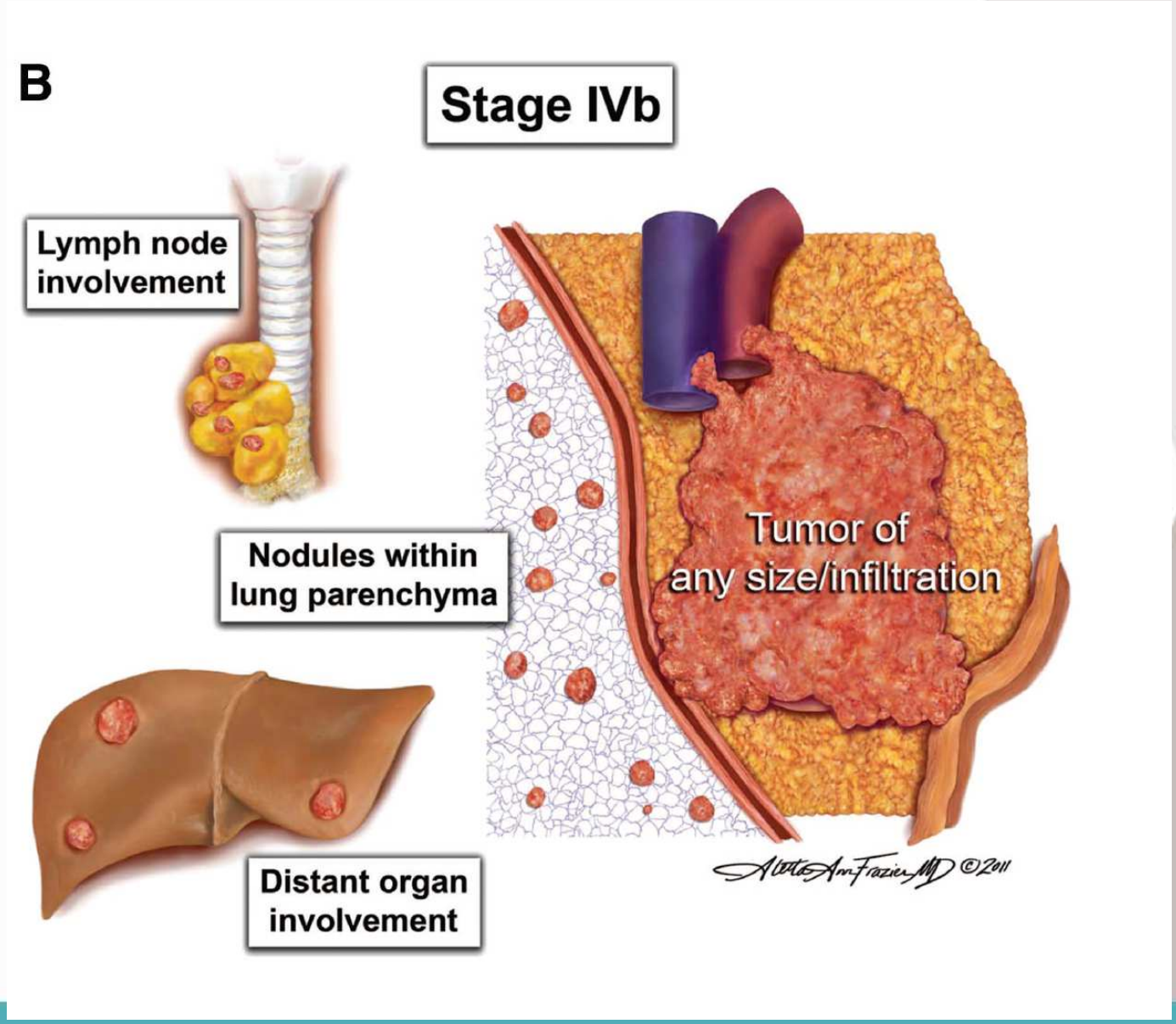


Detterbeck et al. J Thorac Oncol 2011;6:S1710



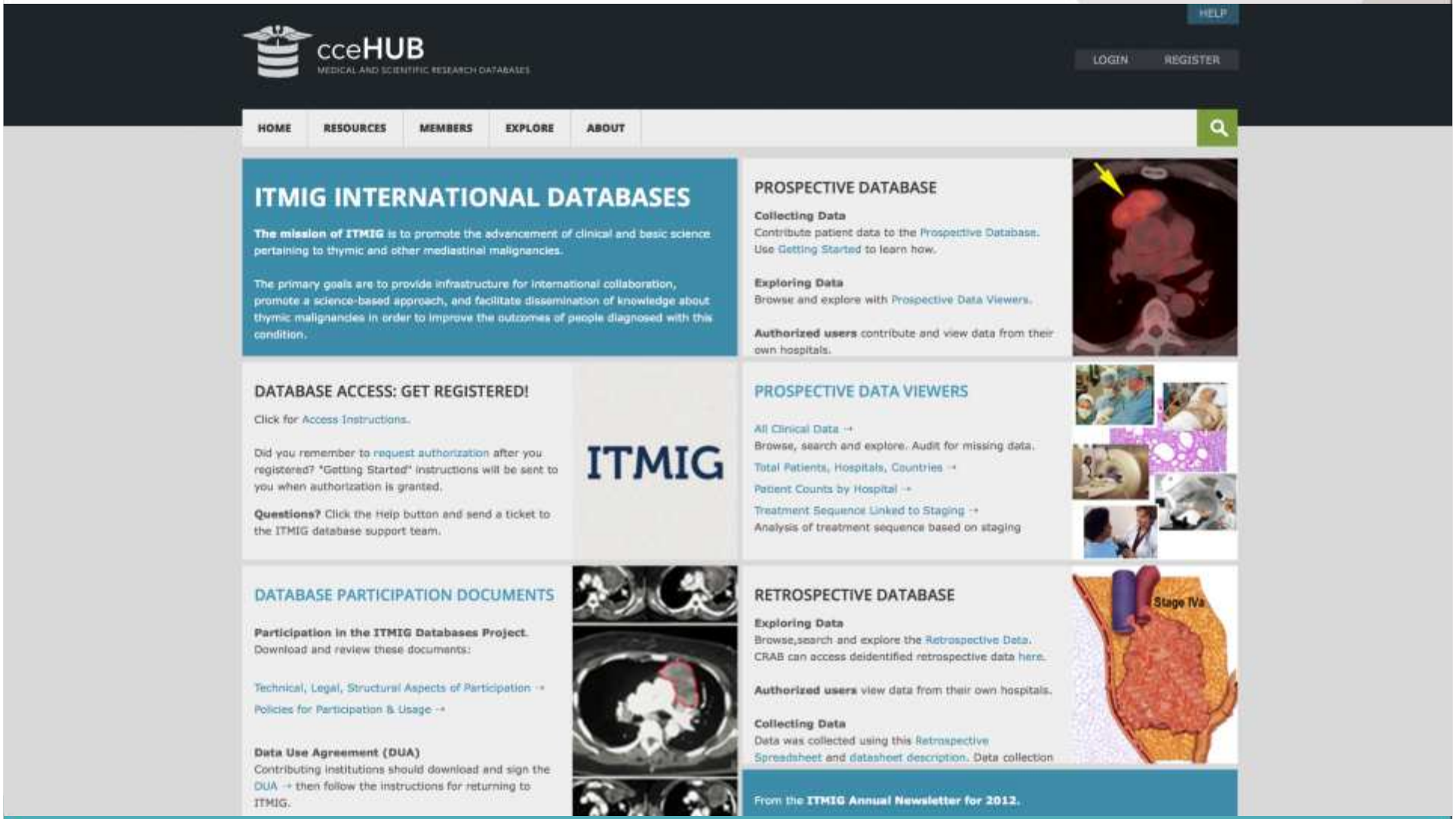


Detterbeck et al. J Thorac Oncol 2011;6:S1710



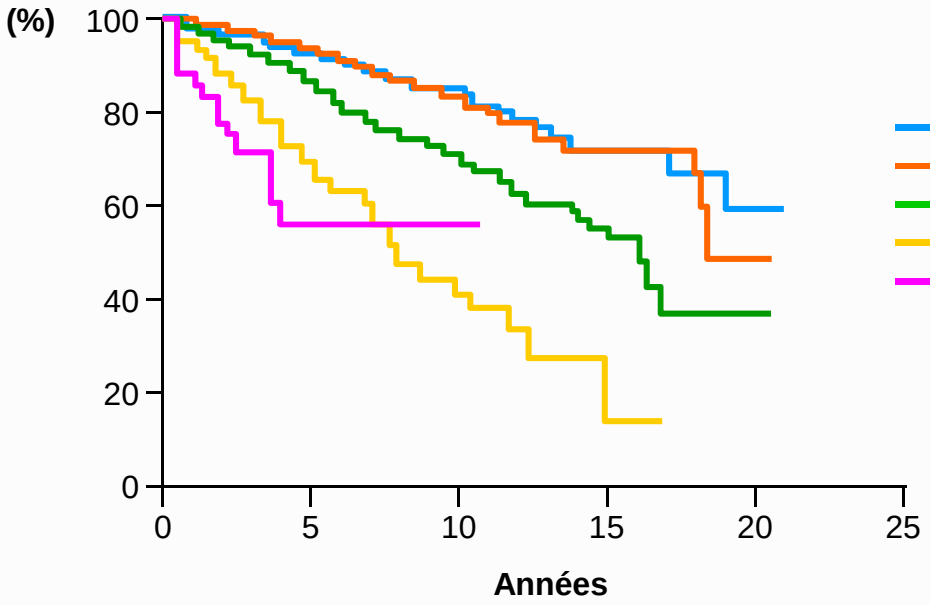
Detterbeck et al. J Thorac Oncol 2011;6:S1710

ITMIG DATABASE



Prognostic Value Of Masaoka-Koga staging

- **ITMIG database**



	Events/n	10 yrs OS, % (IC_{95})
Stage I	30/1 292	84 (81-86)
Stage II	78/1 878	83 (79-87)
Stage III	135/629	70 (64-75)
Stage IVA	40/106	42 (26-58)
Stage IVB	14/40	53 (32-73)

➜ **Same survival for stage I and II**

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

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

Frank C. Detterbeck, MD, Kelly Stratton, MS,† Dorothy Giroux, MS,† Hisao Asamura, MD,‡ John Crowley, PhD,† Conrad Falkson, MBChB,§, Pier Luigi Filosso, MD,‖, Aletta A. Frazier, MD,‖‖‖ Giuseppe Giaccone, MD,¶, James Huang, MD,#, Jhingook Kim, MD,**, Kazuya Kondo, MD,††, Marco Lucchi, MD,‡‡, Mirella Marino, MD,§§, Edith M. Marom, MD,‖‖, Andrew G. Nicholson, MD,¶¶, Meinoshin Okumura, MD,##, Enrico Ruffini, MD,‖, Paul Van Schil, MD,*** on behalf of the Staging and Prognostic Factors Committee,††† Members of the Advisory Boards,‡‡‡ and Participating Institutions of the Thymic Domain§§§*

(*J Thorac Oncol.* 2014;9: S65–S72

Upcoming 8th TNM

TABLE 1. T Descriptors

Category	Definition (Involvement of)[a,b]
T1	
a	Encapsulated or unencapsulated, with or without extension into mediastinal fat
b	Extension into mediastinal pleura
T2	Pericardium
T3	Lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar (extrapericardial) pulmonary vessels
T4	Aorta, arch vessels, main pulmonary artery, myocardium, trachea, or esophagus

[a]Involvement must be pathologically proven in pathologic stagi
[b]A tumor is classified according to the highest T level of involv
with or without any invasion of structures of lower T levels.

TABLE 2. N and M Descriptors

Category	Definition (Involvement of)[a]
N0	No nodal involvement
N1	Anterior (perithymic) nodes
N2	Deep intrathoracic or cervical nodes
M0	No metastatic pleural, pericardial, or distant sites
M1	
a	Separate pleural or pericardial nodule(s)
b	Pulmonary intraparenchymal nodule or distant organ metastasis

[a]Involvement must be pathologically proven in pathologic staging.

Detterbeck et al. J Thorac Oncol 2014

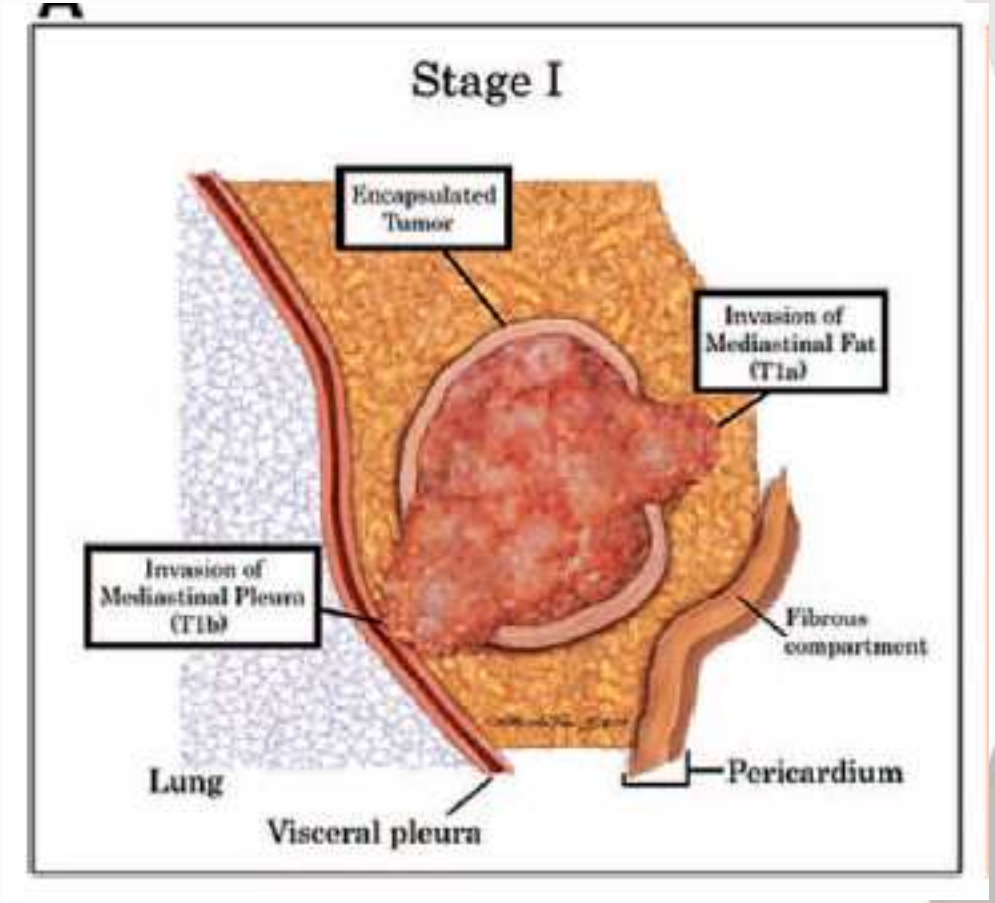
Upcoming 8th TNM

TABLE 3. Stage Grouping

Stage	T	N	M
I	**T1**	N0	M0
II	**T2**	N0	M0
IIIa	**T3**	N0	M0
IIIb	**T4**	N0	M0
IVa	T any	**N1**	M0
	T any	N0,1	**M1a**
IVb	T any	**N2**	M0,1a
	T any	N any	**M1b**

Detterbeck et al. J Thorac Oncol 2014

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

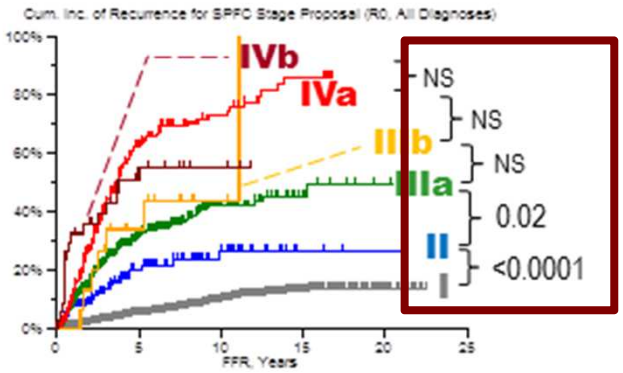
Detterbeck et al. J Thorac Oncol 2014

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

Frank C. Detterbeck, MD, Kelly Stratton, MS,† Dorothy Giroux, MS,† Hisao Asamura, MD,‡ John Crowley, PhD,† Conrad Falkson, MBChB,§, Pier Luigi Filosso, MD,‖, Aletta A. Frazier, MD,‖‖‖*

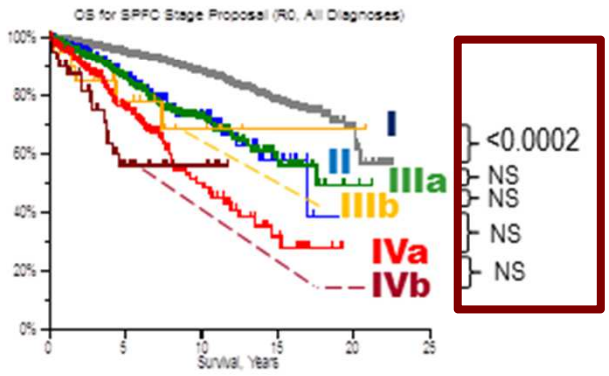
Figure e1: Outcomes of all Patients by Proposed Stage Groups

Recurrence, R0



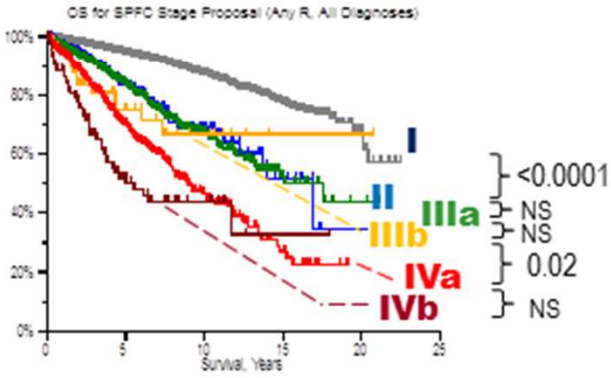
Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
I	192/3659	5.1% (5.1, 5.2)	9.7% (9.5, 9.9)
II	22/124	20% (17.6, 22.8)	27% (22.1, 31.1)
IIIa	142/455	32% (29.6, 34.4)	42% (37.0, 46.9)
IIIb	7/18	34% (10.6, 57.4)	43% (20.0, 66.9)
IVa	119/201	62% (47.4, 77.3)	73% (43.3, 100)
IVb	17/35	51% (23.5, 78.0)	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	86% (82.6, 89.2)	73% (67.3, 77.7)
IIIb	5/23	78% (58.7, 97.6)	68% (43.6, 93.1)
IVa	75/251	75% (68.5, 81.7)	50% (39.9, 60.2)
IVb	14/43	56% (38, 74)	56% (38, 74)

Overall Survival, any R

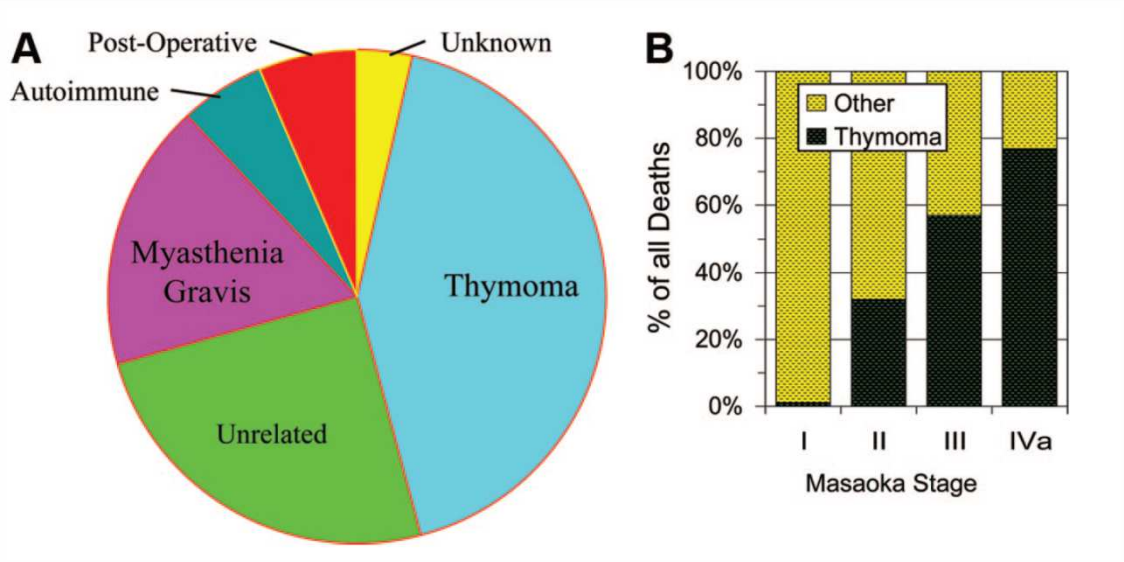


Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
I	405/5487	94% (93.5, 95)	87% (85.5, 88.5)
II	43/239	84% (77.6, 90)	69% (59.7, 78.1)
IIIa	163/778	83% (80.3, 86.5)	67% (62.4, 72.2)
IIIb	13/57	75% (61.8, 88.1)	67% (50.8, 82.6)
IVa	209/654	70% (65.7, 74.4)	46% (40.1, 52.6)
IVb	43/99	52% (40.2, 63.6)	44% (31.5, 55.9)

(*J Thorac Oncol.* 2014;9: S65–S72

Surveillance et cause de décès

- 2,5 % mortalité opératoire



Cause de décès – tous stades

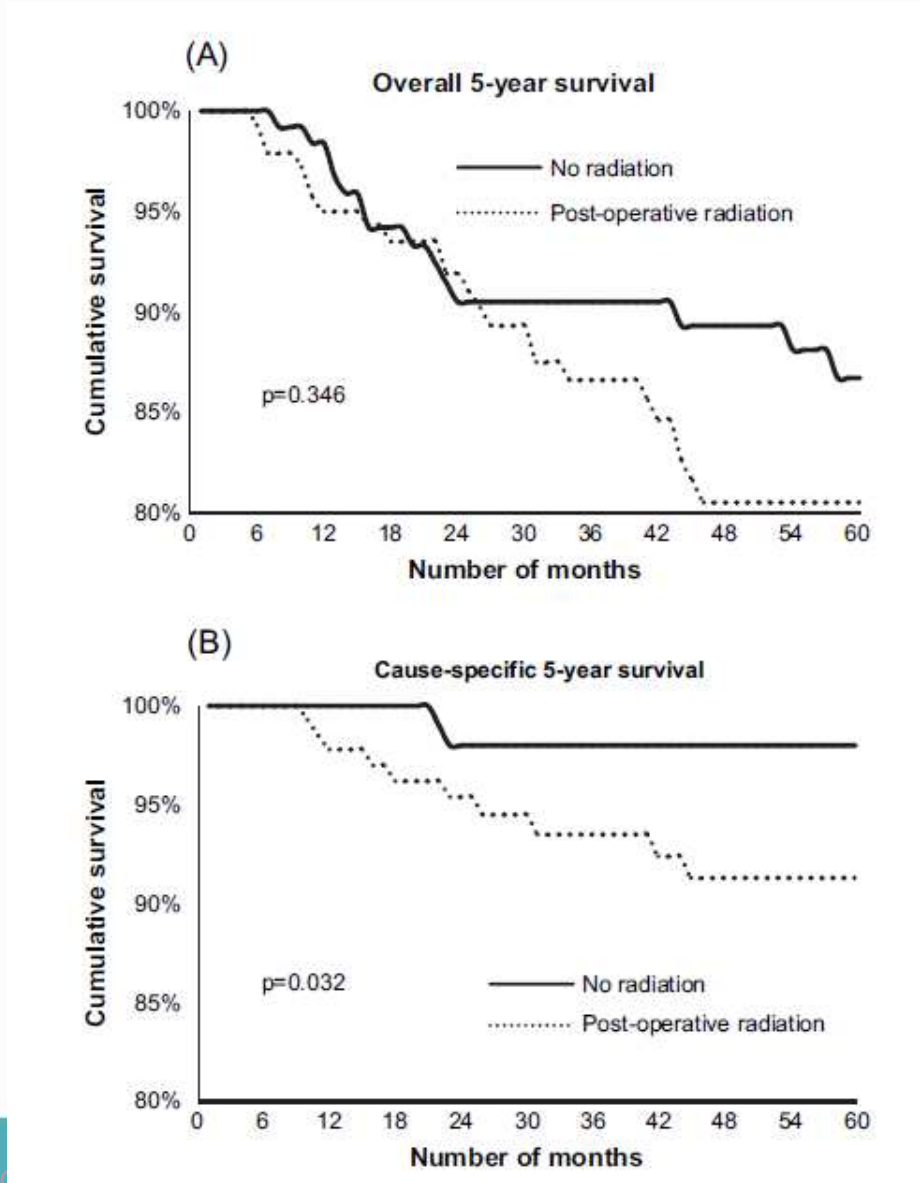
Décès par TET selon le stade Masaoka

- Fréquence d'un second cancer (27 %)
- Récidive tardive possible : 20 % après 10 ans

RT post-opératoire

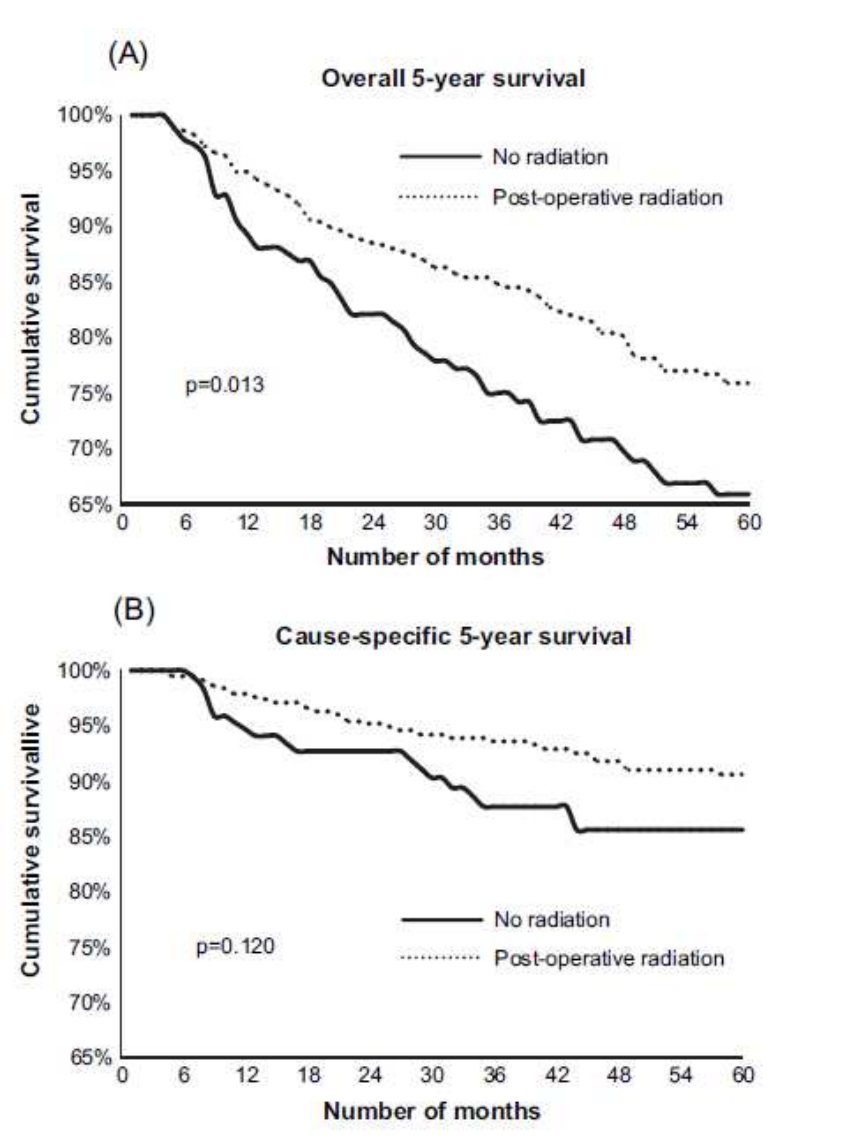
- Base SEER (Surveillance, Epidemiology and End Results) 1973–2005.
- ‘Type A’ ‘historique’ (classif. différente de Masaoka)
- Patients décédés dans les 3 mois après la chirurgie non inclus
- N=901
- 65% traités par RT post opératoire
- 61% type TET non précisée
- Chirurgie radicale 35%

Masaoka stade I (~A localisés)



- N= 275
- Effet délétère
  - **Survie spécifique à 5 ans : 98% (C) vs. 91% (C+RT) p = 0.03**
  - **Survie globale: 87% (C) vs. 81% (C+RT) p = 0.35**

Masaoka stade II-III (=A régionaux)



- N= 626
- Effet bénéfique
  - **Survie spécifique à 5 ans : 86% (C) vs. 91% (C+RT) p = 0.12**
  - **Survie globale: 66% (C) vs. 76% (C+RT) p = 0.01**
- Persiste si chirurgie radicale
  - **Survie globale: 62% (C) vs. 75% (C+RT) p = 0.12**

Radiothérapie post-opératoire

RECOMMANDATIONS : Indication

La proposition de stratégie pour la radiothérapie post-opératoire, à valider en réunion de concertation pluri-disciplinaire, est la suivante[49-51] :

- en cas de résection complète :
  - stade I : pas de radiothérapie post-opératoire
  - stade IIa :
    - types A-B2 : pas de radiothérapie post-opératoire
    - type B3 : discuter une radiothérapie post-opératoire
  - stade IIb
    - types A-B1 : pas de radiothérapie post-opératoire
    - types B2-B3 : discuter une radiothérapie post-opératoire
  - stades III:
    - radiothérapie post-opératoire
- en cas de résection R1 : - radiothérapie post-opératoire
- en cas de carcinome thymique : - radiothérapie post-opératoire

- **Irradier la totalité de la loge thymique ainsi que les éventuelles extensions tumorales**
- **Irradiation creux sus-claviculaires non recommandée**

Radiothérapie post-opératoire

RECOMMANDATIONS: Dose

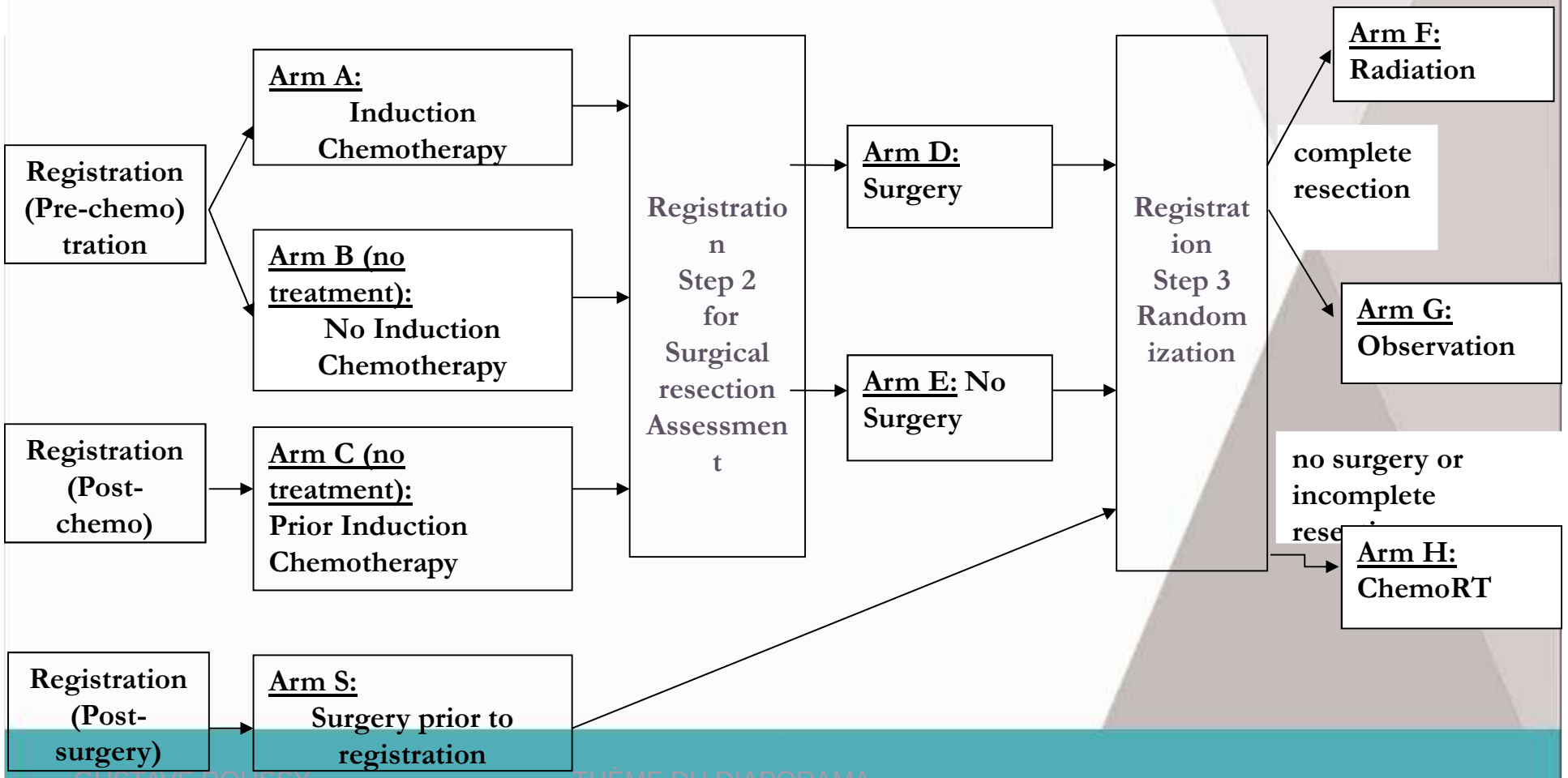
- **Résection complète : 50 à 56 Gy**
- **Résection incomplète :**
  - Planed Target Volume + organes critiques
  - 50 – 56 Gy + surimpression 60 – 66 Gy
  - 66 Gy en cas de simple biopsie

RECOMMANDATIONS: Modalités

- **9 à 10 Gy hebdomadaires en 5 séances**

ECOG-ACRIN & EORTC

Randomized Study of Resected Stage III Invasive Thymoma or Stage II –III Thymic Carcinoma with or without Postoperative Radiation Therapy



Induction chemotherapy

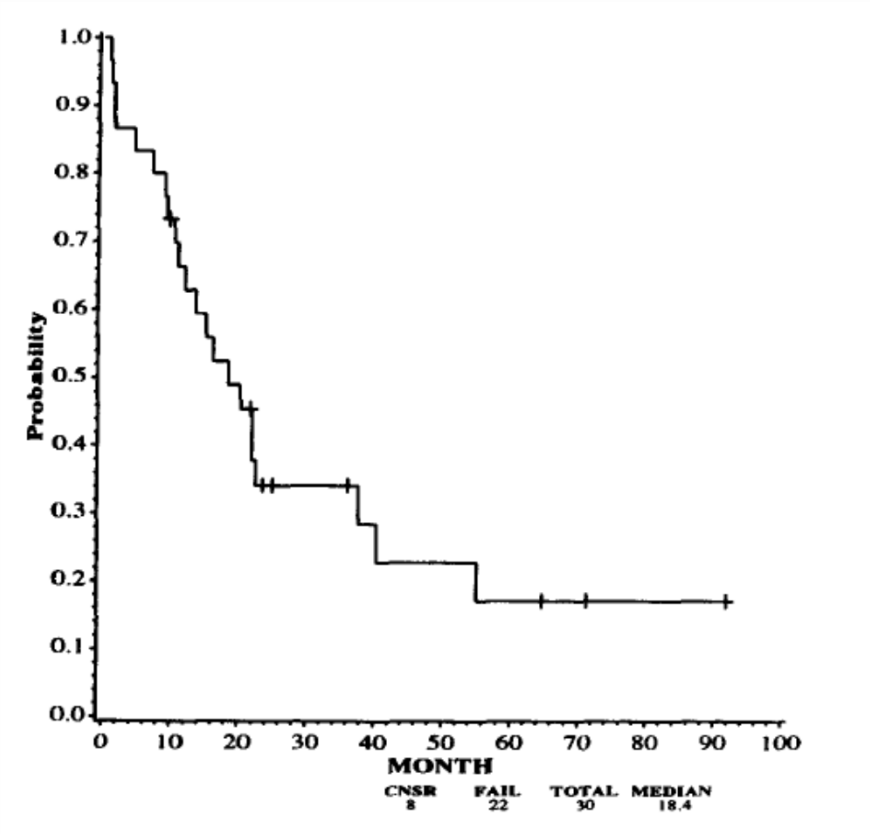
Reference	Primary Chemotherapy Regimen	n	Period of Accrual (yr)	Tumor		Study	Response Rate (%)	Subsequent Treatment (%)			
				Type	Stage			Surgery	Complete Resection	RT (Definitive ChemoRT)	Palliative Chemo-therapy
Chemotherapy											
Macchiarini[14]	CEE	7	2	T/TC	III	Phase II	100	100	57	0	0
Berruti[16]	ADOC	6	2	T	III-IVA	Phase II	83	?	17	?	?
Rea[6]	ADOC	16	6	T	III-IVA	Retrospective	100	100	69	0	0
Venuta[3]	CEE	15	14	T/TC	III	Retrospective	66	100	?	?	?
Bretti[7]	ADOC/PE	25	11	T/TC	III-IVA	Retrospective	72	68	44	?	?
Kim[15]	CAPP	22	10	T		Phase II	77	100	72	0	0
Lucchi[4]	CEE	36	27	T/TC	III-IVA	Retrospective	67	69	78	19	3
Jacot[5]	CAP	5	6	T/TC	III-IVA	Retrospective	75	38	25	50	12
Yokoi[8]	CAMP	14	15	T/TC	III, IVA-B	Retrospective	93	64	14	14	21
Kunitoh[17]	CODE	21	8	T	III	Phase II	62	62	43	24	14
Chemoradiation											
Loehrer[18]	CAP	23	12	T/TC	III-IVA	phase II	70	15	0	70	15
Berruti[19]	ADOC	16	7	T	III-IVA	phase II	81	56	56	31	13
Wright[9]	PE, ADOC, CAP, CEE	10	9	T/TC	III-IVA	Retrospective	40	100	80	0	0

The CAP, ADOC, and PE regimen are described in Table 1. The CODE regimen consists of cisplatin (25 mg/m^2/wk), vincristin (1 mg/m^2/wk), adriamycin (40 mg/m^2/wk), and etoposide (80 mg/m^2×3 d/wk), the CEE regimen of cisplatin (75 mg/m^2/3 wk), epirubicin (100 mg/m^2/3 wk), etoposide (120 mg/m^2×3 d/ 3 wk), and the CAMP regimen of CAP with prednisolone (1000 mg/m^2×4 d and 500 mg/m^2×2 d/3 wk).

T, thymoma; TC, thymic carcinoma; RT, radiotherapy.

Stades métastatiques

CAP (CDDP, Adriamycine, Cyclophosphamide)



- Traitement historique
- CAP X 8
- N=30 (1 carcinome thym.)
- Pas de classification OMS anatomo-pathologique
- Evaluation tumorale OMS (TDM)
- ORR=50%
- TTF=18 mois
- Survie médiane 37 mois

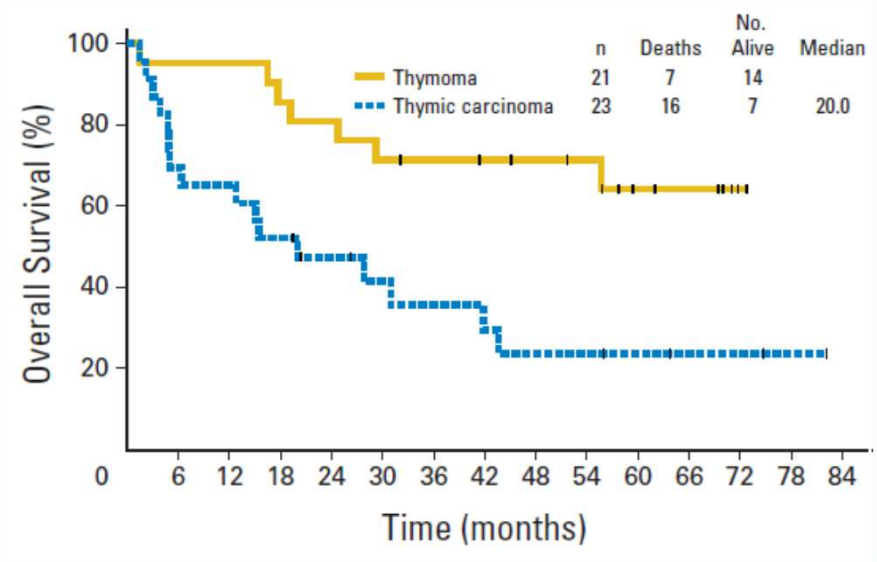
Lehrer, JCO 94

Stades métastatiques
Paclitaxel - carboplatine

Table 1. WHO Classification of Patients With Thymic Neoplasms

WHO Classification		Thymic Tumor No.	Thymic Tumor %
A	N=21	1	2.3
AB		1	2.3
B1		8	18.1
B2		7	15.9
B3	N=23	10	22.7
C		13	29.6
Thymoma-NOS*		4	9.1

*Thymoma-NOS classification indicates not otherwise specified because of limited material.



- Carboplatin AUC 6 + paclitaxel (225 mg/m2) X6
- RECIST

- Thymomes
- PFS = 16.7 mois
- ORR 42.9%
- OS non atteinte

- Carcinomes thymiques
- PFS 5 mois
- ORR = 21.7%
- OS 20.0 mois

Lemma, JCO 11

Stades métastatiques

	Phase	N (%st III, % st IV)	Schéma	Réponses	Survie globale
VIP	Ph II	16 (50%, 50%)	Étoposide 100 mg/m² J1 à J3 Ifosfamide 1500 mg/m² J1 à J3 Cisplatine 30 mg/m² J1 à 3 J1=J21	TR : 25% (75% SD)	SG 78,1% à 2 a 58,6% à 3 a
VIP	Ph II	28 (21%, 79%)	étoposide 75 mg/m² J1 à J4 Ifosfamide 1200 mg/m² J1 à J4 Cisplatine 20 mg/m² J1 à J4 J1=J21	TR 32%	SG méd 31,6 m SG 70% à 2 a
CAP	Ph II	30	Cisplatine 50 mg/m² J1 Doxorubicine 50 mg/m² J1 Cyclophosphamide 500 mg/m² J1 J1=J21	TR 51%	SG méd : 37,7 mo SG 64 ,5% à 2 a
PE	Ph II	16	Cisplatine 60 mg/m² J1 Etoposide 120 mg/m² J1 à J3 J1=J21	TR 56%	SG médiane 4,3 a SG 69% à 3 a
Carbo/ taxol	Ph II	46 (16%, 84%)	Carboplatine AUC 6 J1 Pacltiaxel 225 mg/m² J1 J1=J21	TR 22% (C) TR 43%	SG méd 20 m (C) SG méd NA

Grassin F, J Thorac Oncol. 2010 juin;5(6):893-7. - Loehrer PJ Sr, Cancer. 2001 juin 1;91(11):2010-5.
Loehrer PJ Sr, J. Clin. Oncol. 1994 juin;12(6):1164-8. - Giaccone G, J. Clin. Oncol. 1996 mars;14(3):814-20.
Lemma GL, J. Clin. Oncol. 2011 mai 20;29(15):2060-5.

Stades métastatiques

	Phase	N (% st III, % st IV)	Schéma	Réponses	Survie globale
Monothérapies					
PEM	Phase II	27 (0%, 100.5%)	Pemetrexed 500mg/m² J1= J21	TR : 17%	SSP med 11 mois SG non atteinte
CDDP	Phase II	21 (0,100%)	Cisplatine 50 mg/m² J1=J21	TR : 10% SD : 40%	SG 39% à 2 ans SG méd 19 mois
Oct	Phase II	38 (5%, 95%)	Octreotide 0.5 mg x3/j En continu, 1 a max Ajout prednisone 0,6mg/kg/j si SD à 12 sem	TR : 31.6%	SG 75,7% à 2 ans

Loehrer PJ, ASCO Meeting Abstracts. 2006 juin 16;24(18_suppl):7079.
Bonomi PD, Am. J. Clin. Oncol. 1993 août;16(4):342-5.
Loehrer PJ Sr, J. Clin. Oncol. 2004 janv 15;22(2):293-9.

Etoposide Oral

(25 mg X 3 par jour, 3 semaines / 4)

Patient demographics (N = 13)

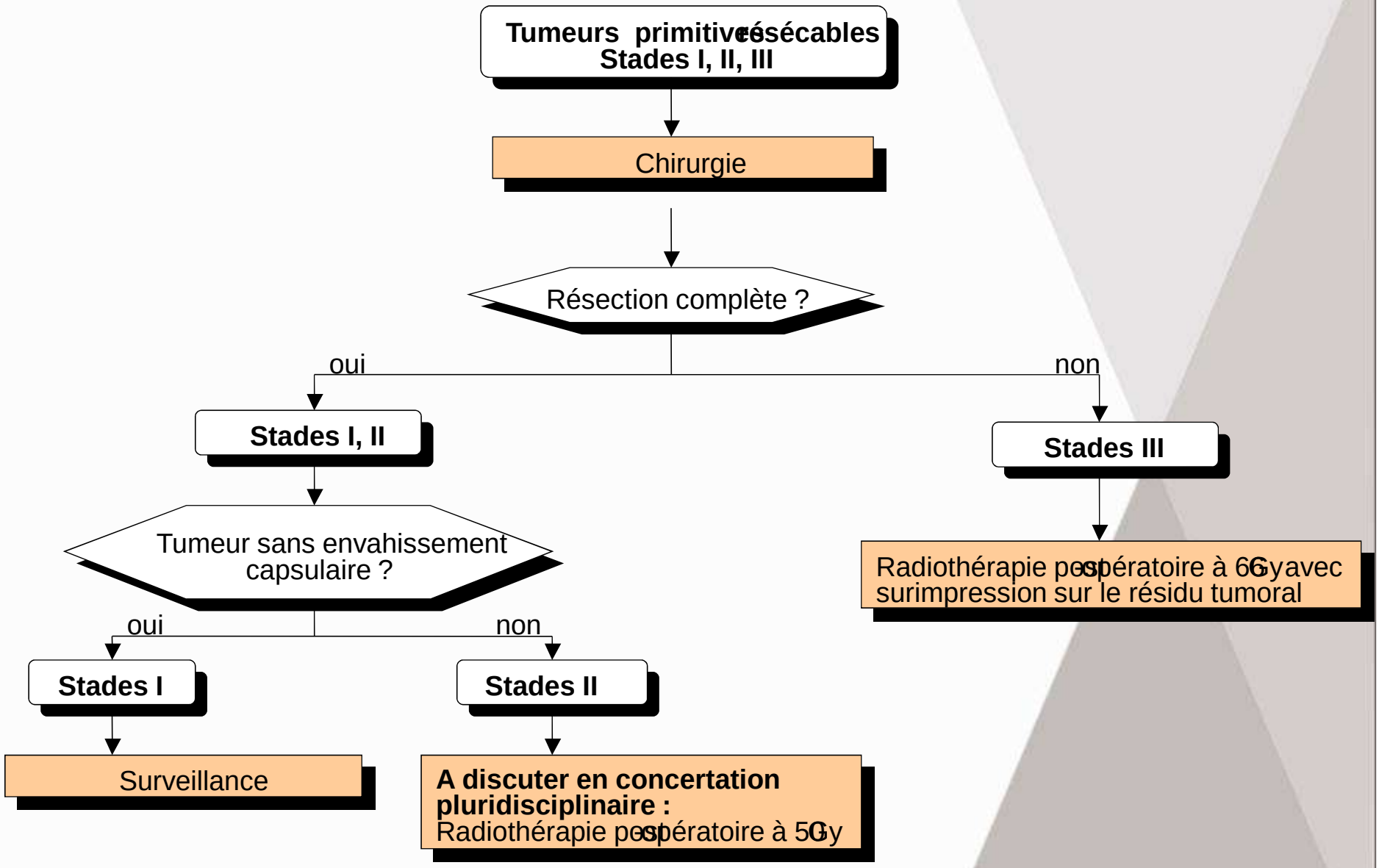
	Frequency	Percentage
Age at etoposide introduction		
Median (range)	59 (33-85)	
Histology		
Thymoma	5	39%
Thymic carcinoma	8	61%
Prior chemotherapy		
Median number of lines (range)	2 (0-8)	

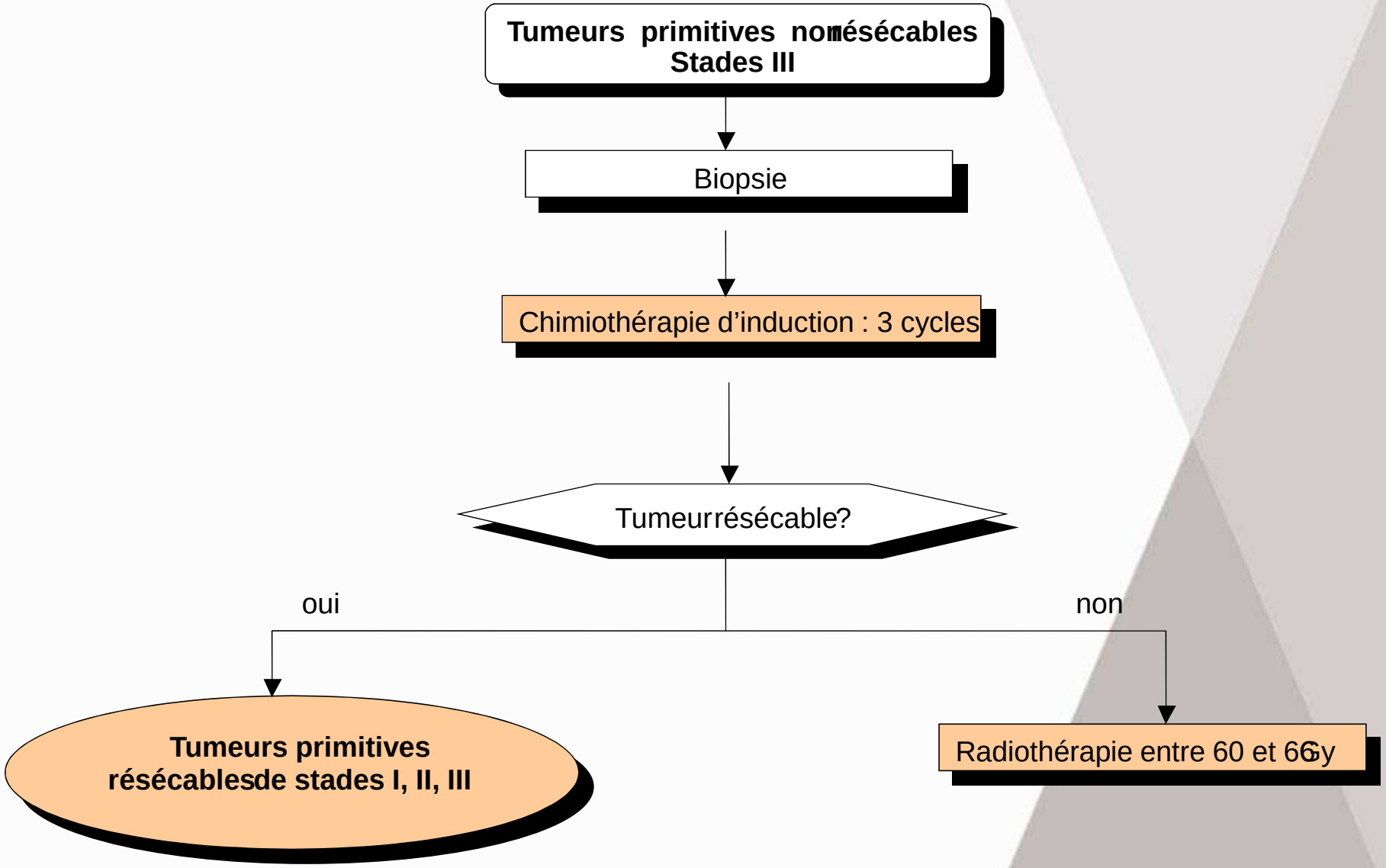
	Grade 3	Grade 4
Anemia	15 %	0 %
Neutropenia	8 %	15 %
Low platelets	0 %	8 %
Fatigue/asthenia	0 %	0 %
Febrile netropenia	8 %	0 %

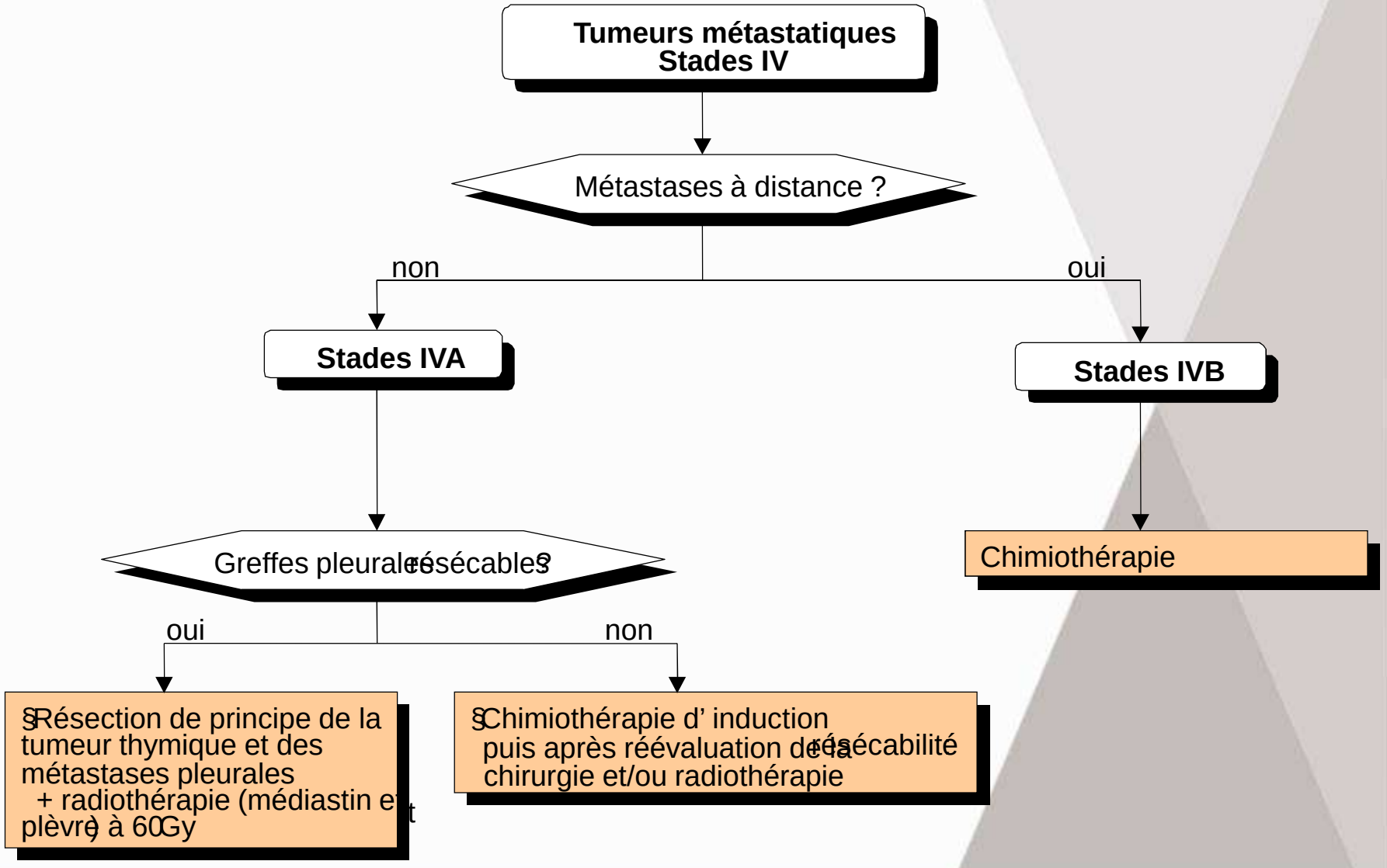
	n	%
Best response		
Partial response	2	15%
Stable disease	9	70%
Progressive disease	2	15%

median OS: 40 months

median PFS: 9 months;


Tumeurs primitives résécables
Stades I, II, III
Chirurgie
Résection complète ?
oui
non
Stades I, II
Stades III
Tumeur sans envahissement capsulaire ?
Radiothérapie post opératoire à 66 Gy avec surimpression sur le résidu tumoral
oui
non
Stades I
Stades II
Surveillance
A discuter en concertation pluridisciplinaire :
Radiothérapie post opératoire à 50 Gy


Tumeurs primitives non résécables
Stades III
Biopsie
Chimiothérapie d'induction : 3 cycles
Tumeur résécable?
oui
non
Tumeurs primitives
résécables de stades I, II, III
Radiothérapie entre 60 et 66 Gy


Tumeurs métastatiques
Stades IV
Métastases à distance ?
non
oui
Stades IVA
Stades IVB
Greffes pleurales résécables ?
Chimiothérapie
oui
non
Résection de principe de la tumeur thymique et des métastases pleurales
+ radiothérapie (médiastin et plèvre) à 60 Gy
Chimiothérapie d' induction
puis après réévaluation de la résécabilité
chirurgie et/ou radiothérapie

Protein or gene alterations

WHO Type	Chromosomal Arm-Level Aberrations	Chromosomal Translocations	Mutations and Copy Number Changes Affecting Selected Genes	Methylation	RNAs MicroRNAs
A	6q25 loss 6p23 loss (FOXC1)		*HRAS* (G13V)		miR-515 upregulation (targets PTEN)
AB	6q25 loss 6p23 loss (FOXC1) 7p15 loss				
B1	1p, 2q, 3q, 6q losses				
B2	6q25 loss 6p23 loss (FOXC1) 1q gain		*KRAS* (G12A)		
B3	6q25 loss 6p23 loss (FOXC1) 11q4 losses 1q gain	t(11;X)	*BCL2* copy number gains (18q21.33) *MCL1* copy number gain *CDKN2A/B* copy number losses (9p21.3) *BCOR* *PHF15*		
TSCC	6q25 loss 6p23 loss (FOXC1) 9p, 13q, 16q, losses 1q, 9q, 17q gains		*KIT* mutations: *E490K* (exon 9), *Y553N*, *W557R, V559A, V560del, L576P, P577-D579del* (exon 11), *H697Y* (exon 14), *D820E* (exon 17) *KRAS* (G12V) *BCL2* copy number gains (18q21.33) *MCL1* copy number gain *CDKN2A/B* copy number losses (9p21.3)	MGMT CDKN2	miR-142-5p down-regulation (targets MYC)

TSCC, Thymic squamous cell carcinoma.

Patients inclus en phase I

- 11 essais; 22 patients entre 94 et 2012 à Gustave Roussy
- Age médian : 41,1 an
- TC 15 / T 7
- Stades Avancés
- Suivi median 22.1 (1.25-77.79 mois)
- Pré-traitement :
  - médiane de 2 lignes,
  - tous prétraités par un sel de platine
  - 12 par anthracycline
  - 5 par Taxanes
  - 12 opérés, 13 irradiés

Diagnostic	Stage	Experimental Treatment	Class
T	IIVB	HKI 272-Temsirolimus	Pan-erbB inhibitor/mTOR inhibitor
TC	IVB	HKI 272-Temsirolimus	Pan-erbB inhibitor/mTOR inhibitor
TC	III	HKI 272 Temsirolimus	Pan-erbB inhibitor/mTOR inhibitor
T	IVB	HKI 272-Temsirolimus	Pan-erbB inhibitor/mTOR inhibitor
TC	IVB	E3810 (VGFR EGFR inhibitor)	AA
T	IVA	AVE 8062	AA
TC	IVB	BMS 514-FOLFIRI	AA
TC	IVB	AVE 8062	AA
TC	IVB	PCB-AG 951	AA
TC	IVB	BMS 690514-FOLFOX	AA
TC	III	DCF/VEGF TRAP	AA
TC	IIIA	CDKO 125 A006	TRK CDK inhibitor
TC	IVB	CDKO 125 A006	TRK CDK inhibitor
T	IVA	CDKO 125 A006	TRK CDK inhibitor
T	IVB	AB1010	KIT/PDGFR inhibitor
TC	IVA	AB1010	KIT/PDGFR inhibitor
T	IIIB	AB1010	KIT/PDGFR inhibitor
TC	IIA	5FU-streptozocine	Cytotoxic agent
TC	IIIB	Aplidine	Cytotoxic agent
TC	IVB	Cystemucine	Cytotoxic agent
TC	IVA	EMD 534085	Antimitotic agent
T	IVA	EMD 534085	Antimitotic agent

Toxicités

- Traitements bien tolérés
- Les toxicités de grade III/IV et I/II ont été rapportées dans respectivement 36% et 77% des patients.
- Aucun décès lié au traitement n'a été rapporté.
- On note une exacerbation aigue de maladie auto-immune chez un patient
- Le type d'effets secondaires et leur incidence étaient similaires à ceux obtenus pour d'autres tumeurs chez les patients.

Resultats (n=17 pts évaluables)

	OS month	PFS month
All treatments	54,5	6,6
mTORi	**31,5**	**11,6**
AA	**65**	**7,0**
Cytotoxic	25	1,3
Other TT	85	6,6

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2013

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

[2] Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center

[3] Foundation Medicine, University of California, San Diego

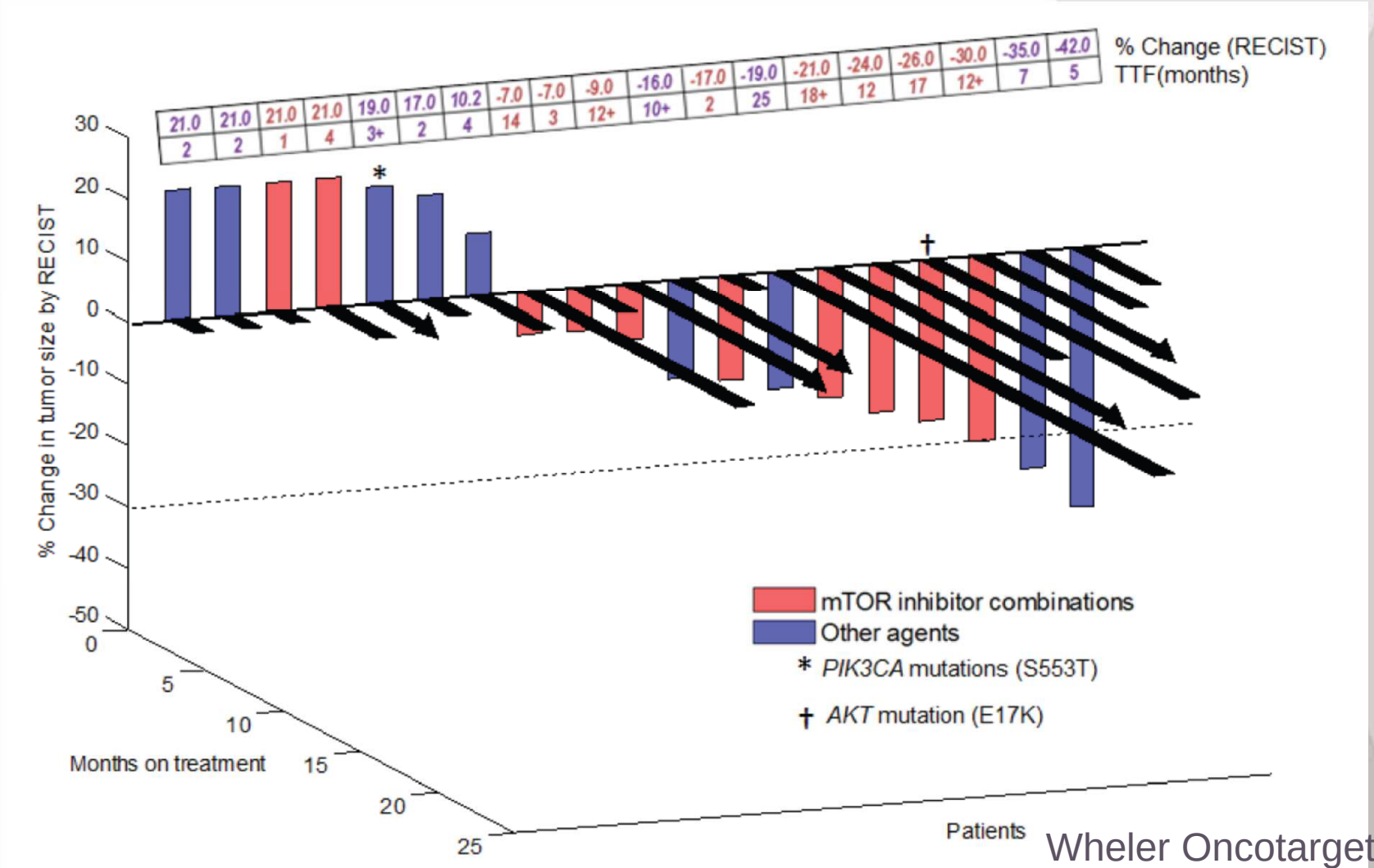
[4] Moores Cancer Center, University of California, San Diego

Correspondence to: *Jennifer Wheler,* ***email:*** *jjwheler@mdanderson.com*

Keywords: advanced thymoma, mTOR inhibitors, response, targeted therapy, thymic carcinoma.

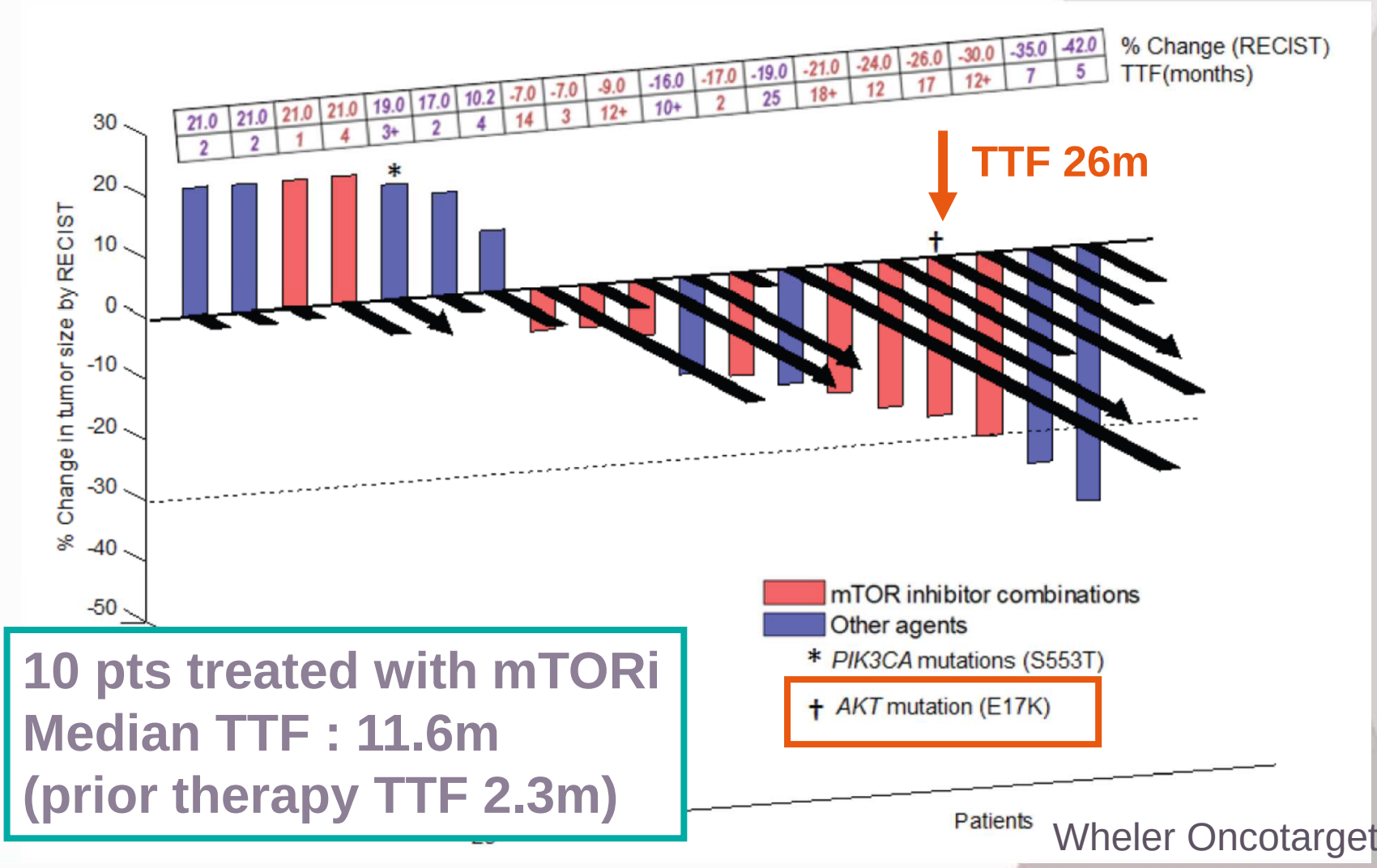
Received: *May 2, 2013* ***Accepted:*** *June 9, 2013* ***Published:*** *June 10, 2013*

Essais de phase I - MDACC



Wheler Oncotarget 13

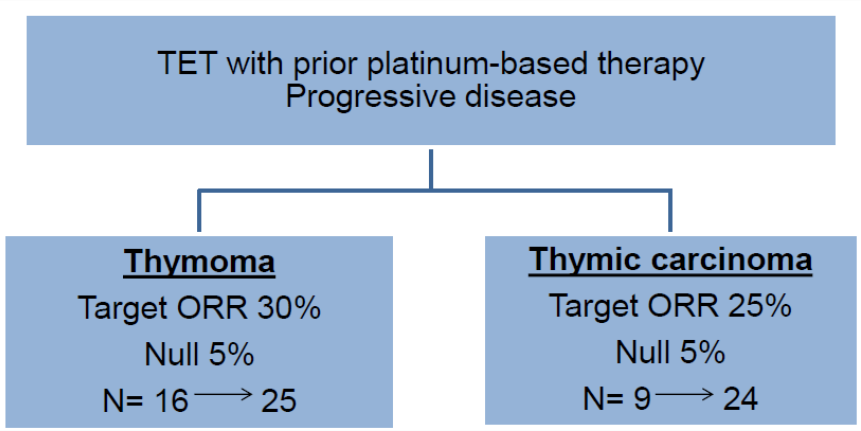
Essais de phase I - MDACC



10 pts treated with mTORi
Median TTF : 11.6m
(prior therapy TTF 2.3m)

Wheler Oncotarget 13

Phase II trial - Sunitinib



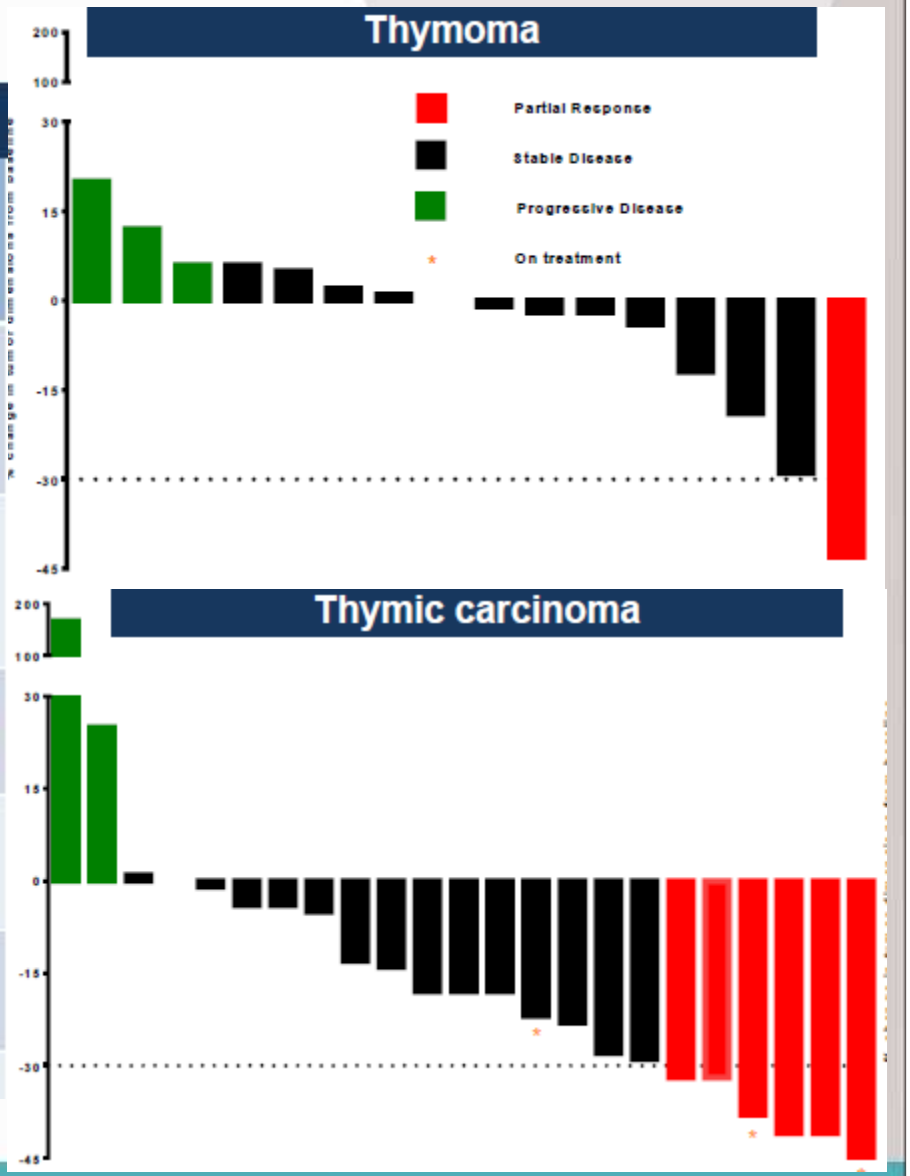
- **Sunitinib 50 mg/d**
- **4 weeks out of 6**

Patient characteristics

	Thymoma	Thymic carcinoma	Total
Number of patients	16	24	40
Age Median (Range)	54 (31-74)	58 (41-81)	57.5 (31-81)
Sex Male Female	7 9	15 9	22 18
ECOG PS 0- 1 2	15 1	21 3	36 4
Race: Caucasian African-American	13 3	23 1	36 4
Histology B1 B2 B3 Uncategorized	2 5 8 1	24	40
Prior systemic therapies Median (Range) ≥ 2 prior therapies	2 (1-7) 13	2 (1-5) 14	2 (1-7) 27
No. of cycles administered Median (Range)	5 (1-13)	4 (1-13)	4 (1-13)

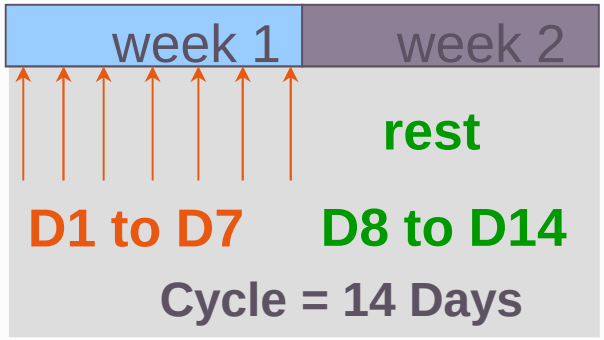
Sunitinib

Responses and survival	Thymoma (n=16)	Thymic carcinoma (n=23)
Objective Response Rate n (%) 95% CI	1 (6%) 0.2-30.2	6 (26%) 10.2-48.4
Disease control rate n (%) 95% CI	13 (81%) 54.4-96.0	21 (91%) 72.0-98.9
Overall survival	Not reached	Not reached
12 month overall survival % 95% CI	86% 60.9-96.1	78% 58.0-90.4
Progression-free survival Median months	8.5	7.2
Median follow up 17 months		



Thomas ASCO 2014

Phase II study - Milciclib

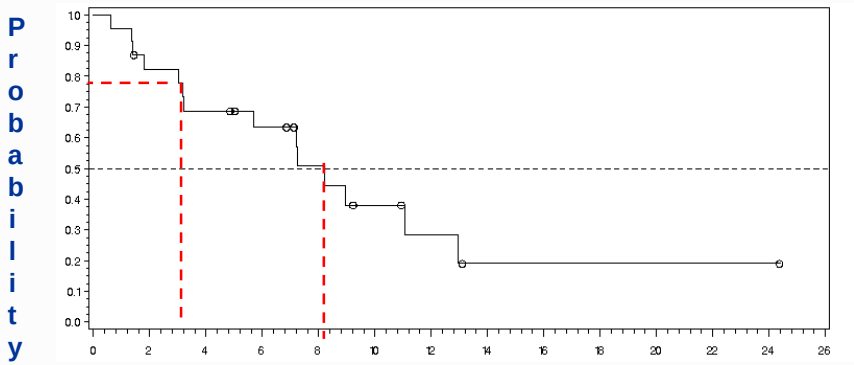


Patients received 150 milciclib orally once daily for 7 days on, 7 days off, in a 2-week cycle

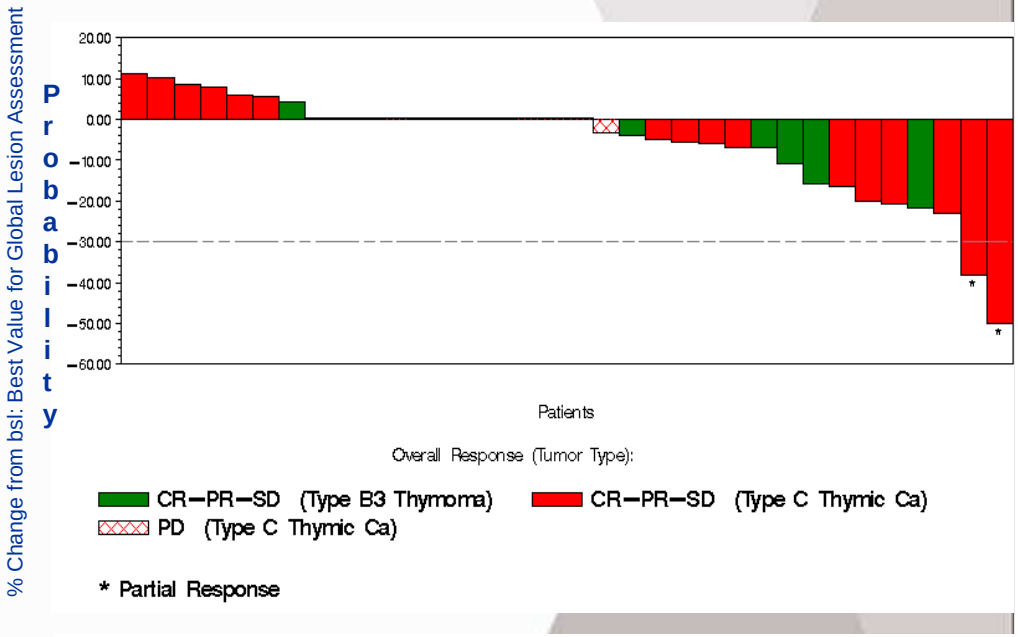
Patients' baseline characteritics (n=49)	
Characteristics	**Value**
Median age, years (range)	55 (21-80)
ECOG PS 0 -1*	22 / 13
Tumor types (WHO classification)* B3 - Well Differentiated Thymic Carcinoma C - Thymic carcinoma	 11 33
Prior therapies* None Systemic only Surgery + Systemic Systemic + Radiotherapy Surgery + Systemic + Radiotherapy	 4 6 9 2 19

Milciclib

Progression-Free Survival



Median PFS (95% CI)
8.2 (3.2- 12.9) mo

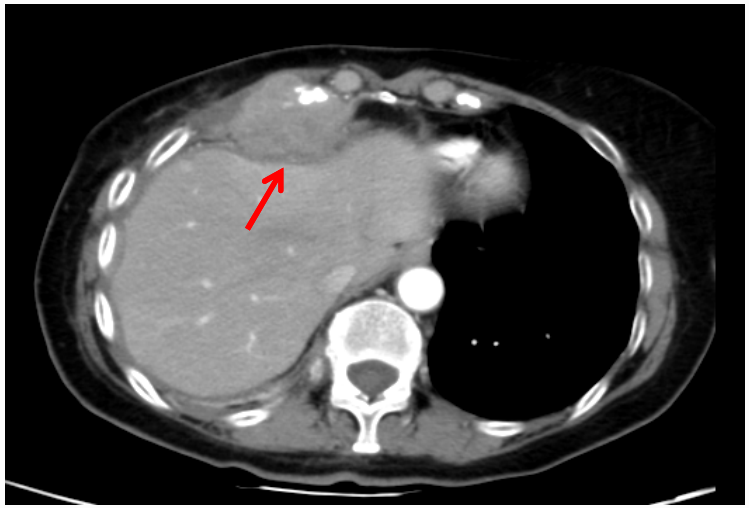


Evaluable pts : 12 SDs + 2 PRs/28 pts
Treated pts : 18 SDs + 2 PRs/39 pts

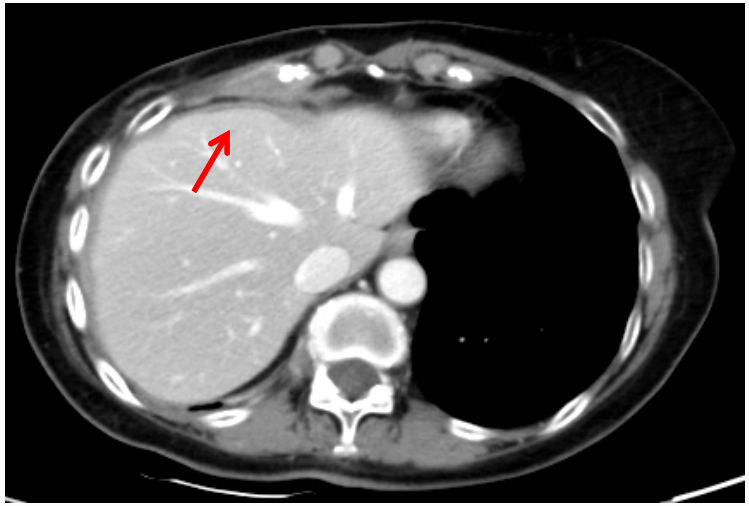
What's new for thymic cancer?

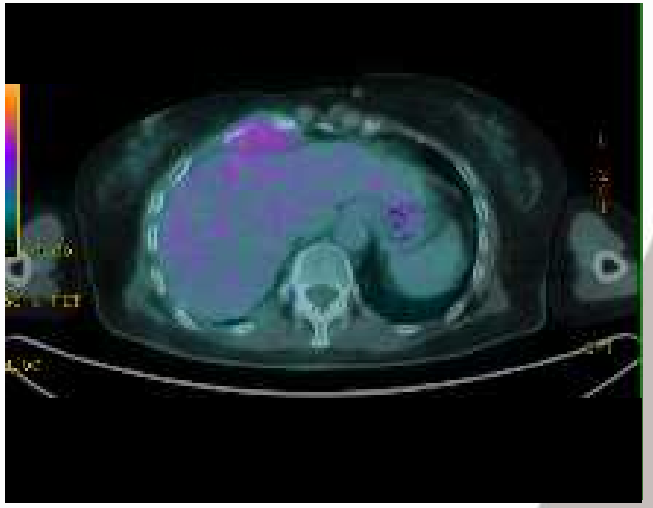
Presentation	Mechanism	Patients	Outcomes
Besse et al #7526 Milciclib	Multi-targeted kinase inhibitor with activity against CDK1,2,4, and 6	49 (B3 and TC)	RR ~7% (2/28 eval) mPFS 8 mo
Thomas et al #7525 Sunitinib	Mult-itargeted kinase inhibitor	24 (TC)	RR 26% (6/23 eval) mPFS 7 mo
Zucali et al **7527** **Everolimus**	**mTOR inhibitor**	**50 (19 TC)**	**RR 20% (10/50)** **mPFS – 6 mo (TC)**

Response to Everolimus



BASELINE





AFTER 6 WKS

RYTHMIC: a regional network of expert centers

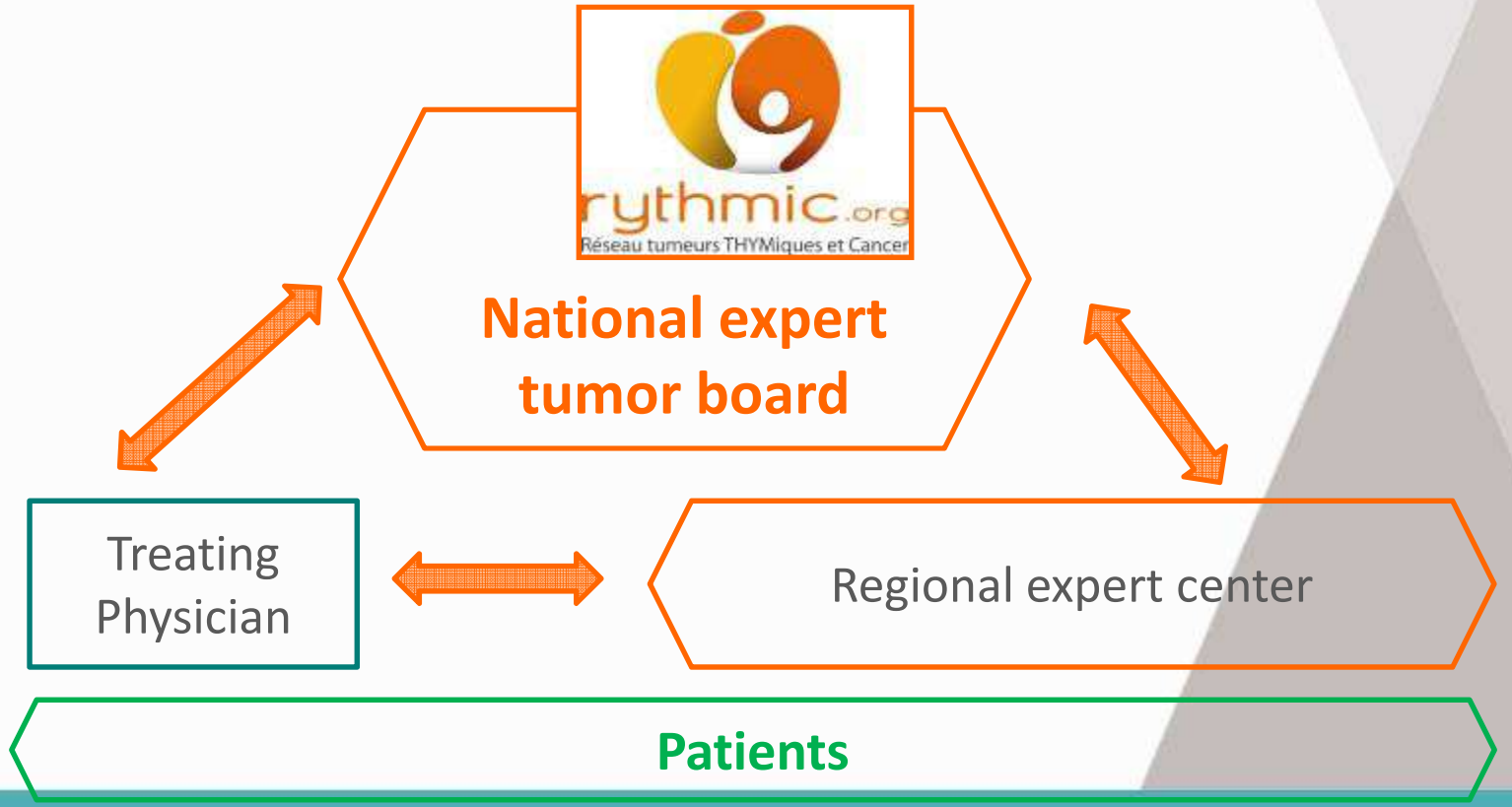
rythmic.org
Réseau tumeurs THYMiques et Cancer

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

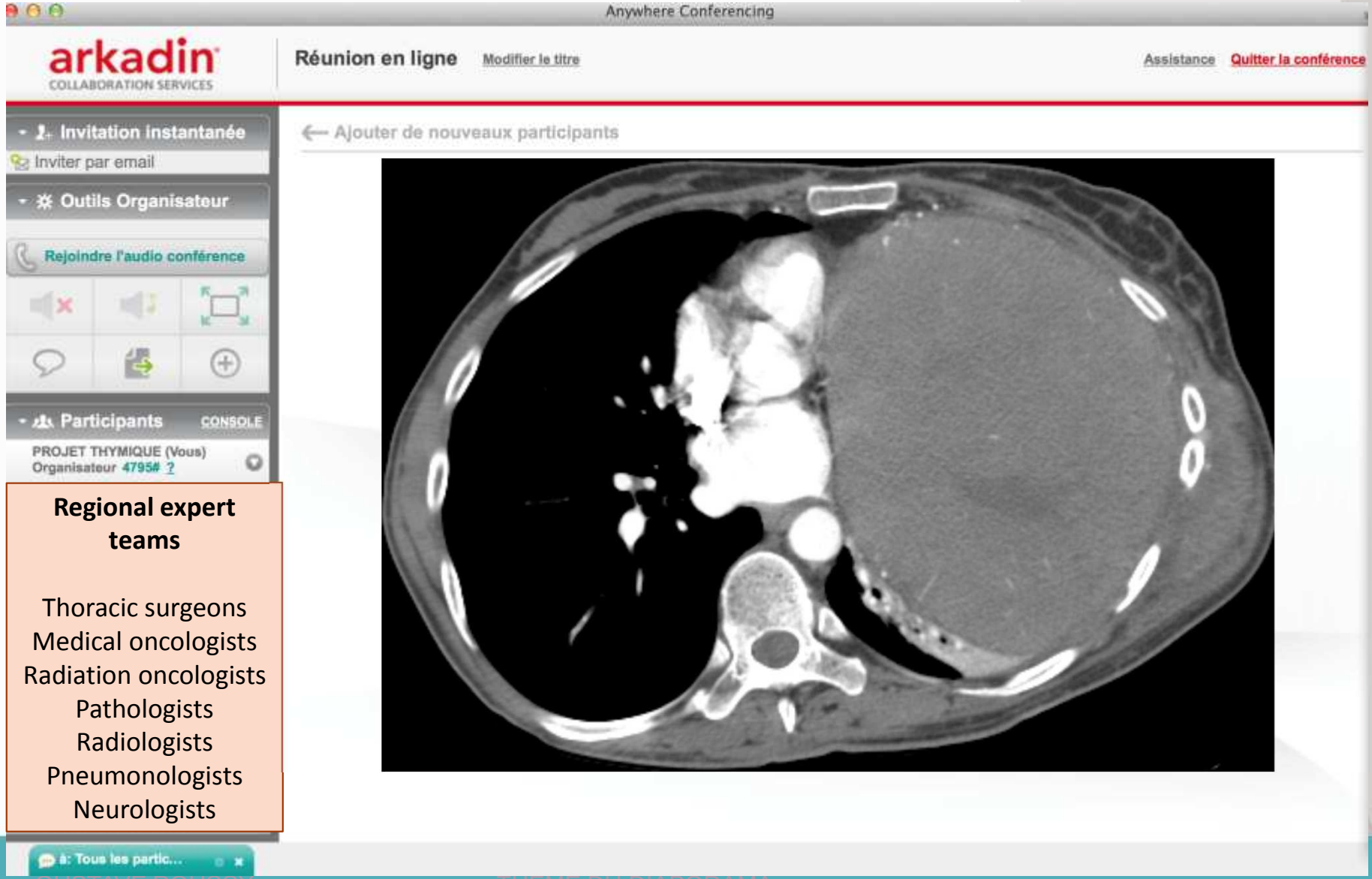
Coordinator:
B. Besse
Gustave Roussy

Hospices Civils de Lyon

RYTHMIC: Infrastructure of the network



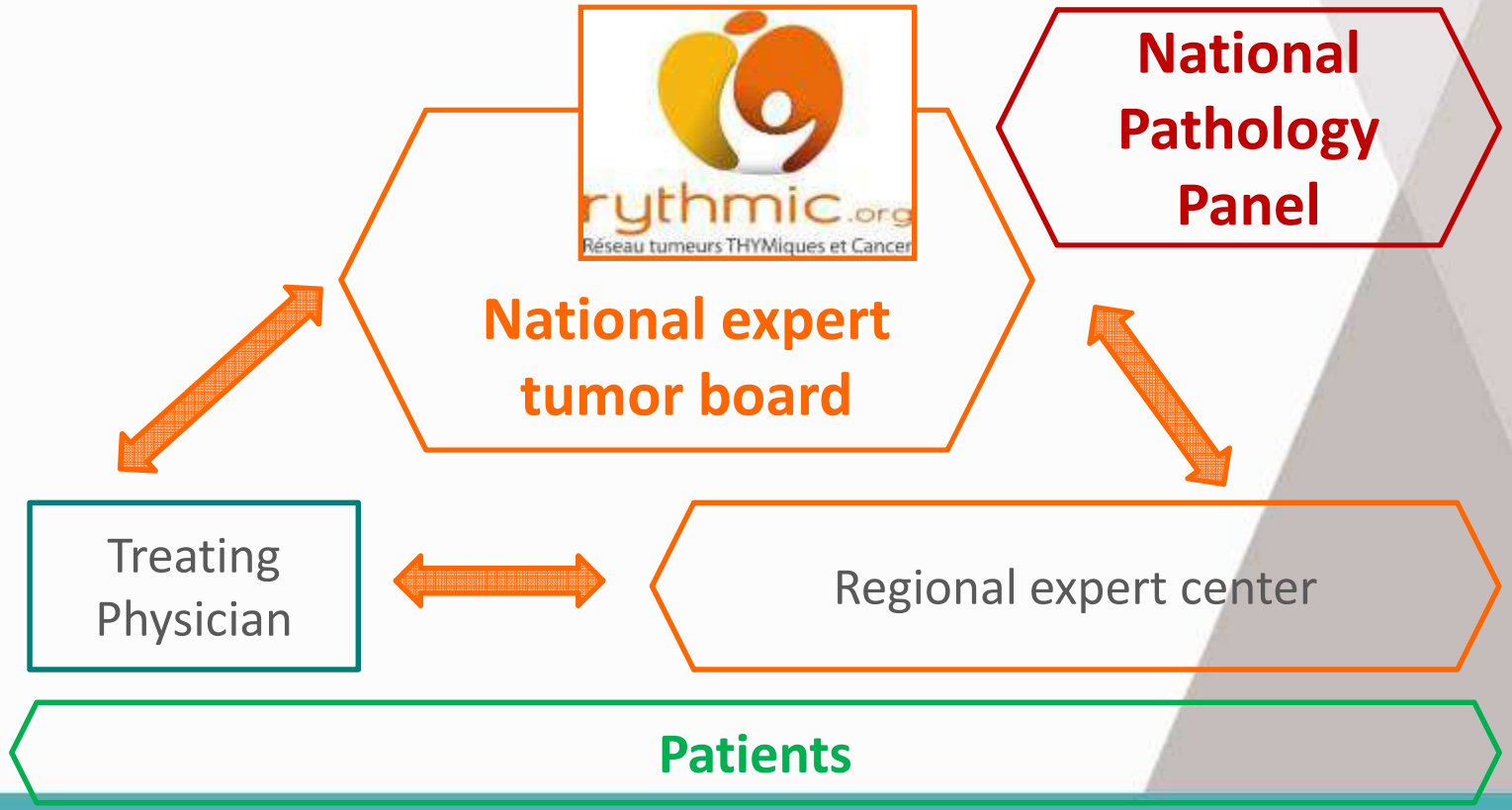
Online virtual tumor board



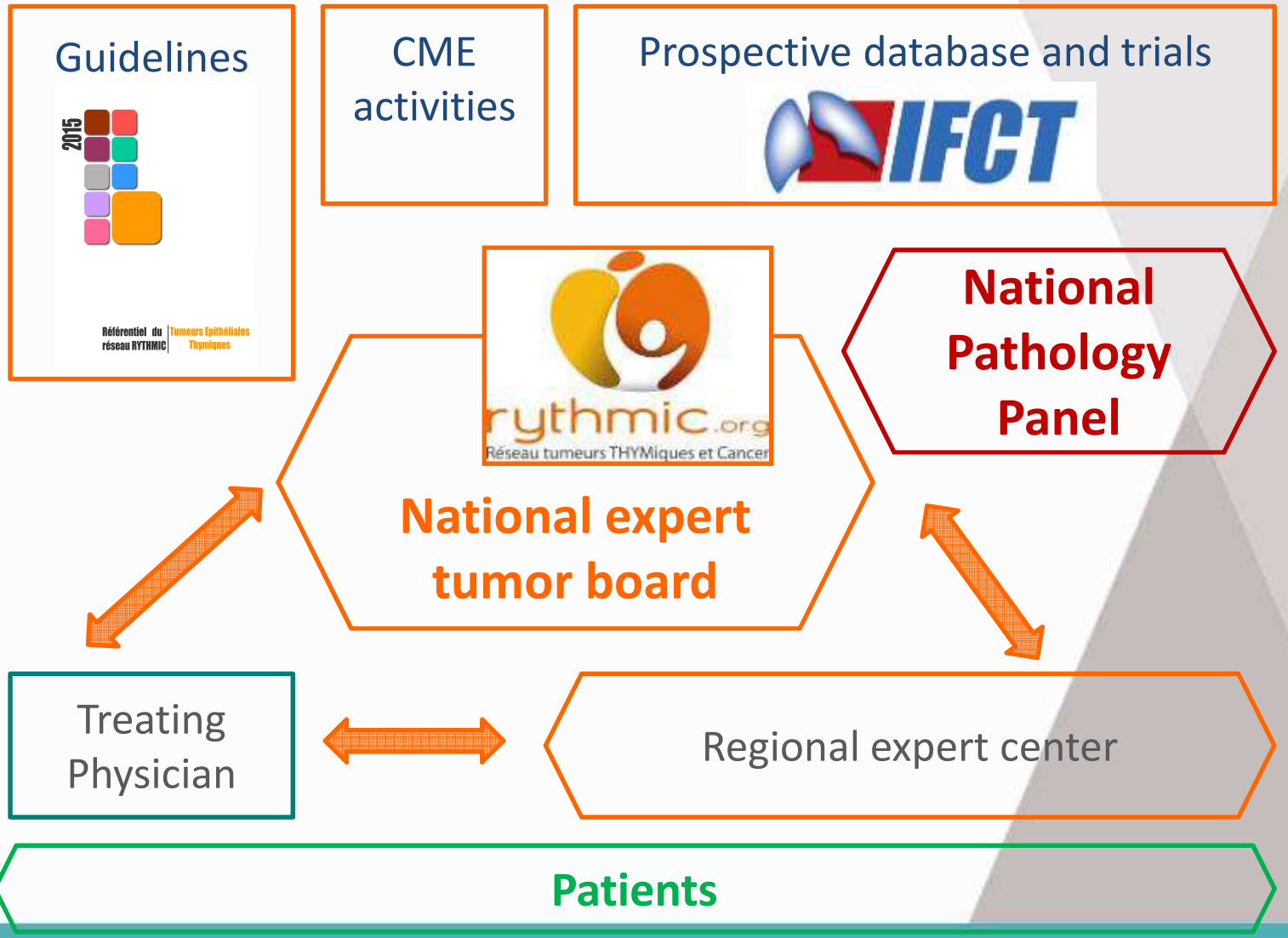
Regional expert teams

Thoracic surgeons
Medical oncologists
Radiation oncologists
Pathologists
Radiologists
Pneumonologists
Neurologists

RYTHMIC: Infrastructure of the network

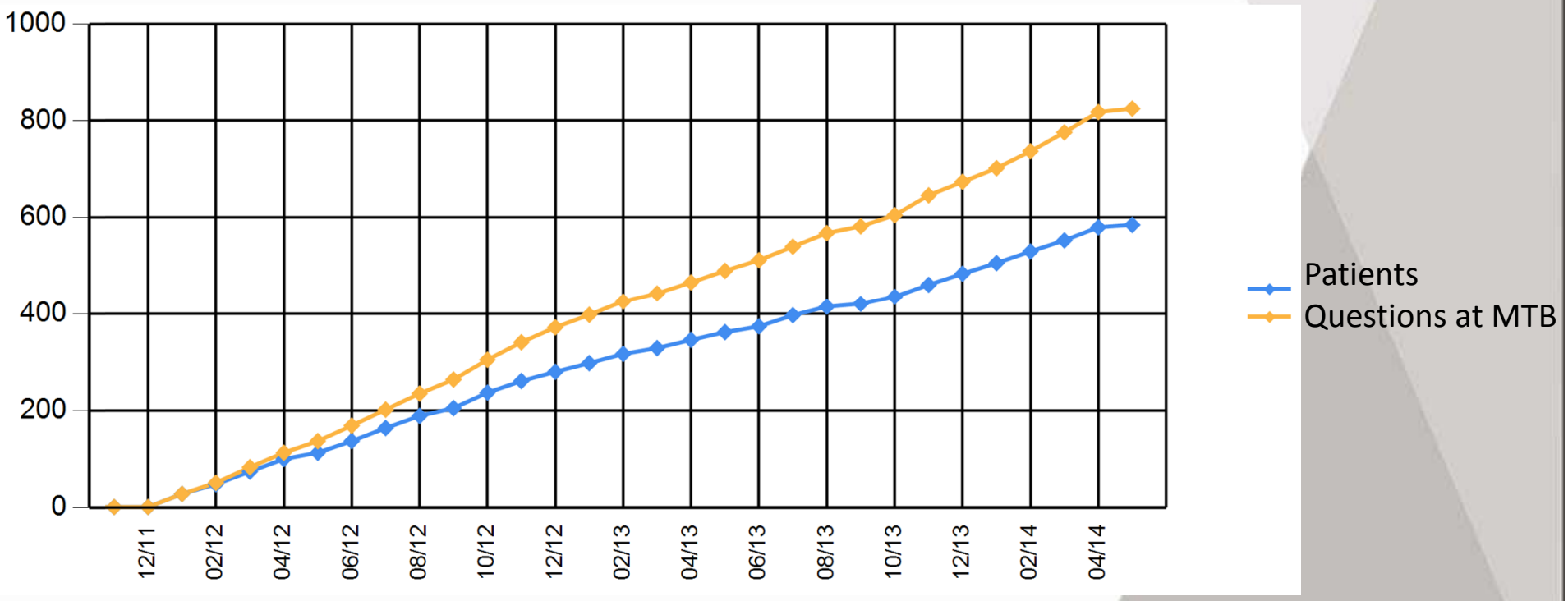


RYTHMIC: Infrastructure of the network



RYTHMIC: Accrual of patients

- **627 patients enrolled from January 2012 to May 2014**
- **825 questions at the national multi-disciplinary tumor board**



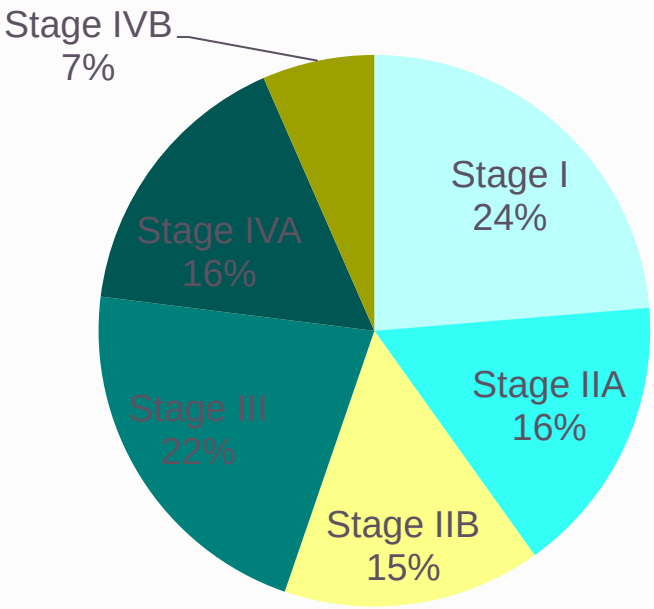
Data cutoff was June 1st, 2014

RYTHMIC: Characteristics of patients

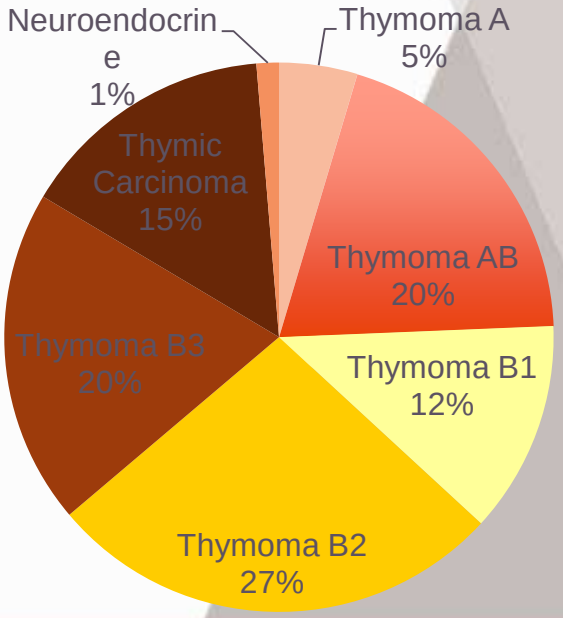
- **A global view of the disease, from early to late stage**
  - 50% of stage III-IV tumors
  - Histology was of higher grade (B2, B3, Carc) in those cases

(p<0.001)

Masaoka-Koga-ITMIG stage



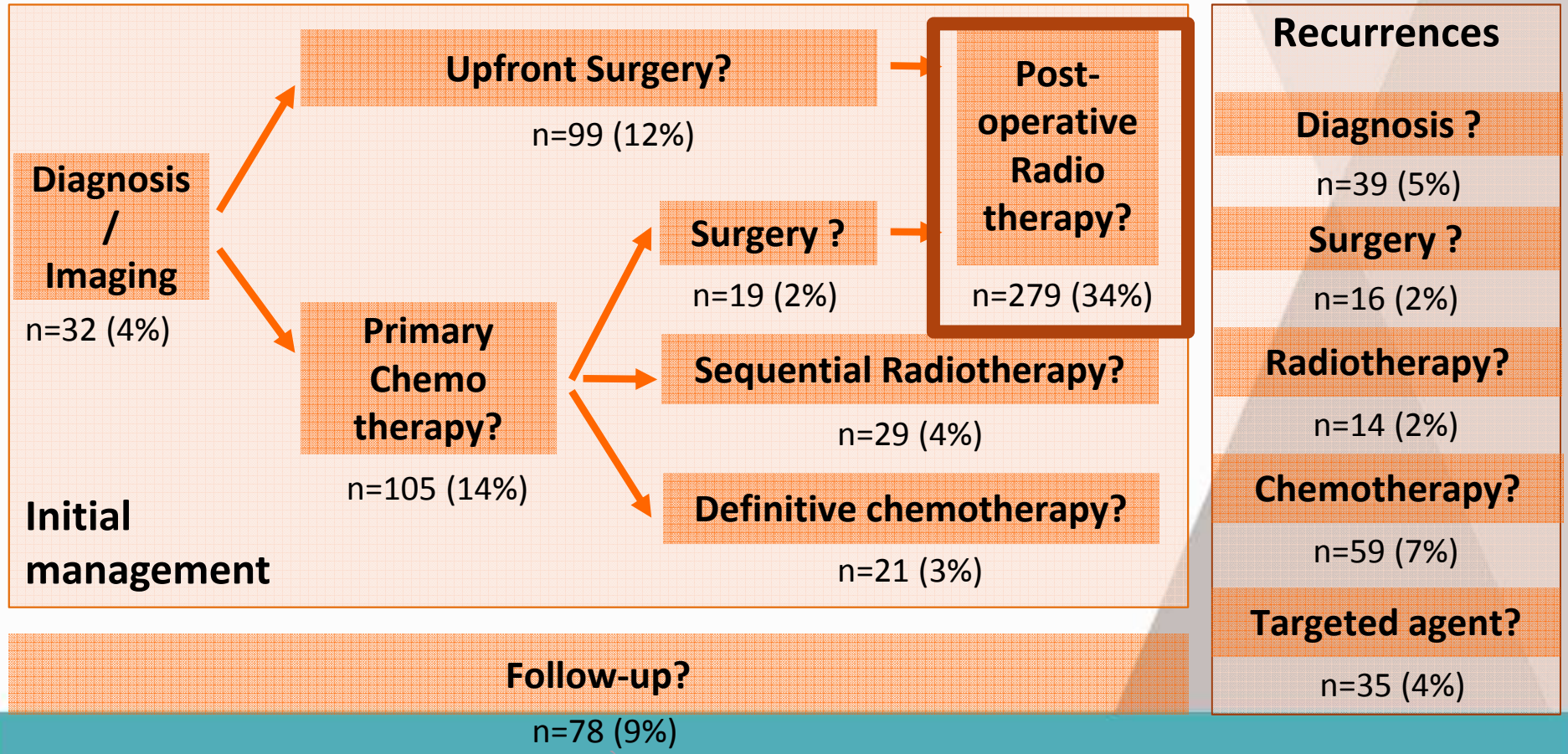
Histology



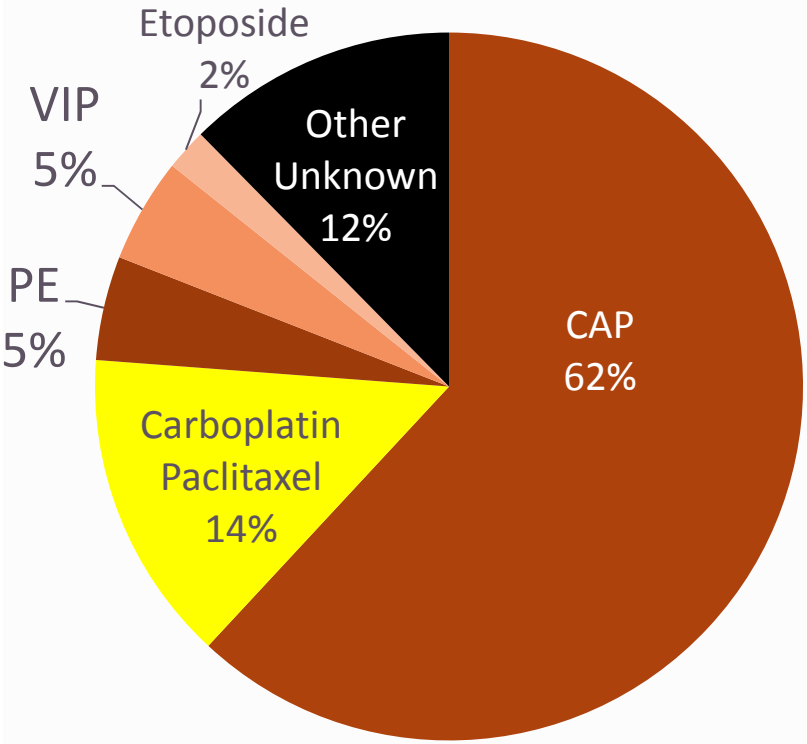
Among 152 fully assessable cases

RYTHMIC: Multidisciplinary tumor board

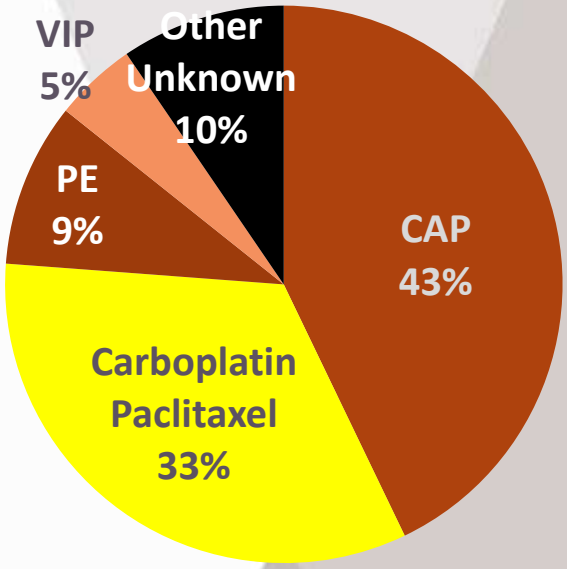
- **Post-operative radiotherapy is the most frequent question raised at the multi-disciplinary tumor board (34% of cases)**



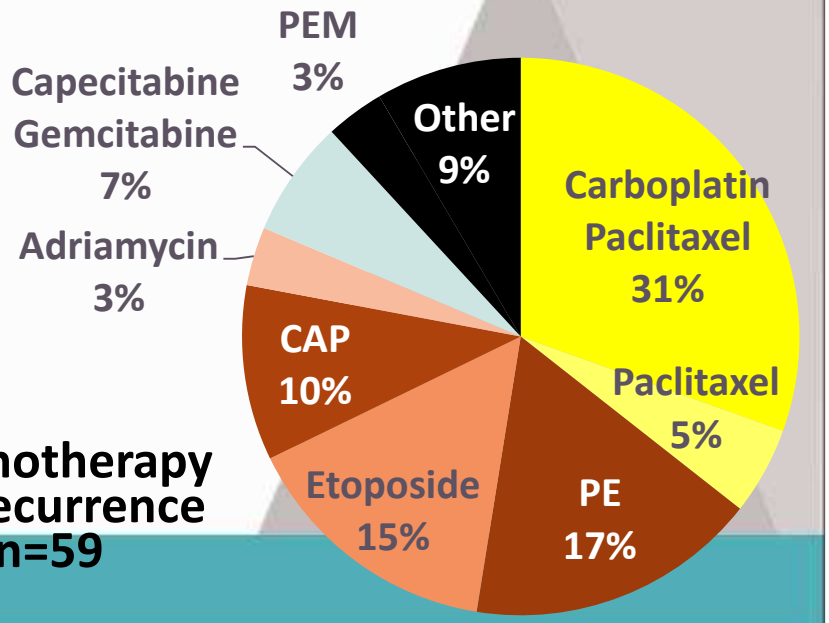
RYTHMIC: Proposed chemotherapy regimens



Primary chemotherapy
n=105



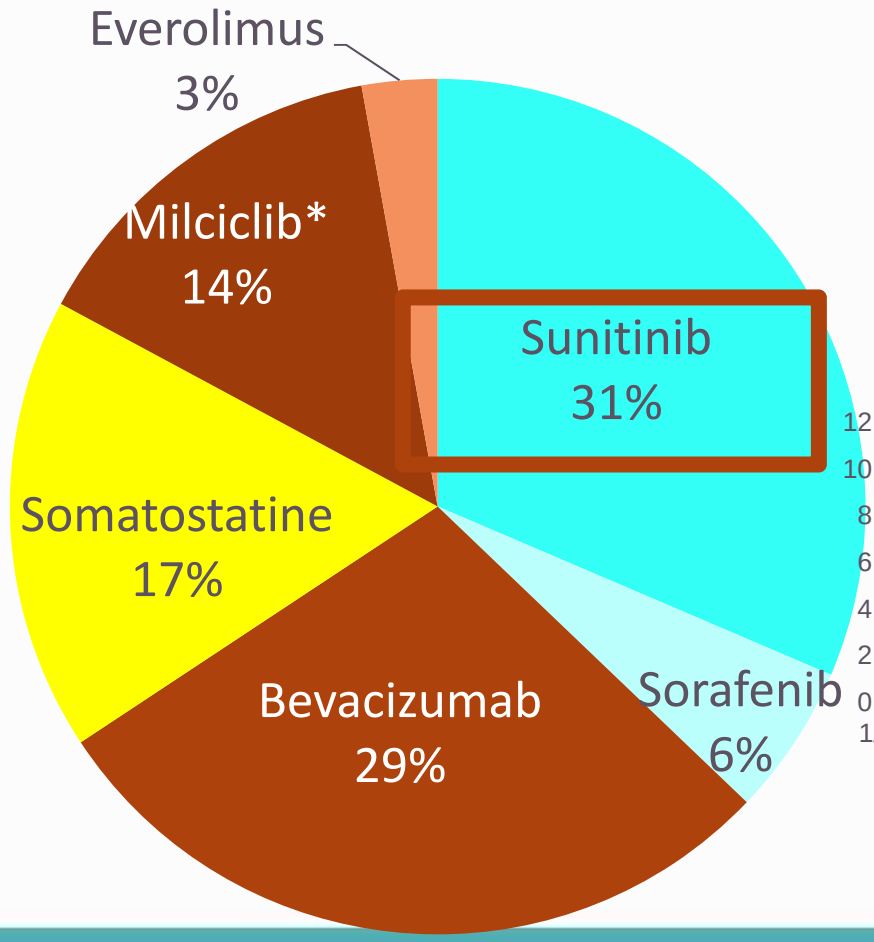
Definitive chemotherapy
n=21



Chemotherapy for recurrence
n=59

RYTHMIC: Proposed targeted agents

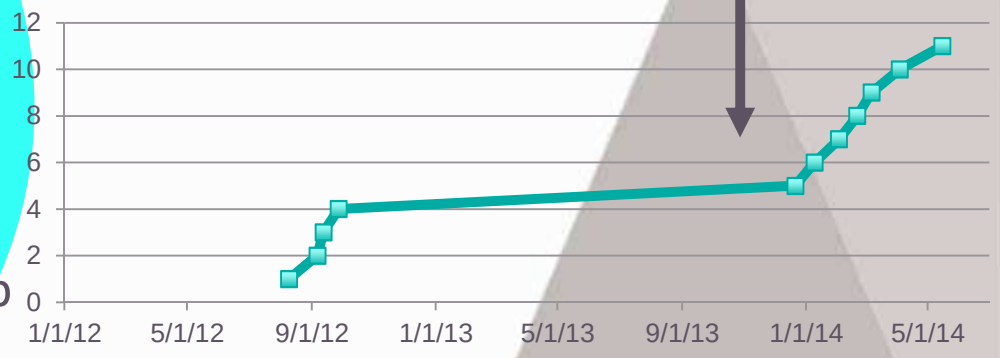
- **35 cases, recurrent tumors: rapid and equal access to innovation**



THYMIC MALIGNANCIES
MONDAY, OCTOBER 28, 2013 - 10:30-12:00

MO03.07 CLINICAL ACTIVITY OF SUNITINIB IN PATIENTS WITH THYMIC CARCINOMA

Anish Thomas[1], Arun Rajan[1], Arlene Berman[1], Barbara Scepura[1], Christina Brzezniak[2], Corey A. Carter[2], Udayan Guha[1], Yisong Wang[1], Eva Szabo[1], Patrick J. Loehrer[3], Giuseppe Giaccone[4]



Number of cases with a proposal of sunitinib accross time

* Phase I/II trial

J Thorac Oncol 2013;8:S268

RYTHMIC: summary

- **RYTHMIC demonstrates the feasibility of a national multidisciplinary tumor board for thymic malignancies.**

- **RYTHMIC is a comprehensive tool for research:**
  - exhaustive registry
  - advanced stage and recurrent tumors

- **RYTHMIC allows a rapid implementation of new results in clinical practice, while ensuring patients an equal access to therapeutic innovation.**

2015

Référentiel du réseau RYTHMIC | Tumeurs Epithéliales Thymiques

www.rythmic.org

Manuel d'oncologie
Appstore & google play