



Mésothéliome 2023

Pr. Nicolas Girard

**Institut Curie,
INSERM U932,
Université Paris-Saclay**



Liens d'intérêt

- Recherche clinique:

- Amgen
- Astra-Zeneca
- Abbvie
- Blue
- BMS
- Boehringer-Ingelheim
- Janssen
- Hoffmann-La Roche
- Lilly
- Merck
- MSD
- Novartis
- Sivan
- Trizell

- Symposia:

- Amgen
- Astra-Zeneca
- BMS
- Janssen
- Mirati
- MSD
- Pfizer

- Congrès:

- Astra-Zeneca
- MSD

- IFCT: Trésorier

- ITMIG: Président

- Réunions d'experts:

- Amgen
- Astra-Zeneca
- BMS
- Boehringer-Ingelheim
- Janssen
- Hoffman-La Roche
- Lilly
- Novartis
- Merck
- MSD
- Pfizer
- Sanofi

Déclaration publique d'intérêt

<https://dpi.sante.gouv.fr/dpi-public-webapp/app/recherche/declarant>

Mesothelioma

Epidemiology and risk factors

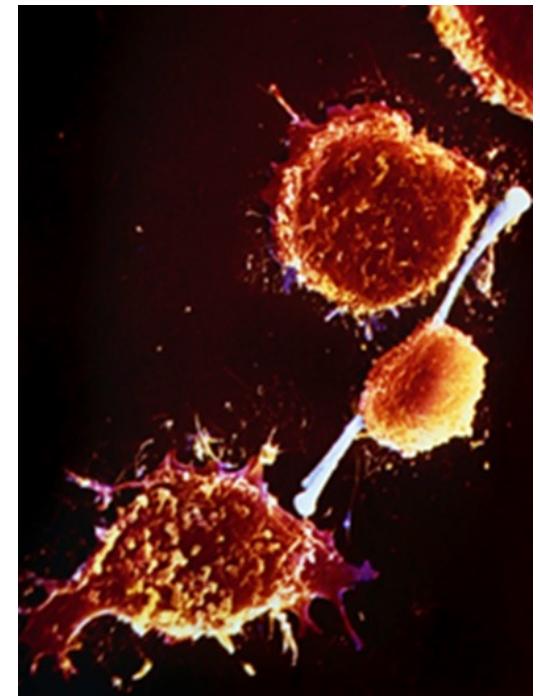
Mésothéliome



- Tumeur demeurant une tumeur rare.
- En France :
 - Incidence relativement stable : ≈ 1000 cas annuels
 - Age moyen au moment du diagnostic de 75 ans, sex ratio de 3,5/1
 - Maladie à déclaration obligatoire (INVS)
 - Réseau NET-MESO : MESOCLIN (clinique) + MESO-PATH (anatomopathologique)

Mésothéliome

- Amiante +++
 - Amphiboles > chrysotile
 - survenue possible après des expositions courtes, indirectes, et faibles (< 5 fibres/mL x années). Pas de dose-seuil.
 - latence importante de 15 à > 40 ans après l'exposition.
- Absence de relation avec le tabac
- Rôle des radiations ionisantes
- Prédisposition génétique : perte expression BAP-1 (BRCA-associated protein 1)



Mesothelioma

Epidemiology and risk factors

Histology

First: distinguish mesothelioma from other pleural diseases

Mesothelial Hyperplasia	Mesothelioma
<ul style="list-style-type: none">Absence of stromal invasion (beware of entrapment and en face cuts)Cellularity may be prominent but is confined to the mesothelial surface/pleural space and is not in the stromaSimple papillae; single cell layersLoose sheets of cells without stromaNecrosis rareInflammation commonUniform growth (highlighted with cytokeratin staining)	<ul style="list-style-type: none">Stromal invasion usually apparent (highlight with pancytokeratin staining)Dense cellularity, including cells surrounded by stromaComplex papillae; tubules and cellular stratificationCells surrounded by stroma ("bulky tumor" may involve the mesothelial space without obvious invasion)Necrosis present (occasionally)Inflammation usually minimalExpansile nodules; disorganized growth (highlighted on cytokeratin staining)
Usually Not Useful	
	<ul style="list-style-type: none">Mitotic activityMild to moderate cytologic atypia

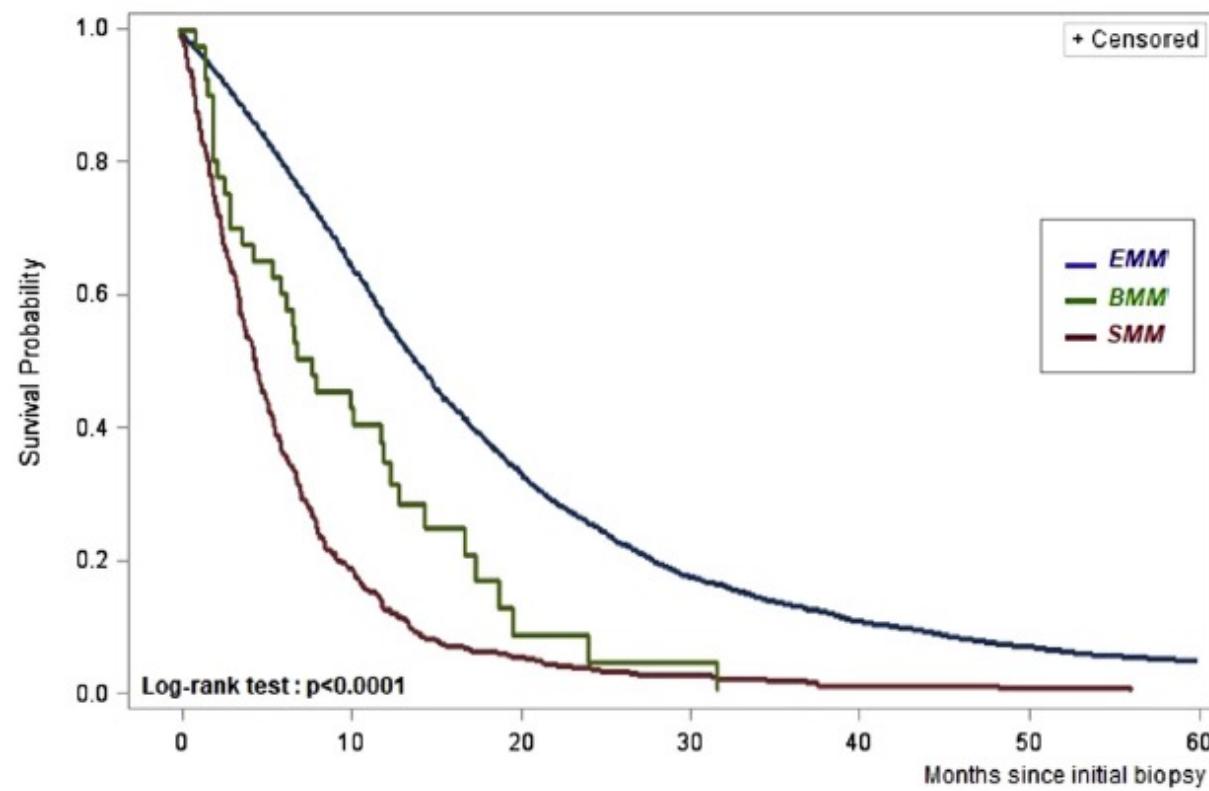
Fibrous Pleurisy	Desmoplastic Mesothelioma
<ul style="list-style-type: none">Storiform pattern not prominentAbsence of stromal invasionNecrosis, if present, is at the surface epithelioid mesothelial cells (where there is often associated acute inflammation)Uniform thickness of the processHypercellularity at the surface with maturation and decreased cellularity deep (so-called zonation)Perpendicularly oriented vessels	<ul style="list-style-type: none">Storiform pattern often prominentStromal invasion present (highlight with pancytokeratin staining)Bland necrosis of paucicellular, collagenized tissueDisorganized growth, with uneven thickness, expansile nodules, and abrupt changes in cellularityLack of maturation from the surface to the depths of the processPaucity of vessels, without orientation
Usually Not Useful	
	<ul style="list-style-type: none">CellularityAtypia (unless severe)Mitotic activity unless numerous atypical mitotic figures

^a Data derived from Mangano et al,¹³⁵ 1998.

Second: Histopathological classification of mesothelioma

<u>Epithelioid mesothelioma</u>	<u>Sarcomatoid mesothelioma</u>
Tubulopapillary	
Trabecular	
Adenomatoid	
Solid	
Micropapillary	
Myxoid	
Clear cell	
Deciduoid	
Small cell	
Rhabdoid	
Lymphohistiocytoid	
	<u>Biphasic mesothelioma</u>
	Any combination of patterns of epithelioid and sarcomatoid mesothelioma
	Transitional
	Pleomorphic

Second: Histopathological classification of mesothelioma



	N	Median	1 yr-survival [CI95%]	2 yrs-survival [CI95%]	5 yrs-survival [CI95%]
EMM	5219	14 mos	55% [53%; 57%]	24% [23%; 26%]	4% [3%; 5%]
BMM	42	8 mos	38% [23%; 53%]	8% [0%; 19%]	0%
SMM	465	4 mos	12% [9%; 15%]	3% [1%; 5%]	0%

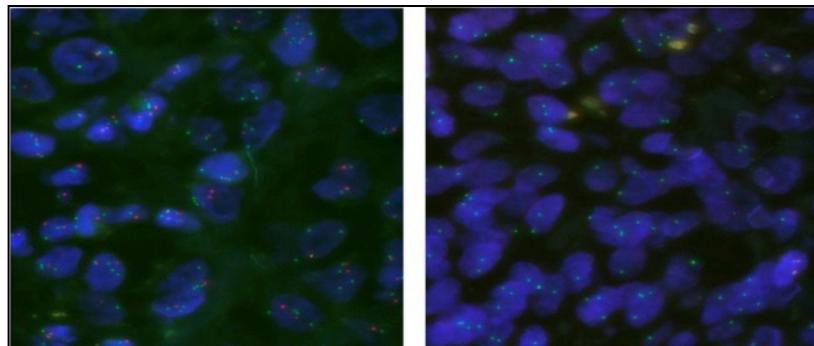
Biomarkers for diagnosis: BAP1 IHC and P16 deletion

Utility of BAP1 Immunohistochemistry and p16 (CDKN2A) FISH in the Diagnosis of Malignant Mesothelioma in Effusion Cytology
Specimens: Hwang HC et al. AJSP 2015 39:977-82

BAP1 Immunohistochemistry and p16 FISH to Separate Benign From Malignant Mesothelial Proliferations.. Sheffield BS et al.
American Journal of Surgical Pathology. 2015 39:977-982. (100% specific, 58% sensitive)

BAP1 immunohistochemistry and p16 FISH analysis provide reliable markers of mesothelial malignancy in effusion cytology specimens, especially where the atypical mesothelial proliferation is well sampled. BAP1 is easier to interpret with scanty specimens.

On the basis of small numbers of cases, use of both markers appears to increase sensitivity.



Examples of p16 retained (A) and p16 deleted (B) mesothelial proliferations. B, TMA core of mesothelioma showing homozygous loss of p16. Majority of cells show green signal(s) without corresponding orange signal.

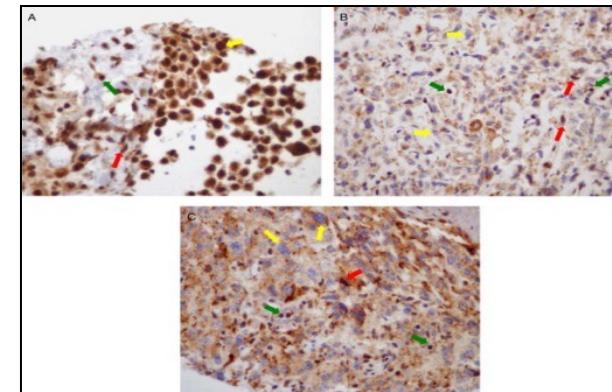


FIGURE 1 . Examples of retained (A) and lost (B and C) BAP1 expression.

Mésothéliome

Etape essentielle : prise en charge thérapeutique et reconnaissance d'une maladie professionnelle

Biopsies de taille suffisante indispensables pour le diagnostic

Morphologie : 70% épithélioïdes, 15% fusiformes ou sarcomatoïdes, 10% biphasiques ou mixtes

Deux étapes :

1. Affirmer la malignité : hyperplasie mésothéliale atypique vs. mésothéliome malin épithélioïde débutant, pachypleurite vs. mésothéliome desmoplastique

- délétion homozygote du gène *CDKN2A* (p16) par FISH = argument important en faveur d'un mésothéliome
- perte d'expression de BAP1 en IHC très spécifique pour affirmer le diagnostic de mésothéliome malin (doute avec hyperplasie mésothéliale atypique)

2. Différencier le mésothéliome malin d'une autre prolifération tumorale pleurale

- formes mixtes avec un synovialo-sarcome
- formes sarcomatoïdes avec un sarcome ou un carcinome sarcomatoïde,
- distinction entre métastase pleurale d'un adénocarcinome et mésothéliome pleural malin

Diagnostic devant être confirmé par l'expertise du réseau MESOPATH pour indemnisation par le FIVA et/ou la CPAM

Mesothelioma

Epidemiology and risk factors

Histology

Staging

Staging of mesothelioma: T

ORIGINAL ARTICLE



The IASLC Mesothelioma Staging Project: Proposals for Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma

Anna K. Nowak, M.B.B.S., PhD,^{a,b,*} Kari Chansky, MS,^c David C. Rice, MBBCh,^d

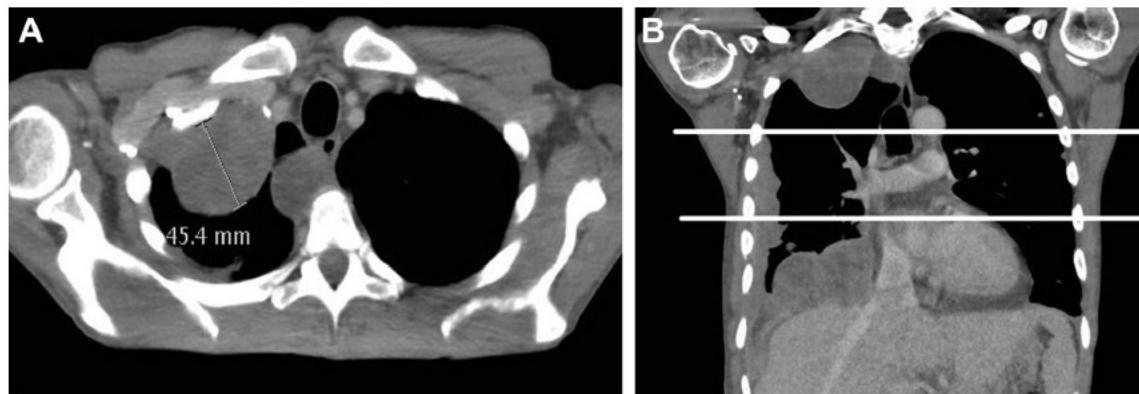


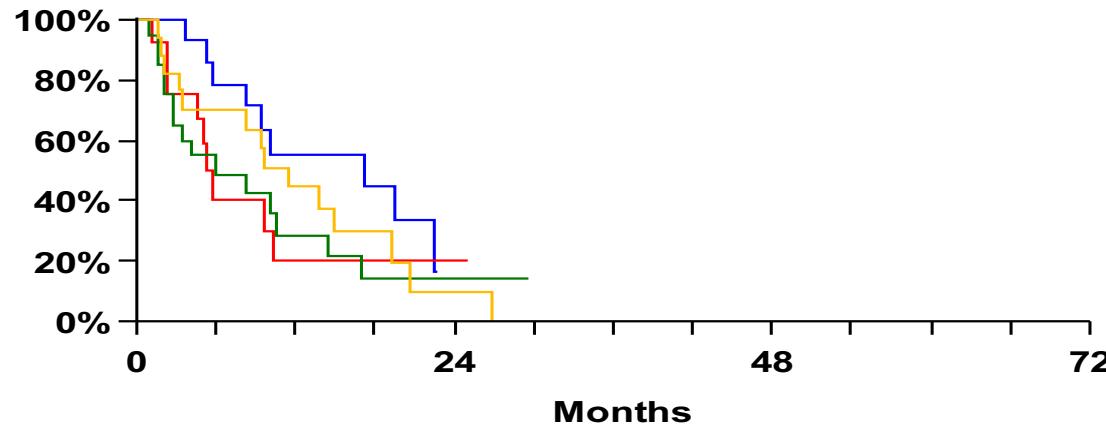
Figure 1. (A) Maximal tumor thickness perpendicular to the chest wall or mediastinum was measured for each of three levels on axial imaging. (B) Measurements of tumor thickness were made on axial slices, representing the upper, middle, and lower third of the hemithorax. These thirds were defined as follows: the upper level extends from the apex of the lung to the inferior margin of the arch of the aorta; the middle level includes the pleura between the upper and lower levels; and the lower level is pleural, including and inferior to the first image on which the left atrium is seen.

Staging of mesothelioma: T

T Component Staging	T Descriptors
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to the ipsilateral parietal \pm visceral \pm mediastinal \pm diaphragmatic pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: <ul style="list-style-type: none">• involvement of diaphragmatic muscle• extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Describes locally advanced but <i>potentially resectable</i> tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: <ul style="list-style-type: none">• involvement of the endothoracic fascia• extension into the mediastinal fat• solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall• nontransmural involvement of the pericardium
T4	Describes locally advanced <i>technically unresectable</i> tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: <ul style="list-style-type: none">• diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction• direct transdiaphragmatic extension of tumor to the peritoneum• direct extension of tumor to the contralateral pleura• direct extension of tumor to mediastinal organs• direct extension of tumor into the spine• tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

Staging of mesothelioma: M

cM1 with Descriptors



	Events / N	MS T	24 Mont h	60 Mont h
1.Single lesion, single site	9 / 18	17.3	0	0
2.Multiple lesions, single site	9 / 14	5.8	20%	0
3.Multiple sites	15 / 21	6.1	14%	0
4.Single site, lesions NOS	14 / 17	11.5	10%	0%

Table 2. Location of Metastatic Sites in 84 Patients with M1 Disease Identified before Any Treatment

Site	n
Contralateral pleura	6
Contralateral lung	13
Peritoneum	9
Intra-abdominal	22
Bone	8
Liver	7
Brain	2
Distant lymph node ^a	23
Other site	7
No descriptors	14

Note: Some patients had multiple sites of disease (see text).

^aIncludes all extrathoracic lymph nodes other than supraclavicular nodes. Specific information regarding these lymph node sites is not available in the database.

Staging of mesothelioma: conclusions

- Most patients with T4 disease
- TNM not used clinically
- Interest for clinical trials with surgical approaches

Mesothelioma

Epidemiology and risk factors

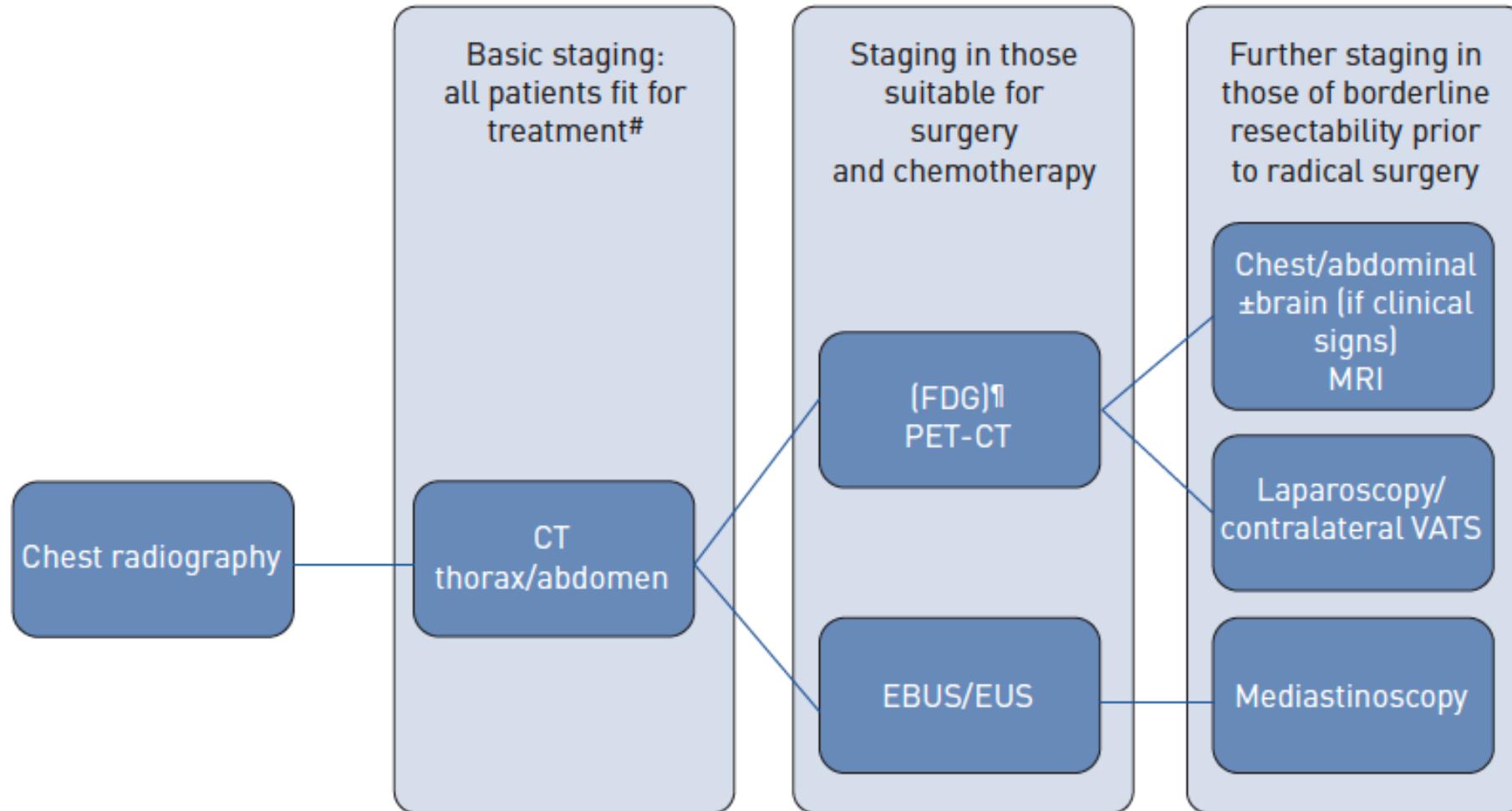
Patient pathway

Histology

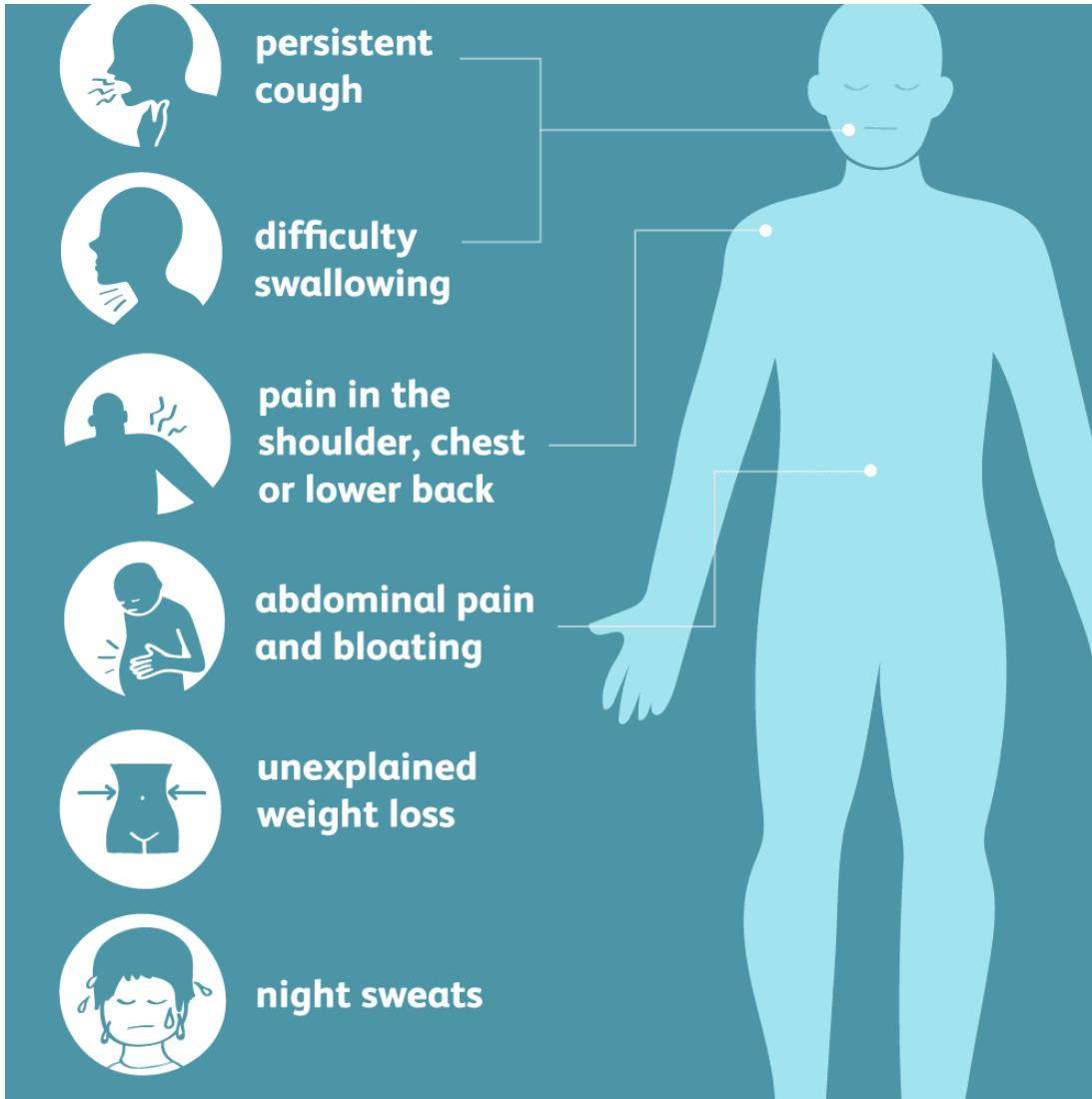
Staging

Prognostic factors

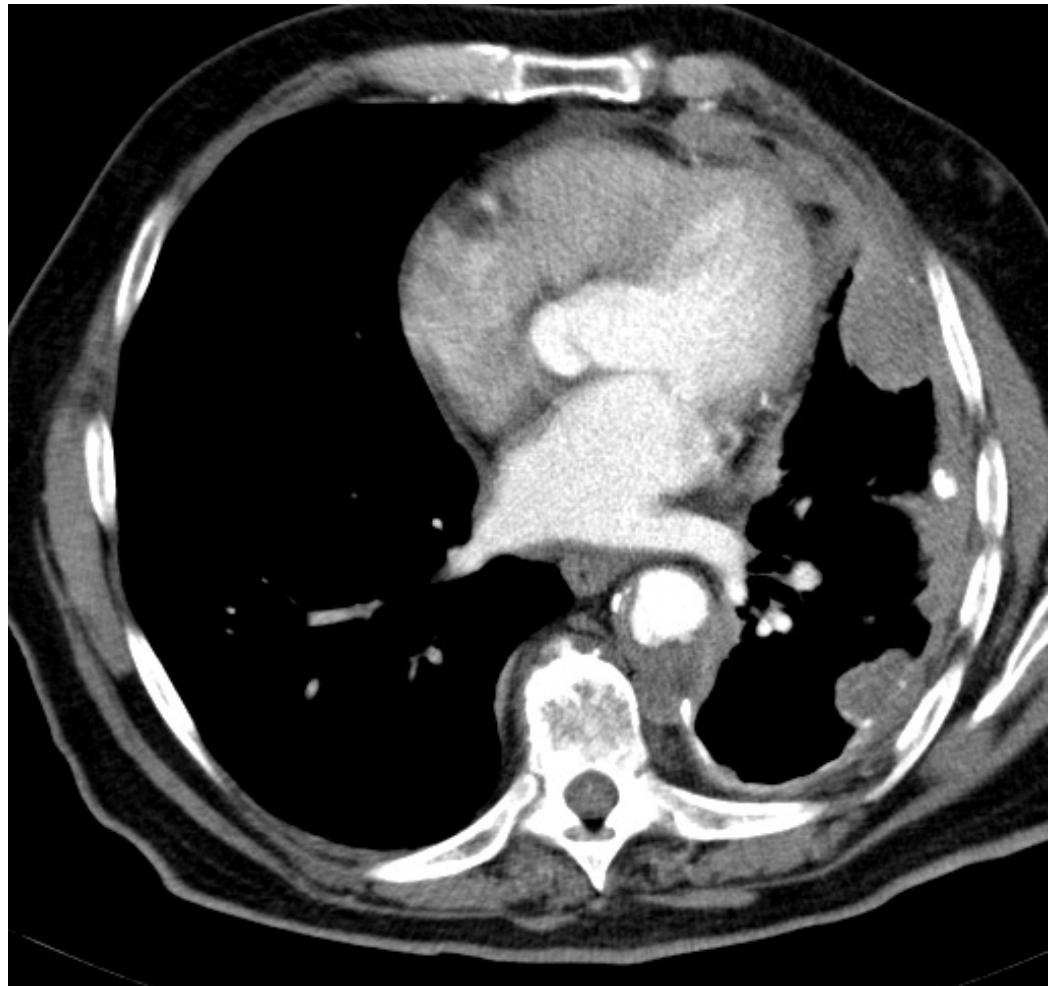
Patient pathway



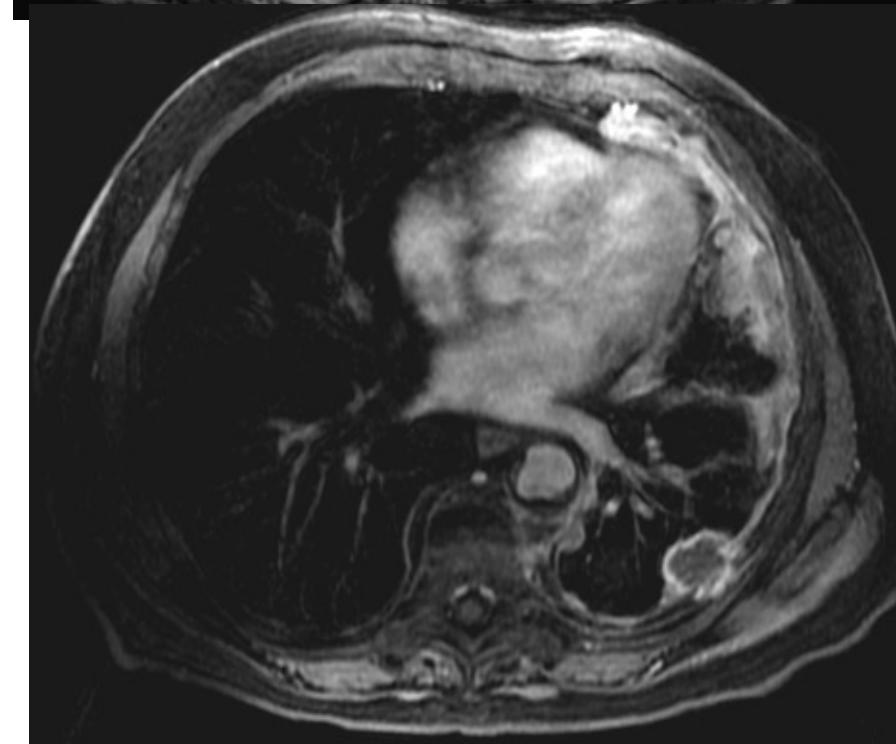
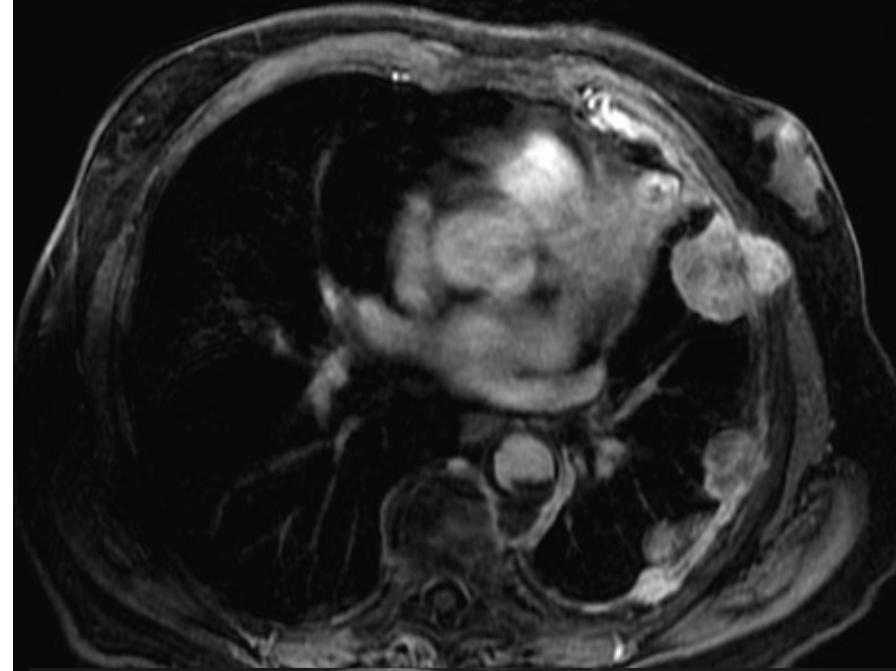
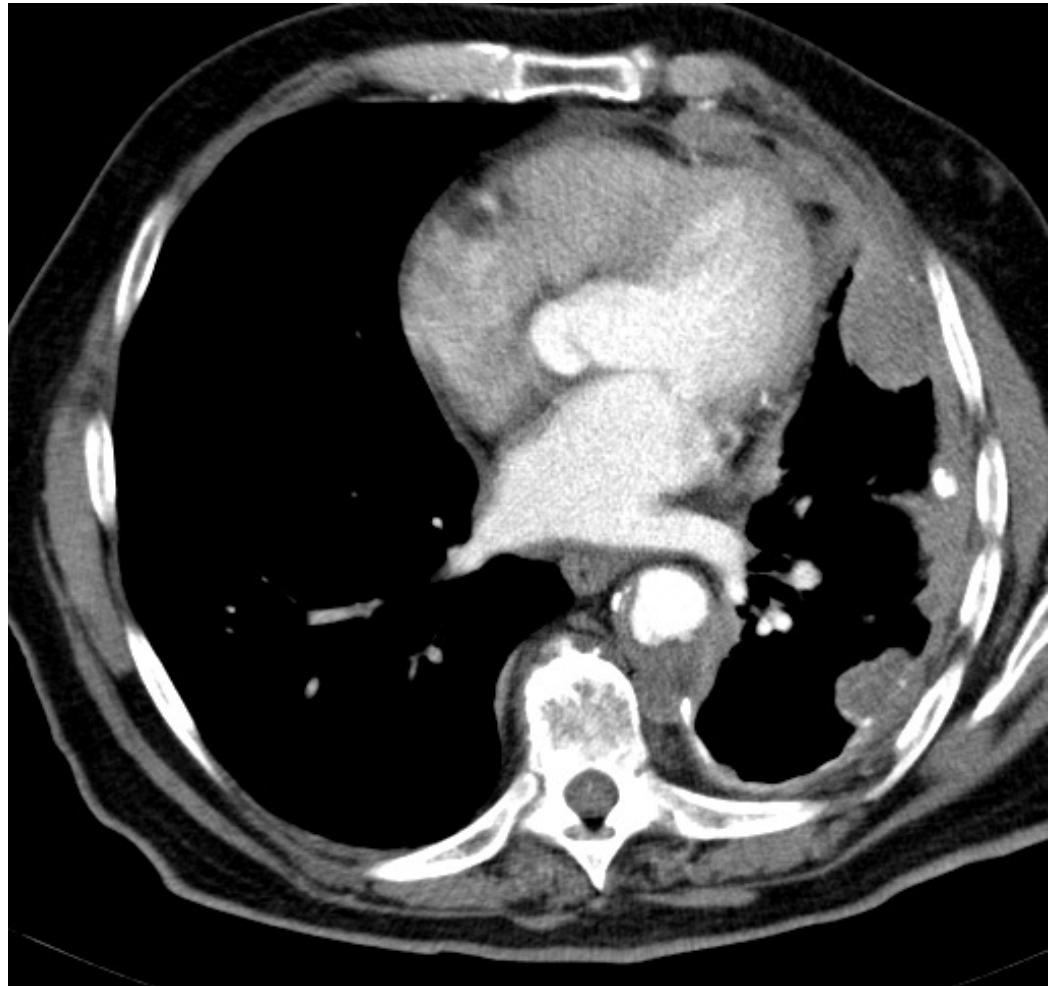
Symptoms



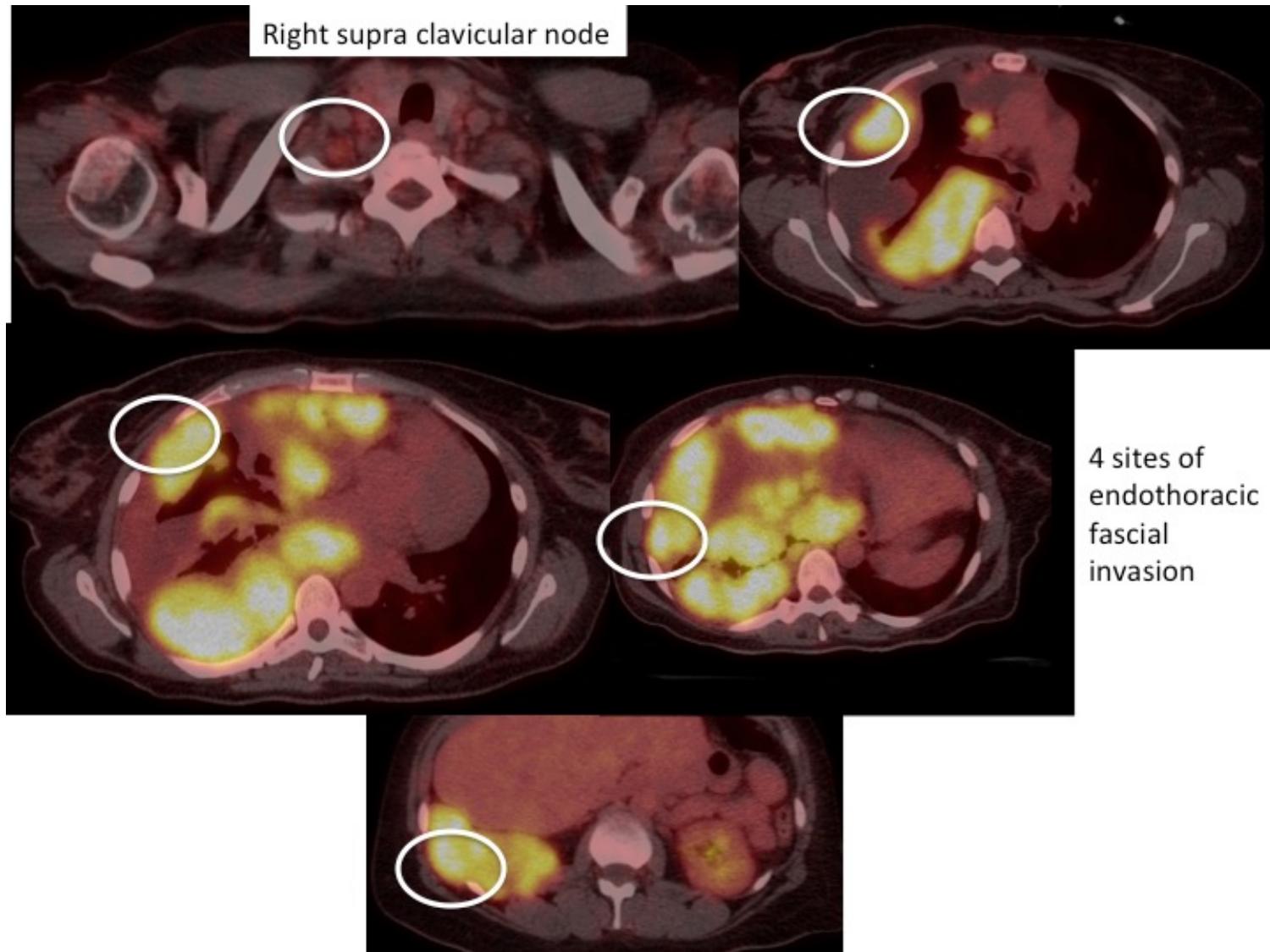
Imaging: Computed tomography scan



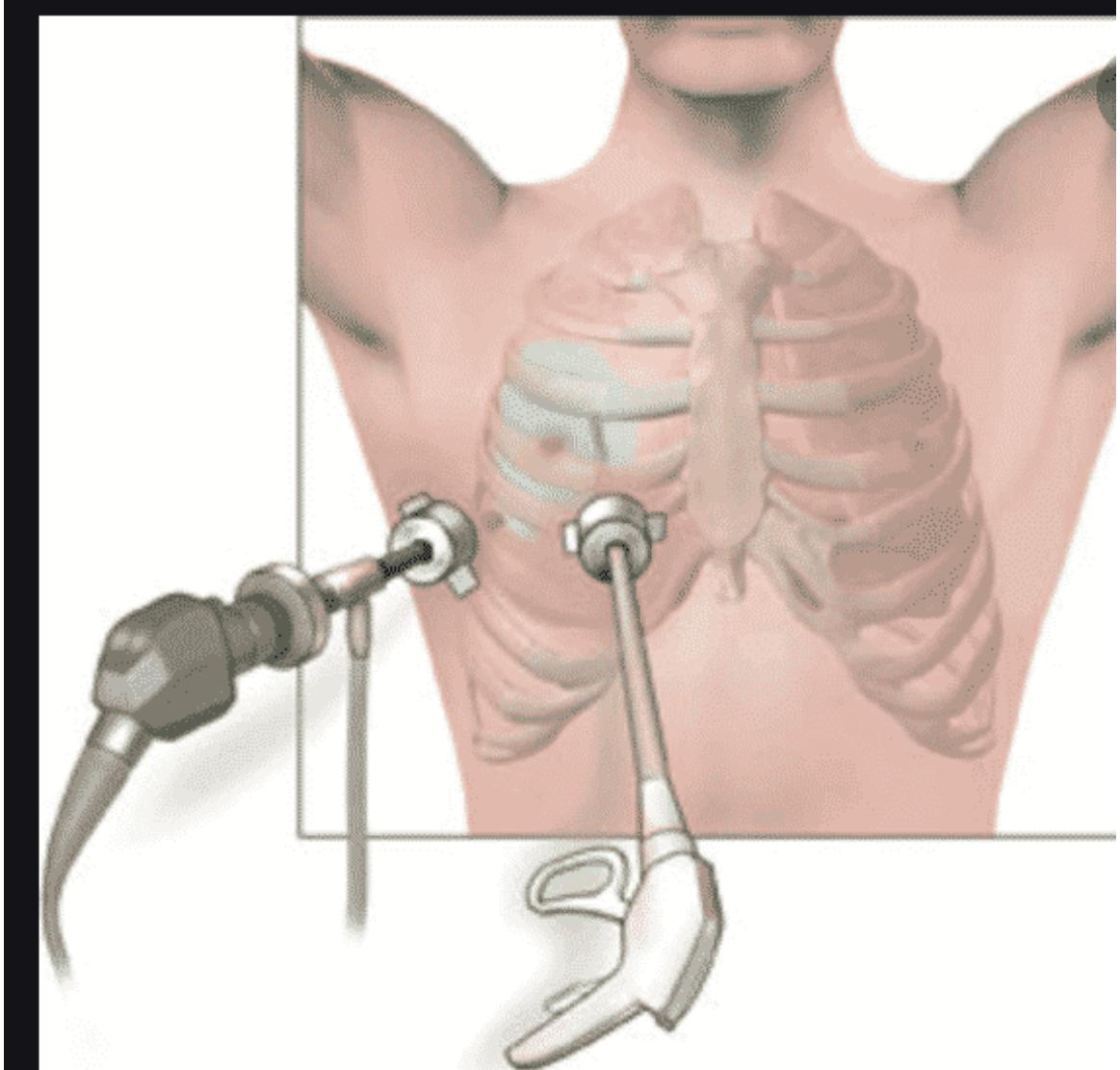
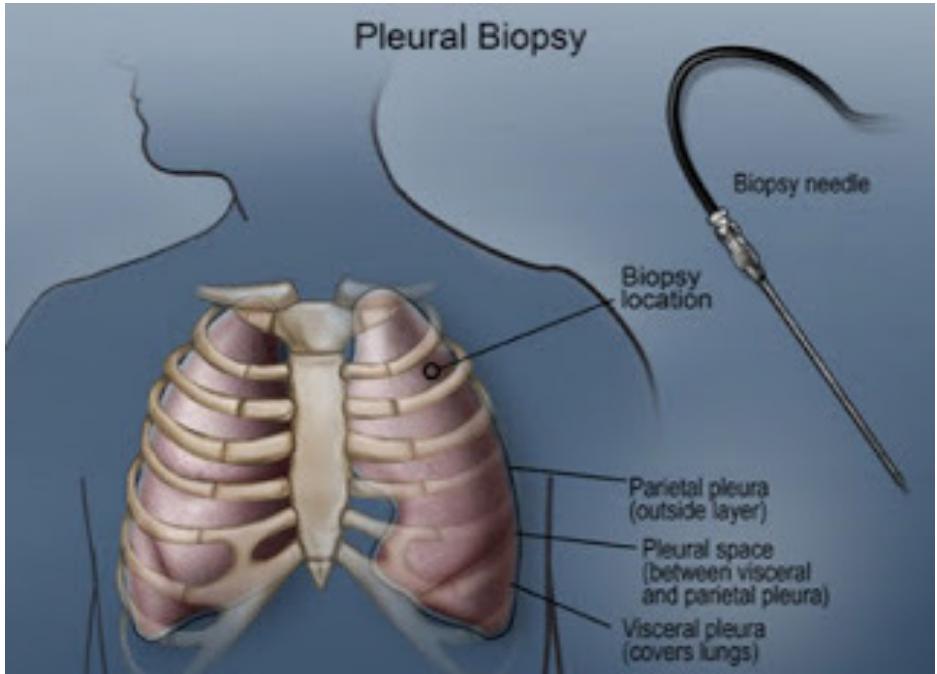
Imaging



Imaging: 18-FDG PET scan



Biopsy



Mesothelioma

Epidemiology and risk factors

Patient pathway

Histology

Guidelines

Staging

Prognostic factors

Mesothelioma: guidelines



Dr. Myriam Locatelli-Sánchez
Coordinatrice

Dr. Pascal Foucher – Dr. Virginie Avrillon
Pr. Arnaud Scherpereel – Pr. Gérard Zalcman
Et le comité de rédaction de l'édition 2021

ERS/ESTS/EACTS/ESTRO GUIDELINES

ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma

Arnaud Scherpereel^{1,2}, Isabelle Opitz³, Thierry Berghmans⁴, Ioannis Psallidas⁵,

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v31–v39, 2015
doi:10.1093/annonc/mdv199
Published online 28 July 2015

Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

P. Baas^{1,2}, D. Fennell³, K. M. Kerr⁴, P. E. Van Schil⁵, R. L. Haas⁶ & S. Peters⁷, on behalf of the ESMO Guidelines Committee*

¹Department of Thoracic Oncology, The Netherlands Cancer Institute, Amsterdam; ²The Academic Medical Center, Amsterdam, The Netherlands; ³Department of Medical Oncology, University of Leicester, Leicester; ⁴Department of Pathology, University of Aberdeen, Aberdeen, UK; ⁵Department of Thoracic and Vascular Surgery, University of Antwerp, Antwerp, Belgium; ⁶Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; ⁷Department of Medical Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Malignant Pleural Mesothelioma

Version 2.2021 — February 16, 2021

NCCN.org

NCCN Guidelines for Patients®

Continue

Mesothelioma

Epidemiology and risk factors

Histology

Staging

Prognostic factors

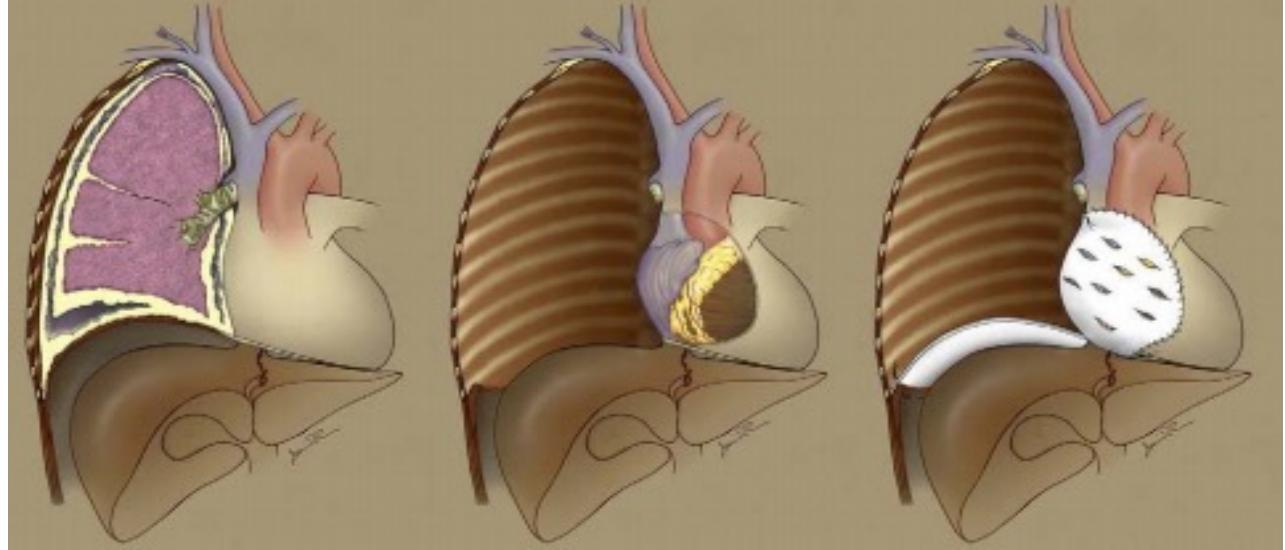
Patient pathway

Guidelines

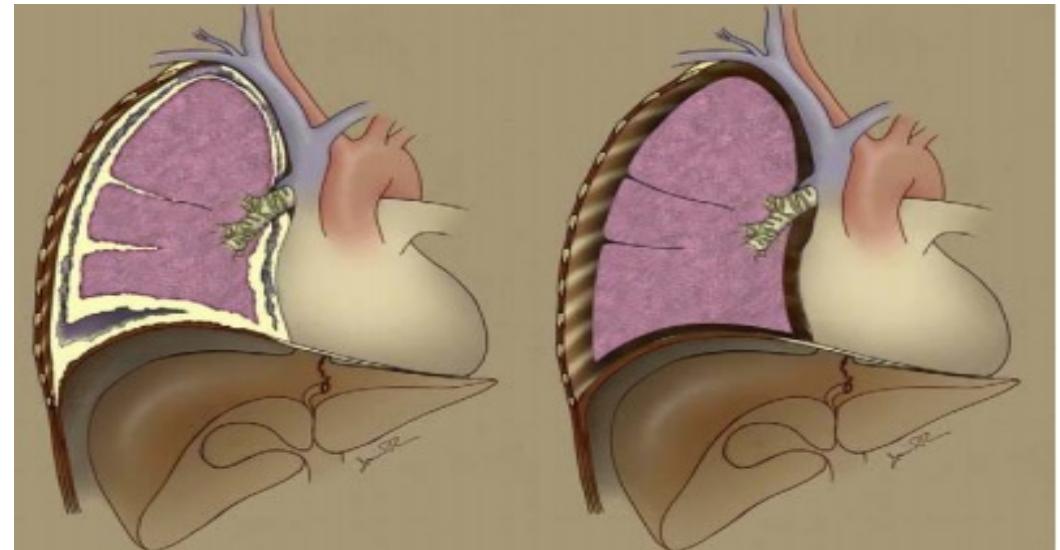
Surgery

Mesothelioma: surgery

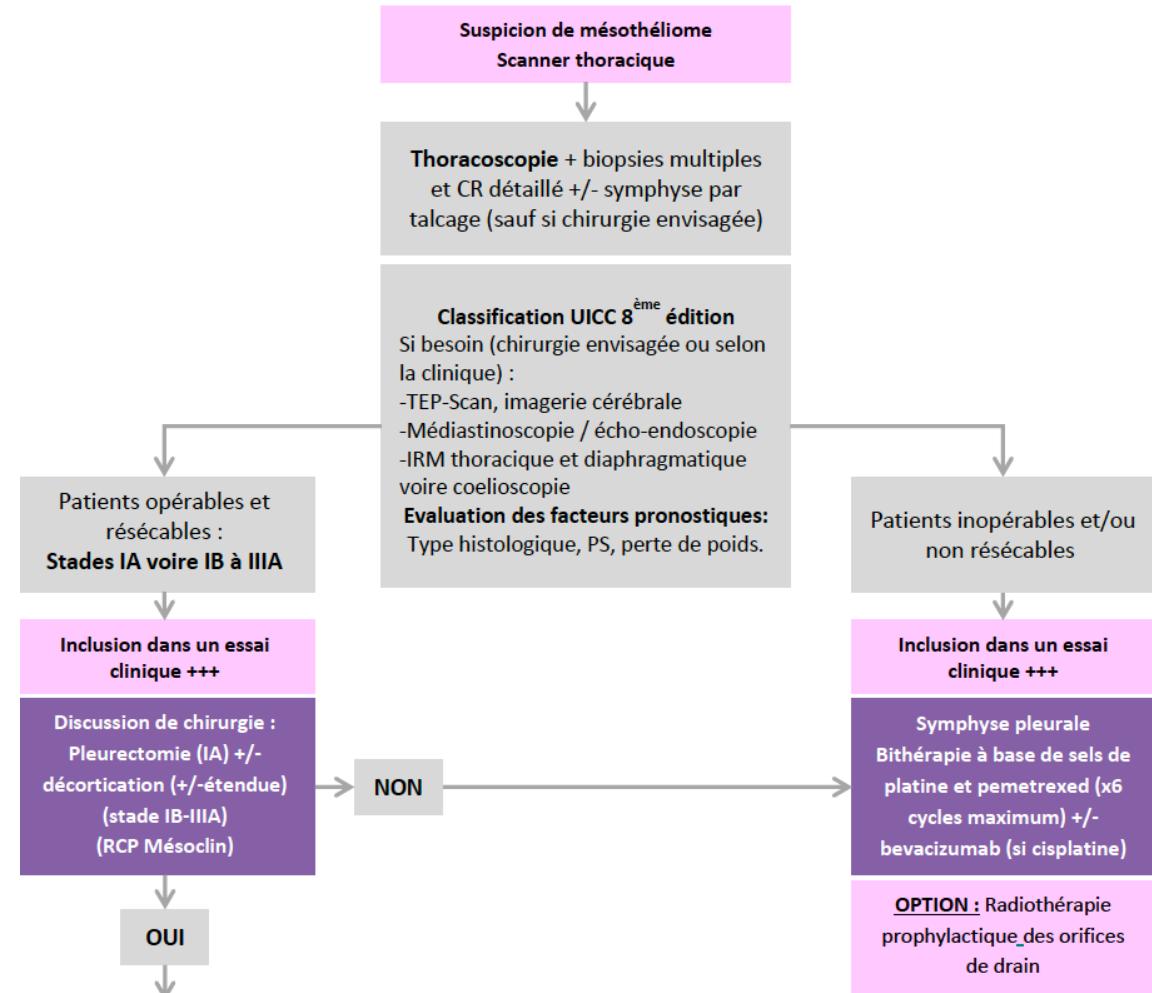
Extrapleural pneumonectomy



Pleurectomy decortication



Référentiel MESOCLIN



Mesothelioma

Epidemiology and risk factors

Histology

Staging

Prognostic factors

Patient pathway

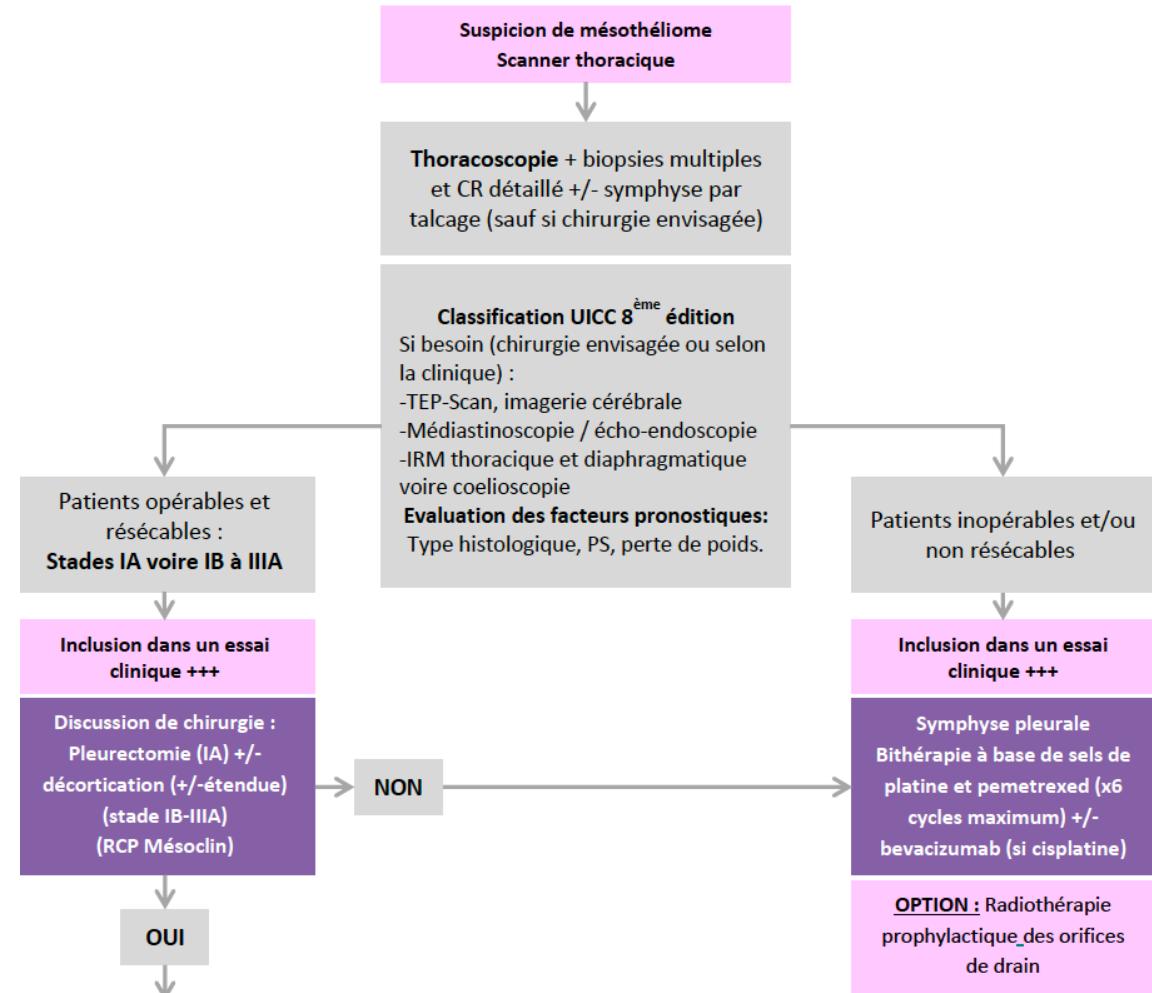
Guidelines

Surgery

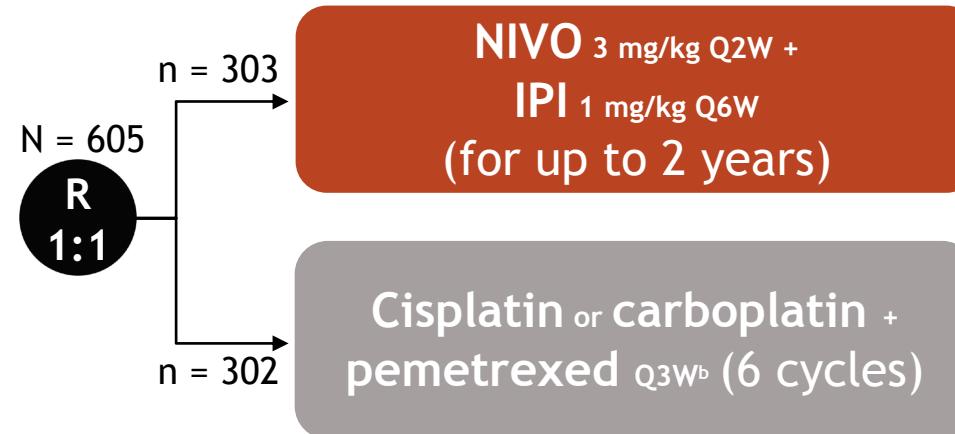
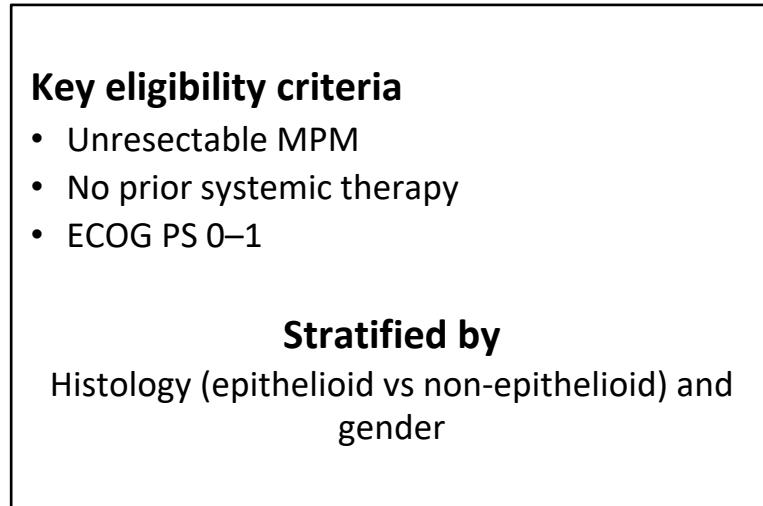
Radiotherapy

Systemic therapies

Référentiel MESOCLIN



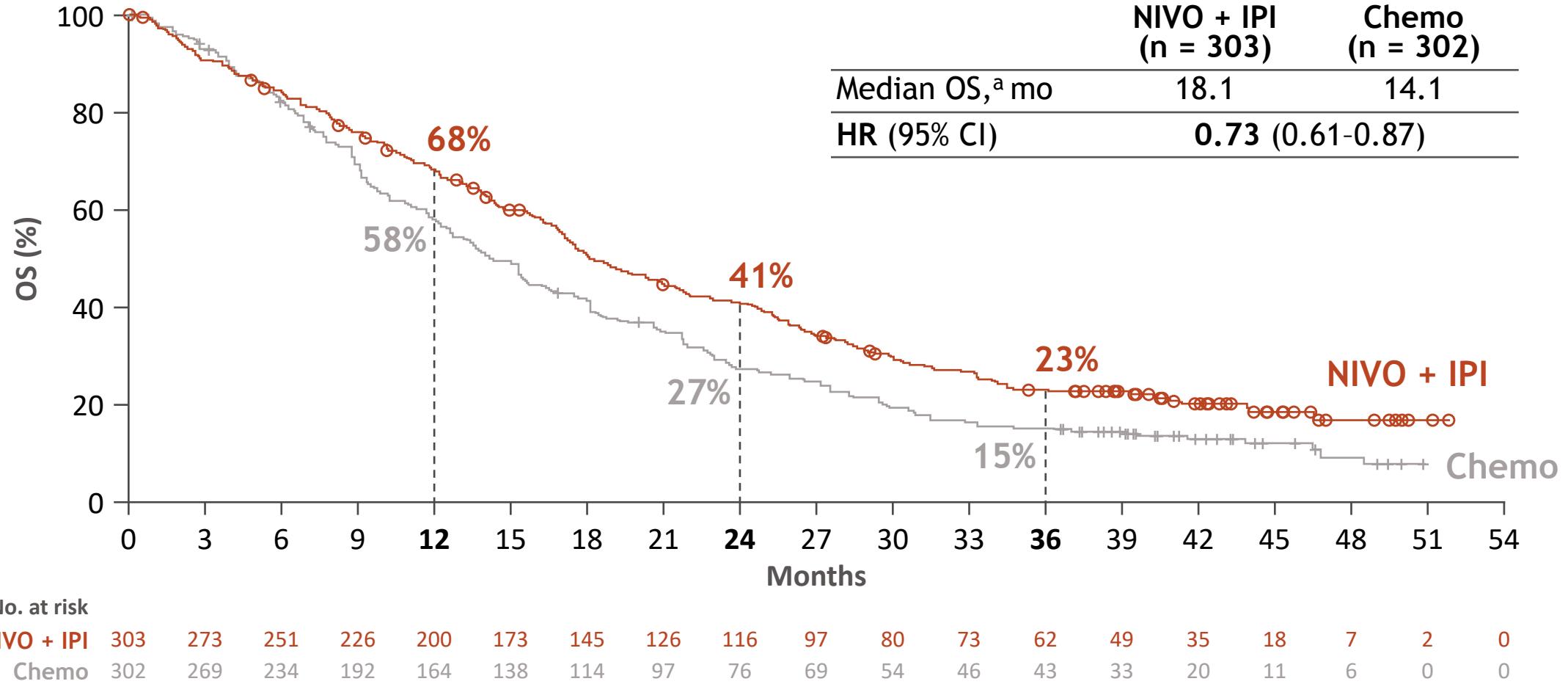
Mesothelioma: First-line immunotherapy as a standard CheckMate-743



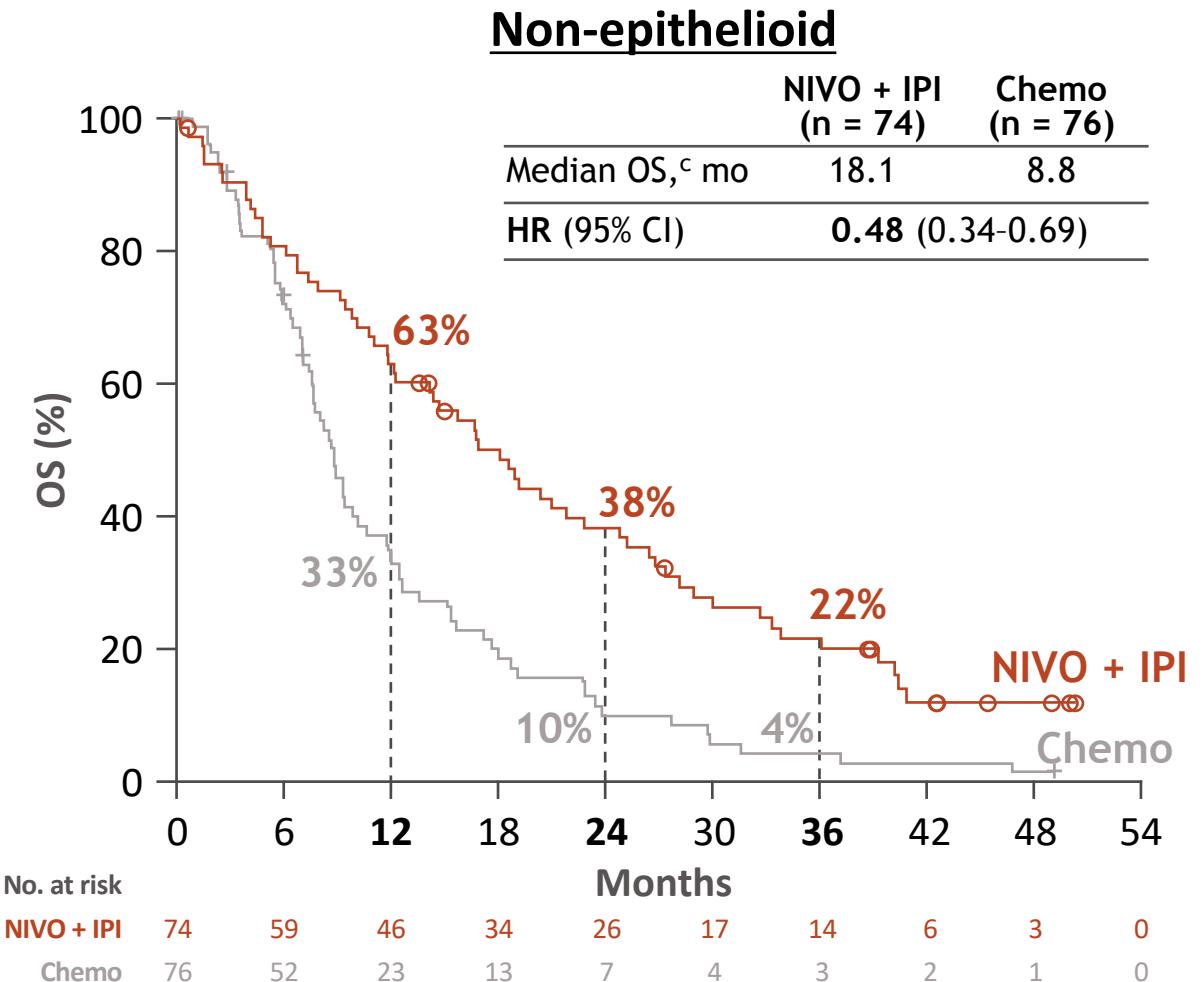
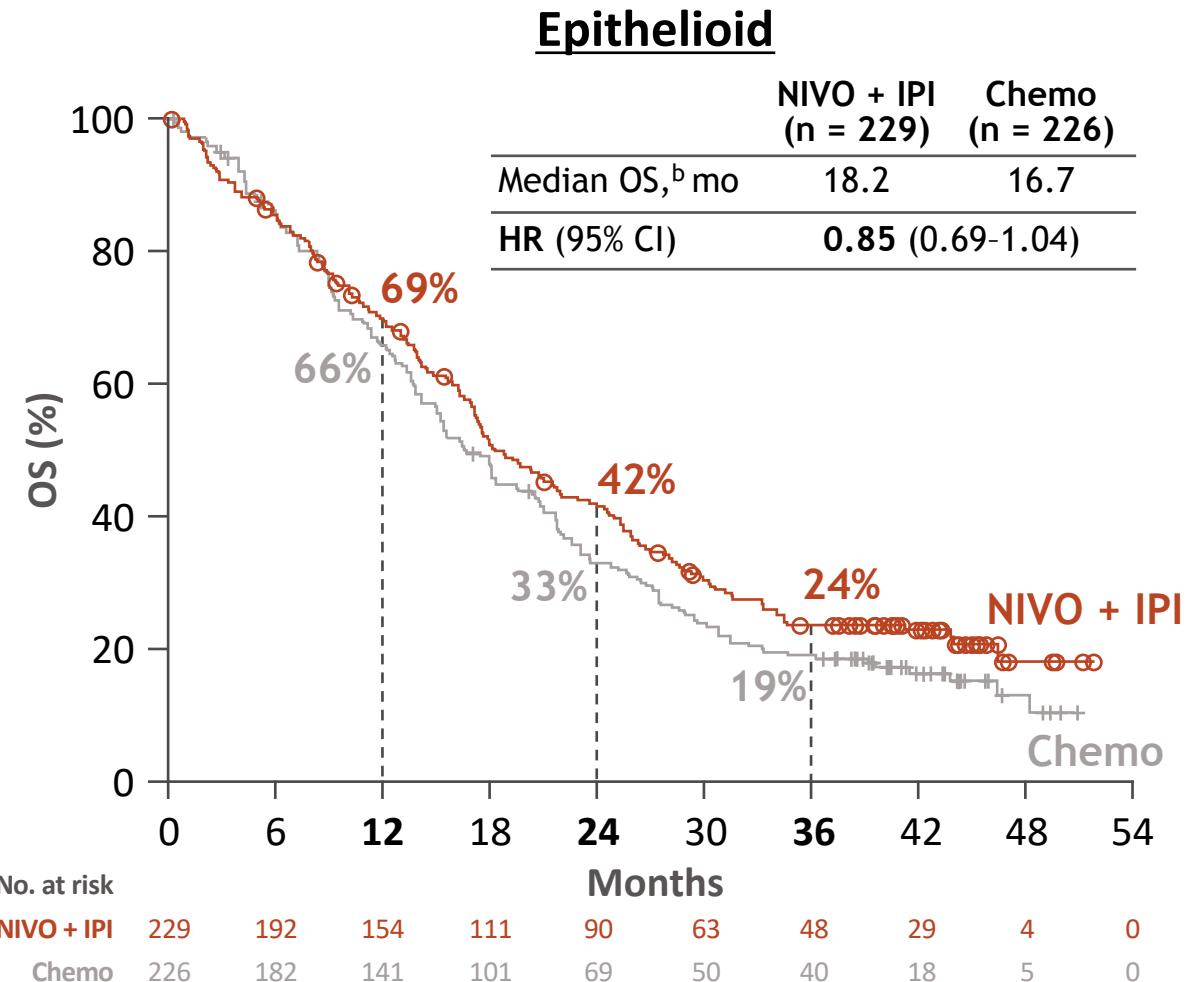
Until disease progression,
unacceptable toxicity,
or for 2 years for
immunotherapy

Primary endpoint	Secondary endpoints	Exploratory endpoints
• OS	• ORR, DCR, and PFS by BICR • Efficacy by PD-L1 ^c expression	• Safety and tolerability • Biomarkers

Mesothelioma: First-line immunotherapy as a standard CheckMate-743



Mesothelioma: First-line immunotherapy as a standard CheckMate-743



Second-line chemotherapy

No standard for 2nd line chemo MPM

vinorelbine

gemcitabine

pemetrexed

cisplatin/pemetrexed

(after initial response/long treatment-free interval)

Author/Year	Regimen	Patients	Stratification?	Survival	RR %
Kindler Command	Defactinib 400mg	372	Yes for merlin	NS	NR
Stopped in October 2015	Placebo	enrolled	status		
Buikhuisen NVALT 5	BSC + thalidomide	111	yes	10.6	NR
<i>Lancet Oncol, 2015</i>	BSC	111		12.9	
Szlosarek	BSC + ADI- PEG20	44	no	390 (days)	NR
<i>J Clin Oncol, 2014 (abstr# 7507)</i>	BSC	24		317 (days)	
Krug Vantage 014	vorinostat	329	no	30.7	NR
<i>Lancet Oncol, 2011</i>	placebo	332		27.1	
Reck	Ranpirnase +doxorubicin	203	yes	11.1	NR
<i>J Clin Oncol, 2009 (abstr# 7507)</i>	doxorubicin	210		10.7	
Jassem	Pemetrexed +BSC	123	yes	8.4	18.7
<i>J Clin Oncol 2008</i>	BSC	120		9.7	1.7

Mesothelioma

Epidemiology and risk factors

Histology

Staging

Prognostic factors

Patient pathway
Guidelines

Surgery

Radiotherapy

Systemic therapies

Merci!



La science pour la santé
From science to health

E-Mail: nicolas.girard2@curie.fr

@nicogirardcurie

@ThoraxParis