Mésothéliome Malin de la Plèvre: Les autres recommandations académiques: quelles différences et pourquoi ?

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Nice St-Paul de Vence 27-29 mars 2019

Déclaration de liens d'intérêt

•Investigateur d'essais cliniques de phases I, II & III des laboratoires Lilly, GSK, Roche, MSD, Merck-Serrono, Pfizer, Astra-Zeneca, Sanofi-Aventis, Pierre Fabre, Borhinger, BMS, Novartis, mais aucune rémunération à titre personnel, l'ensemble des honoraires étant perçu par son Institution (CHU de Caen, Centre de Recherche Clinique puis GH Bichat, CIC), ou jusqu'en juin 2015 l'Association A.D.P, domiciliée au CHU de Caen, conformément à ses statuts puis par la Fondation recherche de l'AP-HP.

SUBVENTION ET AVANTAGES À TITRE COLLECTIF	RÉMUNÉRATION ET AVANTAGES À TITRE PERSONNEL
Lilly, Roche, Pfizer, Astra-Zeneca, Sanofi-Aventis, GSK, BMS, Amgen, Chugaï, Pierre Fabre, Borhinger-Ingelheim, Merck-Serono, Chugai, Novartis, Janssen-Cilag **(Subventions Intergroupe Francophone de Cancérologie Thoracique - IFCT, dont GZ a été président de 2011 à 2015)** Lilly, Roche, Astra-Zeneca, Clovis Oncology, Pfizer, Gsk-bio, Merck, Pierre Fabre: Honoraires pour advisory boards ou présentations versés à **l'Association pour le Développement de la Pneumologie** (ADP, CHU Caen) Astra-Zeneca, Edimark: compensations financières versées à la **Fondation Recherche de l'AP-HP**	Lilly, Roche, Astra-Zeneca, Pfizer, Merck, Pierre Fabre, Borhinger, BMS (**invitations congrès** ASCO, ESMO, ERS, CPLF, WCLC) Honoraires pour participation à des conseils scientifiques/stratégiques (Boards), organisés par les Laboratoires Roche, Lilly, BMS, GSK-Bio, Aventis, Clovis Oncology, Pfizer, Borhinger-Ingelheim, Astra-Zeneca: le montant des sommes perçues ne dépasse pas 10.000 Euros sur les 10 dernières années;

MAIS l'auteur conformément à sa déontologie personnelle, n'a jamais eu et n'aura jamais le moindre partenariat avec l'industrie du Tabac

Les autres recommandations académiques dans le MPM

- ASCO
- BTS
- ESMO
- ERS/EACTS
- NCCN
- SPLF

Société de Pneumologie de Langue Française

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline

Hedy L. Kindler, Nofisat Ismaila, Samuel G. Armato III, Raphael Bueno, Mary Hesdorffer, Thierry Jahan, Clyde Michael Jones, Markku Miettinen, Harvey Pass, Andreas Rimner, Valerie Rusch, Daniel Sterman, Anish Thomas, and Raffit Hassan

JCO 1st May 2018, 36:1343-73

KEY RECOMMENDATIONS

Ponction pleurale explo !

Diagnosis

Recommendation 1.1: Clinicians should perform an initial thoracentesis when patients present with symptomatic pleural effusions and send pleural fluid for cytologic examination for initial assessment for possible mesothelioma (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).!!!!

Non traité dans AURA mais clairement déconseillé dans les recommandations françaises

Recommendation 1.2: In patients for whom antineoplastic treatment is planned, it is strongly recommended that a thoracoscopic biopsy should be performed. This will: (a) enhance the information available for clinical staging; (b) allow for histologic confirmation of diagnosis; (c) enable more accurate determination of the pathologic subtype of mesothelioma (epithelial, sarcomatoid, biphasic); and (d) make material available for additional studies (eg, molecular profiling) (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2.1: When performing a thoracoscopic biopsy, the minimal number of incisions (two or fewer) is recommended and should ideally be placed in areas that would be used for subsequent definitive resection to avoid tumor implantation into the chest wall (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Thoracoscopie diagnostique recommandée et allusion au risque de meta de reperméation

Mais dans la perspective…chirurgicale radicale

Recommendation 2.0: Cytologic evaluation of pleural fluid can be an initial screening test for mesothelioma, but it is not a sufficiently sensitive diagnostic test. Whenever definitive histologic diagnosis is needed, biopsies via thoracoscopy or CT guidance offer a better opportunity to reach a definitive diagnosis (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Non traité dans AURA mais cyto clairement déconseillée dans les recommandations françaises

Recommendation 3.0: Histologic examination should be supplemented by immunohistochemistry using selected markers expected to be positive in mesothelioma (eg, calretinin, keratins 5/6, and nuclear WT1) as well as markers expected to be negative in mesothelioma (eg, CEA, EPCAM, Claudin 4, TTF-1). These markers should be supplemented with other markers that address the differential diagnosis in that particular situation (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.1: Mesothelioma should be reported as epithelial, sarcomatoid, or biphasic, because these subtypes have a clear prognostic significance (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.2: In surgical, thoracoscopic, or open pleural biopsies with sufficient tissue, further subtyping and quantification of epithelial versus sarcomatoid components of mesothelioma may be undertaken (Type of recommendation: informal consensus; Strength of recommendation: moderate).

en accord avec AURA/SPLF: MESOPATH

Recommandations
-Le diagnostic histologique du mésothéliome pleural malin doit être effectué sur des prélèvements biopsiques de taille suffisante (thoracoscopie sauf contre-indications). L'examen extemporané n'est pas accepté pour ce diagnostic. -Le diagnostic morphologique doit toujours être complété par une étude immunohistochimique confirmative. -Le diagnostic histopathologique doit être confirmé par l'expertise du réseau MESOPATH après transmission à un expert régional du réseau, dans l'optique d'une indemnisation par le FIVA et/ou la CPAM.

Recommendation 2.1: The current AJCC/UICC staging classification remains difficult to apply to clinical staging with respect to both T and N components and thus may be imprecise in predicting prognosis. Physicians should recognize that in patients with clinical stage I/II disease, upstaging may occur at surgery (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Vive le pragmatisme US !!

Recommendation 3.1: The optimal approach to mesothelioma measurement requires the expertise of a radiologist to identify measurement sites on CT as per modified RECIST for mesothelioma. This approach requires calculating the sum of up to six measurement sites with at least 1 cm thickness measured perpendicular to the chest wall or mediastinum with no more than two sites on each of three CT sections separated by at least 1 cm axially (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.2: Assessment of tumor volume by CT scan may enhance clinical staging and provide prognostic information but remains investigational and thus is not recommended (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.3: It is recommended that tumor response classification be determined based on RECIST criteria from the comparisons of these sums across serial CT scans (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

comme dans AURA (où moins développé): RECIST méso +++

Chemotherapy

Recommendation 1.1: Chemotherapy should be offered to patients with mesothelioma because it improves survival and quality of life (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.2: In asymptomatic patients with epithelial histology and minimal pleural disease who are not surgical candidates, a trial of close observation may be offered prior to the initiation of chemotherapy (Type of recommendation: informal consensus; Strength of recommendation: moderate).

AURA

-L'introduction précoce de la chimiothérapie dans les formes non résécables paraît préférable à une mise en route différée à l'apparition des symptômes chez les patients non symptomatiques au moment du diagnostic.

Recommendation 2.1: The recommended first-line chemotherapy for patients with mesothelioma is pemetrexed plus platinum. However, patients should also be offered the option of enrolling in a clinical trial (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong)

Recommendation 3.1: The addition of bevacizumab to pemetrexed-based chemotherapy improves survival in select patients and therefore may be offered to patients with no contraindications to bevacizumab. The randomized clinical trial demonstrating benefit with bevacizumab used cisplatin/pemetrexed; data with carboplatin/pemetrexed plus bevacizumab are insufficient for a clear recommendation (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: moderate)

Recommendation 4.0: In patients who may not be able to tolerate cisplatin, carboplatin may be offered as a substitute for cisplatin (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 5.1: Retreatment with pemetrexed-based chemotherapy may be offered in pleural mesothelioma patients who achieved durable (> 6 months) disease control with first-line pemetrexed-based chemotherapy (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Re-challenge par pemetrexed aussi abordé dans AURA

-En seconde ligne, il n'y a pas de traitement validé. Néanmoins, la reprise d'un schéma à base de pemetrexed peut être envisagée en cas d'intervalle libre prolongé (consensus d'experts).

Recommendation 5.2: Given the very limited activity of second-line chemotherapy in patients with mesothelioma, participation in clinical trials is recommended (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 5.3: In patients for whom clinical trials are not an option, vinorelbine may be offered as second-line therapy (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate). ???

Recommendation 6.1: In asymptomatic patients with epithelial mesothelioma and a low disease burden who are not surgical candidates, a trial of expectant observation may be offered before initiation of systemic therapy (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 6.3: There is insufficient evidence to support the use of pemetrexed maintenance in mesothelioma patients, and thus it is not recommended (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: strong).

Non Précisé dans AURA: erreur !

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Surgical Cytoreduction

Recommendation 1.1: In selected patients with early-stage disease, it is strongly recommended that a maximal surgical cytoreduction should be performed (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong). ???!!

Recommendation 1.2: Maximal surgical cytoreduction as a single modality treatment is generally insufficient; additional antineoplastic treatment (chemotherapy and/or radiation therapy) should be administered. It is recommended that this treatment decision should be made with multidisciplinary input involving thoracic surgeons, pulmonologists, medical and radiation oncologists (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

1. Notion de "résécabilité" chirurgicale du mésothéliome pleural malin

La possibilité d'effectuer une résection complète d'un mésothéliome pleural malin est très discutable, voire illusoire sur le plan microscopique. Une première difficulté provient du fait que le staging pré-opératoire sous-estime fréquemment l'extension réelle de la maladie. La seconde difficulté est liée à l'absence de consensus sur les modalités et l'intérêt en termes de survie d'une résection chirurgicale du mésothéliome pleural malin, ce qui implique que la prise en charge des patients va notablement différer d'une équipe multidisciplinaire à l'autre. La chirurgie va donc être effectuée dans l'optique d'une cytoréduction tumorale maximale, l'importance du volume tumoral résiduel ayant une signification pronostique ; la pleurectomie-décortication +/- élargie, chirurgie à visée de réduction tumorale, est envisageable dans les stades I, II et IIIA de la nouvelle classification, lorsque l'atteinte de la plèvre viscérale est focale, non confluente, sans invasion majeure des scissures, après avis RCP MESOCLIN. La pleuro-pneumonectomie élargie est associée à une morbidité-mortalité importante et ne doit être discutée exceptionnellement que dans le cadre d'une RCP pluridisciplinaire nationale MESOCLIN impliquant des équipes expérimentées chez des patients jeunes et médicalement aptes à tolérer une pneumonectomie.

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Recommendation 1.3: Patients with transdiaphragmatic disease, multifocal chest wall invasion, or histologically confirmed contralateral mediastinal or supraclavicular lymph node involvement should undergo neoadjuvant treatment before consideration of maximal surgical cytoreduction. Contralateral (N3) or supraclavicular (N3) disease should be a contraindication to maximal surgical cytoreduction (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.1: Patients with histologically confirmed sarcomatoid mesothelioma should not be offered maximal surgical cytoreduction (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.2: Patients with ipsilateral histologically confirmed mediastinal lymph node involvement should only undergo maximal surgical cytoreduction in the context of multimodality therapy (neoadjuvant or adjuvant chemotherapy). Optimally, these patients should be enrolled in clinical trials. (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Indications éventuelles bien délimitées ici. Non abordées dans AURA

Recommendation 3.0: Maximal surgical cytoreduction involves either extrapleural pneumonectomy (EPP) or lung-sparing options (pleurectomy/decortication [P/D], extended P/D). When offering maximal surgical cytoreduction, lung-sparing options should be the first choice, due to decreased operative and long-term risk. EPP may be offered in highly selected patients when performed in centers of excellence (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

EPP reste dans les recommandations US !!!

Recommendation 4.1.2: In patients who have a symptomatic pleural effusion, who are PS 2 or greater, or in whom a maximal cytoreduction cannot be performed (due to disease extent or comorbid conditions), palliative approaches such as a tunneled permanent catheter placement or thoracoscopic exploration with partial resection and/or pleurodesis should be offered. In the latter case, additional biopsy to confirm pathologic diagnosis should be performed during the procedure. If the patient is being evaluated for investigational therapy, material for additional studies (eg, molecular and/ or immunologic profiling) should be obtained. (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Radiation Therapy

Recommendation 1.1: Prophylactic irradiation of intervention tracts should generally not be offered patients to prevent tract recurrences (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: moderate).

AURA 2018/19

OPTION : Une irradiation prophylactique (3x7Gy) dans les 6 semaines maximum après le geste pleural (drainage, thoracoscopie, thoracotomie) peut être proposée pour réduire la fréquence des nodules thoraciques de perméation. On l'envisagera notamment après une chirurgie du MPM avec mise en évidence d'un envahissement avéré (histologiquement) des orifices thoraciques précédents.

Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial

Lancet Oncol 2016
Published Online
June 23, 2016
http://dx.doi.org/10.1016/S1470-2045(16)30095-X

Amelia O Clive, Hazel Taylor, Lee Dobson, Paula Wilson, Emma de Winton, Niki Panakis, Justin Pepperell, Timothy Howell, Samuel A Stewart, Erika Penz, Nikki Jordan, Anna J Morley, Natalie Zahan-Evans, Sarah Smith, Timothy J P Batchelor, Adrian Marchbank, Lesley Bishop, Alina A Ionescu, Mike Bayne, Samantha Cooper, Anthony Kerry, Peter Jenkins, Elizabeth Toy, Vallipuram Vigneswaran, James Gildersleve, Merina Ahmed, Fiona McDonald, Mick Button, Conrad Lewanski, Charles Comins, Muthukumar Dakshinamoorthy, Y C Gary Lee, Najib M Rahman, Nick A Maskell

- **Mesotheliome Pleural Malin (MPM)**
- Histologiquement prouvé
- PS= 0-3
- Chimio-naïf ou pas
- Age<78
- drain, pleuroscopie medicale ou chir, thoracotomie, pleur-X

R 1:1

A

RT Immédiate des orifices
(dans les 42 jours)
3x 7 Gys + bolus cutané
7cmx 7cm (3cm de marge circonférencielle)
électrons hte énergie(>12MeV)

B

RT à l'émergence d'un nodule
3x 7 Gys + bolus cutané
7cmx7cm dans les 42 jours suivant l'émergence

H: décroitre de **15%** dans le bras RT différée à **2%** l'incidence des métastases de reperméation

=>102 patients x 2 pour puissance = 90%, α=5%, avec 3 % de perdus de vue

Interpretation Routine use of prophylactic radiotherapy in all patients with mesothelioma after large-bore thoracic interventions is not justified.

OR= 0,51; p=0,14

Prophylactic radiotherapy to prevent procedure-tract metastases

Amelia Clive and colleagues' article[1] in *The Lancet Oncology* reports on a randomised trial comparing the use of early systematic radiotherapy for the prevention of procedure-tract metastases (PTM) to deferred radiotherapy in patients with malignant pleural mesothelioma. We think that the main conclusion of their study, emphasised by the accompanying Comment title,[2] could

in eight patients, and three other patients receiving their first fraction beyond the 42-day limit, which is already twice the delay used in the seminal study by Boutin and colleagues.[7] Hence, the per-protocol prespecified analysis clearly showed a significant difference of PTM from 16 (16%) of 99 patients in the deferred radiotherapy group to five (6%) of 84 patients in the immediate radiotherapy group(p=0·037). Supporting this finding, the mean volume of PTM in the deferred radiotherapy group was larger by 1·5 cm, although the distance between the procedure site and the edge of

GZ participated in advisory boards for Roche, Eli Lilly, Bristol-Myers Squibb, Clovis Oncology, AstraZeneca, Boehringer Ingelheim, and Pfizer, all outside the submitted work, and received a research grant from Roche. AS reports grants from Roche. He was an advisory board member for Merck Sharp & Dohme, Bristol-Myers Squibb, Seattle Genetics, Roche, and AstraZeneca; he received research grants from Amgen, Teva, and Roche and received travel grants from Boehringer Ingelheim, all outside the submitted work. SB declares no competing interests.

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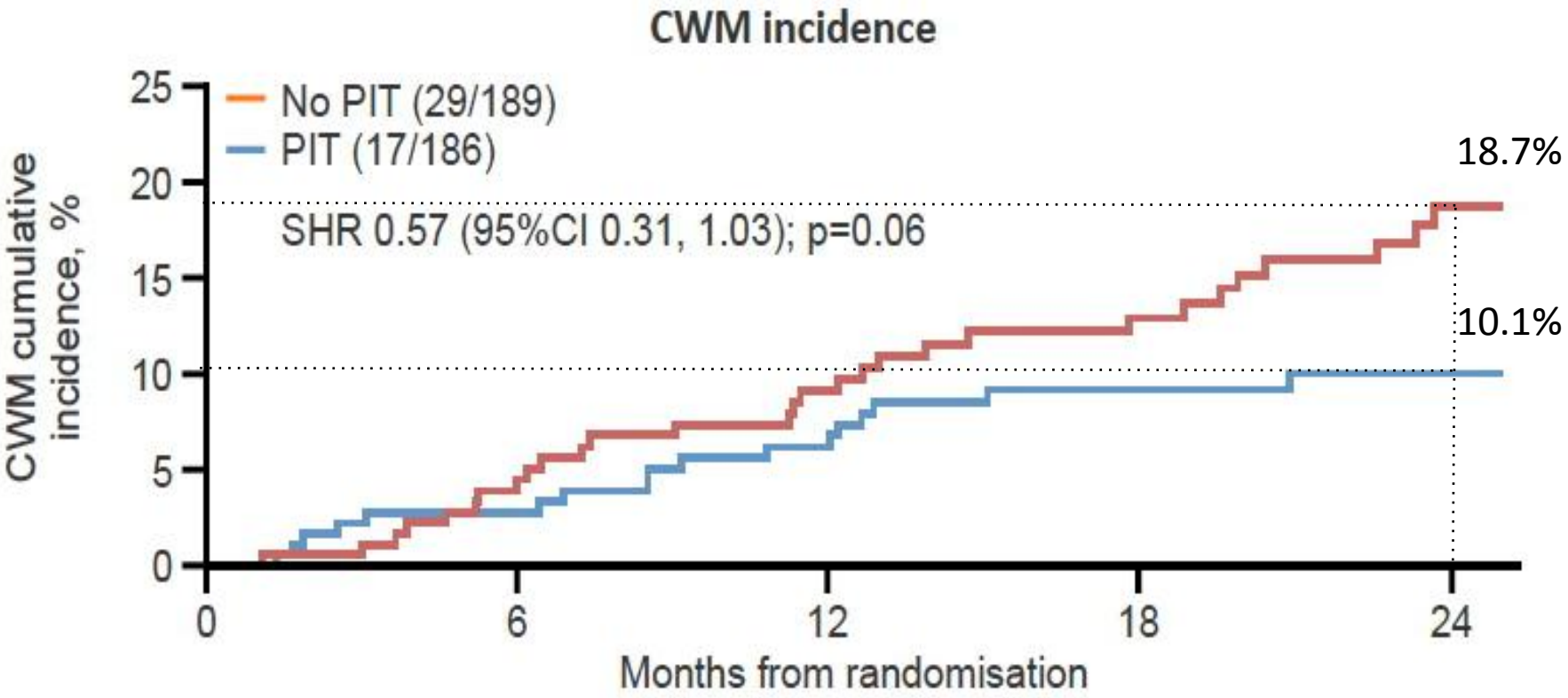
Partly SMART or partly flawed ?

Zalcman G., Brosseau S, Scherpereel A. Lancet Oncol 2016

11% de violations majeures de protocole ! (> 42j, < 7cm, meV < 12meV)

2ème essai britannique: WCLC 2017 : 375 patients randomized, primary endpoint was….6 months
« large thoracotomies, needle biopsy sites were excluded…only VATS, chest drains »
Cumulative incidence at 24 months was 18.7% vs. 10.1%

OA 02.03: Prophylactic Irradiation of Tracts (PIT) in Patients with Pleural Mesothelioma: Results of a Multicentre Phase III Trial – Bayman N, et al



- The cumulative incidence of CWM at 6 or 12 months was 3.2% with PIT vs. 5.3% without at 6 months and 8.1% vs. 10.1% at 12 months, respectively
- The most common radiotherapy-related AE in the PIT arm was mild skin toxicity

Bayman N et al. J Thorac Oncol 2017;12(suppl):Abstr OA 02.03

British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma

Ian Woolhouse,[1] Lesley Bishop,[2] Liz Darlison,[3] Duneesha De Fonseka,[4] Anthony Edey,[5] John Edwards,[6] Corinne Faivre-Finn,[7] Dean A Fennell,[8] Steve Holmes,[9] Keith M Kerr,[10] Apostolos Nakas,[11] Tim Peel,[12] Najib M Rahman,[13] Mark Slade,[14] Jeremy Steele,[15] Selina Tsim,[16] Nick A Maskell[17]

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Section 11: Systemic anticancer treatment Recommendations

- Offer patients with MPM with good PS (WHO 0-1) first-line therapy with cisplatin and pemetrexed. Where licensed (not presently in the UK), bevacizumab should be added to this regime. Raltitrexed is an alternative to permetrexed. Grade A.
- Do not offer pemetrexed or vorinostat as second-line treatment for patients with MPM. Grade A.

Good practice points

- ✓ Where cisplatin is contraindicated, or has adverse risk, offer carboplatin in combination with pemetrexed.
- ✓ First-line clinical trials are an appropriate option for patients with good PS and are recommended above any other option for second-line treatment, providing the patient is of adequate PS.

Research recommendations

The role of immunotherapy in MPM should be further assessed in large phase III randomised controlled trials (RCTs).

Section 10: The role of Recommendations

AURA: Pleuroscopie 1ère

- Do not offer VATS-PP over talc pleurodesis in MPM. Grade A.
- Do not offer Extra-Pleural Pneumonectomy (EPP) in MPM. Grade B.
- Do not offer extended pleurectomy decortication (EPD) outside of a clinical trial. Grade D.

Section 12: Radiotherapy Recommendations

??!!!

- Do not offer prophylactic radiotherapy to chest wall procedure tracts. Grade A.
- Do not offer preoperative or postoperative radiotherapy in MPM. Grade A.
- Do not offer hemithorax radiotherapy for MPM. Grade D.
- Consider palliative radiotherapy for localised pain in MPM, where the pain distribution matches areas of underlying disease. Grade D.

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Table 1 SIGN levels of evidence

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort or studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg, case reports, case series
4	Expert opinion

Table 2 SIGN grades of recommendations

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+
√	*Good practice points* Recommended best practice based on the clinical experience of the guideline development group

Chirurgie du Mesotheliome pour les Britanniques

Evidence statements cf. mauvais essai UK

VAT-PP has no effect on overall survival and results in increased complications and longer hospital stay than talc pleurodesis. Level 1+.

EPP does not improve survival when added to treatment with chemoradiotherapy. Level 1+.

EPD may result in lower perioperative mortality than EPP. Level 1−.

Quality of life and lung function may not deteriorate in patients selected to undergo pleurectomy decortication. Level 2−.

Recommendations

- Do not offer VATS-PP over talc pleurodesis in MPM. Grade A.
- Do not offer EPP in MPM. Grade B.
- Do not offer EPD outside of a clinical trial. Grade D.

Table 15 Randomised phase III trials in first-line treatment of malignant pleural mesothelioma

Trial	Year of publication	Treatment arms	OS (months)	P value
Vogelzang[115]	2003	P/C vs C	12.1 vs 9.3	0.020
van Meerbeeck[116]	2005	R/C vs C	11.4 vs 8.8	0.048
Muers[117]	2008	ASC+ctx vs ASC	8.5 vs 7.6	0.290
Zalcman[119]	2015	P/C/B vs P/C	18.8 vs 16.1	0.017

ASC, active symptom control; B, bevcizumab; C, cisplatin; ctx, chemotherapy; OS, overall survival; P, pemetrexed; R, ralitrexed.

- For patients with MPM with good PS, first-line chemotherapy with cisplatin and pemetrexed leads to longer survival than cisplatin alone. Evidence level 1 + +.
- For patients with MPM with good PS, first-line therapy with cisplatin and pemetrexed and bevacizumab leads to longer survival than cisplatin and pemetrexed alone. Evidence level 1 + +.
- Carboplatin in combination with pemetrexed is a safe and effective alternative to cisplatin in combination with pemetrexed. Evidence level 3.
- Second-line pemetrexed does not improve sur
previously treated with first-line chemotherapy regimens that did not include pemetrexed. Evidence level 1+.

 # AURA: cf. Ceresoli et al.
cf. EAP Pemetexed

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. Fennell[3], K. M. Kerr[4], P. E. Van Schil[5], R. L. Haas[6] & S. Peters[7], on behalf of the ESMO Guidelines Committee*

Recommendation 1

Diagnostic procedures in MPM should encompass at least

- *Occupational history with emphasis on asbestos exposure [II, A]*
- *CT scanning of the thorax [II, A]*
- *In all patients who have a unilateral pleural thickening, with or without fluid and/or calcified asbestos plaques, efforts should be made to obtain a pathological specimen, as there are no specific clinical features of MPM [II, A]*
- *There is no place for screening of persons exposed to asbestos [IV, B]*
- *Tumour markers cannot distinguish MPM [II, B]*

Recommendation 3

Staging for every patient with a confirmed diagnosis of MPM

- *In the absence of a uniform, robust and validated staging system, experts advocate the use of the most recent TNM-based IMIG/UICC classification [III, B].*
- *The use of MRI is only recommended in special situations when tumour delineation is necessary [II, B].*
- *The use of PET scanning is limited and can be used for localisation of tumour sites, distant metastases or early response to treatment, as part of a study protocol [III, B].*

Recommendation 2

A. Definitive diagnosis of MPM on effusion cytology specimens

- *Effusion cytology for definitive diagnosis of MPM remains a controversial topic and is still generally not recommended [IV, C].*
- *If effusion cytology is frankly malignant, the diagnosis may be strongly suggested but confirmation by biopsy, if possible, is recommended [A, no level of evidence].*
- *IHC is invaluable to characterise the nature of atypical effusion cells and sample preparation to facilitate IHC should be carried out if at all possible [A, no level of evidence].*

Plus proche de AURA/MESOCLIN dans l'esprit

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v31–v39, 2015
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Recommendation 4

The first- and second-line treatment of unresectable mesothelioma

- *Anti-folate/platinum doublet is the only approved standard of care [I, A].*
- *Maintenance therapy (switch or continuation) has not yet improved the OS and patients should be included in these studies [II, A].*
- *Patients in good condition should be recommended to join studies in second line [II, A].*

Pas de maintenance Pemetrexed Clairement affirmé….

Mais pas de Bevacizumab suggéré !!! (2015, avant MAPS)

second-line therapy for mesothelioma

There is currently no second-line standard of care. Phase III evaluation of pemetrexed monotherapy in previously treated patients was not associated with longer survival when compared with best supportive care (BSC). Post-study chemotherapy has been shown to be associated with significantly longer survival, with an adjusted hazard ratio of 0.56 [27]. Single agent vinorelbine has shown useful activity in phase II trials [28, 29], demonstrating a trend towards longer survival as was seen in the first-line study (MSO1) [30].

Pas de standard 2ème ligne et notamment pas de re-challenge Pemetrexed… Alors que vinorelbine sugggérée sur la foi de 2 phases 2 non comparatives !!

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. Fennell[3], K. M. Kerr[4], P. E. Van Schil[5], R. L. Haas[6] & S. Peters[7], on behalf of the ESMO Guidelines Committee*

Recommendation 5

RT can be considered in the following cases

- *For palliation of pain related to tumour growth, RT can be considered [II, A].*
- *The use of RT to prevent growth in drainage tracts is not proved to be useful [III, A].*
- *RT can be given in an adjuvant setting after surgery or chemo-surgery to reduce the local failure rate. However, no evidence is available for its use as a standard treatment [II, A].*
- *When postoperative RT is applied, strict constraints must be adhered to in order to avoid toxicity to neighbouring organs, and special, tissue sparing, techniques should be used [II, A].*

En résumé, très daté,
A réactualiser ☺

Surgery

Recommendation 6

The indications for surgery are

Très « jésuite » ☺

- *For palliation of pleural effusions when chest tube drainage is not successful [II, A]*
- *To obtain diagnostic samples of tumour tissue and to stage the patient [II, A]*
- *To be part of a multimodality treatment, preferably as part of a study [II, A]*
- *To perform a macroscopic complete resection by means of P/D or EPP [III, C]*

Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma

Eur respir J 2010

A. Scherpereel, P. Astoul, P. Baas, T. Berghmans, H. Clayson, P. de Vuyst, H. Dienemann, F. Galateau-Salle, C. Hennequin, G. Hillerdal, C. Le Péchoux, L. Mutti, J-C. Pairon, R. Stahel, P. van Houtte, J. van Meerbeeck, D. Waller and W. Weder

En cours de réactualisation : car 2010

- Avant bévacizumab
- Avant Immunothérapie
- Avant l'abandon assez généralisé de l'EPP
- Avant les essais UK de radiothérapie des orifices de ponction/drainage (qui doivent être honnêtement interprétés)

ERS/EACTS statement on the management of malignant pleural effusions

Eur. Respir. J. 2018, 52: 1800349

Anna C. Bibby[1,2], Patrick Dorn[3], Ioannis Psallidas[4], Jose M. Porcel[5], Julius Janssen[6], Marios Froudarakis[7], Dragan Subotic[8], Phillippe Astoul[9], Peter Licht[10], Ralph Schmid[3], Arnaud Scherpereel[11], Najib M. Rahman[4,12], Giuseppe Cardillo[13,14] and Nick A. Maskell[1,2,14]

	Variable	Value	Score
L	Pleural fluid LDH level IU·L^{-1}	<1500	0
		>1500	1
E	ECOG PS	0	0
		1	1
		2	2
		3–4	3
N	NLR	<9	0
		>9	1
T	Tumour type	Mesothelioma	0
		Haematological malignancy	
		Breast cancer	1
		Gynaecological cancer	
		Renal cell cancer	
		Lung cancer	2
		Other tumour types	

Risk category	Total score
Low risk	0–1
Moderate risk	2–4
High risk	5–7

FIGURE 1 The LENT score calculation and prognostic groups [45]. LDH: lactate dehydrogenase; ECOG PS: Eastern Cooperative Oncology Group performance status; NLR: neutrophil lymphocyte ratio.

Un score pronostique insuffisamment connu ou utilisé en France

ERS/EACTS statement on the management of malignant pleural effusions

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n=482 MPM
+ validation cohort

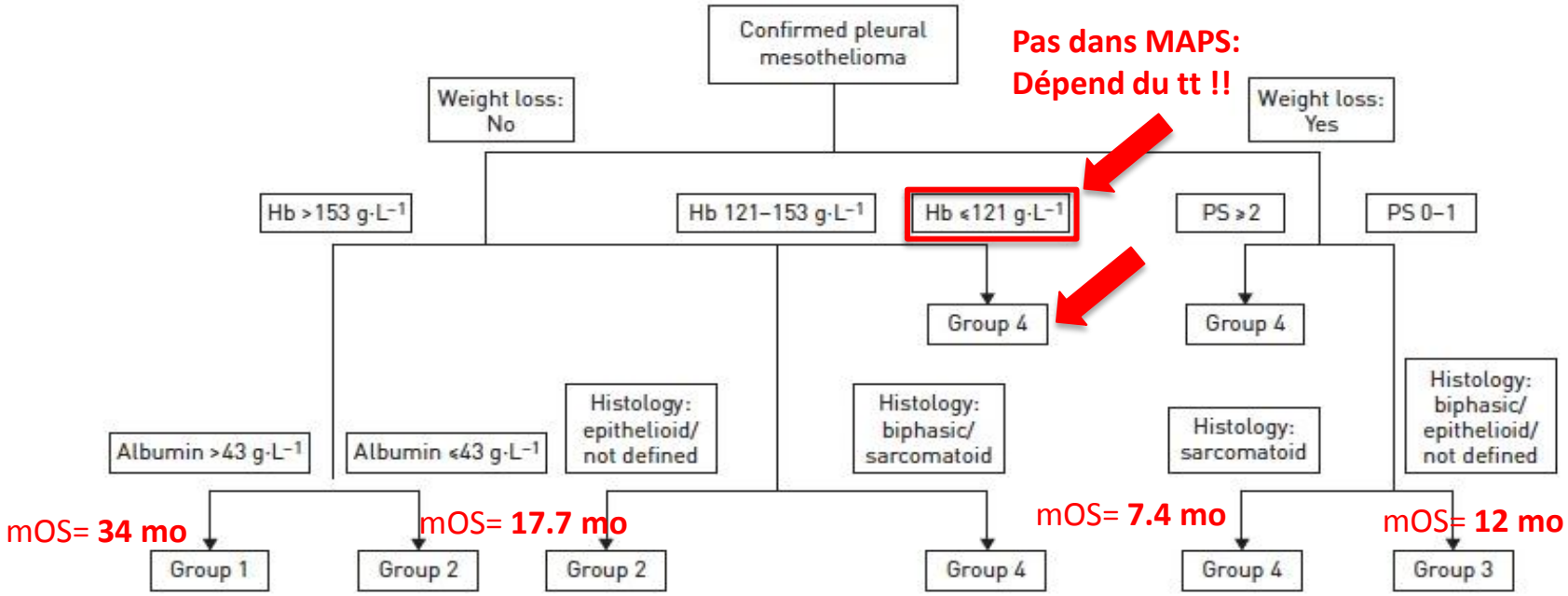


FIGURE 2 Brims' decision tree for predicting mesothelioma prognosis [192]. Hb: haemoglobin; PS: Eastern Cooperative Oncology Group performance status.

Brims FJ, Meniawy TM, Duffus I, *et al.* A novel clinical prediction model for prognosis in malignant pleural mesothelioma using decision tree analysis. *J Thorac Oncol* 2016; 11: 573–582.

National Comprehensive Cancer Network

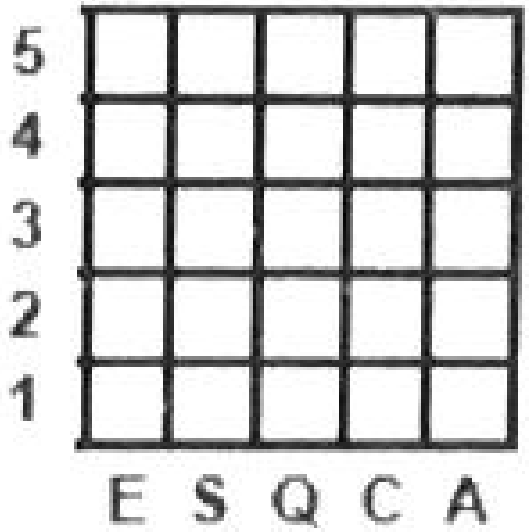
Actualisé chaque année

NCCN Ciinical Practice Guidelines in Oncology (NCCNB Guidelines®)

Malignant Pleural Mesothelioma

version 2.2017 (03/08/2017)

NCCN evidence blocks™

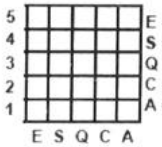


E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Nice St-Paul de Vence 27-29 mars 2019

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Malignant Pleural Mesothelioma
NCCN Evidence Blocks™



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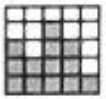
NCCN Guidelines Inde
Table of Content
Discussio

EVIDENCE BLOCKS FOR SYSTEMIC THERAPY

First-Line Combination Chemotherapy

	Clinical stage IV, sarcomatoid, or medically inoperable MPM PS 0-2 (MPM-2)	Induction chemotherapy for medically operable clinical stage I-III (MPM-3)	Unresectable clinical stage I-III (MPM-3)	Postoperative chemotherapy for clinical stage I-III not receiving induction therapy (MPM-3)
Carboplatin + pemetrexed		—		
Cisplatin + pemetrexed				
Cisplatin + pemetrexed + bevacizumab followed by maintenance bevacizumab				
Vinorelbine				

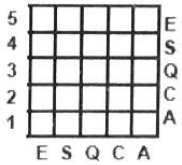
Quality of evidence

Subsequent Systemic Therapy

Pemetrexed	
Vinorelbine	
Gemcitabine	
Nivolumab + ipilimumab	
Nivolumab	
Pembrolizumab	

Une case en moins :
- Safety
- Consistency of evidence
- Affordability

Ph3 UK: vs. BSC=9 months mOS!!!!!



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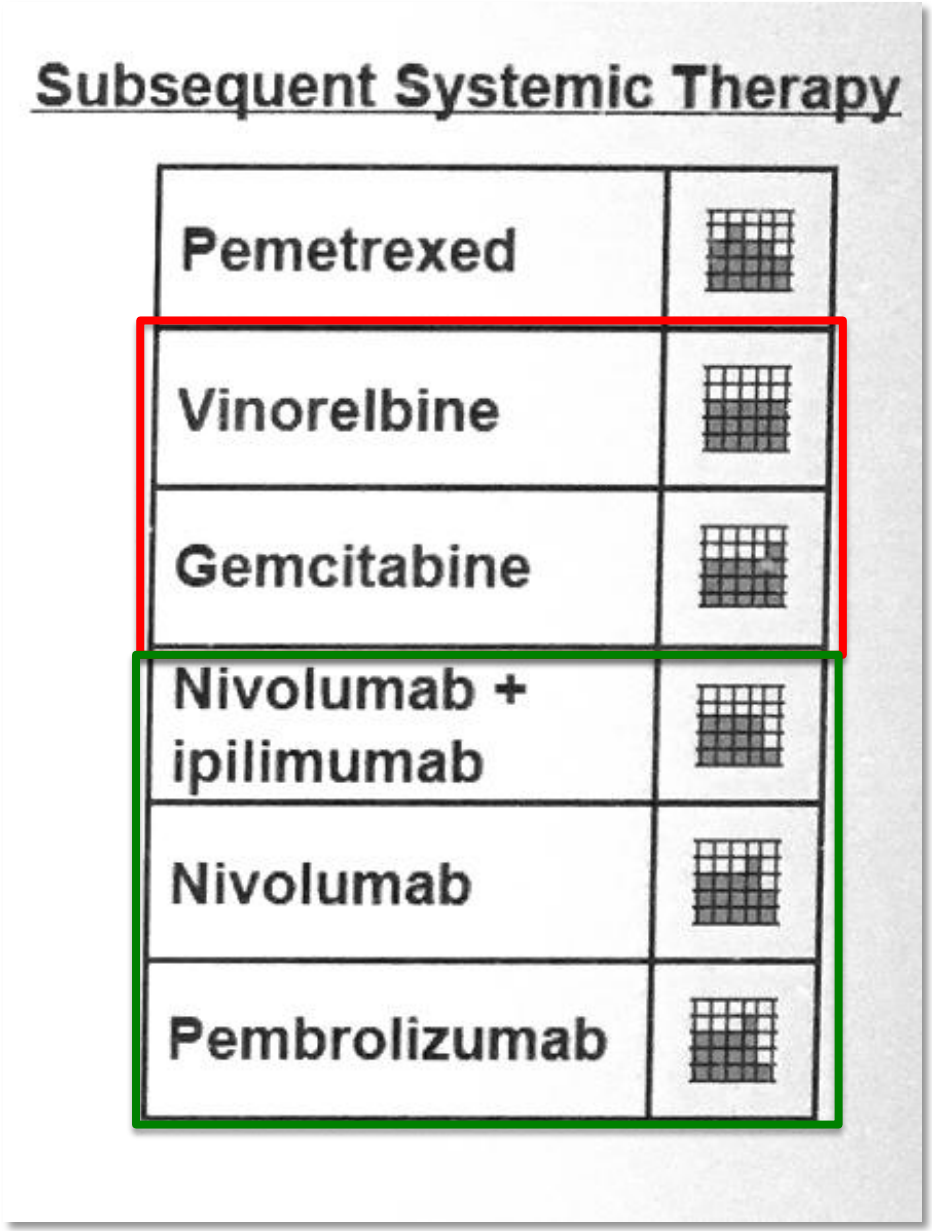
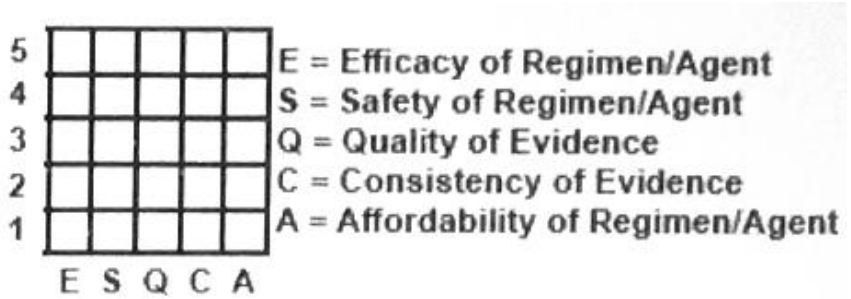
Traitements de 2ème ligne selon NCCN





Consistency of evidence

Ma conclusion

- NCCN & AURA 2019 sont les guidelines les plus récents sur le MPM

- les **guidelines n'évitent pas les partis-pris non evidence-based**:

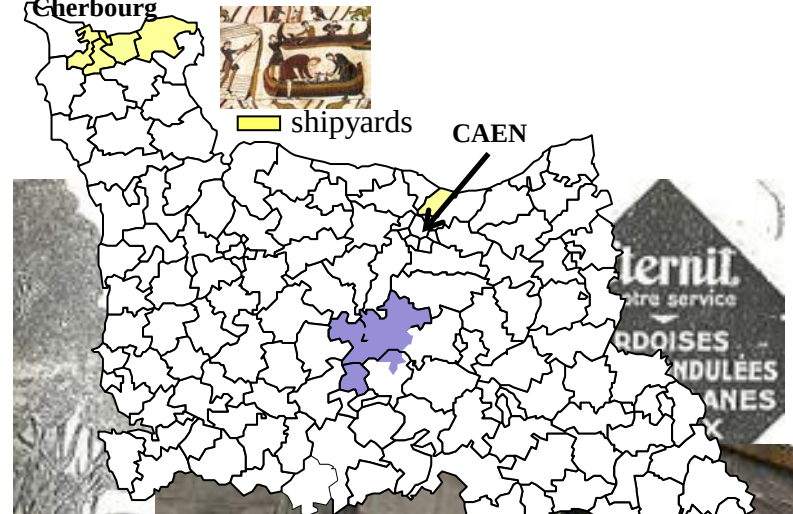
  $\Rightarrow$ *cf*. EPP de certains chirurgiens US et Canadiens

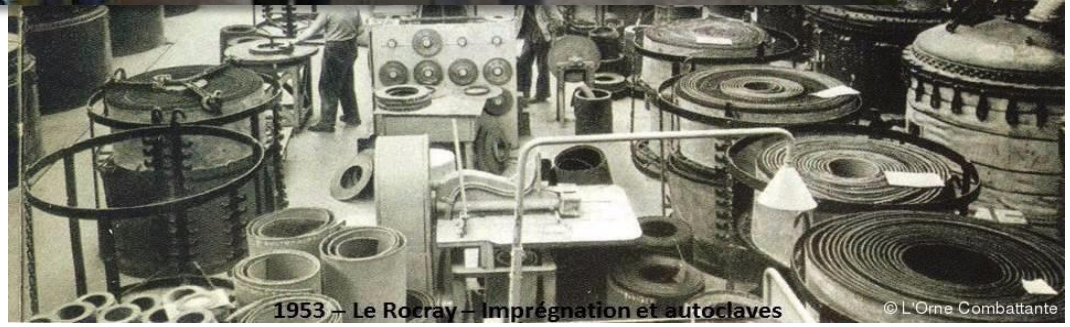
  $\Rightarrow$ *cf*. la RT des points de ponctions et orifices de drainage: 2 essais randomisés mal conçus et non puissants ne font pas l'évidence:

  « L'absence de preuve n'est pas la preuve de l'absence »

- Prise en compte souhaitable par AURA des scores pronostiques, catégorisation pronostique des patients (mais limites liées au sous-Tt UK)

- AURA devrait introduire les notion de niveau de preuve et grade de recommandation +++ d'autant plus quand le niveau de preuve est faible comme dans le Mesotheliome





Merci de votre attention….