Review Article

There is insufficient evidence to support a screening programme for malignant pleural mesothelioma

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Abstract: Malignant pleural mesothelioma (MPM) is an aggressive cancer of the pleura associated with previous asbestos exposure. Patients typically present late in the disease course. At present there is no curative treatment and the median survival is low. In this article, we explore whether MPM meets accepted criteria for initiation of a screening programme and we review potential screening strategies. These include blood-based biomarkers and radiological imaging. We conclude that, at present, there is insufficient evidence to support a screening programme for MPM.

Keywords: Malignant pleural mesothelioma (MPM); screening; biomarkers

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Introduction

Malignant pleural mesothelioma (MPM) is responsible for an estimated 38,400 deaths worldwide annually (1), 95% of which are associated with previous asbestos exposure (2). In the US and many western European countries, including the UK, cases are expected to peak around year 2020. However, MPM is likely to remain a significant issue globally for decades to come due to the on-going and unregulated use of asbestos in a number of industrialised and developing nations including Brazil, India, Russia and China (3). Workers exposed to the highest levels of asbestos include asbestos miners, asbestos factory workers, carpenters, electricians, insulation manufacturers and laggers (4). Men are affected with a 4:1 predominance (3). The lifetime risk of developing MPM is as high as 1.8% in high-risk non-construction occupations (including dockyard workers and marine engineers) (5).

At present, MPM survival is poor with a median survival from diagnosis of only 9.5 months (6), and a 3-year overall survival (OS) rate of around 12%. Up to 50% of patients present as an acute emergency to hospital, frequently due to symptomatic pleural effusion. This referral pathway may contribute to poor outcomes since patients are immediately limited by difficult symptoms and may spend considerable time in hospital resulting in deconditioning and reduced tolerance to cancer therapies. Recent English audit data from the periods 2008–2012 and 2014, show that only 5 and 11% of MPM cases respectively, present with stage 1 disease (7,8). However, these data are significantly confounded by reporting of MPM stage in only 29% of cases during 2008–2012 (7), and 42% of cases in 2014 (8). This uncertainty is consistent across population-based studies with stage being omitted from reports from the Netherlands (n=4,464, 2012) (9), Australia (n=1,258, 2011) (10) and Italy (n=4,100, 2009) (11). Furthermore, surgical series report a low prevalence of early stage disease even in the most radically treated patients. Flores *et al.* reported Stage I disease in <8% of patients (52/663) treated by extra-pleural pneumonectomy (EPP)

or extended pleurectomy/decortication (EP/D) in a multi-centre retrospective study (12). In this analysis, 75% of patients treated by EPP had stage III or IV disease (65% for patients treated by EP/D), which was associated with adverse survival (HR 1.4, 95% CI: 1.28–1.55, P<0.001).

Therefore, there is some evidence that MPM is currently being diagnosed in many patients at a stage at which meaningful treatment, including surgery, is difficult. On this basis, it is reasonable to hypothesise that earlier detection might improve outcomes. In addition, those affected by prior asbestos exposure place great importance on earlier detection. This was recently expressed via the James Lind Alliance Mesothelioma Priority Setting Partnership, which brought together patients, their carers, associated health professionals and mesothelioma support groups in the UK. One of the priority research questions identified through this process was "whether annual CT or CXR in a high-risk population would lead to earlier MPM diagnosis" (13). The Helsinki group also made similar recommendations (14).

In this article, we will appraise the available data regarding development of a screening programme for MPM, based around the criteria first set out in 1968 by Wilson and Jungner (15) and updated by the World Health Organization in 2008 (16). Although Wilson and Jungner originally described 10 criteria, these have been summarised and supplemented by several authors since. Broadly speaking these require that:

(I) The condition should be an important health problem;
(II) There should be a readily available and accepted treatment;
(III) There is a diagnostic test available with sufficient sensitivity and specificity that is acceptable to the population;
(VI) The natural history of the disease should be understood and there should be an early or asymptomatic disease stage during which screening can take place;
(V) Case finding should be a continuous process and not a single event, with the screening programme being economically viable.

Appraising the available data, we highlight that although mesothelioma is a devastating disease, there is insufficient evidence at present to support the introduction of a screening programme.

Clinical importance

Based on their analysis of high quality MPM mortality date from 59 countries in the WHO database, Odgerel *et al.* concluded that "clearly, mesothelioma is a global health issue" based on a best estimate of a global mortality of 38,400 per annum (1). This is reflected in the current epidemics being experienced in the UK, western Europe and North America, which mined, imported or used asbestos extensively in the 1960s–1980s. Continued importation and use of asbestos in highly populated developing nations predicts similar and likely larger, epidemics for decades to come.

Presence of an accepted treatment

Although there is currently no curative treatment for MPM, Phase III randomised controlled trials have demonstrated survival benefit for two platinum-antifolate doublets [cisplatin/pemetrexed (17) and cisplatin/raltitrexed (18)] and for a triplet combination involving cisplatin/pemetrexed and the anti-angiogenic agent, bevacizumab (19). Cisplatin/pemetrexed is available in most health care systems and constitutes the standard of care, which meets the criterion set by Wilson and Jungner. Raltitrexed is no longer available having been discontinued by the manufacturer and the Bevacizumab triplet has yet to be licensed in the UK, Europe or the US.

Nevertheless, treatment options for MPM are likely to increase over coming years, driven in part by greater understanding of the MPM tumour genome (20). Multiple phase III trials of novel therapies are currently in progress following positive phase II studies, including immune check-point inhibitors (21), agents targeting metabolic pathways, particularly arginine deprivation (22) and an alternative anti-angiogenic, nintedanib (23).

To date, surgical treatments have failed to demonstrate any survival benefit in well-designed randomised controlled trials although the outcome of MARS2, which is currently recruiting in the UK, is eagerly awaited (24). In this study, patients can be randomised to EP/D if their disease is confined to the ipsilateral hemithorax and deemed technically resectable by the surgical team. Some authors advocate more stringent surgical selection criteria and recommend staging cervical mediastinoscopy in all cases prior to potentially radical surgery. This constitutes a considerable shift in surgical practice towards earlier stages of disease and MPM screening might facilitate greater access to surgery. However, this argument will only be relevant to MPM patients if MARS2 demonstrates a meaningful survival benefit in subjects randomly allocated

to EP/D. Benefit from earlier treatment would be another argument in favour of MPM screening. In a small pilot study published in 2008, O'Brien *et al.* reported that asymptomatic MPM patients randomised to early treatment with mitomycin, vinblastin, cisplatin (MVP) chemotherapy had a median OS of 14 months, which compared favourably to a median OS of 10 months in those treated upon development of symptoms (delayed treatment) (25). Although this comparison failed to reach statistical significance (P=0.1), this study also showed a trend towards a longer time to symptom progression in patients treated early (25 *vs.* 11 weeks, P=0.1). It was also noted that the opportunity to receive chemotherapy was missed in 23% (5/22) delayed treatment patients because of functional decline. Although underpowered, this data constitutes weak evidence in support of earlier treatment which might be facilitated by screening.

The IASLC mesothelioma staging project collated data from patients with newly diagnosed, cytologically or histologically confirmed MPM to review and revise the current staging manual (26). In total, 3,519 MPM cases were assessed, with stage T1 tumours (with involvement of only the ipsilateral pleura) having a 29.1-month median survival time compared to stage T4 tumours (chest wall, diaphragmatic or pericardial involvement) with a 13.4-month median survival. Whilst on one level this data is suggestive that an earlier MPM diagnosis may lead to prolonged survival, care must be taken to avoid lead-time-bias, whereby screening simply increases the length of time a patient lives with a known cancer without any additional life gained as result of screening.

Diagnostic tests for use in screening

Biomarkers

Collection of circulating blood or exhaled breath is generally acceptable to patients. Biomarker tests are also cheaper and have less potential for off-target false positive results than radiological screening tests. They are therefore attractive screening tools, particularly for enrichment of the population to be screened assuming they exhibit acceptable sensitivity at high specificity. However, few "diagnostic" biomarkers have been tested in low prevalence screening populations, where the negative predictive value of any marker will be lower than in studies recruiting incident cases. Moreover, most diagnostic biomarker studies have been limited by relatively small sample sizes, the retrospective use of stored samples and use of "convenience" cohorts, rather than genuine intention-to-diagnose populations. The DIAPHRAGM study has recently recruited 650 patients presenting with suspected MPM and constitutes the largest intention-to-diagnose biomarker study conducted to date (27). On final analysis in 2018, this study will the report whether two of the markers discussed below (SOMAscan proteomic array and fibulin-3) offer clinically useful diagnostic information relative to the most widely studied MPM marker, mesothelin. However, prospective validation of any candidate screening markers identified will be required in a screening study.

Mesothelin

Mesothelin is formed from a 71-kDa precursor protein, cleaved to form a 45-kDa glycosylphosphatidylinositol (GPI)-anchored cell surface protein (mesothelin) and a soluble protein, megakaryocyte potentiating factor (MPF). Mesothelin is over-expressed in mesothelioma, ovarian and pancreatic cancers (28). It is most sensitive for epithelioid MPM and is rarely expressed by the sarcomatoid subtype (29). Mesothelin has most frequently been studied in incident or prevalent populations of MPM. However, two meta-analyses (30,31) report limited sensitivity, particularly in detecting non-epithelioid and early stage MPM, the latter being particularly relevant to the current question. Hollevoet *et al.* (31) examined data from 16 studies that used the Mesomark ELISA and specifically examined the performance of mesothelin in differentiating 217 patients with stage I/II epithelioid or biphasic MPM from 1,612 high-risk controls. Although the control group included 731 patients with lung cancer, limiting its generalizability to MPM screening, the sensitivity of mesothelin was only 32% (95% CI: 26–40%) at specificity 0.77 (95% CI: 0.73–0.81).

Nevertheless, interest in mesothelin as a screening tool had been raised by Robinson *et al.* (28) who showed elevated levels (>2.18 nM) in 37 of 44 patients (sensitivity 84%, 95% CI: 73–93%) with MPM and in 7 out of 40 healthy asbestos-exposed individuals (specificity 83%, 95% CI: 70–93%). Interestingly, 3 of the 7 healthy individuals subsequently developed MPM, in comparison to none of the 33 individuals with normal results. This prompted the larger Dust Diseases Board Cohort Study, reported by Park *et al.* (29). In this study mesothelin was measured in 538 asbestos-exposed individuals, and those with levels >2.5 nM had further tests. However, no MPM cases were subsequently diagnosed in the 15/538 (2.7%)

positive patients, prompting the authors to conclude that mesothelin is unlikely to be of use in screening.

Fibulin-3

Fibulin-3, a protein that mediates cell-to-cell and cell-to-matrix interactions is over-expressed in mesothelioma compared to surrounding normal pleura and has been shown to have a role in the regulation of MPM cell migration and proliferation (32). In contrast to mesothelin, fibulin-3 levels are not influenced by mesothelioma subtype. Pass *et al.*, examined fibulin-3 levels in 92 MPM and 136 asbestos-exposed people without cancer. Using a cut-off of 53 ng/mL the sensitivity of fibulin-3 for MPM was 97% at specificity of 95%. However, these results were tempered by a validation set sensitivity <40% at 95% specificity area under the curve (AUC) 0.87 (33). A subsequent study compared fibulin-3 and mesothelin in the same samples and demonstrated superior performance using mesothelin (sensitivity 56% at 95% specificity, AUC 0.822) compared with fibulin-3 (sensitivity 22% at 95% specificity, AUC 0.671) (34). Later studies have generally been small and have shown considerable inconsistency (35-38), as reviewed by Creaney *et al.* (39). Further prospective studies are awaited (27,40), although the protein may have a role in disease prognostication (36).

Osteopontin

Osteopontin is a glycoprotein over-expressed in a number of malignancies including lung, breast, gastric and ovarian tumours and correlates to tumour invasion, progression and metastases (41). At a cut-off value of 48.3 ng/mL osteopontin was able to distinguish mesothelioma from benign asbestos related disease with a sensitivity of 77.6% and specificity of 85.5% (AUC of 0.888) (41). A meta-analysis of six studies examining osteopontin as a biomarker in MPM showed a sensitivity of 0.65 and a specificity of 0.81, with an AUC of 0.83 (42), again below that required for a diagnostic test.

Ecto-NOX disulfide-thiol exchanger 2 (ENOX-2)

ENOX-2 proteins belong to a family of cell surface proteins that interact with nicotinamide adenine dinucleotide phosphate (NADPH). Morré *et al.* compared serum samples from 17 patients with mesothelioma with 15 samples from asbestos-exposed healthy individuals (43). All 17 of the MPM patient samples exhibited two ENOX-2 protein variants associated with mesothelioma, whereas in the 15 healthy asbestos-exposed individuals, 9 expressed neither protein, 1 expressed both proteins and 5 expressed one of the two proteins. Interestingly, 7 of the MPM patients had also had serum samples collected over a number of years prior to diagnosis. When analysed for ENOX-2 variants, the proteins could be detected in samples taken 4–10 years prior to MPM diagnosis. These results require external prospective validation but are of potential interest in a screening context.

SOMAmer Technology

Ostroff *et al.* used aptamer-based SOMAmer proteomic technology to compare serum samples from 117 MPM patients with those from 142 asbestos-exposed individuals (44). 13 of 64 differentially expressed proteins were subsequently used in a Forrest classifier to distinguish MPM cases from asbestos-exposed controls. In a training set and subsequent blinded validation studies this resulted in an AUC value of 0.99±0.1, and 0.95±0.4, respectively. However, sensitivity decreased in lower stage disease (77% sensitivity in stage 1 *vs.* 93% in stage 2 MPM) and further prospective validation is required. The 13 proteins in the SOMAmer classifier have not been previously associated with MPM but include molecules implicated in inflammatory and proliferative pathways.

High mobility group box 1 protein (HMGB1)

HMGB1 is released by human mesothelioma cells when exposed to asbestos and initiates a chronic inflammatory response. MPM cells become addicted to HMGB1 for growth and invasion, releasing HMGB1 in an autocrine manner (45,46). Tabata *et al.* initially reported that total serum HMGB1 could be used to differentiate MPM patients from controls with benign asbestos related disease; however the accuracy of this classification was low (AUC 0.674), with a sensitivity of 34% at 100% specificity (47). Differentiating between the hyper-acetylated and non-acetylated isoforms of HMGB1 appears to have greater diagnostic accuracy. Napolitano *et al.* analysed serum samples obtained from 22 MPM patients, 20 asbestos exposed individuals and 20 healthy controls (48). Comparison between total HMGB1 levels in MPM patients with those in asbestos exposed controls resulted in a modest AUC value of 0.830 with a specificity of

100% and sensitivity 73%, but use of the hyper-acetylated isoform was associated with 100% sensitivity and specificity (AUC 1.000). Fibulin-3, mesothelin and osteopontin measured in the same samples could not replicate this impressive performance. A clinical trial is planned in the US to externally validate these findings and depending upon the design, may clarify what appears to be genuine screening potential of HMGB1 (49).

Volatile organic compounds (VOCs)

More than 4,000 different VOCs are detectable in exhaled human breath. These arise from biochemical endogenous pathways or from inhaled exogenous sources (50), where the relative composition is indicative of blood levels due to gaseous exchange at the alveolar interface (51). Levels vary due to infection, inflammation or tumour development and combinations of compounds can potentially be used in the detection of malignancy, including MPM. Several studies albeit with small test sets have examined VOCs (52,53) and although the initial results have been promising, larger cohorts with blinded validation are required.

Imaging

The largest radiological screening program to date for workers exposed to asbestos took place in Finland between 1990–1992. A total of 18,983 ex-asbestos workers, exposed through the construction, shipyard and asbestos industries were screened by chest radiograph (CXR). Although 22% CXRs were abnormal, resulting in 4,133 referrals for further evaluation, the number of MPM cases identified were not reported (54). The low sensitivity of CXR for MPM makes this an unrealistic screening tool.

Based on positive results in lung cancer, low dose CT screening was subsequently tested in two studies. Fasola *et al.* (55) screened 1,045 Italian asbestos-exposed individuals but identified no cases of MPM. Lung nodules were identified in 44% cases (amongst which there were nine lung cancers) and pleural abnormalities were common (70%). Roberts *et al.* (56) screened 516 asbestos-exposed Canadian workers but again reported a low rate of mesothelioma detection (two MPM and two peritoneal mesotheliomas). Similar to the Finnish CXR data, these results are likely to reflect the low sensitivity of the chosen screening test (low dose, non-contrast CT). Using standard dose, contrast-enhanced CT, Hallifax *et al.* recently reported that the negative predictive value of this examination for pleural malignancy was only 65% (sensitivity 68.2%) in 370 patients, all of whom had a pleural effusion (57). Tsim *et al.* replicated these findings in 315 patients recruited to the DIAPHRAGM study and showed a further reduction in sensitivity when either non-thoracic radiologists reported CTs or non-venous contrast enhancement (CT pulmonary angiography) was used (sensitivity 27%) (58). These data demonstrate that up to 4 in 10 patients presenting with incident cases of pleural malignancy may have a "benign" CT report. However, this data is based on patients with symptomatic pleural effusion and is not generalizable to a screening setting, particularly since 0% and 0.6% of patients screened by Fasola and Roberts had pleural effusion (55,56).

An increasing body of evidence suggests that magnetic resonance imaging (MRI) may be more accurate than CT for detecting MPM. This ability, without use of ionising radiation, makes it attractive as a candidate screening tool. Katz *et al.* recently reported that the optimal pleural contrast enhancement delay was 280 seconds using gadolinium enhanced MRI, not 40–60 seconds as is the case for iodinated contrast CT (59). Tsim *et al.* similarly reported a similar peak enhancement time and promising diagnostic performance using MRI-early contrast enhancement (MRI-ECE), with sensitivity of 91% at an 86% specificity in a pilot study of 24 MPM patients (60). Importantly, this performance equaled or exceeded contrast-enhanced CT and MRI-ECE could be applied to areas of minimal pleural thickening. The semi-objective nature of MRI-ECE may also result in greater reproducibility than morphology assessment (59), but the technique needs further assessment in a prospective screening trial.

Natural history and screening window

Although much remains to be discovered about the natural history of the disease, MPM is characterised by a long latent period between exposure to asbestos and symptomatic presentation, typically 30–40 years. This latency period provides a window of opportunity during which patients may be screened. If those at highest risk within the asbestos exposed population could be identified, intervention could occur prior to development of disease, potentially through the use of chemoprophylaxis agents although no such treatments exist at present. Similarly, for those who do develop MPM, earlier detection of the disease might one day allow curative treatment to be offered, with earlier diagnosis leading to individuals having better performance

status thereby allowing access to clinical trials and more aggressive therapies.

Case finding and economics

During development of a screening programme careful thought has to be given as to how best to identify those at highest risk in order to optimise cost-effectiveness whilst avoiding unnecessary anxiety in low risk individuals unlikely to have disease. Estimation of asbestos fibre exposure has been made using risk assessment tools (61), the accuracy of which have been confirmed through fibre counts at surgery and post mortem (62). Such risk assessment tools could be used to enrich participants to be screened thereby reducing costs of a screening programme (61). Such an approach could be employed in new significant at-risk populations now being identified in large parts of Asia including China, the world's largest asbestos consumer, and in India where an upward trend of asbestos usage continues (63). Rapid population growth and the need for housing has prompted this increased use of asbestos, often in an unregulated manner (64).

Assessing such populations will prove challenging, and emphasises the need for a low cost, readily accessible, high sensitivity screening test that could better identify those at-risk. As outlined above, mesothelin, fibulin-3 and osteopontin appeared promising in initial studies but have not been shown to have sufficient sensitivity or specificity in subsequent validation studies. SOMAmer technology, hyperacetylated HMGB1 and ENOX-2 proteins offer potential but initial studies require validation in larger cohorts. The natural history of MPM in the pre-symptomatic period is poorly understood leading to uncertainty about the frequency of radiological or biomarker testing which influences radiation exposure, patient anxiety and costs. An effective biomarker may reduce the risk of harm from multiple screening episodes although none to date have been shown to have the sensitivity and specificity required for this role. Combination models to screen for MPM, initially by risk assessment using an asbestos exposure tool followed by biomarker assessment or imaging also need to be examined.

While introducing a screening programme may offer reassurance to those exposed to asbestos (13), anxiety may increase in the absence of a curative treatment and the minimal gain in life expectancy seen on early diagnosis (65). This needs to be balanced against the anxiety of those in high-risk occupations who know they have a high chance of developing the disease. The psychological impact of screening has been examined in relation to lung cancer screening programmes. Cancer distress is greatest around the period of screening, when, for example, an indeterminate CT finding requires follow up (66), as would likely occur in a MPM screening programme. In the UK lung cancer screening trial, heightened screening distress was seen in women, younger participants, current smokers, lower socioeconomic groups and those with experience of lung cancer (67). These findings are relevant to an asbestos-exposed population who are predominantly from lower socioeconomic groups and often have prior knowledge of mesothelioma from workplace colleagues. The quality of communication in relaying findings from screening studies influences overall wellbeing (68), and would be key in any potential MPM screening programme.

Conclusions

Based on the criteria that Wilson and Jungner recommended for establishing a screening programme there is not enough evidence, at this stage, to support a MPM screening programme. Whilst MPM is undoubtedly an important clinical condition, whose incidence particularly in Asia will rise over the coming years, at present there is no curative treatment, and the best available chemotherapy regimens provide a few months survival benefit at best. The improved clinical survival in early stage MPM seen in the IASLC mesothelioma staging project is likely a result of lead-time-bias, instead of a treatment effect, meaning a patient will simply live longer in the knowledge of their MPM diagnosis, with the associated psychological harms that this may entail. Studies of potential mesothelioma biomarkers have been compromised by small sample sizes, absence of "intention-to-treat" populations and a lack of independent validation studies. Additionally, there have been no good biomarker studies in low incidence populations, where the background MPM risk is low. Although the newer biomarkers including HMGB1 and the SOMAmer technology appear promising these have yet to be validated in either larger cohorts, or in a prospective study. Further evidence of biomarker efficacy is required before their use can be recommended for use as either a single screening test or as a component of combined modality tests. With regard to radiological modalities for screening for MPM the evidence is mixed. There is no data to support the use of CXRs and low dose non-contrast CT imaging has a low sensitivity for detecting MPM (55,56).

However, this may be due to sub-optimal pleural imaging algorithms employed historically. Recent work indicates that MRI may offer advantages over CT for delineating pleural anatomy although this has yet to be assessed in a prospective clinical trial. In addition, the potential benefits of MRI need to be weighed against increased costs and availability compared with CT.

In summary, although there is not enough evidence at present to recommend the development of screening programmes for MPM, there are a number of areas requiring further investigation and these should be examined within the context of feasibility or pilot clinical trials. The rationale for an MPM screening programme could be revisited when this data becomes available.

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Footnote

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References

1. Odgerel CO, Takahashi K, Sorahan T, et al. Estimation of the global burden of mesothelioma deaths from incomplete national mortality data. Occup Environ Med 2017;74:851-8.
2. Brown T, Darnton A, Fortunato L, et al. British Occupational Cancer Burden Study G. Occupational cancer in Britain. Respiratory cancer sites: larynx, lung and mesothelioma. Br J Cancer 2012;107 Suppl 1:S56-70.
3. Bibby AC, Tsim S, Kanellakis N, et al. Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment. Eur Respir Rev 2016;25:472-86.
4. Roggli VL, Sharma A, Butnor KJ, et al. Malignant mesothelioma and occupational exposure to asbestos: a clinicopathological correlation of 1445 cases. Ultrastruct Pathol 2002;26:55-65.
5. HSE. Occupational, domestic and environmental mesothelioma risks in Britain. 2009. Available online: http://www.hse.gov.uk/research/rrpdf/rr696.pdf
6. Beckett P, Edwards J, Fennell D, Hubbard R, Woolhouse I, Peake MD. Demographics, management and survival of patients with malignant pleural mesothelioma in the National Lung Cancer Audit in England and Wales. Lung Cancer 2015;88:344-8.
7. Royal College of Physicians CEaEU. National Lung Cancer Audit Report 2014 Mesothelioma Report. Report for the period 2008-2012. Available online: https://www.rcplondon.ac.uk/file/2140/download?token=6aeWOP23
8. Royal College of Physicians CEaEU. National Lung Cancer Audit pleural mesothelioma report 2016 (for the audit period 2014). Available online: https://www.rcplondon.ac.uk/projects/outputs/national-lung-cancer-audit-pleural-mesothelioma-report-2016-audit-period-2014
9. Damhuis RA, Schroten C, Burgers JA. Population-based survival for malignant mesothelioma after introduction of novel chemotherapy. Eur Respir J 2012;40:185-9.
10. Asbestos Disease Research Institute ADRI 2013 annual report. Available online: http://asbestosresearch.org.au/files/ADRI_Annual_Report_2013.pdf
11. Montanaro F, Rosato R, Gangemi M, et al. Survival of pleural malignant mesothelioma in Italy: a population-based study. Int J Cancer 2009;124:201-7.
12. Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. J Thorac Cardiovasc Surg 2008;135:620-6, 626.e1-3.
13. Stephens RJ, Whiting C, Cowan K, James Lind Alliance Mesothelioma Priority Setting Partnership Steering C. Research priorities in mesothelioma: A James Lind Alliance Priority Setting Partnership. Lung Cancer 2015;89:175-80.
14. Wolff H, Vehmas T, Oksa P, et al. Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations. Scand J Work Environ Health 2015;41:5-15.
15. Wilson JM, Jungner YG. Principles and practice of mass screening for disease. Bol Oficina Sanit Panam 1968;65:281-393.
16. Andermann AB, Beauchamp S, Dery V. Revisiting Wilson and Jungner in the genomic age: a review of screening over the past 40 years World Health Organisation 2017. Available online: http://www.who.int/bulletin/volumes/86/4/07-050112/en/
17. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636-44.
18. van Meerbeeck JP, Gaafar R, Manegold C, et al. Randomized phase III study of cisplatin with or

without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. J Clin Oncol 2005;23:6881-9.
19. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet 2016;387:1405-14.
20. Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. Nat Genet 2016;48:407-16.
21. Calabrò L, Morra A, Fonsatti E, et al. Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. Lancet Respir Med 2015;3:301-9.
22. Szlosarek PW, Steele JP, Nolan L, et al. Arginine Deprivation With Pegylated Arginine Deiminase in Patients With Argininosuccinate Synthetase 1-Deficient Malignant Pleural Mesothelioma: A Randomized Clinical Trial. JAMA Oncol 2017;3:58-66.
23. Grosso F, Steele N, Novello S, et al. Nintedanib Plus Pemetrexed/Cisplatin in Patients With Malignant Pleural Mesothelioma: Phase II Results From the Randomized, Placebo-Controlled LUME-Meso Trial. J Clin Oncol 2017;35:3591-600.
24. MARS 2: A Feasibility Study Comparing (Extended) Pleurectomy Decortication Versus no Pleurectomy Decortication in Patients With Malignant Pleural Mesothelioma (MARS2): U.S. National Library of Medicine, 2014.
25. O'Brien ME, Watkins D, Ryan C, et al. A randomised trial in malignant mesothelioma (M) of early (E) versus delayed (D) chemotherapy in symptomatically stable patients: the MED trial. Ann Oncol 2006;17:270-5.
26. Nowak AK, Chansky K, Rice DC, et al. The IASLC Mesothelioma Staging Project: Proposals for Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma. J Thorac Oncol 2016;11:2089-99.
27. Tsim S, Kelly C, Alexander L, et al. Diagnostic and Prognostic Biomarkers in the Rational Assessment of Mesothelioma (DIAPHRAGM) study: protocol of a prospective, multicentre, observational study. BMJ Open 2016;6:e013324.
28. Robinson BW, Creaney J, Lake R, et al. Mesothelin-family proteins and diagnosis of mesothelioma. Lancet 2003;362:1612-6.
29. Park EK, Sandrini A, Yates DH, et al. Soluble mesothelin-related protein in an asbestos-exposed population: the dust diseases board cohort study. Am J Respir Crit Care Med 2008;178:832-7.
30. Luo L, Shi HZ, Liang QL, et al. Diagnostic value of soluble mesothelin-related peptides for malignant mesothelioma: a meta-analysis. Respir Med 2010;104:149-56.
31. Hollevoet K, Reitsma JB, Creaney J, et al. Serum mesothelin for diagnosing malignant pleural mesothelioma: an individual patient data meta-analysis. J Clin Oncol 2012;30:1541-9.
32. Chen Z, Gaudino G, Pass HI, et al. Diagnostic and prognostic biomarkers for malignant mesothelioma: an update. Transl Lung Cancer Res 2017;6:259-69.
33. Pass HI, Levin SM, Harbut MR, et al. Fibulin-3 as a blood and effusion biomarker for pleural mesothelioma. N Engl J Med 2012;367:1417-27.
34. Creaney J, Dick IM, Meniawy TM, et al. Comparison of fibulin-3 and mesothelin as markers in malignant mesothelioma. Thorax 2014;69:895-902.
35. Kaya H, Demir M, Taylan M, et al. Fibulin-3 as a diagnostic biomarker in patients with malignant mesothelioma. Asian Pac J Cancer Prev 2015;16:1403-7.
36. Kirschner MB, Pulford E, Hoda MA, et al. Fibulin-3 levels in malignant pleural mesothelioma are associated with prognosis but not diagnosis. Br J Cancer 2015;113:963-9.
37. Demir M, Kaya H, Taylan M, et al. Evaluation of New Biomarkers in the Prediction of Malignant Mesothelioma in Subjects with Environmental Asbestos Exposure. Lung 2016;194:409-17.
38. Agha M, El-habashy M, El-Shazly R. Role of fibulin-3 in the diagnosis of malignant mesothelioma. Egypt J Chest Dis Tuberc 2014;44:1701.
39. Creaney J, Dick IM, Robinson BW. Comparison of mesothelin and fibulin-3 in pleural fluid and serum as markers in malignant mesothelioma. Curr Opin Pulm Med 2015;21:352-6.
40. Hooper CE, Lyburn ID, Searle J, et al. The South West Area Mesothelioma and Pemetrexed trial: a multicentre prospective observational study evaluating novel markers of chemotherapy response and prognostication. Br J Cancer 2015;112:1175-82.
41. Pass HI, Lott D, Lonardo F, et al. Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. N

Engl J Med 2005;353:1564-73.
42. Hu ZD, Liu XF, Liu XC, et al. Diagnostic accuracy of osteopontin for malignant pleural mesothelioma: a systematic review and meta-analysis. Clin Chim Acta 2014;433:44-8.
43. Morré DJ, Hostetler B, Taggart DJ, et al. ENOX2-based early detection (ONCOblot) of asbestos-induced malignant mesothelioma 4-10 years in advance of clinical symptoms. Clin Proteomics 2016;13:2.
44. Ostroff RM, Mehan MR, Stewart A, et al. Early detection of malignant pleural mesothelioma in asbestos-exposed individuals with a noninvasive proteomics-based surveillance tool. PLoS One 2012;7:e46091.
45. Jube S, Rivera ZS, Bianchi ME, et al. Cancer cell secretion of the DAMP protein HMGB1 supports progression in malignant mesothelioma. Cancer Res 2012;72:3290-301.
46. Ying S, Jiang Z, He X, et al. Serum HMGB1 as a Potential Biomarker for Patients with Asbestos-Related Diseases. Dis Markers 2017;2017:5756102.
47. Tabata C, Shibata E, Tabata R, et al. Serum HMGB1 as a prognostic marker for malignant pleural mesothelioma. BMC Cancer 2013;13:205.
48. Napolitano A, Antoine DJ, Pellegrini L, et al. HMGB1 and Its Hyperacetylated Isoform are Sensitive and Specific Serum Biomarkers to Detect Asbestos Exposure and to Identify Mesothelioma Patients. Clin Cancer Res 2016;22:3087-96.
49. Carbone M, Yang H. Mesothelioma: recent highlights. Ann Transl Med 2017;5:238.
50. Lagniau S, Lamote K, van Meerbeeck JP, et al. Biomarkers for early diagnosis of malignant mesothelioma: Do we need another moonshot? Oncotarget 2017;8:53751-62.
51. de Gennaro G, Dragonieri S, Longobardi F, et al. Chemical characterization of exhaled breath to differentiate between patients with malignant plueral mesothelioma from subjects with similar professional asbestos exposure. Anal Bioanal Chem 2010;398:3043-50.
52. Chapman EA, Thomas PS, Stone E, et al. A breath test for malignant mesothelioma using an electronic nose. Eur Respir J 2012;40:448-54.
53. Dragonieri S, van der Schee MP, Massaro T, et al. An electronic nose distinguishes exhaled breath of patients with Malignant Pleural Mesothelioma from controls. Lung Cancer 2012;75:326-31.
54. Koskinen K, Zitting A, Tossavainen A, et al. Radiographic abnormalities among Finnish construction, shipyard and asbestos industry workers. Scand J Work Environ Health 1998;24:109-17.
55. Fasola G, Belvedere O, Aita M, et al. Low-dose computed tomography screening for lung cancer and pleural mesothelioma in an asbestos-exposed population: baseline results of a prospective, nonrandomized feasibility trial--an Alpe-adria Thoracic Oncology Multidisciplinary Group Study (ATOM 002). Oncologist 2007;12:1215-24.
56. Roberts HC, Patsios DA, Paul NS, et al. Screening for malignant pleural mesothelioma and lung cancer in individuals with a history of asbestos exposure. J Thorac Oncol 2009;4:620-8.
57. Hallifax RJ, Haris M, Corcoran JP, et al. Role of CT in assessing pleural malignancy prior to thoracoscopy. Thorax 2015;70:192-3.
58. Tsim S, Stobo DB, Alexander L, et al. The diagnostic performance of routinely acquired and reported computed tomography imaging in patients presenting with suspected pleural malignancy. Lung Cancer 2017;103:38-43.
59. Armato SG, Blyth KG, Keating JJ, et al. Imaging in pleural mesothelioma: A review of the 13th International Conference of the International Mesothelioma Interest Group. Lung Cancer 2016;101:48-58.
60. Tsim S, Humphreys CA, Stobo DB, et al. S21 Early Contrast Enhancement: A Perfusion- based Magnetic Resonance Imaging Biomarker of Pleural Malignancy. Thorax 2015;70:A16.1-A16.
61. Cherrie JW, McElvenny D, Blyth KG. Estimating past inhalation exposure to asbestos: A tool for risk attribution and disease screening. Int J Hyg Environ Health 2018;221:27-32.
62. Rasmuson JO, Roggli VL, Boelter FW, et al. Cumulative Retrospective Exposure Assessment (REA) as a predictor of amphibole asbestos lung burden: validation procedures and results for industrial hygiene and pathology estimates. Inhal Toxicol 2014;26:1-13.
63. Le GV, Takahashi K, Park EK, et al. Asbestos use and asbestos-related diseases in Asia: past, present and future. Respirology 2011;16:767-75.
64. Leong SL, Zainudin R, Kazan-Allen L, et al. Asbestos in Asia. Respirology 2015;20:548-55.
65. Wardle J, Pope R. The psychological costs of screening for cancer. J Psychosom Res 1992;36:609-24.
66. van den Bergh KA, Essink-Bot ML, Borsboom GJ, et al. Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). Br J Cancer 2010;102:27-34.
67. Brain K, Lifford KJ, Carter B, et al. Long-term

psychosocial outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised controlled trial. Thorax 2016;71:996-1005.
68. Slatore CG, Golden SE, Ganzini L, et al. Distress and patient-centered communication among veterans with incidental (not screen-detected) pulmonary nodules. A cohort study. Ann Am Thorac Soc 2015;12:184-92.

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