Mesothelioma: Scientific Clues for Prevention, Diagnosis, and Therapy

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Abstract: Mesothelioma affects mostly older individuals who have been occupationally exposed to asbestos. The global mesothelioma incidence and mortality rates are unknown, because data are not available from developing countries that continue to use large amounts of asbestos. The incidence rate of mesothelioma has decreased in Australia, the United States, and Western Europe, where the use of asbestos was banned or strictly regulated in the 1970s and 1980s, demonstrating the value of these preventive measures. However, in these same countries, the overall number of deaths from mesothelioma has not decreased as the size of the population and the percentage of old people have increased. Moreover, hotspots of mesothelioma may occur when carcinogenic fibers that are present in the environment are disturbed as rural areas are being developed. Novel immunohistochemical and molecular markers have improved the accuracy of diagnosis; however, about 14% (high-resource countries) to 50% (developing countries) of mesothelioma diagnoses are incorrect, resulting in inadequate treatment and complicating epidemiological studies. The discovery that germline BRCA1-associated protein 1 (BAP1) mutations cause mesothelioma and other cancers (BAP1 cancer syndrome) elucidated some of the key pathogenic mechanisms, and treatments targeting these molecular mechanisms and/or modulating the immune response are being tested. The role of surgery in pleural mesothelioma is controversial as it is difficult to predict who will benefit from aggressive management, even when local therapies are added to existing or novel systemic treatments. Treatment outcomes are improving, however, for peritoneal mesothelioma. Multidisciplinary international collaboration will be necessary to improve prevention, early detection, and treatment. CA Cancer J Clin 2019;69:402-429. © 2019 American Cancer Society.

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Epidemiology

A marked increase in the age-standardized mesothelioma incidence and mortality rates began in the 1960s after the massive use of asbestos during World War II and thereafter. The widespread use of asbestos continued in high-resource countries (the United States, Europe, Australia) until the late 1970s and early 1980s, when strict regulations were implemented to limit and ban the use of 6 of approximately 400 different mineral fibers present in nature because these 6 fibers (amphiboles fibers [crocidolite, actinolite, tremolite, anthophyllite, and amosite] and serpentine fibers [chrysotile]) were used commercially. For regulatory purposes, these 6 fibers were collectively called “asbestos.” The remaining approximately 400 mineral fibers have not been regulated and can be used freely, although many of them are carcinogenic and have been associated...
with mesothelioma.\textsuperscript{1,2} In addition, germline mutations of BRCA1-associated protein 1 (\textit{BAP1}) and of other tumor suppressor genes have been causally linked to mesothelioma, at times together with exposure to asbestos or other carcinogenic fibers (gene \texttimes\ environment interaction [GxE]).\textsuperscript{2} Also, therapeutic ionizing radiation to the chest, usually to treat lymphomas, has been causally linked to mesothelioma (and sarcomas), especially in young patients.\textsuperscript{3-5}

**Incidence and Mortality in the United States**

Approximately 3000 incident cases of mesothelioma are registered each year in the United States.\textsuperscript{6} The incidence rate varies between less than 1 case per 100,000 persons in states with no asbestos industry to 2 to 3 cases per 100,000 persons in states with an asbestos industry.\textsuperscript{1,2,7} These numbers most likely underestimate the true incidence as, even with the development of the International Classification of Diseases, 10th revision coding system, about 20\% to 25\% of mesotheliomas are not coded correctly and therefore are not captured by statistics.\textsuperscript{8} The causes of incorrect coding have been reviewed.\textsuperscript{8} The age-standardized incidence rates of mesothelioma peaked in the United States in the 1980s and early 1990s, when the Surveillance, Epidemiology, and End Results Cancer Registry reported an age-adjusted incidence rate of 2.5 cases per 100,000 persons.\textsuperscript{9} Since then, the age-standardized incidence rate decreased to 0.97 cases per 100,000 persons in 2009. From 2009 to 2015, the US data show a further slight decrease in age-adjusted incidence rates to 0.88 cases per 100,000 persons in 2015. This modest decrease from 2009 to 2015 has been observed in both males (from 1.87 to 1.7 cases per 100,000 persons) and females (from 0.32 to 0.28 cases per 100,000 persons). The mean age of death from mesothelioma in the United States was 72.8 years, with a male-to-female (M:F) mortality ratio of 4.2:1, as men were traditionally more likely to be employed in trades involving asbestos exposure. Indeed, men and women with equivalent exposure to asbestos have a similar incidence of pleural mesothelioma.\textsuperscript{4} The latency from asbestos exposure to the development of mesothelioma is about 30 to 50 years. The age-specific incidence rates increase past age 60 years, from 0.5 to 1.24 cases (from age 60-85 years) per 100,000 persons and reaches 6.34 cases per 100,000 persons in those older than 85 years. In the United States and in many countries, people are living longer, and the population is getting larger. Thus, despite the decrease in age-adjusted mesothelioma incidence rates per 100,000 persons in the past decades, the overall number of new cases and of deaths per year caused by mesothelioma in the United States has remained stable, at approximately 3000 deaths per year, and continues to steadily increase in many countries because mesothelioma affects mostly older people, and the population is getting older.\textsuperscript{6,10}

**Incidence and Mortality Worldwide**

It has been estimated that, between 1994 and 2008, age-adjusted mesothelioma mortality rates increased by 5.37\% per year worldwide.\textsuperscript{6} According to the World Health Organization,\textsuperscript{11} the highest age-standardized incidence rates in 2018 were observed in the United States, Australia, Russia, Western Europe, Turkey, South Africa, and Argentina. Moreover, Australia, New Zealand, and the
United Kingdom, where there has been a large burden of asbestos exposure, show a temporal decline in mesothelioma mortality rates in males, probably thanks to the introduction of regulatory laws. Instead, the rates in those countries among females are still rising as of 2018. Among the countries that were part of the Soviet Union or the Soviet bloc, where regulations have been limited or introduced in the recent past, data are available only for Kyrgyzstan and Poland: both countries show increases in mesothelioma rates in both sexes. The highest worldwide consumption of asbestos from 1995 to 2003 occurred in Russia, China, Thailand, Brazil, India, Kazakhstan, Iran, and Ukraine. The World Health Organization does not include mesothelioma incidence and mortality data from these countries, with the exception of Kazakhstan, where incidence rates increased from approximately 0 to 0.26 cases per 100,000 persons in the past 10 years. Because the asbestos bans and regulations went into effect during different times in different countries, it is expected that mesothelioma rates will follow dissimilar patterns in the next decades. By 1990, the use of asbestos in most industrialized countries had been reduced by at least 75% from the peak asbestos consumption. Iran, Korea, Chile, and Egypt reached the same level of reduction of asbestos usage in 1999, as did Nigeria, Zimbabwe, the United Arab Emirates, Ukraine, and Kazakhstan between 2000 and 2005. Other countries, such as the Russian Federation, India, and China, where asbestos is still used, are expected to show dramatic increases in age-adjusted mesothelioma incidence and mortality rates in coming years.

Very recently, South America’s largest mesothelioma study reported some characteristics of 302 pleural mesotheliomas from Argentina, Brazil, Colombia, Costa Rica, Panama, Mexico, Peru, Nicaragua, and Venezuela. The median patient age at diagnosis was 61.1 years, 63.2% had stage III disease, and 37.7% had stage IV disease. Compared with patients who had mesotheliomas in the United States and Europe, these Latin American patients were younger, the M:F ratio and the percentage of patients exposed to asbestos were lower, and, surprisingly, median survival was significantly longer than in the United States and Europe despite the advanced stages of all 302 patients. These findings might be consistent with a higher percentage of mesotheliomas linked to genetic predisposition, which are associated with these characteristics (see below), and possibly to better medical care. However, a significant concern when looking at these and other data from developing countries is that the information about methodology and accuracy of diagnosis is minimal. Recent articles indicate that there is a very high rate of incorrect diagnoses, ranging from approximately 14% in the Western world to approximately 50% in some developing countries, which can influence statistics including survival (see Diagnosis and Evaluation, below).

### Asbestos Exposure and Mesothelioma in the 21st Century

A recent meta-analysis explored the association between non-occupational exposure to asbestos and pleural mesothelioma. Eighteen studies in 12 countries comprising 665 cases were included; a significantly increased risk of pleural mesothelioma was reported for both household exposure (odds ratio [OR], 5.4; 95% CI, 2.6–11.2) and neighborhood exposure (OR, 6.9; 95% CI, 4.2–11.4). Different strengths of association were observed according to fiber type, with the strongest associations noted when amphibole was present and the weakest when chrysotile was present. Therefore, the types of fibers to which residents are exposed influence mesothelioma rates. Crocidolite and amosite fibers are considered the main cause of mesothelioma among occupationally exposed individuals.

Toxicological studies in rodents suggest that fiber length influences pathogenesis: the longer the fibers (longer than 5–20 μm), the more carcinogenic they are in rodents. Erionite is the most potent fiber in causing mesothelioma upon inhalation in rodents and humans, yet most erionite fibers are shorter than 5 μm. A possible explanation for this paradox is that only a few longer fibers cause mesothelioma. However, the toxicological studies in rodents showing increased carcinogenicity of fibers longer than 5 μm cannot be extrapolated to human mesothelioma because these studies were conducted by intrapleural or intraperitoneal injection, thus bypassing the natural lung filter, where long fibers are trapped more easily than short ones.

Establishing accurate asbestos exposure is a complicated exercise. Histories of exposure are generally reliable at a cohort level, for example, when studying a cohort of individuals occupationally exposed to asbestos, such as asbestos miners, shipyards workers, etc, but their reliability decreases at the individual level because, within a given category of workers, exposure may vary greatly. Moreover, individuals may not correctly remember events that occurred 30 to 50 years earlier. The naked eye can only detect “dust,” whereas a microscope can establish whether a given dust contains asbestos and/or other carcinogenic fibers. To overcome this limitation, specific questionnaires were developed to capture exposure more reliably. These questionnaires were developed largely to identify different levels of exposure within occupationally exposed individuals—for example, an accountant and a miner both working for the same “asbestos” company, different lengths of employment, etc—but they are less reliable at identifying exposure among non-occupationally
established asbestos exposure with a certain level of reliability. Pleural plaques can be used to determine asbestos levels in the lung tissue (Fig. 1) and prover evidence of exposure, but they are rarely performed because of the lack of availability of lung biopsies, costs, and legal reasons. There was no correlation seen in a study of patients treated at the US National Cancer Institute that compared “asbestos exposure” (as determined by history of exposure obtained from patients with mesothelioma who were interviewed by trained nurses and aided by the American Thoracic Division of Lung Disease Adult Questionnaire) with lung content analyses in the same patients with mesothelioma. Several patients who did not report asbestos exposure contained asbestos levels in their lungs above background, and vice versa. In the absence of lung content analyses, the combination of a history of occupational exposure and radiological evidence of exposure, such as bilateral, calcified pleural plaques, and/or histological evidence of several asbestos fibers in lung tissue (Fig. 1) can be used to establish asbestos exposure with a certain level of reliability at the individual level. Pleural plaques are frequent in patients with mesothelioma; for example, they were found in 88% of asbestos-exposed patients with mesothelioma who had a history of exposure confirmed by lung content analyses.

Environmental Exposure to Asbestos and to Other Carcinogenic Fibers

Erionite is a carcinogenic fiber that has been linked to a mesothelioma epidemic in some Cappadocian villages in Turkey, where it is naturally present in the environment and where it was used to build homes and pave roads. In the United States, there are several deposits of naturally occurring erionite, and, after the discovery of oil in North Dakota, erionite has been increasingly used to pave over 300 miles of dirt roads, resulting in exposure levels measured in the air of transiting school buses similar to those measured in the Cappadocian villages. This is but one example of a recent environmental phenomenon with the development of rural areas in which some communities are inadvertently being exposed to carcinogenic fibers that are present in the environment and are released in the air because of human activities (mining, road construction, off-road driving, etc). Exposure and human disease, including mesothelioma caused by mineral fibers present in the environment, were documented in Turkey (erionite fibers), in Mexico (erionite), in New Caledonia (antigorite fibers) and other countries, and more recently in the states of North Dakota (erionite), Nevada (mainly actinolite asbestos and also the other types of “asbestos” fibers [erionite, winchite, richterite, and antigorite]), and California (mainly chrysotile and tremolite). In some of these countries and states, measures were introduced to reduce or eliminate exposure and prevent mesothelioma in future generations. As environmental exposure often begins at birth and occurs randomly among sexes, mesotheliomas caused by the environment (unlike those caused by occupational exposure) tend to occur at a younger age (<55 years) with an M:F ratio close to 1:1. However, not all mineral fibers are carcinogenic: a recent study demonstrated that palygorskite, a mineral fiber abundantly present in the Mojave Desert in Nevada and present in desert dust storms, is not carcinogenic.

Exposure to simian virus 40 and exposure to talc

Simian virus 40 (SV40) is a DNA tumor virus that causes mesothelioma in 60% of hamsters injected systemically, and that readily transforms human mesothelial cells and astrocytes in vitro. Millions of people were exposed to live, infectious SV40 that contaminated polio vaccines until 1963 in the United States and until at least 1978 in the former Soviet Union and member countries of the Soviet bloc. The possible link between SV40 and human mesothelioma was reviewed by the International Agency for Research on Cancer, which advised that SV40 is not classifiable as to its carcinogenicity to humans (group 3), and by the US National Academy of Medicine, which advised that “because the epidemiologic studies are sufficiently flawed, the evidence was inadequate to conclude whether or not the contaminated (SV40) polio vaccines caused cancer.”

Recently, there has been renewed interest regarding the hypothesis that talc, and/or talc contaminated with asbestos, causes mesothelioma and other cancers. Talc deposits may include asbestos minerals, such as chrysotile and amphiboles, and other mineral fibers that may be carried over into consumer products. Whether talc baby powders,
the use of which has been widespread worldwide in the past decades, are or were contaminated with asbestos or with other carcinogenic fibers, and whether the amounts of this eventual contamination are or were sufficient to cause mesothelioma is an hypothesis largely based on case reports. The authors are not aware of any supporting epidemiological or mechanistic studies or of experimental evidence in animals; however, this hypothesis may also depend on investigation of various talc commercial products. The International Agency for Research on Cancer stated that asbestos-free talc cannot be classified as to its carcinogenicity to humans (category 3), whereas the use of perineal talc is classified as a possible human carcinogen (category 2B), a conclusion that was challenged by a recent meta-analysis.

Summary: exposure to asbestos and to other fibers and mesothelioma

In countries where regulations have been in effect for several decades, there has been a decrease in mesothelioma incidence rates, but the rate of decrease so far has been much lower than predicted. Thus, the hope that mesothelioma would disappear after the implementation of strict regulations on asbestos has not materialized; instead, the number of new mesotheliomas per year and of deaths per year continue to increase both in high-resource countries and worldwide. There are many reasons that, in aggregate, help explain this increase: 1) the aging of the population (as mesothelioma incidence increases with age); 2) the ongoing use of over 2 million tons of asbestos per year, albeit mostly in developing countries where regulations are nonexistent, lax, or implemented only recently; 3) asbestos already “in place” from past industrial use; 4) increased environmental exposure to asbestos or to other carcinogenic fibers from geological sources as rural areas are being developed; and 5) mesotheliomas caused by genetic mutations, as discussed below.

Currently, the majority of pleural mesotheliomas occur in individuals occupationally exposed to asbestos, whereas peritoneal mesothelioma is rarely associated with asbestos exposure (see Unique Characteristics of Peritoneal Mesothelioma, below). However, as the cohorts of asbestos-exposed workers vanish (because of old age) from populations in which strict regulations have been implemented, the number of cases of mesothelioma linked to occupational asbestos exposure will steadily decrease in these populations, whereas the number attributed to the dispersal of geological deposits by new construction and to genetic predisposition (as associations with additional genes are recognized) will increase. Because only 6 of approximately 400 fiber types present in nature are regulated under the generic name of asbestos, many potentially carcinogenic fibers are not regulated and continue to cause human exposure and mesothelioma.

Carcinogenic Mechanisms

How Do Asbestos and Other Carcinogenic Fibers Cause Mesothelioma?

Older studies proposed that asbestos fibers are phagocytosed by, or simply “puncture,” human mesothelial cells and, once inside the cell, they can mechanically interfere with the cell spindle during mitosis, causing chromosomal alterations responsible for carcinogenesis. Although the images were impressive, these were all short-term studies: in these experiments, human mesothelial cells invariably died within 2 to 10 days from exposure because of the extensive genetic damage caused by asbestos, and no immortal cell lines ever emerged to support the hypothesis that such cells could evolve into a cancer. Moreover, mesothelial cells are much more susceptible than other cell types to asbestos cytotoxicity and are also more susceptible than rodent mesothelial cells to asbestos cytotoxicity. This raised an obvious paradox: how could asbestos cause mesothelioma if it kills human mesothelial cells? Numerous studies indicated that the chronic inflammatory process caused by the deposition of mineral fibers in tissues and the related production of mutagenic oxygen radicals induced by asbestos are responsible for asbestos pathogenesis and carcinogenesis. When asbestos and other fibers reach the pleura and peritoneum through lymphatics, they remain in place for months or years, triggering a chronic inflammatory process driven by high mobility group protein B1 (HMGB1) secretion and related inflammasome activation, which induces the activation of nuclear factor kappa-light-chain–enhancer of activated B cells (NF-κB) and the phosphatidylinositol 3-kinase (PI3K) pathways in mesothelial cells. This environment favors the growth of mesothelial cells that have accumulated mutations spontaneously or because they are exposed to mutagenic reactive oxygen species released by inflammatory cells around asbestos deposits. The longer biopersistence of crocidolite and erionite compared with chrysotile likely accounts for their increased pathogenicity.

The Role of Genetics

Cancer is caused by the accumulation of genetic damage. Genetic damage can be inherited, can develop spontaneously, can be caused by exposure to carcinogens and oncogenic infectious agents, or can be caused by the interplay of a combination of these factors. Currently, there is a very active debate about the relative contribution of these factors to human cancer.

Briefly, human cells accumulate approximately 3 or more mutations per division: because billions of cells divide each day, cancer is an inevitable risk in our lives. Some argue that spontaneous cancers, those occurring because cells develop “spontaneous” mutations when they
divide, are the cause of approximately two-thirds of all malignancies; others instead propose that environmental carcinogens, which induce additional genetic damage (“induced mutations,” such as ultraviolet light, asbestos, radiation, etc), cause greater than two-thirds of malignancies and that spontaneous mutations cause “only approximately 10% to 30% of cancers.” This issue is complex. The proportion of “spontaneous” versus “induced” cancers varies among different cancer types and among populations with various prevalence of carcinogenic exposures; thus, it is difficult to quantify the relative contribution of “spontaneous” versus “induced” mutations.

In addition to “spontaneous” and “induced” somatic mutations, a growing percentage of cancers are attributed to inherited mutations of DNA repair genes and of other genes that, when mutated, accelerate the accumulation of DNA damage and/or the percentage of cells carrying DNA damage. Inherited mutations may also increase susceptibility to environmental carcinogens (GxE interaction). Thus, the previous hypothesis, which focused almost exclusively on identifying human carcinogens to understand why cancer developed in some individuals, is now being integrated with studies aimed at including GxE interactions, which may better account for the observation that many are exposed but only few get cancer and that some cancers occur in unexposed individuals.

The concepts outlined above also apply also to mesothelioma, a cancer caused predominantly by occupational or environmental exposure to asbestos and to other carcinogenic fibers. In addition, the discovery that susceptibility to mesothelioma was transmitted in a Mendelian fashion in some families, and the subsequent discovery of a very high mesothelioma risk in family members who are heterozygous for inherited/germline \(BAP1\) mutations, underscore the role of genetics in mesothelioma and in other cancers. Over 600 articles have confirmed and expanded the pathogenic role of \(BAP1\) mutations in mesothelioma and in other cancers.

This condition was named the “\(BAP1\) cancer syndrome,” because affected family members developed multiple malignancies, predominantly mesotheliomas and uveal melanomas, and less frequently, skin melanomas, basal cell carcinomas, renal cell carcinomas of the clear cell type, breast carcinomas, cholangiocarcinomas, sarcomas, and various types of brain tumors. In addition, early in their 20s and 30s, individuals affected by the \(BAP1\) cancer syndrome develop benign melanocytic \(BAP1\)-mutated atypical intradermal tumors, with histological characteristics that clearly distinguish them from atypical Spitz tumors and melanomas. The detection of melanocytic \(BAP1\)-mutated atypical intradermal tumors allows dermatologists to suspect the diagnosis, which is then verified histologically and confirmed by DNA sequencing.

Over 200 families affected by the \(BAP1\) cancer syndrome have been described in the United States, Europe, Australia, and Asia. Moreover, somatically mutated (acquired mutations occurring during tumor cell growth) \(BAP1\) has been found in approximately 60% of mesotheliomas, underscoring the critical role that \(BAP1\) has in preventing mesothelioma growth.

\(BAP1\) is a deubiquitylase that modulates the activity of multiple genes and proteins controlling DNA replication, DNA repair, metabolism, and cell death. Recent reports have elucidated the mechanism responsible for the potent tumor suppressor activity of \(BAP1\). Bononi et al reported that, after DNA damage caused by asbestos, ultraviolet light, radiation, or chemotherapy, \(BAP1\) regulates both DNA repair and apoptosis.

In the cytoplasm, \(BAP1\) modulates the stability of the IP3R3 channel, which allows the flux of \(Ca^{2+}\) from the endoplasmic reticulum into the mitochondria, where \(Ca^{2+}\) is required for the Krebs cycle and, at higher doses, to execute apoptosis. Subsequently, Zhang et al reported that cells with reduced \(BAP1\) activity also have impaired ferroptosis, providing an additional mechanism by which \(BAP1\)-mutated cells escape cell death.
activity accumulate more DNA damage, as they cannot properly repair the DNA and, at the same time, they cannot execute apoptosis, which normally eliminates cells that contain genetic mutations, to prevent cancer (Fig. 3). As a consequence of the altered mitochondrial metabolism caused by reduced Ca\(^{2+}\) levels, cells with BAP1 mutations derive energy largely through aerobic glycolysis, the so-called Warburg effect, a metabolic shift that favors malignant growth.

In summary, BAP1-mutant cells are prone to malignant transformation. Accordingly, all carriers of inherited heterozygous BAP1 mutations have developed at least one and often several cancers during their lifetime. Exposure to asbestos (mesothelioma), ultraviolet light (melanoma), ionizing radiation (any cancer), etc, may further increase the rate of tumor development (see also The Case for Genetic Testing and BAP1 as a Therapeutic Target, below).
Additional Germline Mutations That Predispose to Mesothelioma

In addition to BAP1, other tumor suppressor genes have recently been found to cause a hereditary predisposition to mesothelioma—and to other cancers—in several families in the United States and abroad: overall, at least 12% of mesotheliomas occur in carriers of genetic mutations.67-69 Most of these heterozygous germline mutations occur in genes that regulate DNA repair, such as MLH1, MLH3, TP53, BRCA2,67-69,71 etc. The penetrance and prevalence of different tumor types vary, depending on the gene involved: for example, approximately 100% of carriers of BAP1 and TP53 germline mutations developed one and often multiple cancers during their lifetime. In carriers of germline BAP1 mutations (BAP1 cancer syndrome), approximately one-third of cancers were mesotheliomas, whereas carriers of TP53 mutations (Li-Fraumeni cancer syndrome) mostly developed breast cancer (females), adrenocortical carcinomas, sarcomas and only occasionally developed mesotheliomas.

Similar to mesotheliomas caused by environmental exposure, those linked to inherited germline mutations occur at a younger age and with a M:F ratio close to 1:1.2,67,68 Thus, the combined presence of 1) clusters of mesotheliomas in young individuals, and 2) a M:F ratio of 1:1 is an indication of either environmental exposure, or genetic predisposition, or both. These clusters are difficult to detect from country-level or state-level records, in which the preponderance of asbestos-induced mesotheliomas masks them; instead, these clusters are better identified at the county or city/town level.6 Discovering these clusters of mesothelioma can lead to life-saving measures for prevention and/or early detection of mesothelioma and other syndromic cancers,2 as outlined below (see The Case for Genetic Testing).

Genomics

Because of the carcinogenic “field effect” caused by asbestos, mesotheliomas are often polyclonal.89,90 Recently, The Cancer Genome Atlas program published a study of 74 mesotheliomas that were investigated for genetic alterations using next-generation sequencing (NGS), including whole-exome sequencing (WES), messenger RNA expression, methylation analysis, microRNA expression,
exomes, reverse-phase protein array, and transcription factor analyses.\textsuperscript{91} Confirming a previous comprehensive NGS study by Bueno et al.\textsuperscript{82} Hmeljak et al.\textsuperscript{91} reported frequent mutations of CDKN2A, NF2, TP53, LAT52, and SETD2 (Fig. 4).\textsuperscript{82,91} In addition, they\textsuperscript{91} reported a 57% prevalence of BAP1 mutations, confirming a previous comprehensive analysis that reported a 60% prevalence of BAP1 mutations.\textsuperscript{78} It is both surprising and reassuring that this study did not identify any new common mutations/deletions in mesotheliomas\textsuperscript{91}: thus, the current understanding of genetic lesions in dominant clonal populations in mesotheliomas may be complete.\textsuperscript{78,82,92} However, the study by Bueno et al. was conducted at 100 times sequencing depth with greater than 80% cellularity, and thus 100 reads × 0.8 indicates 80 reads, a sufficient number of reads to reliably identify most genuine mutations. Instead, the WES in the study by Hmeljak et al. was conducted at 30 times sequencing depth (ie, 30 sequence reads) with an estimated 60% tumor cellularity, and thus 30 reads × 0.6 indicates 18 reads.\textsuperscript{91} In other words, a given base could be covered by as few as 18 reads, which is inadequate because approximately 100 reads are necessary for a reliable tumor tissue analysis. Shallower sequencing increases the likelihood of false-negative results (ie, failing
to identify mutations, especially mutations that are present in minor clonal populations). Of note, subclones and microdeletions are difficult to detect in WES and whole-tissue messenger RNA sequencing analysis, whereas targeted NGS, high-density arrays, and single-cell analysis may provide more information. In summary, the study by The Cancer Genome Atlas project confirmed previous findings.78-82,92

Recent work using targeted NGS and high-density arrays by Mansfield et al using mate-pair sequencing analyses and a previous study by Yoshikawa et al using targeted NGS in combination with high-density array comparative genomic hybridization revealed a much higher number of genetic alterations in mesothelioma than detected by NGS, including point mutations, minute deletions, and copy number changes. NGS is a technique designed to identify point mutations; therefore, larger genetic alterations are easily missed using this technique.79 Yoshikawa et al discovered that chromothripsis (ie, chromosome shattering followed by random chromosomal rearrangement) (Fig. 5A) causes some of the genetic alterations in mesothelioma,94 a finding independently confirmed by Mansfield et al93 and most recently by Oey et al. Moreover, Mansfield et al predicted that the vast array of genetic alterations in mesothelioma may lead to the production of neoantigens, which correlates with the clonal expansion of tumor-infiltrating lymphocytes. Early satiety and inability to lean forward can be observed in patients with ascites as a second site of disease.

Diagnosis and Evaluation

Pleural Mesothelioma: Clinical Presentation

Patients with pleural mesothelioma most commonly seek medical attention because of dyspnea, which is frequently associated with dry cough, chest pain, fatigue, and weight loss. Less frequent symptoms include night sweats and fever. Early satiety and inability to lean forward can be observed in patients with ascites as a second site of disease from the pleural mesothelioma (or in patients with peritoneal mesothelioma).

The dyspnea is predominantly related to the development of a pleural effusion. The suspicion of a pleural effusion on physical examination leads to the initial investigations with chest x-ray and computed tomography (CT) scan. The pleural effusion is then drained, and the fluid is examined cytologically. Pleural biopsy is often required for diagnosis, and pleurodesis with talc poudrage is often performed during the same surgical setting. Recognition and rapid investigations of the pleural or peritoneal effusion are key for early diagnosis. Delayed diagnosis will inevitably lead to tumor progression, limiting the therapeutic options.

Dyspnea and dry cough often persist despite the pleurodesis and worsens with disease progression because of progressive compression of the mediastinum and restriction of the involved lung. Signs and symptoms of mesothelioma progression frequently include worsening pain, weight loss, and fatigue. Care should be taken to provide optimal nutritional support to these patients. When possible, pleural effusions should be drained to relieve symptoms such as early satiety, inability to lean forward, and dyspnea. Distant metastases are often delayed or absent. In a postmortem study of 318 patients who had a diagnosis of pleural mesothelioma, distant metastasis was found in 55.4% of patients, and lymph node involvement was identified in 53.3%. Tumor dissemination was observed in the liver (31.9%), spleen (10.8%), thyroid (6.9%), and brain (3.0%). The precise cause of death was established in only 20% of patients, with bronchopneumonia and pulmonary emboli being the main causes. Other causes included cardiac tamponade and invasion of the great vessels. Cachexia was observed in up to 25% of patients and predominated in cases with no specific cause of death.

Mesothelium

A single layer of mesodermal cells resting on a basement membrane covers the celomic cavity. During the second month of human gestation, the celomic cavity is divided by the septum transversum into what will become the thoracic and abdominal cavities. This single layer of mesodermal cells does not further differentiate: postnatally, these cells are called mesothelial cells. The underlying vascularized fibroelastic connective tissue (as a supporting tissue) is important for stability and for separating mesothelium from underlying pulmonary parenchyma/alveoli; otherwise, any superficial mesothelial erosion would lead to pneumothorax. Because the connective tissue layer is not exposed to the surface, these cells are not present in the pleural/peritoneal fluid. Mesothelial cells retain pluripotential ability and can give rise to tumors with an epithelioid, sarcomatoid, or biphasic histology.96,97 This heterogeneity increases the risk of diagnostic errors, often with serious consequences for the patient.

Cytopathology

The reported sensitivity of the cytological diagnosis of mesothelioma is highly variable, ranging from dismal (<5%) to outstanding (>90%). Sarcomatoid mesotheliomas rarely cause an effusion and seldom exfoliate diagnostic cells. Even when there are sarcomatoid cells, they are sparse and difficult to evaluate.98,99 Our view is that cytopathology in experienced hands is very helpful—except with sarcomatoid mesothelioma—as usually the pleural fluid is the first specimen available to a pathologist to...
render or to suggest a diagnosis of mesothelioma or metastatic carcinoma to the pleura. “Normal” benign pleural fluid contains only mesothelial cells and inflammatory cells, and thus the presence of “foreign epithelial cells” is diagnostic of metastatic carcinoma. At times, metastatic carcinoma cells can elicit a florid mesothelial reaction, and they may be difficult to observe among an overwhelming number of reactive mesothelial cells: immunohistochemistry (IHC) for epithelial markers helps to define these metastatic cells. When only inflammatory cells and large numbers of atypical mesothelial cells forming large, 3-dimensional structures are noted—so-called cannon balls—the diagnosis of epithelioid mesothelioma is suspected. The cytopathological diagnosis should be confirmed by thoracoscopy-biopsy whenever possible. For peritoneal malignancies, a biopsy can be obtained more easily by laparoscopy. Importantly, atypical mesothelial cells forming 3-dimensional structures can be noted in several benign conditions, and thus it is critical that the cytopathologist is aware of the patient’s clinical history; we have seen benign conditions misdiagnosed as mesothelioma in children with pneumonia, in patients who had received radiation therapy, and in other pathologies that may cause the accumulation of pleural fluids with very atypical mesothelial cells. In these conditions, BAP1 IHC and fluorescence in situ hybridization or other analyses to detect homozygous deletion of the CDKN2A (p16) are very useful to separate benign mesothelial hyperplasia from mesothelioma.

**IHC and Other Ancillary Diagnostic Tests**

In expert hands, an IHC panel comprising a broad-spectrum antikeratin antibody—we recommend Cam 5.2, which stains approximately 100% of mesotheliomas (but also stains carcinomas)—as well as antibodies for calretinin, WT1, and 2 or more organ-specific epithelial IHC markers, depending on the differential diagnosis, together with histological evaluation and clinical history, usually suffice to correctly diagnose epithelial and biphasic mesothelioma. Only approximately 50% of sarcomatoid mesotheliomas will stain with calretinin or WT1 antibodies, whereas, with rare exceptions, close to 100% of them will stain with Cam5.2; however, Cam5.2 will also stain metastatic sarcomatoid carcinomas and carcinosarcomas. Recently, positive nuclear GATA3 staining in sarcomatoid mesothelioma has been proposed as a useful IHC marker in the differential diagnosis of sarcomatoid carcinomas, which usually are negative for GATA3—except for urothelial tumors, which are GATA3 positive. A new IHC marker, D2-40, for diagnosing epithelialid and sarcomatoid mesothelioma is very sensitive but lacks specificity.

Since 2011, when Carbone’s team reported that a lack of BAP1 nuclear staining reliably identified mesotheliomas with biallelic BAP1 mutation, BAP1 IHC has entered the routine of most pathology laboratories, improving the ability to diagnose mesothelioma. BAP1 wild-type (BAP1WT) is found in the nucleus and the cytoplasm, resulting in strong nuclear staining and less intense cytoplasmic staining. BAP1 mutations and deletions nearly always result either in the complete absence of staining or in cytoplasmic staining without nuclear staining. This is because: 1) deletions that cause truncated BAP1 proteins lack the carboxy terminus that contains the nuclear localization signal, and
2) mutations in the catalytic domain prevent the autodeubiquitylation of BAP1 required to enter the nucleus. All the different truncated and mutated forms of cytoplasmic BAP1 tested thus far have been biologically inactive. Because benign cells always show BAP1 nuclear staining, the absence of BAP1 nuclear staining is a specific and reliable marker to distinguish mesothelioma from benign atypical mesothelial hyperplasia at its earliest stages of development.

Overall, approximately 70% of epithelial and 50% of sarcomatoid mesotheliomas contain somatic BAP1 mutations, resulting in an absence of BAP1 nuclear staining. Unfortunately, positive BAP1 nuclear staining does not help to distinguish mesothelioma from benign mesothelial hyperplasia, because approximately 30% to 40% of mesotheliomas contain BAP1WT, and thus their tumor cells show BAP1 nuclear staining similar to benign lesions. In these cases, fluorescence in situ hybridization analyses for P16 mutations are helpful to identify malignancy. Finally, negative BAP1 staining in spindle cells helps identify biphasic mesothelioma from synovial sarcoma.

Considerations About the Accuracy of Diagnosis
When caring for a patient with mesothelioma, a critical issue is always whether the diagnosis is correct. Most pathologists have limited experience in diagnosing mesothelioma, thus increasing the risk of misdiagnosis. IHC is very helpful to increase the accuracy of diagnosis, yet an incorrect interpretation of IHC is often the cause of misdiagnoses. For example, calretinin and WT1, the most sensitive and specific IHC markers for mesothelioma, can also stain lung carcinomas, triple-negative breast carcinomas, carcinomas of mesonephric origin, etc, thereby underscoring the importance of applying strict criteria when evaluating the results of IHC. A recent study by French pathologists of 5258 mesotheliomas showed 69% concordance with the diagnosis between the collegial expertise of a team of pathologists with proven experience at diagnosing mesothelioma and the pathologists making the initial diagnosis. The expert panel changed the diagnosis of 14% of these 5258 mesotheliomas to either benign lesions, primary pleural or lung sarcomas invading the pleura, metastases from various carcinomas, or direct pleural invasion by lung cancer. The discrepancy regarding the histological subtype of mesothelioma was 16%. That study’s findings were almost identical to those of a previous (2006) study in which one-third of all mesotheliomas diagnosed in France were reviewed by a panel of pathologist with expertise in diagnosing mesothelioma. Therefore, the recent IHC improvements have not yet resulted in a parallel improvement in the accuracy of diagnosis. Similar or more pronounced rates of inaccurate diagnoses have been reported in other countries. In summary, we recommend that a pathologist experienced with diagnosing mesothelioma should confirm all diagnoses.

Staging and Prognosis
Staging Pleural Mesothelioma
There are substantial variations in the methods used for clinical staging. CT of the chest and upper abdomen, preferably performed with intravenous contrast and with slices of 3 mm or less in thickness, is considered the primary imaging modality. The now-routine inclusion of coronal and sagittal as well as axial images on CT helps to delineate tumor invasion of the chest wall and diaphragm, areas that historically have been difficult to evaluate. Positron emission tomography (PET)/CT identifies additional sites of disease not seen on CT in approximately 10% of patients and is also used to assess response in patients receiving systemic therapy. Additional methods used to evaluate the extent of disease include magnetic resonance imaging (MRI), laparoscopy, endobronchial ultrasound (EBUS) with lymph node biopsies, or mediastinoscopy to evaluate hilar and mediastinal lymph nodes. Although some institutions use all of these modalities routinely for pretreatment assessment, there is no universal standard. More frequently, CT and PET studies are obtained, and additional modalities are used selectively to refine clinical staging. MRI may further define chest wall and diaphragmatic tumor invasion, but whether it supersedes the combined value of axial, sagittal, and coronal CT imaging is unclear.

Analyses of a large international mesothelioma database developed by the International Association for the Study of Lung Cancer (IASLC) have refined the staging system for this disease, first proposed in 1995 by the International Mesothelioma Interest Group (IMIG). The current international malignant pleural mesothelioma staging system (eighth edition), based on the most recent analyses of the IASLC database, changed substantially between the sixth and seventh editions of the staging system.
Prognosis: Histology
Histology is a reliable prognostic marker. The Surveillance, Epidemiology, and End Results program documented that median survival was 14, 10, and 4 months for epithelial, biphasic, and sarcomatoid histological types of pleural mesothelioma, respectively (see Diagnosis and Evaluation, above).16 A South Wales study on 910 cases of pleural mesothelioma reported similar findings: the median survival was 13.3 months for epithelial mesothelioma compared with 6.2 months for sarcomatoid and biphasic mesotheliomas.17 Epithelioid mesotheliomas are the least aggressive: among them, some subtypes have a better prognosis than others. For example, Travis et al reported a median survival of 24.9 months and 17.9 months for trabecular and tubular-papillary subtypes, respectively, and 15.8 months and 13.7 months for micropapillary and solid subtypes, respectively.133 Biphasic and sarcomatoid mesotheliomas had a median survival of 7.0 months and 3.8 months, respectively.133 Sarcomatoid mesotheliomas have the worst prognosis, and a subset among them known as pleomorphic mesothelioma also have a dismal prognosis.133 Biphasic mesotheliomas with mixed epithelioid and sarcomatoid histologies behave more or less aggressively, depending on the percentage of the sarcomatoid component.18,21 Rarely, mesotheliomas can originate in the pericardium and in the tunica vaginalis, representing less than 1% of all cases.134 Recent studies using a combination of molecular analyses and histology are fine-tuning the prognostic accuracy of sporadic mesotheliomas.82

Prognosis: Who Are the High-Risk Patients for Surgical Failure in Pleural Mesothelioma?
When patients present with a diagnosis of mesothelioma, validated prognostic models exist in both nonsurgical and surgical patients, including the European Organization for Research and Treatment of Cancer135 and the Cancer and Leukemia Group B136 prognostic indices. Newer models include the Brims Prognostic Index137 and data from the IASLC/IMIG Mesothelioma Registry.138 Brims et al used classification and regression-tree analysis to define prognostic variables for 18-month survival. Four risk groups with clear survival differences were defined. The group with the best survival at 18 months had no weight loss, a hemoglobin level greater than 153 g/L (9.5 mmol/L), and a serum albumin level greater than 43 g/L. Weight loss and sarcomatoid histology identified patients with the poorest survival. The IASLC/IMIG Mesothelioma Registry found that histology, age, sex, and white blood cell and platelet counts stratified survival for 906 patients138; further validation can be found in the eighth edition of the Mesothelioma Staging Registry.130 Greater emphasis on preoperative quantitation imaging studies,131,132 including CT volume of the pleural mesothelioma or linear measurements at 3 levels127,139 or of diaphragm thickness,140 also may add to clinical/laboratory stratification. In the immediate future, greater use of novel IHC, genomic, and immune-based tissue biomarkers may influence whether surgical therapy is indicated.

More Favorable Prognosis in Mesothelioma Developing in Carriers of Germline Mutations
In 2015, Carbone’s team reported that patients with mesothelioma carrying germline mutations had a 7-fold improved survival.141 In a follow-up 2018 publication, this team tested the hypothesis that patients with mesothelioma who had a family history of mesothelioma and/or of other cancers and/or patients with early-onset mesothelioma (at age <50 years) were more likely carriers of inherited germline mutations, and these patients had a much improved survival. A total of 79 patients met these recruitment criteria. Inherited germline mutations were found in 28 of 50 probands (56%).67 Patients with mesothelioma who carried germline mutations experienced a significantly prolonged survival of 5 to ≥10 years, only 28% reported possible asbestos exposure, and the M:F and pleural vs peritoneum ratios were 1:1, underscoring the uniqueness of this subgroup of patients. Among them, 43 of 79 patients had deleterious germline BAP1 mutations: their median age at diagnosis was 54 years, and the median survival was 5 years.67 Among the remaining 36 patients with no BAP1 mutation, the median age at diagnosis was 45 years, the median survival was 9 years, and 12 of 36 patients (33%) had deleterious mutations of other tumor suppressors, such as MLH1 (Lynch syndrome), TP53 (Li-Fraumeni syndrome), and/or mutations in genes that regulate DNA repair or that were previously found mutated in mesothelioma.79,142 Thus, on one hand,
germline mutations favor the development of mesothelioma and of other cancers, but, conversely, for reasons that currently are unclear, these same mutations appear to mitigate aggressive tumor growth as these patients live much longer. Similarly, other malignancies occurring in carriers of various germline mutations are often associated with a prolonged survival.\textsuperscript{143-146}

Mesotheliomas in carriers of \textit{BAP1} mutations are almost exclusively of the epithelioid type, are well differentiated, and have an overall nonaggressive morphology, consistent with prolonged survival (ie, oval cells with bland nuclei, rare mitoses, no necrosis, etc).\textsuperscript{67} Mesotheliomas in carriers of other germline mutations seem to follow a similar trend, although relatively small numbers of them have been studied so far to be sure of this.\textsuperscript{67}

In a parallel 2018 study, Panou et al\textsuperscript{68} reported that 12% of 198 patients with mesothelioma treated at the University of Chicago carried pathogenic germline mutations, especially those with peritoneal mesothelioma, minimal asbestos exposure, young age, and a second cancer diagnosis. Among the germline mutations detected, \textit{BAP1} was the most common, accounting for 3% of all patients. In 2019, Hassan et al\textsuperscript{69} reported that 12% of consecutive patients with mesothelioma from the Thoracic Medical Oncology Clinic of the US National Cancer Institute carried pathogenic germline mutations—and \textit{BAP1} was the most commonly affected gene (7%). Mutations were more common in females and in patients with a second cancer diagnosis or with relatives diagnosed with mesothelioma, melanoma, or breast cancer. The authors observed a significantly improved survival among pleural mesotheliomas in carriers of germline mutations.\textsuperscript{69} Together, the remarkably similar findings of these studies provide compelling evidence that approximately 12% of mesotheliomas occur in carriers of pathogenic germline mutations. Among them, \textit{BAP1} mutations are the most common: in unselected patients, it was initially reported that 5% carried \textit{BAP1} mutations,\textsuperscript{66} and recent studies reported rates from 3% to 7%.\textsuperscript{58,69} The prevalence of \textit{BAP1} and other germline mutations in a population and the presence of asbestos and other fibers in the environment contribute to the incidence of mesothelioma among nonoccupationally exposed patients.\textsuperscript{68,69}

The Case for Genetic Testing
There are several reasons to justify genetic testing for patients with mesothelioma. When mesothelioma develops in carriers of germline mutations, they fare significantly better compared with the majority of mesotheliomas that develop in older patients with asbestos exposure. This information is very important for these patients. Also, in carriers of germline mutations of genes required for DNA repair (\textit{BAP1}, \textit{TP53}, \textit{BRCA1}/\textit{BRCA2}, etc),\textsuperscript{67,69} MRI should be preferred to imaging that uses ionizing radiation, which can cause secondary malignancies.\textsuperscript{147} Because these patients and their relatives who inherited the same mutations (the rate of transmission of heterozygous mutations is approximately 50%) are susceptible to developing multiple malignancies, they should be screened for early detection, which can be life-saving. For example, early detection of melanoma, renal cell carcinoma, and breast carcinoma (tumor types that are frequent in carriers of heterozygous \textit{BAP1} mutations) and of colon, ovarian, and endometrial cancers (frequent in carriers of heterozygous \textit{MLH1} mutations [Lynch syndrome]) can be life-saving.

Even for malignancies that might be difficult to cure by surgical resection, early diagnosis is associated with a better response to therapy and survival of 10 or more years.\textsuperscript{67} In this regard, mesothelioma is considered a malignancy that cannot be cured surgically; however, there are a few cases of patients from families with malignant mesothelioma caused by germline \textit{BAP1} or other tumor suppressor mutations who, because of screening and a high degree of suspicion, underwent surgery at a very early stage, and most of them are alive and apparently tumor-free 10 years post-surgical resection (2 of them at 18 years and 21 years, respectively, postsurgery).\textsuperscript{67} Thus, knowledge about the presence of germline mutations is relevant to patients, their relatives, and the physicians who have to plan their care. Moreover, a proportion of these germline mutations may be actionable, and patients can be enrolled in targeted clinical trials. Therefore, patients who present with clinical indicators denoting heritability (familial history of mesothelioma or other cancers at a young age [\textleq 50 years]) should undergo genetic testing by targeted NGS using a gene panel covering all DNA repair and tumor suppressor genes to test for cancer inheritability.\textsuperscript{67,69,142} Ideally, all patients with mesothelioma should undergo genetic testing together with genetic counseling.

Treatment
Surgery for Pleural Mesothelioma
The surgical management of pleural mesothelioma remains controversial: the reasons are outlined below. There are many unmet needs, different opinions, a modest amount of data, a lack of standardization for recommendation of the best surgical approach, and, most importantly, no proven survival benefit of aggressive surgical interventions. The unmet needs start in the areas of diagnosis. Whereas a diagnosis can sometimes be made from pleural fluid cytology, video-thoracoscopic (VATS) biopsy, preferably through a single port, remains the standard means of obtaining material for definitive pathological diagnosis.\textsuperscript{96} However, there are no surgical guidelines for how many intrathoracic sites should be biopsied or how much tissue should be obtained,
an important issue given the heterogeneity of mesothelioma, which can show different histology in different biopsies. Verification of adequate tissue for diagnosis by frozen section is useful during VATS, but no standards exist.

The selection of patients for surgical procedures is influenced by the patient’s performance status and cardiopulmonary reserve, and by the T and N categories. However, clinical staging methods, EBUS, and mediastinoscopy correlate poorly with pathological staging.

Two operations, extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D), are performed with curative intent. By contrast, partial pleurectomy or VATS with pleurecisis are performed with palliative intent to manage recurrent pleural effusions or to re-expand a partially entrapped lung. Surgery and the type of operation performed are influenced by the extent of disease and by the patient’s physiological reserve, particularly cardiopulmonary function. Both EPP and P/D aim to achieve a macroscopic complete resection of all tumor. EPP involves resection of the pleura along with the underlying lung, usually with the pericardium and diaphragm. P/D involves complete resection of the pleura without the underlying lung. A P/D that also involves resection of the pericardium and diaphragm is termed an extended P/D or EPD. For many years, EPP was regarded as the only potentially curative operation. However, during the past decade, multiple series have shown that the morbidity and mortality of EPP is higher (mortality in the range of 6% for EPP vs 3% for P/D or EPD), and that OS after EPP is probably lower than OS after P/D or EPD. Data from the IASLC database suggest that only a highly select group of younger patients with an epithelioid mesothelioma histological subtype and no lymph node metastases may experience improved long-term OS with EPP. Consequently, P/D and EPD have gradually become the main operations performed for pleural mesothelioma.

The pros and cons of EPP versus P/D or EPD and the role of surgical resection have been the focus of intense controversy. Although surgical resection is currently an accepted part of the treatment for physically fit patients who can have all gross tumor removed, there are many unanswered questions regarding surgery in mesothelioma. There is controversy about whether visually normal pleura, pericardium, and diaphragm (vs obvious gross tumor) should be removed during surgery, whether the visual absence of tumor in apparently normal areas should be confirmed intraoperatively by frozen sections, to what extent lymph nodes should be dissected, and how to describe the extent of residual disease at the end of resection. It is generally hypothesized that an R0 (microscopically negative margins) resection cannot be performed in pleural mesothelioma due to the proximity of the pleura to vital structures, such as the aorta and esophagus, and thus only an R1 or R2 (microscopically or macroscopically positive margins, respectively) resection can be achieved. However, no definitions exist to describe the amount of residual disease after R2 resection. For the purposes of recording data in the IASLC staging database, definitions used for optimal debulking in ovarian cancer surgery (≥1 cm or <1 cm residual tumor) have been empirically adopted. Evidence-based confirmation of the prognostic importance of these definitions is needed.

Finally, narrative operative reports do not capture all of the elements of surgical resection and residual disease. Synoptic operative reports, analogous to those routinely used by pathologists and radiologists, if adopted across the surgical community, may enhance analyses of tumor stage and prognostic factors.

Concerns About the Beneficial Effects of Surgery in Patients With Pleural Mesothelioma

The literature used to justify aggressive surgical resections such as EPP or EPD relies heavily on single-institution series of patients with early-stage, limited disease burden, epithelioid histology mesothelioma who are highly selected for surgical resection, leading to an inherent bias when reporting long-term survival outcomes in this group of patients postoperatively. Despite the selection of patients who are expected to have longer survival times based on baseline clinical characteristics, median survival after a major debulking surgery is routinely cited as 14 to 18 months after either EPP or P/D, which essentially is the same as among nonoperative patients. To date, only one prospective, randomized trial, the Mesothelioma and Radical Surgery (MARS) trial, has attempted to evaluate the added benefit of a surgical resection over chemotherapy alone. Not only did the MARS trial fail to show an added benefit of surgery, it demonstrated worse survival among patients who underwent EPP compared with a similar cohort of early-stage patients who were managed with chemotherapy alone. This trial has been criticized for its small sample size and high (19%) postoperative mortality rate in the EPP group, which impacted OS, and because the operations were done in multiple hospitals, including some with teams that did not have extensive experience with EPP; nevertheless, it remains the only randomized trial to date. An ongoing randomized clinical trial in the United Kingdom, “MARS 2,” should determine whether P/D or EPD after induction chemotherapy leads to superior outcomes compared with chemotherapy alone.

In addition to the lack of a proven benefit, there is also a significant risk of mortality and morbidity after a major surgical resection such as EPP or extended P/D that is often overlooked. Even at the most experienced, high-volume centers, 30-day or in-hospital mortality after EPP
is reported to be 5% to 7%, with postoperative mortality rates at the very best high-volume mesothelioma programs more than doubling to 11% when patients are followed up to 90 days postoperatively. For the patients who do survive surgery, most of the literature cites complication rates as high as 45%, and these studies also do not address the pain and suffering that patients endure to recover from a large thoracotomy, rib shingling or removal, with or without pneumonectomy. For these reasons, many thoracic surgeons have chosen to no longer perform EPP and favor extended P/D for mesothelioma. Survival outcomes improved from 15.6 months to 19.6 months in a center with the same surgeons and patient population when the practice of EPP was abandoned after publication of the MARS trial in 2011. Several meta-analyses have favored EPD over EPP because of the higher mortality after EPP without a survival benefit over EPD. Some thoracic surgeons believe that major surgical resections in mesothelioma do not improve survival and cannot be justified except in rare instances. There are surgeons who still perform EPP or EPDs routinely in the absence of data comparing nonsurgical with surgical patients who are propensity matched or without the results of MARS2, and therefore the role of surgery in mesothelioma remains controversial.

Novel Surgical Multimodality Therapy Approaches for Pleural Mesothelioma

Multimodality therapy is often used for clinical stage I to III pleural mesothelioma. However, the optimal combination therapy remains debated. The outcomes after induction chemotherapy followed by EPP and adjuvant hemithoracic radiation have been disappointing, with median survivals ranging between 16 and 20 months in trials that included more than 40 patients. However, patients who completed adjuvant hemithoracic radiation had a median survival of 29 to 39 months and achieved excellent local control. These results and studies in animal models and in vitro experiments suggest that, in contrast to current belief, mesotheliomas are sensitive to radiation. Cho et al developed a protocol that starts with hemithoracic radiation to deliver an optimal dose of radiation to the tumor before surgical resection. The concept of Surgery for Mesothelioma After Radiation Therapy (SMART) includes: 1) an induction dose of hemithoracic radiation before surgery; and 2) the application of an accelerated, hypofractionated hemithoracic regimen delivering 25 gray (Gy) in 5 fractions associated with a boost of 5 Gy to the gross disease. The results of this SMART approach have been encouraging, with an overall median survival of 36 months in epithelioid mesothelioma. Research in mice demonstrated that nonablative, hypofractionated radiation induces a specific activation of the immune system against mesothelioma with the development of an in situ vaccination, which is maintained through memory T cells directed against the tumor. Evidence from these mouse experiments and from palliative radiation in patients with mesothelioma suggest that a dose of radiation lower than 25 Gy in 5 fractions to the whole hemithorax may still be effective and limit the risks of pneumonitis in the underlying lung. Indeed, in contrast to normally fractionated radiation, hypofractionated radiation exerts its effect on the tumor through immune activation that is not dose-dependent. A lower dose of radiation to the whole hemithorax may boost mesothelioma sensitivity to an ablative dose of radiation and provide an optimal combination to ablate the gross disease and activate the immune system before surgery. The SMART approach may also provide an ideal platform to introduce immunotherapy as part of multimodality therapy.

In addition to radiation, other approaches have been tested in the multimodality setting. The most frequently used combination is tumor resection (P/D or EPP) followed by intraoperative lavage with chemotherapy compounds. Different drugs such as cisplatin, doxorubicin, mitomycin C, and gemcitabine have been used for this procedure. Although long-term survivors have been identified, this procedure is still considered investigational. Heated chemotherapy is often used in peritoneal mesothelioma (see Unique Characteristics of Peritoneal Mesothelioma, below). Unfortunately, no randomized studies have been performed to judge its additional value compared with the standard of care. Photodynamic therapy has had limited success. In this approach, the administration of laser light to the thoracic cavity after administration of a photosensitizing agent leads to a cell kill penetrating up to a few millimeters in the postsurgical tumor bed. Another approach, the application of a cisplatin-containing gel after resection, is currently being evaluated.

Tumor Immunology and Checkpoint Inhibitors in Pleural Mesothelioma

Most patients with mesothelioma are not offered surgery because of the extent of disease, advanced age, comorbidities, or poor performance status and are considered for palliative chemotherapy instead. With US Food and Drug Administration (FDA) approval in 2004, the gold standard of treatment for mesothelioma has been the combination of cisplatin and pemetrexed. A recent clinical trial demonstrated that the addition of bevacizumab improves survival over the use of the platinum-doublet alone, although this regimen has not been approved by the FDA.
to date. However, even with aggressive trimodality or bimodality therapy, the median survival for resectable pleural mesothelioma remains at 17 to 25 months and, for unresectable mesothelioma, it is 9 to 12 months.\textsuperscript{174} It is crucial to identify novel, well defined targets.

The biology of mesothelioma shows significant heterogeneity in both the tumor and the microenvironment. The inflammatory component often found to be associated with mesothelioma may influence survival.\textsuperscript{175,176} A large study performed a semiquantitative assessment of the inflammatory response in the tumor and in the stroma on routine hematoxylin and eosin–stained slides of epithelioid tumors obtained from patients with pleural mesothelioma (n = 175). Patients who had a high-grade chronic inflammatory response in the stroma (n = 59) had improved survival compared with those who had a low-grade chronic inflammatory response (n = 116; median OS, 19.4 months vs 15.0 months; \textit{P} = .01).\textsuperscript{177} A comprehensive investigation of tumor-infiltrating immune cells within the tumor nest and tumor-associated stroma in 230 patients indicated that stage and the presence of tumoral CD20–positive B lymphocytes were independently associated with survival. Tumors with high CD163–positive tumor-associated macrophages and low CD8–positive T-lymphocyte infiltration had the worst prognosis, and patients with low CD163–positive tumor-associated macrophages and high CD20–positive B lymphocyte infiltration had a better prognosis than other groups.\textsuperscript{175} Several studies proposed the prognostic role of T and B lymphocytes and macrophages and the presence of immunosuppression in pleural mesothelioma through analysis of T-cell–inhibitory receptors and chemokines.\textsuperscript{175,176} Bueno et al\textsuperscript{,82} using RNA sequencing, identified 4 different phenotypic clusters of molecular expression with divergent associated survival and mutational characteristics in 212 patients with mesothelioma. Programmed death-ligand 1 (PD-L1) was expressed in 39% of patients and was associated with a worse survival. PD-L1 expression was higher in nonepithelial mesotheliomas.\textsuperscript{82,178}

Clinical trials using cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitors failed to improve survival in mesothelioma.\textsuperscript{179} Subsequent trials suggested that PD-L1 inhibitors may benefit some patients.\textsuperscript{180} Several trials using checkpoint inhibitors in mesothelioma have met accrual goals or are recruiting. The experimental arms of these trials include combinations of PD-L1 inhibitors with CTLA-4 inhibitors, chemotherapy, or anti-body-drug conjugates.

In the first-line metastatic setting, the DREAM study (Durvalumab with First-Line Chemotherapy in Mesothelioma)\textsuperscript{181} investigated the addition of the PD-L1 inhibitor durvalumab to standard-of-care chemotherapy (cisplatin and pemetrexed, up to 6 cycles), followed by maintenance durvalumab every 3 cycles. The primary endpoint of progression-free survival was 57% at 6 months, with a median progression-free survival of 6.9 months. The median duration of response was 6.5 months. The additional toxicity (3 patients with grade 3 autoimmune toxicity requiring corticosteroid therapy) was considered acceptable. These results have led to an international, randomized, phase 3 study that is currently ongoing. In addition, the CheckMate743 study (A Phase III, Randomized, Open Label Trial of Nivolumab in Combination With Ipilimumab Versus Pemetrexed With Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma; ClinicalTrials.gov identifier NCT02899299), which started in 2018, has accrued 600 chemotherapy-naïve patients to test whether there is a benefit of combination immunotherapy (nivolumab plus ipilimumab) over standard-of-care chemotherapy; the results will be available soon. The major concern and limitations of the reported studies include a possible inconsistency in response evaluation because of the lack of a central review of responses or the lack of a control arm. Table 1 presents a summary of these studies. It is estimated that from 20% to 25% of patients with mesothelioma may benefit from checkpoint inhibitors.\textsuperscript{180–182} Most patients, however, do not meet the eligibility criteria to participate in phase 2 or 3 clinical trials. There are still many limitations in selecting patients for these treatments, including lack of predictive tests for benefits, absence of drugs to overcome resistance in initial responders, and therapies to convert nonresponding tumors into responsive tumors.

A priority is the identification of biomarkers that predict benefit or harm from immune checkpoint inhibitors. Reported toxicities are comparable to the use of immunotherapy in other tumors and can be managed with the standard of care.\textsuperscript{179–182} Other aspects of the antitumor immune response are being targeted in smaller studies and include vaccines, autologous T cells, chimeric antigen receptor T cells, and viral therapies. This plethora of trials will establish whether there is a role for immunotherapy and what role immunotherapy may have in mesothelioma.\textsuperscript{183}

**BAP1 as a Therapeutic Target**

As discussed above in the section BAP1 and Mesothelioma, BAP1 is an attractive therapeutic target and prognostic biomarker because it is the most frequently mutated gene in mesothelioma. Several of the pathways controlled by BAP1 already have drugs in development or work is ongoing to create new drugs.

Histones are among the BAP1 targets. The effect of histone deacetylase (HDAC) inhibitors on histone
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BAP1 modulates double-strand DNA damage repair.83,85 Cells with BAP1 mutations are more sensitive to both radiation and treatment with olaparib, a PARP inhibitor.188-190 There is an ongoing phase 2 study of olaparib in mesothelioma (ClinicalTrials.gov identifier NCT03531840). Patients who have been treated with cytotoxic chemotherapy are eligible to receive olaparib and will be analyzed in 3 separate groups: 1) those who have germline mutations in DNA repair genes; 2) those whose tumors have somatic BAP1 mutations; and 3) those who do not fall into group 1 or 2.

Felley-Bosco's team performed a genome-wide silencing screen in mesothelioma cell lines, revealing 11 hits (false discovery rate <0.05) that were more cytotoxic to BAP1-proficient cells.191 Two actionable targets, ribonucleotide reductase regulatory subunit M1 (RRM1) and ribonucleotide reductase regulatory subunit M2 (RRM2), were validated, and their inhibition, mediated by gemcitabine or hydroxyurea, was more cytotoxic to BAP1-proficient cells. A genetically engineered model was established expressing either functional or nonfunctional BAP1, and whole-genome small-interfering RNA screens were performed assessing cytotoxicity induced by gemcitabine and hydroxyurea in a panel of BAP1WT and BAP1-mutant/deleted cell lines. Functional studies were carried out in a BAP1-mutant/deleted cell line reconstituted with BAP1WT or BAP1C91A (catalytically dead mutant), and in a BAP1WT cell line upon small-interfering RNA-mediated BAP1 knockdown. Increased lethality mediated by gemcitabine and hydroxyurea was observed in NCI-H2452 cells reconstituted with BAP1WT, but not with BAP1C91A.191 These data indicate that BAP1 regulates RRM2 levels during replication stress and that patients could be stratified for gemcitabine

### TABLE 1. Overview of Clinical Outcomes of Studies With Immunotherapy in Malignant Mesothelioma

| OUTCOME | PEMBROLIZUMAB | AVENUMMA | NIVOLUMAB | NIVOLUMAB PLUS IPILIMUMAB | TREMELIMUMAB PLUS DURVALUMAB | TREMELIMUMAB PLUS DURVALUMAB | TREMELIMUMAB PLUS DURVALUMAB |
|---------|--------------|-----------|-----------|--------------------------|-----------------------------|-----------------------------|-----------------------------|
| No. of patients analyzed | | | | | | | |
| ORR, % | 20-21 | 15-18 | 9.4 | 15-29 | 26-28 | 7-14 | 10-18 |
| DCR, % | 63-72 | 43-67 | 56.6 | 43-67 | 52-72 | 52-72 | 52-72 |
| mPFS, mo | 4.5-5.5 | 4.5-5.5 | 4.5-5.5 | 4.5-5.5 | 4.5-5.5 | 4.5-5.5 | 4.5-5.5 |
| mOS, mo | | | | | | | |

Abbreviations: DCR, disease control rate; mPFS, median progression-free survival; mOS, median overall survival; NR, not reached; ORR, overall response rate.

A See Nowak A, Kok P, Lesterhuis W, et al. OA08.02 DREAM-a phase 2 trial of durvalumab with first line chemotherapy in mesothelioma: final results. J Thorac Oncol 2018;13(10 suppl):S338-S339 w
treatment, depending on BAP1 status. In a parallel study, Mutti’s team demonstrated that mesothelioma cells with functional BAP1 were more sensitive to gemcitabine treatment compared with cells bearing mutated and non-functional BAP1. Together, these independent studies indicate that it may be possible to identify those patients with mesothelioma—and possibly patients with any cancer—who are more likely to respond to gemcitabine based on BAP1 status.

Unique Characteristics of Peritoneal Mesothelioma
Diffuse malignant peritoneal mesothelioma (MPeM) represents approximately 15% to 20% of all mesothelioma diagnoses. Although it shares many similarities with the pleural form of mesothelioma, it has many unique features. It most often presents as a diffuse process arising from the serosa of the peritoneum. Morbidity and mortality from MPeM is almost always because of its propensity to locoregional progression. In contrast to pleural mesothelioma, MPeM is rarely associated with asbestos exposure; in a large series, only 8% of patients reported exposure, and MPeM afflicts men and women equally—as anticipated when mesothelioma is not caused by occupational exposure (see above). However, when MPeM occurs in individuals exposed to asbestos, they usually have a higher lung fiber burden than those with pleural mesotheliomas, possibly because a higher burden is required for asbestos fibers to bypass the lung filter and reach the peritoneum in sufficient amounts to cause mesothelioma. Proportionally, MPeM is observed in carriers of germline mutations more often than pleural mesothelioma, especially among patients who do not report asbestos exposure. A history of previous abdominal surgeries is common in these patients, supporting the theory that chronic inflammation, caused by asbestos, by other fibers, or after previous surgeries, promotes the malignant growth of mesothelial cells. The age at initial presentation ranges from 40 to 65 years. The average time from the onset of symptoms to diagnosis is approximately 5 months, and patients generally present with vague and ill-defined signs and symptoms, including abdominal pain and increasing abdominal girth secondary to ascites. Other symptoms are weight loss, dyspnea, chest pain, and a palpable abdominal mass on physical examination. In less than 10% of cases, MPeM manifests as a localized or focal circumscribed mass that may invade locally into adjacent organs. MPeM shows the same histological subtypes as pleural mesothelioma; the epithelioid type represents approximately 80% of tumors, and the presence of invasion here is critical. In fact, in addition to the benign/borderline mesothelial proliferation known as well-differentiated papillary mesothelioma and multicystic mesothelioma, MPeM can present an indolent, tubulopapillary, noninvasive histology that must be distinguished from tubulopapillary and solid MPeM with invasion, as the former are characterized by an indolent course, prolonged survival, and rare/no recurrence at 10 years, whereas the latter are much more aggressive. Accordingly, one hallmark feature of MPeM is the heterogeneity of its biological behavior: that is, disease progression is highly variable. A meta-analysis of 20 publications with data on outcomes of 1047 patients with MPeM treated with cytoreductive surgery (CRS) reported a 5-year survival of 42%. However, some patients will progress and die quickly after initial diagnosis and treatment, whereas others will live for years, even with evidence of active disease. Patients who have long survivals are mostly those with no invasion, some carry germline mutations.

In any individual with evidence of a diffuse malignant process in the abdominal cavity, the most likely diagnosis is peritoneal metastases from ovarian cancer in women or gastrointestinal cancer in men. However, the possibility of MPeM must be entertained and can be verified pathologically with an image-guided core needle biopsy or laparoscopic biopsy. Although a diagnosis of MPeM can be made on cytological evaluation, low cellularity is a common problem. As with pleural mesothelioma, a correct IHC assessment is critical for the definitive diagnosis of malignant pleural mesothelioma. Positive antibody staining for pankeratin, cytokeratins 5 and 6, calretinin, and WT1 indicates active disease. Patients who have long survivals are expected to have indolent, tubulopapillary, noninvasive histology that must be distinguished from tubulopapillary and solid MPeM with invasion, as the former are characterized by an indolent course, prolonged survival, and rare/no recurrence at 10 years, whereas the latter are much more aggressive. Accordingly, one hallmark feature of MPeM is the heterogeneity of its biological behavior: that is, disease progression is highly variable. A meta-analysis of 20 publications with data on outcomes of 1047 patients with MPeM treated with cytoreductive surgery (CRS) reported a 5-year survival of 42%. However, some patients will progress and die quickly after initial diagnosis and treatment, whereas others will live for years, even with evidence of active disease. Patients who have long survivals are mostly those with no invasion, some carry germline mutations.

There are no uniformly accepted standards for assessing the extent of disease in patients with MPeM. Although CT scanning is the staging modality most commonly used, MRI with specific acquisition protocols may be increasingly used in the future. The role of PET or PET/CT remains to be defined. Irregular or nodular peritoneal or mesenteric thickening, an omental mass, and ascites are common radiographic features. Unfavorable radiographic findings associated with a poor outcome include nodular thickening of the visceral peritoneal surfaces with marked distortion of the normal architecture of the bowel or signs of bowel obstruction.

There is no uniformly accepted staging system for patients with MPeM, but the peritoneal cancer index (PCI) is commonly used to codify the extent of disease in the abdomen. When using the PCI, the abdominal cavity is divided into a grid of 9 sections: the small bowel and its
mesentery are divided into 4 sections, and each is assigned a value from 0 (no gross disease) to 3 (extensive disease). By convention, the PCI has usually been divided into quartiles (1-10, 11-20, 21-30, and >30) to identify progressively advanced disease.

CRS with some type of regional perioperative chemotherapy is the optimal initial treatment in selected patients with MPeM, and it is associated with survival ranging between 34 and 92 months. Perioperative therapy has been delivered as either hyperthermic intraoperative peritoneal chemotherapy (HIPEC) or early postoperative intraperitoneal chemotherapy (EPIC). Data reporting outcomes of patients treated with CRS and HIPEC are derived from retrospective analyses. Factors important in patient selection for CRS and HIPEC are good performance status, a disease burden and tumor distribution that are favorable for a complete or near complete CRS, young age, female sex, epithelioid histology, and the absence of preoperative thrombocytosis. Age older than 60 years, male sex, biphasic or sarcomatoid histology, tumor invasion into adjacent tissue on histopathology, and pretreatment thrombocytosis are all associated with shortened survival. The largest multicenter retrospective study included results from 29 centers for 405 patients treated in both the United States and Europe. The perioperative treatments administered were not controlled. The actuarial median OS was 53 months. Factors that were independently associated with improved outcome included favorable (epithelioid) histologic subtype, absence of lymph node metastases, completeness of CRS, and the administration of HIPEC. A second large, retrospective review of outcomes of 211 patients with MPeM who were treated at 3 centers in the United States showed similar outcomes. The actuarial median OS was 38 months, and factors that were independently associated with improved outcome were age younger than 60 years, completeness of cytoreduction, favorable tumor histology, and the use of cisplatin versus mitomycin c administered through HIPEC. It was also noted that, in patients who had a suboptimal cytoreduction, HIPEC conferred no clinical benefit. A meta-analysis showed that the use of EPIC and the use of cisplatin were associated with prolonged survival. These studies were conducted before the discovery that patients with MPeM carrying germline mutations almost always had well-differentiated MPeM and prolonged survival, and thus future studies will have to include genetic testing for the proper evaluation of factors influencing survival.

Treatment morbidity from CRS and HIPEC can be significant and should be considered in any patient for whom CRS and HIPEC are contemplated. In 65 patients with MPeM who underwent CRS and HIPEC, major postoperative morbidity was 35%, and the 60-day mortality rate was 6%. On multivariate analysis, postoperative sepsis was significantly associated with shortened survival. Other studies have reported operative mortality rates of less than 2%. Together, these data suggest that careful patient selection and expertise in patient management are essential to optimize outcomes in patients with MPeM who undergo CRS and HIPEC.

The most active chemotherapy regimen for patients with MPeM is a doublet of pemetrexed and cisplatin, as established by data from the US Expanded Access Program: the overall response rate was 26%, and the stable disease rate was 45% for a combined disease control rate of 71%. Systemic therapy is usually reserved for patients who are not operative candidates for CRS and HIPEC. The benefit of systemic chemotherapy in a neoadjuvant or adjuvant setting around CRS and HIPEC has not been established. In general, the use of chemotherapy before or after a planned CRS and HIPEC procedure should be individualized and reserved for those who may not be medically optimized for immediate operative intervention or whose histopathology indicates a very high risk for early recurrence and progression.

**Summary**

After the vast use of asbestos during World War II, the incidence of mesothelioma increased significantly: for decades, almost all patients were asbestos workers. As the cohorts of asbestos workers vanish because of old age, increasing percentages of mesotheliomas, especially peritoneal mesotheliomas, occur in individuals who are not occupationally exposed to asbestos. These mesotheliomas may be caused by environmental exposure, genetic predisposition, or GxE interaction. A careful clinical history can help uncover environmental sources of exposure, alerting local health authorities to implement preventive measures that can be life-saving. Pathogenic germline mutations of BAP1 and, less frequently, of other tumor suppressor genes have been detected in approximately 12% of patients. This subgroup of genetically linked mesotheliomas occurs in younger individuals who rarely report asbestos exposure, with a M:F ratio of 1:1 and survival from 5 to 10 or more years. Genetic testing of relatives helps detect those who inherited the mutations and who will benefit from early detection screening, which can be life-saving. Genomic analyses revealed that BAP1 mutations are also the most commonly acquired mutations in sporadic mesotheliomas, providing a potential specific target. Clinical trials targeting pathways that are altered when BAP1 is mutated are ongoing. The recent evidence of the neoantigenic potential of chromothripsis and other patterns of chromosomal rearrangement in some mesotheliomas provides renewed hope that immunotherapy
may benefit patients with mesothelioma: several trials are being conducted. As we wait for the outcome of the ongoing clinical trials that, we hope, will improve therapeutic options, there are things that can be done to help patients: 1) reduce the percentage of misdiagnosis, estimated at 14% in France and as high as 50% in some developing countries, which leads to delays and inappropriate treatment; and 2) genotype patients to identify carriers of germine mutations and conduct genomic studies on tumor biopsies to identify actionable mutations.

References

1. Baumann F, Ambrosi JP, Carbone M. Asbestos is not just asbestos: an unrecognized health hazard. Lancet Oncol. 2013;14:576-578.
2. Carbone M, Kanodia S, Chao A, et al. Consensus report of the 2015 Weinman International Conference on Mesothelioma. J Thorac Oncol. 2016;11:1246-1262.
3. Goodman JE, Nascarella MA, Valberg DA, et al. Epidemiology of environmental exposure and malignant mesothelioma. J Thorac Oncol. 2017;12:1031-1045.
4. Stayner L, Welch LS, Lemen R. The worldwide epidemiology of asbestos-related diseases. Annu Rev Public Health. 2013;34:205-216.
5. Allen LP, Raze J, Stern MEC, Takahashi K, George F. Trends and the economic effect of asbestos bans and decline in asbestos consumption and production worldwide. Int J Environ Res Public Health. 2018;15 pii: E531.
6. Rojas L, Cardona AF, Trejo-Rosales R, et al. Characteristics and long-term outcomes of advanced pleural mesothelioma in Latin America (MeSO-CLiCaP). Thorac Cancer. 2019;10:508-518.
7. Meyerhoff RR, Yang CF, Speicher PJ, et al. Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database. J Surg Res. 2015;196:23-32.
8. Linton A, Pavlakis N, O’Connell R, et al. Factors associated with survival in a large series of patients with malignant pleural mesothelioma in New South Wales. Br J Cancer. 2014;111:1860-1869.
9. Baumann F, Carbone M. Environmental risk of mesothelioma in the United States: an emerging concern-epidemiological issues. J Toxicol Environ Health B Crit Rev. 2016;19(5-6):231-249.
10. Sun H. North-south gradient of mesothelioma and asbestos consumption-production in the United States-Progresses since the 1st asbestos partial ban in 1973. Am J Ind Med. 2019;62:337-346.
11. Camidge DR, Stockton DL, Bain M. Factors affecting the mesothelioma detection rate within national and international epidemiological studies: insights from Scottish linked cancer registry-mortality data. Br J Cancer. 2006;95:649-652.
12. Liu B, van Gerwen M, Bonassi S, Taioli E. Epidemiology of environmental exposure and malignant mesothelioma. J Thorac Oncol. 2017;12:1031-1045.
13. Stayner L, Welch LS, Lemen R. The worldwide epidemiology of asbestos-related diseases. Annu Rev Public Health. 2013;34:205-216.
14. Allen LP, Raze J, Stern MEC, Takahashi K, George F. Trends and the economic effect of asbestos bans and decline in asbestos consumption and production worldwide. Int J Environ Res Public Health. 2018;15 pii: E531.
15. Rojas L, Cardona AF, Trejo-Rosales R, et al. Characteristics and long-term outcomes of advanced pleural mesothelioma in Latin America (MeSO-CLiCaP). Thorac Cancer. 2019;10:508-518.
16. Meyerhoff RR, Yang CF, Speicher PJ, et al. Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database. J Surg Res. 2015;196:23-32.
17. Linton A, Pavlakis N, O’Connell R, et al. Factors associated with survival in a large series of patients with malignant pleural mesothelioma in New South Wales. Br J Cancer. 2014;111:1860-1869.
18. Galateau Salle F, Le Stang N, Nicholson AG, et al. New insights on diagnostic reproducibility of biphasic mesotheliomas: a multi-institutional evaluation by the International Mesothelioma Panel from the MESOPATH Reference Center. J Thorac Oncol. 2018;13:1189-1203.
19. Mao W, Zhang X, Guo Z, et al. Association of asbestos exposure with malignant mesothelioma incidence in eastern China. JAMA Oncol. 2017;3:562-564.
20. Guo Z, Carbone M, Zhang X, et al. Improving the accuracy of mesothelioma diagnosis in China. J Thorac Oncol. 2017;12:714-723.
21. Gilg Soit Ilg A, Ducamp S, Gramond C, et al. Programme national de surveillance du mesothéliome (PNSM). Actualisation des principaux résultats. Bull Epidemio Hebld (BEH). 2015;(3-4):28-37.
22. Marsh GM, Riordan AS, Keeton KA, Benson SM. Non-occupational exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. Occup Environ Med. 2017;74:838-846.
23. Sluis-Cremer GK, Liddell FD, Logan WP, Beuzidnenhout BN. The mortality of amphibole miners in South Africa, 1946-80. Br J Ind Med. 1992;49:566-575.
24. Dodson RF, O’Sullivan M, Corn CJ, McLarty JW, Hammar SP. Analysis of asbestos fiber burden in lung tissue from mesothelioma patients. Ultrastruct Pathol. 1997;21:321-336.
25. Pierce JS, McKinley MA, Pautenbach DJ, Finley BL. An evaluation of reported no-effect chrysotile asbestos exposures for lung cancer and mesothelioma. Crit Rev Toxicol. 2008;38:191-214.
26. Carbone M, Baris YI, Bertino P, et al. Erionite exposure in North Dakota and Turkish villages with mesothelioma. Proc Natl Acad Sci U S A. 2011;108:13618-13623.
27. Carbone M, Ly BH, Dodson RF, et al. Malignant mesothelioma: facts, myths, and hypotheses. J Cell Physiol. 2012;227:44-58.
28. Carbone M, Emri S, Dogan AU, et al. A mesothelioma epidemic in Cappadocia: scientific developments and unexpected social outcomes. Nat Rev Cancer. 2007;7:147-154.
29. Emri SA. The Cappadocia mesothelioma epidemic: its influence in Turkey and abroad. Ann Transl Med. 2017;5:239.
30. Wolfe C, Buck B, Miller A, et al. Exposure to naturally occurring mineral fibers due to off-road vehicle use: a review. Int J Hyg Environ Health. 2017;220:1230-1241.
31. Ortega-Guerrero MA, Carrasco-Nunez G, Barragan-Campos H, Ortega MR. High incidence of lung cancer and malignant mesothelioma linked to erionite fibre exposure in a rural community in central Mexico. Occup Environ Med. 2015;72:216-218.
32. Baumann F, Buck BJ, Metcalfe RV, McLaurin BT, Merker DJ, Carbone M. The presence of asbestos in the natural environment is likely related to mesothelioma in young individuals and women from southern Nevada. J Thorac Oncol. 2015;10:731-737.
33. Pan XL, Day HW, Wang W, Beckett LA, Schenker MB. Residential proximity to naturally occurring asbestos and mesothelioma risk in California. Am J Respir Crit Care Med. 2005;172:1019-1025.
34. Larson D, Powers A, Ambrosi JP, et al. Investigating palygorskite’s role in the development of mesothelioma in southern Nevada: insights into fiber-induced carcinogenicity. *J Toxicol Environ Health B Crit Rev*. 2016;19(5-6):213-230.

35. Carbone M, Rizzo P, Pass H. Simian virus 40: the link with human malignant mesothelioma is well established. *Anticancer Res.* 2000;20(2A):875-877.

36. Gazdar AF, Butel JS, Carbone M. SV40 and human tumours: myth, association or causality? *Nat Rev Cancer*. 2002;2:957-964.

37. Bocchetta M, Di Resta I, Powers A, et al. Human mesothelial cells are unusually susceptible to simian virus 40-mediated transformation and asbestos cocarcinogenicity. *Proc Natl Acad Sci U S A*. 2000;97:10214-10219.

38. Zhang L, Qi F, Gaudino G, et al. Tissue tropism of SV40 transformation of human cells: role of the viral regulatory region and of cellular oncogenes. *Genes Cancer*. 2010;1:1008-1020.

39. Cutrone R, Lednicky J, Dunn G, et al. Some oral poliovirus vaccines were contaminated with infectious SV40 after 1961. *Cancer Res*. 2005;65:10273-10279.

40. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Malaria and some polyomaviruses (SV40, BK, JC, and Merkel cell viruses). *IARC Monogr Eval Carcinog Risks Hum*. 2014;104:9-350.

41. Institute of Medicine Immunization Safety Review Committee; Stratton K, Almarrio DA, McCormick MC, eds. Immunization Safety Review: SV40 Contamination of Polio Vaccine and Cancer. Washington, DC: The National Academies Press; 2002.

42. Reger R, Morgan WK. On talc, tremolite, and tergiversation. *Br J Ind Med.* 1990;47:505-507.

43. Gordon RE, Fitzgerald S, Millette J. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. *Int J Occup Environ Health*. 2014;20:318-332.

44. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Carbon black, titanium dioxide, and talc. *IARC Monogr Eval Carcinog Risks Hum*. 2010;93:1-413.

45. Berge W, Mundt K, Luu H, Boffetta P. Genital use of talc and risk of ovarian cancer: a meta-analysis. *Eur J Cancer Prev*. 2018;27:248-257.

46. Price B, Ware A. Time trend of mesothelioma incidence in the United States and projection of future cases: an update based on SEER data for 1973 through 2005. *Crit Rev Toxicol*. 2009;39:576-588.

47. Olofsson K, Mark J. Specificity of asbestos-induced chromosomal aberrations in short-term cultured human mesothelial cells. *Cancer Genet Cytogenet*. 1989;41:33-39.

48. Yang H, Bocchetta M, Kroczyńska B, et al. TNF-alpha inhibits asbestos-induced cytotoxicity via NF-kappaB-dependent pathway, a possible mechanism for asbestos-induced oncogenesis. *Proc Natl Acad Sci U S A*. 2006;103:10397-10402.

49. Yang H, Rivera Z, Jube S, et al. Programmed necrosis induced by asbestos in human mesothelial cells causes high-mobility group box 1 protein release and resultant inflammation. *Proc Natl Acad Sci U S A*. 2010;107:12611-12616.

50. Xu A, Wu LJ, Santella RM, Hei TK. Role of oxyradicals in mutagenicity and DNA damage induced by crocidolite asbestos in mammalian cells. *Cancer Res.* 1999;59:5922-5926.

51. Qi F, Okimoto G, Jube S, et al. Continuous exposure to chrysotile asbestos can cause transformation of human mesothelial cells via HMGB1 and TNF-alpha signaling. *Am J Pathol*. 2013;183:1654-1666.

52. Carbone M, Yang H. Molecular pathways: targeting mechanisms of asbestos and erionite carcinogenesis in mesothelioma. *Clin Cancer Res*. 2012;18:598-604.

53. Thompson JK, Shukla A, Leggett AL, et al. Extracellular signal regulated kinase 5 and inflammasome in progression of mesothelioma. *Oncotarget*. 2018;9:293-305.

54. Ramos-Nino ME, Blumen SR, Sabo-Attwood T, et al. HGF mediates cell proliferation of human mesothelioma cells through a PI3K/MEK5/Fra-1 pathway. *Am J Respir Cell Mol Biol*. 2008;39:209-217.

55. Greaves M. Does everyone develop covert cancer? *Nat Rev Cancer*. 2014;14:209-210.

56. Tomasetti C, Vogelstein B. Cancer etiology, Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science*. 2015;347:78-81.

57. Tomasetti C, Li L, Vogelstein B. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science*. 2017;355:1330-1334.

58. Wu S, Powers S, Zhu W, Hannun YA. Substantial contribution of extrinsic risk factors to cancer development. *Nature*. 2016;529:43-47.

59. Wu S, Zhu W, Thompson P, Hannun YA. Evaluating intrinsic and non-intrinsic cancer risk factors. *Nat Commun*. 2018;9:3490.

60. Stahl PL, Stranneheim H, Asplund A, Berglund L, Ponten F, Lundeborg J. Sun-induced nonsynonymous p53 mutations are extensively accumulated and tolerated in normal appearing human skin. *J Invest Dermatol*. 2011;131:504-508.

61. Martincorena I, Roshan A, Gerstung M, et al. Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. *Science*. 2015;348:880-886.

62. Martincorena I, Fowler JC, Wabik A, et al. Somatic mutant clones colonize the human esophagus with age. *Science*. 2018;362:911-917.

63. Carbone M, Amelio I, Affar EB, et al. Consensus report of the 8 and 9th Weinman Symposium on Gene *Ex* Environ Interaction in Carcinogenesis: novel opportunities for precision medicine. *Cell Death Differ*. 2018;25:1885-1904.

64. Carbone M, Klein G, Gruber J, Wong M. Modern criteria to establish human cancer etiology. *Cancer Res*. 2004;64:5518-5524.

65. Roushdy-Hammady I, Siegel J, Emri S, Testa JR, Carbone M. Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. *Lancet*. 2001;357:444-445.

66. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. *Nat Genet*. 2011;43:1022-1025.

67. Pastorino S, Yoshikawa Y, Pass HI, et al. A subset of mesotheliomas with improved survival occurring in carriers of BAP1 and other germline mutations. *J Clin Oncol*. 2018;36:3485-3494.

68. Panou V, Gadiraju M, Wolin A, et al. Frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. *J Clin Oncol*. 2019;37:2863-2871.

69. Hassan R, Morrow B, Thomas A, et al. Inherited predisposition to malignant mesothelioma and overall survival following platinum chemotherapy. *Proc Natl Acad Sci U S A*. 2019;116:9008-9013.

70. Dey A, Seshasayee D, Noubade R, et al. Loss of the tumor suppressor BAP1 causes myeloid transformation. *Science*. 2012;337:1541-1546.

71. Ostrander GK, Cheng KC, Wolf JC, Wolfe MJ. Shark cartilage, cancer and the growing threat of pseudoscience. *Cancer Res*. 2004;64:8485-8491.
72. Carbone M, Ferris LK, Baumann F, et al. BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBATs. J Transl Med. 2012;10:179.

73. Carbone M, Flores EG, Emi M, et al. Combined genetic and genealogic studies uncover a large BAP1 cancer syndrome kindred tracing back nine generations to a common ancestor from the 1700s. PLoS Genet. 2015;11:e1005633.

74. Haugh AM, Njuw CN, Buhley JA, et al. Genotypic and phenotypic features of BAP1 cancer syndrome: a report of 8 new families and review of cases in the literature. JAMA Dermatol. 2017;153:999-1006.

75. Walpole S, Pritchard AL, Cebulla CM, et al. Comprehensive study of the clinical phenotype of germline BAP1 variant-carrying families worldwide. J Natl Cancer Inst. 2018;110:1328-1341.

76. Carbone M, Yang H, Pass HI, Krausz T, Testa JR, Gaudino G. BAP1 and cancer. Nat Rev Cancer. 2013;13:153-159.

77. Piris A, Mihm MC Jr, Hoang MP, et al. BAP1 and BRAFV600E expression in benign and malignant melanocytic proliferations. Hum Pathol. 2015;46:239-245.

78. Nasu M, Emi M, Pastorino S, et al. High incidence of somatic BAP1 alterations in sporadic malignant mesothelioma. Thorac Oncol. 2015;10:565-576.

79. Yoshikawa Y, Emi M, Hashimoto-Tamaoki T, et al. High-density array-CGH with targeted NGS unmasks multiple non-contiguous minute deletions on chromosome 3p21 in mesothelioma. Proc Natl Acad Sci U S A. 2016;113:13432-13437.

80. Guo G, Chmielecki J, Goparaju C, et al. Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma. Cancer Res. 2015;75:264-269.

81. Lo Iacono M, Monica V, Righi L, et al. Targeted next-generation sequencing of cancer genes in advanced stage malignant pleural mesothelioma: a retrospective study. J Thorac Oncol. 2015;10:492-499.

82. 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;48:407-416.

83. Yu H, Pak H, Hammond-Martel I, et al. Tumor suppressor and deubiquitinase BAP1 promotes DNA double-strand break repair. Proc Natl Acad Sci U S A. 2014;111:285-290.

84. Bononi A, Yang H, Giorgi C, et al. Germline BAP1 mutations induce a Warburg effect. Cell Death Differ. 2017;24:1694-1704.

85. Bononi A, Giorgi C, Patergnani S, et al. BAP1 regulates IP3R3-mediated Ca(2+) flux to mitochondria suppressing cell transformation. Nature. 2017;546:549-553.

86. Zhang Y, Shi J, Liu X, et al. BAP1 links metabolic regulation of ferroptosis to tumour suppression. Nat Cell Biol. 2018;20:1181-1192.

87. Affar EB, Carbone M. BAP1 regulates different mechanisms of cell death. Cell Death Dis. 2018;9:1151.

88. Napolitano A, Pellegrini L, Dey A, et al. Minimal asbestos exposure in germline BAP1 heterozygous mice is associated with deregulated inflammatory response and increased risk of mesothelioma. Oncogene. 2016;35:1996-2002.

89. Comertpay S, Pastorino S, Tanji M, et al. Evaluation of clonal origin of malignant mesothelioma. J Thorac Surg. 2014;12:301.

90. Oey H, Daniels M, Relan V, et al. Whole-genome sequencing of human malignant mesothelioma tumours and cell lines [published online April 25, 2019]. Carcinogenesis. doi:10.1093/carcin/bgz066

91. Hmeljak J, Sanchez-Vega F, Hoadley KA, et al. Integrative molecular characterization of malignant pleural mesothelioma. Cancer Discov. 2018;8:1548-1565.

92. Ugurluer G, Chang K, Gamez ME, et al. Genome-based mutational analysis by next generation sequencing in patients with malignant pleural and peritoneal mesothelioma. Anticancer Res. 2016;36:2331-2338.

93. Mansfield AS, Peikert T, Smadbeck JB, et al. Neoantigenic potential of complex chromosomal rearrangements in mesothelioma. J Thorac Oncol. 2019;14:276-287.

94. Carbone M, Yang H, Gaudino G. BAP1 and cancer. J Thorac Oncol. 2015;10:565-576.

95. Guo G, Chmielecki J, Goparaju C, et al. Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma. Cancer Res. 2015;75:264-269.

96. Lo Iacono M, Monica V, Righi L, et al. Targeted next-generation sequencing of cancer genes in advanced stage malignant pleural mesothelioma: a retrospective study. J Thorac Oncol. 2015;10:492-499.

97. 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;48:407-416.

98. Yu H, Pak H, Hammond-Martel I, et al. Tumor suppressor and deubiquitinase BAP1 promotes DNA double-strand break repair. Proc Natl Acad Sci U S A. 2014;111:285-290.

99. DeMay RM. The Art & Science of Cytopathology. Vol 1. Exfoliative Cytopathology. 2nd ed. Chicago, IL: American Society of Clinical Pathologists; 2011.

100. DeMay RM. The Art & Science of Cytopathology. Vol 3. Deep Aspiration Cytopathology. 2nd ed. Chicago, IL: American Society of Clinical Pathologists; 2011.
atypical ubiquitin ligase UBE2O. Mol Cell. 2014;54:392-406.

109. Churg A, Sheffield BS, Galateau-Salle F. New markers for separating benign from malignant mesothelial proliferations: are we there yet? Arch Pathol Lab Med. 2016;140:318-321.

110. Sheffield BS, Hwang HC, Lee AF, et al. BAP1 immunohistochemistry and p16 FISH to separate benign from malignant mesothelial proliferations. Am J Surg Pathol. 2015;39:977-982.

111. Churg A, Hwang H, Tan L, et al. Malignant mesothelioma in situ. Histopathology. 2018;72:1033-1038.

112. Righi L, Duregon E, Vatrano S, et al. BRCA1-associated protein 1 (BAP1) immunohistochemical expression as a diagnostic tool in malignant pleural mesothelioma classification: a large retrospective study. J Thorac Oncol. 2016;11:2006-2017.

113. Hwang HC, Pyott S, Rodriguez S, et al. BAP1 Immunohistochemistry and p16 FISH in the diagnosis of sarcomatous and desmoplastic mesotheliomas. Am J Surg Pathol. 2016;40:714-718.

114. Fresco R. Malignant mesothelioma electron microscopy. In: Pass HI, Vogelzang NJ, Carbone M, eds. Malignant Mesothelioma: Advances in Pathogenesis, Diagnosis, and Translational Therapies. New York, NY: Springer; 2005:508-516.

115. Carbone M, Rizzo P, Powers A, Fresco R, Krausz T. Molecular analyses, morphology and immunohistochemistry together differentiate pleural synovial sarcomas from mesotheliomas: clinical implications. Anticancer Res. 2002;22(6B):3443-3448.

116. Flores RM, Akhurst T, Gonen M, et al. Positron emission tomography predicts survival in malignant pleural mesothelioma. J Thorac Cardiovasc Surg. 2006;132:763-768.

117. Lee HY, Hyun SH, Lee KS, et al. Volumebased parameter of 18F-FDG PET/CT in malignant pleural mesothelioma: prediction of therapeutic response and prognostic implications. Ann Surg Oncol. 2010;17:2787-2794.

118. Erasmus JJ, Truong MT, Smythe WR, et al. Integrated computed tomography positron emission tomography in patients with potentially resectable malignant pleural mesothelioma: staging implications. J Thorac Cardiovasc Surg. 2005;129:1364-1370.

119. Conlon KC, Rusch VW, Gillern S. Laparoscopy: an important tool in the staging of malignant pleural mesothelioma. Ann Surg Oncol. 1996;3:489-494.

120. Pilling JE, Stewart DJ, Martin-Ulcar AE, Muller S, O’Byrne KJ, Waller DA. The case for routine cervical mediastinoscopy prior to radical surgery for malignant pleural mesothelioma. Eur J Cardiothorac Surg. 2004;25:497-501.

121. Tournoy KG, Burgers SA, Annema JT, et al. Transesophageal endoscopic ultrasound with fine needle aspiration in the preoperative staging of malignant pleural mesothelioma. Clin Cancer Res. 2008;14:6259-6263.

122. Giesel FL, Bischoff H, von Tengg-Kobligk H, et al. Dynamic contrast-enhanced MRI of malignant pleural mesothelioma: a feasibility study of noninvasive assessment, therapeutic follow-up, and possible predictor of improved outcome. Chest. 2006;129:1570-1576.

123. Coolen J, De Keyzer F, Nafeux P, et al. Malignant pleural disease: diagnosis by using diffusion-weighted and dynamic contrast-enhanced MR imaging—initial experience. Radiology. 2012;263:884-892.

124. Heelan RT, Rusch VW, Begg CB, Panicek DM, Caravelli JF, Eisen C. Staging of malignant pleural mesothelioma: comparison of CT and MR imaging. AJR Am J Roentgenol. 1999;172:1039-1047.

125. Rice DC, Stelig MA, Stewart J, et al. Endoscopic ultrasound-guided fine needle aspiration for staging of malignant pleural mesothelioma. Ann Thorac Surg. 2009;88:862-868; discussion 868-869.

126. Rusch VW, Giroux D, Kennedy C, et al. Initial analysis of the International Association for the Study of Lung Cancer Mesothelioma database. J Thorac Oncol. 2012;7:1631-1639.

127. 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;11:2089-2099.

128. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma. From the International Mesothelioma Interest Group. Chest. 1995;108:1122-1128.

129. Rice D, Chansky K, Nowak A, et al. The IASLC Mesothelioma Staging Project: proposals for revisions of the N descriptors in the forthcoming eighth edition of the TNM classification for pleural mesothelioma. J Thorac Oncol. 2016;11:2100-2111.

130. Rusch VW, Chansky K, Kindler HL, et al. The IASLC Mesothelioma Staging Project: proposals for the M descriptors and for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for mesothelioma. J Thorac Oncol. 2016;11:2112-2119.

131. Rusch VW, Gill R, Mitchell A, et al. A multicenter study of volumetric computed tomography for staging malignant pleural mesothelioma. Ann Thorac Surg. 2016;102:1059-1066.

132. Gill RR, Naidich DP, Mitchell A, et al. North American multicenter volumetric CT study for clinical staging of malignant pleural mesothelioma: feasibility and logistics of setting up a quantitative imaging study. J Thorac Oncol. 2016;11:1335-1344.

133. Kadota K, Suzuki K, Sima CS, Rusch VW, Adusumilli PS, Travis WD. Pleomorphic epithelioid diffuse malignant pleural mesothelioma: a clinicopathological review and conceptual proposal to reclassify as biphasic or desmocellular mesothelioma. J Thorac Oncol. 2011;6:896-904.

134. Mezei G, Chang ET, Mowat FS, Moolgavkar SH. Epidemiology of mesothelioma of the pericardium and tunica vaginalis testis. Ann Epidemiol. 2017;27:348-359.e11.

135. Curran D, Sahmoud T, Therasse P, Van MJ, Postmus PE, Giaccone G. Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. J Clin Oncol. 1998;16:145-152.

136. Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuky Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. Chest. 1998;113:723-731.

137. 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.

138. Pass HI, Giroux D, Kennedy C, et al. Supplementary prognostic variables for pleural mesothelioma: a report from the IASLC Staging Committee. J Thorac Oncol. 2014;9:856-864.

139. Armato SG 3rd, 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.

140. de Perrot M, Dong Z, Bradbury P, et al. Impact of tumour thickness on survival after radical radiation and surgery in malignant pleural mesothelioma. Eur Respir J. 2017;49 pii: 1601428.

141. Baumann F, Flores E, Napolitano A, et al. Mesotheliomapatients withgermine
BAP1 mutations have 7-fold improved long-term survival. *Carcinogenesis.* 2015; 36:76-81.

142. Betti M, Casalone E, Ferrante D, et al. Germline mutations in DNA repair genes predispose asbestos-exposed patients to malignant pleural mesothelioma. *Cancer Lett.* 2017;405:38-45.

143. Copson ER, Maishman TA, Tapper WJ, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. *Lancet Oncol.* 2018;19:169-180.

144. Helfferich J, Nijmeijer R, Brouwer OF, et al. Trimodality strategy for treating epithelioid malignant pleural mesothelioma: results in 285 patients. *Ann Thorac Surg.* 2008;85:257-264; discussion 264.

145. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol.* 2011;12:763-772.

146. Meclan RR, Berger A, Sima CS, et al. Thirty-day mortality underestimates the risk of early death after major resections for thoracic malignancies. *Ann Thorac Surg.* 2014;98:1769-1774; discussion 1774-1765.

147. Batirel HF, Metintas M, Caglar HB, et al. Adoption of pleurectomy and decortication for malignant mesothelioma leads to similar survival as extrapleural pneumonectomy. *J Thorac Cardiovasc Surg.* 2016;151:478-484.

148. Rice D, Rusch V, Pass H, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group. *J Thorac Oncol.* 2011;6:1304-1312.

149. Sugarbaker DJ, Richards WG, Bueno R. Extrapleural pneumonectomy in the treatment of epithelialoid malignant pleural mesothelioma: novel prognostic implications of combined N1 and N2 nodal involvement based on experience in 529 patients. *Ann Surg.* 2014;260:577-580; discussion 580-572.

150. 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;135:620-626, 626.e1-e3.

151. Kindler HL, Ismaila N, Armato SG 3rd, et al. Treatment of malignant pleural mesothelioma: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2018;36:1343-1373.

152. Flores RM, Zakowski M, Venkatraman E, et al. Prognostic factors in the treatment of malignant pleural mesothelioma at a large tertiary referral center. *J Thorac Oncol.* 2007;2:957-965.

153. Cao C, Tian D, Park J, Allan J, Pataky KA, Yan TD. A systematic review and meta-analysis of surgical treatments for malignant pleural mesothelioma. *Lung Cancer.* 2014;83:240-245.

154. Schipper PH, Nichols FC, Thomse KM, et al. Malignant pleural mesothelioma: surgical management in 285 patients. *Ann Thorac Surg.* 2008;85:257-264; discussion 264.

155. Perrot M, Wu L, Wu M, Cho BCJ. Radiotherapy for the treatment of malignant pleural mesothelioma. *Lancet Oncol.* 2017;18:e532-e542.

156. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol.* 2016;17:e473.

157. Alexander HR Jr, Bartlett DL, PINGPANK JF, et al. Treatment factors associated with long-term survival after cytoreductive surgery and regional chemotherapy for patients with peritoneal mesothelioma. *Surgery.* 2013;153:779-786.

158. Pass HI, DeLaney TF, Tochner Z, et al. Intraoperative photodynamic therapy: results of a phase I trial. *Ann Surg Oncol.* 1994;1:28-37.

159. Baas P, Murer L, Zoetmulder FA, et al. Photodynamic therapy as adjuvant therapy in surgically treated pleural malignancies. *Br J Cancer.* 1997;76:819-826.

160. University of Zurich. Intracavitary Cisplatin-Fibrin Localized Chemotherapy After P/D or EPP for Malignant Pleural Mesothelioma. ClinicalTrials.gov identifier NCT01644994. ClinicalTrials.gov/show/NCT01644994.

161. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. A phase I study of Foscan-mediated photodynamic therapy and surgery in patients with mesothelioma. *Ann Thorac Surg.* 2003;75:952-959.

162. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma and Radical Surgery (MARS) randomised, controlled, open-label, phase 3 trial. *Lancet.* 2016;387:1405-1414.
174. Tsao AS, Lindwasser OW, Adjei AA, et al. Current and future management of malignant mesothelioma: a consensus report from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation. J Thorac Oncol. 2018;13:1655-1667.

175. Suzuki K, Kadota K, Sima CS, et al. Durvalumab with first line chemotherapy for malignant pleural mesothelioma (KEYNOTE-028): preliminary analysis. J Thorac Oncol. 2018;13:606-623.

176. Ujiie H, Kadota K, Nitadori JI, et al. Monoubiquitination of ASXL1 controls the deubiquitinating activity of the tumor suppressor BAP1. Nat Commun. 2018;9:4385.

177. McCambridge AJ, Napolitano A, Mansfield AS, et al. Progress in the management of malignant pleural mesothelioma in 2017. J Thorac Oncol. 2018;13:1765-1773.

178. Mutti L, Peikert T, Robinson BWS, et al. Scientific advances and new frontiers in mesothelioma therapeutics. J Thorac Oncol. 2018;13:1269-1283.

179. Metaxas Y, Rivalland G, Gauti LA, et al. Pembrolizumab as palliative immunotherapy in malignant pleural mesothelioma. J Thorac Oncol. 2018;13(10 suppl):S338-S339.

180. Dozier J, Zheng H, Adusumilli PS. Clinical results of cytoreduction and HIPEC for malignant peritoneal mesothelioma: a systematic review and meta-analysis. Ann Surg Oncol. 2015;22:1686-1693.

181. Parrotta R, Okonska A, Ronner M, et al. A novel BRCAl-associated protein-1 isoform affects response of mesothelioma cells to drugs impairing BRCAl-mediated DNA repair. J Thorac Oncol. 2017;12:1309-1319.

182. Krug LM, Kindler HL, Calvert H, et al. Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Oncol. 2015;16:447-456.

183. LaFave LM, Beguelin W, Koche R, et al. Loss of BAP1 function leads to EZH2-dependent transformation. Nat Med. 2015;21:1344-1349.

184. Reid A, de Klerk N, Ambrosini G, Olsen N, Pang SC, Musk AW. The additional risk of malignant mesothelioma in former workers and residents of Wittenoom with benign pleural disease or asbestosis. Occup Environ Med. 2005;62:665-669.

185. Ujiie H, Kadota K, Nitadori JI, et al. Identification of ALK rearrangements in malignant peritoneal mesothelioma. JAMA Oncol. 2018;4:235-238.

186. Hung YP, Dong F, Watkins JC, et al. Progression of BAP1 loss or inactivation in malignant mesothelioma. J Thorac Cancer. 2018;10:315-324.

187. Krug LM, Kindler HL, Calvert H, et al. Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Oncol. 2015;16:447-456.

188. Krug LM, Kindler HL, Calvert H, et al. Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Oncol. 2015;16:447-456.

189. Tsao AS, Lindwasser OW, Adjei AA, et al. Current and future management of malignant mesothelioma: a consensus report from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation. J Thorac Oncol. 2018;13:1655-1667.
207. Janne PA, Wozniak AJ, Belani CP, et al. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. *Clin Lung Cancer.* 2005;7:40-46.

208. Deraco M, Baratti D, Hutanu I, Bertuli R, Kusamura S. The role of perioperative systemic chemotherapy in diffuse malignant peritoneal mesothelioma patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol.* 2013;20:1093-1100.

209. Kepenekian V, Elias D, Passot G, et al. Diffuse malignant peritoneal mesothelioma: evaluation of systemic chemotherapy with comprehensive treatment through the RENAPE database: multi-institutional retrospective study. *Eur J Cancer.* 2016;65:69-79.