Malignant Pleural Mesothelioma: Factors Influencing the Prognosis

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Here we examine recent advances in the knowledge of this severe and heterogeneous malignancy, and we analyze the clinical significance of prognostic factors.

Introduction

Among the primary neoplasms of the chest, malignant pleural mesothelioma (MPM) has benefited less than others from the multidisciplinary advances of the past few decades. MPM is highly aggressive and still has a very poor prognosis. The majority of patients are diagnosed in advanced stages; thus, they are not candidates for surgical care and die within 10 to 17 months of first symptom onset, with a median survival of less than 12 months.[1]

Because of the difficulty in diagnosing and staging the tumor, especially in its initial clinical manifestations, management remains challenging. The unsatisfactory results obtained so far by surgery and multimodality combinations of conventional oncologic treatments have awakened interest in new and intriguing aspects of the disease.

Great efforts have recently been made to improve our knowledge of the molecular pathways and genetic changes involved in the disease, in order to enable researchers to paint a more accurate picture of the tumor—ideally, a true “fingerprint” of the neoplasm, with a high probability of predicting prognosis and facilitating the individualization of targeted therapies.

Here we examine recent advances in the knowledge of this severe and heterogeneous malignancy, and we analyze the clinical significance of prognostic factors.

Clinical Factors

The clinical factors relevant to management of MPM include basic epidemiologic variables, clinical condition, common blood assays, imaging assessment, and gross tumor features, as well as the anatomic extent of the disease. Many of these variables have been combined into prognostic categories to reinforce their predictive power.

Gender and age

Male gender is conventionally considered to be a predictor of poorer prognosis. Men are more likely to have had occupational exposure and to have had greater asbestos exposure, which results in more aggressive disease.[2]

Age is a potential prognostic factor, but its precise impact is difficult to define. Nonetheless, the onset of MPM in a young person is generally considered the result of an elevated asbestos exposure, thus implying a more aggressive disease. Older age is therefore considered a good predictor of longer survival, with an arbitrary cut-off that varies from 50 to 75 years.[2,3]

Asbestos exposure

Asbestos is the principal etiologic agent of MPM, leading to disease within a period of 10 to 30 years of exposure.[1,4] Although exposure to asbestos fibers should be considered as a risk factor more than a prognosticator, it has been suggested that longer duration and higher intensity of exposure to asbestos can lead to the development of more aggressive tumors.[4]

Symptoms

Severity of symptoms is generally related to extent of disease. Dyspnea and chest pain are simple but reliable clues to lung and chest wall invasion, related to a worse prognosis.[5,6] Loss of appetite and weight, likely resulting from tumor production of cachexia-inducing cytokines,[1] are included as negative factors in the European Organisation for Research and Treatment of Cancer (EORTC)
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Performance status and quality of life

Performance status is usually one of the strongest prognosticators of good surgical outcome. It is included in the two main prognostic scoring systems, the Cancer and Leukemia Group B (CALGB)[5] and EORTC[6] systems. Performance status has been measured by a variety of scales: that of the Eastern Cooperative Oncology Group (ECOG), that of the World Health Organization, and the Karnofsky index; the last of these is the most frequently used indicator of prognosis.[7] The introduction of scientific quantification of quality of life allowed a more precise evaluation of the influence quality of life has on prognosis. Scales of general health, such as the SF-36 Health Survey or the EORTC questionnaires, have been widely used to quantitate quality of life. Significant improvement in the physical component summary of the SF-36 Survey after extrapleural pneumonectomy has been associated with longer survival.[8]

Computed tomography (CT) scanning

The use of CT scanning as a prognostic tool has recently emerged as a result of the development of software that allows the quantification of tumor volume.[9] The Prospective Mesothelioma Staging Project, as part of their efforts to establish the bases of a new staging system, took into account CT evidence, using as a reference cutoff an estimated tumor volume of 500 cm³.[10]

Positron emission tomography (PET) scanning

An elevated standardized uptake value (SUV) on PET scanning is significantly associated with shorter survival, with a threshold value ranging from 4 to 10. [11,12] Furthermore, a correlation between a decrease in SUV after midterm chemotherapy and slower disease progression has been described.[12]

Histology

Three histological subtypes of MPM have been defined. Definitive diagnosis requires a panel of stains.[13] The epithelioid subtype accounts for 50% of cases, whereas the mixed and sarcomatoid types represent 34% and 16%, respectively.[13] A diagnosis of epithelioid subtype has the most clinical relevance. It influences the choice of therapeutic strategy, typically resulting in more aggressive surgical and medical procedures. The presence of an inflammatory stromal response demonstrated an association with improved survival.[14] Nonepithelioid subtypes have a worse prognosis and may be related to a higher amount and longer duration of exposure to asbestos. The sarcomatoid subtype categorically excludes patients from surgery, primarily because of the historic short postoperative survival in this patient subgroup.

Hematological disorders

The EORTC score includes an increase in the white blood cell count as a negative prognostic factor, due to the production of granulocyte colony-stimulating factors associated with this finding; the threshold used is \(8.3 \times 10^9/L\).[6] A poor prognosis is also seen in patients with a high blood neutrophil-to-lymphocyte ratio.[15] Increased platelet aggregation was included as a negative prognosticator in both the CALGB[5] and EORTC[6] scoring systems, with cut-off values of \(400 \times 10^9/L\) and \(350 \times 10^9/L\), respectively. It is theorized that platelet-derived growth factor (PDGF) and megakaryocyte potentiating factor (MPF) have roles in this phenomenon. Low hemoglobin level is another variable proposed as a negative predictor.[16] The cut-off value is indicated as 1 g/dL below the sex baseline (ie, 16 g/dL in males and 14 g/dL in females). Anemia (hemoglobin level below 10 g/dL) was recently shown to be a strong negative prognosticator.[17]

Enzyme disturbances

A shift of the metabolism towards aerobic glycolysis (resulting in the production of lactate) is characteristic of the most aggressive tumors. As a consequence, an elevated serum lactate dehydrogenase (LDH) level has been correlated with poor prognosis.[5] The CALGB score includes high levels of LDH as an indicator of poor prognosis, using as a threshold a level of 500 IU/L. 

FIGURE 1
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Staging

Staging describes the anatomical extent of the neoplasm. A variety of staging systems have been proposed.[18-20] To date, two retrospectively-based staging systems have been widely utilized: the Brigham and Women's Hospital system (Table 1), formulated according to the results of extrapleural pneumonectomy in trimodal therapy,[19] and the TNM classification developed by the International Mesothelioma Interest Group (Figure 1).[20] The majority of the studies using these two systems have assigned a prognostic value to the stage.[21-23] In the TNM classification, T status is not as strong a prognostic factor as N status. Mediastinal nodal involvement has been recognized as a critical component of staging, with a detrimental effect on survival.[19-23]TABLE 1

The Proposed International TNM Staging System for Malignant Pleural Mesothelioma

A recent review has proposed limiting use of the TNM classification just to MPM with epithelioid histology [21]; the authors also proposed adjustments to the T status classification criteria (Table 2). These new criteria improved the distribution of the stages and survival stratification: median survival values were 51, 26, 15, and 8 months in stages I, II, III, and IV, respectively.[21] A study of a larger group of patients from multiple centers enrolled in a prospective manner is presently ongoing by the International Association for the Study of Lung Cancer (IASLC).TABLE 2

Proposed Changes to IMIG TNM Staging System for Malignant Pleural Mesothelioma
Surgical radical resection

The completeness of surgical resection is an important prognostic factor.[23] Classic extrapleural pneumonectomy with en bloc hemidiaphragm and pericardium removal and mediastinal lymph node sampling is generally regarded as the most radical procedure. Although associated with greater morbidity and perioperative mortality, it may result in longer survival, especially when combined with multimodality therapies.[19] More recently, the National Comprehensive Cancer Network guidelines stated that radical pleurectomy/decortication represents the first surgical option for tumor not growing within the parenchyma.[24] This lung-sparing procedure entails resection of involved pleura, pericardium, and diaphragm, along with mediastinal lymph node sampling, and provides good symptomatic relief.[25]

To date, there has been a general consensus that these two operations are not comparable because they target different patients with different degrees of neoplastic local extension. However, we can assume that any surgery able to achieve radical eradication of all gross tumor is likely to have a survival benefit. Patients suitable for surgical resection should be at earlier stages, with good preoperative performance status and few comorbidities; such patients form a group that by definition has a better prognosis. The removal of all microscopic tumor is difficult to achieve.[19] The presence of occult disease can be demonstrated by immunohistochemistry and has been significantly associated with rapid macroscopic recurrence and a worse prognosis.[26]

Treatment-dependent factors

Complete eradication of microscopic disease has been shown to improve survival.[19] National Comprehensive Cancer Network [24] and European Society of Medical Oncology [27] guidelines indicate that multimodality treatment carried out by an experienced multidisciplinary team can achieve better outcomes. Patients who received complete adjuvant therapy demonstrated a longer survival compared with those who underwent surgery alone.[23] Chemotherapy and radiotherapy alone have very poor results,[24] underscoring the pivotal role of surgery. However, when surgical resection of all gross tumor is feasible, adjuvant and/or neoadjuvant therapies must always be planned.[27] The use of intraoperative hyperthermic intrapleural chemotherapy has been proposed as well and has been shown to have a significant survival advantage.[28]

The prognostic impact of including radiotherapy in the multimodality approach to MPM is currently under investigation. To improve local control after radical resection, it has been shown that both 3D conformal and intensity-modulated radiotherapy can be delivered at doses of > 45 Gy.[27] It has been documented that use of cisplatin as single-agent chemotherapy has unsatisfactory results.[27] Improvement in survival, along with a benefit in symptom control, has been achieved when platinum derivatives have been combined with new antifolate drugs such as pemetrexed (Alimta) or raltitrexed.[29] Chemosensitivity varies widely among individuals, and this may represent an important prognostic factor.[30] High expression of thymidylate synthase predicts a poor response to pemetrexed, and it has been documented as a prognosticator of shorter survival.[1]

Excision repair cross-complementation group 1 (ERCC1) is a protein involved in DNA nucleotide repair. Low expression of ERCC1 might predict increased sensitivity to platinum-based chemotherapy, thus implying a longer survival.[31]TABLE 3
**Prognostic scoring systems**

The difficulty in finding a single prognostic predictor has favored the development of clinical scoring systems. The CALGB system,[5] the EORTC system,[6] and the modified version of the latter[17] are summarized in **Table 3**. These systems identify low- and high-risk subgroups with different survival rates. A new combined prognostic system is currently being developed by IASLC using a database of more than 3000 surgically managed patients. It considers an initial group of prognostic factors called “core” factors, together with supplementary prognostic variables (**Table 3**). Apart from staging, the IASLC found that the most significant variables on multivariate analysis were histology, sex, age, white blood cell count, and platelet count.[32]

**Serum biomarkers**

Serum biomarkers are used primarily for early diagnosis, but they should also be used to monitor the evolution of the disease and to predict prognosis. Serum mesothelin is a three-form (variants 1, 2, and 3) differentiation antigen in mesothelial cells that is highly expressed in MPM. Abnormal serum levels are associated with a large tumor volume and have proved effective as a prognostic indicator.[33] MPF, mentioned above, is a soluble protein produced by proteolytic cleavage of the amyloid precursor protein mesothelin. It is secreted by MPM cells and has recently been shown to have a negative prognostic value.[33] Osteopontin is a glycoprotein involved in the adhesion of cells to the bone matrix. Serum levels of osteopontin are higher in MPM and are related to the duration of exposure to asbestos. Low serum levels of osteopontin are associated with a better overall survival.[33] More diffuse oncomarkers, such as soluble cytokeratin fragments (CYFRA) 21-1 and tissue polypeptide antigen (TPA) have been shown to have only a limited diagnostic or prognostic role.[1]

**Genetic Prognostic Factors**

The scant effectiveness of all conventional antitumor therapies in MPM has supported efforts to increase our knowledge of unidentified mechanisms involved in the genesis and development of the neoplasm. Tumor growth is controlled by several pathways, which are regulated by the activity of both intrinsic and extrinsic factors. Accordingly, a number of chromosomal, DNA, RNA, and gene abnormalities have recently been identified.[1,34] Their role as predictors of prognosis is currently under investigation and should be validated in larger and controlled studies.

**Chromosomal alterations**

Many chromosomal abnormalities found in MPM are correlated with patient survival.[1,34] Poor prognosis was found to be correlated with chromosome copy number deletions and alterations on the short arm of chromosome 7.[34] Homozygous **CDKN2A** deletion, detected by fluorescent in situ hybridization (FISH) analysis, is another significant independent adverse prognostic factor. This locus encodes both p16INK4a and p14ARF and may be altered in MPM.[35,36] An association has been hypothesized between 9p21.3 deletion encompassing the CDKN2A locus and short-term recurrence.[34]

**DNA methylation**

DNA methylation implies a downregulation of individual genes and is associated with a poor prognosis.[37] Patients with a low frequency of DNA methylation had significantly longer survival. Classification based on the methylation profile of patients identified subgroups characterized by different clinical outcomes.[37]

**MicroRNA expression**

MicroRNA expression has been shown to exhibit different and specific patterns in different histologic subtypes.[38] Downregulation of microRNA-17 and microRNA-30c in sarcomatoid MPM and upregulation of microRNA-29c in epithelioid-type MPM are significantly associated with better survival.[14] Increased expression of microRNA downregulates DNA methyltransferase and increases the demethylating genes, resulting in a significant decrease in proliferation, migration, invasion, and colony formation.[1]

**Gene mutations**

Gene mutations can interact with specific pathways that can be altered in MPM cells, paving the way
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for future targeted therapies. The \textit{TP53} gene, a tumor suppressor gene located at 17p13.1 that controls cell cycle and apoptosis, is mutated in many human cancers. \textit{TP53} alterations are considered a negative prognostic factor.[1]

Homozygous deletions of the locus \textit{INK4a/ARF} located on chromosome 9p21 may result in a deficiency of p14\textsuperscript{ARF}, an inhibitor of murine double minute 2 (MDM2); MDM2 inactivates the p53 pathway, thus limiting its tumor-suppressing effect.[35] The same locus encodes the p16\textsubscript{INK4a} protein, which inhibits the retinoblastoma protein (pRb), thereby inducing cell-cycle arrest in G1 phase. These mutations impede the functioning of the tumor suppressor pathway and are associated with poor survival.[36]

Another frequent gene mutation is that of the neurofibromatosis 2 (\textit{NF2}) gene. Mutations of this gene could be related to shorter survival.[34]

Four-gene signatures, which include \textit{KIAA097}, guanosine diphosphate–dissociation inhibitor 1, cytosolic thyroid hormone-binding protein, and an expressed sequence tag similar to the tumor antigen L6, correlated with good and poor prognostic groups.[34] In addition, an 11-gene, oncogene-driven pathway signature is associated with a poor prognosis.[1]

\textbf{Gene expression profiling}

Data from array-based studies indicate deregulation of gene expression in MPM.[39] Gene expression analyses (transcriptome and/or quantitative reverse transcriptase–polymerase chain reaction) lead to an improvement of prognostic power. Three ratios of gene expression (\textit{TM4SF1/PKM2, TM4SF1/ARHDDIA, COBLL1/ARHDDIA}) have proved capable of discriminating between high- and low-risk patients.[40]

Aurora kinases are serine/threonine kinases that play a crucial role in cell division by controlling the segregation of chromatids. Defects in the separation process can cause genetic instability, a condition that is highly associated with tumorigenesis and poor prognosis.[36]

Maternal embryonic leucine zipper kinase (MELK); BIRC5, an inhibitor of apoptosis; KIF4A, an adenosine triphosphate–dependent microtubule-based motor protein; and SEPT9, a member of the septin family involved in cytokinesis and cell-cycle control, are upregulated in some patients with MPM, and all are associated with poor prognosis.[36]

\textbf{Molecular Pathway Factors}

Tumor onset and growth is also related to a large number of deregulated molecular pathways. These involve various cell mechanisms, including growth factors, cell-cycle regulators, apoptosis, and angiogenesis. The major molecular pathways involved in MPM and their prognostic implications are summarized in Table 4.

\textbf{Oxidative stress}

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\textbf{Principal Prognostic Biomarkers} & \\
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The carcinogenic effects of asbestos fibers are the result both of direct action and of the creation of an induced inflammatory environment containing reactive oxygen and nitrogen species.[1] These reactive species are able to affect the equilibrium between mitosis and apoptosis, moving it toward excessive cell proliferation and the onset of cancer. Genes overexpressed in this cascade are mitogen-activated protein kinase (\textit{MAPK}), also known as extracellular signal–regulated kinase
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(ERK),[41] transcription factor activator protein 1, nuclear transcription factor κ light chain–enhancer of activated B cells (NF-κB),[42] and protein kinase C. Activations of the phosphatidylinositol 3 kinase plus protein kinase B (PI3K-AKT) and ERK pathways result in neoplastic cell survival and proliferation. The hyperactivation of the above-named genes may be associated with a poorer prognosis.[1] Cyclooxygenase-2 (COX-2) is implicated in many events in the tumorigenic process, producing highly reactive products that can affect cell growth, immune response, apoptosis, and angioneogenesis.[43] High COX-2 expression is a marker of poor prognosis in MPM, and may be a target for selective COX-2 inhibitors (eg, celecoxib [Celebrex], rofecoxib [Vioxx]).[43]

Growth factor receptors

Many growth factors appear to be highly expressed in MPM, and these may have some prognostic significance.[1,34] Epidermal growth factor (EGF) and its receptor (EGFR), a membrane receptor tyrosine kinase (RTK), are highly expressed in MPM and are statistically associated with unfavorable prognosis.[44] In vitro inhibition of EGF by specific RTK inhibitors resulted in control of tumor growth and inhibition of angiogenesis.[44] High expression of platelet-derived growth factor (PDGF) and/or its receptor (PDGFR) is strongly associated with shorter survival.[45] PDGFR is also an RTK that can be inactivated by selective inhibitors.

Vascular endothelial growth factor (VEGF) is a growth factor linked to angiogenesis and is overexpressed in MPM.[46] High expressions of VEGF and of its receptor (VEFGR) are correlated with the density of microvessels and high tumor necrosis.[46] An inverse relationship between placental growth factor (PIGF) expression and survival has recently been demonstrated in operated MPM, suggesting a central role for this factor in the recurrence and progression of disease.[47] Hepatocyte growth factor (HGF) is a multifunctional factor that induces cell proliferation. The receptor for HGF is synthesized from c-MET, a proto-oncogene with an RTK located on chromosome 7q31. Overexpression of HGF and c-MET is associated with increased angiogenesis.[48] Many attempts at using RTK inhibitors as MPM therapy have failed.[1] These unsatisfactory outcomes show that inhibition of a single factor is probably not sufficient to obtain a tumor suppressor effect; rather, the use of multiple inhibitors should be considered.[34]

Matrix metalloproteinases

Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, play a role in tumor angiogenesis and invasion. Increases in the inactive proprotein form of MMP-2 and total MMP-2 have been associated with poor survival on multivariate analysis.[49] High expression of MMP-14 has been associated with lower survival, and the MMP14 gene has been proposed as a potential MPM biomarker.[34]

Wnt signaling pathway

The Wnt signaling pathway is a network of proteins that transfers signals from cell surface receptors to DNA using β-catenin protein (Figure 2), thereby stimulating developmental processes, cell proliferation, and cell polarity. This pathway may be altered in MPM because of promoter hypermethylation of regulatory genes.[50] Its inhibition results in tumor reduction and apoptosis, whereas overexpression may portend a less favorable prognosis.[34]

Hippo pathway

The Hippo pathway is a novel and promising cell growth inhibitor pathway[34]; it involves signal transduction from membrane receptors (Fat) into the nucleus (Figure 2). Alterations in the Hippo pathway predispose to cell overgrowth. Merlin, the protein encoded by NF2, regulates cell growth by signaling via the Hippo pathway to inhibit the function of the transcriptional coactivator and candidate oncogene yes-associated protein 1 (YAP1),[51] which also interferes with the Wnt pathway. NF2 normally acts as a tumor suppressor gene and as a gatekeeper in asbestos-related MPM.[1] Disruption of NF2 signaling plays a major role in the development of MPM as demonstrated by the high rate of mutations seen in this tumor.

Ubiquitin/proteasome pathway

This pathway is related to many other pathways, including the NF-κB pathway, and to inhibitors of apoptosis. Complex proteasome subunits are upregulated in MPM,[34] whereas other proteins, such
as FAS-associated factor 1 (FAF1), are downregulated[52] and tend to be associated with a poorer prognosis.[34]

**Cell-cycle regulation**

The cell cycle is organized into many checkpoints regulated by the combination of proteins called cyclins with cyclin D–dependent kinases (CDKs).[1] These multimeric complexes are inhibited by CDK inhibitors such as p21 and p27 (Figure 2). The p53 tumor suppressor pathway is also involved in cell-cycle regulation, providing transcriptional control of various cell-cycle regulatory proteins, including p21, which is induced by activation of the p21 gene.[1] p27[53] and p21[54] have been associated with a statistically significant decrease in survival. As mentioned above, inactivation of genes located on the INK4/ARF locus and encoding the p14ARF and p16INK4a proteins leads to cell-cycle deregulation with uncontrolled proliferation. These events are associated with a poorer prognosis.[36]

The monoclonal antibody MIB-1 recognizes a nuclear protein, antigen Ki67, that is expressed in proliferating cells; MIB-1 can be used to assess the growth fraction in normal and neoplastic tissues. A close correlation between high expression of MIB-1 and aggressive biological behavior of MPM has been demonstrated.[55]

**Apoptosis**

Apoptosis is a process characterized by programmed cell death; it is used to control cellular proliferation and destruction. In MPM, the expression of genes that regulates apoptosis is altered.[1] Apoptosis is normally induced by extrinsic and intrinsic pathways (Figure 2). The extrinsic pathway is activated by ligands of the tumor necrosis factor family, the tumor-related apoptosis-inducing ligands (TRAIL). Most MPM cells are resistant to apoptosis induced by TRAIL; this may be due to overexpression of the caspase-8 inhibitor FLIP/CFLAR and by methylation of TRAIL receptors.[56]

Downregulation of TRAIL,[56] as well as overexpression of NF-κB, which protects the cell from apoptosis,[42] may have an impact on the prognosis.

**FIGURE 2**

Molecular Pathways of Potential Prognostic Value in Malignant Pleural Mesothelioma

The intrinsic pathway is triggered by internal apoptotic signals and involves release of cytochrome c from the mitochondrial intermembrane space. Mitochondrial membrane permeability is regulated by the B-cell lymphoma 2 (Bcl-2) family of proteins, which includes proapoptotic proteins (eg, Bax, Bak, Bad, Bid, Bim) and antiapoptotic proteins (eg, Bcl-2, Bcl-xL, and Mcl-1). Elevated expression of Bcl-xL was seen in all MPM cell lines,[57] and downregulation of Bcl-xL improves sensitivity to chemotherapeutic agents, thereby influencing prognosis. Conversely, reduced levels of Bax protein, which has proapoptotic activity, have been associated with a poor outcome.[58]

The phosphatase and tensin homolog (PTEN) enzyme is a tumor suppressor that functions as a negative regulator of the combined PI3K-AKT pathway and mammalian target of rapamycin (mTOR) pathway, which promote cell growth and impede apoptosis (Figure 2).[59] Hence, PTEN inhibits cell division and directs cells to programmed death. High expression of PTEN has been correlated with better survival,[59] and its inactivation may account for poorer prognosis.

Another apoptotic protein is glucose transporter-1 (GLUT1), which regulates glycolysis. Its overexpression, measured with immunohistochemistry in MPM samples, has proved to be correlated with lower survival.[60]

**Telomerase activity**

The length of human telomeres is believed to be directly proportional to the number of possible cell divisions and is therefore correlated with cell life expectancy. Telomere lengthening is promoted by...
the enzyme telomerase, which can prolong the cell lifespan. Deregulated telomerase activity could be at the basis of unlimited growth of the tumor cell. Telomerase activity was found overexpressed in MPM, and a significant correlation with tumor relapse and short disease-free survival has been documented.[61]

**Aquaporin 1 (AQP1)**

AQP1 is a protein in the cell membrane that is involved in the transport of water, in cell motility, and in proliferation. Its expression in ≥ 50% of tumor cells proved an independent prognostic factor in MPM regardless of treatment.[62] Labeling immunohistochemistry for AQP1 should be included in the routine work-up of patients with MPM. An agonist or blocker of AQP1 may be found to be useful for treatment.[62]

**Calretinin**

Calretinin is a vitamin D–dependent calcium-binding protein involved in calcium signaling. This protein plays a role in message targeting and intracellular calcium buffering. Low expression of calretinin was independently associated with a poor prognosis in MPM patients undergoing extrapleural pneumonectomy.[63]

**Conclusions**

A body of literature has developed covering the numerous investigations that have been conducted on MPM. Despite relevant advances in many areas, including improvements in diagnosis, staging, and the clinical course of treated patients, MPM remains a rare but highly lethal disease characterized by a markedly aggressive local evolution with progressive loss of pulmonary function. Thus, MPM is a continuing challenge for thoracic surgeons and for medical and radiation oncologists. More recently, geneticists and biologists interested in better understanding the behavior of the disease have joined the ranks of those attempting to address the challenges of MPM.

The therapeutic role of surgery is still vigorously debated, despite a remarkable decrease in operative morbidity and mortality. The decision to operate is dependent on many factors, which necessarily include specific features and effects of the disease, along with the experience of the surgeon and the results of the preoperative and intraoperative evaluations. Now, in selected patients, surgery combined with chemotherapy and radiation therapy seems to provide the greatest benefit in terms of survival and quality of life.

Attention should also be paid to the study of prognostic factors, novel biomarkers, and genetic abnormalities. These all might be of help in formulating an early diagnosis as well as in selecting a more accurately targeted treatment. Until the suggested novel gene and immunologic therapies have demonstrated their effectiveness, the best approach that can be offered to patients remains as extensive a surgical cytoreduction as possible, followed by adjuvant chemo- and radiotherapy. Still, an adequate knowledge and evaluation of prognostic factors can help in defining the multidisciplinary approach to therapy in order to reduce the mortality from this lethal disease. Finally, it is important that the rarity of this neoplasm not be an obstacle to research into the optimal general approach to treatment and management.

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