13 Advances in Clinical Research and Management of Diffuse Peritoneal Mesothelioma

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Diffuse malignant mesothelioma is a tumor arising from the serosal surfaces of the pleura, peritoneum, pericardium, or tunica vaginalis testis. Although the tumor is exceedingly uncommon, there is a substantial interest in this disease, as either biological or occupational and medical-legal issues are concerned: Asbestos is the principal carcinogen associated with malignant mesothelioma, and up to 8 million living persons in the USA have been occupationally exposed to asbestos over the last five decades (Robinson and Lake 2005).

Diffuse malignant peritoneal mesothelioma (DMPM) is a rapidly fatal disease for which conventional therapy, such as palliative surgery, radiotherapy, and systemic or intraperitoneal (IP) chemotherapy is unsatisfactory. Only in recent years have prospective trials of multimodality treatment consisting of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) reportedly resulted in a survival advantage for selected patients.

13.1 Epidemiology

About 2,500 new cases of mesothelioma are registered each year in the United States (Price 1997). The incidence of malignant mesothelioma has been rising worldwide since 1970, and it has been estimated that a 5%–10% increase in annual mortality rate will be observed worldwide at least until 2020 (Peto et al. 1995). The disease has likely already reached the incidence peak in the USA (Archer and Rom 1983). In contrast, in Europe (Peto et al. 1999) and Australia (Leigh and Robinson 2002) the peaks are not expected to occur for another 10–15 years. In Japan, as well as in other countries where wide use of asbestos was observed later then in the western world, peak incidence of mesothelioma is delaying (Murajama 2004). Moreover, the increased use of asbestos in developing countries is expected to result in an increase of mesothelioma incidence unless stringent occupational controls are put in place (Takayhashi 2004).

Mesothelioma is approximately threefold more common in males than in females. Incidence rises with age and is about 10-fold higher in individuals 60 to 64 years old than in those 30 to 34 years old (Price 1997).

Peritoneal mesothelioma accounts for 10% to 20% of all forms of malignant mesothelioma. A recent analysis of the Surveillance Epidemiology and End Results (SEER) database estimated a yearly incidence of 250 cases in the USA (Price 2003).

13.2 Etiology

The link between malignant mesothelioma and asbestos exposure was first reported by Wagner in 1960 in South Africa's Cape Prov-

ince (Wagner et al 1960). In the 1960s and 1970s many case-controlled studies confirmed the association between both occupational and occasional asbestos exposure and this neoplasm (Spirtas et al. 2004). McDonald summarized data from 43 cohort studies and observed an overall proportional cancer-specific mortality rate of 2.5 to 102.3 in individuals exposed to asbestos (McDonald 2000). Subjects at risk for developing asbestos-related mesothelioma can be categorized as follows: workers directly exposed to asbestos during its mining or milling; workers exposed during use or manufacture of asbestos products, such as plumbers, carpenters, defense personnel, and insulation installers; people exposed incidentally to environmental asbestos contamination (Leigh and Robinson 2002).

No asbestos exposure can be documented in approximately 20% to 40% of patients with mesothelioma. Furthermore, the neoplasm is characterized by a long latency (up to 40 years) from asbestos exposure (McDonald 1985). These data suggest that other etiological factors may be determinant and that multiple somatic genetic events are required for mesothelioma oncogenesis.

13.2.1 Asbestos-Induced Oncogenesis

Asbestos induces mesothelioma by means of the following mechanisms: (1) asbestos fibers penetrate into the lung and hence enter the pleura, originating scarring (plaques) and malignant disease; (2) asbestos fibers may sever or pierce the mitotic spindle and disrupt mitosis, resulting in aneuploidy or other chromosomal damage; (3) asbestos induces the generation of iron-related reactive oxygen species that cause DNA alterations; (4) asbestos induces phosphorylation of the mitogen-activated protein kinases and the extracellular signal-regulated kinases. Such alterations increase the expression of early-response proto-oncogenes (Robinson et al. 2005). Crocidolite fiber is the most oncogenic form of asbestos; other fibers have less convincing evidence for causing mesothelioma (Pisick and Salgia 2005).

The role of asbestos exposure in the origin of DMPM has not been as well established as in pleural mesothelioma, especially in women. Spirtas et al. recorded in a case-control study 88% of pleural mesothelioma and 58% of peritoneal mesothelioma directly related to past asbestos exposure among men. By contrast, only 20% of women with peritoneal mesothelioma had past asbestos exposure (Spirtas et al. 1994). Several epidemiological studies have reported increased incidence of DMPM in men working in crocidolite mines and in male insulation workers. Risk of developing DMPM was significantly related to intensity of exposure to asbestos (Hassan and Alexander 2005). A case-control study was conducted at the Washington Cancer Institute on 40 patients with confirmed diagnosis of DMPM; 16 of them were females. A strong association between occupational asbestos exposure and DMPM was observed in men but not in women. Therefore, it has been suggested that the epidemiology and progress of DMPM may differ between men and women (Sugarbaker et al. 2003). Other possible etiologies of DMPM are abdominal external beam radiation for testicular carcinoma or cervical cancer (Antman et al. 1983), chronic peritonitis, and administration of thorotrast (Maurer and Egloff 1975).

13.2.2 Oncogenesis Not Related to Asbestos

Simian virus 40 (SV40) is a DNA virus that has been implicated as a possible cofactor in mesothelioma oncogenesis, although its role remains controversial. SV40 has demonstrated to be an oncogenic virus in rodent and human cells by a mechanism of tumor-suppressor gene blocking; SV40 DNA sequences have been found in malignant mesothelioma as well as in atypical mesothelial proliferation and noninvasive mesothelial lesions (Gazdar and Carbone 2004).

The hypothesis of a genetic susceptibility with an autosomal dominant pattern is based on the observations gathered in Cappadocia. Among inhabitants of two villages built from stone that contains a large amount of asbestos fibers, it has been documented that approximately 50% of deaths can be attributed to malignant mesothelioma (Baris et al. 1978).

Interestingly, in a nearby town that was built with stone from the same cave, no cases of mesothelioma were recorded. The researcher found that about 50% of descendants of affected parents develop the disease; when a person from an unaffected family marries a member of an affected family, their descendants develop mesothelioma (Roushdy-Hammady et al. 2001).

13.2.3 Molecular Biology

The biology of peritoneal mesothelioma is largely unknown, and the cellular and molecular bases for its proliferative potential and relative resistance to therapy have not yet been elucidated. One of the hallmarks of cancer cells is their limitless replicative potential. In a high percentage of human tumors the attainment of immortality is due to the reactivation of telomerase, an RNA-dependent DNA polymerase that stabilizes telomeres and allows cells to avoid the senescence checkpoint (Blackburn 2001), and may therefore contribute to tumorigenesis and neoplastic progression (Hahn et al. 1999). The core enzyme consists of an RNA component (hTR) that provides the template for the de novo synthesis of telomeric DNA and a catalytic subunit (hTERT, human telomerase reverse transcriptase) with reverse transcriptase activity (Cong et al. 2002). Some tumors, however, maintain their telomeres by one or more mechanisms referred to as alternative lengthening of telomeres (ALT) (Bryan et al. 1997). Telomere dynamics in ALT cells are consistent with a recombination-based mechanism, and characteristics of ALT cells include unusually long and heterogeneous telomeres and subnuclear structures termed ALT-associated promyelocytic leukemia (PML) bodies (APBs) that contain telomeric DNA, telomere-specific binding proteins. and proteins involved in DNA recombination and replication (Dunham et al. 2000). Based on the limited information available thus far, it appears that ALT is more frequently present in tumors of mesenchymal origin than in those of epithelial origin, possibly because of a tighter repression of telomerase in normal mesenchymal than in epithelial cells (Henson et al. 2002). Although it is well known that telomerase is largely expressed in pleural mesotheliomas (Kumaki et al. 2002), no information is available thus far concerning the presence of telomere maintenance mechanisms in DMPM. In this context, we analyzed the expression of telomere maintenance mechanisms in 28 DMPM specimens obtained from patients who underwent cytoreductive surgery at our Institute. Telomerase activity, as detected by the Telomeric Repeat Amplification Protocol (TRAP) assay, was present in 19 of 28 cases (67.9%). Moreover, in all telomerase-positive specimens a full-length hTERT transcript was detected. All telomerase-negative cases were characterized by the presence of APBs, as assessed by a combined PML immunofluorescence/telomere FISH approach, in sufficient percentage of cells (>0.5%) to be defined as ALT-positive according to Henson (Henson et al. 2005). Moreover, when we measured telomere length in individual cases by gel electrophoresis and Southern blot hybridization we found that telomeres were significantly longer in ALT-positive than in telomerase-positive specimens (unpublished observations). Overall, these preliminary results indicate the presence of multiple telomere maintenance mechanisms in peritoneal mesothelioma and suggest the requirement for telomere maintenance during the development of this malignancy.

Since apoptotic cell death is the major mode by which chemical and physical anticancer agents kill tumor cells, it is likely that dysregulation of the apoptotic pathways plays a role in sustaining peritoneal mesothelioma cell chemoresistance as already demonstrated for pleural mesothelioma. In fact, previous investigations have shown overexpression of antiapoptotic proteins belonging to the Bcl-2 family (Bcl-2 and Bcl-XL) and inhibitors of apoptosis protein (IAP) family (IAP-1 and survivin) in pleural mesothelioma cell lines and surgical specimens (Gordon et al. 2002). Moreover, through the use of antisense-mediated inhibition approaches, these studies also demonstrated a cytoprotective role of such proteins toward spontaneous and anticancer drug-induced apoptosis (Xia et al. 2002). The identification of points in the apoptotic path-

ways at which dysregulation occurs in DMPM could open new opportunities for the design of novel therapeutic strategies targeting the molecular determinants of treatment resistance of this malignancy. For this purpose, we examined the expression of antiapoptotic proteins belonging to the IAP family (survivin, c-IAP1, c-IAP2 and X-IAP), as well as proapoptotic proteins such as SMAC/Diablo, by immunohistochemistry in 32 peritoneal mesothelioma specimens. Overexpression of survivin and other IAP proteins was observed in a high percentage of tumors, ranging from 69% to 100%, and in an elevated fraction of tumor cells within individual specimens. Conversely, SMAC/Diablo immunostaining was detectable in only 34% of tumors. Accordingly, a low apoptotic index (median percentage of apoptotic cells, 0.45%; range, 0.01%–5.8%) was consistently observed (unpublished observations). To investigate whether antiapoptotic proteins represent potential targets for new therapeutic interventions in this disease, we tested the effects of survivin knockdown accomplished through RNA interference in a peritoneal mesothelioma cell line. Survivin is a structurally unique member of the IAP family whose expression is associated with clinical progression in some tumor types. Accumulating evidence supports the existence of a multifunctional survivin pathway positioned at the interface between mitotic progression and apoptosis inhibition and required to preserve the viability of proliferating tumor cells (Altieri 2003). Survivin also appears to be involved in tumor cell resistance to some anticancer agents as well as ionizing radiation. On the basis of these findings, survivin has been proposed as a promising target for new anticancer interventions (Altieri 2003). In this context, we transfected peritoneal mesothelioma cells with a 21-mer double-stranded small interfering RNA (siRNA) targeting survivin mRNA and observed a strong inhibition of survivin expression at mRNA and protein levels, which was followed by a time-dependent reduction of cell growth and a significant increase of caspase-9-mediated apoptotic rate. Moreover, sequential exposure of siRNA-transfected mesothelioma cells to anticancer drugs (cisplatin and doxorubicin) induced additive antiproliferative effects and markedly increased the apoptotic response to individual drug treatment (unpublished observations). Overall, our results indicate that peritoneal mesothelioma is characterized by dysregulation of apoptosis pathways, in terms of increased expression of antiapoptotic proteins, and suggest that strategies aimed at interfering with such proteins may provide a novel approach for the treatment of this malignancy.

13.3 Pathology

The histological features of malignant peritoneal mesothelioma are usually the same as their pleural counterparts and may be subdivided into epithelial, sarcomatoid, and biphasic tumors. Epithelial tumors predominate in both pleural and peritoneal locations. In a series of 82 peritoneal tumors, 75.6% were epithelial, 22% biphasic, and 2.4% sarcomatoid (Kannerstein and Churg 1977). The data are similar in our experience. Immunohistochemistry is an important ancillary technique in the diagnosis of mesothelioma. Mesotheliomas demonstrate a similar immunohistochemical profile, regardless of the site of origin (pleura or peritoneum). The more common antigens expressed in mesotheliomas are calretinin, cytokeratin 5/6, HMBME, N-cadherin, and thrombomodulin (Ordonez 1998).

The diagnostic microscopy and immunohistochemistry features of peritoneal mesothelioma along with a detailed pathological description of its different morphological types and subtypes is comprehensively described in Chap. 12 of this book.

13.4 Natural History

Patients are usually diagnosed with peritoneal mesothelioma when presenting signs and symptoms of advanced disease (see Fig. 13.1). DMPM growth is characterized by peritoneal seeding, eventually leading to the patient's death due

to tumor encasement, bowel obstruction, and intractable malignant ascites (Moertel 1972). This pattern of spread supports the potential usefulness of selectively increasing cytotoxic drug concentrations by direct IP chemotherapy administration (Antman et al. 1980).

13.4.1 Clinical Presentation

The clinical presentation of DMPM can be varied. Signs and symptoms may last for months before the disease is diagnosed. Patients typically present with abdominal pain, increasing abdominal girth, bloating, weight loss, alteration in bowel habits, abdominal masses, ascites, or fever (Chan et al. 1975). The initial symptoms of DMPM were outlined in a series of 68 patients (Sugarbaker et al. 2003). Increased abdominal girth was the most common sign, reported in 56% of cases. The second most common initial symptom was pain, reported in 44% of patients. A new-onset hernia was seen in 13% of patients and was statistically more common in men. Occasionally DMPM may be discovered in asymptomatic individuals undergoing abdominal exploration or laparoscopy for other causes. In the above-mentioned series, incidental diagnosis was reported in 38% of the women and in 19% of the men; this difference was statistically significant (P=0.016). Clinical presentation was related to survival after surgical cytoreduction and HIPEC, since patients with DMPM diagnosed by incidental findings had significantly longer survival than those with symptomatic mesothelioma.

13.4.2 Pattern of Spread

Intraperitoneal malignancies spread according to three different patterns: direct extension, cell dissemination via peritoneal fluid, and surgical manipulation (Carmignani et al. 2003). As a consequence of the latter modality, viable exfoliated tumor cells become entrapped in avascular scar tissue, thus becoming relatively resistant to intravenous chemotherapy (CT). The dissemination within the peritoneal cavity was defined by Sugarbaker as a redistribution phenomenon, indicating a complete

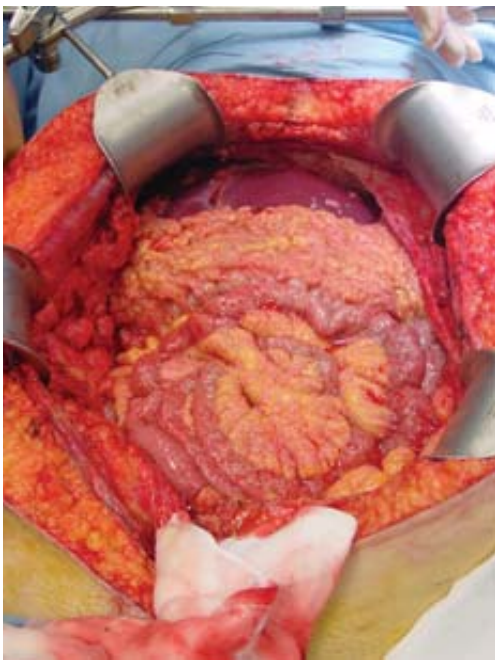

Fig. 13.1 Peritoneal carcinomatosis due to diffuse malignant peritoneal mesothelioma

and sequential invasion of the peritoneal cavity with large tumor volume localization at predetermined anatomical sites and minimal invasion at other sites (Sugarbaker 1994). Large pores are present on the peritoneal surface of the omentum, and lymphatic lacunae are open at the diaphragm undersurface. Consequently, a large volume of tumor rapidly localizes at these anatomical sites. Cells then settle by gravity within the abdomen, with accumulation in the pelvis, in the right retrohepatic space, in the left abdominal gutter, and at the Treitz ligament, while the ileum usually remains tumor free. Progression will eventually compromise gastrointestinal function because of bowel compression (Deraco et al. 1999).

The disease is generally confined to the peritoneal cavity and rarely metastasizes to the liver. Only in advanced stages may direct extension to the pleural cavity and distant spread be noted. An autopsy study demonstrated that two-thirds of the examined patients had tumor only in the abdominal cavity and

that 78% of patients had died because of complications directly related to intra-abdominal disease, such as bowel obstruction (Antman et al. 1980).

13.5 Diagnosis

Definitive diagnosis of peritoneal mesothelioma is usually a difficult clinical problem (Whitaker 2000). Cytological diagnosis in ascitic fluid is often inconclusive, since cells frequently resemble elements with mesothelial hyperplasia. Only in recent years have cytological and ultrastructural methods enhanced the diagnostic accuracy of cytological assessment (Robinson et al. 2005). In the series of the Washington Cancer Institute, diagnosis was made by fluid sampling in none of 68 patients. Laparotomy was required in 44% of patients, laparoscopy in 52%, and US/CT-scan guided biopsy in 4% (Sugarbaker et al. 2003). Mesothelioma has a high propensity to implant in laparoscopic trocar tracts or abdominal incisions. Therefore, biopsies should be performed in the midline along the linea alba, as dissemination within the abdominal wall may result from placement of lateral ports (Brigand et al. 2006).

As discussed in Chap. 12, the differential diagnosis from carcinoma of ovarian or digestive origin may be problematic. Appropriate immunocytochemical stains are required. A positive calretinin, cytokeratin 7, EMA, WT1, and mesothelin stain has significant diagnostic sensitivity. In contrast, negative immunostaining for epithelial antigens such as CEA or B72.3 is highly suggestive of peritoneal mesothelioma (Ordonez 1998).

A clinicopathological study on 35 patients treated with cytoreductive surgery and locoregional hyperthermic CT has been carried out in our institution (Nonaka et al. 2005). Calretinin and WT-1 were expressed in all cases to a variable degree, while expression of polyclonal CEA and Ber-EP4 also were negative in all cases. MMP-2 was expressed in all cases, generally in a diffuse and strong fashion, whereas MMP-9 was expressed in 30 cases but was found to be of variable intensity and distribution. EGFR was expressed in a membranous pattern in all but two cases. Conversely, p16 was found to be only focally positive, with a nuclear staining pattern noted in 21 cases (60%) (see Table 13.1).

13.5.1 Radiological Imaging

The radiological features of peritoneal mesothelioma at CT scan have been reviewed recently. Diffuse disease distribution throughout the peritoneal cavity was observed, with large tumor volume in the midabdomen and in the pelvis in a majority of patients. These findings may raise the suspicion that a patient with malignant ascites could be affected by DMPM. A classification of mesothelioma involvement of small bowel and its mesentery has been proposed (see Table 13.2). Such classification provides important information on the extent of the disease and on the functional bowel impairment that may be expected (Yan et al. 2005).

Table 13.1. Immunohistochemical staining in 35 patients with malignant peritoneal mesothelioma

	No. of patients							
Score	Calretinin	WT-1	pCEA	Ber-Ep4	EGFR	p16	MMP-2	MMP-9
0	0	0	35	35	2	14	0	5
+1	0	5	0	0	1	11	2	9
+2	1	6	0	0	3	6	3	8
+3	6	5	0	0	7	2	7	8
+4	28	19	0	0	22	2	23	5

pCEA, pathological carcinoembryonic antigen; EGFR, epidermal growth factor receptor; MMP, matrix metalloproteinase

Table 13.2. Classification of small bowel and mesentery CT scan features

Class	Presence of ascites	Small bowel and mesentery involvement	Loss of mesenteric vessel clarity	CT scan interpretation
0	No	No	No	Normal appearance
I	Yes	No	No	Ascites only
II	Yes	Thickening, enhancing	No	Solid tumor present
III	Yes	Nodular thickening, segmental obstruction	Yes	Loss of normal architecture

CT, computed tomography

The role of preoperative abdominal and pelvic CT scan in the identification of patients most likely to benefit from a comprehensive treatment of CRS and HIPEC has been assessed. Tumor mass >5 cm in the epigastric region and loss of normal architecture of the small bowel and its mesentery were the radiological features related to failure in adequately removing all the macroscopic tumor. In a composite analysis, none of the patients with both of these radiological features had an adequate cytoreduction. Conversely, patients who lacked these two preoperative CT scan findings had a 94% probability of adequate cytoreduction (Yan et al 2005).

13.5.2 Serum Markers

Serum mesothelin-related proteins are a soluble form of mesothelin that has reported to be elevated in 84% of patients with pleural mesothelioma and in only 2% with other pulmonary diseases (Pass et al. 2005). Serum osteopontin levels were shown to be significantly higher in patients with pleural mesothelioma than in those with asbestos exposure (Robinson et al. 2003). No data are presently available about the clinical utility of these antigens in DMPM management. We conducted a study on the clinical role of serum markers in patients with DMPM. (Baratti et al. 2006). Baseline diagnostic sensitivity was 58% for CA125, 50% for CA15.3, 2.3% for Ca19.9, and 0 for CEA. These data may be of some help in the initial assessment of peritoneal dissemination of unknown origin, since they demonstrate that an elevated CA125 should not exclude a diagnosis of DMPM, although the tumor is less common than ovarian cancer, with which it is easily confused. Serial postoperative CA125 and CA15.3 measurements were effective in assessing response to treatment and disease progression after surgery and HIPEC.

13.6 Staging

In contrast to pleural mesothelioma, no staging system is universally accepted for peritoneal mesothelioma. A standard assessment of tumor burden would be of help in selecting patients for aggressive multimodality treatment, planning cytoreductive surgery, and predicting patient outcome. Furthermore, as addressed in Chap. 8, standard disease staging might assist in comparing results from different investigators.

Currently, four intraoperative staging systems are used in peritoneal malignancies. The Japanese Research Society for Gastric Cancer system was originally proposed to classify carcinomatosis from gastric primary cancer. Such classification is very simple and quantifies peritoneal involvement according to location and number of tumor nodules (Iwamoto et al. 1989). It is described in detail in Chap. 8. Correlation between survival and this classification was found in several studies investigating the impact of cytoreductive surgery followed by HIPEC for gastric cancer (Fujimoto et al. 1997), but it has never been applied to peritoneal mesothelioma.

A major drawback of this staging system is its inaccurate anatomic definition and the lack of size assessment of the cancer implants.

The Gilly peritoneal carcinomatosis staging system was first described in 1994 (Gilly et al. 1994). It is detailed in Chap. 8 (Table 8.1). In a recent paper, Gilly score was related to survival also among patients with peritoneal mesothelioma (Brigand et al. 2006). Simplicity and reproducibility are the main advantages of this system. However, the distribution of peritoneal surface implants, which is a prognostic determinant, is difficult to assess in stages 3 and 4. Large-size peritoneal implants confined to one portion of the abdomen may imply a favorable outcome; conversely, if tumor nodules <5 mm are diffuse all over the abdominal cavity, prognosis may be certainly worse (Harmon and Sugarbaker 2005).

The Peritoneal Cancer Index (PCI) was introduced by Sugarbaker and presently is the most widely used system for staging peritoneal malignancies. The PCI quantitatively combines tumor distribution in 13 abdominal anatomical regions with lesion size (Jacquet et al. 1996). It is described in detail in Chap. 8 (Fig. 8.1). In patients with carcinomatosis from invasive cancer, PCI correlates to the probability of performing a complete cytoreduction and prognosis after CRS with HIPEC (Harmon and Sugarbaker 2005). Sugarbaker and Elias independently established the correlation between PCI and survival in a large number of patients with carcinomatosis from colorectal cancer (Elias et al. 2001; Sugarbaker et al. 1999). Tentes and colleagues validated the PCI for ovarian cancer (Tentes et al. 2003). Sugarbaker reported that PCI>28 correlated to significantly lower survival rates in patients affected by peritoneal mesothelioma undergoing CRS and HIPEC (Sugarbaker et al. 2003). PCI score is presently adopted in our center to stage peritoneal malignancies, but we have not observed correlation to prognosis in patients with DMPM (Deraco et al. 2005). The main drawback of PCI is its complexity. Moreover, complete tumor removal could be difficult to achieve in cases with low PCI, if invasive large tumor is present at crucial anatomic sites, such as the hepatic hilum (Fig. 13.2)

The Simplified Peritoneal Cancer Index (SPCI) was introduced at the Netherlands Cancer Institute and has been used for colorectal and appendiceal cancer staging. There are marked similarities between the SPCI and the PCI. However, in the SPCI, there are seven anatomic regions (see Table 13.3) (Witkamp et al. 2001). Verwaal established that SPCI is able to predict not only patient outcome but also morbidity and mortality rates (Verwaal et al. 2004).

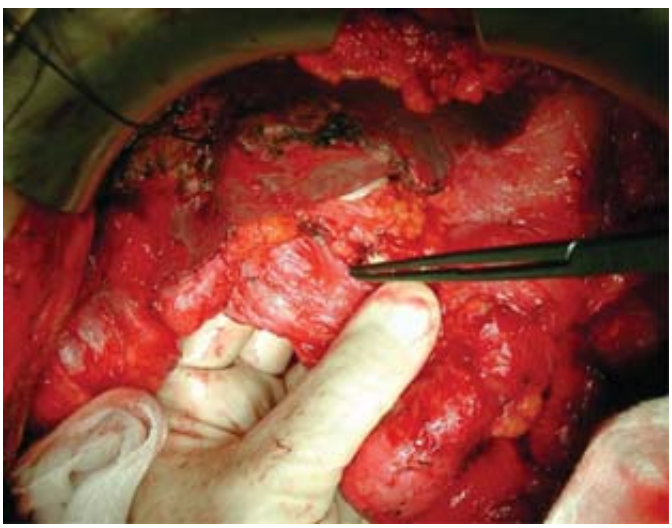

Fig. 13.2 Hepatic hilum dissection

Table 13.3. Simplified peritoneal cancer index (SPCI)

Abdominopelvic regions	Tumor diameter
1. Small pelvis	0=none
2. Ileocecal region	1=≤1 cm
3. Omentum/transverse colon	2=>1 cm, ≤5 cm
4. Small bowel/mesentery	3=>5 cm
5. Subhepatic area/stomach	
6. Left subdiaphragmatic area	
7. Right subdiaphragmatic area	

13.7 Conventional Treatment

13.7.1 Systemic Chemotherapy and Biological Therapies

The optimal chemotherapeutic regimen for DMPM is unclear. Treatment schedules that have been used in this disease include many drugs that have shown activity in pleural mesothelioma, but most of them showed a response rate of 10% to 15% (Krug 2005). Combination schedules have improved the response rate to about 25% (Hassan et al. 2006). Cisplatin has shown a good activity rate as a single agent or in combination; in a systematic meta-analysis including 83 different phase II trials it had the best single-agent activity. Other platinum analogs (i.e., carboplatin or oxaliplatin) have shown comparable results (Berghmans et al. 2002). The combination of cisplatin and gemcitabine has yielded response rates of 48% and 33%, respectively, in two different phase II trials, but these results have not been confirmed in other studies (Krug 2005). Antifolates (pemetrexed and raltitrexed) have shown more favorable results, particularly in combination with platinum compounds. A phase III clinical trial of pemetrexed plus cisplatin versus cisplatin alone showed an increased response rate and overall survival (OS). Median survival in the pemetrexed/cisplatin arm was 12.1 months versus 9.3 months in the control arm (P=0.020, two-sided log-rank test). Median time to progression was significantly longer in the pemetrexed/cisplatin arm: 5.7 months versus 3.9 months. Pemetrexed/cisplatin is currently considered the regimen of choice in the pleural form of the disease by many oncologists (Vogelzang et al. 2003). There is little information on the effectiveness of this combination for DMPM. The preliminary results of a nonrandomized trial started in June 2002 account for an overall objective response rate of 26% among 73 evaluable patients with DMPM. Median survival was 13.1 months for previously treated patients and has not been reached for chemotherapy-naive patients (Janne et al. 2006).

13.7.2 Intraperitoneal Chemotherapy

Since DMPM remains confined to the peritoneal cavity for most of its clinical course, several authors have investigated intraperitoneal chemotherapy (IP CT). Such procedure has the theoretical advantage of increased locoregional concentration along with reduced systemic toxicity. The disadvantages are the poor drug penetration in tumor tissue, the need for indwelling catheters, and intra-abdominal visceral adherences resulting in obstacle to free fluid circulation (Hassan and Alexander 2005). Cisplatin, mitomycin C, 5-fluoruracil, doxorubicin, and paclitaxel have been used in this setting (Vlasveld et al. 1991). In one of the largest series, IP CT with cisplatin and mitomycin was administered to 19 patients; 5-year OS was 10% (Markman and Kelsen 1992). IP CT has never been tested in a randomized fashion; this makes results difficult to evaluate.

13.7.3 Combined Treatment

Although the median survival of patients with DMPM reported in most series is short, long-term survival has been reported. In a series of 10 patients treated with sequential debulking surgery, CT (5IP and 1 intravenous) and whole abdominal irradiation, six patients achieved complete remission at 19–78 months. Conversely, those who did not receive this combined approach died after 2–15 months (Lederman et al. 1987). In Langer's study, 10 patients

were treated with surgical debulking and IP cisplatin, sodium thiosulfate, and etoposide. Median survival was 22 months for patients with residual tumors <2 cm before IP treatment and 5 months for those with residual disease >2 cm; this difference was statistically significant. (Langer et al. 1993). Eltabbakh published a study of 15 women with DMPM treated with various combinations of surgery followed by systemic CT. Patients who underwent CRS survived longer than those who underwent biopsy only (Eltabbakh et al. 1999). Taken together, these data suggest the relevance of extensive debulking surgery on outcome. However, it is impossible to draw conclusions, as these studies were conducted on small series of patients, with a short follow-up, ill-defined eligibility criteria, and an absence of control groups.

13.8 Cytoreductive Surgery and Intraperitoneal Hyperthermic Perfusion

Most therapeutic options have failed to demonstrate significant results in the treatment or palliation of peritoneal mesothelioma. In the 1980s, a new integrated approach to peritoneal surface malignancies renewed the interest of the scientific community in this challenging field (Sugarbaker 2001). It consisted of aggressive cytoreductive surgery by means of peritonectomy procedures and other visceral resections along with HIPEC. Recent phase I and II prospective trials have reported promising results in selected patients undergoing this multimodality treatment protocol (Stewart et al. 2005).

13.8.1 Rationale

In patients with peritoneal mesothelioma the tumor remains confined within the abdominal cavity until advanced stages of the disease occur. This makes a combined locoregional approach attractive. Theoretically, CRS is aimed at removing all the visible tumor deposits and HIPEC is performed to treat microscopic residual disease.

13.8.1.1 Cytoreductive Surgery

The idea of reducing tumor volume for peritoneal surface malignancies was first reported for ovarian cancer as an important factor in achieving tumor response to CT (Eisenkop et al. 1998). The rationale is based on the enhancement of neoplastic chemosensitivity due to the recruitment of tumor cells to the growth phase and the possibility of surgically remove chemoresistant cellular clones. It is well known that the penetration of IP chemotherapy into tumor nodules is limited to 2–5 mm, even when combined with heat. Thus the goal of cytoreductive surgery for curative intent is to achieve maximum reduction of tumor volume (Ruth et al. 2003).

It is important to underline the difference between simple debulking and the surgical cytoreduction included in the combined protocol adopted in our center. We believe that more extensive surgery is required to minimize postoperative residual disease, including parietal peritonectomy and/or multiple organ resection. Such an aggressive surgical approach is an attempt to remove not only all the intracavitary tumor load but also the anatomic structure (i.e., the peritoneum) where the tumor originates and which represents a potential site of disease progression (see Fig. 13.3). In our experience, surgical procedures, such as colectomy, splenectomy, greater and lesser omentectomy, small bowel resection, and cholecystectomy, are frequently performed.

13.8.1.2 Intraperitoneal Chemotherapy

Systemic CT for peritoneal surface malignancies is largely ineffective because of its limited entry into the peritoneum. As with any locoregional antiblastic therapy, the objective of IP drug administration is to expose the tumor to a high drug concentration and to reduce systemic toxicity (Stewart et al. 2005). The presence of a peritoneal-plasma partition has been hypothesized (Dedrick and Flessner 1997). Pharmacokinetic studies have demonstrated that drugs delivered into the peritoneal cavity have a clearance inversely proportional to the square root of their molecular weight. Therefore, hydrophilic properties and

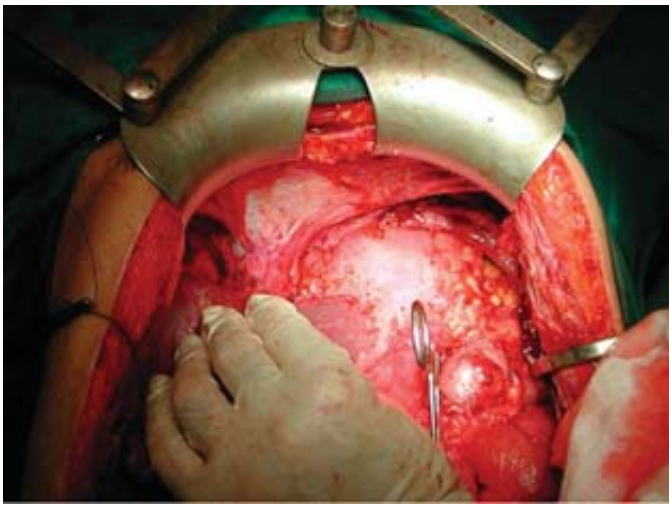

Fig. 13.3 Right diaphragmatic peritonectomy

high molecular weight result in an optimal pharmacokinetic profile for IP use, with low peritoneal absorption rate and rapid systemic clearance (Kuzuya et al. 1994). An optimal ratio between the areas under the curve of mitomycin C, doxorubicin, and cisplatin administered intraperitoneally and those obtained by systemic administration has been demonstrated (Deraco et al. 2003).

Not only the route but also the timing of administration is of relevance. HIPEC is performed before the development of intra-abdominal adhesions, allowing a uniform drug distribution. Moreover, the procedure is carried out before exfoliated tumor cells are entrapped in avascular scar tissue, becoming relatively resistant to CT (Sugarbaker et al. 1990).

13.8.1.3 Antitumor Effect of Hyperthermia

Heat is a fundamental component of this new treatment, because of its own cancericidal property and chemosensitivity-modulating capacity. The direct cytotoxic activity of heat has been demonstrated in vitro at 42°C. The biophysical effects of hyperthermia are not completely understood but probably include membrane protein denaturalization (Arancia et al. 1989), increased vascular permeability (DuBose et al. 1998), alterations in the cytoskeleton and in complexes such as insulin receptors (Calderwood and Hahn 1983), and changes in enzyme complexes for DNA synthesis and repair (Xu et al. 2002). Moreover, the vasculature in solid tumors is chaotic, resulting in regions with low pH, hypoxia, and glucose level. This susceptible microenvironment makes solid tumors more sensitive to hyperthermia (Vaupel 1997). In addition, at 40°C to 42°C, the neoplastic cell becomes more chemosensitive because of an increase of intracellular drug concentration, the drug activation process (especially for alkylating agents), and an alteration in DNA repairing (Ozols and Young 1987). Heating cells to 43°C during platinum (CDDP) exposure has been found to increase drug accumulation in CDDP-resistant cell lines, with little effect on CDDP-sensitive cell lines. Ongoing platinum-DNA adduct formation after the end of CDDP exposure is also enhanced and/or adduct removal is decreased in heated cells, resulting in considerably more DNA damage (Hettinga et al. 1997). Mild hyperthermia increases the antitumor activity also of oxaliplatin, doxorubicin, and mitomycin C (Engelhardt 1987). It has been observed that the synergy between heat and mitomycin C occurs independently of the cell cycle; hence, a relevant tumoricidal effect is obtained even with brief drug exposure (Barlogie et al. 1980).

13.8.2 Patient Selection

The integrated procedure described herein is expensive in terms of financial resources, operative time, and technological facilities. A considerable rate of major morbidity has been reported by some groups (Kusamura et al. 2006). Patient selection is important to maximize the results of treatment, excluding patients who will not benefit from a high-morbidity and potentially life-threatening therapy. Preoperative clinical conditions have been shown to be a relevant prognostic factor for pleural mesothelioma (Robinson et al. 2005). Data from our institution demonstrate that performance status according to the Eastern Cooperative Oncology Group (ECOG) score (Oken et al. 1982) was related to progression-free (PFS) survival in patients with DMPM undergoing CRS and HIPEC (Deraco et al. 2006).

In the management of peritoneal malignancies the extent of previous surgery before definitive cytoreduction with HIPEC may have a negative impact on prognosis (Harmon et al. 2003). According to the cancer cell entrapment hypothesis, the raw surfaces of surgically dissected tissue planes are favorable sites for cancer cell adherence. Cancer progression deep to peritoneal surfaces, especially if imbedded in scar, is difficult or impossible to eradicate (Eggermont et al. 1987). The prior surgical score (PSS) has been introduced by Sugarbaker to rate the extent of surgery prior to definitive combined treatment. The assessment uses a diagram similar to that for PCI but excludes regions 9–12: PSS 0=no prior surgery or only a biopsy was performed; PSS 1=one region with prior surgery; PSS 2=2/5 regions previously dissected; PSS 3=more than 5 regions previously dissected. Five-year OS was 70% in appendiceal cancer patients with PSS=0–2 and 51% in those with PSS=3 (P=0.001) (Sugarbaker et al. 1999). Among patients with DMPM treated with CRS and HIPEC at the Centre Hospitalier Lyon Sud median OS was not statistically different between patients with PSS=0/1 and those with PSS=2/3 (Brigand et al. 2006).

At the National Cancer Institute of Milan inclusion criteria are the following:

- Confirmed pathological diagnosis of DMPM
- Age 75 years
- ECOG performance status 2
- No significant impairment of cardiorespiratory, renal, hepatic, and bone marrow function
- No parenchymal hepatic and/or extra-abdominal metastases
- No massive retroperitoneal disease
- Completely resectable (or at least potentially significantly reducible) peritoneal disease
- Written informed consent statement signed by the patient

13.8.3 Operative Technique

Cytoreductive surgery by means of peritonectomy procedures combined with HIPEC was described by Sugarbaker (Sugarbaker 2003). We present here the procedure adopted in our institution (Deraco et al. 2003, 2004).

13.8.3.1 Cytoreductive Surgery

Patients are placed in a supine position, with gluteal folds advanced to the break in the operating table to allow full access to the perineum. A three-way bladder catheter is inserted for cold lavage during hyperthermia in order to avoid mucosal damage.

The surgical procedure starts with a xyphopubic midline cutaneous incision. The deeper layers of the abdominal wall are dissected until the parietal peritoneum is visualized. The parietal peritoneum is then stripped from the abdominal wall. During this time the peritoneum remains closed to facilitate the procedure. Ureters, iliac arteries and veins, deferent ducts, and gonadal vessels are bilaterally visualized and spared. A 2-mm ball-tip electrosurgical handpiece is used on pure cut at high voltage as the standard tool to dissect peritoneal surfaces. At this point, the peritoneum is opened and lysis of adhesions is performed to allow full exploration of the peritoneal cavity. The Thompson self-retaining retractor is used to achieve generous abdominal exposure.

CRS is carried out on the basis of disease extension by the following steps: (1) greater omentectomy, right parietal peritonectomy, right colon resection; (2) pelvic peritonectomy

with sigmoid colon resection ± hystero-annexectomy; (3) antrectomy, cholecystectomy, lesser omentectomy, and dissection of the duodenal-hepatic ligament; (4) right-upper-quadrant peritonectomy and Glissonian capsule resection; (5) left-upper-quadrant peritonectomy-splenectomy and left parietal peritonectomy; and (6) other intestinal resection and/or abdominal mass resection. In our institution the main goal of cytoreductive surgery is to remove all macroscopic tumor deposits, leaving no residual nodules >2.5 mm. However, not all six peritonectomy procedures are required in all patients. The surgical procedures and visceral resections are planned after careful assessment of disease extent and distribution (see Fig. 8.1). In those locations where only minimal tumor deposits involve parietal or visceral peritoneal surfaces, such as the stomach or bowel, local resection is attempted. Peritonectomies are performed in case of major serosal involvement, and segmental resections are carried out only when massive visceral involvement is observed. Anastomoses are completed before HIPEC; ostomies are constructed at the end of the entire procedure.

13.8.3.2 Hyperthermic Intraperitoneal Chemotherapy

In our institution HIPEC is performed according to the closed abdomen technique. After CRS, two inflow catheters (one in the right subdiaphragmatic cavity and one at deep pelvic level) and two outflow catheters (one in the left subdiaphragmatic cavity and one at superficial pelvic level) are inserted. Six temperature probes are placed in the abdominal cavity. After abdominal skin closure, the catheters are connected to the extracorporeal perfusion circuit [Performer LRT; RAND, Medolla (MO) Italy]. The device consists of a roller pump, a heat exchanger, a reservoir, an integrated control of temperature, flow, and pressure, and software for real time data monitoring, analysis and registration (see Fig. 13.4). The polysaline perfusate consists of a solution of 2/3 of Normosol R and 1/3 of Emagel (4–6 l) containing cisplatin (43 mg/l) plus doxorubicin (15.25 mg/l). The perfusion is carried out at a mean flow of 600 ml/min for 90 min, starting from the true hyperthermic phase (42.5°C).

A major technical variant is represented by the open-abdomen or "coliseum" technique,

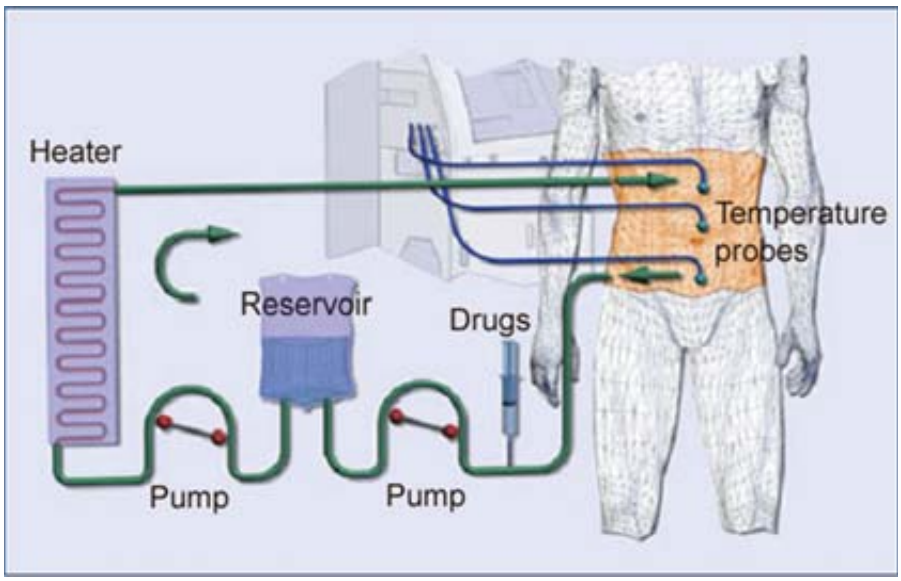

Fig. 13.4 The device and the extracorporeal circuit of hyperthermic intraperitoneal chemotherapy (HIPEC)

which involves covering the abdomen with a plastic sheet during the perfusion (Sugarbaker et al. 1999). Proponents of the open technique report that it provides optimal thermal homogeneity and spatial diffusion. In contrast, proponents of the closed technique suggest that the increased intra-abdominal pressure implies deeper drug penetration (Leunig et al. 1992). To date, no prospective trials have compared the techniques.

13.8.4 Assessment of the Completeness of the Cytoreduction

Presently, two classification systems are used to rate the completeness of cytoreduction. We use the completeness of cytoreduction (CC) score devised by Sugarbaker and colleagues. The extent of the residual disease is scored after the completion of the surgical cytoreduction, as follows: cc-0=no residual disease; CC-1=residual disease 2.5 mm; CC-2=residual disease >2.5 mm 2.5 cm; CC-3=residual disease >2.5 cm (Jacquet and Sugarbaker 1996). Other authors have used the following classification system: R0=no gross disease with negative microscopic margins; R1=no gross disease with positive microscopic margins; R2a=residual tumor 5 mm; R2b=residual tumor >6 mm 2 cm; R2c=residual disease >20 mm (Stewart et al. 2005). The CC-1 nodule size (2.5 mm) is thought to reflect the maximum tissue penetration of locoregionally delivered drugs. Nevertheless, no data in the literature are found to determine the superiority of one system over the other. Complete cytoreduction has been confirmed in all trials of CRS and HIPEC as one of the most relevant determinants of survival and can be defined in both systems as CC-0/1 or R0/1/2a, respectively.

13.9 Results

Few centers have reported prospective nonrandomized trials evaluating surgical cytoreduction and HIPEC in patients affected by peritoneal mesothelioma. The National Cancer Institute in Bethesda, Maryland reported 18 patients included in three consecutive phase I trials (Park et al. 1999) and more recently a larger series of 49 patients with longer follow-up (Feldman et al. 2003). Results on 68 patients treated at the Washington Hospital Center were reported by Sugarbaker (Sugarbaker et al. 2003), updating a previous paper on 33 patients from the same institution (Sebbag et al. 2000). The National Cancer Institute of Milan has published a preliminary report on 19 patients (Deraco et al. 2003), a clinicopathological study on 33 patients (Nonaka et al. 2005), and a recent update on 49 patients with multivariate statistical analysis of prognostic factors (Deraco et al. 2006). Prospective trials on 12 and 15 patients, respectively, were conducted at the Centre Hospitalier Lyon Sud (Brigand et al. 2006) and at Wake Forest University (Loggie et al. 2001). In general, criteria for patient selection and treatment parameters are not consistent from one center to another as far as type, dose, temperature, and duration of hyperthermic chemotherapy are concerned. Furthermore, no standard definition of adequate cytoreduction seems to be universally accepted, as the surgical procedure in the different centers was aimed at obtaining residual disease nodules ranging from 2.5 to 25 mm in diameter. However, these studies demonstrate median survival times of 34 to 67 months, which is a significant improvement over the previously reported median survival time.

Malignant ascites is a common presentation and a major factor in disease-related morbidity and mortality. In the above-mentioned studies, palliation in the form of relief from ascites occurred in 86% to 99% of cases after HIPEC for malignant mesothelioma (Stewart et al. 2005).

13.9.1 Morbidity and Mortality

Because of the complexity of this combined treatment of CRS and HIPEC, morbidity and mortality rates may be significant. Operative mortality ranges from 0% to 11% and major morbidity ranges from 8% to 26% of peritoneal mesothelioma patients (Stewart et al. 2005).

13.9.2 Prognostic Factors

In the study of Sugarbaker the following factors were related to reduced OS: male sex, age>53 years, weight loss, nonincidental diagnosis, PCI>28, sarcomatous/biphasic histology, CC score=3, and presence of metastases (Sugarbaker et al. 2003). Prognostic factors were tested by multivariate analysis in Feldman's paper (Feldman et al. 2003). A history of previous debulking surgery and absence of deep tissue invasion were independent determinant of both improved OS and PFS; residual disease <1 cm and age <60 years were recognized as independent prognostic factors only for improved OS. Immunohistochemical stains for p53, p27, and Ki-67, as well as desmoplasia, were not related to prognosis. In the small series of the centre Hospitalier Lyon Sud, Gilly score 1–2 and CC score 1–2 were related to prolonged OS by univariate analysis (Brigand et al. 2006).

We observed that the CC score and the mitotic count (MC) presented the strongest association with OS at multivariate analysis. The estimated hazard rate was eight times higher for patients with residual disease >2.5 mm than for those with residual disease <2.5 mm, after adjustment for other variables. Whether this survival benefit resulted from lower tumor aggressivity or from the surgical effort itself is difficult to ascertain. However, this series included only the most malignant subtypes of DMPM, an aspect that could support the validity of aggressive surgical approach.

The second variable that remained in the Cox model as a factor influencing the OS was MC. Patients with an MC >5 per 50 HPFs presented a hazard rate 10 times higher compared with those with a lower MC. Data about this issue in the literature are conflicting. In two case series patients with high MC survived for a significantly shorter time than those with low MC (Ramael et al. 1994; Beer et al. 2000), whereas Kerrigan did not reach the same conclusion (Kerrigan et al 2002). However, the prognostic relevance of both variables (CC and MC) should be taken cautiously because the 95% confidence intervals for their respective hazard rates are fairly wide (2.05–36.24 for CC and 1.98–55.23 for MC).

Multivariate analysis of factors influencing PFS showed that performance status and MC remained in the model after the backward-elimination method. Preoperative clinical condition has been largely shown to be a prognostic factor for pleural mesothelioma, but the same finding has not been demonstrated for the peritoneal counterpart. In this series, it is noteworthy that the performance status was not related to OS. This could be attributed to the fact that the great majority of patients (89%) had an ECOG performance status of 0 and the number of deaths due to disease progression was not high enough. The independent association between MC and PFS emerged after the multivariate analysis even in the absence of a significant correlation at univariate analysis. This could have resulted from the presence of a confounding factor among the clinicopathological variables. Other factors possibly related to prognosis according to the literature, such as age at diagnosis, sex, and previous debulking, were not predictive of outcome in our series.

13.9.3 Biological Markers

P16, also known as INK4a, is a tumor-suppressor gene located on chromosome 9 in the region 9p21. Two alternatively spliced gene products are encoded by p16: the proteins P16 and p14ARF. The p16(INK4a) protein, by inhibiting cyclin-dependent kinase, downregulates Rb-E2F and leads to cell cycle arrest in the G1 phase. The p14(ARF) protein interacts with the MDM2 protein and neutralizes MDM2-mediated degradation of p53. Because p53/Rb genes are not altered in malignant mesothelioma, additional components of these pathways, such as p16 (INK4a) and p14(ARF), are candidates for inactivation. The recent molecular genetic study on 45 malignant mesothelioma specimens revealed alterations of p16 in 31% of cases, promoter methylation in 9%, deletion in 22%, and point mutation in 2% (Hirao et al. 2002). In our series, the immunoreaction of p16 was absent or reduced in 25 cases (71%), in agreement with previous reports (Kratzke et al. 1995).

EGFR is a cell surface receptor involved in the regulation of cell growth and differentiation. The binding of the ligand to the recep-

tor causes activation of its intrinsic tyrosine kinase activity and rapid internalization of the receptor-ligand complex into the cell; this leads to an increase in cellular proliferation, an increase in angiogenesis, inhibition of apoptosis, and expression of extracellular matrix proteins. The overexpression of EGFR is associated with a poor prognosis in some cancers. An earlier study showed EGFR immunoexpression in 69% of the epithelial type of diffuse malignant pleural mesothelioma, 44% of the sarcomatoid type, and 22% of the mixed type. No correlation between EGFR overexpression and prognosis was identified. Twenty-two (63%) of 35 cases showed diffuse and strong immunoreactivity for EGFR, a finding consistent with a previous study (Trupiano et al. 2004).

The pattern of DMPM progression within the abdominal cavity suggests an important role of proteases, including the MMPs, in the evolution of the disease. Our study demonstrated the constant expression of MMP-2 and, to a lesser degree, of MMP-9. All the cases expressed MMP-2 to some extent, and 23 patients showed a 4+ staining intensity in DMPM cells. Overexpression of MMPs, particularly MMP-2 (gelatinase A), MMP-9 (gelatinase B), and MMP-11 (stromelysin 3), is related to tumor progression and metastasis in various carcinomas, including gastric, colonic, and pulmonary carcinomas (Cox et al. 2000). In a study of pleural mesotheliomas using semiquantitative gelatin zymography, increasing MMP-2 and pro-MMP-2 activity were independently associated with a poor prognosis, but MMP-9 activity had no prognostic significance (Edwards et al. 2003). Only a few small studies have investigated MMP immunohistochemically on surgical specimens of DMPM. The results were variable and not always consistent with those found by reverse transcriptase-polymerase chain reaction, Western blot, and gelatin zymography on mesothelioma cell lines, as well as fresh tissue (Liu et al. 2002).

13.10 Future Perspectives

Future directions in DMPM research should involve biological studies on tumor pathogenesis to elucidate the molecular mechanisms and the possible etiological role of asbestos in peritoneal mesothelioma oncogenesis. The comprehensive therapeutic approach to DMPM represented by CRS and HIPEC has attracted an increasing consensus as the treatment of choice for this disease in selected patients, but several technical issues need to be rationalized by means of larger prospective, possibly multicentric, trials (Sugarbaker et al. 2006). Since not all the patients with DMPM are candidates for surgery and HIPEC and many of them ultimately relapse, development of novel cytotoxic agents is needed. Promising approaches may be represented by new monoclonal antibodies directed against mesothelium, inhibitors blocking cellular signaling pathways, antiangiogenetic agents, and gene therapy (Hassan et al. 2006).

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