Peritoneal Mesothelioma

17

Marcello Deraco, Dario Baratti, Shigeki Kusamura,
Antonello D. Cabras, Federica Perrone, and Nadia Zaffaroni

17.1 Introduction

Diffuse malignant peritoneal mesothelioma (DMPM) is an exceedingly uncommon tumor arising from mesothelial cells. Macroscopically, the disease is characterized by thousands of small tumor nodules that grow to form plaques, masses, or layers covering all peritoneal surfaces. DMPM has been considered a pathological entity without effective treatment options until the 1990s, when initial surgical experiences integrating cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) showed a significant impact on patient prognosis [1–3]. These encouraging results prompted clinical and basic science researchers to intensify their efforts in an attempt to identify new prognostic factors and therapeutic targets to optimize patient selection for treatment and therapeutic strategies. The translation of these advancements into clinical practice will be the challenge for the coming years [4, 5]. Treatment guidelines and investigational perspectives concerning DMPM were defined by the Consensus Conference, Milan (4–6 December 2006) [6].

17.2 Epidemiology

Epidemiological, biological, and clinical behaviors of DMPM are different from its better know and more frequent pleural counterpart. From the Surveillance, Epidemiology, and End Results (SEER) program and European Cancer Incidence and Mortality (EUROCIM) data [7, 8], age-standardized incidence

M. Deraco (✉)
Department of Surgery, National Cancer Institute,
Milan, Italy
e-mail: marcello.deraco@istitutotumori.mi.it

A. Di Giorgio, E. Pinto (Eds), *Treatment of Peritoneal Surface Malignancies*,
Updates in Surgery
DOI: 10.1007/978-88-470-5711-1_17, © Springer-Verlag Italia 2015

rates among men range from 0.5 to approximately three cases per million population. About 2,500 new cases of mesothelioma are registered each year in the USA. Higher rates are reported in smaller areas with widespread past use of asbestos, such as the harbor city of Genoa, Italy (age-standardized incidence in men in 1995 was 5.5/1,000,000) [9]. According to recent epidemiological data, a 5–10 % increase in annual disease-related mortality will be observed worldwide until 2020. The disease has likely reached its incidence peak in the USA, but in Europe and Australia, the peak is expected during this decade [10].

17.3 Etiology

The role of asbestos exposure in DMPM origin is not clear, as in pleural forms. It was estimate that 58 % of men and only 20 % of women with DMPM had past asbestos exposure [11]. Therefore, it has been suggested that disease etiology may differ between sexes [12]. Since no asbestos exposure is documented in about 20–40 % of patients with DMPM, it has been suggested that other factors, such as Simian virus 40 (SV40), may be implicated as possible cofactors in mesothelioma oncogenesis. Furthermore, observations gathered in Cappadocia, Turkey, resulted in the hypothesis of a genetic susceptibility with an autosomal dominant pattern [13, 14]

17.4 Diagnosis

17.4.1 Clinical Presentation

DMPM growth is characterized by peritoneal seeding, eventually leading to death because of intractable ascites, bowel encasement, and bowel obstruction. Patients are usually diagnosed at an advanced disease stage. In an Italian series of 81 DMPM patients, the most frequent symptoms leading to diagnosis were ascites, abdominal pain, and asthenia. Weight loss, anorexia, abdominal mass, fever, diarrhea, and vomiting were less common; presentation with abdominal hernia occurred in 13 % of patients and thrombocytosis with anemia in 73 %. In about 25 % of female patients, diagnosis was triggered by nonspecific gynecological symptoms [15].

Cytological examination of ascitic fluid is mostly nondiagnostic. In the Washington Cancer Institute series, diagnosis of DMPM was made by fluid sampling in none of 68 patients. In 44 % of patients, diagnosis was obtained by laparotomy, in 52 % by laparoscopy, and in 4 % by ultrasound/computed tomography (US/CT)-guided biopsy [12]. CT-scan is the preferred radiological tool for disease staging and patient selection for treatment [16].

17.4.2 Histology, Immunohistochemistry, and Staging

According to the 2012 update of the Guidelines for Pathologic Diagnosis of Malignant Peritoneal Mesothelioma of the Consensus Statement from the International Mesothelioma Interest Group (iMIG), DMPM can be classified into epithelial, sarcomatoid, and biphasic variants, analogously to the pleural form. Histological subtypes are outlined in Table 17.1 [17]. Epithelial DMPM is further classified by its predominant patterns: tubulopapillary, solid, deciduoid, storiform-like, fascicular-like, papillary, microcystic, and granular. Tubulopapillary areas are sometimes difficult to distinguish from well-differentiated mesothelioma. There is usually some degree of nuclear pleomorphism. [17, 18].

Sarcomatoid DMPM can show the histologic patterns produced by any soft-tissue tumor. A mixture of sarcomatoid and epithelial components gives rise to biphasic or mixed variants (Fig. 17.1), which are usually aggressive tumors. Occasionally, sarcomatous areas may be markedly hypocellular, resulting in small biopsy specimens being misinterpreted as reactive fibrosis [17, 18].

It must be emphasized that conventional pathological techniques have low sensitivity and specificity in the diagnosis of DMPM. Thus, misdiagnosis between neoplasms originating from other abdominal organs is relatively common. Therefore, immunohistochemical studies play an important role in the diagnostic workup. In particular, DMPM must be distinguished from benign reactive lesions and metastatic carcinoma. At present, a specific marker for mesothelioma is not available, and diagnosis relies on the combination of positive [calretinin, cytokeratin (CK)-5/6, monoclonal antibody (MAb) D2-40, podoplanin, mesothelin, and Wilms tumor-1 (WT1)] and negative [claudin-4, carcinoembryonic antigen (CEA), MAbs MOC-31 and B72.3, and antihuman epithelial antigen (Ber-EP4) markers [17].

Table 17.1 Diffuse malignant peritoneal mesothelioma (DMPM) types and subtypes

Types	Subtypes	Percentage
Malignant	Epithelial	75
	Tubulopapillary nonglandular (solid)	13
	Sarcomatous	6
	Biphasic (mixed)	6
	Undifferentiated	Very rare
	Desmoplastic	Very rare
	Lymphohistiocytic	Very rare
	Small cell	Very rare
	Deciduoid	Very rare
Borderline/low malignant	Well-differentiated papillary	Rare
	Multicystic	Rare

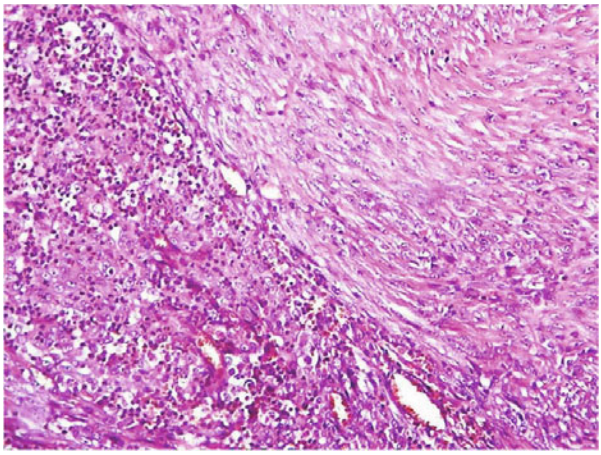

Fig. 17.1 Biphasic diffuse malignant peritoneal mesothelioma (DMPM) histology: combination of an epithelial and a sarcomatoid cells

Thyroid transcription factor 1 (TTF-1) can assist in distinguishing DMPM from lung carcinoma, homeobox protein CDX-2 from colon carcinoma, and cytokeratin (CK)-7 and paired-box (PAX)-8 from ovarian carcinoma or serous papillary peritoneal carcinoma. Renal cell carcinoma marker (RCC-Ma) may be helpful in establishing renal origin [19, 20].

Gathering data from eight international centers, a new tumor/node/metastasis (TNM) staging system for DMPM was recently proposed. Peritoneal cancer index (PCI) was categorized into T1 (PCI 1–10), T2 (PCI 11–20), T3 (PCI 21–30), and T4 (PCI 30–39). T1 N0 M0 was defined as stage I, T2/T3 N0 M0 as stage II, and T4 and/or N1 and/or M1 as stage III. The 5-year survival associated with stage I, II, and III disease was 87 %, 53 %, and 29 %, respectively [21].

17.4.3 Serum Tumor Markers

Although mesothelin and osteopontin showed their potential usefulness in diagnosing and assessing prognosis of pleura mesothelioma patients, no information is available for DMPM [22]. The clinical role of serum markers was studied in 60 patients with DMPM treated at the Istituto Nazionale Tumori (INT) in Milan, Italy. Baseline diagnostic sensitivity was 53.3 % for cancer antigen (CA)125, 0 for CEA, 3.8 % for CA19.9, and 48.5 % for CA15.3 [23]. These data may help in the initial evaluation of peritoneal tumors from unknown site of origin. When therapy response was assessed, CA125 normalized after adequate CRS plus HIPEC in 21/22 patients with elevated baseline levels. CA125 remained high in all patients with persistent macroscopic disease after surgery. Also, CA125 became positive in 12/12 patients with elevated baseline levels, developing disease progression after adequate CRS plus HIPEC. A borderline prognostic significance for baseline CA125 levels was observed only in individuals not previously treated with systemic chemotherapy (sCHT).

17.5 Treatment Results

17.5.1 Systemic Chemotherapy

In our institution, we investigated the role of sCHT in 116 DMPM patients treated with CRS plus HIPEC. No significant survival difference was seen among three subsets of patients: (1) those treated by sCHT before CRS plus HIPEC ($n = 60$), (2) patients who had sCHT after CRS plus HIPEC ($n = 30$), and (3) the group receiving no sCHT ($n = 26$). However, administration of platinum compounds plus pemetrexed was related with a statistically significant borderline survival advantage ($p = 0.09$) [24]. Even looking at other centers' experiences, no high-quality clinical data to define the role of sCHT in DMPM management is available.

DMPM is a poorly chemoresponsive tumor. A systematic meta-analysis of all prospective clinical trials published up to 2001 involving pleural or peritoneal mesothelioma demonstrated that cisplatin was the most active single agent and that cisplatin with doxorubicin was the most active combination in terms of treatment response [25]. However, these results should be interpreted with caution, as comparisons were not made in a randomized framework.

In a German series and the pemetrexed expanded access program, DMPM response rates were comparable with those observed for pleural disease [26, 27]. Other agents showing activity in DMPM are vinorelbine and gemcitabine, either alone or combined with platinum compounds. In historical case series, standard therapy with palliative surgery and systemic/intraperitoneally administered chemotherapy (IP-CHT) was associated with a median survival of ~ 1 year [4]. However, the hypothesis that chemotherapeutic drugs have limited efficacy seems to be confirmed by the poor median survival, ranging from 9 to 15 months, observed in individuals affected by DMPM who receive sCHT alone [2].

17.5.2 Cytoreductive Surgery plus Hyperthermic Intraperitoneal Chemotherapy

The 2006 Milan Consensus Conference on Peritoneal Surface Malignancies concluded that the standard treatment of DMPM is based on the integration of CRS-HIPEC and sCHT [6].

The aim of CRS is complete removal of all neoplastic implants from the abdominal cavity, which is possible only by peritonectomy (PRT) procedures and multivisceral resections. The pattern of DMPM dissemination implies complete distribution on peritoneal surfaces, and most cases are diagnosed with widespread tumor (Fig. 17.2). Also, microscopic disease is frequently identified at pathological examination, even when no evidence of disease is noted at macroscopic intraoperative examination. Therefore, we recommend complete

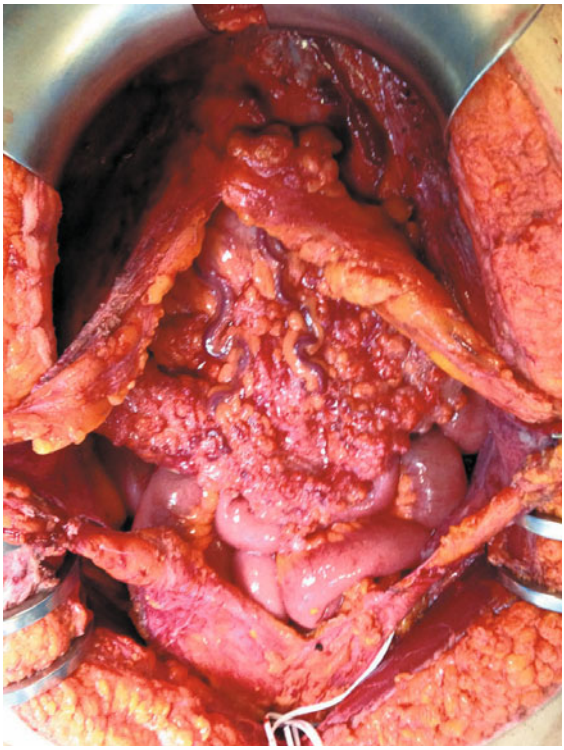

Fig. 17.2 Intraoperative high Peritoneal Cancer Index (PCI) in diffuse malignant peritoneal mesothelioma (DMPM): typical omental cake, peritoneal thickening, abdominal mass, and mesenterial thickening

parietal PRT for this disease [28]. Conversely, organ resections are indicated only in case of their massive involvement.

With the aim of consolidating macroscopic CRS, locoregional treatment allowing high peritoneal (and low systemic) drug concentration is used. This procedure, HIPEC, combines the pharmacological advantage with moderate hyperthermia. CRS is performed according to the technique originally described by Sugarbaker, with minor variations [29, 30] (Fig. 17.3) HIPEC is performed according to the closed-abdomen technique with cisplatin (45 mg/L perfusate) and doxorubicin (15 mg/L perfusate) for 90 min at a temperature of 42.5 C, based on a recent dose-finding study [31]. Perfusate volume is 4–6 L, and mean flow is 700 ml/min. The extracorporeal circulation device, Performer LRT® (RAND, Medolla, Italy), is used.

Analysis of published data allows us to conclude that median survival grew from 12 months with sCHT to 53 months with CRS plus HIPEC plus sCHT [32–34]. In our institutional experience, postoperative quality of life (QoL) was satisfactory, related morbidity and mortality acceptable, and financial cost-effectiveness reasonable [35, 36].

According to our most recent study, median overall (OS) and progression-free

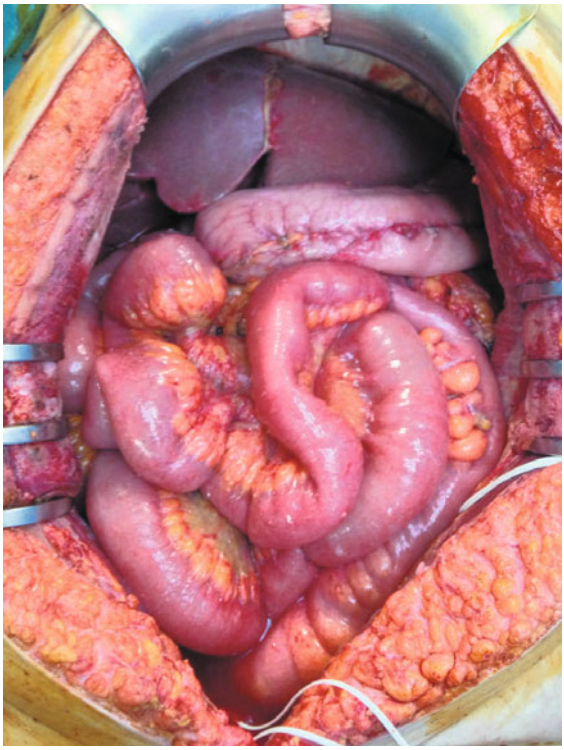

Fig. 17.3 High Peritoneal Cancer Index (PCI) diffuse malignant peritoneal mesothelioma (DMPM): result after mesenteric peritonectomy

(PFS) survival were 63.2 and 25.1 months in 108 patients undergoing complete CRS plus HIPEC (residual tumor < 2.5 mm). The survival curve reached a plateau after 7 years, suggesting that patients surviving > 7 years may be cured. Actual cure rate was 19/39 patients with potential follow-up of 7 years (43.6 %) [37].

17.6 Prognostic Factors

In a large collaborative study, the most significant prognostic factors were epithelial subtype, no node metastases, completeness of cytoreduction (CC), and administration of HIPEC [33]. In pattern-of-failure analysis, the small bowel was the site most commonly involved at recurrence; residual tumor > 2.5 mm was the only independent risk factor for recurrence [38]. CC has consistently been one of the most predominant prognostic factors. It is related to the extent of peritoneal involvement and surgeon skill to remove all peritoneal disease [1–3, 32–34]. Lymph node metastases are rare in DMPM but correlate with poor outcome. This supports the necessity that any suspicious node be systematically removed during the CRS procedure [32, 33].

Biphasic and sarcomatoid histological variants are correlated with poor prognosis, although their clinical utility as prognostic factors is limited by their rarity [1]. Other pathological prognostic variables are nuclear/nucleolar size, depth of tumor invasion, and mitotic count.

In the above-mentioned series, a Ki67-positive cell rate < 10 % correlated at multivariate analysis with better OS and PFS [37]. The role of proliferative index for prognostic stratification was confirmed in an exhaustive clinicopathological analysis by Deraco et al. (personal communication) using the technology of tissue microarray (TMA), results of which were presented at the Ninth International Symposium on Locoregional Cancer Therapies, Steamboat Springs, CO, USA, 15–17 February 2014.

17.7 Molecular Biology

In DMPM, molecular and cellular mechanisms underlying the proliferative potential and resistance to therapy are still poorly understood. The biology of this disease has been thoroughly investigated by clinical and basic science researchers at Milan INT during the last decade. It has been demonstrated that p16 expression is frequently absent or reduced in patients with DMPM and that EGFR overexpression is more common in peritoneal than in pleural forms. However, no correlation with prognosis of overexpression of EGFR and matrix metalloproteases (MMP)-2 and -9 was found in patients treated in our institution [39].

Telomerase activity (TA) is expressed in the majority of DMPM and negatively impacts prognosis [40]. In DMPM specimens from 38 patients undergoing various therapies; we assessed TA using the telomeric repeat amplification protocol. The alternative lengthening of telomeres (ALT) mechanisms were studied by assaying ALT-associated promyelocytic leukemia nuclear bodies. ALT or TA alone was found in 18.2 % and 63.6 % of cases, respectively; both ALT and TA were positive in two cases. In the overall series, TA expression was significantly associated with disease relapse (p = 0.018) and cancer-related death (p =0.045); ALT was not associated with outcome. In a subset analysis, the prognostic relevance of TA was confirmed in patients uniformly treated by CRS plus HIPEC.

Overexpression of cytoprotective factors, including survivin and members of the inhibitors of apoptosis protein (IAP) family, were demonstrated by Zaffaroni et al. [5]. Those authors analyzed DMPM proliferative and apoptotic features and tested a survivin knockdown approach in a human DMPM cell line. DMPM cells were transfected with small-interfering RNA (siRNA) targeting survivin messenger RNA (mRNA). Survivin expression, growth rate, and ability to undergo spontaneous and drug-induced apoptosis was measured, showing low proliferation rates and poor apoptotic activity in DMPM cells. Survivin was expressed in 91 % of cases and the other IAPs in 69–100 %. Transfection of

DMPM cells with survivin siRNA resulted in a survivin inhibition, a time-dependent cell-growth decrease, and an enhancement of spontaneous and drug-induced apoptosis. These results suggest that survivin may be a potential target for biological treatments in DMPM.

We demonstrated by in vitro experiments that nortopsentin heteroanalogs inhibit cyclin-dependent kinase (CDK)-1 activity, reduce cell growth, induce a concentration-dependent cell cycle arrest in the gap 2/mitosis (G2/M) phase, increase apoptotic rate, and downregulate survivin in a DMPM cell line. Additionally, the combined administration of nortopsentin heteroanalogs and paclitaxel further increased the cytotoxic effect.

In surgical samples from 20 DMPM patients undergoing CRS plus HIPEC at our center, Perrone et al. studied the expression of tyrosin kinase receptors (TKR) and the status of TKR downstream pathways, with mTOR and its effectors S6 ribosomal protein (S6), and 4E binding protein 1 (4EBP1), through biochemical and mutational analysis and fluorescent in situ hybridization (FISH). By immunoprecipitation/Western blot, activation/phosphorylation was shown in 90 % of cases for EGFR, 75 % for PDGFRβ, and 45 % of cases for PDGFRα. In 100 % of cases, no EGFR, PDGFRα, or PDGFRβ mutation or gene amplification was demonstrated. Primarily, AKT, extracellular signal-regulated kinase (ERK) 1/2, mTOR, S6, and 4EBP1 were highly expressed and activated. No mutations in *PI3KCA*, *PTEN*, *KRAS*, and *BRAF* genes were seen. The ligand- and heterodimerization-dependent activation/expression of EGFR and PDGFRβ was demonstrated. Taken together, these findings strongly suggest the potential of TKR and their downstream effectors as targets for molecularly tailored treatments. Based on the concurrent activation of TKR and their downstream effectors, we designed a clinicobiological study to test the combination TKR and mTOR inhibitors. In a further analysis, we evaluated the EGFR inhibitor gefitinib, the mTOR inhibitor everolimus (RAD001), and the multiple TKR inhibitor, sorafenib, in a DMPM cell line: gefitinib and RAD001 alone showed poor cytotoxic activity; sorafenib had a stronger effect on cellular proliferation, and sequential treatment with RAD001 followed by sorafenib induced a marked synergistic effect in DMPM cells [41].

17.8 Multicystic and Well-differentiated Papillary Peritoneal Mesothelioma

Multicystic (MPM) and well-differentiated papillary (WDPPM) PM are exceedingly rare tumors with uncertain malignant potential. At Milan NCI, MPM and WDPPM have been treated with CRS plus HIPEC because of their propensity to recur locoregionally and to evolve into truly malignant neoplasms. We treated four women with MPM and eight with WDPPM; one patient underwent a second procedure due to MPM peritoneal recurrence. Seven patients had recurrent disease after prior debulking. Due to the low aggressiveness of these diseases,

uterus and ovaries were spared in four young women. Optimal CRS with microscopic or minimal (≤ 2.5 mm) residual disease was achieved in 12/13 procedures.

After a median follow-up of 27 (range 6–94) months, disease progression developed in two patients and tumor-related death in one. At the time of this writing, the first patient was disease free after the repeated procedure. In the second patient, we documented a transition of typical WDPPM to biphasic DMPM; this woman died of disease progression after incomplete CRS followed by HIPEC. Five-year OS and PFS were 90 % and 79 %, respectively. The difference in PFS after 11 debulking operations carried out in seven patients before referral to the Milan NCI was statistically significant in favor of CRS plus HIPEC ($p = 0.016$). According to these data, definitive tumor eradication by CRS plus HIPEC is recommended as the standard option to prevent disease recurrence or transition into malignant conditions [42].

17.9 Future Perspectives

During the last two decades, CRS plus HIPEC has become the standard treatment for DMPM. Several studies have addressed DMPM biology and natural history, identifying new biological prognostic factors and therapeutic targets. However, there is still a critical need for effective systemic therapies for these patients. Several research lines are currently active at the Milan NCI:

- A prospective study, supported by the Health Ministry, aims to evaluate the potential efficacy of integrating CRS plus HIPEC and systemic treatment into an individualized, comprehensive approach based on molecular characterization of the disease.
- Further investigations on microRNA and other biological markers using the TMA technique aim to identify new prognostic factors and therapeutic targets.
- New efforts should be taken to validate prospectively the proposed TNM staging system.

Acknowledgement
Contents are partially based on Deraco M, Baratti D, Kusumara S (2012) Diffuse malignant peritoneal mesothelioma. In Sugarbaker et al. Cytoreductive Surgery and Perioperative Chemotherapy for Peritoneal Surface Malignancy: Textbook and Video Atlas, Cine-Med, Incorporated, pp 115-126.

References

1. Feldman AL, Libutti SK, Pingpank JF et al (2003) Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. J Clin Oncol 21:4560-4567

2. Sugarbaker PH, Yan TD, Stuart OA, Yoo D (2006) Comprehensive management of diffuse malignant peritoneal mesothelioma. Eur J Surg Oncol 32:686-691
3. Deraco M, Nonaka D, Baratti D et al (2006) Prognostic analysis of clinicopathologic factors in 49 patients with diffuse malignant peritoneal mesothelioma treated with cytoreductive surgery and intraperitoneal hyperthermic perfusion. Ann Surg Oncol 13:229-237
4. Deraco M, Baratti D, Zaffaroni N et al (2007) Advances in clinical research and management of diffuse peritoneal mesothelioma. Recent Results Cancer Res 169:137-155
5. Zaffaroni N, Costa A, Pennati M et al (2007) Survivin is highly expressed and promotes cell survival in malignant peritoneal mesothelioma. Cell Oncol 29:453-466
6. Deraco M, Bartlett D, Kusamura S, Baratti D (2008) Consensus statement on peritoneal mesothelioma. J Surg Oncol 98:268-272
7. European Network of Cancer Registries. Eurocim Version 4.0. European Incidence Database V2.3, CI5 Dictionary (2001). Lyon, France: IARC
8. Surveillance, Epidemiology, and End Results (SEER) Program. http://www.seer.cancer.gov
9. Boffetta P (2007) Epidemiology of peritoneal mesothelioma: a review. Annals of Oncology 18:985-990
10. Peto J, Decarli A, La Vecchia C et al (1999) The European mesothelioma epidemic. Br J Cancer 79:666-672
11. Spirtas R, Heineman EF, Bernstein L et al (1994) Malignant mesothelioma: attributable risk of asbestos exposure. Occup Environ Med 51:804-811
12. Sugarbaker PH, Welch LS, Mohamed F, Glehen O (2003) A review of peritoneal mesothelioma at the Washington Cancer Institute. Surg Oncol Clin North Am 12:605-621
13. Gazdar AF, Carbone M (2003) Molecular pathogenesis of mesotheliom and its relationship to Simian virus 40. Clin Lung Cancer 5:177-181
14. Roushdy-Hammady I, Siegel J, Emri S et al (2001) Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. Lancet 357:444-445
15. de Pangher V, Recchia L, Cafferata M et al (2010) Malignant peritoneal mesothelioma: a multicenter study on 81 cases. Ann Oncol 21:348-353
16. Yan TD, Haveric N, Carmignani CP et al (2005) Abdominal Computed Tomography Scans in the Selection of Patients with Malignant Peritoneal Mesothelioma for Comprehensive Treatment with Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy. Cancer 103:839-849
17. Husain AN, Colby T, Ordonez N et al (2013) Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 137:647-667
18. Weiss SW (1994) World health Organization International Histological Classification of Tumors: Histological typing of soft tissue tumors. Springer-Verlag, Berlin
19. King J, Thatcher N, Pickering C, Hasleton P (2006) Sensitivity and specificity of immunohistochemical antibodies used to distinguish between benign and malignant pleural disease: a systematic review of published reports. Histopathology 49:561-568
20. Deraco M, Baratti D, Cabras AD et al (2010) Experience with peritoneal mesothelioma at the Milan National Cancer Institute. World J Gastrointest Oncol 2:76-84
21. Yan TD, Deraco M, Elias D et al (2011) A novel tumor-node-metastasis (TNM) staging system of diffuse malignant peritoneal mesothelioma using outcome analysis of a multi-institutional database. Cancer 117:1856-63
22. Robinson BWS, Creaney J, Lake R et al (2003) Mesothelin-family proteins and diagnosis of mesothelioma. Lancet 362:1612-6
23. Baratti D, Kusamura S, Martinetti A et al (2007) Circulating CA125 in patients with peritoneal mesothelioma treated with cytoreductive surgery and intraperitoneal hyperthermic perfusion. Ann Surg Oncol 14:500-508
24. Deraco M, Baratti D, Hutanu I et al (2013)The role of perioperative systemic chemotherapy in diffuse malignant peritoneal mesothelioma patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 20:1093-1100
25. Berghmans T, Paesmans M, Lalami Y et al (2002) Activity of chemotherapy and immunother-

apy on malignant mesothelioma: a systematic review of the literature with meta-analysis. Lung Cancer 38:111-121
26. Jänne PA, Wozniak AJ, Belani CP et al (2005) 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 7:40-46
27. Carteni G, Manegold C, Martin Garcia G et al (2009) Malignant peritoneal mesothelioma. Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agent: Lung Cancer 64:211-218
28. Baratti D, Kusamura S, Cabras AD, Deraco M (2012) Cytoreductive surgery with selective versus complete parietal peritonectomy followed by hyperthermic intraperitoneal chemotherapy in patients with diffuse malignant peritoneal mesothelioma: a controlled study. Ann Surg Oncol 19:1416-1424
29. Sugarbaker PH (1995) Peritonectomy Procedures. Ann Surg 221:29-42
30. Deraco M, Baratti D, Kusamura S et al (2009) Surgical technique of parietal and visceral peritonectomy for peritoneal surface malignancies. J Surg Oncol 100:321-328
31. Rossi CR, Foletto M, Mocellin S et al (2002) Hyperthermic intraoperative intraperitoneal chemotherapy with cisplatin and doxorubicin in patients who undergo cytoreductive surgery for peritoneal carcinomatosis and sarcomatosis: phase I study. Cancer 94:492-499
32. Baratti D, Kusamura S, Cabras AD et al (2010) Lymph node metastases in diffuse malignant peritoneal mesothelioma. Ann Surg Oncol 17:45-53
33. Yan TD, Deraco M, Baratti D et al (2009) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol 27:6237-6242
34. Deraco M, Casali P, Inglese MG et al (2003) Peritoneal mesothelioma treated by induction chemotherapy, cytoreductive surgery, and intraperitoneal hyperthermic perfusion. J Surg Oncol 83:147-153
35. Deraco M, Baratti D, Kusamura S (2007) Morbidity and quality of life following cytoreduction and HIPEC. Cancer Treat Res 134:403-418
36. Baratti D, Scivales A, Balestra MR et al (2010) Cost analysis of the combined procedure of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). Eur J Surg Oncol 36:463-469
37. Baratti D, Kusamura S, Cabras AD et al (2013) Diffuse malignant peritoneal mesothelioma: long-term survival with complete cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC). Eur J Cancer 49:3140-148
38. Baratti D, Kusamura S, Cabras AD et al (2009) Diffuse malignant peritoneal mesothelioma: Failure analysis following cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC). Ann Surg Oncol 16:463-472
39. Nonaka D, Kusamura S, Baratti D et al (2005) Diffuse malignant mesothelioma of the peritoneum: a clinicopathological study of 35 patients treated locoregionally at a single institution. Cancer 104:2181-2188
40. Villa R, Daidone MG, Motta R et al (2008) Multiple mechanisms of telomere maintenance exist and differentially affect clinical outcome in diffuse malignant peritoneal mesothelioma. Clin Cancer Res 14:4134-4140
41. Perrone F, Jocollè G, Pennati M et al (2010) Receptor tyrosine kinase and downstream signalling analysis in diffuse malignant peritoneal mesothelioma. Eur J Cancer 46:2837-2848
42. Baratti D, Vaira M, Kusamura S et al (2010) Multicystic peritoneal mesothelioma: outcomes and patho-biological features in a multi-institutional series treated by cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Eur J Surg Oncol 36:1047-1053