Updates in Surgery

Angelo Di Giorgio
Enrico Pinto *Editors*
In collaboration with
Paolo Sammartino and Franco Roviello

Treatment of Peritoneal Surface Malignancies

State of the Art and Perspectives

Springer

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Foreword by
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Springer

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Foreword

On the basis of the latest epidemiological data, peritoneal surface malignancies (PSM) represent a pathology characterized by a high annual incidence, between those of stomach and colorectal cancer.
The integration of cytoreduction surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), variously combined with other adjuvant and neoadjuvant chemotherapeutic regimens, is an example of the increasingly complex care strategy for PSM.

There is a strong rationale behind combining CRS with HIPEC to create a procedure based on the evolutionary history of PSM, once considered to be caused only by locally advanced malignancies of the abdominal cavity free of distant metastases. Over the past 20 years, the consistency of results of this integrated procedure has led to it now being considered the treatment of choice for carcinomatosis from pseudomyxoma peritonei, mesothelioma and, recently, the colon, with low peritoneal spread. Furthermore, the trend in using this procedure is increasingly being applied to treat gastric and ovarian carcinomatosis and rarer forms of peritoneal diseases, such as peritoneal metastases from breast and pancreatic cancer and sarcomatosis.

Experience to date using this treatment modality has identified the most significant prognostic parameters and the most important risk factors associated with the procedure. This monograph is thus based on contributions from some of the major Italian centers devoted to treating PSM. It provides the most significant updates on diagnosis, treatment, and outcomes obtained so far. The text thoroughly summarizes the state of the art on CRS plus HIPEC and identifies future development perspectives on related research.

Rome, September 2014

Giorgio De Toma
President, Italian Society of Surgery

Preface

A variety of tumors originating from intra- or extra-abdominal viscera and, more rarely, from the peritoneal membrane, spread or metastasize to the visceral and parietal peritoneum. The term peritoneal surface malignancy (PSM) encompasses all these forms and thus identifies a heterogeneous family of primary or metastatic tumors with epithelial or mesenchymal origin. The inclusion of various forms of primary and secondary PSM under a unique definition is justified by the substantial uniformity of their clinical evolution within the abdominal and pelvic cavity, leading to production of tumor implants and ascites until fatal obstruction occurs. Prognosis is poor, and palliative therapy has long represented the only treatment option. In the natural history of PSM, evolution can be slow and metastatic development late, so that many forms represent ideal targets for aggressive locoregional therapies.

In the 1980s, Paul Sugarbaker theorized – following countless pharmacokinetic and pharmacodynamic studies – about advantages of the association between maximal surgical cytoreduction [peritonectomy (PRT)], aimed at removing all visible implants, and hyperthermic intraperitoneal chemotherapy (HIPEC), aimed at treating microscopic or millimetric residues. Since the 1990s, this concept has gradually gained acceptance and currently is the intervention of choice for pseudomyxoma peritonei and mesothelioma, but it is also diffusely used to treat carcinomatosis from colorectal, gastric, and ovarian cancer and peritoneal sarcomatosis. For the most common forms of PSM treated with PRT plus HIPEC, experiences available to date consistently show overall results better than or highly competitive with traditional treatment modalities. PSM forms that until two decades ago were considered untreatable surgically and for which progression was fatal within months of diagnosis, today, after appropriate patient selection, are routinely treated with PRT plus HIPEC, resulting in improved patient quality of life and long-term survival rates. The combined procedure achieves acceptable postoperative morbidity and mortality rates in relation to its complexity and duration (median 10 h) similar to those of major abdominal and pelvic surgery.

However, the procedure has limited application considering the high overall incidence of various forms of PSM and is not exempt from criticism. The limited

diffusion of PRT plus HIPEC treatment is related to the long learning curve; availability of relevant human, technical, and economic resources; and skepticism toward its effectiveness, particularly in reference to HIPEC, which is considered potentially risky during the postoperative course. Furthermore, the main criticisms concern the lack of prospective randomized phase III studies to define clearly the role of HIPEC, given that the validity of maximum cytoreduction is accepted worldwide. Indeed, to date, overall results of prospective trials for HIPEC are scarce and heavily criticized for the general treatment approach, lack of homogeneity of surgical techniques, and wide dispersion of enrolled cases. Therefore, results regarding overall significance of this procedure come mainly from multi-institutional studies, reviews, meta-analyses, and studies conducted in single centres with a high volume of PRT plus HIPEC activity. While taking into account the limitations inherent in such studies, the magnitude of experience gained to date reveals the overall trend of results. The great effort made by surgeons, oncologists, and specialized centers dedicated to treating PSM using PRT plus HIPEC has brought about the possibility of successfully treating aggressive locoregional tumors such as PSMs. It now remains for the inevitable upcoming prospective studies to confirm the promising results obtained thus far with this combined treatment modality and to determine the most appropriate ways to address treatment for PSM.

The purpose of this monograph is to provide a summary of the knowledge base supporting the rationale of associating maximum cytoreduction with HIPEC, pathological assessment and diagnostic workup of patients with PSM, surgical and HIPEC techniques, and management results of the most common forms of PSM. In the world that revolves around PSM management, Italy plays a significant role, as demonstrated by case series treated by the various PSM centers in this country and the vast scientific contribution drawn from the literature and from acts of the major international conventions. Collaboration between many of the most important specialized Italian surgeons and treatment centers has helped provide an overall picture that illustrates the state of the art regarding PSM management. The topics discussed, and the opinions, experiences, and conclusions expressed by the various authors of these chapters, provide an in-depth summary of experiences pertaining to the most critical issues and outline goals to be achieved in the coming years through collective and coordinated efforts.

Rome, September 2014

Angelo Di Giorgio
Enrico Pinto

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Part I

Background

Peritoneal Surface Malignancies

1

Angelo Di Giorgio

1.1 Definition

The term Peritoneal Surface Malignancies (PSMs) identifies a wide range of epithelial or mesenchymal neoplasms that originate from the primitive structure of the peritoneum or spread over and through the peritoneum membrane as metastases deriving from tumors of intra-abdominal, retroperitoneal, or extra-abdominal organs or viscera (Table 1.1). PSM evolution depends on the degree of aggressiveness of the various neoplastic forms: in contrast with benign or low malignant forms, aggressive forms are able to produce fast and fatal disease progression. The primitive forms are much rarer than secondary forms, and mesotheliomas and serous tumors of the peritoneum are the most common among them. Colorectal, gastric, and ovarian peritoneal carcinomatosis (PC) are the most frequent forms of PSM arising from intraperitoneal viscera. PSMs originating from retroperitoneal tumors, such as the pancreas, kidneys, or adrenals, are rare and even less frequent are those originating from extra-abdominal tumors, such as breast or lung cancer. Epithelial forms are far more frequent than mesenchymal forms. Primary tumors of the peritoneum and carcinomatosis from gynecological or gastrointestinal tumors are overall the most widespread and common PSMs treated in surgery and oncology. Irrespective of histological differences, most PSMs have a common tendency to grow for a relatively long period of time exclusively in the abdominal cavity, thus representing an ideal target for aggressive locoregional treatments.

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Table 1.1 Peritoneal surface malignancies

	Malignant	Borderline/low grade
Primary	DMPM (Diffuse Malignant Peritoneal Mesothelioma)	WDPM (Well-differentiated Papillary Mesothelioma); MPM (Multicystic Peritoneal Mesothelioma)
	PPSPC (Primary Peritoneal Serous Papillary Carcinoma)	
	DSRCT (Desmoplastic Small Round Cell Tumor)	
Secondary	***Intra-abdominal origin***	
	Colorectal cancer	
	Gastric cancer	
	Ovarian cancer	Ovarian cancer
	PMCA (Peritoneal Mucinous Adenocarcinoma): pseudomyxoma peritonei from mucinous adenocarcinoma of appendix	DPAM (Diffuse Peritoneal Adenomucinosis): pseudomyxoma peritonei from low-grade mucinous tumors of appendix
	Adenocarcinoid of appendix	
	Small-bowel adenocarcinoma	
	GIST (Gastrointestinal Stromal Tumor)	
	Retroperitoneal origin	
	Pancreatic cancer	
	Kidney, ureter, adrenal, bladder cancer	
	Sarcomas	
	Extra-abdominal origin	
	Breast cancer	
	Lung cancer	

Epidemiology: Extent of the Problem

2

Simone Sibio, Joseph Maher Fouad Atta, Alessio Impagnatiello, Bianca Maria Sollazzo, and Daniele Marrelli

2.1 Introduction

Peritoneal carcinomatosis (PC) most commonly represents local or regional evolution of an abdominal carcinoma. Sometimes it can be synchronous with the primary tumor (primary carcinomatosis) but more often is present as recurrent disease (metachronous or secondary) after first-line treatment of the originating tumor. Patients with tumors from colon, ovary, and stomach cancer are more likely to present with PC during their clinical course. Less frequently, other abdominal malignancies, such as uterus, pancreas, small bowel, biliary, or urinary tract, can involve the peritoneum. Tumors originating from the peritoneum itself are definitely rarer: mesothelioma, pseudomyxoma peritonei (PMP), primitive peritoneal carcinoma, and desmoplastic small-round-cell tumor. PC from extra-abdominal tumors, such as lung, breast, melanoma, or peritoneal sarcomatosis, is exceptional, and few epidemiological data are available on them. Statistical analysis of worldwide cancer incidence, prevalence, and mortality rate is available on GLOBOCAN 2012 [1]. In Italy, most epidemiological data are available in the reports from the Italian Association of Tumor Registries (AIRTUM) [2], which collects data regarding incidence, prevalence, and mortality rates from all local and regional tumor registries, covering at least 34% of total population. This data is considered a high-quality regional coverage by and international ranking system (GLOBOCAN 2012 rate B). An overview of available data suggests a global general consideration: mortality related to cancer in general decreased from 75% of global incidence of cancers in 1970 to 47% in 2010 despite a global increased incidence of 25%

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in the same 40-year period in Western countries; these data appear related to the strong impact on survival of new treatment strategies and drugs and concur with observations for PC. In Italy 30,000–40,000 new cases of PC from various primary tumors are expected every year. Table 2.1 shows the incidence of PC (primary or secondary) in Italy in 2012 by age [Italian National Institute of Statistics (ISTAT)]. Mortality rate for PC as first cause of death (Table 2.2) or as one of multiple causes of death (Table 2.3) are reported for the previous 6 years in Italy; data are extracted from hospital discharge records by ISTAT and include primary and secondary tumors.

Table 2.1 Incidence of primary (ICD-9-CM 1588–1589) or secondary (ICD-9-CM 1976) peritoneal carcinomatosis in Italy by age

Year 2012						
Description	Age					
	0–44	45–54	55–64	65–74	75+	Total
Malignant neoplasm of peritoneum or retroperitoneum (primary)	133	264	518	665	732	2,312
Malignant neoplasm of peritoneum or retroperitoneum (secondary)	2,862	6,028	10,364	13,605	11,753	44,612

ICD-9-CM International Classification of Diseases, 9th Revision – Clinical Modification

Table 2.2 Mortality for peritoneal carcinomatosis (PC) in Italy (first cause)

ICD-10	Years					
	2006	2007	2008	2009	2010	2011
C48.0	270	222	286	261	257	230
C48.1	15	14	11	17	14	9
C48.2	159	155	198	182	124	125
C48.8	1					
C78.6	272	288	233	276	302	316
Total	717	679	728	736	697	680

ICD-10 International Classification of Diseases, 10th Revision

2.2 Peritoneal Carcinomatosis from Colorectal Cancer

Globally, colorectal cancer (CRC) is the third most common cancer and ranks as the fourth most common cancer-related cause of mortality [1]: it is the third most common cancer in men [746,000 (10 %) cases] and the second most com-

Table 2.3 Mortality for peritoneal carcinomatosis (PC) in Italy (multiple causes)

ICD-10	Years					
	2006	2007	2008	2009	2010	2011
C48.0	297	257	312	289	282	251
C48.1	17	17	15	19	19	11
C48.2	253	252	251	302	210	170
C48.8	1					1
C78.6	8,219	8,648	8,557	9,060	9,505	9,626
Total	8,787	9,174	9,235	9,670	10,016	10,059

ICD-10 International Classification of Diseases, 10th Revision
C48 Malignant neoplasm of peritoneum or retroperitoneum (primary)
C48.1 specified site
C48.2 unspecified site
C48.8 overlapping sites
C78.6 malignant neoplasm of peritoneum or retroperitoneum (secondary)

mon in women [614,000 (9.2%) cases]. Almost 55 % of cases occur in more developed regions. There is wide geographical variation in incidence across the world, and geographical patterns are very similar in men and women: incidence rates vary tenfold in both sexes worldwide, the highest estimated rates being in Australia/New Zealand and the lowest in western Africa (4.5 and 3.8 per 100,000, respectively). Mortality rate is lower [694,000 (8.5 %) deaths] but with more deaths (52 %) in the less developed regions of the world, reflecting a poorer survival in these regions. There is less variability in mortality rates worldwide (sixfold in men, fourfold in women), with the highest estimated mortality rates in both sexes in central and eastern Europe (20.3 per 100,000 for men; 11.7 per 100,000 for women) and the lowest in western Africa (3.5 and 3.0, respectively) [1].

In United States, the incidence of CRC is about 149.000 new cases per year, with a related mortality rate reaching 30 % [3]. A major component of treatment failure is cancer dissemination within the peritoneal cavity appearing as local recurrence of primary tumor or peritoneal metastases, which is estimated to account for 40 % of all patients with CRC [4].

Thomassen et al. [5] studied the incidence of synchronous PC in patients affected by CRC; data were extracted from the Eindhoven Cancer Registry over a period of 15 years; results are reported in Fig. 2.1. In Italy, CRC has an incidence of 38,000–41,000 new cases per year, with a 33 % mortality rate (13,000 deaths per year). Among these patients, about 15 % (6,000 per year) present with primary PC, whereas 35 % of all mortality (4,600 per year) is related to peritoneal recurrence alone, or 11 % of all patients with CRC [2]. Table 2.4 summarizes the more significant experiences in the literature regarding PC incidence and local recurrence from CRC in different series of patients [6–17].

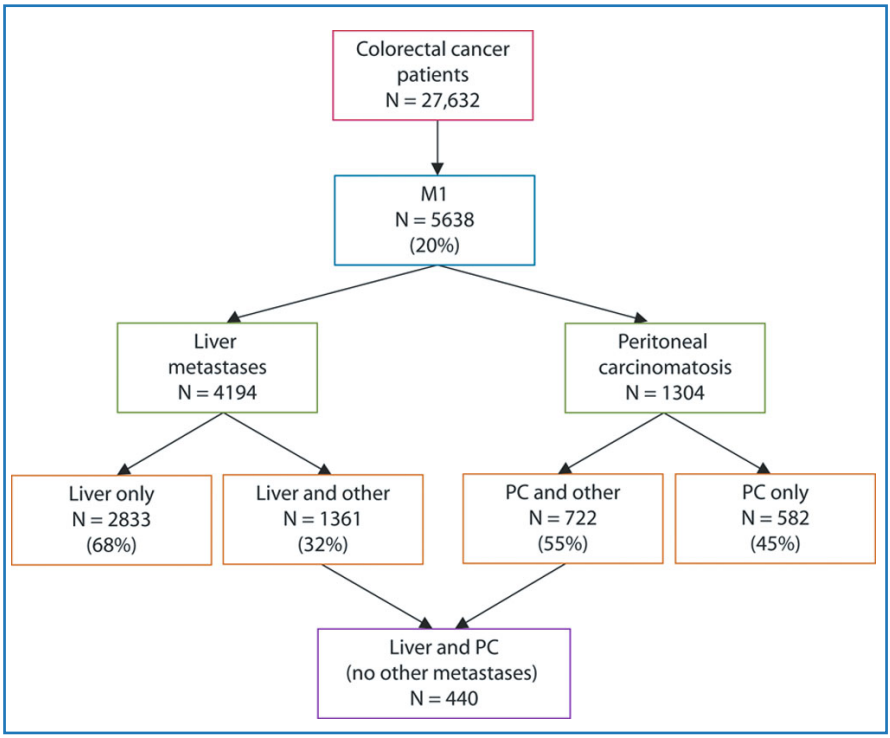

Fig. 2.1 Incidence of synchronous peritoneal carcinomatosis (PC) in patients with colorectal cancer (CRC) in a large, population-based study from Eindhoven Cancer Registry [5]

Table 2.4 Incidence of local recurrence and peritoneal carcinomatosis (PC) from colorectal cancers reported in the literature

Study [Reference]	No. patients	Local recurrence (%)	PC (%)
	Clinical series		
Malcolm et al. [9]	285	3.9	13
Cass et al. [6]	280	23	28
Russell et al. [13]	94	7	12
Mendenhall et al. [10]	140	29	3
Olson et al. [12]	281	9	-
Minsky et al. [11]	294	9	4
Gilbert et al. [8]	31	36	3
Jayne et al. [17]	2,756	-4.9	
	Reoperation series		
Gunderson et al. [14]	91	48	21
Tong et al. [15]	64	48	44
	Autopsy series		
Russell et al. [16]	53	38	36
Gilbert [8]	45	-	40

2.3 Peritoneal Carcinomatosis from Gastric Cancer

Although the incidence of gastric cancer (GC) has decreased in recent years, it is still the fourth most common newly diagnosed cancer worldwide and the second leading cause of cancer-related death [5]. There are major differences in the incidence of GC across countries and continents. Global incidence, as well as primary tumor location and histological type, are constantly changing. In the US and most of western Europe, there has been a marked decline in distal intestinal GC, whereas the incidence of proximal and Barrett's adenocarcinoma of the gastric cardia and esophageal–gastric junction has been increasing. The incidence of diffuse adenocarcinoma, on the other hand, is largely unchanged. Adenocarcinoma of the body of the stomach and antrum predominates in developing countries, among African Americans, and in lower socioeconomic groups, whereas proximal tumors are more common in developed countries, among Caucasians, and in higher socioeconomic classes [18]. Nevertheless, GC is common throughout Europe. In 2000, there were 192,000 new diagnoses, with 158,000 deaths [19].

In Italy, the incidence accounts for 17,000 new patients per year, with higher mortality rates [10,900 (60 %) per year] [1, 2]. Outcome remains poor despite advances in therapy, and an overall 5-year survival rate of about 20% compares very unfavorably with that of 70% achieved in Japan [19]. Peritoneal dissemination is the most frequent pattern of metastasis from GC and commonly occurs via intracoelomic dissemination or tumor spillage during surgery [20]. PC is present at diagnosis in 5–20 % of patients and can affect 60 % after curative treatment [21, 22]. Despite radical surgery and extended lymphadenectomy, 20–50 % of patients will develop peritoneal recurrence during their follow-up. Serosal involvement, Lauren diffuse histotype, and positive peritoneal cytology are the most important risk factors for peritoneal recurrence after radical surgery [23]. Multicenter studies indicate a decrease in locoregional recurrence and an increase in peritoneal recurrence of GC in recent years, with approximately one third having total recurrences after curative surgery [24]. Although there are few data available from cancer registries, PC form GC in Italy is likely to reach 3,500–4,000 cases per year, with a very high mortality rate [3,100 (30 %) of all deaths per year].

2.4 Peritoneal Carcinomatosis from Ovarian Cancer

Epithelial ovarian cancer (EOC) affects > 200,000 women and causes 125,000 deaths annually worldwide [25]. In the USA, the incidence is ~ 22,000 cases per year and is the fifth most common cause of cancer death (15,500). In Italy, there are 4,400 new cases every year, and there is a global mortality rate of 67.7 %. Worldwide, only 40–47 % of patients with EOC can be expected to survive > 5 years. Lifetime risk for OC is one in 70, but some women have a much

higher risk, especially those with germ-line mutations of *BRCA1* and *BRCA2* tumor suppressor genes [26]. The incidence is low before menopause, but after this, the incidence rises progressively. Median age at diagnosis is 63 years worldwide [1, 27]. More than 70 % of EOC patients present with peritoneal spread at first diagnosis (82 % in Italy), and > 80 % of deaths are due to PC. Family history is the strongest risk factor for hereditary OC.

Three clinical manifestations of hereditary OC are recognized: site-specific OC, breast and OC syndrome, and the hereditary nonpolyposis CRC (HNP-CC; Lynch II) syndrome. The first two groups are associated with germ-line mutations in the *BRCA1* and *BRCA2* tumor suppressor genes, whereas HNP-CC is associated with germ-line mutations in the DNA mismatch repair (*MMR*) genes, primarily *hMLH1* and *hMSH2*. At least 10 % of all epithelial OC is hereditary, with mutations in the *BRCA* genes accounting for ~ 90 % of cases and most of the remaining 10 % being attributable to HNP-CC [26]. There are no certain risk factors for sporadic EOC, although a study by Peterson et al. of 581 US patients found lower socioeconomic status, estimated by neighborhood socioeconomic status, is associated with OC tumor characteristics indicative of more advanced and aggressive disease; however, reasons for this remain unclear [28]. Interestingly, another study by Bristow et al. demonstrated that prognosis in EOC is highly dependent from epidemiological variables, such as socioeconomic status, and access to high-volume care centers: high-volume physician and annual hospital case volumes are associated with improved OC survival, although access to high-volume care centers is yet limited [29].

2.5 Peritoneal Mesothelioma

Data on descriptive epidemiology of diffuse malignant peritoneal mesothelioma (MPM) are available from many national registries, such as EUROCIM [30], the US Surveillance, Epidemiology, and End Results Cancer Registry (SEER) [27], and in Italy, AIRTUM [2]; diagnostic criteria have changed widely over recent years, which complicates adequate description of epidemiological data. Age-standardized incidence rates range from 0.5 to ~ 3 cases per million worldwide, with 2,500 new cases per year. However, higher rates are reported in smaller areas with widespread past use of asbestos, such as the harbor of Genoa, where the incidence rate is 5.5 per million [31]. In Italy, incidence varies from 0.1 to 6.4 per million, with 1,000 expected new cases per year [2]. Peritoneal mesothelioma must be considered an increasing public health problem because its incidence has been rising worldwide since 1970; an increasing in mortality rate of 5–10 % is expected until 2020 [32]. Mesothelioma is three times more common in men than in women, and incidence increases with age, being tenfold higher in 60–64-year-old individuals than in 30–40-year-olds. Asbestos is the main known cause of the disease, but other risk factors are likely to be involved in its etiology and pathogenesis, such

as radiation, viruses, or genetics [31]. SEER median survival data is 10 months, and relative 5-year survival is 16 %. Survival is positively influenced by female gender (related to asbestos exposure), younger age at diagnosis, and epithelioid histology [33].

2.6 Pseudomyxoma Peritonei

In 1884, Werth [34] introduced the term pseudomyxoma peritonei, literally translated as an untrue mucinous tumor of the peritoneum. PMP is a very rare disease, with an incidence of one to two per million per year worldwide; it is characterized by disseminated intraperitoneal mucous and mucinous implants on peritoneal surfaces and omentum and in the subdiaphragmatic space. Global overall 10-year survival is ~ 70 %.

PMP is thought to be associated with appendiceal mucinous neoplasms (AMN). Because ovarian involvement is seen in the majority of female patients, an ovarian primary has long been suggested as the cause of PMP. However, results of several clinical, histopathological, immunohistochemical, and molecular genetic studies strongly suggest that in patient with PMP, ovarian tumor deposits are almost always metastases of an appendiceal primary, although other origins have been described as well [35]. It has also been reported rarely in association with mucinous carcinomas of other organs, such as gallbladder and bile ducts, stomach, pancreas, colon, Fallopian tube, uterine corpus, urachus, urinary bladder, breast, and lung. Although PMP may on rare occasions arise from benign mucinous tumors, it is most commonly associated with well-differentiated malignant tumors or those of borderline malignancy.PMP occurs in approximately two of every 10,000 laparotomies and is more common in women; 75 % of patients are women, with an average age of 53 years [34].

A large population-based study in The Netherlands considered > 167,000 appendectomies performed in that nation in a 10-year period and found 1,482 of them presenting appendiceal neoplastic lesions (nine per 1 million) (Table 2.5), which is higher than worldwide general incidence, with a three- to eight-fold incidence in women compared with men [36]. PMP can be synchronous with the appendiceal lesion (77 %) or metachronous; median evolution time from an appendiceal neoplasm to PMP is ~ 2 years but can be > 10 years.

2.7 Other Secondary Peritoneal Carcinomatosis

Occasionally, every solid tumor originating in the peritoneal cavity can involve the peritoneal surface, such as urinary tract, pancreas, biliary tract, and uterus. Among them, pancreatic carcinoma represents the most frequent histotype. In a large population-based study, Thomassen et al. found 265 (9 %) of 2,924 patients

Table 2.5 Incidence and gender distribution of appendiceal lesions and pseudomyxoma peritonei (PMP) in 167,744 appendectomies in The Netherlands (by age)

Lesion type	Appendiceal		PMP	
	M/F	Ratio	M/F	ratio
Mucocele	186/269	1:1.4	3/8	1:2.7
Mucinous neoplasms	203/371	1:1.8	31/83	1:2.7
Adenoma	153/268	1:1.7	18/52	1:2.9
Adenocarcinoma	50/103	1:2.1	13/31	1:2.4
Nonmucinous neoplasms	219/234	1:1.1	2/11	1:6.0
Adenoma	112/130	1:1.2	1/8	1:8.0
Adenocarcinoma	107/104	1:1.0	1/3	1:3.0
Total	608/874	1:1.4	36/102	1:2.8

M/F, male/female

affected by pancreatic cancer presenting with synchronous PC and observed an increasing trend in patients treated with chemotherapy in more recent years (11 % in 1995–1999 and 22 % in 2005–2009) [37]. PC from extra-abdominal tumors is very rare, and most current literature is based on case reports; among them, breast and lung cancer represent the most frequent tumors associated with PC. In a large study of 1,628 patients with breast cancer, Tuthill et al. identified 44 patients (2.7 %) with PC who had a very poor prognosis (1.57 months) in the UK [38]. Another study of PC from lung cancer in an autopsy series showed a global incidence ranging from 2.7 % to 16 %, together with other sites of metastasis [39].

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Mechanism of Intraperitoneal Spread of Free Cancer Cells

3

Giovanni Corso, Daniele Marrelli, and Franco Roviello

3.1 Introduction

Peritoneal carcinomatosis (PC) from cancer cell dissemination from a primary tumor is considered a local cancer rather than systemic spread. Multiple primary cancers are responsible of peritoneal metastasis (PM). Patients affected by primary epithelial tumors plus PM can benefit from an aggressive surgical approach, such as the cytoreductive surgery (CRS), combined with hyperthermic intraperitoneal chemotherapy (HIPEC), which can result in long-term survival rates in selected patients [1]. Targeted indications are important for the success of these treatments. Patient selection is performed routinely depending on clinical parameters, preoperative tumor staging, and intraoperative findings. However, the origin mechanism of PM underlying specific biological aspects; in fact, some targeted molecules are responsible of tumor spread and peritoneal cancer cells adhesion. These molecular biomarkers are introduced in clinical practice to identify patients eligible for targeted therapies.

This chapter specifically focuses on describing cellular pathogenesis in PM to evaluate its potential role in clinical application.

3.2 Pathophysiology

In PM, three independent mechanisms are responsible for cancer-cell implantation in the peritoneum:

- The primary pathway is dissemination of free cancer cells from a primary

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tumor, with exfoliation and direct peritoneal invasion [2]. Free cancer cells cleave to the peritoneal surface via adhesion molecules [3];
- The second mechanism is dissemination of tumor cells through lymphatic or venous vessels within the peritoneal cavity [2];
- The third mechanism is surgical manipulation or trauma [2].

Neoplastic redistribution is a PC that originates from transparietal spread in individuals with low-grade tumors. This diffusion is associated with a nonrandom mechanism of metastasization due to gravity on biological fluids (i.e., ascites). This redistribution plays a preponderant role on the effect of viscosity. Free cancer cells float into the peritoneal space forming cell aggregation in spotted areas as a consequence of gravity and concentration in places of peritoneal fluid absorption. Reabsorption of peritoneal fluids takes place at the omentum and diaphragmatic peritoneum. The most frequently affected locations are pelvis, subphrenic areas, parietocolic grooves, and the Morrison's pouch [3]. In the absence of tumor fluid production, cancer cell motility is limited, implanting close to the primary site. Distant areas are affected when the fluid carrier is presents, such as at the Treitz ligament and the lesser omentum; in the absence of fluid carriers, these sites are unaffected.

In general, in the early stage, the mesenteric surfaces and serosa of the small intestine are spared; the presence of peristaltic motility inhibits cancer cell adhesion. Conversely, fixed areas, such as the duodenum, ileocecal, and rectosigmoid passages, are frequently involved by PM. The association of multiple factors, such as peristalsis, gravity, fluid reabsorption, tumor histotype, and biological features, defined this pattern of peritoneal invasion known as neoplastic redistribution [4].

3.3 Molecular and Cellular Pathology

The pathophysiology of cancer spread, specifically peritoneal dissemination, comprises different stages: (1) detachment of cancer cells from the primary cancer; (2) migration to distant sites, and (3) colonization and adaption in a new microenvironment—in this case, the peritoneum [5]. PM pathophysiology is depicted in Fig. 3.1.

3.3.1 Loss of Cell Adhesion and Increased Motility

After detachment from the primary cancer, free tumor cells show reduced adhesion and increased motility to the peritoneum. In this phase, inactivation of cell–cell adhesion molecules (CAMs) plays a pivotal role in changing the cytoskeletal structure [6]. The CAM group comprises integrins, cadherins, selectins, and some members of the immunoglobulin family. Moreover, among