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Primary Peritoneal Carcinoma: A Review of the Literature

Christina S. Chu, Andrew W. Menzin, Debra G.B. Leonard, Stephen C. Rubin and James E. Wheeler

Departments of Obstetrics and Gynecology (C.S.C., S.C.R.) and Pathology and Laboratory Medicine (D.G.B.L., J.E.W.), University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; and Department of Obstetrics and Gynecology, North Shore University Hospital (A.W.M.), Manhasset, New York

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader will be able to understand the similarities and differences between primary peritoneal carcinoma and epithelial ovarian cancer, the criteria used to define primary peritoneal carcinomas, and the differences in presentation between a low malignant potential tumor of the peritoneum and an ovarian low malignant potential tumor.

In 1959, Swerdlow (1) reported a case of a 27-year-old woman with a tumor of the pelvic peritoneum, histologically resembling papillary serous carcinoma of the ovary. Since Swerdlow's report, primary peritoneal carcinoma (PPC) has been called by many names including mesothelioma, papillary carcinoma of the peritoneum, serous surface papillary carcinoma, and extraovarian papillary serous carcinoma, reflecting the controversy surrounding its histogenesis and clinical behavior. Initially, these tumors were classified as mesotheliomas because of their purported common ancestry (2), despite the apparent epidemiological differences.

PPC is a tumor that diffusely involves the peritoneal surface while sparing or only minimally involving the ovaries. It is histologically indistinguishable from primary epithelial ovarian carcinoma (EOC), and is diagnosed in the absence of another identifiable primary. Upon retrospective review, approximately 10 percent of the patients initially felt to have EOC are reclassified instead as PPC (196 of 1958 patients in five different series) (3–7). With its increased recognition and subsequent studies, it seems timely to review the past and current literature pertaining to PPC.

Reprint requests to: Christina S. Chu, MD, 106 Dulles, 3400 Spruce Street, University of Pennsylvania Medical Center, Philadelphia, PA 19104. E-mail: chuc@mail.med.upenn.edu

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EPIDEMIOLOGY

PPC was initially distinguished from malignant mesothelioma (MM) on the basis of differing epidemiologic profiles. Approximately 63 percent of patients diagnosed with peritoneal MM are men and up to 83 percent involve a history of asbestos exposure (8–11). In contrast, PPC has been described exclusively in women, with a single recent exception (12). No association with asbestos exposure has been reported in PPC.

Patients with PPC are older at diagnosis than those with EOC, with weighted mean ages at presentation of 61 and 56, respectively, calculated from multiple series (3–6, 9, 10, 13–21 for PPC; 20, 22 for EOC). MM usually develops at a median age of 50 to 60 (23). Eltabbakh et al. (20) examined over 40 epidemiologic features of 50 women with PPC and 503 women with EOC. The authors concluded that the mean age at diagnosis is significantly older (63.8 vs.

TABLE 1 A comparison of primary epithelial ovarian carcinoma (EOC), primary peritoneal carcinoma (PPC), and malignant mesothelioma (MM)

	EOC*	PPC*	Single reported case of PPC in a male (Ref. 74)	MM of the Peritoneum*
% Female	100	>99	NA†	37–46
Mean age at diagnosis	56	61	74	53
Age range	14–92	4–92	NA	38–82
Mean age at menarche	12.8	13.3	NA	‡
Median parity	2	3–4	NA	‡
Asbestos exposure	‡	‡	none	50–83%
Talc exposure	48%	26%	‡	‡
Median survival (months)	27–30	12–24	3	4–18§

* The numbers in parentheses indicate the cited references for each. EOC (20,22,24,25), PPC (3–6,9,10,13–19,21,22,24–27), and MM (8–11,23,28,29).

† NA, not applicable.

‡ Data not available.

§ Survival for patients with peritoneal and/or pleural mesothelioma.

55.0 years, respectively, $P < .001$), menarche later (13.3 vs. 12.8 years, $P = .024$), and talc use less (26 vs. 48.1 percent, $P = .003$) in patients with PPC. The use of hormone replacement therapy and oral contraceptives was similar, as was parity. Table 1 summarizes selected epidemiologic features of PPC, EOC, and MM.

The racial distribution of PPC has rarely been reported. Fromm et al. (5) reviewed all referrals to the M. D. Anderson Cancer Center (MDACC) and identified 74 patients with PPC: 91 percent white, 5 percent African American, 3 percent Hispanic, and 1 percent Asian. In comparison, Morgan et al. (30) reviewed 221 patients diagnosed with EOC at the Hospital of the University of Pennsylvania and found patients to be 91 percent white and 9 percent African American.

CLINICAL PRESENTATION

Patients with PPC, as with EOC, usually present with abdominal distention, pain, or pressure often associated with ascites (3, 6, 10, 13, 14, 17, 31). The symptoms may be vague and mild until the disease is advanced. Fromm et al. (5) categorized the symptoms of women with PPC presenting to the MDACC: 55 percent reported abdominal pain, 52 percent distention, and 19 percent gastrointestinal symptoms (i.e., nausea, vomiting, loss of appetite). Only 6 percent of patients were asymptomatic. Ransom et al. (17) noted that although 76 percent of women complained of pain, distention, or palpable abdominal mass, 21 percent of their 33 patients had normal pelvic examinations at the time of initial presentation. Occasionally, PPC is detected after the identification of psammoma bodies on routine Pap smear (9) or during exploratory surgery for other reasons (17).

PRESURGICAL EVALUATION

Because the symptoms of PPC are similar to those of EOC, the preoperative assessment is the same as that of a woman suspected of having ovarian cancer. This should include a thorough history and physical examination, as well as radiologic and laboratory studies. A chest radiograph is usually obtained as part of presurgical assessment, to rule out metastases or pleural effusion as well as potential anesthetic risks. Additional studies are obtained as dictated by the review of systems, particularly those referable to the gastrointestinal tract. Although PPC cannot reliably be distinguished from EOC by preoperative testing, an ultrasound revealing normal-sized ovaries with evidence of carcinomatosis may raise suspicion. A computed tomography (CT) scan provides an assessment of peritoneal disease, retroperitoneal and hepatic lesion, and may identify obstructive uropathy. Laboratory studies should include an evaluation of hematologic, renal, hepatic, and electrolyte parameters. With any suspicion of ovarian or peritoneal cancer, serum CA-125 determination should be performed.

In any patient presenting with diffuse abdominal tumor, preoperative assessment should be directed at identifying potential primary sites in addition to the ovary, including mammary, pancreatic, and gastrointestinal lesions. Identification of the correct primary site is critical because the surgical management of PPC is vastly different from that of carcinomatosis associated with other malignancies. Although PPC may be considered in the differential, it is not a diagnosis made preoperatively. The diagnosis of PPC is typically made by exclusion after both operative assessment and pathologic study.

Paracentesis may provide short-term relief of symptoms caused by massive ascites. Although the positive predictive value of cytologic evaluation of ascitic fluid is quite high, the sensitivity is rather low (32); furthermore, even when cytologic evidence of malignancy is present, a definitive identification of the primary lesion is typically not possible. Unless the information will alter the management of an

individual patient, diagnostic paracentesis is not warranted. Thoracentesis may also provide short-term relief of pulmonary symptoms in a woman with a pleural effusion. Cytologic evaluation of the effusion is important because it changes the stage, and to some degree, the prognosis of the patient.

PATHOLOGY

The central problem in diagnosis is separation of PPC with some ovarian involvement from primary EOC. The Gynecologic Oncology Group (GOG) defined "extraovarian peritoneal serous papillary carcinoma" according to the following criteria:

1. Both ovaries must be either physiologically normal in size or enlarged by a benign process.
2. The involvement in the extraovarian sites must be greater than the involvement on the surface of either ovary.
3. Microscopically, the ovarian component must be one of the following:
   - nonexistent
   - confined to ovarian surface epithelium with no evidence of cortical invasion,
   - involving ovarian surface epithelium and underlying cortical stroma but with any given tumor size less than 5 × 5 mm,
   - tumor less than 5 × 5 mm within ovarian substance associated with or without surface disease
4. The histological and cytological characteristics of the tumor must be predominantly of the serous type that is similar or identical to ovarian serous papillary adenocarcinoma, any grade.

In 1994, Mulhollan et al. (24) defined a "serous surface papillary carcinoma" (PPC) characterized by tumors on the ovary of 5.0 mm or less in greatest dimension with only surface ovarian involvement or minimal superficial invasion of the ovarian cortex (maximum depth of invasion 3.0 mm). Mills et al. (25) rejected the diagnosis of PPC in any patient with ovaries greater than 3.0 cm in largest dimension, whereas Fromm et al. (5) allowed a maximum ovarian diameter of 4.0 cm. A comparison of various definitions is presented in Table 2. We recommend use of the GOG's definition of PPC, expanding it to include nonserous types of PPC with a histological appearance identical to other subtypes of EOC (i.e., mucinous, clear cell, etc.). We also propose that even a large implant on the surface of an otherwise normal ovary be recognized as PPC if histologic examination reveals invasion less than 5 × 5 mm.

Grossly, the tumor often appears gritty and hard, diffusely studding pelvic and abdominal peritoneal surfaces. PPC demonstrates light microscopic, histochemical, and immunohistochemical features similar to EOC (Table 3) (9, 13, 15). Whereas papillary serous differentiation is the overwhelm-

TABLE 2 **Different criteria for the diagnosis of PPC**

Author	Name	Criteria
Mills et al. (25) 1988	Serous surface papillary carcinoma	1. Grossly normal ovaries, ≤3.0 cm 2. No ovarian involvement, or involvement confined to the surface, or only minimally invasive tumor
Fromm et al. (5) 1990	Papillary serous carcinoma of the peritoneum	1. Ovaries ≤4.0 cm 2. Ovarian involvement minimal with only 1–15 mm implants
Gynecologic Oncology Group, 1993*	Extraovarian peritoneal serous papillary carcinoma	1. Ovaries normal in size, or enlarged by benign process 2. Involvement in extraovarian sites greater than ovarian involvement 3. No ovarian involvement, or surface involvement without microscopic invasion, or involving ovarian surface and stroma with tumor <5 × 5 mm in size 4. Histology must be predominantly serous
Mulhollan et al. (24) 1994	Serous surface papillary carcinoma (small type)	1. Ovaries ≤3.0 cm in greatest dimension 2. Tumor ≤5.0 mm in greatest dimension 3. Only surface ovarian involvement, or superficial invasion ≤3.0 mm

* AS specified in GOG Protocol #138.

TABLE 3 A comparison of the staining properties of primary EOC, PPC, and MM (Refs. 9,10,13,27,33-36)

	EOC	PP	MM
PAS-D (%)	90	75	0-5
EMA	100	100	80-100
Cytokeratin	100	100	100
LeuM1	73	45	11*
B72.3	91	85	0
CEA	54	14-25	0
S100	100	100	0-11
PLAP	29-45	38	0
CA-125	100	75	0-14
Lewis Y	71	88	0

* Denotes only minute foci of staining.

ingly predominant histology (99 vs. 36 percent for EOC) (37), other varieties of müllerian differentiation have been reported including clear cell, endometrioid, mucinous, and mixed müllerian mesodermal tumor. A review of 21 series with a total of 530 patients revealed only 5 cases of nonserous histology (1, 3–7, 9, 10, 13–19, 24, 31, 38–41).

Microscopically, the tumor may demonstrate solid, cribriform, or cystic growth patterns. Papillary structures and epithelial tufting with areas of gland formation may also be prominent. Psammoma bodies, a desmoplastic reaction, and necrosis are common features. Cytologic features are often high grade with markedly atypical cells displaying prominent nucleoli, crowded irregular nuclei, high N:C ratio, and mitoses ranging from 20 to 60/10 high power field (hpf) (Fig. 1) (5). Dalrymple et al. (4) reviewed 31 cases of PPC and noted the distribution of low-, moderate-, and high-grade tumors to be 13, 45, and 42 percent, respectively, using standard criteria (42). In comparison, Dvoretsky et al. (22) noted a similar distribution of grade among 100 cases of EOC (6, 52, and 42 percent, respectively). Hyperplasia of the ovarian surface epithelium may be present, and a transition may sometimes be seen from normal to atypical to frankly malignant epithelium (13, 14, 19). Histochemical studies reveal the almost universal presence of neutral or acidic mucin either in the cytoplasm or on the cell surface. Immunohistochemical studies show characteristic positive staining for cytokeratin and epithelial membrane antigen (EMA). Wick et al. (43) concluded that the lesions they termed "serous surface papillary carcinoma" and "serous ovarian papillary carcinoma" are virtually identical morphologically and immunophenotypically based on analysis of cytokeratin, EMA, B72.3, CEA, Leu M1, CA-125, LN1, LN2, MB2, S100, PLAP, and amylase staining (see Table 3).

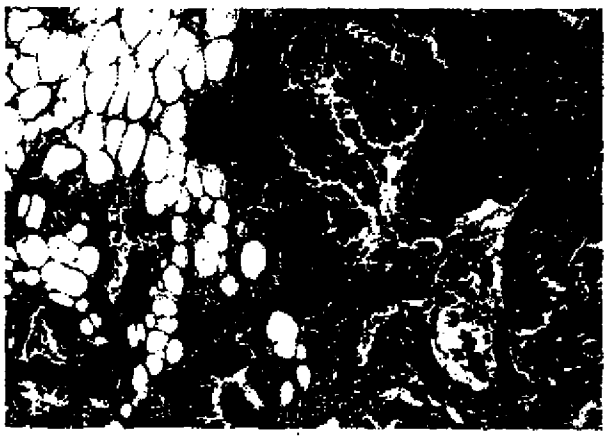

Fig. 1. Primary peritoneal carcinoma invading omentum. The ovaries were not involved.

Although MM of the peritoneum is grossly indistinguishable from carcinomatosis peritonei, histologically, the tumor may present with a wide spectrum of appearances. The epithelial type is characterized by papillary structures lined by uniform, cuboidal cells with pink cytoplasm and round, bland nuclei displaying infrequent mitotic figures and nucleoli. A spindle cell or sarcomatoid component is common, and psammoma bodies are usually absent (detected in only 3.5 percent) (8). A variant of MM, termed well-differentiated papillary mesothelioma, may develop in the peritoneum of women most commonly during the third and fourth decades (44). This type of MM may also occur in the pericardium and pleura, grossly appearing as multiple peritoneal nodules covering the omentum, mesentery, and pelvic peritoneum, with occasional involvement of the ovarian surface. Psammoma bodies may be present in approximately 5 percent (8).

Because of similarities in the gross and microscopic appearance of PPC and MM (especially the well-differentiated papillary subtype), the use of histochemical and immunohistochemical stains may aid in the characterization of these tumors. Unlike PPC, MM virtually never stains for mucin (9, 13). Immunohistochemical stains for EMA and keratin are positive in both. PPC, however, displays staining for many other markers which tend to be negative in MM: S100, CEA, LeuM1, B72.3, placental alkaline phosphatase, CA-125, and Lewis Y. Staining for either S100 and placental alkaline phosphatase, or S100 and B72.3 characterizes the majority of serous PPC and EOC (45). Others have reported that if at least two of the

markers, S100, B72.3, and BerEP4 are positive with the appropriate histologic appearance, serous carcinoma can be assumed (46). Positive staining for carcinoembryonic antigen (CEA), placental alkaline phosphatase, or B72.3 effectively excludes peritoneal mesothelioma (47). Histochemical properties are summarized in Table 3. Electron microscopy has also been utilized to further characterize the differences between PPC and MM: the PPCs possess taller, ciliated cells, but lack tonofilaments; MMs have long microvilli (14, 19, 48).

INTRAOPERATIVE ASSESSMENT AND STAGING

Surgical abdominal exploration provides the means for both diagnosis and staging evaluation of patients with PPC. The procedure should parallel that described for EOC (Table 4). A vertical incision provides adequate exposure to the upper abdomen for exploration and sampling. If ovaries seem normal with widespread disease elsewhere in the abdomen, PPC becomes a leading diagnostic possibility. However, because surface involvement of the ovaries is present in approximately 96 percent of the cases, the distinction between PPC and EOC may only be made after histologic examination to evaluate the extent of ovarian invasion by tumor.

The International Federation of Gynecology and Obstetrics (FIGO) has not yet adopted a specific staging system for PPC. The surgical staging classification scheme as outlined for ovarian carcinoma is typically applied to women found to have PPC (although, by definition, there can be no stage I disease) (3, 4, 6, 19, 21, 41). PPC tends to present in advanced stages. The distribution by stage of PPC and EOC, for multiple series and FIGO data, respectively, is summarized in Table 5.

When disease seems confined to the pelvis (apparent stage II), sampling the omentum, abdominal peritoneal surfaces, and retroperitoneal lymph nodes is advocated to rule out occult abdominal disease (stage III). In cases of small volume disease (<2 cm nodules) abdominal and pelvic lymph node sampling is also recommended. The majority of patients will present with diffuse abdominal disease (>2 cm nodules), and the extent of disease will be determined by inspection rather than surgical sampling.

Of patients with stage IV disease, common sites of extraperitoneal involvement include malignant pleural effusions and parenchymal liver metastases. More rare sites include the pleura, the axillary lymph nodes, the anterior abdominal wall, the vagina, and the skin (4, 5, 40, 50). An autopsy study of 57 patients with PPC conducted by Rothacker and Mobius (7) revealed blood-borne metastases to the lung parenchyma in two cases and to the brain in one case.

TABLE 4 **Surgical staging for PPC***

Vertical incision
Thorough abdominal and pelvic examination
BSO
TAH
Omentectomy
Sampling of gross lesions in the abdomen and pelvis
Peritoneal biopsies of the paracolic gutters and subdiapgragmatic regions, bilaterally
Retroperitoneal lymph node sampling in the pelvis and parasortic regions, bilaterally

* Adapted from GOG Surgical Staging Procedure, Specifications Protocol GOG#157.

TABLE 5 **Distribution by stage of PPC and EOC**

Stage	PPC* (%)	EOC† (%)
I		23
II	2	13
III	73	47
IV	25	16

* References 3,4,6,14,15,17,21,25,41 (weighted average).
† Reference 49.

CYTOREDUCTION

Surgery remains critically important for both the diagnosis and the therapy of PPC. Once the diagnosis is established and the extent of disease documented, maximal cytoreduction becomes the primary goal of the procedure. Excision of all visible implants is the hallmark of cytoreductive efforts. The omentum contains evidence of tumor in 89 to 100 percent of patients (5, 6, 13) and should be resected if possible. Grossly enlarged lymph nodes should be excised, even when a diagnostic sampling is not needed, and bowel resection or splenectomy may be indicated for a maximal surgical excision, or to prevent obstruction or control hemorrhage.

EOC is unusual among solid tumors in having a survival benefit associated with cytoreduction in the setting of carcinomatosis. The first quantitative evidence of the importance of "residual disease" on the outcome of women with EOC came from Griffiths in 1975 (51). He demonstrated that the diameter of the largest remaining nodule after tumor resection correlated with survival. This phenomenon has been supported by numerous retrospective series, although cytoreduction, per se, has never been studied in a randomized, prospective trial.

The terms "optimal" and "suboptimal" used to characterized the burden of disease after cytoreduction in women with EOC have also been applied to PPC. Criteria defining optimal residual disease have varied widely among authors (from 0–3 cm of largest remaining implant). A widely accepted cutoff is that used by the GOG: less than a 1-cm diameter of the largest residual nodule. There is also evidence that the number of residual lesions may have prognostic significance, particularly in the setting of optimal disease status among women with EOC (52); it is advisable, therefore, to include this information in the operative record.

In light of the pathological and clinical similarity between EOC and PPC, it is inferred that a similar or equivalent benefit might be seen in women with PPC. The feasibility of cytoreduction of PPC has been addressed in several retrospective series. The ability to achieve significant cytoreduction may vary widely from surgeon to surgeon, but available data suggest that PPC may be debulked as well as EOC (6, 21) with one exception (53). Factors that may preclude optimal debulking include extensive nodular infiltration of mesenteric, visceral, and peritoneal surfaces (6) and higher paraaortic lymph node disease, involvement of the liver, porta-hepatis, and the mesentery of the small bowel and stomach (21). The only case-control study (53) that demonstrates PPC to be significantly ($P < .0001$) more difficult to debulk than EOC should be confirmed by additional studies. Several studies suggest that approximately 40 percent of patients with either PPC (5) or EOC (54, 55) may be optimally debulked.

ADJUVANT THERAPY

Given the similarities between PPC and EOC, physicians have used therapies for PPC that have proven effective in EOC. In the past two decades, chemotherapy has predominantly consisted of platinum-based regimens. Fromm et al. (5) documented a significant increase ($P = .02$) in median survival in patients treated with platinum-based combination chemotherapy (31.5 months) versus patients treated with nonplatinum-based regimens (19.5 months). First-line agents for PPC have resulted in an overall clinical response rate of 60 percent (5, 15), which is comparable to the response rates for EOC to similar regimes (56, 57). A recent phase II GOG trial directly compared response rates after cisplatin/cyclophosphamide therapy for groups of women with PPC and EOC (58). The authors found similar clinical response rates (65 vs. 59 percent, respectively), and identical complete surgical response rates of 20 percent.

More recently, therapy for EOC has evolved to include use of paclitaxel, an antimicrotubule agent, in combination with platinum analogues. In 1992, Wall et al. (38) reported the effectiveness of paclitaxel as a single agent salvage therapy in a young woman with relapsed PPC, and in 1996, Menzin et al. (31) first documented surgically confirmed responses to the combination of paclitaxel and cisplatin. Among four patients with suboptimal residual disease, one complete and three partial (but marked) responses were noted after six courses of therapy. Recent evidence (59) suggests that regimens of paclitaxel/cisplatinol and cyclophosphamide/cisplatinol may have similar efficacy as first-line therapy in women with suboptimal residual PPC after primary debulking surgery. In patients known to be sensitive to paclitaxel/platinum as a first-line regimen, paclitaxel/carboplatinum has been shown to be an effective second-line regimen after disease recurrence (60). With new GOG protocols that previously included only women with EOC now often also open to patients with PPC, more data regarding the efficacy of various regimens should become available in the coming years.

CLINICAL FOLLOW-UP

Considering the relapse rates following remission after platinum-based therapy among women with EOC, continued surveillance of those with PPC is warranted. Serial CA-125 determination may assist in follow-up if levels were elevated at the time of diagnosis. The vast majority of women will indeed have elevated values, and the regression usually parallels response to therapy (25, 31). Routine imaging studies in asymptomatic patients with normal examinations and normal CA-125 levels are not warranted. A schedule of periodic examinations is determined on an individual basis, with most clinicians favoring visits at 3-month intervals during the early years after initial therapy, during which recurrence rates are highest. When symptoms, examination, or CA-125 levels arouse suspicion, radiologic evaluation is indicated.

SURVIVAL

Median survival among women with PPC has been reported to range from 12 to 25 months (5, 6, 24, 25). Multiple studies, including a retrospective case-control study with close matching of clinical characteristics (53), have suggested that PPC and EOC have

similar survival rates (4–6, 17, 21, 61). However, others have concluded survival for patients with PPC is worse, (24, 25), although it is difficult to interpret these studies inasmuch as the authors did not consider variables such as age and residual disease in one study (24), and the analysis in the second included only 10 patients with PPC (25).

The preponderance of evidence in women with EOC suggests that residual disease burden is inversely correlated with response rates, progression-free interval, survival, and the likelihood of achieving a negative surgical reassessment (21, 54, 55, 62). Similar statistics of women with PPC also indicates a trend toward improved survival with optimal cytoreduction (21, 63–65). Ben-Baruch et al. (21) noted a median survival of 20.5 months for suboptimally debulked patients as opposed to 46.0 months for those optimally debulked, although the study was too small to show statistical significance. Similarly, Fowler et al. (64), Strnad et al. (65), and Taus et al. (27) demonstrated prolonged survival in patients after optimal cytoreduction, but again, their results were not statistically significant. Fromm et al. (5) reported the largest series with 74 patients treated with surgery and adjuvant therapy at a single institution and found no difference in survival (25.5 months for those suboptimally debulked and 26.0 months for those optimally debulked, $P = .51$). Of note, Eltabbakh et al. (63) studied 75 patients with PPC and on multivariate analysis noted a significant survival advantage for those with residual disease ≤ 1 cm ($P = .03$) and for those with performance status ≤ 1 ($P < .001$). A comparison of survival rates for EOC and PPC stratified by presence of residual disease is presented in Table 6.

Some authors have considered a number of potential prognostic factors on survival. Mulhollan et al. (24) noted that the use of multiagent versus single-

TABLE 6 **Survival for EOC and PPC by volume of residual disease**

Author	Residual disease (cm)	Median survival (months)	P Value
EOC			
Conte et al. (66) (*N* = 125)	0	>42	.001
	<2	>42	
	2–5	17	
	>5	15	
Redman et al. (67) (*N* = 86)	<10 cm^3	38	.00085
	10–80 cm^3	36	
	>80 cm^3	19	
Vogl et al. (68) (*N* = 38)	≤2	>40	.003
	>2	15	
Wharton and Herson (69) (*N* = 104)	≤2	28	.0057
	>2	15	
Piver et al. (70) (*N* = 40)	≤2 cm	48	Not stated
	>2 cm	21	
Neijt et al. (71) (*N* = 179)	Microscopic	>36	.0001
	≤1	42	
	1–2	22	
	2–5	20	
	>5	18	
Delgado et al. (72) (*N* = 75)	0	(Mean survival) 45	Not stated
	<2	45	
	>2	16	
PPC			
Ben-Baruch et al. (21) (*N* = 22)	<2	46	NS*
	>2	20	
Fowler et al. (64) (*N* = 34)	<1.5	18	NS
	>1.5	17	
Strnad et al. (65) (*N* = 18)	<3	31	Not stated
	>3	11	
Fromm et al. (5) (*N* = 74)	≤2	25	NS
	>2	26	
Eltabbakh et al. (63) (*N* = 75)	≤1	40	0.03
	>1	18.6	

* NS, not significant, $P > .05$.

agent chemotherapy, the use of platinum- versus nonplatinum-based regimens, and the absence of mitoses predicted an improved survival in women with PPC. Age (age greater than or less than 50), the presence of residual disease (as mentioned above), the percent of papillary component (more than or less than 10 percent), and the presence of vascular invasion did not correlate significantly with differences in survival. Although the authors did not cite data regarding flow cytometric analysis, they did comment that their preliminary results suggest "a greater diversity of ploidy" in cases of PPC. In contrast, Kowalski et al. (73) noted no significant difference in aneuploidy between 44 patients with PPC and 44 patients with EOC matched for age, stage, histology, grade, cytoreduction, and survival.

LOW MALIGNANT POTENTIAL TUMORS OF THE PERITONEUM

In 1979, a tumor with diffuse peritoneal involvement and a histologic appearance similar to EOC of low malignant potential (LMP) was reported and termed "atypical endosalpingiosis" (74). In 1987, the term "serous papillary borderline tumor" was used to describe similar lesions (75). Only three large series of patients with LMP tumors of the peritoneum have been reported (76–78).

TABLE 7 **A comparison of LMP tumors of the peritoneum (76–78) and the ovary (79–89) (weighted means)**

	Peritoneal LMP	Ovarian LMP
Mean age (years)	34	43
Presenting complaint (%)		
Pain	26	31
Distension	0	52
Infertility	13	1
Abnormal bleeding	7	10
No symptoms	35–50	12
5-Year survival (%)	95	95–100
Serous histology (%)	100	42 (52% mucinous, 4% endometrioid, 2% mixed)
Stage at presentation (%)		
I	0	74
II	54	8
III	41	17
IV	0	1
Elevated serum CA-125 (%)	Unknown	22
Presence of ascites (%)	0	37–43% of patients with stage III disease

Peritoneal tumors of LMP present in young women (mean age 34) (76–78). Many patients are asymptomatic at the time of diagnosis, with the tumor incidentally found either at the time of surgery (36 percent) or by the presence of psammoma bodies on routine Pap tests (10 percent) (76–78). Of the remaining patients, infertility and abdominal pain are the most common presenting complaints (Table 7).

Peritoneal LMP tumors display serous histology identical to noninvasive implants of ovarian serous borderline tumors, and show minimal or no ovarian surface involvement (76). Reported involvement has been either focal or diffuse. Grossly, the disease process may resemble miliary granules or peritoneal carcinomatosis, or appear as small nodules, diffuse adhesions, irregular peritoneal blebs, or solitary cystic and solid lesions (77). Histologically, well-differentiated papillary structures may be seen lined by tall pseudostratified columnar cells often demonstrating epithelial tufting. Mitoses are rare and invasion is not evident (Fig. 2). The differential diagnosis may include endosalpingiosis, mesothelial hyperplasia, low-grade mesothelioma, or adenocarcinoma, either primary or metastatic.

Because patients with peritoneal tumors of LMP present at a younger age and often with infertility, conservative treatment may be advocated until childbearing is complete. At surgery, an LMP lesion cannot reliably be distinguished from its invasive counterpart by gross examination alone. As with ovarian LMP tumors, definitive treatment may await permanent section diagnosis, because frozen-section diagnosis of an LMP tumor may not be representative.

Fig. 2. Low malignant potential peritoneal tumor on peritoneal surface. Papillary groups of cells with a serous histology lie on the surface surrounded by scattered chronic inflammatory cells and a few fibroblasts. No invasion is present.

Overall survival is excellent. Bell and Scully (76) reported a 95 percent survival rate among 25 patients followed for a mean of 8 years. Similarly, Biscotti and Hart (77) reported on 14 patients with long-term follow up: 12 were alive with a mean survival of 7.5 years, 1 patient died of an intercurrent illness, and the remaining patient died 7 weeks postoperatively of suspected complications of therapy. Weir et al. (78) identified 14 patients, all alive at a mean of 3 years of follow up: 10 were without evidence of disease, 2 were alive with minimal residual disease, and 2 were subsequently diagnosed with PPC. Of these two patients, one was near death secondary to bowel obstruction. But this patient's diagnosis of peritoneal LMP tumor was based on biopsy only. PPC may have been diagnosed if tumor sampling had been adequate. Adjuvant chemotherapy and/or radiation (with their attendant complications) are not recommended by the authors of these studies.

FAMILIAL PREDISPOSITION AND *BRCA* STATUS

In 1982, Tobacman et al. (39) from the National Cancer Institute reported three cases of intraabdominal carcinomatosis resembling metastatic ovarian cancer among 28 women who had undergone prophylactic oophorectomy from 16 families at high risk of ovarian carcinoma. These authors noted the similarity between their cases and those described as primary peritoneal carcinoma by Foyle et al. (90). The authors recommend a thorough exploration at the time of prophylactic surgery to rule out the presence of an occult malignancy. Inadequate examination of the patient or the pathologic specimens may be responsible for the apparent diagnosis of PPC shortly after removal of the ovaries. The occurrence of PPC itself suggests that the protection afforded women from prophylactic surgery may not be complete.

Piver et al. (91) reporting on data from the Gilda Radner Familial Ovarian Cancer Registry identified six cases of PPC in 324 women who had undergone prophylactic oophorectomy based on a family history of ovarian cancer. These cases developed 1 to 27 years after prophylactic surgery. Although the authors state that the incidence of PPC in this high-risk population cannot be inferred, 1.85 percent of these women in this series developed PPC. In comparison, the lifetime incidence of PPC is calculated to be approximately 0.14 percent (1 in 70 women develop EOC, (92) and approximately 10 percent of these cases may actually be PPC). These figures raise the suspicion that PPC may occur with 10-fold increased frequency in women with hereditary ovarian cancer. Furthermore, study is needed to better define the risks for this population of women and their relatives.

Approximately 5 to -10 percent of all cases of EOC are thought to occur on the basis of a hereditary predisposition (55, 93–97). Although germline mutations in *BRCA1* are felt to be responsible in 90 percent of these cases, (98) mutations in this gene have been reported to occur in only 3 to 6 percent of all patients with epithelial ovarian carcinoma (99, 100). Bandera et al. (101) screened 17 patients with PPC using single strand conformation polymorphism analysis with sequencing of shifted bands, and identified two patients (11 percent) with germline mutations in *BRCA1*. This preliminary work suggests that hereditary predisposition may play a role in the development of PPC with a frequency similar to that in EOC.

PATHOGENESIS

The pathogenesis of PPC is not well characterized. In 1972, Lauchlan (102) pointed out that the female peritoneum should be considered a part of what he termed the "secondary müllerian system," noting (as did Swerdlow) that both the germinal (surface) epithelium of the ovary and the mesothelium of the peritoneum arise from the same embryologic origin and retain the multipotentiality of the müllerian system. Multipotentiality supports the hypothesis that metaplasia of the peritoneum may account for conditions such as squamous metaplasia, endometriosis, and endosalpingiosis. Based on the epidemiological findings and concerns over potential differences in biologic behavior coupled with this concept of müllerian multipotentiality, in 1977 Kannerstein et al. (16) proposed a distinction between mesothelioma and papillary tumors of the peritoneum. Additional information acquired since then strengthens the case for PPC as a separate clinical, histologic, immunohistochemical, and ultrastructural entity (9, 10, 13, 41).

Although PPC is not always a predominant pelvic tumor, and because simultaneous carcinomas of the endosalpinx and endometrium have been documented, Truong et al. (13) hypothesized that a "field effect" involving the entire müllerian system may play a role in the pathogenesis of PPC. Because PPC occurs almost exclusively in women, hormonal influences on the susceptible müllerian system have been speculated to play a role. However, although LH and hCG receptors have been demonstrated in one case report of PPC (103), estrogen (ER) and

progesterone (PR) receptors are not a common finding in cases of PPC. Unpublished data by Chu and co-workers on 14 cases of PPC have demonstrated positive staining for ER and PR in only 21 and 36 percent of tumors, respectively. Eltabbakh et al. (63) demonstrated staining in 50 percent for ER and 6 percent for PR. Rates of immunohistochemical staining for ER and PR in cases of PPC is similar to those for EOC with 38 and 32 percent of cases of EOC exhibiting positive staining, respectively (104, 105).

Others have suggested that irritants such as talc ascending through the female genital tract may contribute to carcinogenesis. Although talc use has been documented to be significantly increased in women with PPC when compared with those with EOC (20), talc has not been a notable finding upon histologic review of pathologic specimens (106), and a causal relationship has not yet been proven.

MOLECULAR GENETICS

Although EOC has been demonstrated to be a monoclonal expansion of tumor cells (107–112), the clonality of PPC is debated: some propose that the tumor arises from the ovarian surface epithelium and then spreads throughout the peritoneum whereas others propose a multifocal malignant transformation process. Only Kupryjanczyk et al. (107) have concluded that PPC is a monoclonal entity, although their conclusions are based on the examination of p53 gene mutations in only two cases of PPC. The remainder of the literature supports a multifocal origin in at least some cases of PPC (41, 113–116).

Mutations in the p53 tumor suppressor gene on chromosome 17 are demonstrated both in EOC (44–57 percent) (115, 117) and in PPC (75 percent) (115). Overexpression of the protein results in malignant transformation in several human cancers (118–120). Frequent nuclear accumulation may correlate with more aggressive biologic behavior and poorer clinical prognosis (121, 122). Marchenko and Moll (123) have concluded that PPC is one of a growing number of tumors which demonstrates p53 nuclear accumulation in the absence of a p53 gene mutation. This phenomenon is also observed in other tumors, including head and neck squamous cell carcinoma, endometrial carcinoma, uterine papillary serous carcinoma, and acute myelogenous leukemia (123). The mechanism underlying this observation is not understood, although hypotheses include inactivation and nuclear accumulation of p53 by interaction with a second abnormal protein, or the ability of the cell to transiently increase and decrease nuclear p53 with levels of DNA damage (123).

Additional molecular studies have reported similar rates of expression of HER-2/*neu*, BCL-2, and nm23-H1 for cases of PPC and EOC (73, 124). LOH at 17q also seems similar (97, 114, 125–130).

CONCLUSIONS

Primary peritoneal carcinoma (PPC) is a tumor of the peritoneum, distinct from malignant mesothelioma (MM), but similar in many ways to primary epithelial ovarian carcinoma (EOC). PPC seems histologically identical to EOC and is differentiated from EOC based on the extent of gross ovarian involvement and microscopic invasion of the cortex. Currently, PPC is evaluated, staged and treated in the same fashion as EOC, with GOG trials for the treatment of EOC now open to patients with PPC. PPC is currently managed surgically in the same way as EOC with the shared goal of optimal cytoreduction. Although the preponderance of evidence supports the benefit of maximal cytoreductive efforts for EOC, only limited data are available for debulking in PPC. On a molecular level, other differences between PPC and POC are becoming apparent as well: although EOC is a clonal proliferation, PPC seems to be multifocal in many patients. PPC and EOC seem to share similar hereditary risks, with the rates of *BRCA1* germline mutations comparable in both entities. The clinician should keep in mind that PPC may develop after bilateral salpingo-oophorectomy for either benign disease or ovarian cancer prophylaxis. Women at risk for hereditary EOC may, in fact, still be at an elevated risk of developing PPC over the baseline population.

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