Introduction

In 10-15% of female patients with serous peritoneal carcinomatosis, no malignant pathology is evident in the ovaries or fallopian tubes (1). In these conditions, a diagnosis of primary peritoneal carcinoma can be suggested. Primary peritoneal carcinoma (PPC), also known as serous papillary peritoneal carcinoma or extraovarian serous papillary carcinoma, is a separate entity arising from the extraovarian peritoneum with Müllerian potential, but closely associated with epithelial ovarian carcinoma (EOC) (2-6).

Epidemiology and Risk Factors

Over 90% of the patients with PPC are Caucasians, and age at diagnosis is usually in the 5th-6th decades (4,7-9), with an average age at diagnosis 3-7 year older than that of EOC (10). There are no significant differences between PPC and EOC with respect to age at menarche, oral contraceptive use, infertility, parity, menopausal status and hormonal replacement therapy (7,9,10).

Similar to EOC, PPC might be part of the breast-ovarian cancer syndrome. No differences were found between PPC and EOC in the frequency of BRCA mutation carriers (about 30%), neither in the distribution of different mutations. In BRCA mutation carriers, the lifetime risk of developing PPC has been estimated to be 1.3% and this figure must be considered when counseling patients for prophylactic oophorectomy (11).

Pathology

The large predominance of PPC cases reported in the literature showed serous histology, indistinguishable from serous papillary ovarian carcinoma, probably due to common embryologic origin from the Müllerian ductal system. Nevertheless, other Müllerian variants of the system that have been reported include endometrioid, clear cell, mucinous, Brenner, and mixed Müllerian tumors (6,12). 7-20% of patients previously classified as primary EOC (29% in advanced stages) may be re-classified as having PPC (2-4,13), according to the following Gynecologic Oncology Group (GOG) diagnostic criteria (14):

1. Both ovaries either physiologically normal in size (4.0 cm in largest diameter) or enlarged by a benign process;
2. Involvement in the extraovarian sites greater than on the surface of either ovary;
3. Microscopically, ovarian component (a) nonexistent, (b) confined to the ovarian surface epithelium with no evidence of cortical invasion, (c) involving ovarian epithelium and the underlying stroma but with any given tumor size less than 5x5mm, (d) tumor less than 5x5mm within ovarian substance associated with or without surface disease;
4. Histological and cytological characteristics of the tumor predominantly of the serous type and similar or identical to ovarian serous papillary adenocarcinoma, any grade.

The PPC has no major antigenic differentiation from the Müllerian neoplastic ovarian epithelium. Nevertheless, immunohistochemistry or PCR-based assays showed some subtle differences from EOC, as loss of heterozygosity at several chromosomal loci and more overexpression of the HER2 oncogene (10). In particular, the Müllerian markers CA-125, S100, LN1, LN2, EMA, MB2 are present in 70-100% of PPC, according to the reported expression profile of EOC. Moreover, PPC harbors similar rates of tumor suppressor gene dysfunction (p53, BRCA1, WT1) as the ovarian counterparts and exhibits similar angiogenic activity, as witnessed by immunohistochemical CD34 endothelial clusters and thymidine phosphorylase activity. An interesting finding reported by several investigators is the 35-55% incidence of HER2 overexpression in serous PPC, consistently higher than the 5-30% overexpression rate seen in EOC (9).

Finally, recent pathological studies have reported the association of PPC with serous tubal intraepithelial carcinoma in the majority of cases in which the fallopian tubes are comprehensively examined. These new findings suggest that PPC is probably derived from tubal epithelium, in particular, from occult high-grade serous carcinoma of the fallopian tube (15,16).

Clinical Presentation

The clinical presentation of PPC is indistinguishable from advanced EOC. The most common presenting symptoms are weight loss and abdominal enlargement. Abdominal pain is present in more than half of cases and ascites is a common finding on physical examination. According to a clinical series of 95 PPC cases, a higher rate of abdominal distention, volume of ascites, and malignant cells in ascitic fluid, and a lower rate of pelvic palpable mass and personal breast cancer history are found in the PPC compared with the EOC group (5). On the contrary, in a recent systematic review...
of 579 patients with PPC (25 clinical series, 1980-2008), no significant clinical differences with serous ovarian cancer were found. Patients in both groups commonly presented at diagnosis with abdominal pain and distention, ascites, mass lesions, intestinal obstruction, and markedly elevated serum Ca-125 levels. In particular, ascites and high serum Ca-125 levels were present in 70-90% of cases of the PPC population (10).

**Screening**

No effective screening is available.

**Diagnosis**

PPC could not be preoperatively suspected or distinguished from EOC, with the rare exception of women undergoing prophylactic oophorectomy for a familial neoplastic syndrome showing an evident carcinomatosis and having ruled out a gastro-intestinal tumor. Consequently, the diagnosis is based on histopathology examination according to the GOG criteria for PPC. Ascites, peritoneal thickening and enhancement, and peritoneal nodules or bulky masses are the most frequent findings of PPC at magnetic resonance imaging (MRI) or computed tomography (CT) scan.

A differential diagnosis must be made with ovarian/fallopian tube cancer, gastro-intestinal cancer, breast cancer, pancreatic cancer, and, more rarely, with mesotheliomas or other lesions of Müllerian type (endosalpingiosis, primary peritoneal serous borderline tumor, primary peritoneal serous psammocarcinoma). Therefore, histopathology (GOG criteria), immunohistochemistry (similar to EOC), gastroscopy/colonoscopy, mammography/breast MRI, and abdominal CT/MRI can be helpful in some cases to differentiate PPC from metastatic diseases.

**Evaluation After Diagnosis**

The clinical process after diagnosis is similar to EOC. At the moment we have no sufficient data concerning the clinical impact of interval debulking surgery (IDS) in PPC patients.

**Tumor Spread and Staging Procedures**

The tumor spread of PPC is similar to EOC and involve mainly the peritoneal, mesenteric and omental surfaces of the abdomen and pelvis (ovarian surface involvement 70-100%), but with a distinct pattern of diffuse micronodular involvement of the upper abdomen and diaphragmatic surfaces with dense adhesions and intense fibrosis; liver and viscera are involved in 5-13% of cases (10). Bilateral ovarian involvement at gross examination reveals tumor growing exophytically from the surfaces of the ovary, with slight to moderate invasion of the underlying parenchyma. In 89% of patients there is an omental involvement (5). Lymphatic spread is frequent (63-73%) and, similar to pattern of EOC, involving the pelvic and/or paraaortic lymph nodes (17,18).

The pattern of spread comparable to EOC implies that staging process of PPC is completely equal. A specific staging system has not been developed for PPC, therefore, it is staged using the American Joint Committee on Cancer (AJCC) TNM staging system for ovarian cancer (19). Almost all patients have disseminated tumor, equivalent to ovarian FIGO Stage III-IV, while less than 12% have disease confined to the pelvis (5).

**Management**

PPC patients are managed similarly to patients with advanced EOC and enrolled in ovarian cancer clinical trials. Therefore, PPC should be managed by surgical cytoreduction, where possible, and postoperative chemotherapy (20).

As well as in advanced EOC, only the optimal surgical cytoreduction and the performance status appear to be significant prognostic factors in PPC. Complete surgical cytoreduction may be more difficult to be achieved because of the widespread peritoneal disease without a single or predominant ovarian or pelvic mass. Moreover, due to lymphatic spread pattern similar to EOC, pelvic and aortic lymphadenectomy can be considered in those patients with a complete intraperitoneal cytoreduction with or without retroperitoneal bulky disease (18).

Preoperative Ca-125 do not predict the primary cytoreductive outcome of patients with advanced PPC. According to the Memorial Sloan-Kettering Cancer Center experience, with a preoperative Ca-125 >500U/mL, extensive upper abdominal procedures are necessary in 50% of cases to achieve residual disease ≤1 cm. These data may be useful as part of preoperative surgical counseling and planning (21).

The quantification of intraperitoneal tumor at the time of surgical exploration has proven to be of value in the assessment of prognosis and treatment planning. The Peritoneal Cancer Index (PCI) is computed assigning a lesion size score (no implants, LS=0; <0.5 cm, LS=1; <5 cm, LS=2; >5 cm, LS=3) to 13 abdominopelvic regions: 9 regions divided as part of preoperative surgical counseling and planning (21).

The Peritoneal Cancer Index (PCI) is computed assigning a lesion size score (no implants, LS=0; <0.5 cm, LS=1; <5 cm, LS=2; >5 cm, LS=3) to 13 abdominopelvic regions: 9 regions divided by two transverse and two sagittal planes, plus 4 regions of the small bowel (22). The PCI serves as an estimate of probability of complete cytoreduction and has been found to be an accurate assessment of survival when cytoreductive surgery is performed. Currently, a PCI >20 is regarded as a relative contraindication to an elective surgical cytoreduction for carcinomatosis from colon cancer (23). The PCI is also validated for EOC as significant prognostic factor (p=0.025) and can be applied to PPC (24).

In PPC, “optimal” debulking at surgery is reported in 28-67% of cases with most studies having described a rate of roughly 40% (9). In fact, in older series, the rate of minimal residual disease (maximum deposits <2 cm) was as low as 30-50%, but in most recent series after 1995, the acknowledgement of the importance of maximal surgical effort led to management in reference centres and in a 60-80% incidence of optimal debulking (residual lesions <1cm) (10). In particular, Zivanovic et al. reported a significant increase in optimal cytoreduction in patients with bulky upper abdominal tumor after 2001 (40% before 2001 vs. 78% after 2001; p<0.001), and this progress, along with the advent
of platinum-taxane regimens, allowed to achieve a better median survival times in patients with advanced PPC (25).

Chemotherapy regimen are similar to EOC: the standard treatment is carboplatin AUC 5-6 and paclitaxel 175 mg/m² administered every 21 days (26). Intraperitoneal therapy, and platinum-based compared with non platinum-based regimens (4).

The series published after the introduction of taxane (8 clinical series, 1997-2008) are listed in Table 1 (10) and showed a similar outcome in PPC vs. EOC in most papers (28-31), although some authors suggest that complete cytoreduction is more difficult in PPC (32,33). The median survival ranges between 15-42 months and 5 year overall survival between 18-52% (9,10,25). Nevertheless, in spite of differences between women with extraovarian primary peritoneal carcinoma and women with epithelial ovarian cancer. Obstet Gynecol 1998;91:254-9.

Follow-Up

Follow-up in case of PPC is similar to the EOC patients.

References

Primary Peritoneal Carcinoma


