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# Low-grade serous primary peritoneal carcinoma ☆,☆☆

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ABSTRACT

*Objective.* 10% of women with serous ovarian cancer have low-grade carcinomas. These patients are diagnosed at a younger age, have a longer overall survival and a lower response rate to platinum-based chemotherapy compared to women with high-grade serous ovarian carcinoma. It remains unclear if these features are similar in women with low-grade primary peritoneal cancer (PPC). To further explore this issue, a retrospective analysis of the clinical and pathologic characteristics of women with low-grade serous PPC was performed.

*Methods.* A retrospective study of 53 patients with low-grade serous PPC evaluated at a single institution from 1986 to 2009 was performed. All cases were reviewed by a gynecologic pathologist to confirm low-grade serous PPC.

*Results.* Median age at diagnosis was 51.7 years (range 27.1–82.4). 46 patients (86.8%) underwent primary surgery, with optimal tumor reduction achieved in 30 patients (65.2%). 48 patients (90.6%) received chemotherapy as part of their initial treatment. At the completion of primary treatment, 66.7% of patients were noted to have persistent or progressive disease. With a median follow-up of 66.1 months, the 5-year PFS was 16%, yet the 5-year OS was 69%.

*Conclusion.* To our knowledge, this is the first report of women with low-grade serous PPC. Similar to low-grade serous ovarian carcinoma, patients with low-grade serous PPC have high rates of persistent disease at the completion of primary treatment yet a long overall survival. Further study focusing specifically on low-grade serous ovarian and primary peritoneal carcinomas is needed to determine the optimal treatment of these diseases.



## Introduction

Primary peritoneal carcinoma (PPC) is a malignancy that diffusely involves the peritoneal surfaces while sparing or minimally involving the ovaries [1–4]. It is histologically indistinguishable from epithelial ovarian cancer, and has similar clinical characteristics, patterns of spread, response to treatment, and survival rates [3,5–9]. Previous reports have suggested that women with PPC have similar epidemiologic features to women with epithelial ovarian cancer, with the exception of an older age at diagnosis and increased rate of obesity [8,10–14]. The recommended treatment for serous PPC is similar to that for serous ovarian carcinoma; however, optimal cytoreduction may be more difficult to achieve in women with PPC due to widespread peritoneal disease without the presence of a predominant pelvic or ovarian mass [15].

To date, most of the literature evaluating PPC has focused on patients with high-grade serous tumors, with little published about low-grade serous PPC. There is now an increasing body of literature on low-grade serous ovarian carcinomas. Low-grade serous ovarian carcinomas represent approximately 10% of ovarian carcinomas [16] and have distinct histologic, pathologic and clinical features [17–27]. Previous studies have reported that women with low-grade serous ovarian carcinomas are diagnosed at a younger age, have a longer overall survival, and yet have a lower response rate to platinum-based chemotherapy compared with women with high-grade serous ovarian carcinoma [28–30]. However, it remains unclear if these features are similar in women with low-grade PPC. A systematic MEDLINE search (keywords *primary peritoneal cancer*, *low-grade serous ovarian and peritoneal cancer*, English language, 1950 to 2010) revealed no reports of low-grade serous PPC. To further explore this issue, we retrospectively evaluated the clinical and pathologic characteristics of women with low-grade serous PPC.

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## Materials and methods

Following the approval from The University of Texas MD Anderson Cancer Center Institutional Review Board, we searched the institutional databases of the Departments of Gynecologic Oncology and Pathology to identify patients with low-grade serous primary peritoneal carcinoma. Although a histopathologic review of all cases had been performed at the time of original diagnosis and/or presentation to MD Anderson Cancer Center, all cases were re-reviewed by a gynecologic pathologist for the purposes of this study. Patients with non-serous histotypes, serous tumors of low-malignant potential (LMP), psammocarcinomas and high-grade serous carcinomas were excluded. Confirmation of a low-grade serous carcinoma was based on the following previously published criteria: 1) frank destructive invasion; 2) relatively uniform round to oval nuclei with mild to moderate atypia and evenly distributed chromatin; and 3) no more than 12 mitoses per 10 high-power fields [17]. Primary peritoneal carcinoma was defined according to the Gynecologic Oncology Group (GOG) criteria [9]: the ovarian component must be: 1) nonexistent; 2) confined to the surface with no cortical invasion; or 3) involving the ovarian surface and underlying cortical stroma without any single focus in the stroma measuring >5 mm in depth and width.

Medical records were reviewed for age at diagnosis, ethnicity, body mass index (BMI), surgical treatment, type and number of chemotherapy cycles administered, imaging study findings, pre- and post-treatment serum CA 125 levels, and residual disease at the completion of surgery. Given the prolonged study period and multiple previously used definitions, optimal cytoreductive surgery was defined as <2 cm of residual disease. Progression-free survival (PFS) and overall survival (OS) times were estimated using the method of Kaplan and Meier [31]. OS was defined as the time from diagnosis to the date of the patient's death or date of last known contact. PFS was defined as the time from diagnosis to disease progression or recurrence or to the date of death or date of last known contact, whichever occurred first. Data were analyzed using SPSS 15.0 software (Chicago, IL).

## Results

Our database search identified 53 eligible patients with low-grade serous PPC evaluated at The University of Texas MD Anderson Cancer Center between 1986 and 2009. Patient demographics are shown in Table 1. Eighteen patients (34%) had undergone previous bilateral salpingo-oophorectomy (BSO) a median of 12.8 years (range, 3.0 to 27.7) prior to the diagnosis of PPC. The findings at BSO included endometriosis (n = 5), ovarian serous cystadenoma (n = 1), and normal ovaries removed at the time of hysterectomy for uterine fibroids (n = 3), dysfunctional uterine bleeding (n = 3), endometrial cancer (n = 1), and persistent cervical dysplasia (n = 1). The pathology from previous BSO was not available for review for four patients.

Clinical and pathologic characteristics are shown in Table 2. The majority of patients were diagnosed with stage III disease (n = 47, 88.7%). Five patients (9.4%) were diagnosed with stage IV disease, 3 due to pleural effusion, 1 due to liver metastases, and 1 due to pulmonary metastases. Median CA 125 value at diagnosis was 70 U/ml (range, 15–3035). Co-existent tumor of low malignant potential (LMP) was noted in 7 (13.2%) patients. Primary surgery was performed in 46 patients (86.8%), with optimal cytoreduction achieved in 30 patients (65.2%) (Table 3). Fifty patients received systemic therapy as part of their primary treatment. Forty-four patients (88.0%) received chemotherapy (n = 38 adjuvant, n = 6 neoadjuvant), with the majority of patients (n = 39, 78.0%) receiving a taxane/platinum drug combination. Four patients (8.0%) received hormonal treatment in conjunction with chemotherapeutic agents (n = 3 leuprolide acetate, n = 1 letrozole), and two patients (4.0%) received hormonal therapy alone (n = 1 anastrozole and n = 1 tamoxifen). At the completion of primary treatment, 66.7% of patients were noted to have persistent or progressive disease. Eighteen patients (34.0%) underwent additional cytoreductive surgery for persistent or recurrent disease, with 16 patients undergoing one additional surgery and two patients undergoing two additional surgeries.

At the time of the analysis, 19 patients (35.6%) were deceased. Twenty-eight patients (52.8%) are currently alive with disease, and 5 patients (9.4%) are alive without evidence of disease. The mean and median follow-up times for all 53 patients are 67.7 and 52.7 months, respectively (range, 0.80 to 235.6). The mean and median follow-up times for patients who were alive at last contact were 77.9 and 66.1 months, respectively (range, 0.80 to 235.6). The median PFS was 30.5 months (95% CI [13.3, 47.8]) with a 5-year PFS rate of 16%. The

**Table 1**
Demographic characteristics (N = 53).

| | |
|---|---|
| Age at diagnosis (years) | |
| Median | 51.7 |
| Mean | 52.6 |
| Range | 27.1 to 82.4 |
| Body mass index (BMI) at diagnosis (kg/m$^2$)[a]: | |
| Median | 27.2 |
| Mean | 28.9 |
| Range | 20.8 to 51.3 |
| BMI category, n (%)[a]: | |
| Underweight (<18.5 kg/m$^2$) | 0 (0%) |
| Normal (18.5–24.9 kg/m$^2$) | 12 (31%) |
| Overweight (25–29.9 kg/m$^2$) | 12 (31%) |
| Obese (>30 kg/m$^2$) | 15 (38%) |
| Ethnicity, n (%): | |
| African American | 2 (4%) |
| Hispanic | 6 (11%) |
| White | 45 (85%) |
| Parity, n (%)[b]: | |
| 0 | 11 (22%) |
| 1–2 | 26 (52%) |
| 3+ | 13 (26%) |
| Prior use of oral contraceptives (OCP) | 11 (21%) |
| Hormone replacement therapy (HRT) | 20 (37%) |
| OCP + HRT | 12 (23%) |
| Smoking history, n (%)[c]: | |
| Ever | 18 (35%) |
| Never | 34 (65%) |
| No. (%) of women with previous BSO for benign reasons | 18 (34%) |
| No. (%) of women with previous USO for benign reasons | 3 (6%) |
| Time from BSO to low-grade PPC diagnosis (years) (n = 18): | |
| Median | 12.8 |
| Mean | 13.4 |
| Range | 3.0 to 27.7 |

[a] BMI data at diagnosis missing for 14 patients.
[b] Parity data missing for 3 patients.
[c] Smoking data missing for 1 patient.

**Table 2**
Clinical and pathologic characteristics (N = 53).

| | |
|---|---|
| Stage at diagnosis, n (%) | |
| II | 1 (2%) |
| III | 47 (89%) |
| IV | 5 (9%) |
| CA 125 at diagnosis (U/ml): | |
| Median | 70 |
| Mean | 386 |
| Range | 15 to 3035 |
| Coexistent pathologic findings, n (%): | |
| Cystadenoma/adenofibroma | 5 (10%) |
| Endosalpingiosis | 11 (21%) |
| Low malignant potential/borderline tumor | 7 (13%) |
| Psammoma bodies | 29 (56%) |