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Patterns of recurrence and role of adjuvant chemotherapy in stage II–IV serous ovarian borderline tumors

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ABSTRACT

Objective. The objective of this study was to evaluate patterns of recurrence and prognostic factors as well as the role of adjuvant chemotherapy in stage II–IV ovarian SBT.

Methods. We performed a retrospective review of all patients with advanced-stage SBT treated at our institution from 1979 to 2008. Advanced stage was defined as FIGO stage II–IV. Progression-free survival (PFS) was defined as the time of diagnosis to time of recurrence/death or last follow-up. Kaplan–Meier method was used to report the PFS rate.

Results. A total of 80 stage II–IV patients were identified, of which 15 (19%) were stage II, 63 (79%) were stage III, and 2 (2.5%) were stage IV. The site of metastasis was pelvis in 15 patients (19%), omentum in 29 patients (36%), isolated lymph nodes in 2 patients (2.5%), lung in 1 patient (1%), axilla in 1 patient (1%), and multiple sites in 32 patients (40%). With a median follow-up of 4.8 years, 17 patients (21%) developed recurrent disease. Only patients with metastasis to the omentum or multiple sites developed recurrent disease. Of the 65 stage III/IV patients, 17 patients (26%) received adjuvant chemotherapy following diagnosis. The 3-year progression-free survival (PFS) was 89.9% (95% CI, 77.3–95.7) for patients who did not receive adjuvant chemotherapy compared with 70.6% (95% CI, 43.1–86.6) for patients who received adjuvant chemotherapy.

Conclusions. While advanced-stage ovarian SBT generally has a good prognosis, nearly 21% of patients develop recurrent disease with intermediate follow-up. It is unclear from these data if adjuvant chemotherapy influenced PFS.

Introduction

Ovarian serous borderline tumors (SBTs) are a separate subset of ovarian epithelial neoplasms. They differ from invasive ovarian epithelial neoplasms both in pathologic characteristics and clinical behavior [1–4], and they have an excellent prognosis overall. Various risk factors for recurrence include the presence of invasive implants, micropapillary pattern histology, DNA ploidy, and age [5–13].

Most ovarian SBTs present with stage I disease; however, SBTs can be associated with advanced-stage disease [14]. The optimal management of advanced-stage ovarian SBTs relies mainly on surgery. The role of adjuvant chemotherapy is debatable, particularly in stage III–IV cases. Surgery is an integral component to management of advanced-stage ovarian SBT. Some early studies have shown that chemotherapy in the adjuvant setting provides some treatment benefit [15,16], but other studies have refuted this [17,18].

The objective of this study was to evaluate clinical characteristics, patterns of recurrence, and outcomes of patients with advanced-stage SBTs, and to describe the role of adjuvant chemotherapy in this select group of patients.

Methods

After Institutional Review Board (IRB) approval, we identified all patients with ovarian SBTs treated at our institution from 1979 to 2008. Not all patients were diagnosed at our institution; some patients presented for further management after initial surgery and diagnosis at an outside institution. We reviewed medical records, including operative reports, pathology and laboratory reports, and chemotherapy records, and extracted the relevant data. The pathology

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specimens from patients who were diagnosed at an outside institution were all reviewed at our institution.

Stage at initial diagnosis was designated based on the International Federation of Gynecology and Obstetrics (FIGO) staging system for ovarian carcinoma [19]. We defined advanced-stage disease as stage II–IV. Histology information was obtained from institutional pathology reports, and only patients with tumors of serous histology were included in this cohort. It is our hospital policy to confirm all outside pathology reports by institutional review of submitted specimens. From the pathology reports, sites of metastasis, presence of micropapillary features, presence of invasive or non-invasive implants, and spread to lymph nodes were noted. We reviewed operative reports to determine which procedures had been performed and to note any intraoperative findings, including presence of ascites and residual disease.

Progression-free survival (PFS) was defined as the time of diagnosis to time of recurrence/death or last follow-up. Recurrence was defined with clinical or CA-125 criteria according to the Rustin criteria [20]. The Kaplan–Meier method was used to estimate PFS rates, and univariate analysis with *P* values were generated using the log-rank test. Statistical analyses were performed using SAS® analytical software.

Results

A total of 80 stage II–IV patients were identified. The clinicopathologic characteristics for this cohort are described in Table 1. The median age at diagnosis was 41 years (range, 16–80 years). Fifteen patients (19%) had stage II disease, 63 (79%) had stage III disease, and 2 (2.5%) had stage IV disease at diagnosis. At the time of initial diagnosis, the site of metastasis was the pelvis in 15 patients (19%), omentum in 29 patients (36%), isolated lymph nodes in 2 patients (2.5%), lung in 1 patient (1%), axilla in 1 patient (1%), and multiple sites in 32 patients (40%). Of the 80 patients in the cohort, 25 (31%) had tumor histology with micropapillary features and 19 (24%) had invasive implants. Forty-four patients (55%) had lymph node sampling at the time of surgery. Of these 44 patients, 28 (64%) had positive lymph nodes. Adjuvant chemotherapy was given in 17 patients (21%). Because our cohort of patients was treated over a 30-year time period, a variety of intravenous and intraperitoneal chemotherapy regimens were given. Intravenous chemotherapy agents included cytoxan, cisplatin, adriamycin, paclitaxel, and carboplatin. Intraperitoneal chemotherapy agents included mitoxantrone, etoposide, carboplatin, cisplatin, and paclitaxel.

Table 1
Clinicopathologic characteristics.

	n (%)
Total number of patients	80
Median age at diagnosis, years (range)	41.1 (16.8–79.6)
Stage	
II	15 (19)
III	63 (79)
IV	2 (2.5)
Sites of metastasis	
Pelvis	15 (19)
Omentum	29 (36)
Isolated lymph nodes	2 (2.5)
Lung	1 (1)
Axilla	1 (1)
Multiple	32 (40)
Micropapillary features	
Yes	25 (31)
No	55 (69)
Implants	
Invasive	19 (24)
Non-invasive	60 (75)
Unknown	1 (1)
Lymph nodes	
Positive	28 (35)
Negative	16 (20)
Not done	36 (45)
Ascites	
Yes	32 (40)
No	48 (60)
Residual disease	
Yes	8 (10)
No	69 (86)
Unknown	3 (4)
Adjuvant chemotherapy	
Yes	17 (21)
No	63 (79)

Table 2 outlines the follow-up and recurrence data. The median follow-up time was 4.8 years (range, 0.05–22.84 years). At the time of last follow-up, 50 patients (62.5%) had no evidence of disease, 10 (12.5%) were alive with disease, 4 (5%) were dead of disease, 4 (5%) were dead of other causes, and 12 (15%) were lost to follow-up. Of the 80 patients in the cohort, 17 (21%) developed recurrent disease—11 (65%) developed recurrent disease with invasive or low-grade serous carcinoma, 5 (29%) developed recurrent disease with borderline histology, and 1 (6%) developed recurrent disease with unknown histology.

The 3-year PFS rate for the entire cohort was 84.9% (95% CI, 73.8–91.6). Univariate analysis of various factors was assessed with RFS. These factors are outlined in Table 3. The 3-year PFS rate was 91.7% (95% CI, 53.9–98.8) for stage II patients and 83.6% (95% CI, 70.8–91.1) for stage III/IV patients ($P=0.093$). The 3-year PFS rate was 72.4 (95% CI, 48.3–86.6) for patients with tumors of micropapillary features and 91.1 (95% CI, 78–96.6) for patients without micropapillary features ($P=0.023$). The 3-year PFS rate was 66.7 (95% CI, 40.4–83.4) for patients with invasive implants and 93.6 (95% CI, 81.5–97.9) for patients with non-invasive implants ($P=0.005$). We further characterized patients according to residual disease. Eight patients (10%) had residual disease at initial surgery, 69 (86%) had no residual disease, and for 3 (4%) patients, it was unclear if there was residual disease at initial surgery. The 3-year PFS rate was 71.4 (95% CI, 25.8–92) for patients with residual disease and 89.4 (95% CI, 77.9–95.1) for patients with no residual disease at initial surgery. Univariate analysis for residual disease was not performed as the number of patients with residual disease was small.

None of the patients with stage II disease received adjuvant chemotherapy. The 3-year PFS rate was 89.9% (95% CI, 77.3–95.7) for patients who did not receive adjuvant chemotherapy compared with 70.6% (95% CI, 43.1–86.6) for patients who received adjuvant chemotherapy. As demonstrated in Fig. 1, there is no benefit of adjuvant chemotherapy for RFS. Interestingly, none of the patients with residual disease at initial surgery received chemotherapy. Of the 69 patients with no residual disease, the 3-year PFS rate was 80% (95% CI, 50–93.1) for patients who received chemotherapy and 92.7% (95% CI, 79–97.6) for patients who did not receive adjuvant chemotherapy.

Table 2
Follow-up data.

Median 3-year RFS rate	84.9 (73.8–91.6)
Median follow-up, years (range)	4.8 (0.05–22.84)
Status at time of last follow-up*	
NED	50 (62.5)
AWD	10 (12.5)
DOD	4 (5)
DOO	4 (5)
Lost to follow-up	12 (15)
Recurrence	
Yes	17 (21)
No	63 (79)

RFS, recurrence-free survival; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; DOO, dead of other causes.