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Characteristics of 10-year survivors of high-grade serous ovarian carcinoma

Fanny Dao [a,1], Brooke A. Schlappe [a,1], Jill Tseng [a], Jenny Lester [b], Alpa M. Nick [c], Susan K. Lutgendorf [d], Scott McMeekin [e,2], Robert L. Coleman [c], Kathleen N. Moore [e], Beth Y. Karlan [b], Anil K. Sood [c], Douglas A. Levine [a,*]

[a] Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, NY, New York, United States
[b] Women's Cancer Program, Samuel Oschin Comprehensive Cancer Institute, Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, CA, United States
[c] Departments of Gynecologic Oncology, Cancer Biology, Center for RNA Interference and Noncoding RNA, University of Texas, M.D. Anderson Cancer Center, United States
[d] Departments of Psychological and Brain Sciences, Obstetrics and Gynecology and Urology, Holden Comprehensive Cancer Center, University of Iowa, United States
[e] Stephenson Oklahoma Cancer Center, University of Oklahoma, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Oklahoma City, OK, United States

HIGHLIGHTS

- Ovarian cancer survivors who live for 10 or more years comprise a heterogeneous patient population with and without recurrent disease.
- Long-term survivors may have suboptimal cytoreduction or short platinum free intervals.
- *BRCA1* and *BRCA2* germline mutations appear common among long-term survivors.

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ABSTRACT

Objective. High-grade serous carcinoma (HGSC) generally presents at an advanced stage with poor long-term (LT) survival. Here we describe clinical features found in women surviving HGSC for ten or more years.

Methods. A multi-center research consortium was established between five participating academic centers. Patient selection criteria included high-grade serous ovarian, fallopian tube, or peritoneal carcinoma with at least ten years of follow up. Non-serous, borderline tumors and low-grade serous subtypes were excluded.

Results. The 203 identified LT ten-year survivors with HGSC were diagnosed at a median age of 57 years (range 37–84 years). The majority of patients had stage IIIC (72.4%) disease at presentation. Of those who underwent primary cytoreductive surgery, optimal cytoreduction was achieved in 143 (85.6%) patients. After a median follow up of 144 months, 88 (46.8%) patients did not develop recurrent disease after initial treatment. Unexpected findings from this survey of LT survivors includes 14% of patients having had suboptimal cytoreduction, 11% of patients having an initial platinum free interval of <12 months, and nearly 53% of patients having recurrent disease, yet still surviving more than ten years after diagnosis.

Conclusions. LT survivors of HGSC of the ovary generally have favorable clinical features including optimal surgical cytoreduction and primary platinum sensitive disease. The majority of patients will develop recurrent disease, however many remained disease free for more than 10 years. Future work will compare the clinical features of this unusual cohort of LT survivors with the characteristics of HGSC patients having less favorable outcomes.

1. Introduction

Ovarian cancer has extensive heterogeneity within and between histologic subtypes [1]. High-grade serous carcinoma is the most aggressive subtype and accounts for the majority of advanced stage cases [2]. Ten-year survival for all ovarian cancer is approximately 30–40% according to the SEER registry and other studies [3,4]. Long-term (LT) survival of women with high-grade serous carcinoma (HGSC) is low and often associated with completely resected disease (no gross residual).

* Corresponding author at: Gynecology Research Laboratory, Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, United States.
E-mail address: levine2@mskcc.org (D.A. Levine).
[1] These authors contributed equally.
[2] Deceased.

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While many factors have been reported to have prognostic value for HGSC beyond the current FIGO staging system, most have limited value for patients with advanced stage disease [5,6]. Nonetheless, the use of intraperitoneal therapy in patients with microscopic and small volume residual disease after cytoreductive surgery has been associated with long-term survival [7]. Nomograms have potential superiority over traditional staging systems to predict individual probabilities of survival [8,9]. Many studies have demonstrated that molecular markers may improve outcome prediction alone or in combination with clinical variables, however, none have been sufficiently robust to incorporate into clinical practice to date [10–13]. Although many recently developed resources are tremendously valuable for studying HGSC, in general, they contain few LT survivors and those that are included often lack detailed clinical and pathologic data [14]. The goal of this pilot report is to describe clinical variables, alone or in combination, that are found among ten year survivors of HGSC with the overall goal of identifying approaches for improving the outcome of patients with shorter survival.

2. Methods

A multi-center research consortium was established between five participating academic centers: Memorial Sloan Kettering Cancer Center, MD Anderson Cancer Center, Cedars-Sinai Medical Center, Stephenson Oklahoma Cancer Center at the University of Oklahoma, and University of Iowa. IRB approval was obtained locally at each center. Study criteria were established that included patients with a diagnosis of high-grade serous ovarian, fallopian tube, or peritoneal carcinoma with at least ten years of follow up from the date of initial diagnosis to the date of death or last follow-up. All stages of cancer were permitted. Diagnosis dates for patients in this study range from 1979 to 2005. Non-serous, borderline tumors and low-grade serous subtypes were excluded in addition to any patients with insufficient follow up data. Grade 2 tumors were excluded unless they were re-reviewed and met contemporary criteria for high-grade serous carcinoma. Clinical and disease characteristics, including age at diagnosis, stage, residual disease after primary surgery, treatment history, recurrence history, and results of *BRCA1* and *BRCA2* germline genetic testing were collected from medical records. Major components (primary surgery and/or adjuvant chemotherapy) of initial treatment were performed at one of the five participating consortium centers. Cytoreductive surgery was characterized as optimal if there was ≤1 cm of residual disease and suboptimal if >1 cm of disease remained at the end of the surgical procedure. Consult cases or other cases referred after the completion of initial therapy were excluded. Data are reported in a descriptive fashion with summary statistics provided, as appropriate. An overall survival analysis using the method of Kaplan and Meier was performed using the time from diagnosis to last follow-up for patients who did not recur and the landmark event of recurrence to define the start of the overall survival interval for patients who had recurred. Statistical analysis and visualization was performed using R (http://www.R-project.org).

3. Results

3.1. Patient characteristics

Across the five centers, 203 patients were identified as LT ten-year survivors and included in this study. Demographic and clinical characteristics of the study group are shown in the Table 1. All patients were diagnosed with high-grade serous carcinoma of the ovary, fallopian tube, or peritoneum at their respective institution. The median age of patients was 57 years (range 37–84 years). Twenty-eight patients (13.8%) were older than 70 years at the time of diagnosis. The majority of patients were white (88.7%) and diagnosed with stage IIIC (72.4%) disease at presentation.

Of the 23 patients with stage IV disease, 12 (52%) had available data that indicated 5 had stage IV disease based on pleural effusion only. Of the seven patients with distant metastases or solid organ involvement, 3 patients had parenchymal liver metastases, two patients had supraclavicular nodal involvement and one patient each had pleural metastasis or abdominal wall involvement. All three patients with liver metastases remained progression free for more than 10 years and have not developed recurrence. Available data for 157 (96%) of 164 stage III patients indicate that 26 (17%) had stage III disease due to lymph node only disease.

Table 1
Demographic and clinical characteristics of long-term survivors

	N[a]	%
Age at diagnosis (years)		
Median (range)	57 (37–84)	
FIGO stage		
I	7	3.5
II	9	4.4
III	164	80.8
IV	23	11.3
Grade		
High	203	100
Histology		
Serous	203	100
BRCA mutations		
BRCA1	22	27.8
BRCA2	21	26.6
None	36	45.6
Residual disease		
None	76	46.6
≤1 cm	61	37.4
>1 cm	26	16.0
Neoadjuvant therapy		
No	184	92.9
Yes	14	7.1
Intraperitoneal therapy		
No	145	79.2
Yes	38	20.8
Number of recurrences		
0	88	46.6
1	21	11.2
2	19	10.1
>2	60	31.9
Platinum-free interval		
<6 months	5	3.6
6–12 months	11	7.9
>12 months	124	88.6

FIGO, International Federation of Gynecology and Obstetrics.
[a] Numbers do not sum to the total for some variables due to missing values.

Of the 198 patients with available treatment information, 92.9% underwent primary cytoreductive surgery and 7.1% received neoadjuvant chemotherapy prior to interval cytoreductive surgery. Of those who underwent primary cytoreductive surgery, optimal cytoreduction, defined as residual disease of less than or equal to 1 cm in maximum diameter, was achieved in 143 (85.6%) patients. A complete gross resection to no macroscopic residual disease was achieved in 70 (47.0%) patients. Ascites was present at the time of surgery in 103 (70.5%) patients. All but one patient (99.5%) received a platinum agent as part of their adjuvant or neoadjuvant treatment regimens. Intraperitoneal chemotherapy was given to 38 (20.8%) patients, with most of these patients receiving IP treatment as part of consolidation therapy.

3.2. Treatment outcome

After a median follow up of 144 months, 88 (46.8%) patients did not develop recurrent disease after initial treatment. This group was characterized by a high optimal cytoreduction rate (93%, 78/84) and a low rate of neoadjuvant chemotherapy (6%, 5/88). The majority of patients in the entire cohort were reported to be platinum sensitive (96.4%) with a platinum-free interval of >12 months for 124 (88.6%) patients. The median progression-free survival (PFS) of the entire cohort was 147 months. Twenty-one (11.2%) patients had one recurrence during