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Review Article

Who are the long-term survivors of high grade serous ovarian cancer?

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HIGHLIGHTS

- Long-term survivors of advanced-stage EOC are a heterogeneous group.
- Clinical and pathologic factors are not sufficient to predict long-term survival.
- Germline genetic mutations are not associated with long-term survival.
- Models based on differential gene expression can classify long-term survivors.
- More research on genomics, transcriptomics, and epigenomics of LTS is needed.

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ABSTRACT

Although the median survival for epithelial ovarian cancer (EOC) is <5 years, approximately 15% of patients will survive for >10 years. A better understanding of these exceptional responders could reveal opportunities to improve the dismal prognosis of most EOC patients. In this review, we examine the clinical and genomic features that have been associated with long-term survival, which is generally defined as survival of >7–10 years after initial diagnosis. Clinical features influencing long-term survival have been best reported in large retrospective population-based studies. These studies find that long-term survival is associated with previously validated prognostic factors, including younger age at diagnosis, earlier clinicopathologic stage, lower grade, non-serous histology, absence of ascites, primary debulking surgery, and optimal cytoreduction at primary surgery. Duration of survival after a recurrence also contributes to long-term survival and depends both on recurrence location and response to subsequent chemotherapy or surgery. Germline *BRCA* mutations, although associated with short-term chemosensitivity, do not appear to improve long-term survival. Unfortunately, the relative lack of recurrent somatic mutations in EOC has made the identification of genomic signatures associated with long-term survival difficult. Although six independent gene expression analyses of long-term survivors (LTS) have identified signatures associated with prolonged survival, different gene sets are identified in each study. Genes differentially expressed in tumors of LTS are broadly involved in cell proliferation, tumor-stromal interactions, the cytoskeleton, metabolism of nutrients, and immune/stress response. We anticipate that consistent selection of control and LTS groups, combined with the use of emerging transcriptomic, epigenomic, and proteomic platforms, is likely to identify conserved features associated with long-term survival. Further elucidating the factors contributing to long-term survival has the potential to contribute to our understanding of the biology of ovarian cancer, with the goal of improving the survival of all EOC patients.

Contents

Abbreviations: EOC, epithelial ovarian cancer; HGSOC, high-grade serous ovarian cancer; LTS, long-term survivor; OCPP, Ovarian Cancer Prognostic Profile; OS, overall survival; SEER, Surveillance, Epidemiology and End Results; STS, short-term survivors.

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1. Introduction

Advanced stage epithelial ovarian cancer (EOC) is generally considered an incurable disease. However, approximately 15% of EOC patients will survive more than ten years [1–4]. Although we currently do not understand why these patients have better survival, identifying what is unique about these patients could be used to benefit the 85% who will succumb earlier to the disease. This review will summarize the current literature on long-term survivors (LTS) of advanced stage EOC and assess what can be learned from this specific group of patients. We will primarily focus on serous EOC. The term EOC in this review includes tumors arising in the ovary, fallopian tube, and the peritoneum (primary peritoneal cancer).

Advanced high-grade serous EOC is characterized by an 85% response rate to initial chemotherapy. Unfortunately, 75% subsequently have a recurrence, which is rarely curable [5]. Five-year survival rates for advanced-stage serous EOC average about 30% world-wide, ranging from 15 to 35% across Europe, 40% in Japan, 20–40% in Australia and 30–40% in North America [2,6], and the median overall survival (OS) ranges from 29 to 44 months [7,8]: 41–45 months for stage III [9,10] and 26–29 months for stage IV [9]. The longest median survival in the literature is 100 months in a Japanese study of dose-dense chemotherapy [11]; these favorable results have, unfortunately, not been replicated outside of these two study environments [7–10].

Yet there are some women with stage III or IV cancer who have prolonged survival. Large studies reported by the Surveillance, Epidemiology and End Results (SEER) database [1], National Cancer Database [2], California Cancer Registry [3], and Swedish registries [4] found 10-year survival rates for stage III EOC of 23%, 20%, 19%, and 25%, respectively. In stage IV patients, 10-year survival rates decreased to 8% [1], 10–15% [2], 7% [3], and <5% [4]. In a subgroup with advanced-stage high-grade serous EOC, 10-year survival was 16% [3].

LTS are commonly defined as those surviving at least 10 years after diagnosis. They constitute a heterogeneous group and each study defines LTS slightly differently. How LTS are defined is critical in determining the aspect of survival that is being measured. Some studies examine patients whose cancer does not recur [12,13], but most focus on a survival threshold regardless of recurrence when they assign a patient to the LTS group [14]. Comparison groups include all other patients [15] or, more commonly, those with a survival of <3 years, which many studies define as short-term survivors (STS) [16]. We find that LTS can be classified into three groups (Table 1): (a) patients whose cancer never recurs, (b) patients whose cancer recurs and who are treated with secondary surgery and then remain free of disease or go on to multiple cycles of chemotherapy, and (c) patients whose cancer recurs and remains sensitive to repeated cycles of chemotherapy ("multiple responders").

Disease outcome is influenced by both patient and tumor characteristics. In this review, we will first examine the clinicopathologic factors associated with prolonged survival. We will then shift focus to the genetic factors that may predict long-term survival. The combined knowledge from these studies could be used to assist physicians in prognostication at the time of diagnosis, help us to better understand EOC and chemosensitivity and, ideally, help us apply what we learn from the biology of LTS to prolong the life of STS.

Table 1
Definitions of survivorship.

Long-term survivor	A woman alive at least 5 [46], 7 [49] or 10 years [3,4,17,23] after diagnosis of stage III or IV high-grade serous ovarian cancer. - With recurrent intraperitoneal disease treated with surgery ± chemotherapy - With recurrent intraperitoneal disease repeatedly responsive to chemotherapy - With isolated lymph node recurrence - With late recurrence and subsequent long or short survival
Cured of HGSOC	Recurrence-free with close follow-up for at least 5 years after diagnosis of stage III or IV high-grade serous ovarian cancer [12]. Cured by surgery and/or chemotherapy.
Short-term survivor	- Overall survival after diagnosis of high-grade serous ovarian cancer of <3 years [49] - Recurrent patients with overall survival > 5 years after diagnosis [12] - Upper versus lower extremes of survival within a given patient population [46].

2. Clinical factors associated with LTS in ovarian cancer

Research on clinical predictors of prognosis and long-term survival relies on retrospective studies. Clinical factors associated with overall survival in EOC include younger age, stage I or II disease, grade I histology, and microscopic residual disease after cytoreductive surgery (Table 2a). Although retrospective studies of factors associated specifically with long-term survival allow large sample sizes and long follow-up, they are limited by changes in treatments and reporting of clinicopathologic factors, as well as by selection bias. Still, they provide valuable clinical information on factors associated with long-term survival and on clinical characteristics of LTS.

Disease-related clinicopathologic factors associated with LTS generally parallel commonly used predictors of a more favorable prognosis (Table 2b, Table S1). In 2004, a reanalysis of two phase III clinical trials in the UK that included women with FIGO 1988 stage IIB to IV EOC found a 13.5% 10-year and 12% 15-year survival [17]. Long-term survival was associated with grade 1 histology (40% 12-year survival vs. <10% for grade 3) and good ECOG performance status at diagnosis. Similarly, a comprehensive registry of patients with EOC in Sweden found differences in 10-year survival based on stage, age, post-operative CA-125 and residual tumor after surgery [4]. Prospective clinical phase III study data supports the association between microscopic residual disease at the end of surgery and long-term survival: 30–45% of FIGO 1988 stage III/IV patients survive 8–10 years after optimal cytoreduction, compared to 10–15% of patients with residual disease [9,15,17–20]. It is important to note that complete cytoreduction does not completely mitigate the effects of disease volume at diagnosis, which is not always reflected in staging [5,18,21]. Each cycle of adjuvant intraperitoneal chemotherapy is also associated with improved 10-year survival, but residual disease continues to play a strong role regardless of the route of chemotherapy [22]. In summary, these studies indicate that prognostic factors of long-term survival overlap with factors clinically associated with improved prognosis.

Yet on an individual basis, we cannot rely exclusively on clinical factors. In 2015, Cress et al. used the California Cancer Registry to examine how clinical prognostic factors were represented among LTS [3]. Surprisingly, LTS included many patients with poor clinical prognostic factors: 32% of LTS had stage III/IV disease, 6% were older than 75 years, 33% had high-grade disease, and 37% had serous histology. The high prevalence of poor prognostic factors among LTS suggests that survival was not determined solely by clinical and pathologic factors observed at

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