Gynecologic Oncology 152 (2019) 228–234

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

The road to long-term survival: Surgical approach and longitudinal treatments of long-term survivors of advanced-stage serous ovarian cancer

Melissa Javellana, Claire Hoppenot, Ernst Lengyel *

Department of Obstetrics and Gynecology/Section of Gynecologic Oncology/Center for Integrated Science, University of Chicago, Chicago, IL 60637, United States of America

HIGHLIGHTS

- A heterogeneous group of women survive ovarian cancer >7 years and become long-term survivors (LTS).
- LTS undergo more aggressive surgical treatment and have lower initial disease burden than short-term survivor counterparts.
- Most LTS maintain platinum sensitivity and/or have oligometastatic recurrences, allowing for repeat debulkings.

ARTICLE INFO

Article history:
Received 14 July 2018
Received in revised form 30 October 2018
Accepted 6 November 2018
Available online 22 November 2018

Keywords:
Ovarian cancer
High grade serous cancer
Long-term survival
Prognostic factors
Surgical treatment

ABSTRACT

Objective. It is unclear if the types of surgical procedures performed on long-term survivors (LTS) of high-grade serous ovarian carcinoma (HGSOC) contribute to prolonged survival. In this case-control study we review the surgical procedures performed on LTS and describe their individual longitudinal disease courses.

Methods. Women with FIGO stage III–IV high-grade serous cancer of the ovary, fallopian tube or peritoneum were selected from the University of Chicago ovarian cancer database. LTS were those surviving >7 years and controls were short-term survivors (STS) living 1–2 years. Patients with non-serous histology, low grade, and low malignant potential tumors were excluded.

Results. We identified 450 women with stage III/IV HGSOC including 45 LTS and 78 STS. LTS showed a trend towards lower disease burden, yet underwent more aggressive surgical treatment. Interestingly, only 15 LTS (34%) were debulked to microscopic disease and 9 LTS (21%) underwent suboptimal debulking. Two LTS (5%) recurred within 12 months. LTS had heterogeneous clinical courses with 13 (29%) never experiencing a recurrence with 143 months median follow-up and 32 (71%) experiencing a recurrence with 115 months median follow-up. Of the women who recurred, 19 (59%) underwent at least one surgery for recurrence.

Conclusions. Aggressive surgical treatment intended to achieve microscopic disease, primary debulking surgery, preservation of sensitivity to chemotherapy, and recurrence amenable to secondary debulking are associated with long-term survival. However, clinicopathologic data are insufficient to predict long-term survival of HGSOC. Biologic characterization of these patient's tumors likely holds the key to understanding their unusually favorable courses.

Abbreviations: ASA, American Society of Anesthesiology; BMI, Body mass index; CS, Surgical complexity score; DS, Disease score; EBL, Estimated blood loss; FIGO, International Federation of Obstetrics and Gynecology; HGSOC, High-grade serous ovarian carcinoma; LTS, Long-term survivors; PARP, Poly-ADP ribose polymerase; STS, Short-term survivor.

* Corresponding author at: University of Chicago, Department of Obstetrics and Gynecology/Section of Gynecologic Oncology, MC 2050, 5841 South Maryland Avenue, Chicago, IL 60637, United States of America.
E-mail address: elengyel@uchicago.edu (E. Lengyel).

https://doi.org/10.1016/j.ygyno.2018.11.007
0090-8258/

MesH terms

Ovarian neoplasms
Survivors
Prognosis
Gynecologic surgical procedures
Treatment outcome

1. Introduction

Ovarian cancer carries an ominous prognosis; it is predicted that approximately 14,000 women in the United States will die of the disease in 2018 [1]. Because localized disease has few symptoms and screening has not been shown to be effective in the general population [2], >80% of women with high-grade serous ovarian cancer (HGSOC) are diagnosed with advanced FIGO stage III/IV disease [3]. Overall survival is highly dependent on stage, with five-year survival ranging from 90% for stage I to 22% for stage IV HGSOC [4,5]. Only a scant 15% of women with advanced-stage HGSOC survive >7–10 years after diagnosis, making them long-term survivors (LTS) of their disease [6–8].

Prior investigations of LTS of HGSOC have established that these patients generally have favorable baseline clinical and pathologic features, including primary surgical treatment, optimal surgical cytoreduction and platinum-sensitive disease [6,9–11]. However, there is a paucity of information in the literature on the specific surgical procedures performed on LTS and whether pre-operative disease burden and aspects of surgery other than residual disease affect long-term survival. Additionally, some patients with very poor prognostic indicators become LTS [7,8] and many LTS have at least one recurrence [9]. The heterogeneous clinical courses of LTS with advanced stage HGSOC can be divided into three categories: (1) those who never experience a recurrence (cured by surgery and/or chemotherapy), (2) those who recur and undergo a second surgery ± chemotherapy, and (3) those who are multiple responders to repeated chemotherapy cycles, often including platinum [12].

We sought to investigate who LTS are and what medical or surgical treatments may have contributed to their prolonged survival. Most prior studies of LTS have used patient registries, which do not contain detailed information about the exact surgical and chemotherapy regimens these patient undergo [6–8]. Understanding interventions more prevalent in LTS could help direct future recommendations for extent of surgery during a debulking procedure and subsequent treatments to maximize the chance of converting patients into LTS. We took advantage of the high level of detail available in the prospectively collected clinicopathologic ovarian cancer database at the University of Chicago to explore the specifics of the care given to LTS, with a focus on intraoperative data. We present a comparison of demographic traits, clinical features, surgical findings and operations performed on long and short-term survivors of HGSOC and detail the longitudinal treatment courses of LTS within our database.

2. Materials and methods

Subjects were selected from the University of Chicago IRB approved Microsoft Access ovarian cancer database, which has archived data on patients treated for ovarian neoplasms since 1992. Data is prospectively collected at the time of initial treatment and regularly updated using a two-tiered review system, with data initially extracted by a nurse and then confirmed by a gynecologic oncologist. The database contains detailed demographic, clinical and pathologic characteristics, including age, race, performance status, extent of disease, surgical procedures performed, and chemotherapy administered. Any missing or incomplete information was supplemented by re-review of electronic and paper medical records, contacting the treating physician, or social security death records.

We identified consecutive patients with International Federation of Gynecology and Obstetrics (FIGO 2014) [13] stage III or IV high-grade serous cancer of the ovary, fallopian tube, or peritoneum diagnosed between 1992 and 2017. Patients with non-serous histology, low-grade serous tumors, or low malignant potential tumors were excluded. One patient had insufficient data and was excluded. All patients had surgery performed by a gynecologic oncologist. Among these patients, we selected long and short-term survivors for further analysis. We defined long-term survival as death or last follow-up >7 years after the date of primary debulking or first cycle of neoadjuvant chemotherapy [12]. Short-term survivors (STS) were patients who died between 1 and 2 years after primary debulking or first cycle of neoadjuvant chemotherapy. We choose this as a comparison group to avoid including women unable to complete their initial treatment course.

Previously published scoring systems were used to calculate a preoperative disease score (DS) [4,14] and surgical complexity score (CS) [15]. The preoperative disease score is defined as "DS low" for tumor involving pelvic and retroperitoneal regions, "DS moderate" for additional spread to the abdomen that spares the upper abdomen, and "DS high" for the upper abdominal disease affecting the diaphragm, spleen, liver, or pancreas. The surgical complexity score was calculated using a published scoring system [15] in which each procedure is assigned a weighted score from 1 to 3. A composite score is generated, which represents the number and complexity of procedures performed during the patient's debulking surgery (see appendix Table S1).

Univariate comparisons between the LTS and the reference STS group were performed on demographic and clinical characteristics, surgical findings and surgical procedures using Wilcoxon and Fisher's exact test as appropriate. Statistical significance was defined as a P value < 0.05. Two logistic regression models were used to identify independent prognostic factors for LTS. Descriptive statistics and a visual representation are presented to describe the clinical courses of the long-term survivors. Analyses were generated using Stata 15 (StataCorp., College Station, TX).

3. Results

3.1. Baseline patient characteristics

We identified 45 long-term survivors and 78 short-term survivors out of 450 consecutive patients with stage III or IV HGSOC. Baseline demographic and clinical characteristics for both groups, divided by all patients and only those who underwent primary debulking surgery, are displayed in Table 1. Age, BMI, pre-operative CA-125 and ASA class were similar between the groups. LTS surgical dates ranged from 5/1993 to 10/2010 and STS surgical dates ranged from 10/1992 to 10/2015. Out of the 2 LTS patients with stage IVB disease, 1 had liver parenchymal metastases and 1 had abdominal wall involvement. Of the 11 STS patients with stage IVB disease, 9 had liver parenchymal metastases, 2 had splenic parenchymal involvement and 1 had breast and axillary metastasis. More LTS than STS were debulked to microscopic disease regardless if they received primary surgery, but in both groups this represented a minority of patients. Of all LTS debulked to microscopic disease, 4 had high DS, 10 had moderate DS, and 1 had low DS. Nine LTS (21%) had residual disease >1 cm, of whom 6 had high DS and 3 had moderate DS. All patients received a platinum agent, and all but 1 LTS and 2 STS also received a taxane as part of their initial treatment course.

3.2. Comparative surgical courses

The operative findings at the time of initial debulking divided into all patients and primary surgery patients are shown in Table 2. STS presented with more involved disease sites, but this finding was significant for fewer disease sites in the primary surgery only patients. The majority of patients in both groups had a high DS, but there was a trend towards higher DS in STS [3]. Table 3 lists the procedures performed during

Table 1
Clinico-pathologic baseline characteristics.

	All patients			Primary debulking only		
	LTS ($N = 45$)[a]	STS ($N = 78$)[a]	*P*-value	LTS ($N = 41$)[a]	STS ($N = 48$)[a]	*P*-value
Age at diagnosis (yrs)						
Median	61	64.5	0.07	59	65.5	0.07
Range	37–81	33–88		38–80	33–88	
BMI (kg/m^2)			0.83			0.5
Median	26.6	25.7		26.6	26.8	
Range	18.8–42.4	18.8–53		18.8–42.4	18.8–53	
Race			0.04			0.05
White	38 (84%)	58 (74%)		34 (83%)	34 (71%)	
African American	3 (7%)	16 (21%)		3 (7%)	11 (23%)	
Hispanic	0	2 (2.5%)		0	2 (4%)	
Asian	4 (9%)	2 (2.5%)		4 (10%)	2 (2%)	
ASA class			0.51			0.34
I	2 (5%)	8 (10%)		2 (5%)	7 (15%)	
II	24 (54%)	37 (48%)		23 (57%)	26 (54%)	
I II	18 (41%)	33 (42%)		15 (38%)	15 (31%)	
Neoadjuvant chemotherapy	4 (9%)	30 (38%)	<0.01	n/a	n/a	n/a
Intraperitoneal chemotherapy	14 (31%)	7 (9%)	<0.01	14 (34%)	6 (13%)	0.02
Pre-operative CA-125 (U/mL)			0.19			0.68
Median	1070	429		1104	606	
Range	12–6884	11–9311		12–6884	45–9311	
FIGO stage			0.04			0.09
IIIA	2 (4.5%)	0		2 (5%)	0	
IIIB	5 (11%)	3 (4%)		5 (12%)	1 (2%)	
IIIC	31 (69%)	48 (62%)		27 (66%)	35 (73%)	
IVA	5 (11%)	16 (20%)		5 (12%)	9 (19%)	
IVB	2 (4.5%)	11 (14%)		2 (5%)	3 (6%)	
Primary disease site			0.34			0.27
Ovary	35 (78%)	50 (64%)		33 (80%)	32 (67%)	
Fallopian tube	3 (7%)	9 (12%)		2 (5%)	7 (14%)	
Peritoneum	7 (15%)	19 (24%)		6 (15%)	9 (19%)	
Residual disease			0.02			<0.01
Microscopic	15 (34%)	18 (23%)		14 (35%)	5 (10%)	
<1 cm	20 (45%)	25 (32%)		18 (45%)	25 (40%)	
>1 cm	9 (21%)	35 (45%)		8 (20%)	24 (50%)	
Primary platinum free interval			<0.01			<0.01
<6 months	1 (2%)	60 (78%)		1 (2.5%)	36 (77%)	
6–12 months	1 (2%)	14 (18%)		1 (2.5%)	10 (21%)	
>12 months	42 (96%)	3 (4%)		38 (95%)	1 (2%)	

[a] Not all numbers sum to total due to missing data.

initial debulking surgery for both groups, divided into all patients and patients undergoing primary surgery only. All patients underwent similar surgeries; only pelvic and paraaortic lymph node dissections were more common in LTS. LTS had higher surgical complexity scores despite having a trend towards lower disease scores.

3.3. Multivariate regression analysis

Table 4 includes two logistic regression models. Model #1 demonstrates that an increase in surgical complexity score is correlated with higher odds of LTS, independent of disease status. Model #2 shows that receiving neoadjuvant chemotherapy lowers the odds of LTS and optimal debulking to minimal residual disease increases the odds of LTS, independent of disease status. Neither model demonstrates an independent association of stage or disease status with LTS. Our models were limited to 5 variables each to avoid overfitting in the setting of only 45 LTS.

3.4. Categories and treatment courses of long term survivors

Out of the 45 LTS, 13 (29%) remained disease free at a median follow up time of 143 months. This represents only a 3% cure rate for 450 consecutive patients with stage III/IV HGSOC. Nine of these patient were still living at the time of study cut off (March 2018) with a median follow-up of 143 months and 4 had died of other causes, with median survival of 124 months. There was no difference in age, BMI, pre-operative CA-125, ASA class, FIGO stage, tumor site, race, blood loss at surgery, optimal cytoreduction, neoadjuvant chemotherapy, IP chemotherapy or platinum sensitivity between patients who did and did not experience disease recurrence.

Thirty-two LTS (71%) experienced a recurrence with a median follow-up time of 115 months. Nineteen of these patients were still living at the time of study cut off, with median time to recurrence of 46 months and median follow-up of 118 months. Thirteen died of disease with a median time to recurrence of 43 months and median survival of 111 months. After their first recurrence, 28 women received chemotherapy, with 24 patients (86%) receiving platinum-based therapy. The 4 patients who received alternate therapy received taxol with liposomal doxorubicin, single agent taxol, single agent liposomal doxorubicin, or tamoxifen.

Nineteen LTS (59%) underwent a secondary debulking (14 to microscopic disease, 5 to <1 cm of disease), 5 (17%) underwent a tertiary debulking (all to microscopic disease), and 1 (3%) underwent a quaternary debulking (to <1 cm of disease). These surgeries were performed because the patient had low-volume, oligometastatic disease deemed to be completely removable by their surgeon. Fourteen out of 19 women (74%) received chemotherapy after their secondary debulking.

In Fig. 1, the treatment courses of LTS are displayed and subdivided into the categories proposed by Hoppenot et al. [12]. Of the patients with no recurrence, patient 13 survived a remarkable 22 years. In patients with recurrence treated with surgery, patient 23 stands out for undergoing a total of 3 repeat debulking surgeries for single-site recurrences, including a celiac trunk lymph node dissection, a mediastinal tumor excision and a chest wall with partial rib resection. Patient 36 is

Table 2
Extent of disease at initial debulking surgery.

	All patients			Primary debulking only		
	LTS (*N* = 45)[a]	STS (*N* = 78)[a]	*P*-value	LTS (*N* = 41)[a]	STS (*N* = 48)[a]	*P*-value
Ovary						
Involved	37 (86%)	77 (99%)	0.01	35 (90%)	48 (100%)	0.04
Prior oophorectomy	3 (7%)	1 (1%)		2 (5%)	0	
Fallopian tube			<0.01			0.07
Involved	30 (70%)	72 (92%)		28 (72%)	43 (90%)	
Prior Salpingectomy	3 (7%)	1 (1%)		2 (5%)	0	
Uterine serosa			<0.01			<0.01
Involved	25 (58%)	56 (72%)		23 (59%)	35 (73%)	
Prior hysterectomy	5 (12%)	17 (22%)		5 (13%)	11 (23%)	
Omentum involved	37 (86%)	76 (97%)	0.02	33 (85%)	46 (96%)	0.13
Small bowel implants	19 (45%)	54 (69%)	0.01	18 (47%)	33 (69%)	0.05
Large bowel implants	22 (52%)	61 (78%)	<0.01	20 (53%)	37 (77%)	0.02
Appendix			0.04			0.30
Involved	7 (17%)	29 (37%)		7 (18%)	16 (33%)	
Prior appendectomy	4 (9%)	9 (12)		4 (11%)	5 (10%)	
Spleen or splenic hilum	5 (12%)	14 (18%)	0.44	4 (11%)	9 (19%)	0.37
Liver parenchyma or surface	12 (29%)	27 (35%)	0.55	11 (29%)	17 (35%)	0.64
Diaphragm nodules			0.51			0.52
>5 mm	7 (16%)	20 (26%)		7 (18%)	14 (29%)	
<5 mm	15 (36%)	22 (28%)		12 (32%)	13 (27%)	
None	20 (48%)	36 (46%)		19 (50%)	21 (44%)	
Malignant pleural effusion	6 (14%)	21 (27%)	0.17	6 (16%)	8 (17%)	1
Ascites > 500 cc	15 (36%)	58 (74%)	<0.01	12 (32%)	42 (88%)	<0.01
Disease score (DS)			0.06			0.06
Low	5 (12%)	2 (3%)		5 (13%)	2 (4%)	
Moderate	14 (33%)	21 (27%)		13 (34%)	13 (27%)	
High	23 (55%)	55 (70%)		20 (53%)	33 (69%)	

[a] Not all numbers sum to total due to missing data.

Table 4
Logistic regression models of prognostic factors.

	Odds Ratio	95% CI	*P*-value
Model 1			
FIGO stage 4 (vs. 3)	0.38	0.13–1.09	0.07
CS (per 1 point increase)	1.24	1.01–1.51	0.04
Age (per 1 year increase)	0.98	0.94–1.02	0.31
Race (vs. White)			0.22
African American	0.31	0.08–1.21	
Other	1.22	0.23–6.39	
DS (vs. low)			0.12
Moderate	0.44	0.07–2.97	
High	0.21	0.03–1.33	
Model 2			
FIGO stage 4 (vs. 3)	0.50	0.17–1.46	0.21
Neoadjuvant chemotherapy	0.16	0.05–0.56	<0.01
Age (per 1 year increase)	0.97	0.94–1.01	0.20
DS (vs. low)			0.89
Moderate	0.72	0.11–4.89	
High	0.65	0.10–4.07	
Residual disease (vs. >1 cm)			0.05
<1 cm	2.69	0.95–7.58	
Micro	4.31	1.26–14.74	

notable among those receiving chemotherapy, as she had 3 recurrences treated to no evidence of disease. Out of the 12 patients who recurred and went on to survive >10 years, 9 (75%) underwent surgical treatment of their recurrence.

4. Conclusions

In this case-control study we highlight the preoperative disease burden, surgical procedures performed on, and treatment courses of LTS of HGSOC. Several disease and surgical factors similar to those found in previous studies are more prevalent in our LTS. LTS underwent higher complexity surgeries than STS and were more likely to be resected to R0 at the end of their procedure [4]. LTS also had a trend towards lower disease burden at presentation, and other authors have demonstrated that low DS is a predictor of long-term survival [4,16]. Similar to the findings in a SEER registry study of women surviving >10 years, our patients who received neoadjuvant treatment were more likely to be STS [6]. A multi-center consortium study of patients surviving

Table 3
Procedures performed at initial debulking surgery.

	All patients			Primary debulking only		
	LTS (*N* = 45)[a]	STS (*N* = 78)[a]	*P*-value	LTS (*N* = 41)[a]	STS (*N* = 48)[a]	*P*-value
Hysterectomy			0.29			0.38
Performed	38 (84%)	59 (76%)		34 (83%)	35 (73%)	
Previously removed	5 (11%)	17 (22%)		5 (12%)	11 (23%)	
Salpingo-oophorectomy			0.25			0.46
Performed	41 (91%)	76 (97%)		38 (93%)	47 (98%)	
Previously removed	3 (7%)	1 (1%)		2 (5%)	0	
Omentectomy	42 (93%)	73 (94%)	1	37 (90%)	43 (90%)	1
Pelvic lymph node dissection	20 (47%)	18 (23%)	0.01	20 (51%)	10 (21%)	<0.01
Paraaortic lymph node dissection	16 (37%)	9 (12%)	<0.01	16 (41%)	5 (10%)	<0.01
Pelvic peritoneum stripping	19 (44%)	41 (53%)	0.45	18 (46%)	23 (48%)	1
Abdominal peritoneum stripping	7 (16%)	10 (13%)	0.6	7 (18%)	7 (15%)	0.77
Diaphragm stripping	7 (16%)	10 (13%)	0.79	7 (18%)	5 (10%)	0.37
Appendectomy			0.89			1
Performed	16 (37%)	31 (40%)		14 (36%)	17 (35%)	
Previously removed	4 (9%)	9 (12%)		4 (10%)	5 (10%)	
Small bowel resection	3 (7%)	6 (8%)	1	2 (5%)	4 (8%)	0.68
Large bowel resection	11(24%)	15 (19%)	0.5	10 (24%)	10 (21%)	0.8
Splenectomy	2 (4%)	3 (4%)	1	2 (5%)	2 (4%)	1
Liver resection	2 (4%)	2 (3%)	0.62	2 (5%)	1 (2%)	0.59
Surgical complexity score (CS)			0.02			<0.01
Median	4	3		4	3	
Range	0–11	0–10		0–11	0–10	

[a] Not all numbers sum to total due to missing data.

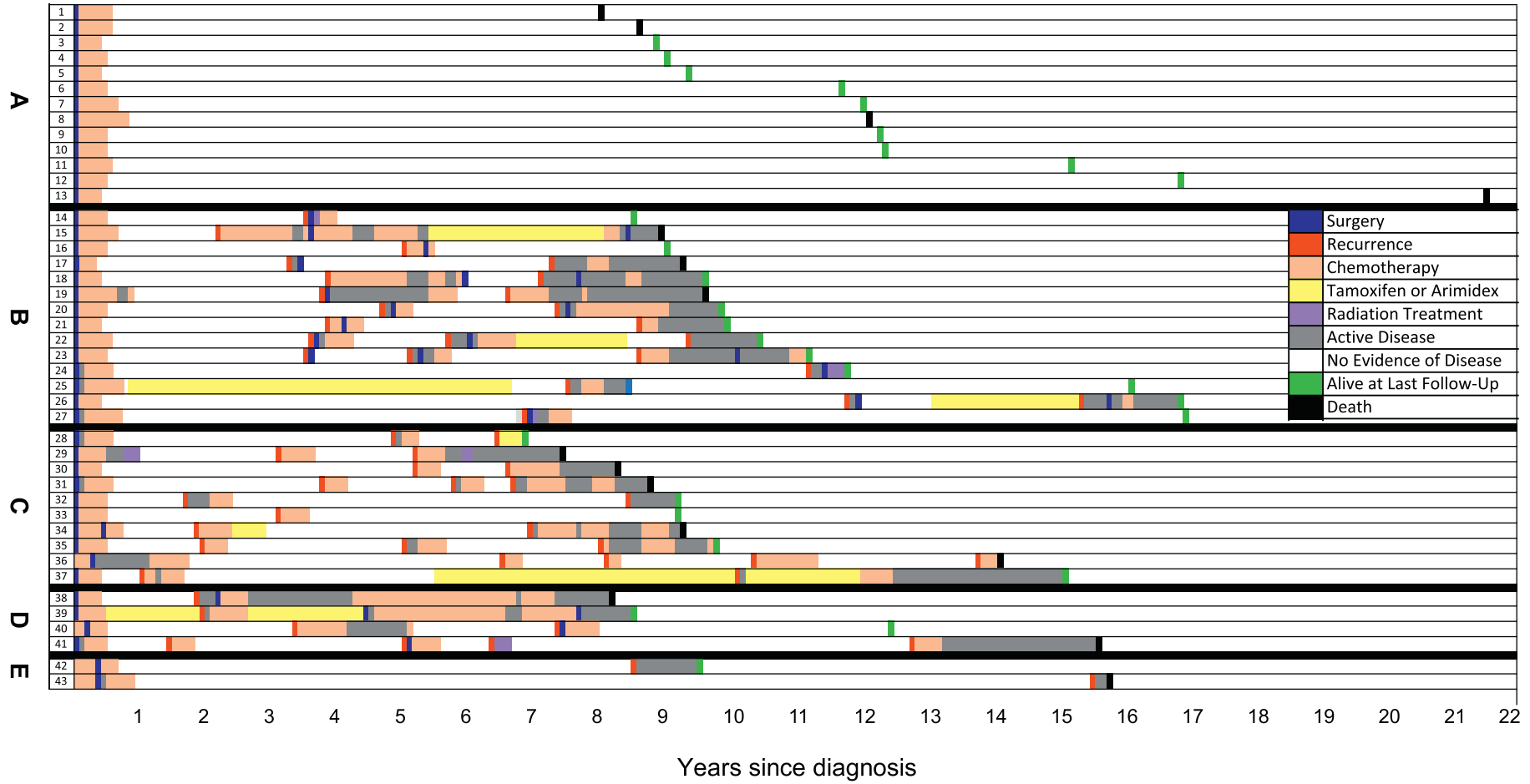

Fig. 1. Patients were categorized into different types of long-term survivors. Group A patients did not experience a recurrence. Group B contains 14 women who underwent a second surgery as their primary recurrence treatment modality. Group C contains 10 women who responded to multiple rounds of chemotherapy, but never had a second surgery. Group D contains 4 women who were a hybrid of category C and D. Group E contains women who elected to not to receive treatment for their recurrence after a lengthy disease free interval. 2 women with recurrence had inadequate follow-up data to categorize and are not included.

>10 years showed that 14% of patients were sub-optimally debulked and 11% were platinum resistant [9]. In contrast, our LTS population only demonstrated a 4% platinum resistance rate, but a notable 21% had >1 cm residual disease. Despite our data suggesting that secondary debulking is associated with LTS, GOG 213 has shown this is likely to be a confounding factor. This fact combined with our surprising number of sub-optimally debulked patients is a compelling argument that unless a patient is cured by initial surgery, platinum-sensitivity decides a patient's disease course. The biologic factors driving platinum-sensitivity are not adequately characterized by clinico-pathologic data.

When we visualized the disease courses of LTS (Fig. 1) we showed that there are multiple treatment paths to long-term survival and that no single clinical and/or pathologic factor is sufficient for its prediction. Our prospectively collected database allowed us to create this unique representation following LTS for up to 22 years and demonstrating several patterns of survival. We do not currently know if the different patterns of long-term survival are characterized by distinct genetic or epigenetic changes. We believe that major progress towards understanding the biology of LTS can be made through the investigation of these factors. We were not able to comment on the effect of BRCA status in our population due to incomplete data. While prior work has shown that BRCA increases survival and length of platinum free interval, it has not been associated with long-term survival [17,18]. Studies in RNA expression have begun to create predictive models for HGSOC. Spentzos and colleagues identified an Ovarian Cancer Prognostic Profile gene panel associated with long-term survival [19]. Berchuck and colleagues subsequently evaluated 24 LTS (median OS 107.5 months) and 30 STS (median survival OS 17.5) and identified 186 genes associated with long-term survival [20]. Riester and colleagues analyzed 1525 samples to create signatures to predict prognosis and the ability to achieve optimal debulking for serous ovarian cancer prior to validating these markers on large public data sets [21]. A recent study by Garsed and colleagues demonstrated an association between concurrent homologous recombination deficiency and retinoblastoma protein loss and long-term survival [22]. The different assay platforms and large number of genes surveyed in these studies has led to a lack of reproducibility, making it difficult to apply any molecular marker in the clinical arena. However, the pathways highlighted by these studies, including proliferative markers, hormone receptors, and stromal genes, can help generate hypotheses to explain and experimentally test the molecular mechanism (s) of LTS. Recently, we have shown that cancer testis 45 (CT45) mediates platinum sensitivity and predicts long-term survival. CT45's mechanism of action is through impairment of DNA repair after platinum treatment and activation of cytotoxic T-cells [23].

Aggressive surgical treatment and platinum sensitivity are consistently associated with LTS of advanced stage HGSOC. In summary, there are multiple avenues to becoming a LTS, but most patients are either cured with their first surgical attempt, have oligo-metastatic recurrences that are amenable to secondary debulking, or have disease that remains sensitive to multiple rounds of platinum treatment. Our study was limited by small numbers, restriction to a single institution and information available in patient's charts. As we looked at all LTS and STS in our database, patients in the 2 groups are not perfectly matched. STS were, on average, treated 5 years later than LTS, which may have introduced to temporal biases. Further exploration of the gene and protein expression profiles of exceptional survivor's tumors and integration of this knowledge with identifiable clinical factors will hopefully point the way to improved survival for all HGSOC patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.11.007.

Acknowledgments

We thank Gail Isenberg for editing the manuscript and Kristen Wroblewski for assistance with statistics.

Conflicts of interest

All authors report no conflicts of interest.

Author contribution

Melissa Javellana, MD and Ernst Lengyel, MD designed the study, collected data, performed statistical analysis and wrote the manuscript. Claire Hoppenot, MD assisted with the initial study design and critically edited the manuscript. Ernst Lengyel, MD supervised the project.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, CA Cancer J. Clin. 68 (2018) 7–30.
[2] National Academies of Sciences, Engineering, and Medicine. Ovarian Cancers: Evolving Paradigms in Research and Care, The National Academies Press, 2016.
[3] N. Howlader, A.M. Noone, M. Krapcho, D. Miller, K. Bishop, C.L. Kosary, M. Yu, J. Ruhl, Z. Tatalovich, A. Mariotto, D.R. Lewis, H.S. Chen, E.J. Feuer, SEER Cancer Statistics Review, 1975–2015, National Cancer Institute, 2018.
[4] N.S. Horowitz, A. Miller, B. Rungruang, S.D. Richard, N. Rodriguez, M.A. Bookman, C.A. Hamilton, T.C. Krivak, G.L. Maxwell, Does aggressive surgery improve outcomes? Interaction between preoperative disease burden and complex surgery in patients with advanced-stage ovarian cancer: an analysis of GOG 182, J. Clin. Oncol. 33 (2015) 937–943.
[5] N. Howlader, A.M. Noone, M. Krapcho, D. Miller, K. Bishop, C.L. Kosary, M. Yu, J. Ruhl, Z. Tatalovich, A. Mariotto, D.R. Lewis, H.S. Chen, E.J. Feuer, National Cancer Institute SEER Cancer Statistics Review 1975–2014, National Cancer Institute, 2017.
[6] L.A. Baldwin, B. Huang, R.W. Miller, T. Tucker, S.T. Goodrich, I. Podzielinski, C.P. Desimone, F.R. Ueland, J.R. Van Nagell, L.G. Seamon, Ten-year relative survival for epithelial ovarian cancer, Obstet. Gynecol. 120 (2012) 612–618.
[7] R.D. Cress, Y.S. Chen, C.R. Morris, M. Petersen, G.S. Leiserowitz, Characteristics of long-term survivors of epithelial ovarian cancer, Obstet. Gynecol. 126 (2015) 491–497.
[8] M. Åkeson, A.M. Jakobsen, B.M. Zetterqvist, E. Holmberg, M. Brännström, G. Horvath, A population-based 5-year cohort study including all cases of epithelial ovarian cancer in western Sweden: 10-year survival and prognostic factors, Int. J. Gynecol. Cancer 19 (2009) 116–123.
[9] F. Dao, B.A. Schlappe, J. Tseng, J. Lester, A.M. Nick, S.K. Lutgendorf, S. Mcmeekin, R.L. Coleman, K.N. Moore, B.Y. Karlan, A.K. Sood, D.A. Levine, Characteristics of 10-year survivors of high-grade serous ovarian carcinoma, Gynecol. Oncol. 141 (2016) 260–263.
[10] W.E. Winter, G.L. Maxwell, C. Tian, J.W. Carlson, R.F. Ozols, P.G. Rose, M. Markman, D.K. Armstrong, F. Muggia, W.P. McGuire, Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group study, J. Clin. Oncol. 25 (2007) 3621–3627.
[11] R.E. Bristow, R.S. Tomacruz, D.K. Armstrong, E.L. Trimble, F.J. Montz, Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis, J. Clin. Oncol. 20 (2002) 1248–1259.
[12] C. Hoppenot, M.A. Eckert, S.M. Tienda, E. Lengyel, Who are the long-term survivors of high grade serous ovarian cancer? Gynecol. Oncol. 148 (2018) 204–212.
[13] J. Prat, et al., International Journal of Gynecology and Obstetrics staging classification for cancer of the ovary, fallopian tube, and peritoneum, Int. J. Gynecol. Obstet. 124 (2013) 1–5.
[14] C.A. Hamilton, A. Miller, C. Miller, T.C. Krivak, J.H. Farley, M.R. Chernofsky, M.P. Stany, G.S. Rose, M. Markman, R.F. Ozols, D.K. Armstrong, G.L. Maxwell, The impact of disease distribution on survival in patients with stage III epithelial ovarian cancer cytoreduced to microscopic residual: a Gynecologic Oncology Group study, Gynecol. Oncol. 122 (2011) 521–526.
[15] G.D. Aletti, S.C. Dowdy, K.C. Podratz, W.A. Cliby, Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer, Am. J. Obstet. Gynecol. 197 (2007) 1–7.
[16] C.A. Hamilton, A. Miller, Y. Casablanca, N.S. Horowitz, B. Rungruang, T.C. Krivak, S.D. Richard, N. Rodriguez, M.J. Birrer, F.J. Backes, M.A. Geller, M. Quinn, M.J. Goodheart, D.G. Mutch, J.J. Kavanagh, G.L. Maxwell, M.A. Bookman, Clinicopathologic Characteristics Associated with Long-term Survival in Advanced Epithelial Ovarian Cancer: An NRG Oncology/Gynecologic Oncology Group Ancillary Data Study, 2017.
[17] I. Cass, R.L. Baldwin, T. Varkey, R. Moslehi, S.A. Narod, B.Y. Karlan, Improved survival in women with BRCA-associated ovarian carcinoma, Cancer 97 (2003) 2187–2195.
[18] J. Kotsopoulos, B. Rosen, I. Fan, J. Moody, J.R. McLaughlin, H. Risch, T. May, P. Sun, S.A. Narod, Ten-year survival after epithelial ovarian cancer is not associated with BRCA mutation status, Gynecol. Oncol. 140 (2016) 42–47.
[19] D. Spentzos, D.A. Levine, M.F. Ramoni, M. Joseph, X. Gu, J. Boyd, T.A. Libermann, S.A. Cannistra, Gene expression signature with independent prognostic significance in epithelial ovarian cancer, J. Clin. Oncol. 22 (2004) 4648–4658.
[20] A. Berchuck, E. Iversen, J. Lancaster, Patterns of gene expression that characterize long-term survival in advanced stage serous ovarian cancers, Clin. Cancer Res. 11 (2005) 3686–3696.
[21] M. Riester, W. Wei, L. Waldron, A.C. Culhane, L. Trippa, E. Oliva, S.H. Kim, F. Michor, C. Huttenhower, G. Parmigiani, M.J. Birrer, Risk prediction for late-stage ovarian cancer by meta-analysis of 1525 patient samples, J. Natl. Cancer Inst. 106 (2014) 1–12.
[22] D.W. Garsed, K. Alsop, S. Fereday, C. Emmanuel, C.J. Kennedy, D. Etemadmoghadam, B. Gao, V. Gebski, K. Amarasinghe, S.M. Grimmond, J.V. Pearson, N. Waddell,

Homologous recombination DNA repair pathway disruption and retinoblastoma protein loss are associated with exceptional survival in high-grade serous ovarian cancer, Clin. Cancer Res. (2018) 569–581.
[23] F. Coscia, E. Lengyel, J. Duraiswamy, B. Ashcroft, M. Bassani-Sternberg, M. Wierer, A. Johnson, K. Wroblewski, A. Montag, S.D. Yamada, B. López-Méndez, J. Nilsson, A. Mund, M. Mann, M. Curtis, Multi-level proteomics identifies CT45 as a chemosensitivity mediator and immunotherapy target in ovarian cancer, Cell (2018) 159–170.