What Characterizes Long-term Survivors of Recurrent Ovarian Cancer? Case Report and Review of the Literature

ZIAD HILAL¹, BEATE SCHULTHEIS², FRANZISKA HARTMANN³, ASKIN DOGAN¹,
CEM CETIN¹, HARALD KRENTTEL⁴, SVEN SCHIERMEIER⁵ and CLEMENS B. TEMPFER¹

Departments of ¹Obstetrics and Gynecology, ²Hematology/Oncology and

³Pathology, Ruhr University Bochum, Bochum, Germany;

⁴Department of Obstetrics and Gynecology, St. Anna Hospital, Herne, Germany;

⁵Department of Obstetrics and Gynecology, University of Witten/Herdecke, Witten, Germany

Abstract. *Background:* Women with recurrent ovarian cancer have a poor prognosis and short survival. However, some women are long-term survivors and it is unclear whether they share specific common characteristics. *Case Report:* We present the case of a 63-year-old woman with histologically-proven recurrent ovarian cancer and a survival time of 16 years after the diagnosis of recurrence. She underwent initial debulking surgery in 1994, followed by 6 cycles of adjuvant chemotherapy with cisplatin and paclitaxel. After recurrent disease was diagnosed by re-laparotomy in 2000, she underwent four lines of systemic chemotherapy from 2000 to 2009 (carboplatin/paclitaxel, topotecan, etoposide/treosulfan and liposomal doxorubicin) and four lines of endocrine therapy between 2002 and 2014 (tamoxifen, goserelin, tamoxifen and exemestane). In 2014, she underwent secondary debulking surgery and was tumor-free until 2015. Upon progression, she was then started on the fifth-line of endocrine therapy, fulvestrant, which was changed to the mTOR inhibitor everolimus in June 2016. In a PUBMED literature search, 360 cases of long-term survivors of recurrent ovarian cancer (LTSROC), defined as women with survival >5 years after the diagnosis of recurrence, were identified with a mean post-recurrence survival time of 7.5 years. Comparing the patient and therapy details of these women, we identified common characteristics of LTSROC, i.e. young age and optimal debulking at initial surgery, a long time span between first-

line therapy and first recurrence and the combined use of optimal cytoreductive surgery and systemic chemotherapy. Conclusion: LTSROC are rare, with 360 cases described in the literature. LTSROC are characterized by young age, low tumor stage, long recurrence-free interval and combined modality treatment with optimal cytoreductive surgery and systemic chemotherapy.

Ovarian cancer is a rare disease with a life-time risk of 1.7% (1). The prognosis of women with ovarian cancer is poor, since approximately 75% of women with ovarian cancer are initially diagnosed at an advanced disease stage with the tumor having spread to the abdomen or even to more distant sites, such as the pleural space (1, 2). In accordance with the predominantly late stage at first presentation, ovarian cancer is the most lethal of all pelvic malignancies. High recurrence rates between 60 and 85% within five years are typical for this disease despite aggressive primary treatment with debulking surgery and systemic platinum-based chemotherapy, today combined in many cases with targeted angiogenesis inhibition with bevacizumab (1-3). Long-term survival and cure after primary therapy is possible in women with early- and late-stage disease. Long-term survivors of ovarian cancer are characterized by specific features. For example, Dao *et al.* identified 203 long-term survivors of ovarian cancer from the database of a multicenter research consortium (4). They found that long-term survivors of ovarian cancer generally had favorable clinical features at the time of primary therapy, including optimal surgical cytoreduction and primary platinum-sensitive disease. In accordance, Sczcesny *et al.* identified extensive primary surgery, platinum sensitivity, young age and good performance status as predictors of long-term survival in a cohort of 174 women from the Norwegian National Cancer Registry (5). In addition to clinical and pathological characteristics, genomic stability also seems to be a hallmark

Correspondence to: Clemens B. Tempfer, MD, MBA, Department of Obstetrics and Gynecology, Ruhr University Bochum, Marienhospital Herne, Hoelkeskampring 40, 44625 Herne, Germany. Tel: +49 23234991801, Fax: +49 23234993393, e-mail: clemens.tempfer@rub.de

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of long-term survival. For example, Stalberg *et al.* assessed genomic profiles in an integrative genetic analysis of patients with serous ovarian cancer (6). Using single nucleotide polymorphism (SNP) arrays and targeted next-generation sequencing of 26 genes, they observed an increased genomic stability, a lower proportion of somatic copy number alterations and a lower average ploidy among ovarian cancer patients with long-term survival compared to those with early cancer-specific death.

In contrast to these well-described predictors for long-term survival in the primary situation, less is known on the predictors of long-term survival in women with ovarian cancer recurrence. Ovarian cancer recurrence predominantly occurs within the abdomen and is characterized by peritoneal carcinomatosis and ascites (1, 2, 4). Clearly, the prognosis for women with recurrent ovarian cancer is poor with a median survival time of less than 2 years (2, 3). It is assumed that there is no cure for women with recurrent ovarian cancer and palliative systemic chemotherapy is, therefore, the standard of care. In the recurrent situation, intravenous systemic chemotherapy with platinum compounds, taxanes, anthracyclines, gemcitabine, topotecan and trabectedine in various combinations and sequences are typically used. These regimens achieve median overall survival times after the first, second, third, fourth and fifth relapse of 17.6 (95% confidence interval (CI)=16.4-18.6), 11.3 (95% CI=10.4-12.9), 8.9 (95% CI=0.8-9.9), 6.2 (95% CI=5.1-7.7), and 5.0 (95% CI=3.8-10.4) months, respectively (2). Recent developments in the treatment of recurrent ovarian cancer include the neoangiogenesis inhibitor bevacizumab and the poly ADP ribose polymerase (PARP) inhibitor olaparib added to mono- or polychemotherapy regimens (7, 8). Due to the poor prognostic outlook of women with recurrent disease and median survival times between 5 and 17 months (2), women with recurrent ovarian cancer rarely survive for a long time. However, in rare cases, women do survive for a long time after having been treated with chemotherapy, endocrine therapy, secondary debulking, exenterative surgery or a combination of these modalities. There is no definition of long-term survivors of recurrent ovarian cancer (LTSROC); however, many case reports and case series of LTSROC published in the literature typically refer to women who survive for more than five years after the diagnosis of recurrence (4, 5).

To highlight the characteristics of LTSROC, we report the rare case of a woman with histologically-verified recurrent ovarian cancer and a survival time of 16 years after recurrence. We describe her tumor's characteristics and multiple consecutive treatment regimens. In addition, we present a literature review of case reports and case series of LTSROC and discuss common characteristics shared by these women.

Case Report

We present the case of a 63-year-old woman with histologically proven recurrent ovarian cancer and a post-recurrence survival time of 16 years. The patient was first diagnosed with ovarian cancer in January 1994 as a chance finding. At that time, she underwent hysterectomy and bilateral salpingo-oophorectomy. Subsequently, staging surgery with removal of the omentum and the pelvic and paraaortic lymph nodes was performed in March 1994. Histology showed a serous cystadenocarcinoma of the ovary with moderately differentiated tumor cells. The International Federation of Gynecology and Obstetrics (FIGO) stage was IIIC. After surgery, the patient was macroscopically tumor-free and adjuvant systemic chemotherapy with six cycles of cisplatin and paclitaxel was administered. The patient tolerated the chemotherapy well and subsequently had no evidence of disease until 2000. At that time, a rise of the tumor marker carbohydrate antigen (CA) 125 was observed and recurrent disease was confirmed by re-laparotomy. Histology showed a serous adenocarcinoma consistent with recurrence of the formerly diagnosed ovarian cancer. Then, secondary tumor debulking was performed with non-resectable residual disease left behind in the pelvic side wall and on the small bowel. Subsequently, the patient underwent four different lines of systemic chemotherapy between 2000 and 2009, starting with re-induction chemotherapy with carboplatin and paclitaxel, followed by a monotherapy regimen with topotecan, then followed by a combination chemotherapy with etoposide and treosulfan and, finally, the patient underwent a monotherapy regimen with liposomal doxorubicin. Between 2001 and 2016, the patient also underwent four lines of endocrine therapy (tamoxifen, goserelin acetate, tamoxifen and exemestane). In April 2014, anterior exenteration was performed with removal of a bulky tumor in the pelvis, cystectomy and creation of an ileum conduit pouch and an ileostoma. In May 2014, the patient experienced a multi-level thrombosis below the level of the vena femoralis communis, treated with the anticoagulant rivaroxabane. Subsequently, in June 2014, she had acute renal failure after a renal infection with *Klebsiella oxytoca*. Ileostomy reversal was performed in August 2014. The patient had no evidence of disease until November 2015, when tumor progress in the pelvis and lungs was observed by computed tomography of the chest and abdomen. She was started on the fifth-line of endocrine therapy, this time with the estrogen receptor antagonist fulvestrant. In June 2016, the therapy was changed to the mTOR inhibitor everolimus due to progressive disease in the abdomen evidenced by CT. This therapy is ongoing at the time of this report with stable disease evidenced by a computed tomography of the chest and abdomen in June 2016. Figure 1 shows hematoxylin-eosin stains of tumor specimens sampled at the time of

Figure 1. Hematoxylin-eosin staining of a recurrent ovarian cancer specimen sampled in 2014 demonstrating serous cystadenocarcinoma. Black bar represents 100 μ m.

secondary tumor debulking in 2014. Figure 2 shows estrogen and progesterone receptor expression of a tumor specimen sampled in 2014.

Literature Review

In a systematic literature search of the databases PubMed and Cochrane Central Register of Controlled Trials (search date: 16-06-2016) using the search terms "ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] AND "neoplasms"[All Fields]) OR "ovarian neoplasms"[All Fields] OR ("ovarian"[All Fields] AND "cancer"[All Fields]) OR "ovarian cancer"[All Fields] AND recurrent[All Fields] AND ("survivors"[MeSH Terms] OR "survivors"[All Fields] OR ("long"[All Fields] AND "term"[All Fields] AND "survivor"[All Fields]) OR "long term survivor"[All Fields] we identified 46 studies. After screening all abstracts, 9 studies

were identified reporting on women with LTSROC, defined for the purpose of this review as a documented survival time >5 years after the diagnosis of ovarian cancer recurrence (4, 9-16). Studies not reporting on long-term survival after ovarian cancer recurrence and studies reporting on women with borderline ovarian tumors or germ cell tumors of the ovary were excluded. After cross-searching the references of the 9 studies identified using this strategy, 8 additional studies were identified (17-24). In summary, 17 studies were included in this review. Figure 3 shows a diagram of the literature search. Table I shows the study characteristics and outcomes of the patients described in the 17 studies identified describing 360 cases of LTSROC. Specifically, 237 (66%) of LTSROC experienced one recurrence, whereas 2 and ≥ 3 recurrences were experienced by 52 (15%) and 71 (20%) of LTSROC, respectively. The mean time of post-recurrence overall survival was 7.5 ± 6.9 years.

Figure 2. Immunohistochemical staining of recurrent ovarian cancer specimens sampled in 2014 demonstrating the expression of estrogen (upper panel) and progesterone receptors (lower panel). Black bars representing 20 μ m. ER, Estrogen receptor; PR, progesterone receptor.

The largest series of LTSROC was published by Dao *et al.* (4). In a large series of 203 ovarian cancer survivors with a history of high-grade serous adenocarcinoma, the authors identified 100 women with a survival time of at least 10 years post-recurrence (4). They found that LTSROC generally had favorable clinical features, including optimal initial cytoreductive surgery (CRS) and primary platinum-sensitive disease. Of note, there was no uniform pattern of time to recurrence in the 100 women described in this cohort study. Some of the patients recurred early and continued to have long-term survival, whereas other patients recurred late and also had long-term survival after recurrence. Both situations were common and equally represented in this cohort of LTSROC.

Optimal surgical cytoreduction at the time of recurrence with no residual tumor left behind was described as a reliable predictor of post-recurrence LTSROC in four studies (7, 10,

12, 18). For example, in a series of 87 women with recurrence after early-stage ovarian cancer, Gadducci *et al.* identified two independent predictors of post recurrence survival, *i.e.* young patient age and successful surgical cytoreduction at the time of recurrence (7). Likewise, Tentes *et al.* stressed the fact that complete cytoreduction at the time of recurrence best predicted overall survival in their analysis of 29 women with recurrent ovarian cancer who underwent cytoreductive surgery (CRS) combined with perioperative intraperitoneal chemotherapy (10). Also, Petrillo *et al.*, assessing 70 women with platinum-sensitive recurrence, found that optimal cytoreduction, in these cases combined with hyperthermic intraperitoneal chemotherapy (HIPEC), resulted in favorable 5- and 7-year survival rates (18).

Radiotherapy in combination with CRS or systemic chemotherapy has been described as an effective therapeutic

Figure 3. Flow diagram of the literature search algorithm.

strategy in 4 studies (15, 16, 17, 21). Firat *et al.* used selective radiotherapy in the management of 28 women with recurrent ovarian cancer involving the vagina or rectum achieving long-term survival >5 years in 4 of them (15). Albuquerque *et al.* described 8 LTSROC among a group of 27 women with localized extraperitoneal recurrences from epithelial ovarian cancer who received tumor volume-directed involved field radiation therapy at the time of recurrence (17). Eight of 14 LTSROC described by Iwase *et al.* received radiotherapy in combination with surgery and/or systemic chemotherapy (21). Finally, Martinez-Monge *et al.*

reported one case of LTSROC after intraoperative radiotherapy combined with CRS and external beam irradiation, as well as systemic chemotherapy (16). Taken together, radiotherapy at the time of ovarian cancer recurrence was effectively used in 57/360 (16%) LTSROC.

Systemic chemotherapy is the standard of care for women with recurrent ovarian cancer (1, 2). In accordance with that, in 14/17 (82%) studies and in 328/360 (91%) patients identified in our literature review, systemic chemotherapy was used as the sole treatment modality or as part of the therapeutic concept. In 15/16 studies, CRS was also performed and in 4/16 studies some form of radiotherapy (RXT) was added to CRS and systemic chemotherapy. Therefore, one characteristic feature of LTSROC seems to be the combination of therapeutic modalities with systemic chemotherapy, CRS and RXT being the most often cited combinations.

Only a minority of the reports identified in this literature review discussed endocrine therapy. For example, Chudecka-Glaz *et al.* described one patient with 9 years of survival post-recurrence solely treated with a gonadotropin releasing hormone agonist (11). Likewise, our own patient described in the present case report successfully underwent and responded to five consecutive lines of endocrine therapy, including tamoxifen, goserelin acetate, exemestane and fulvestrant.

Discussion

In this case report and review of the literature, we describe a woman with histologically-proven recurrent ovarian cancer and a post-recurrence survival time of 16 years. During that time, the patient underwent a series of treatments, including five lines of systemic chemotherapy, two CRS and five lines of endocrine therapy. In a systematic literature search, we identified 17 studies with 360 patients identified as LTSROC. Common characteristics shared by LTSROC were young age and optimal debulking at the time of initial surgery, a long recurrence-free interval and the combined use of optimal cytoreductive surgery and systemic chemotherapy. In a minority of LTSROC, durable responses to endocrine therapies were noted.

Many treatments and treatment combinations for LTSROC were used in the 17 studies analyzed in this review. The individual management strategies are outlined in Table I demonstrating that there is no specific therapy that is characteristic for LTSROC. However, a combination of CRS, systemic chemotherapy and -in some studies- radiotherapy has been used in the majority of successfully treated patients. When looking for common characteristics of LTSROC shared by a majority of women, we identified the following parameters:

- i) optimal debulking at initial surgery,
- ii) young patient age at initial surgery,

Table I. Clinical studies describing cases of women with long-term survival of >5 years after ovarian cancer recurrence.

Author	Year	Number of cases (n)	One/two/≥three recurrences (n)	Initial FIGO stage	Histology	Treatment regimens	Survival time after recurrence-years (n)
Martinez-Monge <i>et al.</i>	1993	1	1/-/-	-	EOC	CRS, RXT, CHXT	7 (1)
Eltabbakh <i>et al.</i>	1998	11	6/5/-	I-IV	EOC	CRS, CHXT-M	9 (11)
Firat <i>et al.</i>	2001	4	1/3/	I-III	EOC	CRS, CHXT, RXT	10 (1); 19 (1); 27 (1); 6 (1)
Chan <i>et al.</i>	2004	2	-/-/2	III	EOC, SAC	CRS, CHXT, ET	7.6 (1); 10.5 (1)
Jha <i>et al.</i>	2005	1	1/-/-	I	AS	Surgery, CHXT	5 (1)
Fleisch <i>et al.</i>	2007	1	1/-/-	III	EOC	CRS, CHXT	5 (1)
Legge <i>et al.</i>	2008	16	-/10/6	II-IV	EOC	Surgery, CHXT	5 (16)
Chudecka-Glaz <i>et al.</i>	2009	1	1/-/-	-	EOC	ET	9 (1)
Tentes <i>et al.</i>	2010	14	14/-/-	-	-	CRS, ICHXT	5 (14)
Kajiyama <i>et al.</i>	2012	102	102/-/-	II-IV	EOC	CRS, CHXT	5 (102)
Gaducci <i>et al.</i>	2013	30	30/-/-	II-IV	EOC	CHXT, CRS, RXT	5 (4); 7 (26)
Bacalbasa <i>et al.</i>	2015	4	1/1/2	I-III	EOC	CRS, CHXT	5.5 (3); 10 (1)
Bentivegna <i>et al.</i>	2015	13	12/1/-	I-II	EOC	Surgery, CRS	15.5 (11); 24 (1); 19 (1)
Iwase <i>et al.</i>	2015	14	14/-/-	I-III	EOC	CRS, CHXT, RXT	>5 (14)
Dao <i>et al.</i>	2016	100	21/19/60	I - IV	EOC	CHXT, CRS	10 (100)
Albuquerque <i>et al.</i>	2016	8	8/-/-	-	EOC	CRS, RXT	5 (3); 10 (5)
Petrillo <i>et al.</i>	2016	37	24/13/-	I-IV	EOC	CRS, HIPEC, CHXT	5 (6); 7 (31)
Hilal <i>et al.</i>	2016	1	-/-/1	III	EOC	CRS, CHXT, ET	16 (1)
Pooled Analysis	-	360	237 (66%)/52 (14%)/71 (20%)	-	-	-	Mean 7.5 (360)

n, Number of cases; EOC, epithelial ovarian cancer; CRS, cytoreductive surgery; RXT, radiotherapy; CHXT-M, maintenance chemotherapy; CHXT, chemotherapy; SAC, serous adenocarcinoma; AS, angiosarcoma; ET, endocrine therapy; ICHXT, intraoperative chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy.

iii) a long time span between the end of the first-line therapy and the first recurrence, and

iv) successful application of multi-modality treatment with optimal cytoreduction and systemic chemotherapy and/or radiotherapy.

In contrast to our expectation, endocrine therapy did not play an important role in the treatment of LTSROC. We could only identify two cases of LTSROC effectively treated with endocrine therapy in this literature review. Therefore, based on the literature search performed, endocrine therapy clearly is not a typical treatment effectively used in LTSROC.

Based on personal experience, women surviving ovarian cancer recurrence for more than 5 years are a rare clinical finding. Therefore, it was surprising to identify the high number of 360 cases in the literature. Although still rare, these cases demonstrate that the chance of LTSROC is considerable and that the assumption of recurrent ovarian cancer being definitively incurable should be seen critically. Obviously, there is a small subset of women with certain characteristics –as identified in our literature review– for whom LTSROC is possible. These women have tumors occurring early in life and are well debulkable and platinum-sensitive. In these women, aggressive treatment strategies at the time of recurrence, including CRS combined with radiotherapy and systemic chemotherapy, may be justified.

Conclusion

In conclusion, we describe the case of a woman with a survival time of 16 years after ovarian cancer recurrence. In a systematic review of the literature, we identified 360 LTSROC with specific characteristics shared by a majority of them. Based on the data available in the literature, we conclude that LTSROC is rare but possible and characterized by biological variables, such as young age at the time of initial diagnosis and management-dependent variables, such as optimal debulking at initial surgery, optimal CRS at the time of recurrence and application of multi-modality treatments combining CRS, radiotherapy and systemic chemotherapy.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

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