Thieme

Low-grade Serous Ovarian Carcinoma

Low-grade seröse Ovarialkarzinome

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Key words

ovarian cancer, low-grade serous, rare tumour

Schlüsselwörter

Ovarialkarzinom, Low-grade serös, seltener Tumor

received 14.8.2018
revised 24.8.2018
accepted 26.8.2018

Bibliography

DOI https://doi.org/10.1055/a-0717-5411
Geburtsh Frauenheilk 2018; 78: 972–976 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0016-5751

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ABSTRACT

In the early 2000s a two-tier grading system was introduced for serous ovarian cancer. Since then, we have increasingly come to accept that low-grade serous ovarian carcinoma (LGSOC) is a separate entity with a unique mutational landscape and clinical behaviour. As less than 10% of serous carcinomas of the ovary are low-grade, they are present in only a small number of patients in clinical trials for ovarian cancer. Therefore the current treatment of LGSOC is based on smaller trials, retrospective series, and subgroup analysis of large clinical trials on ovarian cancer. Surgery plays a major role in the treatment of patients with LGSOC. In the systemic treatment of LGSOC, hormonal treatment and targeted therapies seem to play an important role.

ZUSAMMENFASSUNG

Kurz nach der Jahrtausendwende wurde ein 2-stufiges Klassifizierungssystem zur Einstufung von serösen Ovarialkarzinomen eingeführt. Seither wird zunehmend akzeptiert, dass das Low-grade seröse Ovarialkarzinom (LGSOC) eine eigenständige Einheit mit eigener Mutationslandschaft und klinischem Verhalten bildet. Weniger als 10% aller serösen Karzinome des Ovars werden dem Low-Grade-Subtyp zugeordnet, und in den klinischen Studien zum Ovarialkrebs tritt diese Form nur in wenigen Patientinnen auf. Die aktuelle Therapie für das LGSOC basiert daher auf den Ergebnissen kleinerer Studien und retrospektiver Serien sowie auf der Subgruppenanalyse von großen klinischen Studien zum Ovarialkarzinom. Die operative Therapie spielt eine wichtige Rolle für die Behandlung von Patientinnen mit LGSOC. Bei der systemischen Therapie des LGSOC scheinen sowohl hormonelle Therapien als auch gezielte Therapien eine wichtige Rolle zu spielen.

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Introduction

Ovarian cancer is the second most lethal gynaecological malignancy [1]. The World Health Organisation (WHO) classifies ovarian cancer as epithelial, non-epithelial (germ cell and sex cord-stromal cell), and metastatic (from other primary cancers such as gastric, colon, breast and other cancers) [2]. The most common histotype is serous ovarian carcinoma, which is subdivided into high-grade serous (HGSOC) and low-grade serous ovarian carcinoma (LGSOC). For this classification a two-tier system based on nuclear atypia was introduced in 2004, which led to the recognition of two separate entities in term of their genetic landscape, clinical behaviour, prognosis and management [3]. LGSOC accounts for 5–10% of patients diagnosed with serous carcinoma

of the ovary, Fallopian tube and peritoneum [4]. Similar to HGSOC, approximately 70% of LGSOC are diagnosed at an advanced stage (FIGO III–IV) [5]. Interestingly, LGSOC seems to have a better prognosis, with a mean 5-year survival for FIGO III–IV disease of 32.1% for HGSOC vs. 54.2% for LGSOC [6]. LGSOC also differs from HGSOC in having a lower age at presentation, with a median age at diagnosis of 46.9 years compared to 63 years for HGSOC [7].

The clinical presentation of LGSOC is comparable to that of HGSOC and includes abdominal or pelvic pain, bloating, or dysfunction of the bowel or bladder. Diagnostic workup typically includes clinical examination including pelvic examination, CA125, ultrasound or other imaging modalities such as computed tomography (CT) scan of the thorax, abdomen and pelvis or whole body magnetic resonance imaging (MRI). LGSOC may develop de novo or in the context of a borderline tumour (BOT, low malignant potential tumour). A retrospective series from the MD Anderson Cancer Centre showed that about 60% of LGSOC are found in the context of a serous borderline tumour at diagnosis (sBOT) [8]. Gene expression profiling supports the idea of a developmental relationship in which sBOT can transform into LGSOC [9]. The current WHO classification considers sBOT with invasive implants as low-grade carcinomas [10]. Malignant transformation from low-grade to high-grade serous ovarian cancer has been described in the literature, although it is difficult to explain from a molecular perspective [11]. LGSOC display a p53 wild-type phenotype (p53 is a typical marker of HGSOC which is typically absent in LGSOC) with possible K-*ras* and BRAF mutations [12]. Additionally, DNA copy number changes have been reported as a key event in the transition from BOT to carcinoma [13].

LGSOC has a significantly higher expression of ER and PR compared to HGSOC, which makes LGSOC a possible target for endocrine therapy [14]. Mutations in the KRAS/BRAF/MAPK signalling pathway seem to have a favourable influence on survival in LGSOC and could possibly be used as a target for systemic treatment [4]. BRAF mutations are rare among LGSOC relative to sBOT and their presence usually does not affect prognosis, in contrast to the presence of a K-ras mutation which has been characterised as an adverse prognostic factor [15].

According to the guidelines on epithelial ovarian cancer, genetic testing should be offered to all women diagnosed with LGSOC, even though germline BRCA mutations are less common in LGSOC compared to HGSOC. The Gynaecologic Oncology Group (GOG) 218 study showed that among 1915 women with epithelial ovarian cancer, only 4 out of 70 women with low-grade serous carcinoma carried a pathogenic mutation in the BRCA1 or BRCA2 gene [16].

Review

A key role for primary cytoreductive surgery in LGSOC

Surgery is the cornerstone of the treatment of LGSOC. We should therefore aim for complete resection at primary cytoreductive surgery, even in advanced stage LGSOC. If disease is unresectable or the patient is in a poor general health (including comorbidities, age and nutritional status), neoadjuvant chemotherapy followed by interval debulking surgery may be considered after histological confirmation of disease.

An exploratory case control study of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) meta-database confirmed that microscopic residual disease at primary cytoreductive surgery results in a better overall survival (median: 97 vs. 35 months) compared with women with residual disease > 1 cm [17]. When compared to the group with residual disease of between 1 and 10 mm, the group with no residual disease had a markedly longer progression-free survival (median: 32 vs. 92 months). At upfront surgery, complete cytoreduction was achieved in 51.7% of patients [17]. Other authors reported similar findings [18]. Since many patients are affected at a young age, fertility and sexuality should be discussed [5]. Fertility-preserving options can be offered safely to women with FIGO IA disease and IC1 LGSOC [5, 19]. Ovarian preservation should not be offered to women with invasive epithelial ovarian cancer higher than FIGO I, even after complete staging. This discussion is currently ongoing for patients with serous borderline tumour of the ovary with invasive implants of BOT.

First-line treatment: should we use the same regimen as for HGSOC?

Adjuvant chemotherapy is recommended for all patients with LGSOC not limited to the ovary. For FIGO IC–IIA LGSOC, carboplatin monotherapy should be considered; a combination regimen containing carboplatin and paclitaxel is recommended for more advanced cases [20]. However, it is commonly accepted that LGSOC is not as chemo-sensitive as HGSOC [19, 21, 22]. The estimated response to paclitaxel-carboplatin in previously untreated LGSOC is less than 25% [22]. The case control study of the AGO meta-database found a response rate of 23.1% [17].

Bevacizumab is commonly used as an anti-angiogenic agent in combination with carboplatin-paclitaxel in patients with previously untreated advanced ovarian cancer according to the data of AGO-OVAR 11/ICON 7 [23]. Eighty patients with advanced LGSOC were included in this randomised study. The addition of bevacizumab resulted in a non-significant HR of 0.78 (95% CI: 0.31–1.97; $p = 0.07$) in this sub-analysis, favouring the addition of bevacizumab [23]. We do have to note that this study is too underpowered to detect any therapeutic effect of bevacizumab in this subgroup, and studies on relapsed LGSOC show an advantage for patients receiving bevacizumab as will be discussed in the section on recurrence of LGSOC.

Gershenson et al. recently published a retrospective study of 203 patients with LGSOC who received primary cytoreductive surgery followed by platinum-based chemotherapy [24]. The authors compared 70 patients of this cohort who received hormonal maintenance therapy after chemotherapy with 133 patients who received routine follow-up. Median progression-free survival (PFS) of patients who received hormonal treatment was 64.9 months (95% CI: 43.5–86.3) vs. 26.4 months (95% CI: 21.8–31.0) in the observation group ($p < 0.001$). Both patients with and without persistent disease at the end of platinum-based chemotherapy had a better PFS in the hormonal maintenance therapy group [24]. In this study, oestrogen receptor (ER) and progesterone receptor (PR) status was known for less than half of patients who received hormonal maintenance therapy. Of the tested patients,

96% were ER-positive and 58% were PR-positive. In a sub-analysis, a PFS advantage was observed for patients who received hormonal maintenance therapy irrespective of PR status. As only one patient who received hormonal maintenance therapy was ER-negative, it is not possible to evaluate the treatment effect in an ER-negative population [24]. Fader et al. published a series on 27 patients who were treated with anti-hormonal treatment (tamoxifen, letrozole or anastrozole) after cytoreductive surgery instead of platinum-based chemotherapy [18]. In this series, median PFS and overall survival (OS) had not yet been reached; the authors reported a 3-year PFS of 79% and 3-year OS of 92.6% [18]. Notably, all patients who currently recurred had a PR status of 0–40%, suggesting that hormonal treatment, as a monotherapy, might be less effective in this subgroup [18, 25].

Management of recurrent or metastatic disease

Common options for the management of this subset of patients are:

- secondary cytoreduction
- chemotherapy
- bevacizumab
- hormonal therapies
- targeted agents (in the context of clinical trials)

Role of surgery for recurrent LGSOC

Despite radical first-line treatment, LGSOC may recur at some point [26]. Secondary cytoreductive surgery requires careful patient selection [27]. Defining precise criteria to select the appropriate surgical candidate is clearly difficult, as is the case for every ovarian cancer histotype. Generally, time to recurrence, localisation of disease and number of metastatic sites should be considered when attempting secondary cytoreduction.

Due to the infiltrative nature of LGSOC, surgical expertise is necessary to achieve macroscopic complete resection during secondary cytoreductive surgery (SCRS) for LGSOC. A retrospective study at the MD Anderson Cancer Centre of 41 patients with recurrent disease showed that cytoreduction without macroscopic residual disease could only be achieved in 22% of patients. The median PFS for patients without residual disease after SCRS was 60.3 months, compared to 10.7 months for patients with macroscopic residual disease. Median survival after a diagnosis of LGSOC for patients with complete resection during SCRS was 167.5 months vs. 88.9 months in patients with residual disease. Median survival from the time of SCRS for patients with no gross residual disease was 93.6 months compared to 45.8 months [28].

Complete resection during secondary cytoreductive surgery can improve PFS and possibly also OS for patients with recurrent LGSOC. We should therefore discuss the option of secondary cytoreductive surgery with maximal surgical resection in patients with recurrent disease.

Systemic treatment for recurrent LGSOC

In recurrent platinum-resistant HGSOC, the objective response rates (ORR) for non-platinum monotherapy vary between 17 and 19.7% [25]. In contrast, the ORR for LGSOC is approximately 4.9% for platinum-sensitive disease and 2.1% for platinum-resistant patients [21]. Despite these poor ORR, 60% of patients achieved stable disease during chemotherapy for recurrent LGSOC. Median time to progression was 34.7 weeks (range: 4.3–232.4 weeks) for platinum-sensitive patients and 26.4 (range: 8.4–149 weeks) for platinum-resistant patients. Pegylated liposomal doxorubicin (PLD) seems to be the most active regimen for LGSOC [29]. There is no data which compares the different regimens for platinum-based therapy to treat LGSOC.

As PARP inhibitors are very efficient to treat high-grade ovarian cancer, LGSOC were not included in the last phase III trials [30–32].

The addition of bevacizumab to standard chemotherapy for recurrent LGSOC can improve response rates. Schmeler et al. were the first to publish a report on the possibly beneficial effect of bevacizumab for LGSOC with a partial response in 5/13 patients treated with chemotherapy in combination with bevacizumab for recurrent LGSOC [33]. This finding was confirmed by Dalton et al. in a series of 40 patients in which they observed an ORR of 47.5% for bevacizumab-containing regimens, with a median PFS of 10.2 months (95% CI: 7.9–14.4 months) [34]. Some reports even suggest that bevacizumab might be effective as monotherapy for LGSOC [35, 36].

Hormonal treatment might be an alternative to chemotherapy for recurrent LGSOC. In a series of 64 patients with recurrent LGSOC, an overall response rate of 9% was observed, with stable disease achieved in 61.8% of cases [37].

Based on the known mutation in the KRAS/BRAF/MAPK and the PI3K/AKT/mTOR signalling pathway, several clinical trials have been designed, using targeted agents to target these pathways. In the GOG 0239 trial Farley et al. treated 52 patients with selumetinib, a MEK1/2 inhibitor. They observed an objective response rate of 15%, with stable disease in 65% of patients and an acceptable toxicity profile [38]. Based on this study, the AGO-OVAR 2.24/MILO trial was initiated, a randomised trial in which patients received either physician's choice of chemotherapy (PLD, paclitaxel q1w or topotecan) vs. MEK162. The results of this study have not been published to date but are expected in the near future. A second trial (NCT01936363) combined the MEK inhibitor pimasertib with a PI3K/mTOR inhibitor (SAR245409) or placebo. There is also a third trial which is still ongoing, in which patients are randomised between trametinib (MEK inhibitor) and physician's choice of therapy (letrozole, tamoxifen, PLD, paclitaxel q1w or topotecan).

Conclusions

Low-grade serous carcinoma is relatively chemo-resistant. Surgery is therefore the cornerstone of treatment for LGSOC, both as first-line therapy and to treat recurrence. Standard of care in first-line therapy remains primary cytoreductive surgery followed by platinum-based chemotherapy with or without bevacizumab. Hormonal therapy (e.g., aromatase inhibitors) could be considered as a maintenance therapy after end of chemotherapy for LGSOC. If there is recurrence of disease, the feasibility of secondary cytoreductive surgery should be evaluated and discussed with the patient. Chemotherapy could be offered as a systemic treatment for recurrent LGSOC in accordance with treatment recommendations for high-grade serous ovarian cancers. Endocrine

treatment seems to show similar effects as standard chemotherapy in this tumour entity.

Conflict of Interest

The authors have no conflict of interest concerning this paper.
General conflict of interest:
TB: research funding: Amgen; conference travel expenses: Amgen, Roche;
PH: advisory board: Astra Zeneca, Roche, Clovis, Tesaro, Pharmamar, Lily; honoraria: Astra Zeneca, Roche, Tesaro, Styker;
AdB: advisory board: Pfizer, Astra Zeneca, Roche, Tesaro, Genmab, Pharmamar; honoraria: Astra Zeneca, Roche, MSD, Pharmamar;
FH: advisory board: Tesaro, Roche; travel expenses: Boehringer Ingelheim, Astra Zeneca, Roche;
BA: advisory board: Roche, Amgen, Tesaro; honorarium: Roche; travel expenses: Roche, Tesaro.

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