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LOW-GRADE SEROUS CARCINOMA OVARY: A REVIEW

Dr. Tarini Sonwani [1*], Dr. Mala Sinha[2], Dr. Gaurav Khanna[3], Dr. Rashmi Rekha Bora[4]

[1*]Associate Consultant, Department of Gynecological Oncology, Fortis memorial research Iinstitute, Haryana, India

[2]Senior Registrar, Department of Gynecological Oncology, Fortis memorial research institute, Haryana, India

[3]Assistant Professor, Department of Pathology, Amrita institute of medical sciences, Haryana, India

[4]Senior Consultant, Department of Gynecological Oncology, Fortis memorial research institute, Haryana, India

***Corresponding Author:** Dr. Tarini Sonwani
*Associate Consultant, Department of Gynecological Oncology, Fortis memorial research institute, Haryana, India

Abstract
Low-grade serous carcinoma (LGSC) is a rare subtype of epithelial ovarian carcinoma with unique clinical characteristics and molecular features. Unlike high-grade serous carcinoma, LGSC typically occurs in younger women, follows an indolent course, and is associated with better long-term survival. It can develop de novo or arise from a precursor lesion known as a serous borderline tumor. Accurate pathological differentiation between LGSC and other histological subtypes of ovarian carcinoma is crucial for appropriate management. Several factors can impact the overall prognosis of LGSC. The age at diagnosis, current smoking status, elevated body mass index, mutational status, expression of hormonal receptors, and the Ki-67 proliferation index are all potential prognostic indicators. Surgical intervention plays a central role in the treatment of LGSC to achieve complete microscopic removal of the tumor in cases of metastatic disease. Despite its relative resistance to chemotherapy, adjuvant platinum-based chemotherapy is the current standard of care for LGSC. Hormonal maintenance therapy following adjuvant chemotherapy has demonstrated improved outcomes. In cases of disease recurrence, treatment options include secondary cytoreductive surgery, chemotherapy, hormonal therapy, targeted therapy, and participation in clinical trials. The evolving field of genomic studies and targeted therapies hold promise for transforming the treatment landscape of LGSC. Continued research and advancements in these areas are expected to significantly improve outcomes for patients with LGSC.

Keywords: low-grade serous carcinoma, ovarian epithelial carcinoma, disease recurrence, targeted therapies

Introduction
Ovarian cancer is acknowledged as the most fatal gynecologic malignancy [1]. Epithelial ovarian carcinoma (EOC) represents the predominant histological subtype, which can be further classified into five main subtypes: high-grade serous carcinomas (HGSC), endometrioid carcinomas, clear-cell carcinomas, mucinous carcinomas, and low-grade serous carcinomas (LGSC) [2]. While HGSC is the most common form of EOC, LGSC is relatively rare, accounting for approximately 2-5% of ovarian carcinomas and 5-10% of serous ovarian carcinomas [3, 4]. Due to its low prevalence, there is limited available data regarding the distribution of the disease, factors influencing outcomes, and patients' experiences.

Previously, it was believed that HGSC and LGSC existed along a continuum, but recent evidence has revealed that they are distinct entities. They follow separate pathways and exhibit differential clinical behavior and overall prognosis. LGSC exhibits unique clinical characteristics and possesses a distinctive molecular profile. It is typically diagnosed at a younger age and demonstrates a more indolent progression, relative resistance to chemotherapy, and prolonged survival compared to HGSC. The average age at diagnosis for LGSC is 55.5 years, compared to 62.6 years for HGSC [5]. Most

patients diagnosed with LGSC of the ovary are in advanced stages, similar to HGSC. Approximately 80% of LGSC cases are diagnosed when cancer has already spread beyond the ovaries to other pelvic or abdominal regions. [6]

Histological classification

Previously, serous ovarian carcinomas were classified using three grading systems: the International Federation of Gynaecology and Obstetrics (FIGO) system, the World Health Organization (WHO) system, and the Shimizu/Silverberg system. The FIGO system assessed the tumor's architectural features [7], while the WHO considered architectural and cytologic features [8]. On the other hand, the Shimizu/Silverberg system evaluated glandular architecture, degree of nuclear atypia, and mitotic index [9]. Based on their criteria, these systems categorized serous carcinoma as grade one, two, or three.

However, in 2004, a new two-tier grading system for serous ovarian carcinoma was introduced by Malpica et al. [10]. This novel system aimed to distinguish between HGSC and LGSC. The degree of nuclear atypia was used as the primary criterion in this system, while the mitotic rate was used as a supplementary criterion. This binary method categorized tumors exhibiting moderate nuclear atypia and a mitotic index of up to 12 mitoses per 10 high-powered fields as LGSC. On the other hand, high-grade serous tumors were characterized by extensive nuclear atypia and a mitotic index of more than 12 mitoses per 10 high-power fields. The two-tier grading method has proven superior in predicting clinical outcomes [10, 11, 12] and has good repeatability across various observers. This standardized grading method has been widely adopted for diagnosing LGSC and has prompted substantial research into the differences between HGSC and LGSC in molecular biology and clinical behavior.

Tumorigenesis

The fallopian tube has been hypothesized as a possible LGSC origin by a number of researchers [10, 13, 14]. Persistent inflammation, ovulation, and disturbances of the ovarian surface are all thought to contribute to the fimbriated end of the fallopian tube adhering to the ovarian surface. Ovarian epithelial inclusions are formed when tubal epithelia attach to and invaginate into the ovarian cortex. Serous cystadenoma, serous borderline tumour (SBT), and LGSC can develop from these inclusions [13, 14].

Vang et al. proposed a pathogenic pathway in the tubal system for SBT and LGSC. They suggest that papillary tubal hyperplasia (PTH) is the root cause of SBT and endosalpingiosis. If papillary tufts and clusters of epithelial cells separate from PTH and implant on the ovary or peritoneum, lesions may form. Another non-PTH tubal pathway that may play a role in the development of these lesions is the exfoliation and implantation of normal tubal epithelium on the peritoneum or ovary. [14].

De novo LGSC development is possible, as is LGSC development via SBT. A serous cystadenoma or adenofibroma forms the first step in LGSC development, followed by establishing an SBT by invasive or noninvasive implants. LGSC can sometimes evolve directly from a classic SBT, skipping over intermediate processes [10], even though development is typically sequential. Recurrence is seen in about 11% of previously treated SBTs, and malignancy develops in 2-4% [15]. The malignancy risk in SBT instances may reach 6.9%, as shown by a review by Longacre et al. [16]. LGSC, on the other hand, frequently manifests in repeated SBTs that involve peritoneal implants. Patients with LGSC are less likely than those with HGSC [17] to have a first- or second-degree relative with ovarian cancer. That the two tumors are not closely related is supported by these findings. Being overweight or obese may further increase the risk of LGSC [18].

Molecular profile

Mutations in the genes KRAS, BRAF, ERBB2, and NRAS, all of which are a part of the mitogen-activated protein kinase (MAPK) pathway, are frequently seen in low-grade serous ovarian cancer (LGSOC). However, mutations in PIK3CA, FFAR1, USP9X, and EIF1AX, associated with the AKT-

mTOR pathway, may also be present [19–22]. Among LGSOC samples, Grisham et al. found independent but significant rates of RAS and BRAF mutations (38% and 31%, respectively). BRAF mutations were more common in early-stage than advanced-stage disease, suggesting that serous borderline ovarian tumors (SBOTs) without BRAF mutation can give rise to aggressive LGSOCs [23, 24]. Insulin-like growth factor 1 (IGF-1) overexpression and a much-reduced frequency of p53 mutations are hallmarks of LGSOCs [25, 26]. Rare BRCA mutations have been seen in LGSOC [27]. However, a BRCA test is recommended for all women diagnosed with ovarian cancer (except mucinous and borderline), fallopian tube carcinoma, or primary peritoneal carcinoma [28]. Recent research has shown that LGSOCs lack the proteins MRE11, RAD50, and NBS1; this suggests that these cells have a mismatch repair defect [29].

Table 1: Molecular landscape of LGSC vs. HGSC [30]

LGSC	**HGSC**
KRAS mutation	TP53 mutation
BRAF mutation	BRCA 1 & 2 mutation
NRAS mutation	P16 expression
PIK3CA mutation	NF1 mutation
USP9X mutation	PB1 mutation
IGF-1 overexpression	CDK12 mutation
PAX-2 expression	
Inactivation of PTEN mutation	

Pathology

LGSOCs tend to be bilateral and multicystic, with papillary excrescences on a gross level. The fluid inside can be mucinous, serous, or serosanguinous. The cytoplasm of LGSOCs is amphiphilic or faintly eosinophilic, while the cells themselves are cuboidal, low-columnar, and infrequently flattened. Mild to moderate nuclear atypia and a mitotic index of less than 12 per 10 high-power fields are also characteristic of these cells. Micropapillary, cribriform, elongated papillae, glandular, medium-sized papillae, nests, macro-papillae, cell clusters, solitary cells, and a combination of these architectural patterns are all possible. We also observe psammoma bodies. (30,31,32)

Table 2: IHC profile of LGSC vs HGSC [30]

Biomarker	**LGSC**	**HGSC**
WT-1	Positive	Positive
PAX-8	positive	Positive
ER.	Mostly positive	Mostly positive
PR.	Possibly positive (~50%)	Possibly positive (~30%)
MIB1	Mainly negative	Possibly positive (~50%)
E-cadherin	Possibly positive	Mainly negative
PAX-2	Positive (~50%)	Negative
Her-2/neu	Possibly positive (~30%)	Possibly positive (~20%)
P16	Mainly patchy or negative	Diffusely positive
P53	Mainly patchy or negative	Diffusely positive (~90%)
Ki-67	Low	High

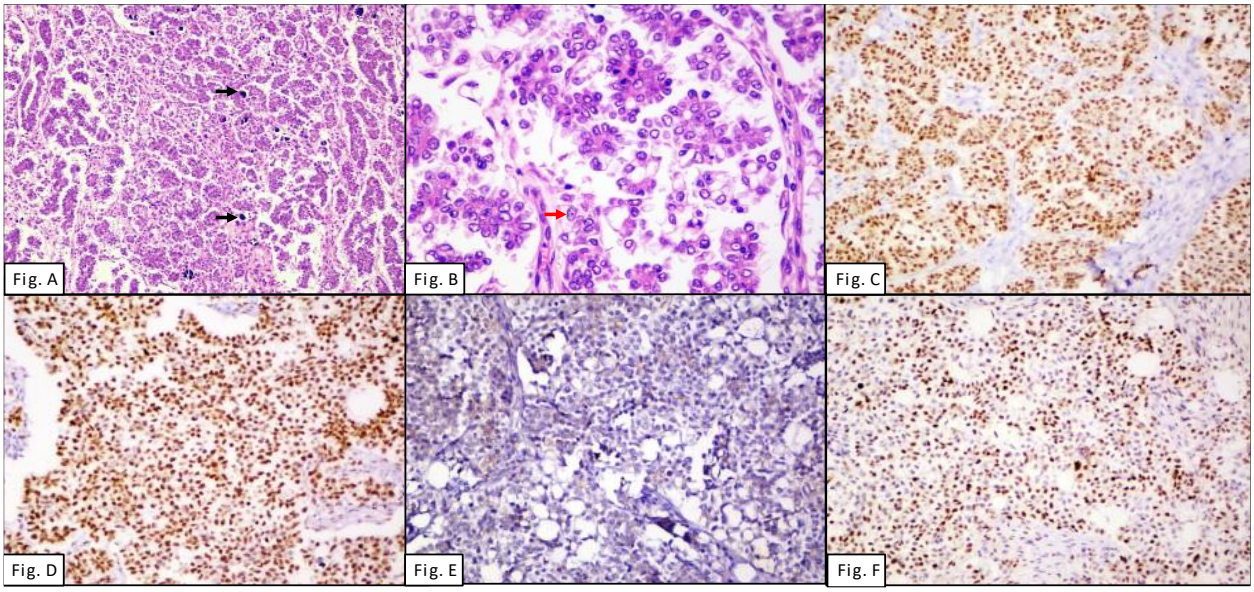

Fig A: Hematoxylin & eosin (H&E) stained section at low power (40x) showing small nests, glands, papillae, and micro-papillae surrounded by clear spaces, with many psammoma bodies (black arrow), Fig. B: H&E at high power (400x) reveals only mild to moderate grade of nuclear atypia with occasional nucleoli (red arrow), Fig. C & Fig. D: Immunohistochemistry (IHC) for Pax8 and WT 1 showing nuclear expression respectively, Fig E: IHC for P 16 is Negative, Fig. F: IHC for P53 showing wild type expression.

Prognosis and Treatment

Low-grade serous ovarian carcinoma typically exhibits a more favorable prognosis compared to HGSC. LGSC tends to be diagnosed at an earlier stage, with lower rates of lymph node involvement and distant metastasis. The 5-year overall survival (OS) rate for LGSC patients ranges from 70% to 90%, varying based on the stage at diagnosis [31]. However, it is crucial to recognize that LGSC can still experience disease recurrence and progression over time.

LGSC treatment involves a multimodal approach incorporating surgery, chemotherapy, and targeted therapies. Surgical intervention plays a central role and aims to achieve optimal cytoreduction, removing as much tumor tissue as possible. Chemotherapy, although LGSC is relatively less sensitive to it, is still utilized as adjuvant therapy and typically involves platinum-based regimens. Additionally, targeted therapies are being explored and may include agents targeting the molecular alterations observed in LGSC, such as MEK and CDK inhibitors.

It is important to plan comprehensive and individualized management for patients with LGSC, considering factors such as disease stage, patient characteristics, and molecular profile. Ongoing research and clinical trials are essential in further improving the understanding and treatment options for LGSC. The primary treatment for localized disease is surgical resection, aiming for optimal debulking and removing all visible tumors. This typically involves a hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Lymph node dissection may be performed if there is suspicion of nodal involvement. In advanced or recurrent diseases, cytoreductive surgery may still be considered to reduce tumor burden and improve response to chemotherapy.

Chemotherapy regimens commonly used for LGSC include platinum-based agents (cisplatin or carboplatin) in combination with taxanes (paclitaxel or docetaxel). These regimens are similar to those used for HGSC. However, LGSC has shown relative resistance to chemotherapy compared to HGSC; therefore, alternative treatment options are being explored.

Targeted therapies have emerged as a promising approach for managing LGSC. Mutations in the MAPK pathway, specifically KRAS and BRAF mutations, are frequently observed in LGSC. Consequently, extensive research has been conducted to explore targeted therapies that effectively

inhibit this pathway. MEK inhibitors, such as selumetinib, have shown efficacy in clinical trials and have been granted breakthrough therapy designation by the US Food and Drug Administration for advanced or recurrent LGSC with BRAF V600E mutations. Other targeted therapies, such as PI3K/AKT/mTOR pathway inhibitors and hormone receptor-targeted therapies, are also being studied in clinical trials [30].

Due to the rarity of LGSC, there is still ongoing research to understand its biology better, identify prognostic factors, and develop more effective treatment strategies. Clinical trials and collaborative research efforts are essential for advancing the knowledge and management of this disease.

Diagnosis and Preoperative Work-up: [30]

Diagnosing LGSC requires a comprehensive approach that involves clinical evaluation, tumor markers, and various imaging techniques. The following outlines the diagnostic and preoperative work-up for LGSC:

1. Clinical Presentation: Abdominal or pelvic pain, early satiety, bloating, and alterations in bowel or urine function are all symptoms shared by both HGSC and LGSC. LGSC, on the other hand, tends to manifest in younger people with greater body mass indexes and less typically presents with ascites than HGSC. It is also possible to get a pleural effusion or bowel obstruction.
2. Tumor Marker (CA-125): Patients with EOC often have elevated levels of CA-125 and other tumor indicators in their blood. Although CA-125 is typically raised in ovarian cancer patients, LGSC patients usually have lower median pretreatment CA-125 values and fewer patients with elevated levels than HGSC patients. CA-125 aids in the diagnosis of EOC, the assessment of prognosis, and the monitoring of treatment response.
3. Ultrasonography: Pelvic ultrasonography is the gold standard for diagnosing and evaluating ovarian lesions. Multilocular cystic lesions with solid components are the most common presentation of LGSC. Calcifications often originate in psammoma bodies. However, HGSCs don't have papillary structures and instead appear as solid masses with areas of cystic transformation, necrosis, and hemorrhage. The vascularity of LGSC and HGSC allows them to be distinguished by Doppler ultrasonography.
4. Computed Tomography (CT) Scan: The diagnostic accuracy of CT for metastatic disease, lymphadenopathies, and peritoneal metastases is 89% or higher, making it the gold standard. Differentiating LGSC from calcified adnexal masses, including leiomyomas, Brenner tumors, fibromas, and teratomas, is easier with imaging tools like CT scans. Necrosis, papillary projections, peritoneal implants, and lymph node calcification suggest carcinoma.
5. Magnetic Resonance Imaging (MRI): MRI provides excellent soft tissue resolution without radiation exposure. It helps confirm large adnexal masses detected on ultrasound or CT. LGSC may exhibit early enhancement on dynamic contrast-enhanced MRI and high signal intensity on diffusion-weighted images.
6. Positron Emission Tomography Scan: As a first-line diagnostic tool, FDG Positron Emission Tomography (PET) scans for ovarian cancer have limited utility. Histological grade and FDG uptake do not appear to be related. LGSCs may have a higher FDG uptake compared to some HGSCs. PET scans are best used for monitoring disease recurrence rather than diagnosing it.

Table 3: Imaging modalities in detecting recurrence [32]

	PET/CT	CT	CA-125
Sensitivity	94%	89%	68%
Specificity	100%	95%	89%
Accuracy	97%	93%	73%

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Management

Surgery

Surgical resection is the gold standard for treating EOCs like LGSC. In the earliest stages of the disease, ovarian cancer patients typically undergo a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and omentectomy as part of the routine surgical staging process. Cytoreductive surgery, which may involve multiple resections, is necessary for optimal debulking in more advanced instances. When operating on early EOCs, a systemic lymphadenectomy is always done for staging. Lymph node involvement is discovered in about 10% of people with initially diagnosed early-stage LGSC, and about 5% of cases are upstaged solely based on positive lymph nodes [33].

Extensive surgical removal of cancerous tissue is crucial in managing metastatic disease and reducing residual disease (RD). Several studies have investigated RD's impact on low-grade serous ovarian cancer (LGSOC) outcomes. Fader et al., in their analysis of GOG 182, examined the survival rates of 189 LGSC patients and identified RD status as the sole significant predictor of survival. Patients with microscopic residuals, residuals less than 1 cm, and residuals greater than 1 cm had median progression-free survival (PFS) of 32.2 months, 14.65 months, and 14.1 months, respectively. In the corresponding groups, the median overall survival (OS) was 96.6 months, 45 months, and 42 months. The adjusted hazard ratios (HR) for disease progression and death in individuals with LGSC and measurable RD after initial cytoreductive surgery were 2.28 and 2.12, respectively [34], similar to those observed in high-grade serous carcinoma (HGSC) with measurable disease. Gershenson et al. [35] found that measurable disease at the end of primary cytoreductive surgery was associated with a 1.79-fold increased likelihood of progression or recurrence and a 1.78-fold increased hazard of death. Additionally, Grabowski et al., in an analysis of four phase-three trials involving 145 LGSC patients, reported significant differences in OS and PFS among subgroups with microscopic residuals, residuals measuring 1-10 mm, and residuals greater than 1 cm. The 5-year OS in patients with residuals >1 cm was 32% (median 35 months, range 31–39 months), whereas it was 85% (median 97 months, range 60-124 months) in women with complete cytoreduction [36].

For women of childbearing age diagnosed with stage 1A-C1 ovarian cancer, fertility-sparing surgery (FSS) may be a suitable option. A retrospective study by Jiang et al. examined FSS and conventional surgery outcomes in 108 reproductive-age patients with epithelial ovarian cancers (EOCs). The study suggested that FSS was feasible for low-grade and stage I diseases in patients of childbearing age [37]. Similarly, Fruscio et al., in a follow-up study of 1031 patients with early-stage EOC, observed that women with grade three disease had a poorer overall outcome and a higher risk of distant recurrence [38]. Moreover, Melamed et al., in a cohort analysis using the National Cancer Database, found that among 1726 women with stage 1A-C EOC, 825 (47.2%) underwent FSS. The study indicated that compared to major surgery, the conservative technique of FSS did not increase the risk of death in young women with stage I EOC [39].

Treatment options for recurrent ovarian cancer include secondary cytoreduction, chemotherapy, bevacizumab, hormonal treatments, targeted therapies, and participation in clinical trials. Each recurrent case requires an individualized assessment of treatment choices, as there is no universally applicable approach.

There is some evidence supporting the effectiveness of secondary cytoreductive surgery (SCS) in treating recurrent low-grade serous ovarian cancer (LGSOC) [41, 42]. A retrospective analysis at Johns Hopkins Medical Institution examined 26 patients with ovarian micropapillary serous carcinoma, of whom 21 underwent SCS. Successful cytoreduction, defined as RDs less than 1 cm, was achieved in 15 (71.4%) patients [41]. The median survival of patients with optimal SCS was 61.2 months following recurrence, compared to 25.5 months for those with suboptimal SCS ($p = 0.02$) and 29.9 months for those who did not undergo surgical treatment ($p = 0.01$).

At MD Anderson Cancer Center, 41 patients with recurrent LGSOC underwent SCS after a median of 33.2 months post-primary debulking surgery (PDS). When comparing nine patients without

macroscopic RD to 32 patients with substantial RD, those without macroscopic RD had a longer median survival following SCS (93.6 months vs. 45.8 months, p = 0.04). The median survival of women who received SCS as their first treatment upon cancer recurrence was 83.3 months, compared to 33.2 months for those who received chemotherapy first and then SCS (p = 0.09).

Neoadjuvant Chemotherapy

Interval debulking surgery (IDS) after neoadjuvant chemotherapy (NACT) is an option when optimal debulking is not feasible or when the patient's health prevents substantial cytoreductive surgery. Histological confirmation of the disease by tissue biopsy is used to guide the administration of chemotherapy before surgery.

Response to NACT in 25 patients with advanced LGSC was assessed retrospectively by Schmeler et al. [42]. The median number of cycles of platinum-based chemotherapy given to each patient was six. Stable disease (SD) was reported by 88% of patients, a complete response (CR) was seen in 4%, and no partial responses were seen. The condition worsened in two cases (8%).

Similarly, Cobb et al. [43] compared the efficacy of NACT in LGSC and HGSC. The researchers analyzed 36 LGSC patients who had NACT. The response rate in LGSC was much lower than in HGSC, although CA-125 levels dropped dramatically. The majority of patients with LGSC had stable disease (83%), four patients (11%) showed partial responses, and two patients (6%) suffered disease progression, similar to the prior study.

These results imply that LGSC may be less susceptible to NACT than HGSC, suggesting that care must be taken while contemplating this strategy for LGSC.

Adjuvant Chemotherapy

All patients diagnosed with LGSC beyond the ovary should get adjuvant treatment. Adjuvant therapy is not recommended for LGSC at stages IA and IB, as per the 2020 National Comprehensive Cancer Network (NCCN) guidelines. There is no standard accepted treatment for stage IC disease; nevertheless, observation, chemotherapy, or hormone therapy are all viable choices [44].

Although LGSC resists chemotherapy, carboplatin and paclitaxel remain the drugs of choice for adjuvant therapy. Grabowski et al. discovered a dismal response rate of LGSC to conventional treatment. After debulking surgery, 23.1% of patients with RD larger than 1 cm showed complete or partial remission, 69.2% remained stable, and 7.7% saw disease progression [45].

After the first platinum-based treatment, Gershenson et al. [46] found that 52% of 112 LGSC patients were declared clinically disease-free. In contrast, after receiving platinum-based chemotherapy, nearly 80% of patients with HGSC showed no evidence of disease [47]. These results underline that the response rate of LGSC to chemotherapy is significantly lower than that of HGSC.

Bristow et al. [40] reported an ORR of 25.0% and a stable disease rate of 25.0% using platinum-based regimens for salvage chemotherapy in LGSC. The overall response rate (ORR) in LGSC patients was 3.7%, ranging from 2.1% in platinum-resistant patients to 4.9% in platinum-sensitive patients at MD Anderson Cancer Centre. Sixty percent of patients had stable disease, with a median time to progression of 29 weeks [41].

Pegylated liposomal doxorubicin (PLD) was the most effective chemotherapeutic agent in recurrent LGSC. A complete response rate of 14.3% was observed by Rose et al. after PLD therapy. In 78.6% of patients, PLD treatment resulted in a statistically significant increase in PFS [48]. With encouraging response rates and prolonged progression-free survival, PLD may be a viable choice for patients with recurrent LGSC.

Hormonal therapy

In a study by Gershenson et al. involving 203 patients with FIGO stage II-IV LGSOC who underwent primary debulking surgery (PDS) and platinum-based chemotherapy, maintenance endocrine therapy showed a significant improvement in progression-free survival (PFS) compared to observation alone

(median, 64.9 months vs. 26.4 months, $p < 0.001$). However, there was no significant difference in overall survival (OS) between the two groups (115.7 months vs. 102.7 months, $p = 0.42$) [49].
Another study conducted by researchers from Johns Hopkins University School of Medicine, the Cleveland Clinic, and Memorial Sloan Kettering Cancer Center compared the outcomes of primary debulking surgery (PDS) (n = 26) and neoadjuvant chemotherapy followed by interval debulking surgery (n = 1) in 27 patients with FIGO stage II-IV LGSOC. These patients were subsequently treated with endocrine therapy for a median of 18 months, including letrozole (55.5% of cases), anastrozole (37.1% of cases), or tamoxifen (7.3%). The study reported a three-year progression-free survival (PFS) of 79.0% and overall survival (OS) of 92.6%. Importantly, genetic analysis of recurrent tumor samples from these patients did not reveal ESR1 mutations associated with resistance to aromatase inhibitors in estrogen receptor-positive metastatic breast cancer [50].
The NRG-GY-019 randomized phase III trial compares carboplatin and paclitaxel followed by maintenance letrozole with letrozole monotherapy in women with stages II-IV LGSOC.
MD Anderson Cancer Center analyzed 89 different hormone regimens for recurrent LGSOC based on data from 64 patients. Overall, the overall response rate (ORR) was 9.0% for the entire cohort, 2.7% for platinum-resistant cases, and 13.5% for platinum-sensitive cases. Letrozole showed responses in 6 out of 33 patients (18.2%), anastrozole showed a response in 1 out of 21 patients (4.8%), and tamoxifen showed a response in 1 out of 17 cases (5.7%). However, no responses were observed with leuprolide alone or in combination with other agents, fulvestrant, megestrol acetate, or raloxifene. The median time to progression was 7.4 months for the overall cohort, 8.9 months for patients with ER+/PR+ disease, and 6.2 months for those without these receptors [52].
In a study involving postmenopausal women with recurrent/metastatic LGSOCs and SBOTs (ER+/PR+), treatment with anastrozole resulted in a partial response in 5 cases (13.9%) and a 3-month clinical benefit (partial response + stable disease) in 23 patients (63.9%) [53]. Additionally, a phase II trial (NCT03909152) is currently recruiting patients with recurrent LGSOC, ovarian granulosa cell tumors, or endometrioid endometrial cancer that are progesterone receptor-positive (PR+) to assess the efficacy of oral progesterone antagonist onapristone.

Molecularly Targeted Agents

Bevacizumab

Bevacizumab, either alone or in combination with other chemotherapeutics, was effective in treating recurrent LGSOC in 17 patients, according to a retrospective study conducted at Memorial Sloan Kettering Cancer Centre [56]. Six (40%) of the 15 evaluable patients had a partial response, and 5 (33.3%) had stable illness for at least three months. Five-year overall survival was calculated to be 61.8%. The most common combination chemotherapy regimen with bevacizumab resulted in five partial responses and consisted of weekly paclitaxel.
Twelve patients with LGSOC were investigated by Rose et al. [57]. They all received bevacizumab either as a monotherapy (n = 11) or combined with another treatment. Only one patient achieved a partial response (8.3%), whereas three individuals (25.0%) had stable illness. In other cases, the secondary PFS far exceeded the primary PFS.
Dalton et al. [58] investigated bevacizumab in a cohort of 40 individuals with recurrent LGSOC; 5 patients received bevacizumab twice. The overall response rate (ORR) was 47.5%, with 3 CRs, 16 PRs, and 12 PDs, while 30% of patients maintained stable disease. The median survival time was 34.6 months, and the progression-free survival time was 10.2 months. Two patients developed intestinal perforations due to their treatment, while another developed an entero-cutaneous fistula.

MEK Inhibitors

Activation of the mitogen-activated protein kinase (MAPK) pathway is a hallmark of LGSC. MEK, an important downstream protein in the MAPK pathway, can be a target for inhibitor therapy [59].

Farley et al. (GOG 0239) looked into the effectiveness and safety of selumetinib (MEKi) in 52 individuals with recurrent LGSC after intensive prior treatment. The overall response rate in the study was 15%, with most responses being partial. In addition, 65 percent of patients had stable disease. 63% of patients had a PFS of more than six months, and the median PFS was 11 months. Interestingly, there was no association between KRAS or BRAF mutant status and tumor response [60].

Trametinib was tested in a randomized phase II/III trial (GOG 281) for recurrent or progressive LGSC. Trametinib was studied alongside standard agents such as letrozole, tamoxifen, PLD, paclitaxel, and topotecan. Compared to the gold standard of treatment, median PFS was considerably longer for patients treated with trametinib (13 months vs. 7.2 months; HR 0.48; p 0.0001). When comparing trametinib and other treatments, the ORR was 26.2% versus 6.2% [61].

Monk et al. studied the effects of the powerful MEK1/2 inhibitor binimetinib in patients with recurrent or chronic LGSC. Three hundred three patients were enrolled in the MILO/ENGOT-ov11 trial and randomly selected to receive either binimetinib or the investigator's preferred treatment. Median progression-free survival (PFS) with binimetinib was 9.1 months; for chemotherapy, it was 10.6 months, although the study was stopped early because there was little to no difference between the two groups concerning objective response rates, median duration of response, or median OS. KRAS mutation was associated with binimetinib responsiveness in a post hoc analysis [62].

Sixty-five patients with recurrent LGSC or SBOT were randomly assigned to receive either pimasertib + voxtalisib or pimasertib alone in a phase II research. No statistically significant differences were seen between the two therapy groups concerning partial response rate (12.1% vs. 9.4%), stable disease rate (36.4% vs. 50.0%), or 6-month progression-free survival (70.8% vs. 63.5%). The trial was stopped early because of poor response and high discontinuation rates [63].

New evidence reveals that there may be racial differences in the primary carcinogenic signaling pathway. It has been hypothesized that the KRAS/BRAF/ERK pathway is more common in Western women (16-54% mutation rate), while the PIK3CA/AKT pathway is more common in Asian women (60%). This racial difference raises the possibility that molecularly targeted medicines' efficacy is affected by race [64, 65].

By stimulating AMP-activated protein kinase (AMPK) and blocking the PI3K-mTOR pathway, the diabetes medication metformin has shown promise as an anticancer agent. In addition to its anti-mitotic and anti-angiogenic actions, metformin also decreases insulin, IGF-1, and vascular endothelial growth factor production. Metformin suppresses the growth of all LGSOC cell lines in vitro, but trametinib inhibits the growth of RAS-mutated LGSOC cell lines in particular. As a result, metformin, either on its own or in conjunction with MEK inhibitors, may prove helpful in treating LGSC [66-68].

Cyclin-Dependent Kinases Inhibitors

The utilization of targeted treatments for recurrent LGSOC is the subject of several ongoing clinical trials. Letrozole (2.5 mg orally once daily) with ribociclib (600 mg orally daily for three weeks with a one-week break) is being studied in women with recurrent LGSOC in a phase II study (NCT03673124).

Patients with stage III-IV LGSOC are being evaluated in a separate pilot phase II research (NCT03531645) that is looking at the effects of neoadjuvant fulvestrant (500 mg intramuscular on days 1 and 15 of cycle 1 and day 1 of cycles 2-4) in combination with abemaciclib (150 mg oral daily on days 1-28 of each cycle).

Targeted treatments, such as CDK4/6 and hormone receptor inhibitors, are now being tested in clinical studies to treat recurrent LGSOC. Potential biomarkers and biological mechanisms related to therapy response and outcomes are also investigated.

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Table 4: Molecularly targeted agents

Anti-angiogenic agent	Bevacizumab
MEK inhibitors	Trametinib
	Selumetinib
	Pimasertib
	Binimetinib
PI3K inhibitor	Voxtalisib
Cyclin-dependent kinase (CDK) 4/6 inhibitors	Ribociclib
	Abemaciclib

Prognostic factors

Low-grade serous ovarian cancer (LGSOC) has a better prognosis than high-grade serous ovarian cancer (HGSOC). For instance, when comparing LGSOC with HGSOC, the average overall survival (OS) was 99 months for LGSOC and 57 months for HGSOC [5]. Furthermore, Okoye et al. found that patients with LGSOC had better overall survival (OS) rates at 5 years than those with HGSOC (62.3% vs. 43.9%), but this benefit waned over time, i.e., 10 years (21.2% vs. 22.7%). [70].

In advanced LGSOC, the degree of RD after cytoreductive surgery is an important prognostic marker. Patients with RD >1 cm had considerably worse 5-year OS rates than those with complete cytoreduction. For instance, patients who achieved complete cytoreduction had a 5-year OS of 85%, whereas patients with RD> 1 cm had a 32% OS, according to research based on the AGO-metadatabase [71]. Furthermore, patients with RD> 1 cm had a 4.31-fold increased risk of recurrence and a 5.35-fold increased mortality risk compared to those with RD = 0 in another Canadian study [72].

An ancillary analysis of the GOG 182 trial looked at the predictive effect of pretreatment CA 125 levels in LGSOC and found that they did not possess significant prognostic value. Patients whose CA 125 levels normalized after two or three chemotherapy cycles had a considerably decreased probability of progression than those whose levels remained elevated or became normal after four cycles [73].

Another factor related to survival outcomes in LGSOC is the age at diagnosis. MD Anderson Cancer Centre research shows that women over 35 had better PFS and OS than younger women [74].

Smoking has been linked to poor outcomes in LGSOC, including an increased risk of death and a shorter OS. The median OS is substantially lower in current smokers than in never or ex-smokers [75]. Further, a body mass index (BMI)≥ 35 kg/m2 is related to an increased mortality risk [75].

LGSOC histopathological characteristics can also be used as a prognostic indicator. Patients whose tumors exhibited invasive patterns such as cribriform glands, micropapillae, complex papillae, or compact cell nests fared worse than those lacking these features, according to research by Ahn et al. [76]. Patients with a high composite estrogen receptor (ER) Allred score have a better prognosis. In contrast, those with a low progesterone receptor (PR) level tend to have a more rapid disease progression [72].

Compared to tumors without these mutations, better survival (OS) has been observed when KRAS or BRAF mutations are present in LGSOC [77]. A higher proliferation rate, as shown by a higher Ki-67 expression level, is related to a shorter OS. It has been found that a Ki-67 cutoff of 6.28% is associated with poor results [78]. Increased sensitivity to chemotherapy has been observed with high Ki-67 expression levels [38]. Longer therapy-free intervals are related to low Ki-67 expression levels. These prognostic indicators help in treatment decisions and patient care.

Conclusions

LGSOC is characterized by an indolent course and a more favorable clinical outcome than HGSOC. Surgery is the mainstay of treatment, emphasizing maximal primary cytoreduction due to its relatively low chemosensitivity. The treatment approach for LGSOC varies based on the disease stage.

Patients with stage IA-IB disease can be observed and regularly followed after comprehensive surgical staging. In cases of stage IC disease, treatment options may include observation, chemotherapy, or endocrine therapy.

Patients with stage II-IV disease have several treatment options. A common approach is administering six cycles of chemotherapy using carboplatin and paclitaxel, followed by endocrine therapy, often with aromatase inhibitors. Alternatively, endocrine therapy alone can be given until disease progression or unacceptable toxicity.

In the case of recurrent LGSOC, surgery, chemotherapy, and endocrine therapy are utilized. Ongoing research is focused on molecularly targeted agents, particularly MEK and CDK inhibitors, to evaluate their effectiveness in this clinical setting. Further exploration of LGSOC genomics is necessary to understand better the gene mutations involved in its development. Clinical trials investigating combinations of MEK inhibitors with hormonal agents, other targeted agents (such as BRAF inhibitors, PI3K/mTOR inhibitors, and IGF-1R-targeted therapy), or metformin is crucial for improving the prognosis of LGSOC patients. These efforts aim to refine treatment strategies and ultimately enhance outcomes for individuals affected by this type of cancer.

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