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REVIEW ARTICLE

Low-grade epithelial ovarian cancer: what a radiologist should know

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ABSTRACT

Ovarian cancer accounts for the death of over 100,000 females every year and is the most lethal gynecological malignancy. Low-grade serous ovarian carcinoma (LGSOC) and high-grade serous ovarian carcinoma (HGSOC) have been found to represent two distinct entities based on their molecular differences, clinical course, and response to chemotherapy. Currently, all ovarian cancers are staged according to the revised staging system of the International Federation of Gynecology and Obstetrics (FIGO). Imaging plays an integral role in the diagnosis, staging, and follow-up of ovarian cancers. This review will be based on the two-tier grading system of epithelial ovarian cancers, with the main emphasis on serous ovarian cancer, and the role of imaging to characterize low-grade vs high-grade tumors and monitor disease recurrence during follow-up.

EPIDEMIOLOGY

Ovarian cancer is responsible for the death of over 100,000 females annually.¹ Much of the published medical literature regards the various histologically distinct subtypes of epithelial ovarian neoplasms as one group, and almost all patients with advanced stage disease are treated with the standard therapy of debulking surgery followed by platinum-based adjuvant chemotherapy. However, recent studies have questioned this “one-size-fits-all” concept and advocated for another theory that ovarian cancer comprise of a spectrum of diverse tumors, each with characteristic histological and molecular features that determine its behavior and prognosis.^{1–3}

In 2004, Malpica and colleagues at the MD Anderson Cancer Center (MDACC) proposed a novel binary grading system for serous ovarian carcinoma, the most common histological subtype of ovarian cancer. This MDACC binary grading system was mainly based on nuclear atypia, in addition to the mitotic index. They found substantial correlation between tumor grade and survival rate. Bodurka et al² assessed the two-tier grading system in 290 patients with Stage III serous ovarian carcinoma and found that this grading system had minimal interobserver variability as it was reproducible among pathologists. Their study supported the theory that grade II and III tumors were better grouped together as they have a similar clinical

outcome and prognosis.² Low-grade serous ovarian carcinomas are a distinct group with a longer progression-free survival (PFS) and overall survival (OS) compared to high-grade serous ovarian carcinomas (45 vs 19.8 and 126.2 vs 53.8, respectively).² Since the binary grading system helps to stratify the clinical outcomes and treatment strategies of ovarian neoplasms, the two-tier MDACC grading system is currently used for grading of serous ovarian carcinoma rather than the traditional three-tier grading system.^{2,4,5} This article reviews the recent literature addressing the staging and follow-up of low-grade epithelial ovarian cancer with the main emphasis on serous ovarian cancer.

CLASSIFICATION

Embryologically, ovarian tumors are grouped into three major categories based on their origin: epithelial-stromal tumors, sex cord-stromal tumors, and germ cell tumors. Malignant epithelial tumors account for 90–98% of ovarian cancer and can be subdivided into five main groups: high-grade serous ovarian carcinoma (HGSOC) (70%), low-grade serous ovarian carcinoma (LGSOC) (<5%), clear cell carcinoma (10%), endometrioid carcinoma (EC) (10%) and mucinous carcinoma (1.5–3%).^{6,7} Other less common subtypes of malignant epithelial neoplasms that are included in the new 2014 WHO Classification of Ovarian Cancer⁸ include malignant Brenner tumors and seromucinous carcinoma.⁹

Table 1. Genomic alterations of different subtypes of low-grade epithelial ovarian cancers (LGEOCs) compared to high-grade serous ovarian carcinoma (HGSOC)^{1,5,6,11,12,16–22}

	Low-grade epithelial ovarian cancer (LGEOC)			High-grade serous ovarian carcinoma (HGSOC)
	Low-grade serous ovarian carcinoma (LGSOC)	Low-grade endometrioid carcinoma	Low-grade mucinous carcinoma	
KRAS	0 to 55% ^{6,16}	>1 to 20% ^{12,17}	43 to 57% ¹¹	0 to 0.6% ^{5,22}
BRAF	0 to 38% ^{1,16}	24% ¹⁷	0 to 23% ¹⁷	0 to 0.6% ^{5,22}
BRAF+KRAS	0 to 68% ⁶	–	–	0 to 14% ⁶
PIK3CA	40% ^{11,18}	11 to 12% ^{12,17}	14% ¹⁷	–
TP53	8.3% ⁶	0 to 25% ¹²	57% ¹⁷	73 to 96% ^{5,22}
ARID1A	–	30% ¹²	9% ¹⁷	–
PTEN/LOH	3 to 8% ¹⁸	20 to 46% ¹²	3% ¹⁷	0.6% ²²
CTNNB1	–	25–60% ¹²	5% ¹⁷	–
MSI	–	60% ¹²	–	–
HER2	–	–	18% ¹¹	0% ⁶
CK7	–	–	80% ¹	–
CK20	–	–	65% ¹	–
USP9X	11% ¹⁶	–	–	–
EIF1AX	15% ¹⁶	–	–	–
BRCA1	–	–	–	12% ²²
BRCA2	–	–	–	11% ²²
NF1	–	–	–	4% ²²

HGSOC, high-grade serous ovarian carcinoma; LGEOC, low-grade epithelial ovarian cancers ; LGSOC, low-grade serous ovarian carcinoma.

GRADING

LGSOC is considered to be a separate entity from HGSOC given the clear discrepancy with respect to their genetics, clinical behavior, and sensitivity to chemotherapy. Regarding other histological subtypes of EOC, it is now suggested that low-grade endometrioid carcinoma and mucinous carcinoma have a discrete behavior and better survival rates compared to high-grade endometrioid carcinoma and mucinous carcinoma.¹⁰ Some investigators suggest that endometriosis-associated ECs are likely low-grade tumors while ECs not associated with endometriosis tend to be high-grade tumors.¹¹ Moreover, malignant Brenner tumor is considered a low-grade tumor, while clear cell carcinoma is a high-grade tumor.⁶

PATHOLOGY AND GENOMIC ANALYSIS

Low-grade epithelial ovarian cancers (LGEOCs) are usually diagnosed at a younger age compared to high-grade epithelial ovarian cancers (HGEOCs) and are characterized by an indolent clinical course.^{12,13} Histopathologically, LGSOCs are characterized by uniform nuclei and occasionally psammoma bodies.¹ Unlike HGSOCs which are believed to develop *de novo* from tubal or ovarian surface epithelium, LGSOCs have different tumorigenesis with a characteristic continuum model in which there is progression of benign tumor to atypical proliferation to carcinoma *in situ* and finally to LGSOC.^{10,14,15}

Genomic analysis (Table 1) can identify distinct genomic signatures (gene mutation, deletion or amplification) which enable us to understand the molecular pathology of different subtypes of LGEOCs and can help to tailor treatment to these subtypes with the potential to improve prognosis and overall survival.^{1,4,5,10,11,15–22} LGSOCs show B-RAF and K-RAS genetic mutations in 0–33% and 19–55% of cases, respectively, and unlike HGSOCs are not associated with BRCA mutations.²³

LGSOCs more commonly express greater levels of estrogen and progesterone receptors than HGSOCs and it has been shown that those positive for hormone receptors expression tend to have a better prognosis compared to hormone-receptor-negative LGSOC patients.³

UTILITY OF DIAGNOSTIC IMAGING IN THE CHARACTERIZATION OF OVARIAN MASSES

The pre-operative discrimination between LGSOC and HGSOC is pivotal in guiding the management of these distinct entities and both LGSOC and HGSOC patients should receive individualized treatment. LGSOC grows slowly, spreads late in the course of the disease and is relatively chemoresistant and therefore the mainstay management is optimum surgical resection. On the contrary, HGSOC is a much more aggressive tumor that needs to be detected early before the appearance of recognizable disease for the treatment to be effective in addition to being much more chemosensitive and therefore patients usually receive

chemotherapy after surgery.^{24,25} As a result, imaging is not only a diagnostic tool but rather a major determinant that provides a roadmap in triaging these patients to tailored treatment.²⁶

Ultrasound

Ultrasound plays a crucial role in the initial assessment of an adnexal mass. Thick irregular walls, papillary projections, and solid echogenic nodules which demonstrate flow on color Doppler are considered predictors of malignancy. Ultrasound findings with the menopausal status and serum Cancer Antigen 125 (CA-125) level are used to calculate the risk of malignancy index used to stratify adnexal lesions into likely benign or malignant.^{6,27} 3D power Doppler ultrasound provides additional information about vascularity of suspicious adnexal mass and boosts the sensitivity for malignancy prediction from 88 to 99%.²⁸ The International Ovarian Tumor Analysis (IOTA) ADNEX model is a risk prediction model using nine predictors; six ultrasound variables and three clinical variables. This model can categorize adnexal tumors in females considered to require surgery into five subtypes: benign; borderline; Stage I tumors; Stage II-IV; and metastatic tumors.^{29,30} The IOTA ADNEX model can discriminate between benign and malignant adnexal lesions with a 97% sensitivity and 71% specificity.³⁰ In addition, it offers fair to excellent differentiation between early-stage and late-stage ovarian cancer, and between primary and secondary ovarian neoplasms.³⁰ However, it is estimated that 5–20% of adnexal masses evaluated by sonography will still remain unclassified or indeterminate, even if the examinations were assessed by experienced professionals.²⁹

Ultrasound has a crucial role to pre-operatively distinguish LGSOC from HGSOC.²⁴ On ultrasound, non-invasive LGSOCs usually appear as multilocular cystic lesions with papillary projections. Invasive LGSOCs are more likely to present as multilocular cysts with solid component or papillary projections and often with extensive calcification while HGSOCs are more likely to present as non-papillary solid masses with scattered areas of cystic change, hemorrhage or necrosis.^{24,31}

Elastography can be used an adjunct tool to conventional ultrasound to discriminate LGSOC from HGSOC as LGSOC appear more stiffer and less elastic compared to HGSOC. This can be explained by the rapid development of necrosis in the solid lesions of HGSOC making them less stiff. One study reported 56.0% sensitivity, 100% specificity, 100% positive predictive value, 78.0% negative predictive value, and 82.8% accuracy when elasticity score of 4 was used for the diagnosis of LGSOC.²⁵

CT

On multidetector computed tomography (MDCT), certain radiological features predominate for each subtype of ovarian cancer. The knowledge of these key imaging features might aid in the characterization of ovarian masses.³²

LGSOC can appear as a solid, mixed solid cystic, or complex primarily cystic adnexal mass. Nodal calcification, peritoneal implants, papillary projections in cystic lesion, and necrosis in solid mass are all characteristic features suggestive of malignancy

and help to differentiate LGSOCs from benign masses.^{6,33} Ascites is not commonly associated with LGSOC, unlike HGSOC which typically present with massive ascites and diffuse peritoneal metastases.^{29,33} LGSOC can calcify and should be differentiated from other adnexal lesions that tend to calcify such as broad ligament fibroids, Brenner tumors, fibromas, and dermoids.³³

Dual-energy CT can also help to differentiate benign vs malignant ovarian tumors using various parameters as iodine content, water content, and atomic number. Pang et al reported threshold value of iodine content of 10.92 (100ug/cm³) to differentiate between benign and malignant ovarian tumors with 0.90 area under receiver operating characteristic curve, 88.9% sensitivity, and 94.7% specificity.³⁴

FDG PET/CT

The role of Fluorodeoxyglucose positron emission tomography/CT (FDG PET/CT) in the initial diagnosis of ovarian cancer is limited as bowel loops can be associated with increased FDG uptake physiologically and can occasionally challenge the anatomical differentiation between bowel loops and the adnexal structures. The use of oral contrast in PET/CT may help to decrease this limitation.^{6,35} Furthermore, PET/CT can show false positive results in follicular cysts, corpus luteum cysts or some benign ovarian tumors.³⁶ One study had shown no statistically significant correlation between the degree of tumor FDG uptake and the histological grade of ovarian tumors. Thus, some LGSOCs might have high FDG uptake, whereas some HGSOCs might have low FDG uptake.³⁷

MRI

Magnetic resonance imaging (MRI) is a valuable imaging modality due to its lack of radiation exposure and the superior soft tissue characterization. MRI features of malignancy are similar to those seen on ultrasound and CT. In addition, the tumor may show early enhancement in dynamic contrast-enhanced MRI and high signal intensity in diffusion-weighted MR images.^{6,31} Moreover, MRI can be used in the assessment of indeterminate lesions seen on ultrasound or CT with sensitivity, specificity, and diagnostic accuracy of 83%, 84%, and 83%.^{6,35} The ADNEX MR scoring system has been proved reliable for evaluation of adnexal lesions with 95% sensitivity, 98% specificity, 97% accuracy, 95% positive predictive value, and 97% negative predictive value.³⁸ This scoring system enables the standardization of pre-operative imaging evaluation similar to the BI-RADS and LI-RADS. Scores higher than four should undergo immediate surgery, while scores of two or three are suggestive of a higher possibility of benign lesions, indicating either follow-up or minimally invasive surgery. One of the limitations of the ADNEX MR system is the lack of widespread use of perfusion MRI in standard clinical practice in many regions.³⁸ Another limitation is that the ADNEX MR scoring system incorporates post-processing techniques that can be complex.³⁸

STAGING

Staging is a crucial step in the management of cancer patients as it helps the physicians to assess the severity of the disease, predict the prognosis, and formulate the management plan. In 2014, the

Figure 1. Illustration of the current FIGO staging system for ovarian cancer.^{6,13,27,39} Stage I ovarian tumors are subdivided into three major subtypes. Stage IA (a) is for tumors found in one ovary (with an intact capsule) or fallopian tube. Stage IB is designated for tumors involving either both ovaries (with intact capsules) or fallopian tubes. Stage IC (b) include the findings in any of the previous two stages in addition to either intraoperative surgical spill (IC1), pre-operative capsule rupture (IC2) or malignant ascites/peritoneal washing (IC3). Stage II involves tumors in one or both ovaries or fallopian tubes extending either to the surface of the uterus or the fallopian tube, which is Stage IIA (c) or to the pelvic intraperitoneal organs below the pelvic brim such as the rectum and urinary bladder, which is Stage IIB (d). Stage III ovarian tumor (e) spread to the abdominal area through peritoneal spread. Stage IIIA1 involves spread to the retroperitoneal lymph nodes and it is further subdivided, based on the size of the metastases in the lymph nodes, into Stage IIIA1(i) if it is <10 mm and Stage IIIA1(ii) if it is >10 mm. Patients with microscopic extrapelvic peritoneal spread (above the pelvic brim) are considered Stage IIIA2, regardless of the state of retroperitoneal lymph node involvement. While females with macroscopic extrapelvic peritoneal spread are staged according to the size of these metastases into Stage IIIB if <2 cm and IIIC if >2 cm, with or without positive retroperitoneal lymph nodes. Furthermore, tumor spread to the capsule of the liver or spleen is within the scope of Stage IIIC as long as the parenchyma is spared. Stage IV includes distant metastases, and it is further subdivided into two stages. Stage IVA (f) includes patients with malignant pleural effusion and a positive cytology, while Stage IVB encompasses metastases to visceral organs such as the liver, spleen, and intestine, including parenchymal or transmural extension, in addition to extra abdominal spread as supraclavicular and inguinal lymph nodes. FIGO, International Federation of Gynecology and Obstetrics.

Figure 2. 48-year-old female with low-grade serous ovarian carcinoma that presented with a back pain of 1 year duration. (a) and (b) Axial contrast-enhanced CT images of the pelvis demonstrate a complex cystic and solid mass (dotted white arrow) within the right adnexa measuring approximately 6×6 cm, with associated calcification (black arrowhead) in the mass. Diffuse largely calcified omental thickening (white arrows) is also noted, representing peritoneal carcinomatosis. (c) and (d) Axial contrast-enhanced CT images of the pelvis, 2 months after the patient underwent optimal tumor reductive surgery and started chemotherapy, depict residual calcified peritoneal implants in the gastrohepatic ligament region (black arrowhead), anterior to the gallbladder fossa (white arrowhead), and anterior to the spleen (white arrow). (e) and (f) Axial contrast-enhanced CT image (e) and Axial fused PET/CT image (f) of the pelvis, 4 months later, show small regression in the size of the previously noted calcified peritoneal implants anterior to the gallbladder fossa (white arrowhead) and anterior to the spleen (white arrow) without evidence of F-18 FDG avidity. No evidence of new metastatic disease. PET, positron emission tomography.

Figure 3. 45-year-old female with low-grade serous ovarian carcinoma that presented with vague abdominal pain. (a), and (b), Axial contrast-enhanced CT images of the pelvis demonstrate bilateral adnexal masses; large left adnexal mass (white arrow) with focal areas of calcifications (black arrow-head) and calcified right ovarian mass (black arrow). Calcified implants (white arrowhead) are also seen along the peritoneal lining representing peritoneal carcinomatosis.

International Federation of Gynecology and Obstetrics (FIGO) proposed an update to the staging of ovarian cancer (Figure 1) based on new evidence-based data.³⁹

For Stage I cancer, one study reports mean overall survival for LGSOCs of 123 months compared to 108 months in HGSOCS with mean overall survival for metastatic disease (Stage III and IV) quoted as 84 months for LGSOCs and 52 months for HGSOCS.⁴⁰

Plaxe⁴⁰ found that the ratio of advanced to early disease was 1.9 for LGSOCs and 10.2 for HGSOCS.⁴⁰ This finding correlates with the less aggressive nature and better prognosis of LGSOCs.⁴⁰ Malpica and colleagues⁴¹ reported a significantly better prognosis in LGSOCs compared to HGSOCS, with a 5-year survival rate of 75 vs 40%.⁴¹ Similarly, in Plaxe's study, the mean survival of LGSOCs was 99 months, whereas the mean survival of HGSOCS was 57 months.⁴⁰

STAGE I

Although Stage I patients usually have a good prognosis, 30–33% of Stage IB or IC ovarian tumors with bilateral tumors present with metastases. Rupture of the capsule of ovarian carcinoma either before or during the operation is an independent unfavorable factor for disease-free survival. In patients with suspected Stage I ovarian carcinoma, it is recommended that the capsule is not ruptured during surgery or during cyst aspiration.^{6,13,42}

Ahmed et al⁴³ found that tumor grade played an important role in the prognosis of ovarian carcinoma although it was not included in the FIGO classification. They reported relapse and survival hazard ratios of Stage I LGEOCs compared to Stage I HGEOCs as 0.26 and 0.39, respectively.⁴³ Moreover, positive peritoneal washing, ascites, and ovarian rupture were also strongly linked to a worse outcome. However, these findings were not statistically significant.¹³

Dembo et al⁴⁴ reported a 5-year relapse-free rate as high as 98% for Stage I LGEOCs with no ascites or adhesions.⁴⁴ Therefore, the majority of these patients did not receive post-operative adjuvant therapy. Another important finding noticed by this group was the interaction between tumor grade and cell histology. The prognostic effect of tumor grade was the most significant in serous ovarian cancers, followed by endometrioid carcinoma and clear cell carcinoma, and was the least significant in mucinous carcinoma.⁴⁴ Other factors such as tumor suppressor genes, oncogenes, DNA ploidy, and serum CA-125 levels might have an impact on the survival of LGEOC patients but need further evaluation.^{42,44}

STAGE II

It is debatable whether the extension of ovarian tumor to the peritoneum should be upstaged to Stage III or it is justified to separate pelvic peritoneum anatomically from the extrapelvic peritoneum. The advocates of the latter view, base their opinion on the survival differences between Stage II and Stage III tumors. According to the current FIGO staging, the involvement of the sigmoid colon below the pelvic brim is considered Stage II, whereas infiltration into the bowel upstages the tumor to Stage IVB.^{6,13,27,39}

STAGE III AND IV

Patients who only have retroperitoneal adenopathy have a better outcome than those with abdominal peritoneal extension. Therefore, the involvement of retroperitoneal lymph nodes is considered a separate stage which is Stage IIIA1.⁶

Ayhan et al⁴⁵ found out that LGEOCs were less common to have nodal spread compared to HGEOCs.⁴⁵ The significant factor in the prognosis of EOCs is the presence of lymphatic metastases rather than the number of metastatic lymph nodes as their number was found to be non-significant in terms of the overall or disease-free survival.^{6,46}

THE ROLE OF IMAGING MODALITIES IN STAGING

Imaging plays a paramount role for treatment stratification of ovarian cancer as it helps in evaluating the tumor stage pre-operatively and predicting its respectability.²⁶ This is particularly important in LGSOC as these tumors are generally chemoresistant and optimal cytoreduction is the current best management option.^{10,24}

MDCT (Figures 2–4) is the modality of choice for ovarian cancer staging as it provides a quick information about the primary tumor, lymphadenopathy and peritoneal implants with an overall diagnostic accuracy of 89%.^{6,31} The use of oral contrast helps to differentiate peritoneal implants from the bowel and to detect bowel invasion as well. However, CT has a low sensitivity in the detection of peritoneal deposits less than 1 cm.³⁶ Noncontrast CT may help identify calcified implants. DECT with iodinated oral contrast may be helpful such that the virtual non-contrast portion of the study may help identify calcified implants.⁴⁷

MRI (Figures 5 and 6) has a staging accuracy similar to CT and PET/CT.^{29,48} Conversely, Low et al⁴⁹ suggested the superiority

Figure 4. 65-year-old female with recurrent LGSOC. The recurrent disease was treated with chemotherapy, hormonal therapy, and recently radiotherapy. (a) and (b) Follow-up axial contrast-enhanced CT images of the pelvis shows metastatic calcified peritoneal implants (black arrowheads). There is also a large mass of high attenuation (black arrow) within the pelvis. (c) and (d) Follow-up axial contrast-enhanced CT images of the pelvis, after 6 months, demonstrate a reduction in the size of the previously noted calcified implants (black arrowheads) in the pelvis. Implant identified anterior to the rectum (black arrowhead) is also significantly smaller in comparison to the prior study. (e) and (f) Follow-up axial T_2 weighted (e) and sagittal T_2 weighted (f) MR images of the pelvis, after 2 years, show disease progression with the metastatic implant (black arrows) in the left mesorectum appearing larger in size. LGSOC, low-grade serous ovarian carcinoma.

Figure 5. 34-year-old female with low-grade mucinous carcinoma of the ovary that presented with pelvic pressure. (a) and (b) Axial T_1 weighted Fat sat (a) and axial T_2 weighted (b) pelvic MR images show a complex multicystic, multiseptated right ovarian mass (white arrows) measuring approximately 14×9 cm. The mass is displacing surrounding structures and depicts varying regions of signal intensity consisting of hemorrhage components (black asterisks). The patient underwent optimal cytoreductive surgery and completed four cycles of chemotherapy. She had regular follow-up with no evidence of the disease. (c) and (d) Axial contrast-enhanced CT images of the pelvis obtained nearly 5 years later when the patient presented to the ER with acute abdominal pain. The images show stranding and nodularity within the right lower quadrant adjacent to the cecum (black arrowhead). Some haziness is also noted within the transverse mesocolon (white arrowhead). The findings are suggestive of a recurrent disease.

of MRI to CT for the selection of candidates for cytoreductive surgery and also in the prediction of the tumor resectability as MRI has a sensitivity, specificity, and accuracy for resectability prediction of 95%, 70%, and 88% compared with 55%, 86%, and 63%, for CT⁴⁹. However, the limited number of patients (five patients with ovarian cancer) is one of the shortcomings of this study.⁴⁹

PET/CT (Figure 2) can help in the detection of any recurrent or residual disease in addition to distant metastases and also in the selection of the patient for the most appropriate therapy.^{6,31,36} Castelluccia *et al*⁵⁰ reported a better diagnostic accuracy of PDG PET/CT compared to CT (69% *vs* 53%, respectively) in the staging of ovarian cancer, particularly in stage IV disease⁵⁰. Ultrasound cannot accurately stage ovarian cancer due to its low sensitivity in the detection of peritoneal metastases in addition to being operator dependent.

Figure 6. 34-year-old female with low-grade endometrioid adenocarcinoma involving the left ovary. (a) and (b) Pre-treatment axial T_1 weighted fat sat (a) and axial T_2 weighted (b) MR images of the pelvis shows a large mass (white arrows) within the left ovary, which has solid and cystic components and has some internal hemorrhage (white arrowhead). The patient underwent bilateral salpingo-oophorectomy and omentectomy. (b) Follow-up axial T_2 weighted MR image of the pelvis shows the uterus (U) with no pelvic mass lesions identified.

TREATMENT

Aggressive surgical debulking, including total abdominal hysterectomy, salpingo-oophorectomy, lymphadenectomy, and resection of all visible macroscopic disease, is the mainstay intervention for LGSOCs.¹⁰ In selected young patients with unilateral Stage I LGSOC, fertility-sparing surgery might be feasible.⁵¹ Most retrospective studies suggest that LGSOCs are less sensitive to conventional platinum-based chemotherapy with a response rate of 23.1–25%.^{10,52,53} Nevertheless, hormonal therapy such as follicle-stimulating hormone receptor (FSHR) and gonadotropin-releasing hormone receptor (GnRHR) targeted agents in addition to targeted molecular therapies as bevacizumab (anti-angiogenesis) and selumetinib (MEK inhibitor) are novel therapeutic approaches that might represent promising alternatives in the treatment of these tumors.^{3,10}

Recurrence and follow-up

Until now, the follow-up strategies for LGSOCs are the same as those used for ovarian cancer in general, including measuring of serum CA-125 levels, single energy and dual energy CT and FDG PET/CT (Figures 2, 4 and 5). Surveillance of females with ovarian tumors usually starts with a clinical evaluation. Serum CA-125 measurement is performed every 3 months for 2 years, then every 6 months until the fifth year or the recurrence.^{15,54} In one study, LGSOC patients who underwent complete cytoreduction had 63% 5-year PFS and 85% 5-year OS *vs* 30%, and 61%,

respectively, in HGSOC.⁵⁵ However, in residual disease ≥ 1 cm, there was no reported difference between LGSOC and HGSOC.⁵⁵

The Gynecological Cancer Intergroup defined progression or recurrence of ovarian tumors based on serum CA-125 levels on the basis of progressive serial elevation of serum CA-125. This rising level must be confirmed with two separate measurements with a 1-week interval at least. However, the efficacy of measuring CA-125 level during the follow-up phase is questionable as some studies failed to show a significant survival difference of early CA-125-directed retreatment. Therefore, many clinicians prefer to delay the retreatment till the appearance of symptoms when the CA-125 level is rising as long as the patient is stable and the tumor volume is small on CT.^{54,56}

Normal CA-125 level during the follow-up of LGSOC cannot exclude recurrence as CA-125 has low sensitivity (68%) in the detection of recurrent disease.⁵⁷ In Takeuchi et al⁵⁷ study, 32% of patients with recurrent disease had normal CA-125 levels.⁵⁷ Another study showed a 50% reduction of CA-125 levels in half of the patients with LGSOCs receiving chemotherapy in spite of showing minimal change radiologically.⁵³ However, this controversy might be attributed to the calcification or fibrosis commonly seen with LGSOCs.⁵³

Although the superior role of MRI to CT in the detection of recurrent tumors is debatable, MRI can be used for patients with increasing serum CA-125 with negative finding on abdominopelvic CT. In such cases, MRI has a sensitivity, specificity, and accuracy of 84%, 100%, and 84%, respectively.⁶ Dynamic contrast-enhanced MRI can be used for assessing treatment response during the follow-up of cases using antiangiogenic drugs.³¹

PET/CT scans may reveal sites of disease not visible on CT scans. The principal role of this imaging modality is to help the selection of patients for secondary debulking surgery by excluding additional sites of disease not seen on CT scans and not amenable to cytoreduction. In one study, PET/CT changed the treatment plan in 30% of patients with recurrent LGSOCs with a reported sensitivity, specificity, and accuracy in recurrence detection of 94%, 100%, and 97%, respectively suggesting that PET/CT may be a valuable modality in assessing recurrence in LGSOC.⁵⁷ These numbers are significantly higher than those in CT and CA-125 levels.^{57,58} Furthermore, the use of maximum standardized uptake value (SUVmax) and total lesion glycolysis (TLG) on PET/CT may help determine the aggressiveness of the tumor and predict the outcome. Recurrent LGSOC patients with TLG value more than 67.7 g are associated with poor prognosis.^{54,57}

PET/CT can be associated with false negative results in recurrent LGSOCs such as in mucinous carcinoma. Recurrent disease that is < 5 mm in size and centrally necrotic tumor may not show FDG uptake.^{59–61} Furthermore, it may yield false positive results in inflammatory and infectious processes during follow-up.⁶¹

Tumor calcification in metastatic LGSOCs is common with reported incidence on CT of 8–16%.⁶² Although post-therapy

calcification is considered a positive prognostic sign indicating a response to treatment in certain malignancies such as lymphoma, colorectal carcinoma, and glioblastoma, Ganesan and colleagues reported that progression of LGSOCs may be linked to progressive calcification after therapy in 77% of patients.⁶² Therefore, it is not recommended to use post-therapy calcification, detected on CT in peritoneal metastases, as an indicator of treatment response for LGSOCs.⁶²

For recurrent LGSOCs, secondary cytoreductive surgery (SCRS) should be considered based on the time to recurrence, disease localization, number of metastases, and patient general condition.⁵² SCRS without macroscopic residual disease is associated with significant better PFS and OS of 60.3 months and 167.5 months, respectively, compared to 10.7 months and 88.9 months, respectively, in patients with macroscopic residual disease after SCRS.⁵²

LGSOCs have poor response to conventional chemotherapy; as a result, some studies have suggested the use of bevacizumab in conjunction with platinum-based and non-platinum-based chemotherapy.⁶³ Schmeler and colleagues⁶⁴ evaluated 17 patients with recurrent LGSOCs, treated with a combination of bevacizumab with chemotherapy and/or hormonal therapy. Of the 13 patients evaluable for response, five patients (39%) had a partial response and three patients (23%) had stable disease with a clinical benefit rate of 62%.⁶⁴ Hormonal therapy can be an alternative for chemotherapy in recurrent LGSOCs.⁵² Gershenson et al⁶⁵ studied the efficacy of hormonal therapy in recurrent LGSOCs and reported PFS of at least 6 months in 61% of patients with a better prognosis for ER- and PR-positive tumors.⁶⁵ Moreover, the use of selective inhibitors of the mitogen-activated protein kinase (MAPK) signaling pathway as BRAF and MEK inhibitors has been associated with promising results in some patients.⁶⁶ Further prospective studies are warranted to determine the optimal use of hormonal and targeted therapies for recurrent LGSOCs.⁴

CONCLUSION

In summary, low-grade epithelial ovarian cancers represent a subtype of ovarian cancer with clinical behavior and molecular signature distinct from high-grade epithelial ovarian cancers. Staging of low-grade epithelial ovarian cancers is a cornerstone of the management as it helps to predict the disease outcome and plan the most adequate treatment. The appearance of calcification in LGSOC may be a sign of progression rather than response. The knowledge of pathology, tumor biology, and tumor markers will help a radiologist to optimally interpret cross-sectional images. Lastly, further prospective clinical trials are needed for a profound understanding of this distinctive group of ovarian tumors and to develop tailored treatment for a better outcome for females with low-grade epithelial ovarian cancers.

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