

Advanced Low grade serous ovarian cancer

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Hierarchy of aggression of ovarian tumors

BIOLOGY

1. Benign

2. Serous borderline tumor/Atypical proliferative Serous tumor

(Mild to moderate cytological atypia , no stromal invasion, detached cell clusters)

3. Micropapillary variant Serous borderline tumor/ Noninvasive implants

4. Low grade Serous carcinoma (new WHO: invasive implants is LGCS)

5. High grade serous ovarian cancer

Types of ovarian serous carcinomas

- **Low grade**

mild to moderate nuclear atypia, uniform nuclei

mitoses 1-2/10hpf,

no necrosis or multinucleate tumour cells

SBOT with invasive implant is LGCS (new WHO)

- **High grade**

marked nuclear atypia,

mitoses 12/10hpf

Presence of necrosis and multinucleate tumour cells

Molecular signatures and markers

	LGCS	SBOT	HGCS
Molecular abnormalities	20-40%-KRAS, 5%-BRAF	60%-KRAS, BRAF	80%-TP53 mutated, BRCA1, BRCA2
IHC	WT1, PAX8, ER /PR positive	WT1, PAX8, ER/PR positive	WT1, PAX8, Mostly ER, PR negative P53 mutated
Central mechanism	MAP kinase path activation	MAP kinase path activation	P53 mutation, chromosomal instability

Clinical scenario

	Low grade Serous	Borderline Serous	High grade Serous
Median Age at presentation	4 th decade	3 rd -4 th decade	6 th decade
Symptom	Similar to HGSC, lesser volume ascites General condition very good	Pelvic pressure and mass	Ascites, metastatic disease
Precursor lesion ???	Serous borderline tumor (60%)/ de novo in ovarian cortex	Cystadenoma/ de novo in ovarian cortex	Tubal intraepithelial Carcinoma
Stage at presentation	90 % stage III/IV	75% stage I	90% stage III/IV
ca125	Raised in >80%	Raised in 25 %	Raised in >90%
CT/USG Stage versus stage	No distinguishing features	No distinguishing features	No distinguishing features

Determinants of Survival in ovarian cancer

- Stage of disease
- Grade of tumor (biology)

Based primarily of nuclear atypia (< 3 fold variation)

Secondary criteria – mitotic index (<12 MF/10HPF)

- Residual disease at the end of treatment

	Low grade Serous	Borderline Serous	High grade Serous
Median OS	85 months	97% 10 yr survival	36months
Recurrence	Recur as LGSC	80% recur as borderline/LGSC	recur as HGSC

Management Options & efficacy

	Low grade Serous	Borderline	High grade Serous
Surgery	Mainstay ? Fertility preservation	Mainstay- fertility/hormone preservation	mainstay
Traditional Chemo	10- 20% response, largely not responsive	No role	90%
Hormonal therapy ? Maintenance	? Prolonging dfs/os	No role	Metronomic
Recurrence rate	30-45%	15%	85%
Median time to recur	2-3yr	3-8yr	1-2yr

Treatment option for Recurrent disease

- Secondary cytoreduction
- Traditional chemotherapy
 - 4% response rate.
- Hormonal therapy
 - 10 % response rate
 - Aromatase inhibitor
 - Tamoxifene
 - Fluvestrant
 - Leuprolide
- Targetted agents :
 - MEK inhibitors (Selumetinib phase2 study: 20% response)
- ? Bevacizumab