

The continuum of serous tumors of low malignant potential and low-grade serous carcinomas of the ovary

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Abstract. The role of serous tumors of low malignant potential (LMP) in the development of invasive epithelial cancer of the ovary is debatable. This review summarizes the current clinical, genetic, and genomic evidence for the existence of a continuum comprising both LMP serous tumors and low-grade serous ovarian carcinomas.

Keywords: K-Ras, B-Raf, Ki-67, p53, low malignant potential, low-grade serous ovarian carcinoma, genomics

1. Introduction

Histopathologically, epithelial ovarian carcinoma can be classified into serous, mucinous, endometrioid, clear cell, and transitional cell types [65]. Serous ovarian carcinoma is the major histological subtype of all ovarian cancers, and its prognosis is very dismal if detected at a late stage. In 1929, Howard Taylor described a group of women of reproductive age who had large ovarian tumors whose course was rather indolent [76]. In the early 1970s, the Federation of Gynecologists and Obstetricians defined these “semi-malignant” tumors as borderline ovarian tumors (BOTs) [1]. Later on, at the 2003 World Health Organization workshop, the term low malignant potential (LMP) became an accepted synonym for BOTs [6]. In a recent review of the clinical outcome of 276 patients with LMP tumors, approximately 7% of the patients had recurrent disease that was classified as low-grade serous carcinoma [43]. Thus, whether an LMP tumor progresses to invasive

ovarian tumor or recurs as a de novo primary low-grade tumor is still a debatable point.

In 2004, a two-tier system for classifying invasive serous ovarian tumors into low-grade and high-grade serous ovarian carcinoma (OSC) was proposed and is gaining increasing acceptance [45]. More recently, a clinical review of 112 patients with late-stage low-grade serous ovarian tumors at our institution identified two characteristics of affected patients: young age at diagnosis and prolonged overall survival [25]. Thus, from a clinical standpoint and in terms of age at diagnosis, histopathology, and clinical outcome, low-grade OSC may belong to a continuum that includes LMP serous tumors. Recent advances in the molecular and genomic analysis of ovarian tumors also suggest that low-grade and high-grade OSCs develop along two different pathways and, and more important for this review, that low-grade OSCs and LMP tumors may lie along the same developmental continuum. In this review, we summarize the current evidence in support of the particular hypothesis that low-grade OSCs and LMP ovarian tumors do indeed lie on a continuum.

2. Clinical and pathological evidence

A mixture of low-grade and LMP tumor elements are commonly observed in low-grade OSCs (Fig. 1).

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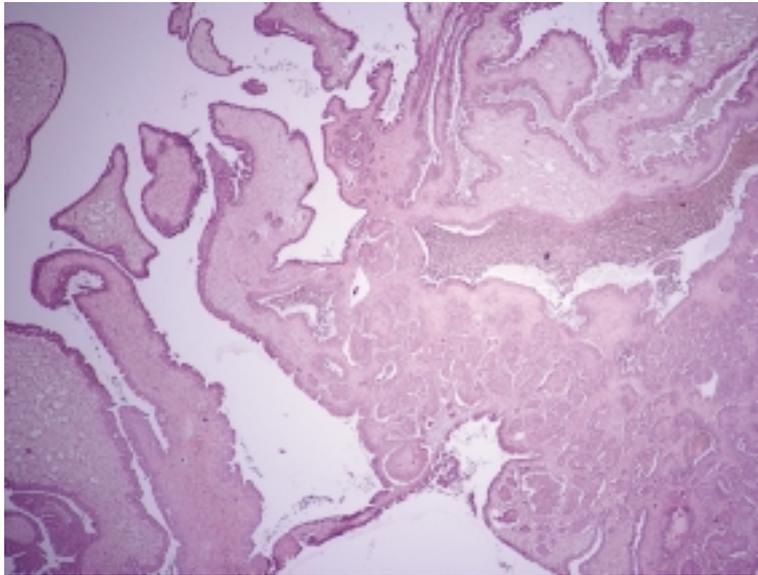


Fig. 1. Ovarian tumor showing low-grade serous carcinoma arising in the background of a serous tumor of low malignant potential (Hematoxylin and eosin; original magnification X40.).

However, it is extremely rare to observe LMP tumor elements in association with a high-grade OSC.

2.1. Clinical observations regarding the relationship between serous tumors of low malignant potential and low-grade serous ovarian carcinomas

A number of clinical observations strongly support the hypothesis that LMP serous tumors and low-grade OSCs exist on a continuum and are distinct from the more common high-grade OSCs. The story of this relationship continues to unfold in the published literature and in ongoing studies at our institution.

For decades now, it has been recognized that, despite the absence of demonstrable stromal invasion (except for microinvasion) in primary LMP serous tumors, approximately 30% of these tumors contain invasive or noninvasive extraovarian peritoneal implants or both [6, 22–24, 48, 52, 62]. These peritoneal implants have been classified as either noninvasive or invasive on the basis of very specific histopathologic criteria, and those of the invasive type have been found to closely resemble low-grade OSC. Moreover, there are molecular studies, albeit based on a relatively small number of cases, that suggest that these peritoneal implants may in fact be independent primary tumors from the primary ovarian tumor [28, 44]. However, the true nature of the relationship between peritoneal implants and primary LMP serous tumors remains unclear.

What is clear is that the type of peritoneal implant (i.e., invasive versus noninvasive) is related to the lifetime risk of relapse in women with LMP serous tumors. As we discovered in a recent literature review, the risk of relapse is markedly lower in women with noninvasive peritoneal implants than in those with invasive ones (at least 20% versus at least 35%); likewise, the related mortality (at least 5% versus at least 25%) [21]. Although the M.D. Anderson experience is not population-based because of referral bias, our most recent review of 80 patients with noninvasive peritoneal implants and at least 5 years of follow-up has nevertheless revealed a relapse rate of 44% [68]. This suggests that the longer ovarian cancer patients with noninvasive peritoneal implants are followed up, the higher the relapse rate. It is also clear that there are two different types of LMP serous tumor – the typical and the micropapillary [9, 14, 17, 43, 64, 73]. Although both types may be associated with relapse, the micropapillary type is more frequently associated with invasive peritoneal implants and relapse.

A second clinical observation that appears to link serous LMP tumors with low-grade OSCs is the pattern of relapse. In approximately 70–80% of patients who experience a relapse after receiving an initial diagnosis of LMP serous tumor, the relapsing tumor is low-grade OSC [12, 43, 68]. Whether such so-called “recurrences” are related to the primary ovarian tumor or represent independent primary tumors remains unknown. At least one study suggests that they may not be related to the

primary ovarian tumor at all [57]. Nor has their relationship to peritoneal implants been adequately studied.

Yet another piece of clinical evidence for the association between LMP serous and low-grade tumor cell types is their coexistence in ovarian tumors that predominantly exhibit the characteristics of a low-grade OSC. In describing their two-tier grading system for OSC, Malpica et al. observed that 60% of low-grade OSCs also contained an associated area of LMP serous tumor, whereas only 2% of high-grade OSCs (1/50) did so [45]. Malpica et al. also noted that when the LMP serous tumor type was found in association with a low-grade OSC, it involved 10% to 99% of the ovarian tumor, and that in 28 of 30 such cases (93%), the LMP serous tumor was of the micropapillary type.

Finally, in an as yet unpublished study in which we compared cases of newly diagnosed metastatic low-grade OSCs with cases of LMP serous tumors that subsequently recurred as low-grade OSCs, we observed that the age distributions and survival curves were very similar. This information suggests that (a) there is an association between these two entities and (b) at least in some cases, a newly diagnosed low-grade OSC may represent a previous, clinically undetected LMP serous tumor. Clearly, further studies are warranted to elucidate the true association.

2.2. *Clinical observations suggesting that low-grade serous ovarian carcinomas lack chemosensitivity*

There is also an unfolding story suggesting that low-grade OSCs may not be as responsive to conventional cytotoxic chemotherapeutic agents as ovarian cancers in general (ie, high-grade OSCs). Potential measures of chemosensitivity include response to primary chemotherapy, percentage of patients who are clinically disease-free at completion of primary chemotherapy, negative second-look rate, response to neoadjuvant chemotherapy, response to salvage chemotherapy, and survival.

In a study of 112 patients with newly diagnosed stage II-IV low-grade OSCs at our institution, we evaluated the response to primary surgery and chemotherapy [25]. Although only 10 patients had measurable disease after therapy, their overall response was 80% (4 complete responses, 4 partial responses, and 2 cases of progressive disease). This response rate is consistent with those reported in phase III trials involving ovarian cancers in general (i.e., 40–75%) [49,53,55]. However, because most patients with low-grade OSCs

appear to have small-volume residual disease after primary surgery, the numbers in the M. D. Anderson study are too small to allow any definitive judgment to be made. Further study will be necessary to resolve this question. We are currently analyzing the response to salvage chemotherapy and hormonal therapies in patients with recurrent low-grade OSCs, and our findings should provide a much broader and clearer assessment of the relative chemosensitivity of these tumors.

In that same study, we also determined that only 56 of 107 evaluable patients (52%) were clinically disease-free after primary treatment [25]. This percentage appears to be lower than those reported in phase III trials involving ovarian cancers in general (ie, 70–80%) [2, 50]. This provides indirect evidence that low-grade OSCs may be less responsive to standard platinum-based chemotherapy administered as frontline treatment.

Although second-look surgery is no longer routinely included in the primary treatment of patients with newly diagnosed advanced ovarian cancer at our institution, we do have historical data with which to compare negative second-look rates in patients with low-grade OSCs versus ovarian cancers in general. In our review of 112 patients with stage II–IV low-grade OSCs cited above, we found that 39 patients underwent second-look surgery; however, the negative second-look rate was only 5% (2/39) and the microscopically positive second-look rate, 33% (13/39) [25]. This compares unfavorably with negative second-look rates of 20–53% in phase III trials [2,47,50,59]. Together, these data appear to be consistent with the observation that a significant proportion of patients with low-grade OSCs still have persistent disease at the completion of primary surgery.

As for evaluation of chemosensitivity in the setting of neoadjuvant chemotherapy setting, our preliminary analysis of patients with low-grade OSCs who received neoadjuvant platinum-based chemotherapy has revealed a response rate significantly lower than that observed by others in previous ovarian cancer cohorts.

2.3. *Therapeutic options for patients with serous tumors of low malignant potential and low-grade serous ovarian carcinomas*

For patients with stage I LMP serous tumors, the standard treatment is surgery alone since the cure rate for such tumors approaches 100% [4]. In older women who have completed childbearing, hysterectomy and bilateral salpingo-oophorectomy are recommend-

ed. However, for women who have not completed childbearing, fertility-sparing surgery – either unilateral salpingo-oophorectomy or ovarian cystectomy – is an option. While comprehensive surgical staging of apparent early-stage cases is recommended by our group, it remains somewhat controversial. Clearly, most patients with these tumors are not operated on by gynecologic oncologists and do not undergo surgical staging [42]. The argument against surgical staging is that most patients with LMP serous tumors have an excellent prognosis and that, even if peritoneal implants are documented, postoperative therapy is ineffective (see below). Advocates of surgical staging argue that (1) the information gained will further elucidate the biological behavior of these tumors, (2) precise staging information will allow patients and their families to better understand the prognosis because the risk of relapse and death is clearly higher in patients with peritoneal implants, and (3) in some cases in which frozen-section examination suggests a LMP serous tumor, the final diagnosis will indicate invasive ovarian cancer. In addition, once an effective therapy for advanced LMP serous tumors has been discovered, there will be even more justification for comprehensive surgical staging. There is also no consensus about the degree of surgical staging. While some advocate the use of procedures identical to those used to stage apparent early-stage invasive ovarian cancers, others recommend cytologic washings, omentectomy, and peritoneal biopsies, but without retroperitoneal lymphadenectomy [61].

For patients referred to gynecologic oncologists with a diagnosis of LMP serous tumor after incomplete or, more commonly, no surgical staging, a frequent clinical dilemma is whether to recommend restaging surgery – either laparoscopic or open [32,74,79]. At least one study has shown no benefit of restaging surgery in reducing relapse rates [18]. Our current recommendation is to provide such patients with comprehensive counseling that presents the potential benefits and disadvantages of restaging surgery versus surveillance.

Factors that appear to influence outcome – either progression-free survival or overall survival – in patients with LMP serous tumors include FIGO stage [8, 41], presence and type of peritoneal implants [5,21,22, 43], patient age at diagnosis [21,22], presence of residual disease after primary surgery [5,8,41], and presence of the micropapillary tumor type [9,14,17,43]. Whether microinvasion in the primary ovarian tumor is prognostic remains controversial. To date, there are still no molecular or genomic biomarkers available that can be used to accurately segregate patients with LMP serous tumors into low- and high-risk groups.

Considerable controversy surrounds the role of postoperative therapy for patients with stage II–IV LMP serous tumors. In our institution's series of retrospective studies, we have been unable to demonstrate any benefit of postoperative therapy for patients with either noninvasive or invasive peritoneal implants [22, 23]. Other groups have also been unable to show a benefit [11,20,37,41,54]. Nevertheless, it is still possible that some benefit of postoperative therapy may be found since most published studies have been retrospective, have involved relatively small numbers of patients, and have varied in terms of follow-up times. Moreover, we do believe that peritoneal implants may be relatively chemoresistant; hence, the search continues for novel, active agents against them. Indeed, there are in the literature hints of chemotherapeutic activity. In the original M.D. Anderson report on LMP serous tumors associated with peritoneal implants, comparison of surgical findings at completion of primary surgery and second-look surgery findings revealed that some tumor implants appeared to respond to chemotherapy (both platinum-based and non-platinum-based) [22]. Similar observations were subsequently reported by the Memorial Sloan-Kettering group in patients given platinum-based chemotherapy [3].

The current practice at our institution is to treat patients who have noninvasive peritoneal implants with surgery alone. On the other hand, despite the lack of a demonstrable benefit, postoperative chemotherapy consisting of a taxane and platinum combination is recommended for patients who have invasive peritoneal implants since their prognosis is worse. However, the lack of proven benefit for this approach is a critical component of counseling for such patients. Regardless of the treatment strategy, all patients are also counselled about prognosis and the risk of relapse.

Patients with stage II–IV low-grade OSCs are currently treated in exactly the same way as patients with high-grade cancers – i.e., with a postoperative taxane-platinum chemotherapy – simply because there is at the moment no better therapy available. Likewise, for patients with recurrent low-grade OSCs – whether resulting from a LMP serous tumor at relapse or a de novo low-grade OSC at relapse – the recommended treatments are no different from those for patients with high-grade tumors. However, as noted above, there is mounting evidence that low-grade OSCs may be relatively more chemoresistant than their high-grade serous counterparts. Nevertheless, patients with recurrent low-grade OSCs tend to have prolonged survival [25].

Clearly, there is emerging evidence that LMP serous tumors and low-grade OSCs follow a distinctly different pathogenetic pathway than do high-grade OSCs, and this certainly warrants the continued search for novel therapies for low-grade OSCs. Therefore, we believe that, in future clinical trial designs, it will be important to segregate patients with low-grade OSCs from those with ovarian tumors of other types. Through the Gynecologic Oncology Group, the Rare Tumor Working Group is developing a clinical trial for patients with recurrent low-grade OSCs. Among the candidate drugs for early study – drugs that have been identified by analyzing the genes and pathways involved in the pathogenesis of these tumors – are the Ras-Raf-MEK inhibitors, such as sorafenib. In addition, according to anecdotal reports, a variety of hormonal agents – i.e., tamoxifen, leuprolide acetate, and letrozole – have shown activity against low-grade OSCs and so may be targets of future research interest.

3. Molecular evidence

Besides the clinical observations described above, several recent molecular and genomic data also strongly support the hypothesis that LMP serous tumors and low-grade OSCs exist on a continuum and are distinct from the more common high-grade OSCs.

3.1. Mutational analysis

The accumulation of mutations in genes that are involved in cell proliferation, differentiation, DNA repair, and cell death is frequently seen in various neoplasms. In ovarian tumors, these mutations include those of the *BRAF*, *KRAS*, *p53*, and *CHEK2* genes [10,39,67,71,72,75]. The most common of these mutations occur in the oncogenic forms of *BRAF* and *KRAS*, a serine-threonine kinase and a GTPase, respectively. Both of these genes are involved in the RAS-RAF-mitogen/extracellular signal-regulated kinase (MEK), extracellular signal-regulated kinase (ERK), and mitogen-activated protein kinase (MAPK) pathway that regulates cell division [40].

Several studies have reported on the frequency of *KRAS* and *BRAF* mutation in LMP, low-grade, and high-grade ovarian tumors (Table 1). Both *KRAS* and *BRAF* mutations are detected in approximately a third of BOTs (i.e., LMP serous tumors) [15,29,69] and a third of low-grade OSCs [70,71]. However, *KRAS* and *BRAF* mutations never occur in the same tumor,

which suggests that they are mutually exclusive. On the other hand, in high-grade OSCs, *KRAS* mutations occur rarely (Table 1) and *BRAF* mutations not at all [47,67]. Moreover, *KRAS* and *BRAF* mutations occur with similar frequency in both LMP serous tumors and low-grade OSCs and have been identified in microdissected areas of benign serous cystadenoma adjacent to serous borderline neoplasms, which suggests that these mutations are early events in the development of low-grade OSCs [70] and that LMP serous tumors and low-grade OSCs do lie on a continuum. Finally, the downstream target of the *KRAS-BRAF* pathway, MAPK, is expressed more often in low-grade than in high-grade OSCs [33].

p53 mutation occurs in more than 50% of human cancers [30], and ovarian cancers are no exception. Mutations in the human *TP53* gene occur frequently in high-grade OSCs but rarely in low-grade OSCs or LMP ovarian tumors [56,75]. In at least one study, *p53* immunoreactivity was found to be enhanced in inclusion cysts adjacent to high-grade OSCs [34]. Thus, as others have proposed, it is likely that high-grade OSCs arise de novo from the ovarian epithelium or the epithelium of cortical inclusion cysts [19,66]. Moreover, the infrequent mutation of *TP53* in LMP serous tumors or low-grade OSCs suggests that these two types of neoplasm develop along a different pathway than do high-grade OSCs.

CHEK2, a protein kinase, is involved in cell-cycle arrest and is activated in response to DNA damage [46]. Polish investigators have identified two types of *CHEK2* mutation: the first involving two founder alleles (1100delC and IVS2 + 1G > A) whose expression results in a truncated *CHEK2* protein, and the second involving a missense substitution that leads to the replacement of a threonine with an isoleucine (I157T) [13]. In their studies, the Polish investigators were able to associate *CHEK2* variants with various types of ovarian tumors by genotyping the *CHEK2* alleles in ovarian tumor samples from 1108 Polish women and control samples from 4000 normal subjects. This genotyping revealed a strong positive association between the *CHEK2* I157T missense variant and ovarian cystadenomas, BOTs, and low-grade invasive OSCs. However, no association was found between this missense variant and high-grade OSCs. Together, these data indicate that *CHEK2* variants may predispose to the development of LMP serous tumors and low-grade OSCs but not high-grade OSCs [75]. In summary, low-grade and high-grade OSCs exhibit different types of gene mutations, whereas LMP serous tumors and low-

Table 1
Mutation analysis of serous ovarian tumors

<i>KRAS</i> (% bearing mutation)			<i>BRAF</i> (% bearing mutation)			Reference
LMP ^a	LGOSC	HGOSC	LMP	LGOSC	HGOSC	
30% (6/20)		4% (1/23)				Teneriello et al., 1993 [77]
33% (17/51)	36% ^b (8/22)	0% (0/69)	28% (14/51)	33% (7/22)	0% (0/67)	Singer et al., 2003 [71]
29% (26/89)	0% ^b (0/1)	12% (6/49)	37% (33/89)	0% (0/1)	0% (0/49)	Sieben et al., 2004 [67]
22% (4/18)		2.5% (1/39)	31% (5/16)		0% (0/38)	Mayr et al., 2006 [47]

^aLMP = serous tumor of low malignant potential; LGOSC = low-grade serous ovarian carcinoma; HGOSC = high-grade serous ovarian carcinoma.

^bAll of the LGOSCs analyzed were invasive micropapillary serous carcinomas.

grade OSCs exhibit gene mutations of similar type and frequency. Together, these genetic data support the hypothesis of a continuum between LMP serous tumors and low-grade OSCs.

3.2. Allelic imbalance analysis

A number of studies have evaluated the allelic imbalances in ovarian tumors and revealed an increase in the frequency of genetic abnormalities with increasing tumor grade from LMP serous tumors and low-grade ovarian tumors to high-grade tumors [16,31,35, 38]. These allelic imbalances, as analyzed in terms of loss of heterozygosity (LOH) and chromosome copy number gain or loss, have been detected by a variety of methods.

Allelic changes are rarely detectable, if at all, in LMP serous tumors but are usually frequent and extensive in high-grade OSCs. As shown by a cytogenetic analysis of 13 borderline (i.e., LMP serous) tumors by comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), or both, only three of the tumors had detectable abnormalities [78]. In another cytogenetic study, the only anomaly detected in three of five borderline (i.e., LMP serous) and grade 1 tumors was trisomy 12 [16]. Similar results were reported by Pejovic et al. [60].

Allelic imbalance has also been assessed by CGH in atypical proliferative tumors, noninvasive micropapillary serous carcinoma (MPSCs) (considered to be a variant of LMP serous tumors), and invasive MPSCs (considered to be a variant of low-grade OSCs) [69]. In brief, allelic imbalances in chromosomes 1p, 5q, 8p, 18q, 22q, and Xp (especially chromosome 1p) increased from LMP serous tumors to low-grade OSCs (i.e., invasive MPSCs). In contrast, all high-grade OSCs including the very earliest tumors confined to one ovary showed extensive allelic imbalance [69].

In two other, more comprehensive CGH analyses, allelic imbalances increased progressively with increas-

ing tumor grade. For example, Kiechle et al. reported observing a median of 6 abnormalities in grade 1 ovarian tumors ($n = 6$ tumors, 3 of which showed no abnormalities at all), 19 abnormalities in grade 2 tumors ($n = 42$), and 21 abnormalities in grade 3 tumors ($n = 55$) [38]. In another study, Iwabuchi et al. [35] assessed 56 benign, low-grade, and high-grade ovarian tumors for the presence of DNA sequence copy number abnormalities (CNAs) and found no CNAs in the benign tumors, some in the low-grade tumors, and comparatively more in the high-grade tumors. The most common CNAs were increased copy number at chromosomes 3q25-26 and 20q13 in low-grade tumors and increased copy number at chromosome 8q24 in high-grade tumors [35].

In a study in which restriction fragment length polymorphisms and microsatellite markers were used to detect LOH in low-grade OSCs ($n = 20$), high-grade OSCs ($n = 34$), and borderline tumors ($n = 4$) [16], LOH was infrequent in most low-grade OSCs (65%) and all of the borderline tumors. Moreover, borderline and invasive tumors shared few if any abnormalities. Together, these findings suggest that most low-grade OSCs and LMP serous tumors may arise from an alternative mechanism, or mechanisms, that cannot be detected by LOH analysis [16].

In summary, allelic imbalances become progressively more frequent as tumor grade increases from LMP serous tumor and low-grade OSC to high-grade OSC. Many LMP serous tumors and low-grade OSCs exhibit no detectable allelic imbalances, which suggests that these two tumor types may lie on a continuum and that the mechanism or mechanisms by which both types are initiated and develop differ from those at work in high-grade OSCs.

3.3. Expression profiling

Besides exhibiting different genetic abnormalities, low-grade and high-grade OSCs have distinctly differ-

Table 2
Expression profiling comparison of various grades

LMP ^a (no. of cases analyzed)	LGOSC (no. of cases analyzed)	HGOSC (no. of cases analyzed)	Reference
0	4	8	Jazaeri et al., 2003 [36]
10	1	12	Gilks et al., 2005 [27]
0	3	38	Schwartz et al., 2002 [63]
8	7	37	Meinhold-Heerlein et al., 2005 [51]
20	6	54	Bonome et al., 2005 [7]

^aLMP = serous tumor of low malignant potential; LGOSC = low-grade serous ovarian carcinoma; HGOSC = high-grade serous ovarian carcinoma.

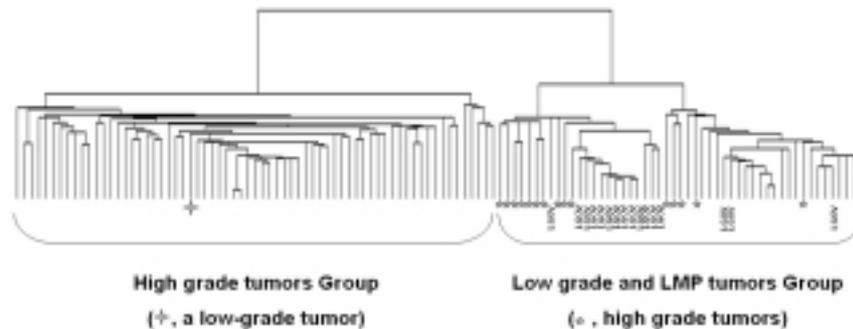


Fig. 2. Unsupervised clustering analysis of 118 ovarian serous tumor samples, including 20 serous tumors of low malignant potential tumors (LMP), 17 low-grade serous ovarian carcinomas (LGOSC), and 81 high-grade serous ovarian carcinomas (HGOSC). Expression values were normalized with a quantile algorithm by using dChip2006 software, a Windows-based program developed for the analysis of gene expression microarrays and SNP microarrays. Clustering analysis was performed on 432 genes having a coefficient of variation (CV) between 1 and 1000 and revealed two major tumor groups. The first group (“High-Grade Tumor Group”) was composed of one LGOSCs and 65 HGOSCs; the second group (“Low-Grade and LMP Tumor Group”) was composed of all 20 LMP tumors, 16 of 17 LGOSCs, and 15 of 81 HGOSCs. Note that LMP is not labelled in the figure. Of the 15 patients having HGOSC associated with LMP/LGOSC, six died after 83, 48, 21, 15, 11, and 9 months of follow-up, respectively (the cause of death in the patients who died after 21 and 15 months of follow-up was suboptimal debulking); the remaining nine patients with HGOSC are still alive (median follow-up, 36 months; longest follow-up, >115 months in three cases).

ent gene expression profiles; on the other hand, LMP tumors and low-grade OSCs have similar expression profiles [7,27,36,51,58,63]. Several studies have compared the gene expression profiles of serous tumors of different grades (Table 2). In one of these studies, which compared the gene expression profiles of eight high-grade OSCs and four low-grade OSCs [36], 99 separate genes were found to be significantly differentially expressed. Forty-nine of those genes were more highly expressed in low-grade tumors, while the other 50 were more highly expressed in high-grade tumors. Interestingly, a high percentage of the upregulated genes in the high-grade tumors were related to centrosome function, which is probably deregulated and related to the poorly differentiated phenotype in those tumors [36].

In another expression profiling analysis of 8 LMP, 7 low-grade, and 37 high-grade ovarian tumors, unsupervised and supervised analyses showed that (a) LMP lesions were distinct from high-grade OSCs and (b)

the expression profiles of well-differentiated low-grade OSCs were strikingly more similar to those of LMP tumors than to those of high-grade OSCs [51]. In a combined CGH and expression profiling analyses of five LMP tumors and 63 invasive carcinomas of varying grades, the expression profiles of LMP and low-grade tumors were again similar and exhibited significantly fewer chromosomal abnormalities than high-grade OSCs. In fact, most of the LMP and low-grade tumors were characterized by high levels of p21/WAF1 and concomitant expression of the cell growth suppressors gadd34 and BTG-2. In contrast, high-grade OSCs characteristically expressed high levels of cell-cycle-related genes and STAT-1-, STAT-3/JAK-1/2-induced genes [51].

Thus, it may be that LMP and low-grade tumors on the one hand and high-grade tumors on the other develop along different biochemical pathways. Indeed, high-grade tumors overexpress genes that control various cell functions related to the tumorigenesis. Con-

versely, LMP tumors characteristically express genes, such as cellular p53, that are involved in growth control pathways. Together, these findings suggest that (a) the initiation of LMP and high-grade tumors involve distinctly different biological mechanisms and (a) some LMP tumors may give rise to invasive low-grade ovarian tumors [26].

In yet another, larger gene expression profiling study in which 80 ovarian tumors (20 LMP tumors, 6 low-grade OSCs, and 54 high-grade OSCs) were subjected to unsupervised clustering analysis [7], the gene expression profiles of the low-grade OSCs were again more like those of LMP tumors than those of high-grade OSCs. Moreover, when we added an additional 11 cases of low-grade OSC and 27 cases of high-grade OSC to the original dataset [26] and subjected this new combined set of 118 tumors to unsupervised clustering analysis, all of the LMP tumors and low-grade OSCs again clustered together in a group separate from the majority of the high-grade OSCs (Fig. 2). Interestingly, however, a subset of 15 high-grade OSCs clustered with tumors of LMP or low grade. Of the 15 patients with these particular high-grade OSCs, nine are still alive (median follow-up, 36 months; longest follow-up, > 115 months in three cases), and six have died after surviving for 48, 21, 15, 11, and 9 months of follow-up, respectively. Together, these mortality and survival data suggest that high-grade OSCs whose gene expression profiles are similar to, as opposed to distinctly different from, those of LMP or low-grade ovarian tumors may be associated with better survival.

In summary, the expression profiles of LMP serous tumors, low-grade OSCs, and high-grade OSCs suggest that LMP tumors are distinct from high-grade tumors but remarkably similar to low-grade tumors.

4. Conclusion

There is intriguing clinical and molecular evidence that LMP serous tumors and low-grade OSCs lie on the same developmental continuum. Genomic and genetic analyses should shed further light on progression from the one tumor type to the other, which may lead in turn to the development of novel therapeutic strategies to prevent that progression. Moreover, further genomic analysis of LMP serous tumors may identify molecular markers of late-stage LMP serous tumors that are likely to develop into low-grade OSCs. Still, none of the available clinical and molecular evidence rules out the possibility that some low-grade OSCs may arise

de novo from an unknown precursor. Indeed, analysis of p53 mutations in eight paired LMP serous tumors and recurrent low-grade OSCs from the same patients has revealed different patterns of p53 mutation in late-stage LMP serous tumors versus recurrent low-grade OSCs [57]. Thus, the potential existence of a continuum from LMP serous tumor to low-grade OSC does not necessarily rule out other pathways of tumorigenesis.

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