Toward the Development of a Universal Grading System for Ovarian Epithelial Carcinoma

Testing of a Proposed System in a Series of 461 Patients with Uniform Treatment and Follow-Up

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BACKGROUND. Most published series of ovarian carcinoma find a correlation between histologic grade and survival, but the grading system used commonly is not specified, and several different systems exist, some of which use different criteria for different histologic types. However, several studies have shown marked interobserver variability in distinguishing among the histologic types of ovarian carcinoma. The authors attempted to derive a universal grading system for all invasive ovarian carcinomas (IOC), based on the Nottingham system for grading all types of mammary carcinoma.

METHODS. The authors studied 461 patients with IOC of different histologic types and clinicopathologic stages who were treated in a uniform manner between 1980 and 1994 with surgery and cisplatin-based chemotherapy. All slides were reviewed and the tumors graded as follows: Architectural pattern (predominant): Glandular = 1, Papillary = 2, and Solid = 3; Nuclear pleomorphism: Slight = 1, Moderate = 2, and Marked = 3; Mitotic activity (mitotic figures per 10 high-power fields [1 HPF = 0.345 mm^2]) in most active region: 0–9 = 1, 10–24 = 2, and ≥25 = 3; Grade 1 = total score (adding three values obtained earlier) 3–5, Grade 2 = 6 or 7, and Grade 3 = 8 or 9.

RESULTS. Tumor grade correlated with survival in both early and advanced stage disease and for all major histologic types of IOC except clear cell carcinoma (CCC). Results for CCC approached but did not reach clinical significance. By multivariate analysis, only this tumor grade and performance status were significant in Stage I/II IOC. For Stage III/IV tumors, the new tumor grade also was significant, as were performance status, residual tumor size, response to chemotherapy, and mucinous (unfavorable) or transitional cell (favorable) histologic type. International Federation of Gynecology and Obstetrics grade (based primarily on architectural features) did not correlate significantly with survival except in Stage III/IV serous and Stage I/II mucinous carcinomas.

CONCLUSIONS. The new grading system reported is simple, reproducible (among the current study authors), and useful for all histologic types and clinical stages of IOC. Further testing for reproducibility and clinical utility is recommended. ***Cancer* 1998;82:893–901.** © *1998 American Cancer Society.*

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The International Federation of Gynecology and Obstetrics (FIGO) stage defined by comprehensive surgery[1] has been the most important prognostic factor for patients with ovarian carcinoma and the basis of the comparison of patient prognosis in different reports. In stage-matched comparison, both histologic type and histopathologic

grade (or degree of differentiation) may function as significant prognostic factors among many histopathologic variables, although some controversies exist, possibly due to different study populations and treatment modalities.[2–5] A Gynecologic Oncology Group (GOG) study demonstrated that the mucinous and clear cell histologic types, both of which were platinum-resistant, were significantly poor prognostic factors in patients with Stage III and IV ovarian cancer.[5] Conversely, some investigators have reached the conclusion that differences in survival between the histologic subtypes disappeared completely when corrected for stage.[2]

In contrast to such controversies concerning the prognostic significance of histologic type, similar conclusions were reached by many authors with regard to the prognostic significance of histopathologic grade.[2–10] Despite a considerable body of such supportive evidence that tumor grade or degree of differentiation of ovarian carcinoma has provided significant prognostic information, this feature has not yet been included in the staging system defined by FIGO,[1,11] nor by the World Health Organization (WHO),[12] mainly because of perceived problems with reproducibility and consistency. Different grading systems have been used at different institutions, producing both interinstitutional and intrainstitutional variabilities.

Among many proposed grading systems, three are the most popular. The FIGO grading system primarily is based on architectural features.[11] The WHO grading system is dependent on observers' impressions derived possibly from both architectural and nuclear features, but not defined in a quantitative manner.[12] The GOG grading system primarily considers architectural and, to a lesser extent, nuclear features, but varies depending on the histologic type of the tumor being graded.[13] It should be noted that clear cell carcinoma of the ovary cannot be graded by either the FIGO or GOG grading system. In addition to these systems, several other challenging systems also have been reported to date, which consider more detailed cytopathologic variables in addition to both architectural and nuclear features.[14] Some authors reporting series of ovarian carcinomas have described the details of the grading procedures used but the majority have not, leading to great difficulties in making comparisons between grading systems. However, it is interesting to note that many of the published series have come to the same conclusion with regard to the prognostic significance of histopathologic grade despite the use of different grading methods.

We previously reported that architectural grade (scored by a system proposed by us), nuclear pleomorphism, and mitotic counts were independent and statistically significant prognostic variables for patients with primary ovarian carcinoma; among these nuclear pleomorphism was the most significant (unpublished data). In that report, we proposed that a new grading system considering these three independent variables, modified from a similar system used for breast carcinoma, that might be applicable for all histologic types of ovarian carcinoma should be established. The current report documents a universal histopathologic grading method for all patients with ovarian carcinoma and demonstrates its value as an independent prognostic factor.

MATERIALS AND METHODS

Patients

We identified patients who initially were diagnosed with malignant ovarian tumors at the Department of Surgical Pathology of the Cancer Institute Hospital in Tokyo, Japan from January 1980 through December 1994, when platinum-based chemotherapy was incorporated into the treatment modality. All cases with available histopathologic slides were entered into the study. Histologic analysis utilized hematoxylin and eosin-stained sections cut from a median of 28 tissue blocks per case (range, 3–68 blocks per case).

All slides for each patient were screened by one of us (Y.S.) and at least three slides suitable for histologic typing and grading of the primary ovarian tumor for each patient were selected. These selected slides were reviewed for histologic typing and grading concurrently by three observers (S.G.S., S.K., and Y.S.) without knowledge of the clinical course of the patients. When a consensus for diagnosis was not reached, a final decision regarding the histologic subtype, architectural grade, and nuclear grade was made by one observer (S.G.S.). Mitotic counts were decided based on consensus reached by the three observers using a multiheaded microscope.

Treatment Modality

Our treatment policy for ovarian carcinoma has been similar to the standard treatment modality. For apparent T1 or T2 ovarian carcinoma, Wertheim's hysterectomy with bilateral adnexectomy, omentectomy, and pelvic to paraaortic lymphadenectomy up to the level of the upper part of the renal vein was the basic procedure (in occasional cases, more extensive surgery, including Douglas peritonectomy, was performed), followed by five to six courses of platinum-based chemotherapy. Patients with apparent T3 or T4 disease had initial maximal surgical debulking with the basic procedure described earlier or more extensive surgery including Douglas peritonectomy, bowel resection, sple-

nectomy, diaphragm resection, and resection or removal of other organs. Thereafter, they received five to six courses of platinum-based chemotherapy and underwent subsequent second surgery (including second look) followed by an individualized treatment program.

The chemotherapy regimen used basically was comprised of cyclophosphamide (500 mg/m^2), doxorubicin (40 mg/m^2), and cisplatin (70 mg/m^2).

Procedure for Histopathologic Typing and Grading

Histologic Subtype

Histologic types were diagnosed according to the WHO classification of surface epithelial-stromal tumors.[12] Histopathologic grading was directed principally at invasive epithelial ovarian carcinomas; tumors diagnosed initially or on review as low malignant potential or of nonepithelial origin were excluded from the current study population.

Grading

The grade for an individual tumor was determined as follows:

Architectural pattern

All parts of each block were scanned and the proportions of glandular, papillary, and solid growth were assessed. A predominant glandular, papillary, or solid structure was assigned a score of 1, 2, or 3, respectively.

Nuclear pleomorphism

For determination of nuclear pleomorphism, we chose the area of the tumor comprising at least 50% of a low-power (4 × 10X) microscopic field with the greatest degree of atypicality. The nuclear grade was determined by the variation in nuclear size and shape, chromatin texture, the nuclear:cytoplasmic ratio, and the presence and prominence of nucleoli. Scoring was as follows:

Score 1: relatively uniform vesicular nuclei (variation in diameter $\leq$ 2:1), a low nuclear:cytoplasmic ratio, with no chromatin clumping or prominent nucleoli.

Score 2: intermediate variation in nuclear size (between 2:1 and 4:1) and shape, nucleoli recognizable but small, some chromatin clumping, with no bizarre cells.

Score 3: marked variation in nuclear size (>4:1) and shape, a high nuclear:cytoplasmic ratio, prominent chromatin clumping, thick nuclear membranes, and large eosinophilic nucleoli; bizarre cells may be present.

Mitotic count

Mitotic activity basically is an independent histologic variable but it generally is increased with increasing nuclear grade, as are abnormal mitotic figures (MF). We counted the most brisk area for mitoses. Thus, mitotic activity was best assessed at the periphery of the tumor at which active growth was most likely, but in many cases the periphery was unidentifiable. Strict criteria for the identification of MF were employed, and only nuclei with definite morphologic features of metaphase, anaphase, or telophase were counted. Hyperchromatic and apoptotic nuclei were excluded. A minimum of 30 fields was assessed and the highest count of MF per 10 high-power microscopic fields (MF/10 HPF) was recorded using a Nikon Optiphot (10× wide field eyepiece, 40× objective) with field diameter and area being 0.663 mm and 0.345 mm^2, respectively. Up to 9 MF/10 HPF scored 1 point, 10–24 MF/10 HPF scored 2 points, and ≥25 MF/10 HPF scored 3 points.

Final grading

For determination of overall grade for each tumor, the scores for the three independent categories provided earlier were added together, giving a possible total score of 3–9. Final tumor grade then was allocated on the following basis: 3–5 points: Grade 1 (well differentiated); 6 or 7 points: Grade 2 (moderately differentiated); and 8 or 9 points: Grade 3 (poorly differentiated).

FIGO grade

For comparison, the FIGO grade based on the ratio of glandular or papillary structures versus solid tumor growth (Grade 1: < 5% solid tumor; Grade 2: 5–50% solid tumor, Grade 3: > 50% solid tumor) also was determined concurrently on the same tumors except those diagnosed as clear cell adenocarcinoma.

Statistical Considerations

Statistical analyses were performed using SAS software.[15] Distributions of patients assigned to FIGO surgical stage and to histopathologic grade by histologic subtype were analyzed by the chi-square test[16] and Wilcoxon rank sum test.[17] Correlations among scored histopathologic variables including FIGO grade, our architectural grade, nuclear grade, and mitotic count grade were assessed by Pearson's product moment correlation coefficients, of which values >0.7 indicated high correlation, values between 0.4–0.7 indicated moderate correlation, and those <0.4 indicated low correlation. The duration of survival was measured up to the date of death or the date of last follow-up if the patient was alive at the time of the last follow-up. All causes of death were used to calculate survival, and estimates of the cumulative proportion surviving were based on Kaplan–Meier procedures.[18] Differences in

TABLE 1
Patients with Ovarian Carcinoma Studied for Possible Histopathologic Grading System

Histologic subtype	FIGO Stage I	II	III	IV	Total
Serous	34	29	93	29	185 (40.1%)
Clear cell	43	15	26	4	88 (19.1%)
Endometrioid	35	13	24	6	78 (16.9%)
Mucinous	31	4	26	3	64 (13.9%)
Transitional cell	3	5	23	3	34 (7.4%)
MMT/Sarcoma	0	2	5	0	7 (1.5%)
Malignant Brenner	1	0	0	0	1 (0.2%)
Unclassified	1	0	1	2	4 (0.9%)
Total	148 (32.1%)	68 (14.7%)	198 (43.0%)	47 (10.2%)	461 (100%)

FIGO: International Federation of Gynecology & Obstetrics; MMT: Malignant mixed mecodermal tumor (carcinosarcoma).
Chi-square test for distribution of patients assigned by histologic subtype and stage: Overall: 76.04308; $P = 0.00000$. Among serous, clear cell, endometrioid, mucinous, and transitional cell: 61.35912; $P = 0.00000$. A significant difference was observed for serous vs. clear cell (0.0000), serous vs. endometrioid (0.00006), serous vs. mucinous (0.00002), transitional cell vs. clear cell (0.00016), transitional cell vs. endometrioid (0.00076), transitional cell vs. mucinous (0.00135).

survival time were analyzed using the log rank test.[19] Univariate analyses of prognostic significance of the new grade and FIGO grade with respect to survival were performed using the log rank test,[19] after survival curves were obtained by the Kaplan–Meier method.[18] Multivariate assessment of survival time was performed with the Cox proportional hazards model.[20]

RESULTS

Characteristics of the Patients eligible for the Current Study

Between 1980 and 1994, 570 patients initially were diagnosed with ovarian malignant tumors at the Cancer Institute Hospital in Tokyo. Of these, 461 patients were found to have invasive epithelial ovarian malignant tumors (carcinomas). Of the remaining patients, 67 had low malignant potential epithelial tumors and 42 had malignant tumors of nonepithelial origin. The relation between surgical stage and histologic subtype for the 461 eligible patients is shown in Table 1. Approximately 67% of the serous carcinomas were assigned FIGO Stage III or IV. Conversely, >60% of clear cell and endometrioid carcinomas were assigned to Stage I or II, as were >50% of mucinous carcinomas. The distribution of transitional cell carcinoma (TCC) was very similar to that of serous carcinoma. Thus, the majority of patients with serous carcinoma or TCC had advanced stage disease at the time of diagnosis, whereas >50% of those with clear cell, endometrioid, or mucinous carcinoma were diagnosed in early stages. As previously reported, such interrelationships between the histologic subtypes and surgical stages at the time of diagnosis were statistically significant (unpublished data).

Survival of Patients with Epithelial Ovarian Carcinoma by FIGO Stage

The 5-year survival rate and median survival time of the 461 patients by FIGO stage were as follows: Stage I (148 patients): 91.5% (178 months); Stage II (68 patients): 61.6%, (95 months); Stage III (198 patients): 28.0%, (39 months); Stage IV (47 patients): 29.8% (21 months); and overall (461 patients): 54.5% (94 months). Differences in survival time of these patients stratified by FIGO stage were statistically significant ($P < 0.00001$ by the log rank test). Thus, the current new grading system was investigated for prognostic value in patients stratified by FIGO stage into two groups: early stage (Stage I and II) and advanced stage (Stage III and IV).

Univariate Analysis of the Prognostic Significance of New Grade

Table 2 shows that the new grade worked as a significant predictor of survival in both early and advanced stage disease for all histologic types of ovarian carcinoma combined. It also was prognostically significant in patients with Stage I/II and III/IV serous carcinoma, Stage I/II endometrioid carcinoma, Stage I/II and III/IV mucinous carcinoma, Stage III/IV transitional cell carcinoma, and clear cell carcinoma in all stages combined.

Table 3 shows statistical analysis of the relation between the new grade and FIGO stage in the major histologic types. The grade was significantly lower in patients with Stage I/II and higher in those with Stage III/IV serous, endometrioid, and mucinous carcinomas. The same trend was observed in pa-

TABLE 2
Univariate Analysis of Survival Time by Histologic Subtype

Histologic subtype	Stage	New grade 1	New grade 2	New grade 3	Total	*P* value[a]
All	I–II	NR[b]	5598	1153	NR	0.0000
		(122)[c]	(63)	(31)	(216)	
	III–IV	1947	975	538	666	0.0000
		(40)	(87)	(118)	(245)	
	I–IV	NR	2597	627	2817	0.0000
		(162)	(150)	(149)	(461)	
Serous	I–II	NR	2300	1322	NR	0.0000
		(30)	(19)	(14)	(63)	
	III–IV	NR	1325	544	671	0.0000
		(10)	(44)	(68)	(122)	
	I–IV	NR	2124	616	1415	0.0000
		(40)	(63)	(82)	(185)	
Clear cell	I–II	NR	NR	1094	NR	0.1257
		(31)	(24)	(3)	(58)	
	III–IV	380	267	322	315	0.9032
		(10)	(15)	(5)	(30)	
	I–IV	NR	NR	779	NR	0.0124
		(41)	(39)	(8)	(88)	
Endometrioid	I–II	NR	3482	2413	NR	0.0042
		(33)	(8)	(7)	(48)	
	III–IV	NR	929	739	929	0.1148
		(9)	(9)	(12)	(30)	
	I–IV	NR	2848	1137	NR	0.0000
		(42)	(17)	(19)	(78)	
Mucinous	I–II	NR	2030	748	NR	0.0002
		(27)	(6)	(2)	(35)	
	III–IV	1947	438	212	527	0.0038
		(11)	(9)	(9)	(29)	
	I–IV	NR	849	276	5916	0.0000
		(38)	(15)	(11)	(64)	
Transitional cell	I–II	—	NR	NR	NR	0.8571
		(0)	(5)	(3)	(8)	
	III–IV	—	NR	921	1355	0.0186
		(0)	(7)	(19)	(26)	
	I–IV	—	NR	921	1904	0.0092
		(0)	(12)	(22)	(34)	

NR: not reached.
[a] Calculated by the log rank test.
[b] Median survival days indicated.
[c] Numbers of patients.

tients with clear cell carcinoma, though this was not significant by a chi-square test.

We previously demonstrated that FIGO grade worked as a prognostic indicator only in patients with Stage III/IV serous carcinoma and Stage I/II mucinous carcinoma. Analysis of the distribution of patients assigned to each FIGO grade by histologic subtype showed that FIGO grade was lower in early stage and higher in advanced stage serous and mucinous carcinomas with statistical significance (unpublished data).

Multivariate Analysis of Prognostic Variables using the Cox Proportional Hazards Model

In patients with FIGO Stage I/II ovarian carcinoma, performance status and the new grade were found to be significant prognostic variables (Table 4). In contrast, histologic subtype and FIGO grade were not statistically significant.

As shown in Table 5, in patients with Stage III/IV disease, performance status of 3 and 4, mucinous carcinoma, new Grade 2 and 3, residual tumor size $\geq$0.5 cm, and a response to chemotherapy of no

TABLE 3
Distribution of Patients Assigned to New Histopathologic Grade by Histologic Subtype

Histologic subtype	Chi-square test		Wilcoxon's rank sum test	
	χ^2	*P* value	z	*P* value
Serous	40.81676	0.00000	5.77631	0.00000
Clear cell	4.9226	0.08534	2.07205	0.03826
Endometrioid	11.55015	0.00310	3.34751	0.00082
Mucinous	11.32845	0.00347	3.32118	0.00090
Transitional cell	2.01169	0.15609	1.78956	0.07352
All	94.69524	0.00000	9.65753	0.00000

χ^2: chi-square; z: standard score.

TABLE 4
Multivariate Analysis of Survival Time of Patients with Stage I–II Ovarian Carcinoma Using Cox's Proportional Hazards Model

Covariate	No. of patients	Relative risk	Wald chi-square	Pr > Chi-square
Age	216	1.023	1.8346	0.1756
Performance status				
0/1	178	1.000		
2	38	3.819	12.7357	0.0004
Histologic subtype				
Serous	63	1.000		
Clear cell	58	1.115	0.0627	0.8022
Endometrioid	48	0.511	1.3968	0.2373
Mucinous	35	1.095	0.0239	0.8771
TCC/Unc	8	0.475	1.4812	0.2236
FIGO Grade				
1	98	1.000		
2	21	1.387	0.5039	0.4778
3	39	0.681	0.6173	0.4321
New Grade				
1	122	1.000		
2	63	8.840	20.2793	0.0001
3	31	19.445	24.4413	0.0001

TCC: transitional cell carcinoma; Unc: unclassified; FIGO: International Federation of Gynecology and Obstetrics.

change or progressive disease were found to be significantly poor prognostic factors, whereas TCC was a significantly favorable prognostic variable. Clear cell carcinoma showed a trend toward poor prognosis (relative risk of 1.71 compared with serous carcinoma) but this was not significant ($P = 0.0610$). Thus, the new grade provided significant prognostic information in both early and advanced stage ovarian carcinoma.

DISCUSSION

The question of the clinical utility of histopathologic grading of ovarian epithelial carcinoma has been debated for years, without any universal agreement, especially in methodology. Despite the vagueness in some reports and total absence of criteria in others for assigning tumor grade, many of the published series came to the same conclusion that grading most likely was associated significantly with prognosis in patients with ovarian carcinoma. The main problem was that the authors provided few details of their methodology in their publications, and often accepted the grades from pathology reports without further review. Thus, reproducibility repeatedly has been argued for every grading system. In this connection, it has been demonstrated that both interobserver and intraobserver diagnostic variability could take place not only in the determination of histopathologic grade but also in the diagnosis of histologic subtype.[21–23] If the grading system employed is somewhat different for each subtype (as in the GOG system[13]), or if one or

TABLE 5
Multivariate Analysis of Survival Time of Patients with Stage III–IV Ovarian Carcinoma Using Cox's Proportional Hazards Model

Covariate	No. of cases	Relative risk	Wald chi-square	Pr > chi-square
Age	245	1.004	0.1827	0.6691
Performance status				
0/1	25	1.000		
2	91	1.355	0.6769	0.4106
3/4	129	3.715	13.0168	0.0003
Histologic subtype				
Serous	122	1.000		
Clear cell	30	1.707	3.5091	0.0610
Endometrioid	30	0.949	0.0346	0.8524
Mucinous	29	2.014	5.0812	0.0242
TCC/Unc	26	0.485	5.6905	0.0171
FIGO Grade				
1	53	1.000		
2	51	0.636	2.1766	0.1401
3	111	0.924	0.0664	0.7966
New Grade				
1	40	1.000		
2	87	2.465	7.8858	0.0050
3	118	4.835	19.3149	0.0001
Residuum				
0	13	1.000		
<0.5 cm	15	5.996	2.3877	0.1223
0.5–2 cm	34	13.714	5.4630	0.0194
≥2 cm	183	19.236	6.8196	0.0090
Response to CTX				
CR/PR	122	1.000		
NC/PD	111	4.105	39.5753	0.0001
NE	12	0.000	0.0000	0.9933

TCC: transitional cell carcinoma; Unc: unclassified; FIGO: International Federation of Gynecology and Obstetrics; CTX: chemotherapy; CR: complete response; PR: partial response; NC: no change; PD: progressive disease; NE: not evaluated.

more subtypes are not graded (as with clear cell carcinoma in the FIGO[11] and GOG[13] systems), it is apparent that variability in typing will lead to even greater variability in grading; for example, a tumor diagnosed as serous carcinoma by one pathologist and clear cell carcinoma by another will be graded in one manner by the first and not at all by the second. Such subjectivity in determination of the histopathologic grade has been one of the main reasons that histopathologic grade still is not considered in the FIGO staging system for ovarian carcinoma. It probably also is a major reason for the frequent failure of pathologists to grade ovarian carcinomas in their reports (41% of 785 ovarian carcinomas reviewed from the National Cancer Institute Surveillance and Epidemiology End Results Program in 1991).[24]

As described earlier, various grading methods including those of FIGO,[11] WHO,[12] and GOG[13] have been used in different institutions. These systems are based either on architectural features (with determination of the ratio of glandular or papillary growth pattern vs. solid structure), nuclear grade, a combination of both, or more detailed histopathologic features in addition to both architectural features and nuclear grade.

Mauch et al.[25] and Ozols et al.[6] compared architectural features with nuclear grading and concluded that architectural grading was more important as a prognostic predictor. Conversely, Malkasian et al., in their series of 1938 patients with ovarian carcinoma, found that nuclear grade based on the Broders' system could provide significant prognostic information for patients with ovarian carcinoma stratified by surgical stage.[2] Sorbe et al. also confirmed the importance of nuclear grading in all stages.[7] Moreover, Bichel et al. reported an original grading system taking into account pathologic features of the tumor-host relation in addition to both architectural features and nuclear grading.[14] This grading index was found to be well correlated with both presence of tumor at second look laparotomy and survival of patients. However, compared with other systems, the scoring system was more complicated and the study was limited to patients with Stage

III and IV serous carcinoma. Thus, there is no universally accepted system of histopathologic grading for ovarian carcinoma, with the result that many different systems have been employed and there are great difficulties in making comparisons between reports using different grading systems.[3]

We previously reported that architectural growth pattern, nuclear pleomorphism, and mitotic counts were independent and significant prognostic variables for both early and advanced stage primary ovarian carcinoma, and that among these nuclear pleomorphism was the most significant (unpublished data). However, none of these three variables alone could predict correctly the prognosis of patients with ovarian carcinoma. Based on these results, we designed a new grading system considering these three independent variables that might be applicable for all histologic types of ovarian carcinoma, so that the grade would be independent of the correct diagnosis of histologic type and could be determined easily in tumors of mixed subtypes (e.g., serous/TCC or endometrioid/clear cell). This system is based on a modification of the Nottingham grading system for breast carcinoma, which also awards points for architecture, nuclear atypia, and mitotic activity, and sums the scores for a final grade.[26] The actual scoring in the current system is adapted for the unique features of ovarian rather than breast carcinoma.

As shown in the results, both univariate and multivariate analyses demonstrated that the new grading system worked well both in Stage I/II and Stage III/IV disease. To our knowledge, this may be the first report to demonstrate the efficacy of a grading system applicable for both early and advanced stages of ovarian carcinoma irrespective of histologic subtype.

Characteristic points of the new grading system include the following. First, we introduced a modified architectural grading system in the current study. As mentioned earlier, usual architectural grading was based on the ratio of glandular or papillary growth pattern versus solid structure, in which glandular or papillary growth patterns were considered to have the same prognostic weight. However, in most ovarian adenocarcinomas, tumors with papillary features (serous, TCC) are more aggressive than those that are primarily glandular (mucinous, endometrioid), although there is certainly some overlap (clear cell, villoglandular endometrioid). Thus, we assigned a glandular growth pattern a lower score than papillary, as mentioned earlier. The result was that our architectural grade worked better as a prognostic indicator than the usual architectural grade, although neither was particularly useful in clear cell carcinoma or TCC (unpublished data).

Second, mitotic activity was incorporated into the grading system. MFs are one of the findings observed within the nuclei. Thus, some investigators consider MF as one of the nuclear features and incorporate it into nuclear grade. Our previous study demonstrated that MF/10 HPF was independent from nuclear pleomorphism (unpublished data). Indeed, it often was observed that some tumors with high nuclear grade had low mitotic activity (such as most clear cell carcinomas) and conversely, that occasional tumors with low nuclear grade had high mitotic activity (as in some but not most endometrioid carcinomas).

Third, the new grading system was simplified and highly reproducible compared with others. In the current series, an approximately 90% reproducibility rate was obtained among the results obtained by three observers (data not shown). Further studies on reproducibility among other investigators are planned.

Conversely, some problems remain to be solved. Clear cell carcinoma is perhaps the only histologic subtype in which prognosis is not highly correlated with this grading method. This is probably due both to a reportedly poor correlation of growth pattern with survival in clear cell carcinoma[27,28] and the tendency noted by us for clear cell carcinoma to be relatively uniform in nuclear grade (moderate to high) and mitotic activity (low) from one case to the next. However, a trend toward significance was observed despite the relatively small number of patients with clear cell carcinoma analyzed in the current study. Thus, continued study with larger numbers of such patients may clarify the feasibility of the new grading system for clear cell carcinoma. Because the elimination of clear cell carcinoma from the grading scheme again would demand the correct diagnosis of histologic type before grading could be performed, we continue to include clear cell carcinoma with all other types of carcinoma at the current time.

The prognostic weight of the histopathologic grade may be affected by the treatment modality. In consideration of such problems, we analyzed patients treated by the same modalities, including the same surgical procedures and cisplatin-based chemotherapy. The fact that the new grading system worked in Stage I/II disease, the outcome of which mainly was affected by surgery, indicates that this grade might reflect correctly the biological behavior of tumor cells. Its similar efficacy in Stage III/IV disease, the outcome of which is determined more by response to chemotherapy than by surgery, suggests that this relation is not influenced markedly by the chemotherapy employed in this series (i.e., no tendency for lower grade patients to respond more poorly to chemotherapy and lose their survival advantage, as has been suggested

in some other reports[3]). Whether the current grading system can provide similar prognostic information for patients receiving other treatment modalities remains to be answered by further studies.

Our results suggest that the proposed new grading system may provide useful prognostic information for all histologic types of ovarian carcinoma. We believe that this system warrants further study in the future.

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