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Grading of Ovarian Cancer

- Histologic grade has been found to be an important prognostic factor in cases of ovarian carcinoma
  - However, there is no system that is universally used for grading these neoplasms

- At present, it seems that ovarian cancer represents a heterogeneous group of diseases
  - Different histologic parameters may needed to determine the biological behavior of different tumors

Serous Carcinoma

- Based on the cytologic atypia (primary parameter) and mitotic index (secondary parameter)
  - Two types
    - High grade (marked variation $\geq 3:1$ in nuclear size and shape with irregular chromatin and variable presence of macronucleoli, and a mitotic index $>12$ mitoses per 10 high power fields)
    - Low grade (uniform round or oval nuclei with evenly distributed chromatin and variable
presence of nucleoli and a mitotic index of up to 12 mitoses per 10 high power fields

Endometrioid Carcinoma
- Based on the amount of solid component
  - Three grades
    - Grade 1, up to 5% solid component (non-morular)
    - Grade 2, >5 to 50% solid component (non-morular)
    - Grade 3, more than 50% solid component (non-morular)

Mucinous Carcinoma
- Based on the presence and type of invasion
  - Two types
    - Non-invasive (intraglandular)
    - Invasive
      - Expansile
      - Infiltrative

Clear Cell Carcinoma
- High grade carcinoma

Transitional Cell Carcinoma
- High grade carcinoma

Undifferentiated Carcinoma
- High grade carcinoma
Bibliography


8. Silva EG and Gershenson DM. Standardized histologic grading of epithelial ovarian cancer: Elusive after all
these years. (Editorial) *Gynecologic Oncology*. 1998; 70:1.


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Grading of Ovarian Cancer

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Grading of Ovarian Cancer

• Introduction
  – Traditionally ovarian cancer has been considered one disease
  – Diverse grading systems have been used to grade these neoplasms regardless of the tumor histotype
Grading of Ovarian Cancer

• The FIGO grading system
  – Based on architectural features, grade of the tumor depends on the ratio of glandular or papillary structures to solid tumor
    • Grade 1, < 5% solid
    • Grade 2, 5% to 50% solid
    • Grade 3, >50% solid
Grading of Ovarian Cancer

• The WHO system
  – Based on the pathologist’s impression of both architectural and cytologic features
  – Categories not defined according to a quantitative method
Grading of Ovarian Cancer

• Ovarian carcinoma appears to be a heterogeneous group of tumors, rather than a single disease
• Therefore, a universal grading system for this heterogeneous group most likely would not accommodate the inherent differences among these diverse tumors
• Considering this heterogeneity, it would be more appropriate to use different parameters in order to grade the cases within each histologic type.
Grading of Ovarian Cancer

• Serous Carcinoma
  – The recently proposed two-tier grading system (M.D. Anderson grading system) has emerged as a good method to segregate serous carcinomas that have different molecular, pathogenetic, histologic, immunohistochemical, and clinical features
Grading Ovarian Serous Carcinoma Using a Two-Tier System

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Abstract: In this study, we evaluate a new-tiered system for grading ovarian serous carcinoma. This system is based primarily on the assessment of nuclear morphology with the mitotic rate used as a secondary feature. The study included 91 cases of high-grade ovarian serous carcinoma and 34 cases of low-grade ovarian serous carcinoma retrieved from the files of the Department of Pathology at the University of Texas M. D. Anderson Cancer Center from 1975 to 1991. Cases assigned to the low-grade category were characterized by the presence of bilobed to multinucleated nuclei, an octagonal to squamous shape, and by the absence of small to medium size nuclear antigens. A secondary feature, they tended to show up to 12 min per 10 high-power fields (HPFs), whereas those in the high-grade category had nucleated nuclei, small to medium size nuclear antigens, and a secondary feature of 12 min per 10 HPFs. For comparison, the tumors were also graded using the Shimkin-Silberberg and the FIGO grading systems. Patients in the low-grade ovarian serous carcinoma group ranged in age from 19 to 72 years (mean 46.1) while patients in the high-grade ovarian serous carcinoma group ranged in age from 27 to 95 years (mean 55 years). All of the cases except one were advanced FIGO stage. Using the Shimkin-Silberberg system, the low-grade ovarian serous carcinomas were distributed as follows: grade 1, 47 cases; grade 2, 3 cases. Using the FIGO grading system, 35 cases were grade 1 and 15 cases were grade 2. Regarding the high-grade ovarian serous carcinoma, using the Shimkin-Silberberg system, 14 of the cases were grade 2 and 30 cases were grade 3. Using the FIGO grading system, 3 cases were grade 2 and 11 cases were grade 3. Most of the patients in both groups were treated with radical abdominal hysterectomy and bilateral salpingo-oophorectomy and adjuvant platinum-based chemotherapy. On follow-up, 37 patients in the low-grade ovarian serous carcinoma group had a total of 43 deaths from disease at a median of 4.2 years after diagnosis compared with 16 patients in the high-grade ovarian serous carcinoma group who died of disease at a median of 2.7 years. High patients in the low-grade ovarian serous carcinoma group had a total of 43 deaths from disease at a median of 3.8 years. Patients with low-grade ovarian serous carcinoma were alive and well at last follow-up of 4 to 38.3 years. For patients with low-grade ovarian serous carcinoma, there was no evidence of disease after a follow-up time ranging from 4.3 to 22.6 years (mean 6.8 years) and 55% of the deaths were of other causes. Our findings strongly suggest that the Shimkin-Silberberg system is superior to the FIGO system in grading ovarian serous carcinoma.
Serous Carcinoma

- The two-tier grading system (M.D. Anderson grading system) is based primarily on the assessment of nuclear atypia with the mitotic rate used as a secondary feature.
- Two grades:
  - Low
  - High
Low Grade Serous Carcinoma

• Definition
  – A serous carcinoma characterized by the presence of uniform cells with mild to moderate nuclear atypia, and usually a low mitotic index (≤ 12 mitoses per 10 HPFs)
High Grade Serous Carcinoma

• Definition
  – A serous carcinoma characterized by the presence of pleomorphic cells with marked nuclear atypia ($\geq 3:1$ variation in size and shape), and a high mitotic index ($>12$ mitoses per 10 HPFs)
Low vs. High Grade Serous Carcinoma
Differences in Pathogenesis: Morphologic Evidence

• Association with a serous neoplasm of low malignant potential
  – 60% of the low grade serous carcinomas
  – 2% of the high grade serous carcinomas

Malpica A et al, 2004
Low vs. High Grade Serous Carcinoma
Differences in Pathogenesis: Morphologic Evidence

• Association with serous tumor of low malignant potential
  – 276 pts with serous LMP and long-term (≥ 5-year) f/u
  – Transformation to low grade serous carcinoma in 6.8% of pts
    • Interval range, 7 to 288 months (58% ≥ 60 months)

Longacre TA et al, 2005
Low vs. High Grade Serous Carcinoma
Differences in Pathogenesis: Molecular Evidence

- Ovarian Tumorigenesis Model
  - Type I, tumors that arise in a stepwise manner from borderline (low malignant potential) tumors
    - Low grade serous carcinoma, prototypic type I tumor
    - \textit{BRAF} and \textit{KRAS} mutations

Singer G et al, 2002
Low vs. High Grade Serous Carcinoma Differences in Pathogenesis: Molecular Evidence

- Ovarian Tumorigenesis Model
  - Type II, de novo development (as yet no recognizable precursor lesion identified)
    - High grade serous carcinoma, prototypic type II tumor
    - $p53$ mutation

Singer G et al, 2002
## Low vs. High Grade Serous Carcinoma: Immunohistochemical Differences

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Low Grade Serous Ca</th>
<th>High Grade Serous Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53</td>
<td>18%</td>
<td>64%</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>5%</td>
<td>26%</td>
</tr>
<tr>
<td>MIB1, mean index</td>
<td>23.0%</td>
<td>55.4%</td>
</tr>
<tr>
<td>Her-2 neu</td>
<td>4.5%</td>
<td>36%</td>
</tr>
<tr>
<td>C-Kit</td>
<td>4.5%</td>
<td>30%</td>
</tr>
</tbody>
</table>

O’Neill CJ et al, 2005
Low vs. High Grade Serous Carcinoma: Differences in Biologic Behavior

• Low grade serous carcinoma appears to be less responsive to conventional chemotherapy than high grade serous carcinoma

• Patients with low grade serous carcinoma have a longer overall survival than patients with high grade serous carcinoma

Low vs. High Grade Serous Carcinoma: Frequently Asked Questions

• What is the incidence of low grade serous carcinoma?
  – Uncommon tumor
  – Less than 10% of ovarian serous carcinomas (MDACC unpublished data)
  – 1/102 cases of advanced stage ovarian cancer (Gilks CB, 2004)

• Is the term low grade serous carcinoma used in a standard fashion?
  – No
  – Some gynecological pathologists use this term to designate the micropapillary/cribriform variant of a serous tumor of low malignant potential
Low vs. High Grade Serous Carcinoma: Frequently Asked Questions

• What is the reproducibility of the two-tier grading system for ovarian serous carcinoma?
  – Overall kappa among 9 different observers = 0.909
  – The inter-observer kappas ranged from 0.717 to 1.000 in the first round of the review and from 0.701 to 1.000 in the second review

Malpica A et al, in press 2007
Low vs. High Grade Serous Carcinoma: Frequently Asked Questions

• What is the reproducibility of the two-tier grading system for ovarian serous carcinoma?
  – Eight of 9 participants had an intra-grader kappa ranging from 0.775 to 1.000 (excellent agreement)
  – One participant had an intra-grader kappa of 0.725 (good agreement)

Malpica A et al, in press 2007
Endometrioid Carcinoma

- Grading system similar to the FIGO grading system used for endometrial endometrioid adenocarcinoma
Endometrioid Carcinoma

Grade 1: less than 5% solid areas
Endometrioid Carcinoma

Grade 2: 5 to 50% solid areas
Endometrioid Carcinoma

Grade 3: more than 50% solid areas
Endometrioid Carcinoma

• Survival rate of patients with grade 1 or 2 tumors is higher than those with grade 3 tumors

Kline RC et al, 1990
Clear Cell Carcinoma

- By definition a high grade carcinoma
- The WHO recommendation is not to grade
Clear Cell Carcinoma
Clear Cell Carcinoma

- A high incidence of stage I disease
- Poor response to platinum-based therapy
- Controversial results regarding the survival of patients with this type of tumor when compared to patients with serous carcinoma
Transitional Cell Carcinoma

• The WHO recommendation is to grade according to the criteria used for transitional cell carcinoma of the urinary tract
• In reality, most (if not all) cases are high grade
Transitional Cell Carcinoma

• **WHO criteria**
  – **Low grade**
    • Uniformly enlarged nuclei, with mild alteration of the polarity and mild differences in shape, contour, and chromatin distribution
    • Infrequent mitoses
  – **High grade**
    • Marked variation in nuclear polarity, size, shape, and chromatin distribution
    • Frequent mitoses
Transitional Cell Carcinoma

- Ovarian carcinomas with more than 50% of a TCC component appear to have a better response to chemotherapy
  - Especially if the TCC component is also predominant in the metastases
Mucinous Carcinoma

- Non-invasive carcinoma (Intraepithelial)
  - Marked atypia of the epithelium
- Invasive carcinoma
  - Expansile or confluent type
    - Confluent glandular pattern uninterrupted by normal ovarian stroma occupying an area measuring more than 5 mm in diameter (The Johns Hopkins’ group criterion) or more than 10 mm² (WHO criterion)
  - Infiltrative type
    - Small glands, nest of cells or individual cells infiltrating the stroma in an area measuring more than 5 mm in diameter (The Johns Hopkins’ group criterion) or more than 10 mm² (WHO criterion)
Mucinous Carcinoma

• Prognosis
  – Intraepithelial mucinous carcinoma
    • Risk of recurrence for stage I cases: 5.8%
  – Invasive carcinoma
    • 5-year survival of 91% for stage I cases; advanced stage cases all died of disease (Riopel MA et al, 1999)
    • Infiltrative stromal invasion appears to be more aggressive than expansile invasion (Lee KR and Scully RE, 2000 and Rodriguez IM and Prat J, 2002)
Undifferentiated Carcinoma

- By definition a high grade carcinoma
- The 5-year survival of patients with undifferentiated carcinoma is worse than that of patients with serous carcinoma or transitional cell carcinoma
Grading of Ovarian Cancer

Summary

• Serous Carcinoma
  – Categories:
    • High grade
    • Low grade
  – Criteria: Degree of cytologic atypia (primary feature) and mitotic index (secondary feature)

• Endometrioid Carcinoma
  – Categories: Grades 1, 2, and 3
  – Criterion: amount of solid component
Grading of Ovarian Cancer

Summary

• Mucinous Carcinoma
  – Categories:
    • Non-invasive (intraepithelial)
    • Invasive
      – Expansile or confluent vs. infiltrative
  – Criteria:
    • Marked cytologic atypia (non-invasive carcinoma)
Grading of Ovarian Cancer

Summary

• Mucinous Carcinoma
  – Criteria:
    • Invasion
      – Glandular crowding without intervening ovarian stroma in an area measuring more than 5 mm in diameter (confluent or expansile pattern)
      – Small glands, clusters of cells or individual cells in the stroma in an area measuring more than 5 mm in diameter (infiltrative pattern)
Grading of Ovarian Cancer

Summary

• **Transitional cell carcinoma**
  – Categories:
    • Almost always high grade
    – Criteria: WHO criteria for urothelial carcinoma
  – High grade carcinomas (by definition)
    – Clear cell carcinoma
    – Undifferentiated carcinoma