Introduction

Breast carcinoma is the most common malignant tumor in women in North America and Europe. Invasive mammary carcinoma, like the pre-invasive tumors that typically precede it, can be readily recognized and graded in surgically removed or biopsied tissue samples. The grading and staging of these tumors are of considerable clinical significance and are performed routinely.

Ductal Carcinoma In Situ

Ductal carcinoma in situ (DCIS) is a precursor of invasive carcinoma. Grading for DCIS is meaningful in predicting prognosis and guiding treatment. While there is no universally agreed-upon grading system for ductal carcinoma in situ, current practice is to grade it on the basis of nuclear characteristics in combination with necrosis, and not according to architectural features.

The current grading system published in the World Health Organization (WHO) monograph is a 3-tiered system (Tavassoli and Devilee, 2003). It incorporates the basic tenets of the Van Nuys grading scheme (1) and the approach outlined by Scott et al. (2), and is a refinement of the original classification published by Lagios et al. in 1989 (3). Like the classifications that preceded it, it is based on grading the tumor cell nuclei on a scale from 1 to 3, and by evaluating the intraluminal groups of tumor cells for the presence or absence of necrosis.

The nuclear grade is based on the size of the nuclei, the distribution of chromatin, and the presence or absence of nucleoli.

- **Grade 1.** The nuclei are small, round, and uniform. The nuclei of the tumor cells are of the same size as a red blood cell, or slightly larger. Their diameter does not exceed by more 1.5 times that of normal red blood cells. The nuclei contain uniformly dispersed chromatin, and the nucleoli are not apparent. Mitoses are rare.
- **Grade 2.** The tumor cell nuclei are enlarged and their diameter is equivalent to 1.5 to 2 times the size of red blood cells. The chromatin is coarse, but the nucleoli are infrequently seen. There are sparse mitoses.
- **Grade 3.** The tumor cell nuclei have a diameter greater than 2.5 that of red blood cells. The nuclei are vesicular, filled with irregularly clumped chromatin and of irregular contour. The nuclei contain 1 or more prominent nucleoli. There are frequent mitotic figures, but their presence is not required for grading.

Necrosis is either present or absent; if present, it typically involves the centrally located cells inside the ducts. Necrotic cells undergo karyorrhexis or pyknosis, and these signs of cell death are associated with a loss of nuclear details, clumping of chromatin, and fragmentation of nuclei. Necrosis must be distinguished from inspissated eosinophilic secretions, hemorrhage, foam cells, or debris without karyorrhexis of the tumor cells.

The final grade is assigned as follows:

- **Grade 1, low-grade DCIS.** The tumor cells have a nuclear grade of 1 or 2, and there is no necrosis (Figure 11-1).
- **Grade 2, intermediate-grade DCIS.** The tumor cells have nuclear grade of 1 or 2, but there is also necrosis (Figure 11-2).
- **Grade 3, high-grade DCIS.** The tumor cells have a nuclear grade of 3, with or without necrosis (Figure 11-3).

Ancillary methods may be used but are not essential for grading DCIS. They may be useful under certain circumstances to support the diagnosis and exclude other possibilities, as follows:

- Immunohistochemical stains for myoepithelial cells, including smooth muscle actin, calponin, and collagen...
IV, can be useful in cases where invasion is suspected (4).
- Immunohistochemical stains for E-cadherin and antibody 34βE12 to high molecular–weight keratin can help differentiate low-grade, solid type DCIS (E-cadherin positive, 34βE12 negative) from lobular neoplasia (E-cadherin negative, 34βE12 positive) (5).
- Immunohistochemical staining for estrogen receptor, progesterone receptor, and Her2/neu expression have prognostic, predictive, and therapeutic values.

Comments

1. The architecture pattern of ductal carcinoma in situ (comedo, cribriform, solid, papillary, and micropapillary) should be included in the pathology report, because certain architectural patterns carry independent prognostic significance (6, 7). DCIS with comedo necrosis is associated with a high risk of local recurrence and progression to invasive cancer. Micropapillary DCIS may be associated with more extensive disease in multiple quadrants.

Figure 11-1. Low-grade DCIS, cribriform architecture. A. The ducts are distended by a monotonous population of cells with small, round to oval nuclei. No central necrosis is present. B. The cells have small nuclei (1–1.5 times that of red blood cells), dispersed chromatin, and indistinct nucleoli (nuclear grade 1).

Figure 11-2. Intermediate-grade DCIS, cribriform architecture. A. The overall pattern is similar to low-grade lesions. There is a central area of necrosis. B. The nuclei are moderately enlarged (1.5–2 times that of red blood cells), with coarse chromatin and occasional prominent nucleoli (nuclear grade 2).
2. The margin status and the extent (size) of disease are the other 2 important prognostic factors in the local control of DCIS, and should be documented in the pathology report (8).

3. There is no consensus on the approach to the grading of uncommon types of DCIS, such as apocrine, clear cell, spindle cell, signet ring, and neuroendocrine types.

4. The presence of microcalcifications must be documented and the microscopic findings correlated with mammographic films and/or specimen imaging.

Lobular Carcinoma In Situ

Tavassoli has proposed a 3-level scheme for stratifying lobular intraepithelial neoplasia (LIN 1, LIN 2, and LIN 3) (8). However, no grading system for lobular carcinoma in situ has been endorsed by the WHO expert panel on breast diseases.

Invasive Mammary Carcinoma

The relationship between breast cancer morphology or histology and survival was documented in 1920s and 1930s. Greenhough and his colleagues were the first to propose the idea of histologic grading in 1925. These investigators reviewed 73 cases of radical mastectomy specimens and assessed 8 morphological factors, including the degree of gland formation, the presence of secretory vacuoles, cell size, nuclear size, variation in the size of cells and nuclei, the degree of nuclear hyperchromatism, and the number of mitoses. Based on the overall evaluation of these 8 features, tumors were assigned a grade in a 3-tiered grading system. A clear association between tumor grade and 5-year “cure” was demonstrated. Current breast cancer grading studies stem from this work.

Patey and Scarff (9) followed Greenhough’s method and developed their own grading systems, emphasizing the amount of tubule formation, variation in nuclear size, and hyperchromatism. They also found associations between grade and survival. However, the idea of breast grading did not gain much popularity among clinicians and pathologists at that time, in part due to the complexity and subjectivity of the grading system, and to the limitation of treatment options corresponding to different grades of the tumor.

In 1950, Bloom (ironically, a radiotherapist) reviewed the literature on breast cancer grading and decided to follow the Patey and Scarff method. He divided tumors into low, moderate, or high-grade malignancy according to the following 3 factors: (1) the degree of tubule formation, (2) the regularity in the size, shape, and staining character of the nuclei, and (3) nuclei hyperchromasia and mitotic activity. He found a clear correlation between tumor grading and 5- and 10-year survival. Following this, in 1957, Bloom and Richardson (10) first proposed a numerical scoring system to facilitate the grading effort. Each of the above 3 features was examined and given a score of 1, 2, or 3, with a total possible score of 3 to 9 points. Then the final grade was assigned as grade I for a score of 3 to 5, II for a score of 6 to 7, and III for a score of 8 to 9. This method was later recommended as the preferred grading system for breast cancer by WHO experts in 1968.

Figure 11-3. High-grade DCIS, comedo type. A. Extensive central necrosis is surrounded by a rim of highly anaplastic tumor cells. B. The tumor cells have high-grade nuclei (greater than 2.5 times that of red blood cells in diameter) with marked pleomorphism, prominent nucleoli, and mitotic figures (nuclear grade 3).
In the meantime, Black and colleagues concluded that only nuclear morphology is the most significant prognostic factor. Their nuclear grade evaluation was based on the regularity of the nuclear outline, the delicacy of the chromatin, nucleoli, and the presence and number of mitotic figures. However, this 5-grade system was in reverse numerical order to common practice in that grades 0 and 1 represent the most poorly differentiated nuclei. In 1980, Fisher and colleagues modified Black’s system, reducing it to a 3-grade system and reversing its numerical order to be consistent with other grading schemes. He then combined nuclear grade and tubule formation in evaluating the histologic grade of a tumor.

It was not until the early 1990s that Elston and Ellis (11) re-examined and modified the grading system by combining the Bloom and Richardson system with Black’s approach. The most important modification was to delete the “nuclear hyperchromasia” in the Bloom and Richardson system and introduce an objective and numerical method to assess the mitotic count. They also clearly defined the criteria for the other 2 features examined (tubule formation and nuclear pleomorphism). This Elston and Ellis system, also referred to as the Nottingham modification of the Bloom-Richardson system, soon became popular and widely used. It has held up as a statistically significant prognostic factor. It is currently recommended by the World Health Organization for use in all cases of invasive breast cancers.

Elston and Ellis’s modification of the Scarff-Bloom-Richardson method is the most widely used grading system of invasive breast carcinoma. Recently, it has been recommended by the panel of WHO experts and is outlined in the monograph edited by Tavassoli and Devilee (2003). It includes 3 components: evaluation of the extent of the formation of tubules and glands, an estimation of the degree of nuclear pleomorphism, and the counting of mitoses.

Tubule and gland formation are assessed and given 1 to 3 points, as follows:
- One point. Tubules or glands formed in >75% of the tumor.
- Two points. Tubules or glands formed in 10% to 75% of the tumor.
- Three points. Few, if any, tubules formed, accounting for <10% of the tumor.

Nuclear pleomorphism is assessed and given 1 to 3 points, as follows:
- One point. Tumor nuclei are small, regular, and uniform.
- Two points. Tumor nuclei are moderately increased in size and show variability.
- Three points. Tumor nuclei show marked variation.

Mitotic figures are counted, and the scores are converted into 1 to 3 points, as follows:
- Field diameter (mm) 0.44 0.59 0.63
- Field area (mm²) 0.152 0.274 0.312
- One point. Mitotic count 0–5 0–9 0–11
- Two points. Mitotic count 6–10 10–19 12–22
- Three points. Mitotic count >11 >20 >23

The final grade, combining values of the above 3 features, is calculated as follows:
- **Grade 1, well-differentiated carcinoma.** 3 to 5 points

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**Figure 11-4.** Invasive well-differentiated ductal carcinoma. A. The majority of tumor is formed of well-recognized tubules/glands (tubule formation >75%, score 1). B. Tumor nuclei are small and uniform, with minimal pleomorphism (nuclear grade 1). Mitosis is rare (score 1). The final histologic grade is 3 out of a total score of 9, indicating a grade 1 (well-differentiated) breast carcinoma.
11. Tumors of the Breast

• Grade 2, moderately differentiated carcinoma. 6 to 7 points (Figure 11-5)
• Grade 3, poorly differentiated carcinoma. 8 to 9 points (Figure 11-6)

Ancillary methods are not essential for grading, but they may be used for special purposes, as follows:
• Immunohistochemical stains for epithelial and myoepithelial markers can be helpful in cases when invasion is questionable.
• Immunohistochemical stains for E-cadherin can be useful in differentiating invasive ductal carcinoma (E-cadherin positive) from invasive lobular carcinoma (E-cadherin negative).
• Immunohistochemical staining for estrogen receptor, progesterone receptor, and Her2/neu expression have prognostic and therapeutic values and should be performed in all invasive carcinoma cases.
• Ki-67 has been suggested as an objective substitute for mitotic counts in the grading system (12–14).

Figure 11-5. Invasive moderately differentiated ductal carcinoma. A. Tumor cells grow in solid cords and nests, with occasional recognizable tubules/glands (tubule formation <10%, score 3). B. Tumor nuclei are moderately increased in size, with mild pleomorphism (nuclear grade 2). Rare mitoses are seen (2/10 hpf, 0.59 field diameter, score 1). The final histological grade is 6 out of a total of 9, indicating a grade 2 (moderately differentiated) breast carcinoma.

Figure 11-6. Invasive poorly differentiated ductal carcinoma. A. There is no evidence of glandular formation (tubule formation <10%, score 3). B. Tumor cells are large with marked pleomorphism (nuclear grade 3). Numerous mitoses are seen, with some atypical forms (more than 20 per 10 hpf, 0.59 field diameter, score 3). The final histological grade is 9 out of a total of 9, indicating a grade 3 (poorly differentiated) breast carcinoma.
Measurement of the degree of genomic instability in breast carcinomas may improve grading at the genetic level (15).

Comments

1. Nuclear grade is an independent prognostic marker in addition to the histologic grade, and should be mentioned separately in the pathology report.
2. All invasive carcinomas, including invasive ductal carcinoma, invasive lobular carcinoma, and special types (medullary carcinoma, tubular carcinoma, mucinous carcinoma, and the like) are graded using this system.
3. Tumor size and margin should be documented in the pathology report.

Phyllodes Tumors

Phyllodes tumors are biphasic tumors characterized by leaf-like structures lined by a double-layered epithelial component, surrounded by overgrowing hypercellular stroma. Depending on the cellularity and atypia of the stromal component, they may have features of benign tumors and resemble fibroadenomas, or be malignant and share features with breast sarcoma.

The grading of phyllodes tumors is described in detail in the WHO monograph (Tavassoli and Devilee, 2003). On the basis of stromal cellularity, cellular pleomorphism, mitotic activity, the appearance of margins, and stromal distribution, phyllodes tumors are divided into 3 groups and labeled either benign, borderline, or malignant.

**Benign phyllodes tumor.** This tumor shows modest stromal cellularity, mild cellular pleomorphism, and no or only a few mitoses, and has well-circumscribed pushing margins. The stromal distribution is uniform (Figure 11-7A).

**Borderline phyllodes tumor.** This tumor displays modest stromal cellularity, moderate cellular pleomorphism, and moderate mitotic activity (< 10/10 hpf), and has partially infiltrative margins. There is stromal overgrowth, but it is typically uneven.

**Malignant phyllodes tumor.** This tumor has marked stromal cellularity and cellular pleomorphism, along with numerous mitoses (>10/10 hpf) and widely invasive margins. Invariably, it shows clear stromal overgrowth (Figure 11-7B).

Ancillary methods are not required for grading, but an immunohistochemical stain for indicators of proliferative activity, especially MIB-1 (Ki-67), may be a valuable prognostic factor in malignant phyllodes tumor (16).

Comments

1. The term “cystosarcoma phyllodes” is inappropriate and should be abandoned, because most of these tumors follow a benign course, and thus the term “sarcoma” is misleading.
2. A sampling of 1 block for every 1 cm of maximal tumor dimension is necessary for an accurate grading of phyllodes tumors, due to the presence of structural variability.
3. The tumors should be graded according to the areas of highest cellularity and atypia.
4. Stromal overgrowth is defined as the absence of epithelial elements in at least 1 low-power field (lpf) (40x) (17).

5. It has been suggested that the mitotic count be related to the field diameter instead of high-power fields (hpf), because the size of the high-power fields varies among microscopes (18).

6. In malignant phyllodes tumors, the epithelial component may only be identified after examining multiple sections, due to overgrowth of the sarcomatous component.

7. The sarcomatous component in malignant phyllodes tumor is usually fibrosarcoma. However, heterologous differentiation including liposarcoma, osteosarcoma, chondrosarcoma, or rhabdomyosarcoma may occur, and such changes should be documented in the diagnostic report.

References

Books and Monographs


Tavassoli F, Devilee P, eds. World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of the Breast and Female Genital Organs. Lyon: IARC; 2003.

Articles


