Histological tumour grade (Core and Non-core)

Histological grade is part of current European Society for Medical Oncology (ESMO)-European Society of Gynaecological Oncology (ESGO) management guidelines for endometrioid and mucinous carcinomas.[1] Serous carcinomas are now classified as low grade serous or high grade serous,[2] and despite the names including the term grade, these are two different histotypes rather than low grade and high grade variants of the same tumour type. Hence, grading does not apply to serous carcinomas. Clear cell carcinomas, un-/dedifferentiated carcinomas, anaplastic carcinomas, carcinosarcomas and mesonephric-like carcinomas are aggressive tumours and grading does not apply. There is no grading system for malignant Brenner tumours. If chemotherapy has been administered, tumour grading (and typing) may need to be based on the pre-chemotherapy biopsy.

The independent prognostic significance of grade for ovarian endometrioid carcinomas has only recently been validated.[3] The 1988 International Federation of Gynaecology and Obstetrics (FIGO) grading system is widely used for grading endometrioid carcinomas of ovarian and endometrial origin.[4] The FIGO grading system is based on architecture; tumours with <5% non-squamous solid component are grade 1, those with 5-50% solid areas are grade 2, and tumours with >50% of solid architecture are classified as grade 3.[4] When grade 1 and 2 tumours show severe nuclear atypia in the majority of the tumour cells (grade 3 nuclei), the histological grade is increased by one.[4,5]

Dedifferentiation in endometrioid carcinoma, sometimes with Switch/Sucrose non-fermenting (SWI/SNF) alterations, results in highly aggressive behaviour and such tumours are high grade by definition.[6] A significant majority of ovarian endometrioid carcinomas are grade 1 and 2. However, there is a subset of grade 3 endometrioid carcinomas which should be diagnosed with caution, since a significant proportion of such tumours are in fact high grade serous carcinomas with so called SET features (solid, pseudoendometrioid, transitional cell). Immunohistochemistry (IHC) is useful in this regard (see **ANCILLARY STUDIES)**. The interobserver reproducibility of grading is limited and several studies have attempted to improve on it.[7-12] There are shortcomings of a primarily architecturally based grading system. Certain growth patterns of endometrioid carcinoma such as spindled with bland nuclear features may be over-graded. On the contrary, tumours with non-solid architecture but high grade nuclear atypia may be under-graded. For example, in a recent study a number of p53 abnormal (p53abn) ovarian endometrioid carcinomas with aggressive course were graded as 1.[3]

As compared to the FIGO grading system,[4] the Silverberg grading system[13] was found to correlate better with survival in a multivariate analysis, although outcome in ovarian endometrioid carcinoma is mostly dictated by stage.[5] The Silverberg system (Table 4) takes into account nuclear atypia and mitotic activity in addition to architecture. Thus, the scores for architecture (majority glandular=1, papillary=2, solid=3), nuclear atypia (mild=1, moderate=2, severe=3), mitotic activity per millimetre $(mm)^2$ of tumour area or in 10 high power fields (HPF) (based on each HPF being 0.345 mm^2 in area, as per the original study;[13] 0-3 mitotic figures/mm^2 (or 0 to 9 mitotic figures per 10 HPF) =1, 3-7 mitotic figures/mm^2 (or 10 to 24 mitotic figures per 10 HPF) =2, and >7 mitotic figures/mm^2 (or ≥25 mitotic figures per 10 HPF) =3) are added to obtain a score for determining the final grade (G1: 3 to 5, G2: 6 to 7, G3: 8 to 9). The better performance of the Silverberg system was attributed to the better separation of grade 2 from the grade 3 tumours, which had a poor outcome.[5]

Table 4: The Silverberg grading system.[13]

Criterion	Score
Architecture (majority pattern)	
Glandular	1
Papillary	2
Solid	3
Nuclear atypia	
Mild	1
Moderate	2
Severe	3
Mitotic count per mm^2	
<3 mitotic figures/mm^2	1
3-7 mitotic figures/mm^2	2
>7 mitotic figures/mm^2	3
Final Grade	**Total Score**
Grade 1	3-5
Grade 2	6-7
Grade 3	8-9

The International Collaboration on Cancer Reporting Ovary Carcinoma Dataset Authoring Committee (DAC) panel agrees that there is insufficient evidence for a change in the grading system of endometrioid carcinomas and continues to recommend the FIGO grading system.[4]

In addition to grading, molecular subtype assignment may further improve outcome prediction in the same way as for endometrioid carcinoma of the uterus; this is done with IHC for mismatch repair proteins and p53 and by sequencing for exonuclease domain mutations (EDM) of *Polymerase epsilon* (*POLE*).[3,14]

Some management guidelines for mucinous carcinomas require grading.[1] The DAC previously suggest that if grading of mucinous carcinomas is undertaken (a non-core element rather than a core element), the same grading system for endometrioid carcinomas should be used. However, a recent study showed no prognostic significance of the FIGO grading system and reemphasised that mucinous carcinomas only rarely show a solid growth pattern.[15] In this study, the Silverberg grade was significantly associated with survival, although all mucinous carcinomas were graded as grade 1 or 2 by the Silverberg system, and none as grade 3.[15] The DAC now recommends the Silverberg grading system[13] for mucinous carcinomas as a non-core reporting element.

The same study also proposed a growth-based grading system based on the pattern of invasion.[15] Expansile/confluent invasion or infiltrative invasion ≤10% of the tumour is graded as 1 while infiltrative invasion >10% is graded as 2.[15] This was significantly associated with survival in univariable analysis in this relatively small study of 46 cases.[16] This corroborates earlier studies showing that while infiltrative invasion is associated with higher stage, it also predicts higher risk of recurrence at Stage I.[16-19] It is important to note, however, that an infiltrative pattern of invasion is a characteristic feature of metastatic mucinous carcinoma. In one study, the infiltrative pattern of invasion lost its significant association with survival after metastatic carcinomas to the ovary were excluded.[20] If an infiltrative/destructive pattern is present, metastatic carcinoma should carefully be ruled out. The quantification of the infiltrative component as focal (≤10%) or diffuse (>10%) may be recorded to allow more data to be gathered for future studies.

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