Histological tumour grade (Recommended)

Reason/Evidentiary Support

Grading of cervical carcinoma

Tumour grade is regularly included in histopathology reports of cervical squamous cell carcinoma (SCC) and adenocarcinoma (ACA). However, at present no particular grading system(s) has achieved universal acceptance and grading of these tumours remains of uncertain clinical value.[1-3] For example, grade is not amongst the factors considered in determining the Gynecology Oncology Group (GOG) score which is used to assess the need for adjuvant therapy following surgery for low-stage cervical carcinomas.[4] Not uncommonly, studies that assess grade as a potential prognostic variable provide no details of the grading system employed, and this is also true of large multicentre investigations such as SEER analyses.[5,6] For these and other reasons (discussed below), tumour grading is not listed as a required but rather a recommended element. Furthermore, no particular grading system for squamous carcinoma or adenocarcinoma is recommended.

General considerations

1. As with tumours arising in other anatomical sites, grading of cervical carcinomas has a considerable subjective component and this probably explains, at least in part, the variable proportion of well, moderately, and poorly-differentiated tumours reported in different studies. However, some investigators have demonstrated reasonable intra- and inter-observer agreement using more complex multifactor grading schemes in SCC (discussed below).

2. Almost all cervical SCCs are HPV-associated and given that HPV-associated SCCs very commonly have a “basaloid” morphology with minimal keratinisation, they are very commonly poorly-differentiated.

3. Most clinically advanced cervical carcinomas are treated with primary chemoradiation rather than surgery and histological sampling may be limited to a small diagnostic biopsy. This may not be fully representative due to tumour heterogeneity and could be potentially misleading as regards tumour differentiation or grade.[1] This may be particularly relevant since less differentiated appearing tumour elements may be located more deeply towards the invasive margin.[2]

4. There is an implicit correlation between tumour subtype and grade in certain cervical carcinomas and therefore a separate grade may not be applicable. For example, pure villoglandular ACA of the cervix is by definition a low-grade neoplasm while serous and clear cell carcinoma, as in the endometrium, are considered high-grade by default. Similarly, ‘gastric-type’ cervical ACAs and NECs are clinically aggressive regardless of their histological pattern and therefore are best considered high-grade automatically.[7,8] There is no published grading system for cervical mesonephric ACAs. Several variants of cervical SCC are also recognised, although most do not differ from conventional SCC in terms of prognosis or therapy.[9]

5. It is uncertain whether a truly ‘undifferentiated’ cervical carcinoma should be regarded as a separate tumour subtype analogous, for example, to similar tumours arising in the endometrium.

6. Grading of very small superficially (‘early’) invasive carcinomas of either squamous or glandular type is probably not possible or relevant.

Grading of Cervical SCC

Historically, cervical SCCs were graded using Broder’s system or modifications thereof based upon the degree of keratinisation, cytological atypia and mitotic activity. In some schemes, the pattern of invasion (pushing versus infiltrating) has also been taken into account. Traditionally, SCCs have also been subclassified into large cell keratinising, large cell non-keratinising and small cell non-keratinising categories, with these sometimes being regarded as approximately equivalent to well, moderately and poorly-differentiated, respectively. As noted above, this raises the issue whether such categorisation represents a tumour subtype (arguably not further graded), or a grade within a

spectrum of a single type of tumour. It should be noted that some studies have found that the keratinising variant of large cell SCC actually has a poorer prognosis than the non-keratinising variant, an apparently paradoxical finding if keratinisation is deemed to be evidence of better differentiation. It is also uncertain what proportion of "small cell SCCs" reported in the older literature would now be classified as high-grade NECs (small cell NEC), and this could potentially bias the supposedly poor outcome of this tumour category.

More complex multifactor grading systems (MGS) that include both tumour and host/stromal parameters have been assessed in cervical carcinomas, mainly SCC.[10-14] For example, the system employed by Stendahl et al,[10] based upon that used in head and neck SCC, comprised eight features, 4 of which were tumour-related (growth pattern, differentiation, pleomorphism and mitoses) and four of which were stromal-related (pattern of invasion, stage/depth of invasion, vascular invasion and inflammatory reaction). Each factor was scored from 1 to 3 and thus the potential total MGS score ranged from 8-24 points. Simplified modifications to the MGS have also been described including systems that selectively focus upon the invasive tumour border or the patterns of tumour invasion.[15-18] However, the "cut-off value" for tumour grade has varied in different studies and not all have demonstrated a correlation with prognosis.[2,19,20] At present, none of these grading systems has been widely adopted in routine diagnostic practice.

Grading of Cervical ACA

As with SCC, it is controversial whether grading has independent prognostic value in cervical ACA. Whilst a correlation between higher grade and adverse outcomes has been reported,[21-25] at least for poorly differentiated tumours, this has not been a universal finding.[26,27] It should also be noted that some studies have included a variable proportion of less common histological subtypes such as adenosquamous carcinoma, mesonephric, gastric-type and clear cell carcinoma[21,24,25] and often tumour details are not provided. Therefore, it is not clear whether the reported grading data are applicable to usual-type cervical ACA or have been biased by the inclusion of other more aggressive tumour subtypes (for example, gastric-type ACA).

Most grading systems for cervical ACA have been based upon the relative proportion of glandular differentiation, typically following the FIGO system for endometrial endometrioid adenocarcinoma (EEC). However, the maximum permitted extent of solid growth for a grade 1 cervical ACA has been variably specified to be 5%[28,29] or 10%.[25,30] As with EEC, an upward grade adjustment has been suggested for those tumours exhibiting more marked cytological atypia. However, it is pertinent that usual-type cervical ACAs typically demonstrate more marked nuclear atypia, mitotic and apoptotic activity than architecturally similar EECs. [31] There are no separate grading systems for the various non-HPV related cervical ACAs.

Recently, a system of assessing cervical ACAs based upon their invasive growth pattern has been developed, and this has been shown to be reproducible amongst pathologists and to correlate with the risk of lymph node metastasis and patient outcomes.[32-35] If these findings are confirmed by additional studies it may be argued whether this system could be considered a complement to, or even an alternative to, conventional grading. The latter has traditionally been based upon the cytoarchitectural pattern of the neoplasm itself but as noted above, tumour-stromal relationships including the pattern of stromal invasion have been included in earlier grading schemes of cervical SCC.

Grading of Cervical Adenosquamous Carcinoma

Although it has been suggested that adenosquamous carcinomas are graded on the basis of the degree of differentiation of both the glandular and squamous components, there is no well-established grading system for these neoplasms which has been shown to be of prognostic significance.

References

1 Benda JA (1996). Histopathologic prognostic factors in early stage cervical carcinoma. *J Natl Cancer Inst Monogr*(21):27-34.

2 Zaino R, Ward S, Delgado G, Bundy B, Gore H, Fetter G, Ganjei P and Frauenhofer E (1992). Histopathologic Predictors of the Behavior of Surgically Treated Stage IB Squamous Cell Carcinoma of the Cervix. A Gynecologic Oncology Group Study. *Cancer* 69(7):1750-1758.

3 Tiltman AJ (2005). The pathology of cervical tumours. *Best Pract Res Clin Obstet Gynaecol* 19(4):485-500.

4 Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT and Major F (1990). Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol* 38:352-357.

5 Vinh-Hung V, Bourgain C, Vlastos G, Cserni G, De Ridder M, Storme G and Vlastos AT (2007). Prognostic value of histopathology and trends in cervical cancer: a SEER population study. *BMC Cancer* 7:164.

6 Macdonald OK, Chen J, Dodson M, Lee CM and Gaffney DK (2009). Prognostic significance of histology and positive lymph node involvement following radical hysterectomy in carcinoma of the cervix. *Am J Clin Oncol* 32(4):411-416.

7 Kojima A, Mikami Y, Sudo T, Yamaguchi S, Kusanagi Y, Ito M and Nishimura R (2007). Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of the uterine cervix. *Am J Surg Pathol* 31(5):664-672.

8 Karamurzin YS, Kiyokawa T, Parkash V, Jotwani AR, Patel P, Pike MC, Soslow RA and Park KJ (2015). Gastric-type Endocervical Adenocarcinoma: An Aggressive Tumor With Unusual Metastatic Patterns and Poor Prognosis. *Am J Surg Pathol* 39(11):1449-1457.

9 Stoler M, Bergeron C and Colgan TJ et al (2014). Squamous cell tumours and precursors. In: *WHO Classification of Tumours of Female Reproductive Organs, 4th ed.*, Kurman RJ, Carcangiu ML, Herrington CS and Young RH (eds), IARC, Lyon, 172-182.

10 Stendahl U, Eklund G and Willen R (1983). Prognosis of invasive squamous cell carcinoma of the uterine cervix: a comparative study of the predictive values of clinical staging IB--III and a histopathologic malignancy grading system. *Int J Gynecol Pathol* 2(1):42-54.

11 Bichel P and Jakobsen A (1985). Histopathologic grading and prognosis of uterine cervical carcinoma. *Am J Clin Oncol* 8(3):247-254.

12 Kristensen GB, Abeler VM, Risberg B, Trop C and Bryne M (1999). Tumor size, depth of invasion, and grading of the invasive tumor front are the main prognostic factors in early squamous cell cervical carcinoma. *Gynecol Oncol* 74(2):245-251.

13 Lindahl B, Ranstam J and Willen R (2007). Prospective malignancy grading of invasive squamous carcinoma of the uterine cervix. Prognostic significance in a long-term follow-up. *Anticancer Res* 27(4c):2829-2832.

14 Eggen T, Arnes M, Moe B, Straume B and Orbo A (2007). Prognosis of early cervical cancer (FIGO Stages IA2, IB, and IIA) in northern Norway predicted by malignancy grading score and objective morphometric image analysis. *Int J Gynecol Pathol* 26(4):447-456.

15 Stendahl U, Eklund G and Willen R (1981). Invasive squamous cell carcinoma of the uterine cervix. IV. Analysis of a histopathologic malignancy grading system and construction of a partial index. *Acta Radiol Oncol* 20(5):289-284.

16 Graflund M, Sorbe B, Hussein A, Bryne M and Karlsson M (2002). The prognostic value of histopathologic grading parameters and microvessel density in patients with early squamous cell carcinoma of the uterine cervix. *Int J Gynecol Cancer* 12(1):32-41.

17 Horn LC, Fischer U, Raptis G, Bilek K, Hentschel B, Richter CE, Braumann UD and Einenkel J (2006). Pattern of invasion is of prognostic value in surgically treated cervical cancer patients. *Gynecol Oncol* 103(3):906-911.

18 Horn LC, Hentschel B and Braumann UD (2008). Malignancy grading, pattern of invasion, and juxtatumoral stromal response (desmoplastic change) in squamous cell carcinoma of the uterine cervix. *Int J Gynecol Pathol* 27(4):606-607.

19 Crissman JD, Budhraja M, Aron BS and Cummings G (1987). Histopathologic prognostic factors in stage II and III squamous cell carcinoma of the uterine cervix. An evaluation of 91 patients treated primarily with radiation therapy. *Int J Gynecol Pathol* 6(2):97-103.

20 Samlal RA, van der Velden J, Schilthuis MS, Gonzalez Gonzalez D, Ten Kate FJ, Hart AA and Lammes FB (1997). Identification of high-risk groups among node-positive patients with stage IB and IIA cervical carcinoma. *Gynecol Oncol* 64(3):463-467.

21 McLellan R, Dillon MB, Woodruff JD, Heatley GJ, Fields AL and Rosenshein NB (1994). Long-term follow-up of stage I cervical adenocarcinoma treated by radical surgery. *Gynecol Oncol* 52(2):253-259.

22 Goodman HM, Buttlar CA, Niloff JM, Welch WR, Marck A, Feuer EJ, Lahman EA, Jenison EL and Knapp RC (1989). Adenocarcinoma of the uterine cervix: prognostic factors and patterns of recurrence. *Gynecol Oncol* 33(2):241-247.

23 Lea JS, Sheets EE, Wenham RM, Duska LR, Coleman RL, Miller DS and Schorge JO (2002). Stage IIB-IVB cervical adenocarcinoma: prognostic factors and survival. *Gynecol Oncol* 84(1):115-119.

24 Eifel PJ, Morris M, Oswald MJ, Wharton JT and Delclos L (1990). Adenocarcinoma of the uterine cervix. Prognosis and patterns of failure in 367 cases. *Cancer* 65(11):2507-2514.

25 Baalbergen A, Ewing-Graham PC, Hop WC, Struijk P and Helmerhorst TJ (2004). Prognostic factors in adenocarcinoma of the uterine cervix. *Gynecol Oncol* 92(1):262-267.

26 Alfsen GC, Kristensen GB, Skovlund E, Pettersen EO and Abeler VM (2001). Histologic Subtype Has Minor Importance for Overall Survival in Patients with Adenocarcinoma of the Uterine Cervix. A Population-Based Study of Prognostic Factors in 505 Patients with Nonsquamous Cell Carcinomas of the Cervix. *Cancer* 92(9):2471–2483.

27 Leminen A, Paavonen J, Forss M, Wahlstrom T and Vesterinen E (1990). Adenocarcinoma of the uterine cervix. *Cancer* 65(1):53-59.

28 Silverberg SG and Ioffe OB (2003). Pathology of cervical cancer. *Cancer J* 9(5):335-347.

29 D'Angelo E and Prat J (2014). Cervical glandular neoplasia. In: *Pathology of the Female Reproductive Tract, 3rd edition*, Mutter GL and Prat J (eds), Churchill Livingstone, 251-289.

30 Lawrence WD, Abdul-Karim FW, Crum C and Fu Y-S (2000). Recommendations for the Reporting of Surgical Specimens Containing Uterine Cervical Neoplasms. *Mod Pathol* 13(4):1029-1033.

31 Young RH and Clement PB (2002). Endocervical adenocarcinoma and its variants: their morphology and differential diagnosis. *Histopathology* 41:185-207.

32 Roma AA, Diaz De Vivar A, Park KJ, Alvarado-Cabrero I, Rasty G, Chanona-Vilchis JG, Mikami Y, Hong SR, Teramoto N, Ali-Fehmi R, Rutgers JK, Barbuto D and Silva EG (2015). Invasive endocervical adenocarcinoma: a new pattern-based classification system with important clinical significance. *Am J Surg Pathol* 39(5):667-672.

33 Diaz De Vivar A, Roma AA, Park KJ, Alvarado-Cabrero I, Rasty G, Chanona-Vilchis JG, Mikami Y, Hong SR, Arville B, Teramoto N, Ali-Fehmi R, Rutgers JK, Tabassum F, Barbuto D, Aguilera-Barrantes I, Shaye-Brown A, Daya D and Silva EG (2013). Invasive endocervical adenocarcinoma: proposal for a new pattern-based classification system with significant clinical implications: a multi-institutional study. *Int J Gynecol Pathol* 32(6):592-601.

34 Roma AA, Mistretta TA, De Vivar AD, Park KJ, Alvarado-Cabrero I, Rasty G, Chanona-Vilchis JG, Mikami Y, Hong SR, Teramoto N, Ali-Fehmi R, Barbuto D, Rutgers JK and Silva EG (2016). New pattern-based personalized risk stratification system for endocervical adenocarcinoma with important clinical implications and surgical outcome. *Gynecol Oncol* 141(1):36-42.

35 Rutgers JK, Roma AA, Park KJ, Zaino RJ, Johnson A, Alvarado I, Daya D, Rasty G, Longacre TA, Ronnett BM and Silva EG (2016). Pattern classification of endocervical adenocarcinoma: reproducibility and review of criteria. *Mod Pathol* 29(9):1083-1094.