International Journal of Gynecological Pathology
38:S3–S8, Lippincott Williams & Wilkins, Baltimore

OPEN

Current Practices in the Processing, Diagnosis, and Reporting of Endometrial Carcinoma: Results of a Web-based Survey by the International Society of Gynecological Pathologists (ISGyP)

Vinita Parkash, M.B.B.S., Xavier Matias-Guiu, M.D., Ph.D., Esther Oliva, M.D., Anais Malpica, and W. Glenn McCluggage, F.R.C.Path.

Summary: There have been significant advances in our understanding of the biology and classification of endometrial carcinoma, over the last few years, and the new prediction models proposed for prognostication. To accurately diagnose and stage tumors and apply these prediction models, it is necessary that there be standardized processing of specimens, and a common understanding and usage of the diagnostic terminology of endometrial carcinoma. The International Society of Gynecological Pathologists embarked on an ambitious project to achieve this goal in 2015. An early step in the process was to collect baseline information on existing practices with regard to the processing, diagnosis, and reporting of endometrial carcinomas among the members of the society. This was carried out using a web-based survey comprising 112 questions. The results are presented herein and reveal areas of uniformity but also areas of substantial variation among pathologists. The results of the survey assisted in developing the subsequent recommendations that follow as separate articles in this issue of the journal with regard to processing, diagnosis, and reporting of endometrial carcinomas.
Key Words: Endometrial carcinoma—Processing—Diagnosis—Reporting—Survey.

From the Department of Pathology and Obstetrics and Gynecology, Yale School of Medicine and the Yale School of Public Health, New Haven, Connecticut (V.P.); Department of Pathology, Hospital University Arnau de Vilanova and University de Bellvitge, Irblleida, Idibell, University of Lleida, Ciberonc, Lleida, Spain (X.M.G.); Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (E.O.); Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas (A.M.); and Department of Pathology, Belfast Health and Social Care Trust, Belfast, UK (W.G.M.).

Presented in part at the 105th Annual Meeting of the United States and Canadian Academy of Pathology, March 2016, Seattle, WA.

The authors declare no conflict of interest.

Address correspondence and reprint requests to Vinita Parkash, MBBS, Department of Pathology, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510. E-mail: vinita.parkash@yale.edu.

Endometrial carcinoma is the sixth most common malignancy of women worldwide (www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/endometrial-cancer-cancer-lining-womb-statistics). It is the most common gynecologic cancer in the developed world and the second most common in the developing world (www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/endometrial-cancer-cancer-lining-womb-statistics). Significant advances have been made in our understanding of the biology and classification of endometrial carcinoma over the past few years, and it is now expected that the pathologic evaluation of a cancer resection specimen will inform not only on staging parameters, but also on accurate subtyping and the provision of prognostic parameters to accurately direct management (1).

DOI: 10.1097/PGP.0000000000000515

There have been no large-scale studies documenting the usual practices for processing, diagnosis, reporting, and ancillary testing of endometrial carcinomas among gynecologic pathologists. The International Society of Gynecological Pathologists (ISGyP) undertook a survey of its members, to investigate these parameters and gather baseline information, and the results are presented herein.

MATERIALS AND METHODS

Details of the rationale for the project are presented elsewhere in this issue. A 112-question survey was designed by the 5 members of the steering committee appointed by the Board of Directors of the ISGyP (authors of this paper). The survey was piloted, modified, and approved by the members of the Board of Directors and the education committee of the ISGyP. The approved survey was sent to the membership using the SurveyMonkey platform (www.surveymonkey.com). The series of questions explored current practice and perceptions relating to processing, diagnosing, reporting, and ancillary testing of endometrial carcinoma. The questions varied in format, including some with binary responses (Yes/No or True/False), single-choice responses from a list of possibilities, and multiple possible selections from a list of possibilities. For some questions, respondents were offered the opportunity to expand on their responses.

A link to the survey was e-mailed to all members of the society. Participants were given a 6-wk deadline to complete the survey, with 3 reminders sent over that time period.

Respondents were given the opportunity to identify themselves and provide e-mail addresses.

They were incentivized to undertake the survey by indicating that they would be invited to the upcoming ISGyP consensus conference that was scheduled for Seattle, WA, USA, in March 2016, to coincide with the annual United States and Canadian Academy of Pathology meeting. While demographic information (eg, country of practice) was requested, the responses were broadly analyzed as a single cohort, with some comparisons performed between North American and European pathologists, the 2 regions with the largest cohort of respondents.

RESULTS

There were 242 respondents to the survey representing 47% of the total society membership, with 221 (91.3%) respondents answering all 112 questions. Respondents came from 30 countries with 51% from North America, 19% from Europe (41% of these from the UK), 11% from Asia and Africa, 6% from Oceania, and 2% from South America. Seventy-six percent of respondents self-identified as academics and 24% as pure gynecologic pathologists. The demographics of the respondents are detailed in Table 1.

TABLE 1. *Demographics of respondents to study*

	Responses (%)
Practice parameters	
Monospecialist	25.91
Oligospecialist	52.27
Generalist	21.82
Percentage of practice comprising gynecologic specimens	
0–30	48.00
31–60	49.00
61–100	12.00
Who grosses the hysterectomy specimens of endometrial carcinoma	
You	30.91
Pathology assistant	59.55
Resident/trainee	73.64
Years out of training	
1–10	27.00
11–20	27.00
>20	46.00
No. gynecologic pathologists in practice	
1	19
2–5	69
≥6	12
Percentage of respondents diagnosing only biopsy samples	1

TABLE 2. *Responses regarding intraoperative assessment*

	% Respondents		
Parameters assessed at intraoperative assessment	Always	Never	Sometimes
Grossing performed at intraoperative assessment	30	39	31
Frozen section performed at intraoperative assessment	23	32	45
Following numbers only from respondents performing FS			
Size of tumor given at frozen section	56	44	
Adnexa evaluated grossly	89	11	
Myometrial invasion reported at frozen section	93	7	
Tumor type assessed at frozen section	88	12	
Grading of endometrioid carcinoma performed at frozen section	76	24	
Reporting lymphovascular invasion at frozen section	41	59	
Cervical involvement assessed at frozen section	3	10	87 (37 gross only)
Adnexa evaluated microscopically at frozen section	1	6	92

TABLE 3. *Responses regarding gross assessment of endometrial carcinomas*

Grossing practices	% Respondents answering in affirmative
Inking of serosa	46
Tissue always taken for molecular studies	33
Uterus always fixed in formalin before grossing	67
Entire cervix submitted for microscopic examination	1
Cervical sections taken at 6 and 12 o'clock	81
Vertical sections taken from the lower uterine section	71
Tumor size recorded	99
Tumor location in uterus recorded	94
Entire endometrium submitted in hysterectomy for atypical hyperplasia/ EIN	92
Entire adnexa submitted for microscopic examination	22
Entire adnexa submitted for microscopic examination if high-grade carcinoma	26
Fimbrial-tubal sections (with or without nonfimbrial sections) submitted for microscopic examination	95
Entire grossly normal ovaries submitted for microscopic examination	13
Single section submitted for microscopic examination from grossly normal ovaries	50
Parametrial sections submitted for microscopic examination	70
Clearing solution always used for lymph node assessment	2
Clearing solution never used for lymph node assessment	84
Entire lymph nodes submitted for microscopic examination	95
Residual fat submitted for microscopic examination	53
Residual fat never submitted for microscopic examination	18
No. of nodes per cassette depends on size	83
Sentinel nodes examined	47
Sentinel nodes examined at frozen section if grossly suspicious	21
Sentinel node protocol used for sentinel node assessment	75
No. omental sections if gross tumor involvement present	2–4 (76)
If omentum grossly negative, no. sections depends on tumor type	Yes (31)
Prior biopsy results taken into consideration when assessing hysterectomy	82
Block key used for pathology report	79

EIN indicates endometrial intraepithelial neoplasia.

Responses with regard to intraoperative assessment (including frozen section examination) are tabulated in Table 2. The responses demonstrated substantial variation among pathologists with regard to the use of intraoperative assessment, with 39% of pathologists never assessing hysterectomy specimens for endometrial carcinoma intraoperatively. Of those who did undertake intraoperative assessment, most indicated that this was carried out either at the surgeon's request or to assess staging parameters. There was significant variability in the number of sections examined (1–8) and the parameters assessed at intraoperative assessment, with myometrial invasion being the most commonly evaluated (93% of respondents).

Responses to the grossing practice questions are tabulated in Table 3, and they also revealed significant variability in practice with regard to some parameters. There was broad agreement with respect to several parameters such as recording tumor size and location (99% and 94%, respectively), including fimbrial sections of the fallopian tube for histologic assessment (95%), submission of the entire endometrium in resection specimens for atypical hyperplasia/endometrial intraepithelial neoplasia (92%), and microscopic evaluation of entire lymph nodes (95%). However, there was variability in the number of sections of tumor examined, ranging from 1 to 2 sections per cm of the entire tumor (responses not shown). There was significant disagreement in practice with respect to other parameters, for example, inking of serosa (46%), evaluating a single section from grossly normal ovaries (50%), and lymph node assessment (53% not examining residual fatty tissue and 47% undertaking sentinel node assessment).

Microscopic variables assessed and reported are tabulated in Table 4. As a general observation, there was greater variability in the assessment of microscopic than gross parameters. International federation of gynecology and obstetrics (FIGO) grading was used by 97% of respondents. However, there was variability in the more granular use of the FIGO grading system, with 17% of respondents indicating that they assigned mixed FIGO grades to phenotypically heterogenous tumors. Reporting of background endometrium and cervical gland involvement was performed by 92% and 90% of respondents, respectively. There was significant variability with respect to minimal and necessary criteria to diagnose high-grade subtypes of endometrial carcinoma (serous, clear cell, carcinosarcoma, undifferentiated), with 22% to 60% of respondents variably using morphology alone to histotype tumors. Nine percent of respondents indicated that they did not report tumor stage in pathology reports; of those that did, 94% used the FIGO staging system with or without the TNM stage.

There was also substantial variability in ancillary testing of endometrial carcinomas, although testing for mismatch repair protein abnormalities and possible Lynch syndrome was performed in at least a

TABLE 4. *Responses regarding microscopic assessment of endometrial carcinomas*

Microscopic variables assessed in reporting of uterine carcinoma	
FIGO grading system used for endometrioid carcinomas	97%
Nuclear grade used to upgrade endometrioid carcinomas	2%
Mixed FIGO grades for morphologically different areas	17%
Diagnosis of serous carcinoma based on morphology alone	31%
Diagnosis of clear cell carcinoma based on morphology alone	45%
Diagnosis of undifferentiated carcinoma based on morphology alone	22%
Diagnosis of carcinosarcoma based on morphology alone	60%
Extra sections taken before making a diagnosis of undifferentiated carcinoma	17%
Relative ratios of sarcomatous and carcinomatous components reported for carcinosarcoma	42%
Epithelial component classified when diagnosis of carcinosarcoma rendered	80%
Sarcomatous component classified when diagnosis of carcinosarcoma rendered (heterologous vs. homologous)	93%
Cut-off percentage for minor tumor type in diagnosing mixed carcinoma	Variable (%)
Percentage of myometrial invasion reported	51
Absolute depth of myometrial invasion reported	78
Distance of tumor to serosa recorded	59
Patterns of myometrial invasion reported	49
Lower uterine segment involvement reported	87
Morphology of nontumorous endometrium recorded	90
Cervical gland involvement recorded	92
Depth of cervical stromal invasion recorded	60
Lymphovascular invasion determined on histologic examination alone	90
Lymphovascular invasion quantified	50
Pseudovascular invasion reported	16
Distinction made between lymphatic and blood vessel vascular involvement	22
Tumor in vessels (deep myometrium, parametrium, ovarian hilum, etc.) used to upstage tumor in the absence of tumor outside vascular channels	11
Parametrial involvement reported	68
Tumor involvement of adenomyosis in outer half of myometrium used to upstage tumor	10
Tumor considered stage IA if deep invasion from focus of adenomyosis is present	55
Free floating intraluminal tubal tumor used to upstage disease	5
Keratin granulomas used to upstage tumors	2
Peritoneal washings routinely examined	85
If washings positive, correlation made with other pathologic features and clinical history (use of intrauterine balloon manipulator)	44
Lymph node counts reported based on gross assessment	4
Lymph node counts reported based on microscopic assessment	31
Largest metastatic focus in lymph node measured	45
Isolated tumor cells in lymph node reported	65
Extranodal extension reported routinely	75
Pathologic staging stated in report	91
Classification system used for precursor of endometrioid carcinoma	EIN (13%), WHO 2014 (71%), WHO 2003 (16%)

Comments: questions were not asked regarding parameters, which are essential for staging, for example, cervical stromal involvement, adnexal involvement.

EIN indicates endometrial intraepithelial neoplasia; WHO, World Health Organization.

subset of cases by 82% of respondents (Table 5), with 27% of respondents undertaking the studies in all cases of endometrial carcinoma. Table 6 documents the parameters used to trigger the aforementioned testing.

Some variability in practice was apparent, between North American and European pathologists, as shown in Table 7. Differences included percentage of pathologists involved in grossing of specimens, use of intraoperative assessment, routine use of immunohistochemistry to histotype tumors, and performing studies to assess possible Lynch syndrome. North American pathologists generally used both TNM and FIGO staging systems, whereas European pathologists favored using only the FIGO system.

DISCUSSION

Recent years have witnessed an explosive growth in our understanding of endometrial carcinoma (1). Like ovarian carcinoma, endometrial carcinoma is not 1 entity, or even 2, as proposed by Bokhman (2), but comprises at least 4 distinctive molecular subtypes with differing prognoses (1). Another significant development has been the identification of endometrial carcinoma as a common, and often sentinel, tumor in Lynch syndrome,

TABLE 5. *Responses regarding ancillary testing of endometrial carcinomas*

Studies undertaken in some cases	82%
Studies undertaken in all endometrial carcinoma cases	27%
Studies undertaken in all endometrioid carcinoma cases	8%
Immunohistochemical studies done for Lynch syndrome assessment	94% (12% use 2 antibodies)
Lynch syndrome studies undertaken in all endometrial carcinomas	26%
Entire endometrium examined in prophylactic hysterectomy for Lynch syndrome	50%
Entire adnexa examined in prophylactic hysterectomy for Lynch syndrome	57%
Methylation studies performed if MLH1/PMS2 loss on immunohistochemistry	56%
Molecular analysis never performed	26%
Molecular analysis always performed	9%
Hormone receptor staining always performed	17%
If hormone receptor staining performed, is it used for prediction of response to hormone therapy	26%
Ploidy studies performed	2%
Molecular analysis for synchronous uterine and ovarian carcinomas performed	7%

one of the most common hereditary cancer syndromes. These discoveries have led to recommendations from clinical societies for extended reporting of prognostic factors and for routine screening of endometrial carcinomas for mismatch repair protein abnormalities (3). However, the impact of these advances on the practice of specialist gynecologic pathologists around the world is unknown. The ISGyP therefore undertook a web-based survey to document current practice patterns before convening a consensus conference and issuing guidelines for the diagnoses, reporting, and ancillary testing of endometrial carcinoma.

The results of our survey show certain consistent practices among gynecologic pathologists worldwide. For example, at grossing, recording tumor size and site, examination of the entire endometrium in resection specimens for atypical hyperplasia/endometrial intraepithelial neoplasia, and assessment of the fimbrial end of the fallopian tube appear embedded as routine practice. At microscopic assessment, reporting of tumor grade, pathologic stage, documentation of depth of myometrial invasion, assessment of cervical glandular involvement, and lymphovascular space invasion are near universal practices. There is also widespread acceptance and utilization of the FIGO grading and staging systems. That said, there are also areas of significant practice variability, including the number of sections of tumor, adnexal tissue, omentum, and lymph nodes examined. While FIGO grading is used universally for reporting, the actual usage shows some variability, with 17% of respondents using mixed grading for phenotypically heterogenous endometrioid carcinomas. Histotyping of nonendometrioid carcinomas, not unexpectedly, seems to be a particularly challenging area for gynecologic pathologists, with morphologic criteria alone being used for subtyping in 22% to 60% of cases, depending on the favored subtype, with ancillary studies being used variably. This raises some concerns about the consistency of diagnostic criteria across studies and institutions, especially as several studies have shown

TABLE 6. *Parameters used to trigger testing for possible Lynch syndrome*

Criterion for possible Lynch syndrome testing	% Respondents
Age based	41
Personal and family history based	42
Morphology and topography based	33
Combination	42
At request of clinician	70
Other (please specify)	11

TABLE 7. *Comparison between North American and European pathologists*

	North America (N = 115) (%)	Europe (N = 42) (%)
Percentage of pathologists involved in grossing of specimens	17	61
Pathologist's assistant grossing specimens	83	30
Practices with > 6 gynecologic pathologists	18	1
Intraoperative assessment never performed	17	61
Horizontal sectioning of lower uterine segment	23	53
Sentinel nodes assessed	58	31
Frozen section performed for sentinel nodes	29	53
Morphology alone used for diagnosis of serous carcinoma	8	37
Morphology alone used for diagnosis of clear cell carcinoma	7	29
Morphology alone used for diagnosis of undifferentiated carcinoma	35	56
Classify epithelial component in carcinosarcoma	71	95
Preferred methodology for recording depth of myoinvasion	Percentage (68%)	Inner/outer half (100%)
Distance to serosa recorded (mm)	47	73
Percentage of pathologists not undertaking Lynch syndrome studies	4	26
Lynch syndrome studies undertaken in all endometrial carcinomas	42	0
Methylation studies performed for loss of MLH1/PMS2	66	33

significant variability in the classification and typing of high-grade endometrial carcinoma, even among expert gynecologic pathologists (4–6).

Similarly, there is substantial variability with respect to assessment of risk for Lynch syndrome, with only a subset of pathologists performing these studies on all cases of endometrial adenocarcinomas (27%). Immunohistochemistry is the favored modality for initial investigation.

Our study also documents some practice differences between North American and European pathologists. In North America, there is a greater use of pathology assistants for grossing of specimens, greater use of intraoperative assessment and frozen sections, and an increased propensity to use ancillary studies for subtyping. North American pathologists are also more likely to report a TNM stage than European pathologists. This is not surprising, as in the United States, use of the American Joint Committee on Cancer version of TNM is required for College of Surgeons Cancer Center accreditation, NCCN Clinical decision guidelines implementation, and for the College of American Pathologists accreditation.

A drawback of this survey is that it was only sent to the members of ISGyP, and, as such, the results are skewed toward the practices of specialist gynecologic pathologists at academic centers. In spite of a relatively high participation rate of 47%, the possibility of a self-selection bias cannot be excluded. As always, reporting of the expected ideal rather than the practiced behavior may have influenced the results.

CONCLUSIONS

The survey shows areas of concordance and variability in practice among gynecologic pathologists worldwide in dealing with endometrial carcinoma specimens.

The results of this survey helped identify areas in need of consensus to standardize processing, diagnostic and reporting criteria, and ancillary testing of endometrial carcinoma. These results informed the deliberations of the Endometrial Carcinoma Project subcommittees for the International Society of Gynecological Pathology. The remaining articles in this journal describe the process and the recommendations that emerged from that project.

REFERENCES

1. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. *Nature* 2013;497:67–73.
2. Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol* 1983;15:10–17.
3. Randall LM, Pothuri B, Swisher EM, et al. Multi-disciplinary summit on genetics services for women with gynecologic cancers: a society of gynecologic oncology white paper. *Gynecol Oncol* 2017;146:217–24.
4. Han G, Sidhu D, Duggan MA, et al. Reproducibility of histological cell type in high-grade endometrial carcinoma. *Mod Pathol* 2013;26:1594–604.
5. Hoang LN, McConechy MK, Köbel M, et al. Histotype-genotype correlation in 36 high-grade endometrial carcinomas. *Am J Surg Pathol* 2013;37:1421–32.
6. Gilks CB, Oliva E, Soslow RA. Poor interobserver reproducibility in the diagnosis of high-grade endometrial carcinoma. *Am J Surg Pathol* 2013;37:874–81.