Article

The ISGyP Endocervical Adenocarcinoma Project: Master Plan Summary, Acknowledgment of Participants, and Participant Responses to Final Recommendations of the Expert Panels

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Summary: The International Society of Gynecological Pathologists carried out a multifaceted project with the broad aim of improving the pathological reporting of endocervical adenocarcinoma (EAC). The intentions were to promote and align practices with the WHO 2020 classification, which endorses HPV status-based classification of EAC and the Silva pattern-based assessment of HPV-associated EAC, to promote uniformity in applying the recent FIGO staging revisions on cervical carcinoma, and to provide best practice guidelines on all aspects of EAC pathology reporting. To facilitate the use of the new WHO/IIECC classification and the Silva system, two online educational portals were set up with training and test sets of scanned slides; these remain available to society members on the ISGyP educational website. In addition, a large international collaborative individual data collection project is ongoing, aiming to ascertain the prognostic value of EAC categories, and to provide a database with the potential to address unanswered questions. A single on-site meeting was held on February 29, 2020 in Los Angeles, in advance of the USCAP Annual Meeting; all other correspondence was by email and through electronic surveys. Project participants were invited to vote and comment on the recommendations contained within the practice guideline articles. The project received an enthusiastic response from pathologists across the world. This report includes an overview and summary of all aspects of the project, a list of participants and the results of polling on practice recommendations. Key Words: International Society of Gynecological Pathologists—Endocervical adenocarcinoma—Recommendations.

BACKGROUND

In 2019, under the leadership of its President, Dr Esther Oliva, the International Society of Gynecological Pathologists (ISGyP) embarked on a multifaceted project on endocervical adenocarcinoma (EAC), in part to synchronize with recent updates introduced by the revised FIGO 2018 staging for cervical carcinoma, the fifth edition of the World Health Organization classification of tumors of the female genital tract and the International Collaboration on Cancer Reporting for cervical cancers. In order to develop, promote and facilitate a uniform...
and standardized approach to pathologic reporting, the ISGyP EAC project engaged the ISGyP members and convened an expert panel to survey current practices to identify areas of discordance, construct an online training portal using scanned slides, develop best practice guidelines with recommendations for pathology reporting, assess ISGyP members response to the final recommendations via polling, and conduct an international multicenter outcome study. Herein we document the mechanics and timeline of these various project components and acknowledge the ISGyP members who contributed time, effort, and creative input to one or more of them.

PROJECT OVERVIEW

Project Aims
The overarching aim of the project was to improve the pathologic reporting of EAC. The specific goals are:

- To understand the spectrum of current global practices in the pathologic evaluation (gross specimen management, diagnosis, classification) and reporting (invasiveness, staging, margins) of endocervical cancer.
- To improve the global reproducibility of EAC classification and pathological reporting by:
  - Developing online self-education modules for applying the new International Endocervical Adenocarcinoma Criteria and Classification (IECC) system and Silva classification system of tumor invasiveness.
  - Developing evidence-based best practice guidelines for gross specimen management, tumor classification, staging and reporting, as well as managing problematic and controversial issues.
- To assess the prognostic significance of WHO/IECC EAC classification and Silva pattern-based classification of HPV-associated adenocarcinomas by conducting an international outcome study.

Project Components
An overview of the project components is illustrated in Figure 1.(1) Development of expert panel recommendations. A systematic approach to developing the recommendations was implemented, incorporating efforts to identify areas of problems and
| Recommendation                                                                                           | Agree, core | Agree, noncore | Disagree | Other |
|---------------------------------------------------------------------------------------------------------|-------------|----------------|----------|-------|
| 1. Endocervical adenocarcinomas should be classified according to the forthcoming WHO 2020 classification system, which incorporates the IECC system | 94          | 6              | 0        | 0     |
| 2. Both classification systems categorize endocervical adenocarcinomas into HPV-associated and HPV-independent types using morphology alone | 69          | 13             | 9        | 9     |
| 3. Not all HPV-associated endocervical adenocarcinomas, however, have easily identifiable mitoses and apoptotic bodies; in difficult cases, additional tests may be necessary | 68          | 26             | 0        | 6     |
| 4. The WHO 2020 and IECC systems incorporate newly described microscopic variants of HPV-associated endocervical adenocarcinomas | 67          | 30             | 1        | 2     |
| 5. Both HPV-associated and HPV-independent endocervical adenocarcinomas can be further stratified using existing criteria. Ancillary testing for diagnosis (such as p16) does not need be reflexively performed on all tumors since morphology is tightly linked to HPV status. p16 and high-risk HPV testing should be reserved for difficult or ambiguous cases | 66          | 24             | 5        | 5     |
| 6. If interpretation is difficult, a diagnostic algorithm based on the amount of intracytoplasmic mucin and ancillary analyses (such as HPV testing, p16, and GATA3 immunohistochemistry) may be useful in the differential diagnosis of the various histologic types | 60          | 38             | 0        | 2     |
| 7. RNA-based in situ hybridization for high-risk HPV exhibits higher sensitivity and specificity compared with HPV DNA polymerase chain reaction (PCR) | 26          | 50             | 16       | 8     |
| 8. RNA-based in situ hybridization (although not available in most institutions) for high-risk HPV has superior sensitivity, specificity, and positive and negative predictive values compared with p16 in identifying HPV-associated endocervical adenocarcinomas | 28          | 52             | 14       | 6     |
| 9. HPV-associated endocervical adenocarcinomas: usual-type tumors lacking intracytoplasmic mucin should not be diagnosed as endometrioid-type tumors | 82          | 15             | 2        | 1     |
| 10. HPV-associated endocervical adenocarcinomas: HPV-associated endocervical adenocarcinomas with villoglandular and micropapillary patterns can be designated as usual-type tumors, but these patterns should be noted on the pathology report | 51          | 45             | 1        | 3     |
| 11. HPV-associated endocervical adenocarcinomas: a diagnosis of primary cervical serous carcinoma should not be made; when dealing with serous-like morphology, most examples will represent an HPV-associated endocervical adenocarcinoma with serous-like morphology or a metastasis from the uterine corpus or fallopian tube/ovary | 63          | 30             | 3        | 4     |
| 12. HPV-associated endocervical adenocarcinomas: a micropapillary component of any percentage has a propensity for aggressive behavior and should be reported | 56          | 38             | 2        | 4     |
| 13. HPV-associated endocervical adenocarcinomas: invasive stratified mucinous carcinoma of any percentage has a propensity for aggressive behavior and should be reported | 48          | 42             | 6        | 4     |
| 14. HPV-associated endocervical adenocarcinomas: mucinous-type (including NOS) tumors are likely associated with a worse survival compared with usual-type tumors, so keeping these 2 categories distinct and reporting them separately is recommended until more studies are conducted | 42          | 44             | 8        | 6     |
| 15. HPV-associated endocervical adenocarcinomas: while p16 and HPV testing are not always needed, they may be useful in problematic cases, and in the absence of block-type p16 staining or HPV, a diagnosis of HPV-associated endocervical adenocarcinoma should be questioned | 67          | 26             | 3        | 4     |
| 16. HPV-independent endocervical adenocarcinomas: immunohistochemistry is of limited value in distinguishing between LEGH and well-differentiated variants of gastric-type endocervical adenocarcinoma, and this is a predominantly morphologic diagnosis | 57          | 39             | 3        | 1     |
| 17. HPV-independent endocervical adenocarcinomas: serous carcinoma of the cervix does not exist | 50          | 25             | 15       | 10    |
| 18. HPV-independent endocervical adenocarcinomas: true endometrioid adenocarcinoma of the endocervix is extremely rare and should not be reflexively diagnosed in the presence of a mucin-poor endocervical adenocarcinoma | 73          | 24             | 0        | 3     |
| 19. HPV-independent endocervical adenocarcinomas: immunohistochemical markers are useful for differentiating between the various HPV-independent histologic types, and HPV testing for differentiating between HPV-associated and HPV-independent endocervical adenocarcinomas | 59          | 32             | 8        | 1     |

HPV indicates human papillomavirus; LEGH, lobular endocervical glandular hyperplasia; NOS, not otherwise specified.
controversy in real-world practice and to assess the available peer-reviewed literature. This approach engaged the ISGyP membership and was guided by an expert panel in the following sequence:

(1a) ISGyP member survey on current practices: A survey on current practices for gross specimen management, tumor classification, staging and reporting of EAC was conducted amongst members of ISGyP in 2019 to identify areas of concordance versus discordance. The results are published separately in this issue. The results were presented by the expert panel at a workshop open to ISGyP members in February 2020 in Los Angeles, CA and were used to guide the expert panel’s approach to developing the final guidelines.

(1b) ISGyP evidence-based recommendations for the pathologic reporting of EAC: An expert

| Recommendation                                                                 | Agree, core | Agree, noncore | Disagree | Other |
|-------------------------------------------------------------------------------|------------|----------------|----------|-------|
| 1. The pattern-based classification should be applied to all invasive HPV-associated EAC. The pattern should be included in the final diagnosis and/or comment sections of the surgical pathology report | 71         | 22             | 1        | 6     |
| 2. If pattern C is identified, the presence of the micropapillary subtype should be reported | 54         | 41             | 2        | 3     |
| 3. To increase reproducibility, completion of training modules (such as the ISGyP online module on pattern-based classification) and intradepartmental/interdepartmental consultation with colleagues is encouraged | 49         | 45             | 4        | 2     |
| 4. On excisional specimens, application of the Silva system requires exhaustive microscopic examination of the tumor | 43         | 29             | 15       | 13    |
| 5. On excisional material, a pattern A designation requires first examination of the entire tumor (to exclude destructive invasion) | 82         | 10             | 4        | 4     |
| 6. In biopsy material: if present, pattern C can be reported. Pattern A or B designation is not recommended | 61         | 17             | 10       | 12    |
| 7. As it influences management, it is recommended to report the LVI status in all patients with pattern B and C endocervical adenocarcinoma | 96         | 0              | 1        | 3     |
| 8. A quantitative estimation of LVI extent can be included in a comment (number of foci) | 25         | 55             | 13       | 7     |
| 9. Silva pattern-based classification applies only to HPV-associated invasive endocervical adenocarcinomas. Silva pattern-based classification is not recommended in HPV-independent adenocarcinomas | 76         | 17             | 5        | 2     |
| 10. Invasive adenocarcinoma: in the presence of destructive growth (patterns B and C), diagnosis of invasive adenocarcinoma is warranted | 90         | 3              | 4        | 3     |
| 11. Invasive adenocarcinoma: in the absence of destructive growth, the following diagnoses should be considered: either adenocarcinoma in situ; in the absence of destructive growth, draw attention to the gland distribution and density; if these are within the confines of the normal endocervix, diagnosis of adenocarcinoma in situ is warranted. Comparison with the uninvolved/normal endocervical gland architecture is helpful. OR pattern-A (nondestructive) adenocarcinoma: if a nondestructive lesion exceeds the size and distribution expected for AIS, or such determination cannot be made, the diagnosis of pattern-A adenocarcinoma (with nondestructive growth) is warranted. It is recommended for now to separate these lesions from frankly invasive adenocarcinoma, as their behavior is largely indolent. It is currently not recommended to classify them as AIS until new evidence on their risk of ovarian spread is available. Reporting size, stage, and margin status is still warranted in this category | 84         | 5              | 4        | 7     |
| 12. Distinction between in situ and invasive gastric type endocervical adenocarcinoma: in the absence of destructive growth, the following diagnoses should be considered: (i) AIS: gland distribution and density similar and within the confines of the normal endocervix. Comparison with the uninvolved/normal endocervical mucosa is helpful. (ii) Atypical lobular endocervical glandular hyperplasia: floret-like arrangements with small, acini-like glands surrounding a central duct and nuclear atypia. Invasive gastric type adenocarcinoma, minimal deviation type: haphazard distribution of glands with involvement of the deep cervical stroma, lack of lobular organization, minimal to absent nuclear atypia | 69         | 17             | 4        | 10    |

AIS indicates adenocarcinoma in situ; EAC, endocervical adenocarcinomas; HPV, human papillomavirus.
A panel was established by the ISGyP President to develop evidence-based recommendations for gross specimen management, tumor classification, staging and reporting of EAC. The expert panel was guided in part by input from the ISGyP member survey to identify areas of controversy in real-world practice. The expert panel then identified areas for which a body of peer-reviewed evidence existed and was consistent, areas for which the peer-reviewed evidence was controversial, and areas for which peer-reviewed evidence was lacking. The initial draft of the expert panel recommendations was presented at the workshop open to ISGyP members in February 2020 and open discussion was invited for areas of controversy and areas lacking evidence. Input from these discussions and subsequent deliberations within the expert panel guided the final version of the recommendations, which are published in this issue.

(1c) ISGyP member response to the expert panel final recommendations: In order to formally acknowledge areas of controversy that persist despite expert panel attempts to achieve

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**TABLE 3. Polling results on grading of EAC recommendations** (80 responses)

| Recommendation                                                                 | Response (%) |
|--------------------------------------------------------------------------------|--------------|
| 1. HPV-associated (HPVA) EAC (with some exceptions) should be graded using a combination of architecture and cytology | Agree, core 53 Agree, noncore 21 Disagree 19 Other 7 |
| 2. HPVA EAC with <10% solid growth are grade 1, 11%–50% solid growth grade 2 and >50% solid growth grade 3. Tumors can be upgraded in the presence of marked nuclear atypia involving >50% of the tumor | Agree, core 41 Agree, noncore 20 Disagree 30 Other 9 |
| 3. HPV-independent adenocarcinomas should not be graded; in particular, gastric-type adenocarcinomas should not be graded but considered high-grade regardless of morphology | Agree, core 76 Agree, noncore 9 Disagree 10 Other 5 |
| 4. Endocervical adenocarcinoma admixed with neuroendocrine carcinoma should not be graded but considered high-grade regardless of morphology | Agree, core 83 Agree, noncore 10 Disagree 6 Other 1 |

EAC indicates endocervical adenocarcinomas; HPV, human papillomavirus.

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**TABLE 4. Polling results on predictive biomarkers in EAC recommendations** (79 responses)

| Recommendation                                                                 | Response (%) |
|--------------------------------------------------------------------------------|--------------|
| 1. Expert gynecologic pathologists should take the lead in developing robust guidelines for testing and scoring HER2 and PDL1 immunohistochemistry to facilitate standardization in clinical trials. It is strongly recommended to interpret and report predictive biomarkers to response of treatment in endocervical adenocarcinoma in correlation with well-established pathologic parameters | Agree, core 63 Agree, noncore 28 Disagree 1 Other 7 |
| 2. Until specific recommendations are validated for endocervical adenocarcinoma, prediction of immunotherapy response criteria is identical to that for squamous cervical cancer. At present, PD-L1 immunohistochemistry (CPS of 1 or higher), as determined by the FDA approved companion test, by 22C3 clone, is recommended for pembrolizumab treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy | Agree, core 62 Agree, noncore 28 Disagree 0 Other 10 |
| 3. With the exception of PD-L1, and based on the lack of scientific evidence at the present time, no other biomarker is recommended for prediction of treatment response in endocervical adenocarcinoma | Agree, core 60 Agree, noncore 32 Disagree 3 Other 5 |
| 4. Clinical trials specifically designed for HPV-associated and HPV-independent endocervical adenocarcinoma patients are strongly encouraged to elucidate the predictive value of some biomarkers (ERBB2 PD-L1, and others). Trials combining unbalanced number of patients with adenocarcinoma (including HPV-independent disease) and squamous cell carcinoma may yield results not necessarily applicable to endocervical adenocarcinoma patients | Agree, core 62 Agree, noncore 32 Disagree 3 Other 3 |
| 5. Involvement of expert gynecologic pathologists in the design of future clinical trials is strongly recommended to appropriately identify new predictive biomarkers in cervical adenocarcinoma | Agree, core 80 Agree, noncore 18 Disagree 0 Other 2 |

EAC indicates endocervical adenocarcinomas; HPV, human papillomavirus.
TABLE 5. Polling results on EAC staging recommendations (79 responses)

| Recommendation                                                                 | Agree, core | Agree, noncore | Disagree | Other |
|---------------------------------------------------------------------------------|-------------|----------------|----------|-------|
| 1. Stage should be included in pathology reports as pathologic stage only (pT) based on all available pathologic material | 77          | 10             | 3        | 10    |
| 2. The staging system used (FIGO 2018, TNM/UICC or both) depends on local practice as some institutions require College of American Pathologists (CAP) AJCC reporting. The staging system used should be indicated alongside the assigned stage | 85          | 10             | 3        | 2     |
| 3. Use all available material to best assess tumor size, which may require combined gross and microscopic measurements—do not provide separate gross and microscopic dimensions as this causes confusion | 84          | 5              | 4        | 7     |
| 4. Clinical, pathologic and radiologic assessment can all be used with pathology being the ultimate arbiter of tumor size | 71          | 13             | 10       | 6     |
| 5. Clinical examination should be used to stage if pathology and radiology are not available | 63          | 25             | 6        | 6     |
| 6. Depth of invasion should be reported as measured on each specimen but for final staging purposes, the deepest invasion in any single specimen should be used | 90          | 5              | 1        | 4     |
| 7. Both the largest tumor dimension and depth of stromal infiltration should be provided in the pathology report, with a comment detailing how each measurement was derived | 79          | 13             | 1        | 7     |
| 8. Total cervical wall thickness in the area of deepest invasion should be reported | 61          | 29             | 4        | 6     |
| 9. Exophytic tumors should be staged based on the largest tumor dimension, even if superficially invasive (<5 mm) | 53          | 11             | 23       | 13    |
| 10. Each invasive focus should be measured individually if they are: (i) located in different blocks separated by intervening uninvolved blocks; or (ii) located on separate cervical lips with discontinuous tumor (not involving the curvature of the canal); or (iii) situated at least 2 mm apart in the same section | 58          | 23             | 11       | 8     |
| 11. At least 2 measurements should be reported: (i) depth of invasion, and (ii) largest tumor dimension | 95          | 1              | 0        | 4     |
| 12. For circumferential “barrel”-shaped cervix without grossly visible tumor: (i) if tumor is in every quadrant with full thickness invasion of cervical wall, measure the diameter of cervix as closest approximation of tumor size; (ii) for tumors without full thickness invasion and/or tumor in every quadrant, report the deepest invasion, largest tumor dimension as measured histologically and number of quadrants involved with a comment regarding lack of grossly measurable tumor | 73          | 23             | 3        | 1     |
| 13. Provide entire cervical wall thickness in area of deepest invasion (to calculate % depth of invasion) | 58          | 30             | 5        | 7     |
| 14. Do NOT use the term “microinvasive carcinoma” | 79          | 11             | 6        | 4     |
| 15. Measure the tumor as accurately as possible and use the specific FIGO or TNM stage | 87          | 5              | 3        | 5     |
| 16. For lesions which are a combination of adenocarcinoma in-situ (AIS) and adenocarcinoma: incorporate maximum tumor dimension and assessment of invasive depth as accurately as possible | 77          | 14             | 3        | 6     |
| 17. For lesions which are a combination of AIS and adenocarcinoma: maximum tumor dimension should form basis of staging | 58          | 11             | 22       | 9     |
| 18. Tumors should not be staged IB based only on positive margins of a loop or cone excision specimen | 72          | 18             | 5        | 5     |
| 19. Tumors with positive loop/cone margins should not be staged—in most such cases, there will be a subsequent excision specimen on which the stage can be determined | 42          | 29             | 14       | 5     |
| 20. Tumor involving the anterior or posterior paracervical tissue, including extension to bladder or bowel WITHOUT mucosal involvement, should be staged as IIB (as this is clinically treated as parametrial involvement) | 72          | 19             | 4        | 5     |
| 21. Ovarian involvement does not upstage cervical carcinoma, but this should be documented on the pathology report | 72          | 18             | 1        | 9     |
| 22. Fallopian tube involvement does not upstage cervical carcinoma, but this should be documented on the pathology report; the location of tubal involvement should be documented (mucosal epithelial, mucosal stromal, mural, serosal or intravascular) | 71          | 17             | 1        | 11    |
| 23. The presence or absence of LVSJ should be included in the pathology report | 98          | 2              | 0        | 0     |
| 24. LVSJ at any location, including that seen outside the uterus (eg, parametrial, adnexal) does not upstage a tumor | 77          | 15             | 1        | 7     |
| 25. The presence of isolated tumor cells (ITCs) in lymph nodes should be recorded but this does NOT count as nodal involvement and should not result in tumor upstaging | 68          | 19             | 5        | 8     |
| 26. The number of lymph nodes harboring ITCs/micro/macrometastases should be recorded | 90          | 8              | 1        | 1     |
| 27. When ITCs are scattered throughout the lymph node, measure only contiguous tumor cells to designate ITCs and not aggregate all scattered clusters into a single measurement; however, if multiple collections of ITCs are present, this should be documented in the pathology report | 65          | 23             | 5        | 7     |
| 28. When there is lymph node involvement, the presence or absence of extracapsular spread should be documented | 80          | 19             | 0        | 1     |
| Recommendation                                                                 | Response (%) | Agree, core | Agree, noncore | Disagree | Other |
|--------------------------------------------------------------------------------|--------------|-------------|----------------|----------|-------|
| 1. Fragmented LEEP/LLETZ specimens: The presence of thermal artifact on         | 48           | 30          | 12             | 10       |       |
| microscopic examination of the tissue edges of a fragmented LEEP specimen is   |              |             |                |          |       |
| the best marker of a true surgical margin                                       |              |             |                |          |       |
| 2. Fragmented LEEP/LLETZ specimens: Document the number of tissue fragments    | 62           | 27          | 5              | 6        |       |
| and size range (minimum to maximum)                                           |              |             |                |          |       |
| 3. Fragmented LEEP/LLETZ specimens: Slice the tissue in 2–3 mm thick slices     | 78           | 16          | 4              | 2        |       |
| parallel to the endocervical canal                                              |              |             |                |          |       |
| 4. Fragmented LEEP/LLETZ specimens: Limit the number of slices per cassette in | 61           | 23          | 9              | 7        |       |
| order to avoid incomplete representation due to sectioning artifacts           |              |             |                |          |       |
| 5. Fragmented LEEP/LLETZ specimens: A single H&E-stained section per block is  | 57           | 22          | 3              | 18       |       |
| sufficient for initial microscopic examination, with consideration for          |              |             |                |          |       |
| deeper sections when there is missing mucosa, absence of squamous intraepithelial |              |             |                |          |       |
| lesion/endocervical adenocarcinoma, suspicion for stromal invasion, or findings  |              |             |                |          |       |
| that are discordant with the clinical, colposcopic and/or cytologic findings.   |              |             |                |          |       |
| Alternatively it may be more efficient to routinely examine 2 or more sections  |              |             |                |          |       |
| per block, depending on the local practice                                     |              |             |                |          |       |
| 6. Intact LEEP and cold knife cone specimens: Ink the ectocervical and endocervi| 71           | 21          | 4              | 4        |       |
| cal mucosal margins as well as the deep connective tissue margin                |              |             |                |          |       |
| 7. Intact LEEP and cold knife cone specimens: If anatomic orientation of the    | 75           | 21          | 1              | 3        |       |
| specimen is designated, preserve this orientation in the tissue block           |              |             |                |          |       |
| designations                                                                    |              |             |                |          |       |
| 8. Intact LEEP and cold knife cone specimens: Document length, diameter and wall| 77           | 17          | 1              | 5        |       |
| thickness of the specimen                                                       |              |             |                |          |       |
| 9. Intact LEEP and cold knife cone specimens: Document the anatomic location of | 73           | 20          | 5              | 2        |       |
| tumor in the cervix using positions on a clock or designating anterior versus    |              |             |                |          |       |
| posterior lip of the cervix                                                     |              |             |                |          |       |
| 10. Intact LEEP and cold knife cone specimens: Document the distance of tumor to| 74           | 17          | 4              | 5        |       |
| the endocervical margin, ectocervical margin, and deep connective tissue margin |              |             |                |          |       |
| 11. Intact LEEP and cold knife cone specimens: Document the tumor length (parallel| 74           | 12          | 5              | 9        |       |
| to the endocervical canal), tumor width (perpendicular to the endocervical       |              |             |                |          |       |
| canal), tumor thickness and depth of tumor invasion                             |              |             |                |          |       |
| 12. Intact LEEP and cold knife cone specimens: Fresh intact LEEP/cone specimens | 47           | 38          | 8              | 7        |       |
| can either be opened and pinned before fixation or placed intact in formalin,   |              |             |                |          |       |
| depending on local practice resources                                           |              |             |                |          |       |
| 13. Intact LEEP and cold knife cone specimens: Specimens opened and pinned      | 55           | 27          | 13             | 5        |       |
| before fixation should be thinly sliced parallel to the endocervical canal       |              |             |                |          |       |
| 14. Intact LEEP and cold knife cone specimens: Specimens fixed intact can be    | 55           | 29          | 9              | 7        |       |
| sliced using a radial or a parallel slicing strategy                            |              |             |                |          |       |
| 15. Intact LEEP and cold knife cone specimens: Specimens should be enterly      | 82           | 9           | 2              | 7        |       |
| submitted for microscopic examination, including any excess trimmed pieces      |              |             |                |          |       |
| 16. Intact LEEP and cold knife cone specimens: If an additional so-called top    | 75           | 16          | 1              | 8        |       |
| hat specimen is submitted, it should be inked, sliced using the same strategy   |              |             |                |          |       |
| for the main LEEP specimen, and entirely submitted                             |              |             |                |          |       |
| 17. Intact LEEP and cold knife cone specimens: A single H&E-stained section per | 58           | 21          | 5              | 16       |       |
| block is sufficient for initial microscopic examination, with consideration of   |              |             |                |          |       |
| deeper sections when there is missing mucosa, absence of squamous intraepithelial |              |             |                |          |       |
| lesion/endocervical adenocarcinoma, suspicion for stromal invasion, or findings  |              |             |                |          |       |
| that are discordant with the clinical, colposcopic and/or cytologic findings.   |              |             |                |          |       |
| Alternatively it may be more efficient to routinely examine 2 or more sections  |              |             |                |          |       |
| per block, depending on the local practice                                     |              |             |                |          |       |
| 18. Trachelectomy specimens: Orient the laterality of the parametria and the    | 78           | 17          | 0              | 5        |       |
| anterior/posterior lip of the cervix based on the orientation provided by the    |              |             |                |          |       |
| surgeon                                                                       |              |             |                |          |       |
| 19. Trachelectomy specimens: Ink the endocervical, vaginal, and parametrical     | 81           | 10          | 3              | 6        |       |
| margins, as well as the nonperitonealized connective tissue at the outer surface |              |             |                |          |       |
| of the anterior and posterior cervical walls                                    |              |             |                |          |       |
| 20. Trachelectomy specimens: Measure the cervix length (parallel to the endocervi| 78           | 16          | 0              | 6        |       |
| canal), diameter and wall thickness                                            |              |             |                |          |       |
| 21. Trachelectomy specimens: Measure the parametrial tissue length (from superior | 66           | 25          | 1              | 8        |       |
| to inferior) and lateral dimension (from uterine wall to distal edge)           |              |             |                |          |       |
| 22. Trachelectomy specimens: Measure the vaginal cuff minimal and maximal length  | 74           | 17          | 1              | 8        |       |
| after stretching it out if it is retracted                                     |              |             |                |          |       |
| 23. Trachelectomy specimens: Document the anatomic location of tumor in the     | 73           | 17          | 4              | 6        |       |
| cervix using positions on a clock face and then correlate with the anatomic     |              |             |                |          |       |
| terminology used by the surgeon                                                |              |             |                |          |       |
24. Trachelectomy specimens: Document the distance of tumor to the endocervical margin, vaginal margin, parametrial margin, and nonperitonealized connective tissue at the outer surface of the anterior and posterior cervix walls

25. Trachelectomy specimens: Document the tumor length (parallel to the endocervical canal), tumor width (in the plane perpendicular to the endocervical canal), tumor thickness and depth of tumor invasion

26. Trachelectomy specimens: Remove parametria and place in cassettes before opening specimen

27. Trachelectomy specimens: Open the specimen and obtain measurements (anatomic structures and any lesion) immediately upon receipt

28. Trachelectomy specimens: After intraoperative consultation (if performed), pin the specimen for overnight formalin fixation, taking care to stretch out the vaginal cuff to its full length and pin

29. Trachelectomy specimens: Tumors 2 cm or less should be entirely submitted while tumors larger than 2 cm can be processed using representative sections

30. Trachelectomy specimens: Tissue sections should demonstrate the deepest tumor invasion and the closest approach of the tumor to the vaginal, radial, and parametrial margins

31. Trachelectomy specimens: If there is no grossly visible lesion, the entire cervix should be submitted

32. Trachelectomy specimens: Perpendicular sections of the vaginal margin closest to the tumor should be examined. Whether the remainder of the vaginal margin should be examined entirely en face or by representative perpendicular sections is left to local practice standards. Similarly, if there is no macroscopic tumor, the decision to examine the entire vaginal margin en face or by representative perpendicular sections is left to local practice standards

33. Trachelectomy specimens: The parametria should be entirely submitted

34. Trachelectomy specimens: A single H&E-stained section per block is sufficient for initial microscopic examination

35. Trachelectomy specimens: The protocol for intraoperative evaluation of trachelectomy specimen should be decided at the local practice level using 1 of the 4 published protocols 24–27, in conjunction with discussion with the surgeon regarding their specific intraoperative needs

36. Trachelectomy specimens: The presence or absence of invasive cancer and of in situ carcinoma at the proximal margin (defined as ink on tumor) should be reported for the intraoperative evaluation

37. Hysterectomy specimens: Ink the vaginal and parametrial margins, as well as the nonperitonealized connective tissue at the outer surface of the anterior and posterior cervical walls

38. Hysterectomy specimens: Weigh the uterus

39. Hysterectomy specimens: Measure the cervix length (parallel to the endocervical canal), diameter and wall thickness

40. Hysterectomy specimens: Measure the parametrial tissue length (from superior to inferior) and lateral dimension (from uterine wall to distal edge)

41. Hysterectomy specimens: Measure the vaginal cuff minimal and maximal length after stretching it out if it is retracted

42. Hysterectomy specimens: Measure the uterine corpus from superior to inferior, side to side and anterior to posterior dimensions

43. Hysterectomy specimens: If present, the size of the ovaries and fallopian tubes should be recorded

44. Hysterectomy specimens: If there is no suspicion that the tumor is extending into the parametria, then they can be removed at the interface with the uterine wall, sliced at 2–3 mm intervals and placed in tissue cassettes before opening the uterus. Otherwise the parametria should be left attached and sliced in continuity with the cervix

45. Hysterectomy specimens: Open the uterus immediately upon receipt in the lab in order to begin formalin fixation

46. Hysterectomy specimens: Fresh hysterectomy specimens can be opened either by amputating the cervix and processing it like a trachelectomy or by the conventional bivalve strategy for opening a uterus

47. Hysterectomy specimens: Slice the uterine corpus in parallel thin slices before formalin fixation

48. Hysterectomy specimens: Stretch out the vaginal cuff to its full length and pin in position before formalin fixation

49. Hysterectomy specimens: Overnight formalin fixation is advised before further tissue sampling

50. Hysterectomy specimens: Document tumor involvement in relation to the endocervix, ectocervix, parametria, and uterine corpus
51. Hysterectomy specimens: Document the anatomic location of tumor in the cervix using positions on a clock or designating anterior versus posterior lip of the cervix

52. Hysterectomy specimens: Document distance of tumor to the vaginal margin, parametrial margin, and nonperitonealized connective tissue at the outer surface of the anterior and posterior cervical walls

53. Hysterectomy specimens: Document the tumor length (parallel to the endocervical canal), tumor width (in the plane perpendicular to the endocervical canal), tumor thickness and depth of tumor invasion

54. Hysterectomy specimens: If the cervix was amputated, opened, and pinned out before fixation, then make 2–3 mm slices parallel to the endocervical canal

55. Hysterectomy specimens: If the cervix was not amputated and pinned out before fixation, then perform radial slices at 2–3 mm intervals parallel to the endocervical canal

56. Hysterectomy specimens: Tumors 2 cm or less should be entirely submitted, whereas tumors larger than 2 cm can be representatively sampled

57. Hysterectomy specimens: Tissue sections should particularly target tumor in relation to closest vaginal, paracervical/radial, and parametrial margins

58. Hysterectomy specimens: If there is no grossly visible lesion, the entire cervix should be submitted

59. Hysterectomy specimens: Perpendicular sections of the vaginal margin closest to the tumor should be examined. Whether the remainder of the vaginal margin should be examined entirely en face or by representative perpendicular sections is left to local practice standards. Similarly, if there is no macroscopic tumor, the decision to examine the entire vaginal margin en face or by representative perpendicular sections is left to local practice standards

60. Hysterectomy specimens: The parametria should be entirely submitted

61. Hysterectomy specimens: The full thickness of the anterior and posterior walls of the corpus and of the lower uterine segment should be representatively sampled

62. Hysterectomy specimens: The fallopian tubes should be processed using the SEE-Fim protocol and the fimbriae should be entirely submitted while the ampullary portion can be representatively sampled

63. Hysterectomy specimens: The ovaries can be representatively sampled

64. Pelvic exenteration specimens: Identify all anatomic structures present (cervix, uterine corpus, vagina, urinary bladder, rectum) in conjunction with the operative note or discussion with the surgeon

65. Pelvic exenteration specimens: Margins to ink are the vagina, parametria, urethra, ureters, proximal and distal rectal margins, and soft tissue margins

66. Pelvic exenteration specimens: Measure all the organs in the fresh state

67. Pelvic exenteration specimens: Inflate the urinary bladder and rectum with formalin for several hours or overnight and then hemisect the specimen

68. Pelvic exenteration specimens: Measure the tumor in 3 dimensions and document its relationship to all the organs and margins

69. Pelvic exenteration specimens: Representative sections of the tumor should demonstrate its relationship to all organs and margins

70. Pelvic exenteration specimens: The vaginal and parametrical margins are processed as is done for a hysterectomy specimen

71. Pelvic exenteration specimens: The urethral, ureteral, rectal, and soft tissue margins are processed en face, unless there is tumor nearby in which case perpendicular margins are advised

72. Lymph node specimens: Record the size and number of macroscopically detectable lymph nodes

73. Lymph node specimens: Remove excess adipose tissue from lymph nodes (nonsentinel and sentinel) and slice perpendicular to long axis at 2 mm intervals

74. Lymph node specimens: Submit all slices of each lymph node for microscopic examination unless there is an obvious macroscopic metastasis, in which case representative section is sufficient

75. Lymph node specimens: Tissue sections should particularly target tumor in relation to closest vaginal, paracervical/radial, and parametrial margins

76. Lymph node specimens: If there is no grossly visible lesion, the entire cervix should be submitted for microscopic examination

77. Lymph node specimens: For sentinel nodes, ultrastaging by deeper level sections should be performed; however, the number of levels and the distance between levels should be decided by local practice conditions as there is insufficient evidence to make a specific recommendation
80. Lymph node specimens: Intraoperative evaluation of SLN should be performed only if the surgeon is prepared to alter the intraoperative plan based on the results and is aware of the limitations to diagnostic sensitivity. 

| 80. | 74 | 24 | 1 | 1 |

81. Lymph node specimens: After removing excess adipose tissue, slice the SLN perpendicular to long axis at 2 mm intervals and evaluate all slices by frozen section.

| 81. | 56 | 20 | 13 | 11 |

82. Lymph node specimens: Do not perform deeper levels intraoperatively except to pursue suspicious findings.

| 82. | 52 | 37 | 7 | 4 |

83. Lymph node specimens: Apply the standard ultrastaging protocol for permanent section processing of the remainder of the frozen tissue block.

| 83. | 68 | 23 | 5 | 4 |

EAC indicates endocervical adenocarcinomas; HPV, human papillomavirus; LEEP/LLETZ, loop electrosurgical excision procedure/large loop excision of the transformation zone.

80. Lymph node specimens: Intraoperative evaluation of SLN should be performed only if the surgeon is prepared to alter the intraoperative plan based on the results and is aware of the limitations to diagnostic sensitivity.

81. Lymph node specimens: After removing excess adipose tissue, slice the SLN perpendicular to long axis at 2 mm intervals and evaluate all slices by frozen section.

82. Lymph node specimens: Do not perform deeper levels intraoperatively except to pursue suspicious findings.

83. Lymph node specimens: Apply the standard ultrastaging protocol for permanent section processing of the remainder of the frozen tissue block.

In order to facilitate real-world reproducible application of the new IECC system and Silva system for tumor invasiveness, 2 online training modules were created for self-education by ISGyP members. The modules are hosted on the ISGyP Education Website (www.isgyp.ca) and were made available to ISGyP members in August 2020. Each module contains a description of the diagnostic criteria accompanied by digitally scanned slides organized into a training set of example cases and a separate test set of cases for which the user can submit their interpretation and receive immediate feedback. The reproducibility of the training and test sets among an expert group was evaluated before making the sets available to ISGyP members in August 2020. The results of the reproducibility of the expert group and diagnostic results of participants up to August 2020 are published separately in this issue.

The modules are available at these sites:

IECC system for tumor classification module: http://www.gpec.ubc.ca/eac2.

Silva system for invasiveness module: http://www.gpec.ubc.ca/eac.

(2) Development of online self-education training modules for applying new tumor classification systems.

(3) Development of an international outcome study to evaluate the IECC system and Silva system: In October 2019, the ISGyP Education Committee invited members of ISGyP and the British Association of Gynaecological Pathologists to participate in a collaborative study titled Risk Prediction in Endocervical Adenocarcinoma: International Society of Gynecological Pathologists (ISGyP) Multi Centre Retrospective Observational Study.

The study was designed to evaluate patients with EAC for whom a minimum of 2 yr of follow-up is available and to correlate outcome with the IECC system and Silva system for tumor invasiveness. Assessment of the IECC tumor classification and Silva pattern of invasiveness was performed locally by the contributing institution. Each participating institution was requested to contribute a minimum of 15 consecutive cases with complete data. The project received sponsorship from Queen Mary University of London on December 2, 2019, and ethical approval from the South West-Frenchay Research Ethics Committee on February 26, 2020 (IRAS 273971; REC ref 20/S/0008). Data accrual was closed in October, 2020. Due to delays as a result of the pandemic, completion of paperwork, data cleaning and analysis are currently ongoing and preliminary results are expected in 2021.

Acknowledgement of Project Participants

The success of the ISGyP EAC Project is a result of more than 250 pathologists across the globe who have dedicated time, effort, and creative input to various components of the project. These pathologists are acknowledged in Table 7. Gratitude is also extended to several pathologists who preferred to remain anonymous. All contributors from each Centre participating in the outcome study will be acknowledged in the publication(s) arising from the data; only the pathologists from these Centres are listed in Table 7.
| **TABLE 7.** List of International Society of Gynecological Pathologists (ISGyP) endocervical adenocarcinoma (EAC) expert panel and project participants*, and ISGyP education committee |
|---|
| **ISGyP EAC expert panel** |
| Abu-Rustum Nadeem | USA |
| Alvarado-Cabrero Isabel | Mexico |
| Bosse Tjalling | The Netherlands |
| Ellenson Lora H | USA |
| Gilks C Blake | Canada |
| Kiyokawa Takako | Japan |
| Lax Sigurd | Austria |
| Malpica Anais | USA |
| Matias-Guiu Xavier | Spain |
| McCluggage W Glenn | UK |
| Oliva Esther | USA |
| Oliva Esther | USA |
| Parra-Herran Carlos | Canada |
| Rabban Joseph T | USA |
| Ramiriz Pedro T | USA |
| Roma Andres | USA |
| Singh Naveena | UK |
| Soslow Robert | USA |
| Stolnicu Simona | Romania |
| Talia Karen | Australia |
| Zamoni Gian Franco | Italy |
| **ISGyP EAC Project Participants*** |
| Abu-Sinn Dua | UK |
| Adler Esther | USA |
| Abu-Rustum Nadeem | USA |
| Akakpo Kafui | Ghana |
| Ali-Fehmi Rouba | USA |
| Alvarado-Cabrero Isabel | Mexico |
| Amaker Barbara | USA |
| Anderson Lyndal | Australia |
| Arafa Maria | Saudi Arabia |
| Ardighieri Laura | Italy |
| Arif Saimah | UK |
| Arora Rupali | UK |
| Arsenneau Jocelyne | Canada |
| Atez Deniz | Turkey |
| Attygalle Ayoma | USA |
| Balzer Bonnie | USA |
| Banet Natalie | USA |
| Barroeta Julieta | USA |
| Bartosch Carla | Portugal |
| Bashkesa Neli | North Macedonia |
| Bell Karen | USA |
| Bennett Jennifer | USA |
| Bergeron Christine | France |
| Bhutnagar Anjali | UK |
| Bittinger Sophie | Australia |
| Bleeker Maaike | The Netherlands |
| Bosse Tjalling | The Netherlands |
| Brainard Jennifer | USA |
| Bryant Anna | UK |
| Burandt Eike-Christian | Germany |
| Buza Natalia | USA |
| Cardinell Silvestro | Italy |
| Carlson Joseph | Sweden |
| Chan Joanna | USA |
| Ching Yeow Yein | Singapore |
| Clarke Blaise | Canada |
| Cohen Paul | Australia |
| Colpaert Cecile | Belgium |
| Conlon Niamh | Ireland |
| Costa Ingrid | Spain |
| Coutts Michael | UK |
| Croce Sabrina | France |
| Crum Christopher | USA |
| Culora Giuseppe | UK |
| Cummings Margaret | Australia |
| Desai Sadha | UK |
| Dillon Jessica | USA |
| Djordevic Bojana | Canada |
| Duggan Maire | Canada |
| Dundr Pavel | Czech Republic |
| Eaton Lynn | USA |
| Ellenson Lora H | USA |
| Elliott Victoria | UK |
| Ewing Patricia | The Netherlands |
| Fadare Oluwole | USA |
| Felix Ana | Portugal |
| Ferreira Joana | Portugal |
| Focchi Gustavo | Brazil |
| Ganesan Raja | UK |
| Gao Hongwen | China |
| Garg Karuna | USA |
| Geisinger Kim | USA |
| Giannico Giovanna | USA |
| Gibbs Paul | USA |
| Gilks C Blake | Canada |
| Griffin Brannan | USA |
| Guarch Rosa | Spain |
| Guerra Fernandez Esther | Spain |
| Gupta Mamt | USA |
| Habanabakize Thomas | Rwanda |
| Hadwin Richard | UK |
| Hagemann Ian S | USA |
| Haider Shireen | UK |
| Hardisson David | Spain |
| Hasan Noori | UK |
| Hoang Lynn | Canada |
| Hodgson Anjelica | Canada |
| Horn Lars-Christian | Germany |
| Hui Pi | USA |
| Hyder Paula | UK |
| Hyne Suzanne | Australia |
| Ibrahim Samiya | UK |
| Ip Philip | Hong Kong |
| Irving Julie | Canada |
| Isacson Christina | USA |
| Jacobsen Anne-Marie | Canada |
| Jadav Nupur | USA |
| Jarboe Elke | USA |
| Jaworski Richard | Australia |
| Jaynes Eleanor | UK |
| Jiang Qingping | China |
| Joehlin-Price Amy S | USA |
| Kalinga Nadia | Rwanda |
| Karnezis Anthony | USA |
| Kila Yemisi | Nigeria |
| Kim Kyu-Rae | South Korea |
| Kiyokawa Takako | Japan |
| Kloen David | USA |
| Kong Christina | USA |
| Kooreman Loes | The Netherlands |
| Krisztina Hanley | USA |
| Lax Sigurd | Austria |
| Lebok Patrick | Germany |
| Lean Sarah Lamshang | UK |
| Leras Sofia | Portugal |
| Liao Shu Yuan | USA |
| Lieberman Richard | USA |
| Liu Aijun | China |
| Llamosas Fernando | Paraguay |
| Longacre Tari A | USA |
| Lynn Amy | USA |
| Mahmoud Khalifa | USA |
| Malpica Anaia | USA |
| Mandalia Trupti | UK |

* ISGyP EAC expert panel and project participants. † ISGyP education committee.
*Includes members of the British Association of Gynaecological Pathologists who came forward to participate in outcome study, and invited participants who are not members of either society.
†Some participants preferred to remain anonymous, or their full names/country of work were unavailable at the time of submission. A complete list of participants who contributed to data collection for the outcome study from each participating Centre will be included in future publication(s).
‡ISGyP President and Project Lead.
CONCLUSIONS

The ISGyP EAC Project has now concluded, with the exception of the analysis of the results of the international outcome study. The extensive contributions of pathologists all across the world has enabled the Project to be a success and is a testament to the value of global collaboration. As co-Chairs of the ISGyP Education Committee, the authors take this opportunity to express their gratitude to all participants, whether or not included in the participant list, for making this endeavor a success in the hope that it will contribute to improving the standard of pathology reporting in EAC and thereby improving the clinical outcomes of our patients.