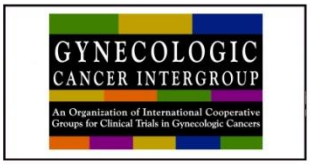

2018 FINAL

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GCIG Pathology Liaison Group: Clinical Trials Pathology Manual

I. IMPORTANCE OF PATHOLOGY IN TRIALS

The results of clinical trials are used to determine best practice, evidence-based therapeutic decisions. However, trial outcomes are heavily influenced by trial design, including pathology-related factors. This manual serves as an outline of pathology issues to consider for trial design in gynecologic tumors.

II. GENERAL GUIDELINES FOR PATHOLOGY IN CLINICAL TRIALS

Pathology-related issues to consider when designing and implementing clinical trials include inclusion criteria (eligibility) with attention to both tissue handling protocols and microscopic diagnostic criteria, stains and molecular tests (ancillary tests), central versus de-centralized pathology review, materials transport and operations, and assessment of treatment response.

Tissue handling protocols

Depending on the site and specific details of the trial, there may need to be recommendations about grossing of the resection specimen or fixation time in formalin if biomarkers are to be used. This is very important in trials where stratification of pathologic features is being investigated in the trial, such as measuring the size of an endometrial or cervical tumor.

Diagnostic criteria

The diagnostic criteria for the tumor to be investigated must be clearly delineated to ensure the validity and integrity of the trial outcomes. Specific pathologic criteria necessary for the diagnosis are required and grade must also be defined. Trial-specific pathology criteria must be included in the protocols.

Ancillary tests

If stains or molecular tests are necessary for inclusion in the study, then it should be clearly defined where the testing will be performed, which assays/antibodies are acceptable, and how the test will be interpreted.

Pathology review

Ideally, all trials looking at specific tumor types would have pathologic review of the materials. Centralized review has the benefit of consistency; however, review at multiple sites is an appropriate alternative when there is coordination between sites. There should be a designated trial-specific lead pathologist who can answer any questions, even if there is not central review. Digital slide scanning is very helpful in this process and should be utilized when possible; this also creates a repository for all the cases considered for the trial. Consideration should be given to compensation of the pathologist for effort in the trial, and authorship inclusion should be determined per section V of this manual.

Material transport and operations

The workflow of the specimen processing (including fixation of tissue) and transport (if applicable) should be addressed in the protocol. This needs to be generic enough to be adapted to multiple sites. Funds must be budgeted for processing and technical fees.

Assessment of treatment response

In some trials, treatment response may be assessed pathologically. In these cases, there should be a scoring system to be used by pathologists to assess the tumor response.

III. PATHOLOGY CHECKLIST

The overall aim is to ensure quality assurance, consistency and comparability and a good robust trial.

- ☐ Lead group trial team includes (at minimum) a trial-specific Lead Pathologist responsible for trial-specific pathology criteria (with rights to inclusion in authorship). When necessary, participating groups include a designated Group Pathologist and participating sites include designated Site Pathologists. Extra pathology-related costs and staff hours should be taken into consideration.

- ☐ Pathology review of trial cases, as defined in the trial protocol, pathology section.

- ☐ Appropriate pathologic term for entity (including synonyms).

- ☐ Literature review of current pathologic understanding of disease, as applicable to trial.

- ☐ Pathologic criteria used to define the entity (helpful to have general and trial-specific criteria, which must be in the protocol).

- ☐ Ancillary tests necessary for inclusion or diagnosis, specifying the type of assay and its interpretation. Specify scanning requirements (including acceptable alternatives for low-resource settings).

- ☐ Defined staging and grading criteria.

- ☐ Defined criteria for lymph node involvement. (i.e. does it include isolated tumor cells and how are these defined?)

- ☐ Tissue handling (grossing procedure, tissue fixatives, lymph nodes, specimen dissection protocol) and transport mechanisms.

- ☐ Harmonization of agreed specimen protocols.

IV. SITE SPECIFIC ISSUES BY ORGAN AND TUMOR TYPE

The design of a clinical trial should include a thorough review of the pathology literature related to the entity to ensure that controversies and challenges in the diagnosis are addressed in the inclusion criteria for the trial. For example, in preparation for a trial involving gynecologic neuroendocrine tumors, pathologist Jackie McDermott drafted the excellent summary shown in the box below. Similar outlines should be prepared by the trial-specific Lead Pathologist for other sites; these summaries can be reviewed by the GCIG Pathology Liaison Group for comments and suggestions for improvement.

Gynecologic Neuroendocrine Tumours

Cervix
Recommended terminology (WHO 2014): same as gastro-enteropancreatic neuroendocrine tumours

LG neuroendocrine tumours
G1 (carcinoid): abundant cytoplasm, granular chromatin, visible nucleoli. Organoid, spindled, nested, islands or trabecular growth patterns. Indolent course
G2 (Atypical carcinoid): greater nuclear atypia, more mitoses, necrosis. Aggressive but few studies exist.
Mitotic count or ki67 staining is not used for grading cervical NET (unlike GI tumours)
IHC: synaptophysin, chromogranin, CD56
High risk HPV association with most cervical NET
3p deletion most common allelic loss in NETs. Rarer: 9p21.

HG neuroendocrine tumours (G3)
Small cell neuroendocrine carcinoma
Monomorphic, hypochromatic granular nuclei, scanty cytoplasm, inconspicuous nucleoli. Nuclear moulding, Rosetting. Abundant mitoses, apoptosis and necrosis. Lymphovascular and perineural invasion common. Associated with high grade HPV, especially 18.
Very aggressive even at low stage.
Can be negative for neuroendocrine markers. TTF1 can be positive (cannot use to rule out pulmonary met).
Large cell neuroendocrine
Pleomorphic, moulded nuclei, eosinophilic cytoplasm, abundant mitoses. Forms islands and sheets.
Larger than small cell neuroendocrine carcinoma. Definitive diagnosis requires neuroendocrine IHC.
Aggressive.

Ovary
Carcinoid (G1). A monodermal teratoma
Insular and/or trabecular pattern. CK7+ CK20- CDX2+/- Invariably benign
Strumal carcinoid: carcinoid with struma ovarii, 40% associated with intestinal type mucinous glands
Mucinous (goblet cell) carcinoid: very rare. CK7-CK20+ . If atypical features, can be aggressive.

Small cell carcinoma, hypercalcemic type
Young women. Very aggressive
Unrelated to small cell carcinoma of the ovary, pulmonary type
SMARCA4 mutation. Now considered to be atypical rhabdoid tumour

Small cell carcinoma, pulmonary type

Post menopausal
Highly aggressive
Same morphology as small cell carcinoma of cervix
Neuroendocrine markers are variably positive. Can express TTF1.

Uterus
Carcinoid (G1) (2 reported cases)
High grade neuroendocrine carcinoma (G3)
Small cell neuroendocrine carcinoma
Large cell neuroendocrine carcinoma
For features see cervix

Vulva
High grade neuroendocrine carcinoma (G3)
Small cell neuroendocrine carcinoma
Large cell neuroendocrine carcinoma
Merkel cell tumour
Most HG NEC in the vulva are Merkel cell tumours:
Cutaneous nodule/s. Intradermal. Hemorrhage and necrosis.
2 types: 1. Resembles small cell carcinoma of lung. 2. G1 NEC
CK20 perinuclear dot positivity
Neuroendocrine markers usually positive. cKit+ and TTF-1-

Vagina
High grade neuroendocrine carcinoma (G3)
Small cell neuroendocrine carcinoma
Large cell neuroendocrine carcinoma
25 cases reported (up to 2004)
For features see cervix

V. STATEMENT OF AUTHORSHIP

Authorship is associated with credit for work performed and responsibility for its integrity. Our position on authorship is based on recommendations from the International Committee of Medical Journal Editors (ICMJE) available at http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

Essentially, there are four key components a contributor must satisfy to be considered an author:

1. He/she must have made a substantial contribution to the conception or design of the work.
2. He/she must have contributed to drafts of the documents.
3. He/she must grant final approval prior to submission of the manuscript.
4. He/she must be accountable for the integrity and accuracy of the work, including resolving any questions regarding the content.

It should be clearly identifiable in the group those portions of contribution attributable to each person. Contributors who do not meet all 4 above criteria are recognized in the acknowledgements section.

Pathologists who have substantially contributed to the collection and/or centralized review of cases in multidisciplinary collaborations should be including the drafting of subsequent manuscripts and included in authorship lists. This recognizes the significant contribution that pathologists make, ensures that where possible diagnoses are reliable and reproducible, and facilitates a high standard of research integrity. Without substantial pathology involvement, misclassification of tumors can occur, either weakening data or corrupting it entirely.

VI. ACKNOWLEDGEMENTS

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Lyndal Anderson (authorship statement)
Jackie McDermott (gynecologic neuroendocrine tumor summary)
Monica Bacon (ops.gcig@gmail.com)
Members of the GCIG Pathology Liaison Group

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