Secretory change within endometrial proliferations: quantitative assessment of Ki-67 index

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Outline:

- [1] Intro: diagnostic issues/pitfalls addressed by Ki-67 index
- [2] Pilot study/manual counts
- [4] Results
- [5] Future Directions
[1.1] Abnormal endometrial proliferations with secretory features/metaplasia:

- Glandular crowding (SEM/polyp)
- Glandular crowding (non-physiological)
- Complex hyperplasia w/o atypia
- Endometrial CA (FIGO 1)
Abnormal endometrial proliferations with secretory features/metaplasia:

- Glandular crowding (SEM/polyp)
- Glandular crowding (non-physiological)
- Hyperplasia w/o atypia
- Endometrial CA (FIGO 1)
Ki67 Rates: counting (gold standard)

1 = secretory endometrium
2 = interval endometrium (neg & positive controls)
3 = focal crowding
4 = hyperplasia w/o atypia
5 = hyperplasia + atypia
6 = endometrial CA
7 = endometrial CA + progestin treatment

*** p ≤ 0.001
ns = not significant

vs. secretory endometrium (1)
Alternate visualization:

Diagnostic ranges based SDx1.93 (95% of all events within a normal distribution)
[3] Methods (& motivation) for followup

• Methods -- manual counts:
  - 3 pre-selected fields ("hot-spots") per case.
  - 200-300 cells per field → up to 900 cells/case
  - 5-10 minutes per case, ~60-80 hours total

• Issues -- manual counts:
  - tedious/repetitive
  - OK for individual cases: not practical for large sets
  - Hard to outsource: a degree of training required

• Alternate methods:
  - ‘eyeball’ estimates: pre-selected fields, whole slide imaging
  - automated counting: software (2 image analysis algorithms)
  - combination (?): human+automated, crowdsourcing
[4.1] Results: ‘Eyeball’ estimates -- PGY-2 AP resident

secretory endometrium  endometrial carcinoma

For secretory endometrium:
- Manual count: 2.5% ± 1.0%
- Selected fields: 2.0% ± 0.5%
- Whole slide: 1.5% ± 0.3%

For endometrial carcinoma:
- Manual count: 75.0% ± 5.0%
- Selected fields: 80.0% ± 4.0%
- Whole slide: 70.0% ± 3.0%

n=12  n=11
‘Eyeball’ estimates: conclusions

- Overall, estimates were accurate (ns for diagnostic category)
- Insufficiently accurate if counts within 5% are required
- At low Ki-67 positivity, estimates were very close, possibly low (underestimates)
- At high Ki-67 positivity, estimates were generally high (overestimates)
‘Eyeball’ estimates: multi-group comparison

endometrial carcinoma

WSI (overall):

n=11
Cell profiler: comparison

secretory endometrium

endometrial carcinoma

n=12

n=11
‘Eyeball’ estimates: conclusions

- Overall, CellProfiler estimates were also accurate (ns for diagnostic category)

- Also insufficiently accurate if counts within 5% are required

- At low Ki-67 positivity, estimates were very close, somewhat high (overestimates)

- At high Ki-67 positivity, estimates were generally low (underestimates)
Ongoing work/future directions: workarround image-related limitations

- OK/easy
- breakdown/secrections
- stromal edema
- overlapping nuclei

[5.1]
[5.2] Solutions?

Other algorithms:

- SIVQ

Human ‘touch’:

Crowdsourcing
[5.3] Future design/applications:

Annotation Production Components

- Interface
- Annotation
- Scoring/verification
- Cross-project tracking
- Data Segmentation

- ID/de-ID
- Templates
- Progress status
- Cross-platform tracking
- User Behavior Tracking

- Modules (integration)
- Web Interface
- Retrieval

- Pathologist
  - Scanned image
- Crowdsourcing
  - manual ID

Database server
[5.4] Ongoing:

Software/Database Engineering collaboration

Front-end interface
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1. Backus et al., Clinical Gastroenterology 2011; 9:509-516