Natural History of HIV-related Anal Dysplasia: A Multi-state Modeling Analysis

Wollelaw Agmas[1], Edward Cachay[1], Christopher Jackson[2], Christopher Mathews[1]
Contact author: C. Mathews (cmathews@ucsd.edu)
[1]University of California San Diego, US. [2]Medical Research Council Biostatistics Unit, UK

Background

The natural history of anal intraepithelial neoplasia (AIN) in the absence of treatment is incompletely understood.

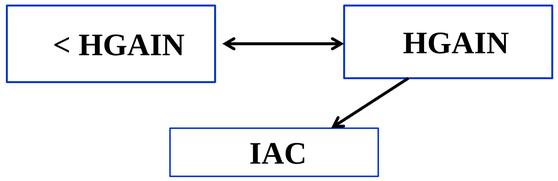
Objective

To estimate progression and regression rates of high grade anal intraepithelial neoplasia (HGAIN) in the absence of treatment in a cohort of HIV-infected adults using multi-state Markov modeling.

Methods

- Retrospective inception cohort analysis of HIV-infected patients under care at UCSD Owen Clinic [2001-2012]
- Inclusion criteria:
  1) Confirmed HIV infection
  2) At least 2 cyto-histologic results available for longitudinal analysis
- Patients diagnosed with invasive anal cancer (IAC) within 180 days of the 1st anal cytology were excluded from the multi-state analysis to avoid incidence-prevalence bias.
- Cytology results were excluded after the 1st treatment for AIN.
- Cytology transition probabilities (corrected for misclassification based on cytology sensitivity & specificity) for 3 states (<HGAIN, HGAIN, IAC) were estimated using the *msm* package implemented in R.
- Transition models were adjusted separately for antiretroviral therapy (ART) use, undetectable viremia (≤ 400 copies/ml), and smoking as time varying covariates.

3-State Transition Model



- HGAIN: high grade anal intraepithelial neoplasia (includes ASC-H results)
- <HGAIN: includes normal, ASCUS, LGSIL cytology categories
- IAC: Invasive anal cancer

Results

- During the study period, 2804 patients underwent ≥ 2 cyto-histologic results.
  - median [range]: 3 [1-18] cytologies
- Median [IQR] follow up was 3.9 [1.9-6.9] years.
- Of 74 patients diagnosed with IAC during the study period, 23 were diagnosed > 180 days after the 1st cytology result.
- The distribution of person-time follow up by selected covariates was:
  - on antiretroviral therapy (88%)
  - HIV viral load ≤ 400 (71%)
  - smoking (30%)

Estimated 2-year Transition Probabilities for Progression and Regression in 3-State Model Adjusted for Cytology Misclassification Assumptions

Model	SE/SP$_1$	2-years Transition Probability (95% C.I.$_3$)		
		<HGAIN→ HGAIN	HGAIN→<HGAIN	HGAIN→IAC$_2$
1	0.66/0.90	0.07 [0.06-0.08]	0.27 [0.21-0.33]	0.022 [0.014-0.033]
2	0.89/0.96	0.12 [0.11-0.13]	0.62 [0.58-0.66]	0.015 [0.001-0.022]
3	0.74/1.0	0.20 [0.18-0.21]	0.61 [0.58-0.65]	0.009 [0.006-0.014]
4	0.47/1.0	0.19 [0.17-0.21]	0.32 [0.28-0.36]	0.009 [0.006-0.013]

1.SE: Sensitivity; SP: Specificity [Reference standard: HRA-directed biopsy]. (Mathews et al. PloS One. 2010;5(8):e12284)
2. HGAIN: high grade anal intraepithelial neoplasia. IAC: invasive anal cancer
3. 95% confidence interval

Person-time Rates

- Estimated HGAIN regression rates (per 100 p-yrs at risk)
  - varied between 16.5 – 64.2
  - depending on assumptions regarding cytology SE & SP
- Estimated HGAIN progression rates to IAC (per 100 p-yrs) varied from 0.5 – 1.3

Discussion

- The validity of our observation of clinically significant likelihood of regression of high grade anal lesions in a HIV-infected cohort is supported by two lines of evidence.
  - Indirectly by analogy with natural history studies of cervical dysplasia demonstrating regression of both CIN2 (43%) and CIN3 (32%) [1]
  - Directly in an independent HIV-infected cohort in which regression of HSIL lesions was estimated at 41 per 100 person-yrs follow-up [2]

Limitations

- Broad range of HSIL regression estimates depending on assumptions regarding cytology operating characteristics
- Model projections assume constant transition rates over time
- Effects of unmeasured risk factors and covariates, including extent and severity of dysplasia assessable at high resolution anoscopy
- Uncertainty regarding optimal width of IAC exclusion interval after baseline cytology to avoid incidence-prevalence bias

Conclusions

- HGAIN regression within 2 years was estimated to vary between 27 - 62% (depending on assumptions regarding cytology accuracy), while progression to IAC was rare (1-2.2%).
- Initial observation without immediate HGAIN treatment may be a reasonable option for some patients after high resolution anoscopy and digital rectal exam, assuming regular follow up is assured.

References

1. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol. 1993; 12:186-92.
2. Grulich et al, The Study of the Prevention of Anal Cancer (SPANC): design and methods of a three-year prospective cohort study. Sexual Health 2013; 10(6):576.