

Global Perspectives: The Quest for Knowledge in Cytopathology

A unique opportunity has emerged with resources that are currently available internationally. The internet has encouraged cytology laboratories around the world to become active and provides access to the American Society of Cytopathology.

Differences in the practice of cytopathology worldwide may facilitate change in laboratories throughout the country. Invited speakers from across the globe will have an opportunity to answer a list of questions provided by the Editorial Board of *The ASC Bulletin*.

Our first author, Nicholas Dudding, FIBMS, is an Advanced Biomedical Scientist Practitioner in Cervical Cytology from Sheffield Teaching Hospitals in the United Kingdom. He describes the cervical cytology experience in England.

Donna K. Russell, M.S., CT(ASCP)HT, The ASC Bulletin, Editor ex officio

Cervical Cytology in England

Nicholas Dudding, FIBMS
Sheffield Teaching Hospitals Foundation Trust
S. Yorks, United Kingdom



Nicholas Dudding, FIBMS

There are approximately 150 laboratories involved with cervical screening in England, reading an estimated 4.5 million samples per annum. Screening here is very different to that in the US. The programme is completely funded by the United Kingdom (UK) government, and women are invited to have a free LBC sample once every three years from the age of 25 and once every five years from the ages 50 to 64. A register of all women is kept by the call/recall agency and it is this organisation that sends letters to women inviting them for screening. Coverage of women has always been challenging, however, and we have always struggled to access more than 80% of the eligible population.

Liquid based Cytology (LBC) was introduced into England in October 2003, largely because of our dreadful unsatisfactory rates and at the present time the market share is probably 50:50 Thinprep®/ Surepath™.

Screening itself is also organised very differently in the UK. Cytotechnologists are allowed to screen for a maximum of five hours per day and must take regular breaks. In addition all slides are either rapidly rescreened or pre-screened, a technique that we find very useful in both reducing the number of false negative samples leaving the laboratory and assessing the individual performance of primary screening. All cytotechnologists have their primary screening sensitivities measured by rapid screening and must not fall below a sensitivity of 90% for all grades and 95% for high grade abnormalities.

In terms of training, all staff who undertakes cervical screening must hold the UK examination and have to undertake an organised training programme www.cityandguilds.com that lasts between 18 and 24 months. The training is portfolio based and takes place largely in the workplace. However, there are eight training centres that run mandatory five week courses for trainees alongside training activities for experienced staff needing update training. Update training is mandatory for all cytotechnologists and they must attend a minimum of a one day update course every year. In addition they undertake proficiency testing, managed and run by an outside agency and comprising tests sets of 10 slides, twice a year.

We also have a grade of cytotechnologists, who once qualified can report out and advise on the management for all abnormal samples, replacing, in some laboratories, the traditional role of the pathologist. The major way to monitor the performance of these staff and of Medical Staff is via positive predictive

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values. This is the proportion of samples that are called high grade by cytology that are confirmed to be high grade on histology. All laboratories submit their individual data to the government annually and 10th – 90th percentiles are calculated. www.ic.nhs.uk The aim is to fall within these figures. For 2007/8 the figure was 70.7% – 88.9%. If your PPV is 89% or above you are an outlier!

Within laboratories it is useful to compare variations between individuals, though it must be noted that positive predictive values are subject to other variables such as type and reporting of any biopsies, regression of lesions, accurate follow up, etc. and care should be taken when assessing data.

Impact of Liquid Based Cytology (LBC)

In terms of sensitivity / specificity and the likely impact on the incidence and mortality of cervical cancer there is little, if any, evidence to say that LBC impacted one way or another in the last five years. What have improved clearly are the unsatisfactory or inadequate rates. Prior to LBC the English mean was 10%; this has fallen to 3% across the entire country and in Sheffield, where we use Surepath™ just 1%. If you couple this with an increase in productivity of around 20 – 30%, then the other age old UK problem of the screening backlog has also started to disappear.

Whilst we can not prove that LBC has impacted positively on disease detection it is clear that sample quality, as indicated by the presence of transformation zone (TZ) cells has improved. Within Sheffield teaching Hospitals we now find that 93% of samples contain TZ cells, a figure matched by that in Manchester¹. Whether this has impacted on overall dyskaryosis rates can be argued, but a recent audit in the North East, Yorkshire & Humber region has shown that it is almost certainly enhanced the pick up of endocervical lesions. The number of cases reported rose from a rate of 2.19 per 10,000 samples to 3.95. This increase of 80% occurred at the same time as positive predictive values (PPV) for samples coded as showing endocervical abnormality with a final histological outcome CGIN (Cervical Glandular Intraepithelial Neoplasia) or invasive endocervical adenocarcinoma increased from 70.4% to 74.4%. More impressively, PPV for an outcome of any high grade disease increased from 92.6% to 95.3%².

Terminology

Another major difference between the US and UK is the terminology used. The UK still uses British Society for Clinical Cytology (BSCC) Terminology. Here HSIL is divided into moderate and severe dyskaryosis whilst ascus equates to the term borderline. LSIL loosely equates to mild dyskaryosis but does not directly cross over since we do not automatically place samples with koilocytes into the category of mild dyskaryosis.

HPV Testing

In England we have seen the beginnings of the introduction of test of cure (ToC) and triage of low grade change and in order to assess their potential six English Sentinel sites for HPV triage and ToC commenced testing in Spring 2008.

Unlike the US, a HPV positive result is recorded on the basis of 2.0 RLU's using the Hybrid Capture 2 (HC2) test qiagen.com.

An ASCUS or LSIL report with a positive HPV test results in referral to colposcopy. A HPV negative result leads to the cytology report being over-ridden and the women remain on normal (3/5 years) recall. At colposcopy women with high grade CIN are treated; those with no CIN on biopsy or a negative colposcopy are returned to normal recall, and those with CIN I or a colposcopic appearance of high grade are invited back for an early repeat (six or 12 months depending on whether the CIN I was treated or not).

Interestingly, because not all koilocytic samples will test positive for high risk HPV types laboratories are “banned” from reporting HPV in the cytology report to avoid any complications of a cytology report stating HPV is present and a HC II result of negative.

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The same sentinel sites are also taking the opportunity to investigate the potential of HPV testing following treatment for CIN. Again using Hybrid Capture II the post-treatment protocol in the sentinel sites comprises:

- Cytology at six months
- If cytology is abnormal, refer for colposcopy
- If cytology is normal perform an HPV test
- If HPV positive refer for colposcopy
- If HPV & cytology negative, return to normal recall.

The results of both triage and ToC in this first year are currently being reviewed by the steering group and at present we do not know when or if it will be rolled out to the rest of the UK.

At present it seems less likely that we will turn to HPV testing for primary screening. Results from the ARTISTIC trial³ were not clearly in favour of this; therefore at present the jury is still out and the trial continues for a further three year period. The result of this trial caused much consternation at the time and close investigation of the protocol. The truth is almost certainly simpler: with its strict training regimes and quality parameters screening in the UK is almost certainly operating at a very high level and it is this that makes it harder for new technologies to compare positively.

In addition all slides are either rapidly rescreened or pre-screened, a technique that we find very useful in both reducing the number of false negative samples leaving the laboratory and assessing the individual performance of primary screening.

Automation

This is the same problem that befell the two automated imaging systems. The introduction of these into the UK was pending the results of the MAVERICK study. The MAVERICK study is a large Health Technology Assessment that took place in the UK to decide if we should move to automated screening or not. Whilst this has yet to formally report, the results were made available at the recent IAC Congress in Edinburgh. As with primary screening with HPV, automation did not make the same impact as it had in other parts of the world with sensitivity for high grade lesions falling by 8%, making its introduction into England less than likely as I write.

Vaccination

Vaccination is now fully integrated into the UK with all girls receiving the Cervarix (GSK) free of charge at the age of 13. A catch up programme that ran for the first two years also vaccinated women up to the age of 18. It is my belief that once these vaccinated women enter the screening programme, in seven years we will see the introduction of primary screening by HPV and the demise of cervical cytology as I know it. ■

References

1. TZ Component in LBC. P. Joseph. J. Marshall. D. Rana. M. Desai. *Cytopathology* 2008;17. (1): 22-24.
2. Glandular Neoplasia and Borderline Endocervical Reporting Rates before and after Conversion to the Surepath™ Liquid Based Cytology System. C. Burnley, N Dudding, M Parker, P Parsons, CJ Whitaker, W Young. Submitted for publication – *Diagnostic Cytopathology*.
3. H Kitchener, M Almonte, C Thompson et al. HPV testing in combination with liquid based cytology in primary screening (ARTISTIC): a randomised controlled trial. *Lancet Oncol* 2009;10:672-82.