

## Review Article

# Interpretation of Pap smear reports

## 柏氏塗片的闡釋

TH Cheung 張德康

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Pap smear screening is a multi-step process that involves recruitment of patients, taking smear, making and reading slides and issuing reports to alert clinicians to take appropriate action. In the last decade, innovative technologies including liquid base cytology, automated screening and human papilloma virus (HPV) tests have revolutionised Pap smear screening. As a quality assurance measure to improve Pap smear reports, Bethesda system (BTS) was developed in 1988 to replace Papanicolaou numeric classes.<sup>1</sup> BTS 1988 is structured and descriptive and is well received in many parts of the world including Hong Kong. Minor modifications were made in 1991 (BTS 1991)<sup>2</sup> to improve the system whilst a major revision was made in 2001 to reflect the current understanding of cervical cytology and use of new technologies in Pap smear screening.<sup>3</sup> This paper will discuss the changes that have been made to BTS 2001 to facilitate interpretation of reports and providing appropriate management.

子宮頸柏氏塗片普查有多項工作步驟，包括：選取病人，子宮頸塗片，塗片的製作與檢查，以及撰寫報告以通知臨床醫生採取適當的治療措施。在過去十年，創新技術如液相細胞學，自動篩查法及人類乳頭狀瘤病毒測試法，均令子宮頸柏氏塗片普查產生革命性變化。為求令柏氏塗片報告的質量更優良，畢士達系統於 1988 年逐步開發，並取代了柏氏計數分類法。1988 年畢士達系統的結構嚴謹，描述仔細，廣為世界各地及本地業界所採用。此系統於 1991 年曾作少許修改。至 2001 年則有大幅修訂，以配合子宮頸細胞學的進展和新科技的應用。

**Keywords:** Bethesda system, Pap smear

**關鍵詞：**畢士達系統，子宮頸柏氏塗片

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Department of Obstetrics and Gynaecology,  
Prince of Wales Hospital, Hong Kong

TH Cheung, FRCOG, FHKAM(O&G)

Correspondence to: Dr. TH Cheung

Department of Obstetrics and Gynaecology, Prince of Wales  
Hospital, Shatin, Hong Kong

## Introduction

Pap smear has been the cornerstone in the cervical cancer prevention programme. A number of innovative technologies has been introduced in the last decade to improve the sensitivity of detecting cervical lesions and Bethesda system

(BTS) has been developed to improve the communication between cytopathologists and clinicians so that the latter can be better informed on the findings on the slides. However, two modifications have been made since the introduction of BTS and changes in the terminologies and definitions may cause confusion and misinterpretation of Pap smear reports. This paper aims at highlighting and explaining the important changes.

### Specimen adequacy

One of the key advantages of the BTS 1988 is that specimen adequacy is commented. However, criteria for evaluation of specimen adequacy was not defined till BTS 1991 was introduced. Patient and specimen identification, pertinent clinical information in the request form, technical interpretability, and cellular composition including the presence of transformation zone (TZ) components are assessed to determine specimen adequacy. Reasons for "Unsatisfactory for evaluation...." should be specified in the BTS report to facilitate appropriate measures be taken before repeating the smear.

A smear is considered unreliable to detect underlying pathology when the cellularity is low. In BTS 1991, slides with less than 10% of its surface covered with cells are deemed inadequate but the number of well visualised squamous cells required is not defined.<sup>4</sup> In BTS 2001, the minimum estimated number of well visualised squamous cells to qualify "Satisfactory for evaluation" for conventional smears and liquid base cytology (LBC) is 8,000 to 12,000 and 5,000 respectively. Paucity of cells is more likely to occur with conventional smears than LBC because deposition of cells from spatula to glass slides is inefficient.<sup>2</sup> Trapping of cells between fibres of wooden spatulas or cotton swabs also contributes to this problem.<sup>5</sup>

Smears are also considered "Unsatisfactory for evaluation...." when it is thick, compromised by drying artefact, and over 75% of the epithelial cells being obscured by blood or inflammatory changes. These problems are minimised with LBC because cells are fixed after immediate transfer into the preservative fluid; inflammatory debris and red blood cells are removed when slides are made.<sup>6</sup> Meta-analysis has confirmed that LBC is less likely to produce smears "Unsatisfactory for evaluation...." compared to conventional methods.<sup>7</sup> Other than using LBC, proper sampling procedure, not taking smear at times of lower genital infection, during menstruation or pregnancy would also reduce the chance of getting unsatisfactory smears. Patients with unsatisfactory smear represent a high risk subset and 16% of them would have squamous intraepithelial lesion (SIL) on subsequent smears.<sup>8</sup> However, smear should not be repeated within days or weeks because false negative rate as high as 60% has been reported for early repeat.<sup>9</sup> The effect is most pronounced when the interval is less than 45 days.<sup>10</sup>

In BTS 1991, presence of two or more clusters of endocervical glandular and/or metaplastic cells, each containing five or more cells, are used as surrogate markers for adequate sampling of TZ. Smears that do not meet the criteria are not regarded as "Unsatisfactory for evaluation...." but would be reported as "Satisfactory for evaluation but limited by....". The latter was deleted in BTS 2001 and smears that do not have sufficient TZ components are accepted as "Satisfactory for evaluation" whilst the inadequacy of TZ component is indicated as addendum.

Such change was made in BTS 2001 because sufficient TZ components could be present though TZ is only partially sampled while proper sampling of TZ may not yield adequate TZ component on smears. If clinicians are confident that the TZ has been sampled with proper inspection of the cervix, inadequate TZ component on smear does not

constitute a problem. Although a cross-sectional study has shown that smears containing TZ component have a higher frequency of finding high grade squamous intraepithelial lesion (HGSIL) than smears that do not,<sup>11</sup> a longitudinal study has not shown patients with normal Pap smear and absence of TZ components have a higher chance of getting HGSIL on subsequent smears.<sup>12</sup> Immediate repeat of Pap smear is therefore not recommended as a routine. However, for patient with history of glandular abnormality, presence of adequate TZ component is essential or "Unsatisfactory for evaluation...." should be reported. To improve TZ sampling and increase the yield of TZ component, spatulas with extended tips or a combination of endocervical brush and spatula should be used.<sup>13</sup>

## General categorisation

This element is optional in the report and is meant to assist laboratory support staff to triage reports. In BTS 2001, "Negative for intraepithelial lesion or malignancy" was introduced to replace "within normal limit" and "benign cellular changes" used in BTS 1991 to avoid confusion that might lead to unnecessary intervention.

"Other" was introduced in BTS 2001 and normal endometrial cells found on smears collected from women above the age of 40 would be reported under this category. This finding is not reported in asymptomatic women below the age of 40 because malignancy is rare.<sup>11</sup> Finding normal endometrial cells on smear is not unusual in the first 10 days of a cycle but the incidence should be less than 2% from day 11 onward.<sup>14,15</sup> Use of intrauterine contraceptive device increases and use of oral contraceptive pills decreases the chance of finding endometrial cells on smears.<sup>14,15</sup> Inadvertent sampling of lower uterine segment with endocervical cytobrush may lead to endometrial cells on smears. Whilst full

investigation is recommended for postmenopausal women because of significant risk of carrying pathology,<sup>15</sup> management could be individualised for premenopausal women. Patients with atypical endometrial cells are reported under "Epithelial cell abnormality" but not "Other".

## Interpretation/Result

Specimens that contain no abnormal epithelial cells are reported as "Negative for intraepithelial lesion or malignancy" in BTS 2001. As sensitivity of Pap smear in detecting underlying SIL is only 50%, one normal Pap smear result has not absolutely ruled out underlying SIL and is less reassuring compared to repeated negative smears.<sup>17</sup> Fortunately, the estimated time taken for carcinoma to develop from SIL is well above 10 years and offers opportunities for subsequent smears to detect the missed SIL. Although annual screening lowers relative risk of developing cervical cancer more than that achieved with longer screening interval,<sup>18</sup> a 3-year screening interval is recommended by the Hong Kong College of Obstetrics & Gynaecology because of cost-effectiveness consideration. As annual screening offers greater protection, this should be recommended to high risk patients.

Smears found to have abnormal squamous or glandular cells are reported under "Epithelial cell abnormalities". In BTS 1991 atypical squamous cell of undetermined significance (ASCUS) is used to describe squamous cells that carry some but not all the criteria requiring to diagnose SIL and are further qualified with favouring reactive change or neoplastic change. As ASCUS favouring reactive changes implies no suspicion of neoplastic process, these smears are reported as normal in BTS 2001 and all atypical cells are therefore suggest presence of neoplasia. In BTS 2001, "atypical squamous cells" (ASC) is qualified with "of undetermined significance" (ASC-US) or

"cannot exclude high grade SIL" (ASC-H) when cells exhibit features suggestive but not conclusive of low grade squamous intraepithelial lesion (LGSIL) and HGSIL respectively. As high grade cervical intraepithelial neoplasm (CIN) can be found in 27-40% patients with ASC-H on smear,<sup>19</sup> immediate referral for colposcopy is recommended.

In BTS 1991, no consensus on the diagnostic criteria for adenocarcinoma in situ (AIS) could be reached and smears suspicious of AIS are reported as "AGUS, probably neoplastic". As cytological criteria for AIS have been defined and shown to have high predictive value and reproducibility in the past 10 years, AIS is introduced to BTS 2001. Furthermore, "atypical glandular cell of undetermined significance" (AGUS) has been removed in BTS 2001 to avoid confusion with ASCUS or ASC-US.

For glandular cells showing some but insufficient features to reach the diagnosis of AIS, "atypical glandular cells" (AGC), "atypical endocervical" or "atypical endometrial" is reported depending the cell origin as suggested by the morphological features. Immediate investigation is recommended for all patients with atypical glandular cells as the risk of underlying pathology is substantial. However, benign glandular cells collected from high endocervix or lower uterine segment with cytobrush may mimic AGC and this is more commonly occur after cone biopsy.<sup>20</sup>

## Automated review and ancillary testing

Automated screening devices can be used for primary screening or to assist in quality control. AutoPap Primary Screening System works by ranking the slides according to the likelihood of underlying abnormalities. The lowest risk 25% of slides can be signed out as "Negative for epithelial lesion or malignancy" without human review whereas the remaining 75% slides need manual

screening. At least 15% of the highest-ranked slides that have been designated as negative after manual screening would be subjected to quality control (QC) manual re-screen. This system has been shown to be superior to conventional practice in identifying slide with ASCUS or above.<sup>21</sup> AutoPap 300 and PapNet Testing System are other automated devices approved by FDA for QC purpose only and they have been shown to be superior to 10% random screen.<sup>22,23</sup> For slides that have been scanned by automated computer system, the instrumentation and the results should be included in the report.

As persistent human papillomavirus (HPV) infection is necessary for the development of CIN and cervical carcinoma.<sup>24</sup> Detection of HPV in the exfoliated cervical cells has been proposed as a primary screening test for SIL or serves as a secondary test to triage patients with mild cytological abnormalities. Hybrid Capture 2 Test (Digene, Gaithersburg, Maryland) detects 13 high-risk HPV and five low-risk types and has been most commonly used for this purpose. HPV test has a 95% sensitivity and is superior to Pap smear in identifying patients with HGSIL.<sup>25</sup> However, HPV infection is exceedingly common in young sexually active women and the 3-year cumulative infection rate reached 44%.<sup>26</sup> In normal smears collected from women between the age 25 to 29, 15% are HPV positive. HPV test therefore has a low specificity for SIL in young women.<sup>27</sup> As HPV positive rate decreases with age and is below 5% in women above the age of 35, HPV test is more useful when applied to elderly women.

For patients with normal Pap smear but have positive HPV test, immediate referral for colposcopy may not be necessary. However, the cumulative risk of developing LGSIL and HGSIL among these women in the next five years was 6.4 and 2.2% respectively compare to 1.1 and 0.3% among women with normal Pap smear and no HPV.<sup>27</sup> Since the median duration of HPV infection is eight months<sup>27</sup> and the one year cumulative rate

of high risk HPV clearance in women with normal smear is 46%,<sup>28</sup> repeat the HPV test 12 months later or Pap smear test every six months can be adopted. Patients with positive HPV test and ASCUS or worse on smear should be referred for colposcopy as risk of SIL is substantial.

## Educational notes and suggestions

Comments are optional and aims at helping clinicians to understand the report and pursue the necessary action. Explanations may also be given for unsatisfactory smears so that appropriate actions can be taken to improve the quality of the repeat smears. However, cytopathologists are limited by the lack of full clinical details and their suggestions are likely applicable to "average" patients only.<sup>29</sup> Clinicians should be prepared to individualise the care according to the patient's situation but not bound by the suggestions given in the report.

## Conclusion

BTS was introduced to improve communication between cytopathologists and clinicians. Familiarisation to the definitions of terminologies is essential to avoid misinterpretation of reports and ensure appropriate action. In case of doubt, direct conversation with the cytopathologist is encouraged.

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