

The Polarprobe—Emerging Technology for Cervical Cancer Screening

S C Quek,*^{MRCOG}, T Mould,*^{MRCOG}, K Canfell,**^{BE (Hons)}, A Singer,***^{PhD, FRCOG},
V Skladnev,†^{BSc, ME}, M Coppleson,‡^{MD, FRACOG, FRCOG}

Abstract

The Polarprobe is a portable non invasive electronic device designed for the detection of cervical precancer and cancer. It measures both electrical and optical properties of cervical tissue to allow a real time comparison with a databank of previously determined cervical tissue types. The need for additional tests to augment or even replace the Papanicolaou smear has partly prompted its development. Indeed it has been shown to be associated with less pain and anxiety than the smear and has the capability of encouraging women to attend for screening. Some of the preliminary clinical trials on the Polarprobe are reported as well as the ongoing developments and modifications to the device.

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Introduction

Cervical cancer is a preventable disease that affects nearly half a million women worldwide. The Papanicolaou smear has been used for screening for over fifty years and the test has the advantage of fast and relatively easy sample collection. However, the performance limitations of the Papanicolaou smear are well understood, and the false negative rate has been reported as between 20% to 40%,¹ and between 6% to 55%.² The technique is subject to human error at many stages between obtaining the specimen and the eventual notification of results.

The specificity of the Papanicolaou test depends on the particular cytology classification system used and the threshold for colposcopy referral. In the USA, the specificity of the test has effectively decreased since the introduction of the Bethesda cytology classification system. The Bethesda System (TBS) introduced a new category, Atypical Squamous Cells of Undetermined Significance (ASCUS). Broadly equivalent cytological categories include morphological changes bordering on mild dyskaryosis, atypical cells, minor atypia and minimal atypia. If the screening programme requires the diagnostic referral of these patients, the overall increase in sensitivity is mitigated by a high false positive rate and lower effective specificity.

One approach is to add additional tests to the screening programmes, and adjunctive testing has been shown to increase overall detection rates.³ Potential candidates include HPV DNA testing, Cervicography and the Polarprobe. If the test utilises complementary technologies to that of the Papanicolaou smear, overall sensitivity will theoretically improve, since the tests may have strengths in different regions of the spectrum of cervical disease. Various methods of combining tests exist and have differing effects on overall sensitivity and specificity of the screening programme. Two tests may be combined in parallel (adjunctive testing) or in series (secondary triage testing). In the case of parallel testing, both tests are performed on all patients and if either test is positive the patient is referred on for further diagnostic testing. In the case of series testing, patients found to test positive on the first test are subject to a second screening test to determine if they should be referred for diagnostic examination. Parallel testing has the effect of increasing overall sensitivity since the true positive results in each test may not be expected to wholly overlap—but at the cost of decreased specificity, since the false positive results will not completely overlap. Therefore the number of true and false positive results, and the number of referrals for diagnostic testing increases. Series testing

* Clinical Research Fellow

*** Professor of Gynaecological Research
Department of Gynaecology
Whittington Hospital, London, UK

** Regulatory and Clinical Trials Coordinator

† Managing Director
Polartechnics Limited, Sydney, Australia

‡ Clinical Professor, Gynaecological Oncology
The University of Sydney, Sydney, Australia

Address for Reprints: Mr Quek Swee Chong, Department of Gynaecology, Whittington Hospital, Highgate Hill, London N19 5NF, United Kingdom.

has the effect of increasing overall specificity at some cost in terms of sensitivity. Positive test results are subject to a further filtering process and the secondary test will reduce the overall false positive rate.

Concerns about the accuracy of current screening methods for cervical cancer and the evident need for an adjunct to the Papanicolaou smear have led to the development of the Polarprobe system.

Polarprobe Technology

The innovative technology utilised in the design of the Polarprobe includes optical elastic backscattering techniques; electrical measurements; and expert system classification of tissue. The instrument provides the operator with instantaneous feedback without requiring tissue sampling for cytological analysis.

The pen-shaped Polarprobe is 170 mm in length, tapering at the distal end to a flat tip approximately 5 mm in diameter which contacts the cervix. The Polarprobe is connected by means of a flexible cable to a console which incorporates a computer-based expert system—a software-implemented classifier (Fig. 1).

As the operator scans the cervix with the Polarprobe, the device delivers low level electrical pulses and optical signals to the cervical tissue (Fig. 2). The measured response, or tissue signature, is digitised and is compared algorithmically in real time to that stored in a databank of cervical tissue types. If a match is found, the results are classified into one of three categories, normal, low grade abnormality, and cancer or high grade abnormality. Currently, seventeen different tissue types are recognised by the system within these three basic categories.

The design of the device has followed a phenomenological approach wherein the responses of different tissue types to various stimuli signals are characterised by the use of a training database. As the Polarprobe system operates to discriminate tissue, a

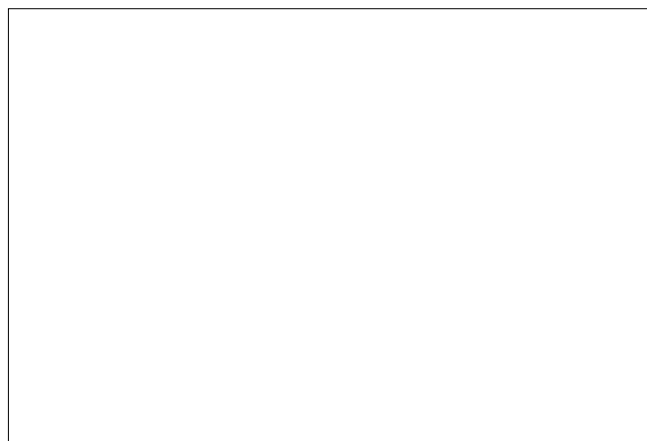


Fig. 1. Polarprobe and console.

statistical matching operation is performed against the training database set. The discriminant parameters which are input to the tissue matching algorithm are chosen from a large array of possibilities on the basis that they demonstrate maximum variability over the range of tissue types of interest and minimum variability within any one tissue type of interest.

The automation provided by this expert system for tissue type classification should make it possible to utilise the technology on a widespread basis, without the need for expert physicians, and therefore it is particularly suited to screening applications. The potential benefits of an expert system approach include faster, simpler, more cost-effective and standardised diagnoses.

The concept of using electrical and optical means to discern cancerous tissue is not new. Fricke and Morse, in 1926, conducted a study involving the electrical measurement of breast tumours.⁴ This was followed by a study of electrical parameters derived from the measurements of cervical tissue by Langman and Burr in 1949, who found “significant differences in cancerous and non-cancerous tissue”.⁵ However, these early techniques were not amenable to *in vivo* testing partly because of the size and amount of equipment required. The rapid advances in electronics, optics and computer power over the last few decades have enabled the miniaturisation of these technologies and have made *in vivo* utilisation a reality.

Description

The Polarprobe system consists of:

- (i) the handpiece, which contains the tissue stimulation and sensor elements;

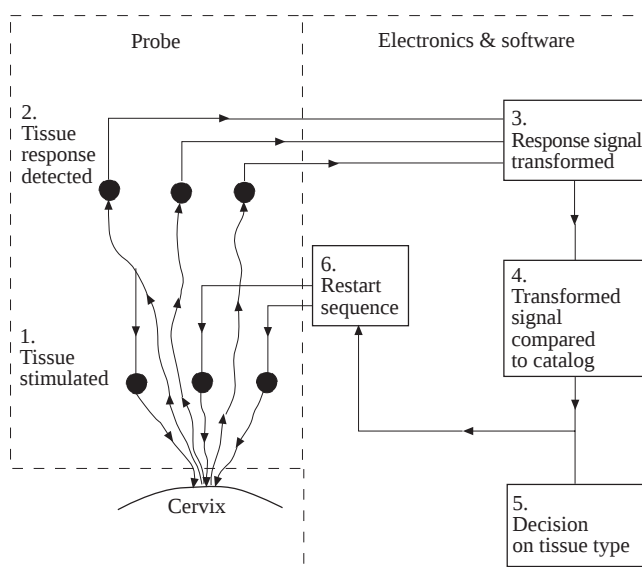


Fig. 2. Polarprobe tissue stimulation and processing (Reproduced with permission from: Coppleston M, Reid B L, Skladnev V N, Dalrymple J C. An electronic approach to the detection of pre-cancer and cancer of the uterine cervix: a preliminary evaluation of the Polarprobe. *Int J Gynecol Cancer* 1994; 4:79-83).

- (ii) the console, which contains a microprocessor control module and a digital signal processor; and
- (iii) a connecting cable between the handpiece and the console. The microprocessor handles the transfer of data to and from the digital signal processor, which implements the complex floating point arithmetic necessary for operation of the tissue classifier. The system also incorporates a keypad to enable entering of patient information, a liquid crystal display and a printer to obtain a hard copy printout of the result. The power supply allows for mains connection or battery pack options, and is designed to operate with 100 to 260 V supplies.

Electrical Tissue Discriminants

The tip of the Polarprobe incorporates three kidney-shaped electrodes (Fig. 3). Low level voltage pulses

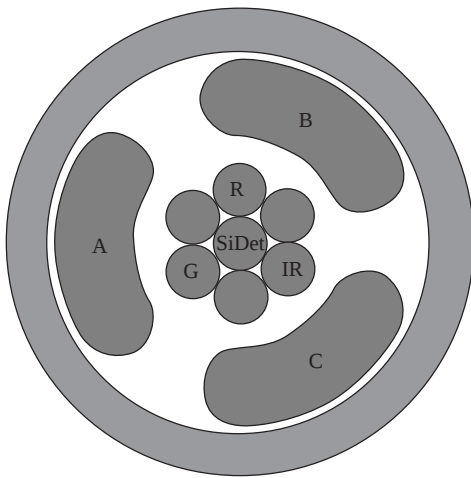


Fig. 3a. The Polarprobe Tip. The kidney-shaped electrodes A, B and C are arranged around the periphery of the 5 mm diameter tip. The optical fibres are mounted in the centre and are labelled R (red), G (green) and IR (infrared). Three optical fibre spacers are also shown (unlabelled). The detector photodiode is labelled SiDet.

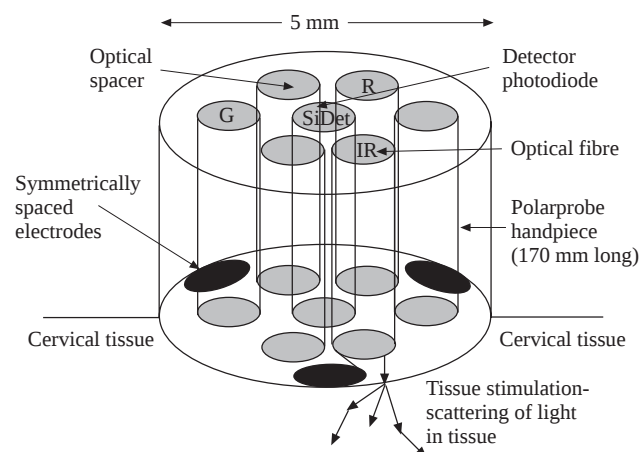


Fig. 3b. Optical fibres are used to convey the optical signals from the red, green and infrared light emitting diodes to the Polarprobe tip, where tissue is stimulated and the response detected by a photodiode.

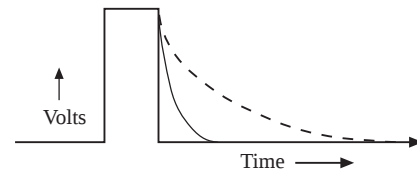


Fig. 4. Polarprobe electrical relaxation curves. Two curves are depicted, each showing different electrical decay constants.

(1.25 V pulses of 260 μ s duration) are applied across various combinations of these electrodes and the response measured. The response is of the form of an electrical decay curve (Fig. 4). The shape of the curve and the decay constant depend on tissue capacitance, the electrode/tissue interface and electronic and ionic conductance.

Optical Tissue Discriminants

In order to discriminate unambiguously between different cervical tissue types, both optical and electrical discriminants are necessary, since there is considerable overlap of the electrical characteristics between tissue types. Accordingly, selective wavelength optical spectroscopy is employed to acquire this complementary information.⁶ The tissue is illuminated by light at various frequencies and the response measured (Fig. 3). The Polarprobe uses a technique known as diffuse reflectance, whereby the tissue response is detected at the excitation frequency as well as off-excitation frequencies. It is thus characterised by the analysis of a relatively broad-band spectral response.

Three light emitting diodes (LEDs) each operate at a different optical frequency—in the red, green and infrared sections of the spectrum respectively. These LEDs are connected by optical fibre links to the probe tip, and as the LEDs are activated, tissue beneath the probe tip is illuminated. The LEDs are activated in sequence and a detector photodiode, which operates across a broad spectral band, records the response. This response results from scattering, reflection and absorption of the incident light by the tissue and these effects are dependent upon cellular and intra-cellular tissue structures.

Clinical Operation

The Polarprobe is subject to a high level disinfection procedure prior to its use, with a standard exposure time, in 2% Glutaraldehyde solution. The cervix is visualised by means of a Cusco's speculum and the probe is gently placed in contact with the cervix and methodically repositioned until the whole ectocervix and everted portion of the endocervix has been covered. This process typically requires between one and two minutes.

The Polarprobe automatically performs fourteen tissue measurements per second with each measurement involving a complex sequence of events, as follows:

- 1) optical and electrical tissue stimulation with subsequent detection of tissue responses;
- 2) extraction of specific parameters from the optical and electrical signals;
- 3) checking for errors and classification of the extracted parameters into various tissue type categories; and
- 4) feedback to the Polarprobe operator.

A total of seventeen tissue types, based on the colposcopic classification of Coppleson and Pixley⁷; and the Reid and Scalzi⁸ abnormality grading system have been programmed into the system. The seventeen tissue type categories have been previously described.⁹ In order for the Polarprobe to be maximally useful as a screening tool, these tissue types are grouped into categories which are of use to the clinician (Normal, Low Grade Abnormality and Cancer or High Grade Abnormality).

The operator is notified of the categorisation result in real time by means of a series of lights positioned on the handle of the Polarprobe and via a liquid crystal display on the console. The operator is also signalled if there is sub-optimal contact with the tissue so that the probe can be adjusted accordingly. At the end of the session, a summary printout of the screening result is provided.

Clinical Trials

The original data on which the classification algorithm is based have been previously reported.¹⁰ This was from 183 patients between the ages of 20 and 50 years who presented with either atypical colposcopic appearances or abnormal Papanicolaou smears, who subsequently underwent Polarprobe examination followed by colposcopy and appropriate biopsies. While these data give a clear indication of tissue mapping accuracy, they do not directly indicate diagnostic accuracy on a per-patient basis. However, a simple extrapolation of those results suggests that false-negative and false-positive rates of 10% respectively are achievable.

The process of tissue classification development is an ongoing one and has been carried out in London, Brazil, Singapore, Beijing, Manila and Sydney. A Research Fellowship has been established at the University of London where much of the clinical work is being carried out at the Whittington Hospital. This process will allow improvements to the accuracy of the probe as well as upgrading of the algorithms used in diagnosis.

The first clinical trial to assess the performance of the Polarprobe on a "patient to patient" basis was conducted by Singer in Recife, Brazil.¹¹ The primary objective of the trial was to determine if the Polarprobe could distinguish subjects with overt clinical cervical cancer from those free of cancer. This was necessary to establish the potential of this method prior to instituting further study into its ability to detect pre-malignant lesions.

The Polarprobe used for this study was programmed to categorise tissue into *Cancer* and *Not Cancer*. Two groups of women were studied. Group 1 comprised 41 women presenting with various stages of symptomatic clinical cervical carcinoma. All of them had tumours that were clearly visible. Group 2 acted as the control group and comprised 45 women, all having had a negative Papanicolaou smear and had not had treatment to the cervix within the previous 12 months. All subjects in the control group were examined colposcopically to ensure that none exhibited any signs of malignancy.

All the subjects had a Polarprobe examination and this was followed by a punch biopsy from those with colposcopically identified invasive cancer. Biopsy specimens were examined by a local pathologist and subsequently reviewed by an independent pathologist in the United Kingdom. In no cases were discrepancies noted between the two sets of pathology results. In this trial, the sensitivity and specificity of the Polarprobe for histologically confirmed invasive cervical carcinoma were found to be 98% and 91% respectively.

Future Trials

The Polarprobe screening classification is based on a reference diagnosis established primarily by review of colposcopic and histologic results. Therefore the Polarprobe tissue group diagnoses do not map directly to cytological classification systems. This will prove a useful feature when the Polarprobe is used as an adjunctive test to cytology, since the device can then be used to resolve cytologically equivocal results. Clinical trials have been planned for evaluation of the Polarprobe in the USA and Europe:

- 1) as a secondary screening tool in a population of Papanicolaou smear positive women (in series with the Papanicolaou smear);
- 2) as an adjunctive test to enhance the accuracy of screening information (in parallel with the Papanicolaou smear), and
- 3) as a primary screening alternative to the Papanicolaou smear.

Acceptability

It is known that cytological screening in the form of the Papanicolaou smear is not uniformly acceptable to all social groups, and is influenced by factors such as the presence of a female smear taker¹² and fear or dislike of the idea of the test.¹³ A survey was carried out at the Whittington Hospital on 152 women attending the colposcopy clinic who had experienced both the Papanicolaou smear and the Polarprobe examination to compare their views on the acceptability, after effects and the delivery of results associated with each of the two tests.¹⁴ They were given a questionnaire which included factors such as anxiety and pain (recorded on a visual analogue

scale), delivery and explanation of the results associated with the two tests. The findings revealed that the women experienced less anxiety (mean anxiety score 2/10 vs 4.5/10), less pain (3% vs 33%) and less after-effects like bleeding and discomfort (12% vs 5%) with the Polarprobe examination. In addition, significantly more women—82% (95% CI 76% to 88%) vs 2% (95% CI 0% to 4%) preferred the Polarprobe examination to the smear. When asked about the effect of having an immediate result and explanation available after the Polarprobe examination, 98% felt that this was reassuring. Importantly, 82% (95% CI 75% to 88%) of women responded that the Polarprobe would encourage them to attend for screening, versus 18% (95% CI 12% to 25%) for the Papanicolaou smear.

Ongoing Developments

Continuing developments are underway to improve the accuracy and clinical utility of the Polarprobe. These include a single-use disposable sheath which will remove the high level disinfection requirement and a smaller diameter probe using hybrid chip miniaturisation technology to enable tissue measurements within the endocervical canal.

The technology utilised by the Polarprobe has great potential for use in other sites of the body and it may be feasible in the future to use a hybrid probe in conjunction with an endoscope for sites like the endometrium, prostate, stomach and colon.

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