# Analysis of digitized cervical images to detect cervical neoplasia

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**Abstract**

Cervical cancer is the second most common malignancy in women worldwide. If diagnosed in the premalignant stage, cure is invariably assured. Although the Papanicolaou (Pap) smear has significantly reduced the incidence of cervical cancer where implemented, the test is only moderately sensitive, highly subjective and skilled-labor intensive. Newer optical screening tests (cervicography, direct visual inspection and speculoscopy), including fluorescent and reflective spectroscopy, are fraught with certain weaknesses. Yet, the integration of optical probes for the detection and discrimination of cervical neoplasia with automated image analysis methods may provide an effective screening tool for early detection of cervical cancer, particularly in resource poor nations. Investigative studies are needed to validate the potential for automated classification and recognition algorithms. By applying image analysis techniques for registration, segmentation, pattern recognition, and classification, cervical neoplasia may be reliably discriminated from normal epithelium. The National Cancer Institute (NCI), in cooperation with the National Library of Medicine (NLM), has embarked on a program to begin this and other similar investigative studies.

**Keywords**: Cervical neoplasia, automated image analysis, digitized cervical images, image processing, registration, segmentation, pattern recognition, classification, wavelet.

## 1. Introduction

### 1.1. Cervical cancer and Papanicolaou smear screening

Cervical cancer is the second most common cancer affecting women worldwide, with rates highest in poor developing nations. In the United States, nearly 15,000 women develop cervical cancer each year. More than twenty times that number of women are found to have premalignant disease. If detected at a precancerous stage, treatment is almost universally successful. Thus, the current goal of cervical cancer prevention is to detect early changes amenable to therapeutic cure.

Use of the Papanicolaou (Pap) smear, a microscopic analysis of exfoliated cervical cells, has reduced the incidence of cervical cancer by 70% in populations where implemented.[1] Yet, the Pap smear is not a perfect test. According to a recent meta-analysis, the true sensitivity of the conventional Pap smear is only 51%.[2] New liquid-based Pap tests offer modest increased sensitivity for detecting cancer precursors mainly because of improved specimen preparation techniques. However, interpretation of these Pap tests remains variable and highly subjective.

### 1.2. Human papillomavirus infection, the initiating event

A persistent infection of the cervical epithelium with oncogenic (high-risk) human papillomavirus (HPV) is necessary, but not sufficient for carcinogenesis. Consequently, the presence of HPV infers women may be at risk for harboring a cervical neoplasia. The recent implementation of HPV DNA testing for triage of women with minor cytologic abnormalities or primary screening offers certain advantages. A woman with a negative HPV DNA (high-risk) test result has merely a 1% chance of having significant disease. However, this test is not specific for cancer precursor lesions and many immunocompetent women resolve the mainly transient HPV infection within two years. Certainly, preliminary results from the HPV 16 and HPV 16/18 vaccine trials suggest that we are on the brink of having a novel method to prevent 50-75% of all cervical cancers.[3] Yet, these agents will not be available for several years and as currently configured, do not convey universal protection from cervical cancer.

### 1.3. Optical detection and diagnosis of cervical neoplasia using Colposcopy

Once a woman has been identified as potentially harboring cervical neoplasia through usual screening methods, a diagnostic examination is conducted. Colposcopy or a magnified transilluminated examination of the cervical epithelium is the current diagnostic technique utilized.[4] Optical or video colposcopes are used by the colposcopist to identify abnormal epithelial and vascular changes. These scopes have magnification complexes ranging from 2x to 25x, intense light sources (halogen/arc lamp), green filters and focusing mechanisms. Colposcopists appraise the cervical epithelium after contrast solutions (5% acetic acid and Lugol's iodine) have been applied. Lesion characteristics such as margin; contour; color; and vessel pattern, type and distribution are used to derive a clinical diagnosis.[5] Biopsy forceps are used for histologic sampling to confirm the colposcopic impression. Yet, colposcopy is a relatively expensive procedure and skills vary because recognition of abnormalities is somewhat subjective.

### 1.3.1 Optical screening tests for cervical neoplasia

Because of the frailties of cervical cytology, optical screening methods, based on colposcopic principles, have evolved. Cervicography, or the analysis of 2x2 Kodachrome images taken of the cervix using a modified 35mm camera with a telephoto lens has been used for both screening and triage purposes.[6,7] However, cost, the proprietary nature and modest performance compared with more modern technology, have limited its use. Direct visual inspection (DVI) of the cervix has been touted for use in third world cancer screening programs.[8] Although inexpensive, the technique is nonspecific and suffers from a significant rate of false positive results. Speculoscopy or essentially low magnification, blue light-enhanced visual inspection of the cervix has limitations similar to those experienced with cervicography.[9] Overall, the previously mentioned optical screening tests lack the necessary magnification to allow critical appraisal of the abnormal morphologic features of cervical neoplasia.

### 1.3.2 Fluorescent and reflective spectroscopy

Fluorescent and reflective spectroscopy devices are currently undergoing trials to determine efficacy in evaluating women with potential lower genital tract neoplasias.[10-14] Fluorescence depends on cellular fluorphores that emit light at particular wavelengths when illuminated with certain different wavelengths of light. These measurements correspond to particular metabolic changes. Reflective technology is based on measurement of the amount and wavelengths of light reflected when tissue is subjected to a broadband light source. Reflective data varies depending upon nuclear content, epithelial thickness and neovascularization. When combined, fluorescent and reflective spectroscopy has been able to discriminate normal from neoplastic epithelium. These systems may detect a greater rate of neoplasia compared with cervicography, HPV DNA testing, colposcopy and cervical cytology. Fluorescent and reflective spectroscopy systems may help triage women with minor cytologic abnormalities, assist colposcopists with lesion detection and biopsy site selection, may serve as an adjunct to cervical cytology, or may be used for primary screening. Although several of these systems are presently undergoing FDA trials, the technology suffers from several potential deficits. Adequacy of examination, endocervical canal inspection, discrimination of immature metaplasia (normal variant) from cervical intraepithelial neoplasia 1 (minimally abnormal) and detection of atypical malignancies are not provided. Furthermore, it is not clear if the independent use of fluorescent and wide-bandwidth hyper-spectral imaging will provide a significantly better screening/diagnostic tool.

### 1.3.3. Advanced cervical image analysis

Clinical evaluation of women with abnormal cervical cytologic results is accomplished by colposcopic examination and targeted biopsy. A clinical diagnosis is derived by a systematic appraisal of specific morphologic features. These features have been objectively measured and analyzed. Computerized, algorithm-based diagnoses derived from automated evaluation of the same morphologic features would benefit society. Such systems could assist less experienced colposcopists to identify and precisely sample pertinent cervical lesions in an adjunctive capacity. Because both use computer-based platforms, automated image analysis could also interface with fluorescent and reflective technology to improve diagnostic performance. Low-cost, hand held image analysis devices would enhance cervical cancer screening in underdeveloped nations. Automated image analyses of the cervix could potentially provide consistent, expert-level diagnoses. However, optimal images are required to develop and operate this system.

The advantages of applying advanced image analysis methodologies to cost-effective RGB images of the cervix in designing improved and on-site noninvasive screening tools is worth investigating. There are different techniques of improving the perceptual quality of the traditional color images of the ectocervix. Pilot studies have already been initiated within an alliance formed from institutions with expertise in cervical cancer, image analysis, and digital archiving.[15,16] This group includes colposcopists from the Medical College of Georgia (MCG) and the National Cancer Institute (NCI), specialists in image analysis from the Computer Vision and Image Analysis Laboratory (CVIAL) at Texas Tech University, and engineers from the Communications Engineering Branch of the National Library of Medicine (NLM).

## 2. Methodologies

### 2.1 NCI cervical image archive and compression

In order to investigate the validity of an automated screening tool for cervical cancer, several preliminary studies are being designed and conducted by the alliance group formed by the NCI. The NCI has collected a vast amount of visual information, 100,000 Cervigrams (35mm color slides), screening thousands of women by this technique. Each of these slides when digitized requires 11 MB to store. A Web-based digital archive for sharing and evaluating these high-quality pictures must be designed for critical evaluation by specialists worldwide. The large sizes of the digitized Cervigrams also make them impractical for efficient storage and processing at a single site. For the effective dissemination of cervical image data from a central repository to various study groups, it is also essential that the file size be reduced through advanced color data compression techniques. This compression must preserve crucial features of color and spatial details indicative of pre-cancerous tissues such as the degree of whiteness in acetowhite regions, delicate lesion margin characteristics and fine vascular structures. A novel hybrid, wavelet-based compression codec has been developed at the CVIAL at TTU with partial support from NLM and other sponsors.[22-24] The details of this multi-spectral codec and its role in designing a web-based educational tool are described in the poster on "A multi-spectral digital cervigram analyzer in the wavelet domain for early detection of cervical cancer," presented at this meeting[16].

A preliminary pilot study for evaluating acceptable compression is currently being conducted using the novel Hybrid Multi-Scale Vector Quantization (HMVQ) developed at Texas Tech[21,25]. Figure 1 shows the average rate-distortion performance graph of HMVQ for 60 cervical images. Compression of cervical images at various levels is seen in figure 2. Important cervical features are seemingly retained at compression ratios approaching 100:1.

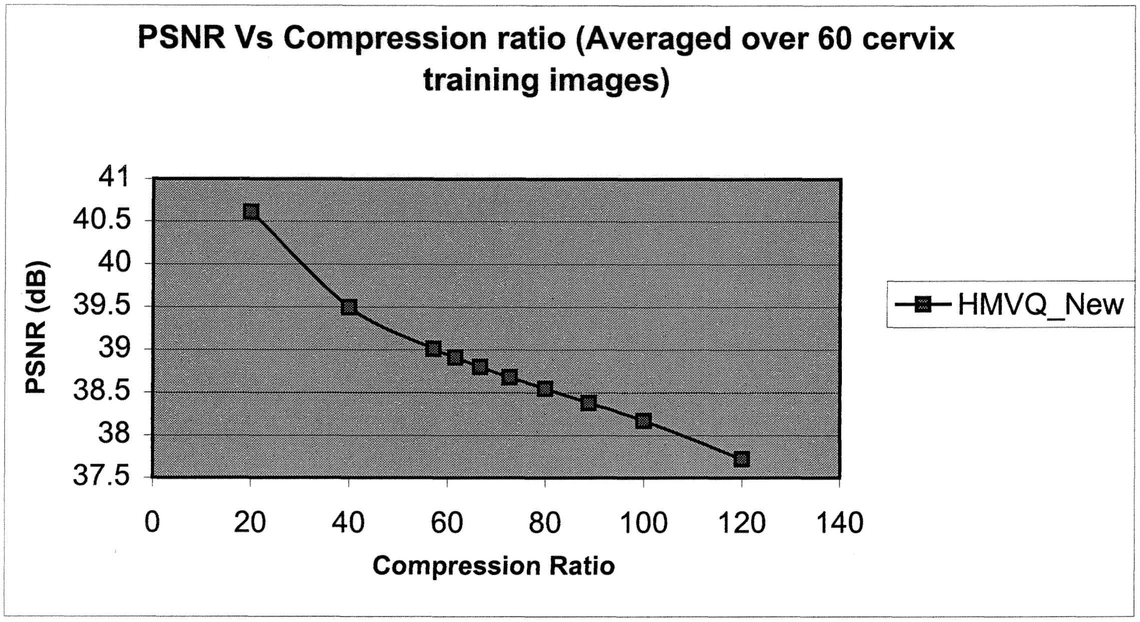



Figure 1. The quality of image as measured by the PSNR against compression levels. PSNR decreases as the compression level increases.

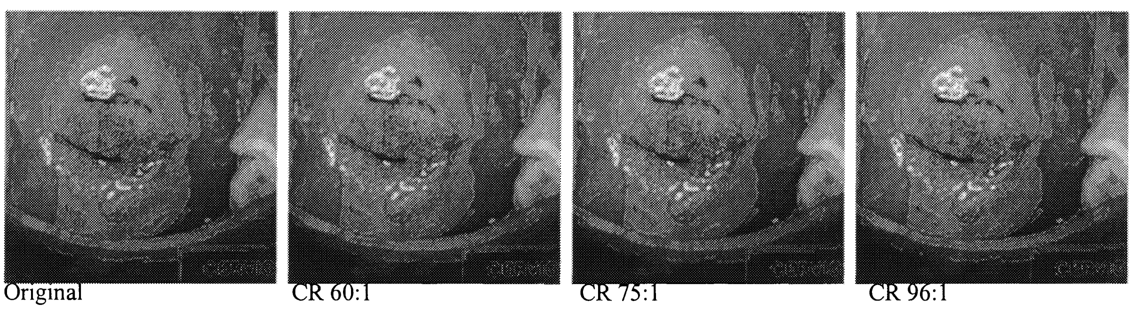


Figure 2. Compression at various levels using a novel wavelet based encoder and optimal color transformation.

However, these results are dependent on image quality. Since the cervical images were not taken by digital cameras directly but were saved as digital images by scanning, image quality was affected by possible film defects and poor scanning processes. Shot noise, film grain noise, blurring, and scratches are generally introduced into the scanning process. Therefore, pre-processing of these noisy images may be considered prior to compression to enhance the image quality.

## 2.2 Image transformation, registration and segmentation

The alliance is presently conducting preliminary studies towards the acceptability of available digitized cervical images under a number of image analysis criteria.

### 2.2.1 Color Transformation

Color transformation is usually among the first of several pre-processing steps prior to the actual compression. This is due to the fact that the high correlations among the red, green and blue color planes of the original image lead to too much redundancy in the compressed data if we compress them simply as they are. YCbCr transform is one of the most efficient color transforms in terms of decreasing the correlation among transformed planes. Hence it becomes one of the most commonly used color transforms in compression. It is also well-known that transformation of an RGB image to YCbCr or L*a*b* results in better perceptual quality [26,27].

The compression codec in development will incorporate multi-spectral mapping for optimum color perception, multi-scale feature extraction, vector quantization codebook training and boundary mark detail-preserving, residual scalar quantization. The modified HMVQ encoder uses YCbCr transform to map the original RGB into YCbCr planes, and then compresses each color plane separately. Under a specified total output bit-rate, HMVQ encoder allocates different bit-rates to different compressed planes. The allocation is based on the two facts: perceptually, human eyes are much more sensitive to the luminance component (Y plane) than chrominance components (Cb and Cr planes); objectively, Y plane contains most of the information from original image, and Cb and Cr planes contain much less information. Hence by allocating higher bit-rate to Y plane data and lower bit-rate to other two planes, the quality of a reconstructed image will be much better than using equal bit-rates for all planes. Preliminary results indicate that a bit-rate ratio of 5:1:1 for Y, Cb and Cr planes performs consistently well in compressing cervigram images. In addition, some cervical images are not captured under optimal viewing conditions, requiring nonlinear transformations for enhancement of image as illustrated in figure 3.

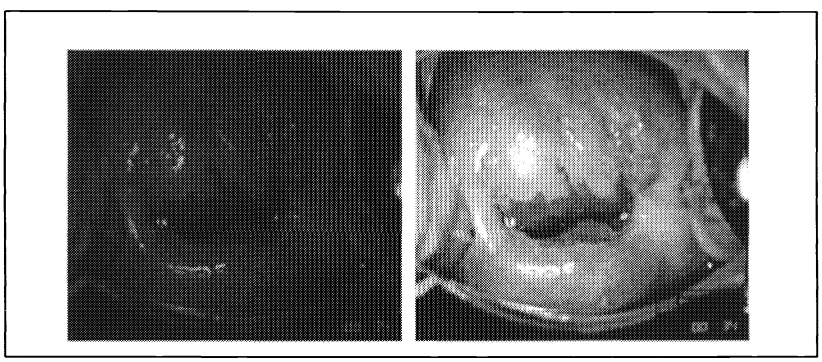


Figure3. The picture on the left shows a section of a digitized cervical image, the right image resulted from a non-linear transformation.

Such image transformations highlight early ectocervical changes and may allow easier detection of neoplasia. However, in the current compression pilot study such color transformations were not included thus restricting the study to only good quality original images.

### 2.2.2 Image Registration

Large clinical trials conducted by NCI have collected serial cervical images from study subjects (figure 4). In order to accurately assess the changing surface area of evolving lesions as shown in figure 4, image registration is required.

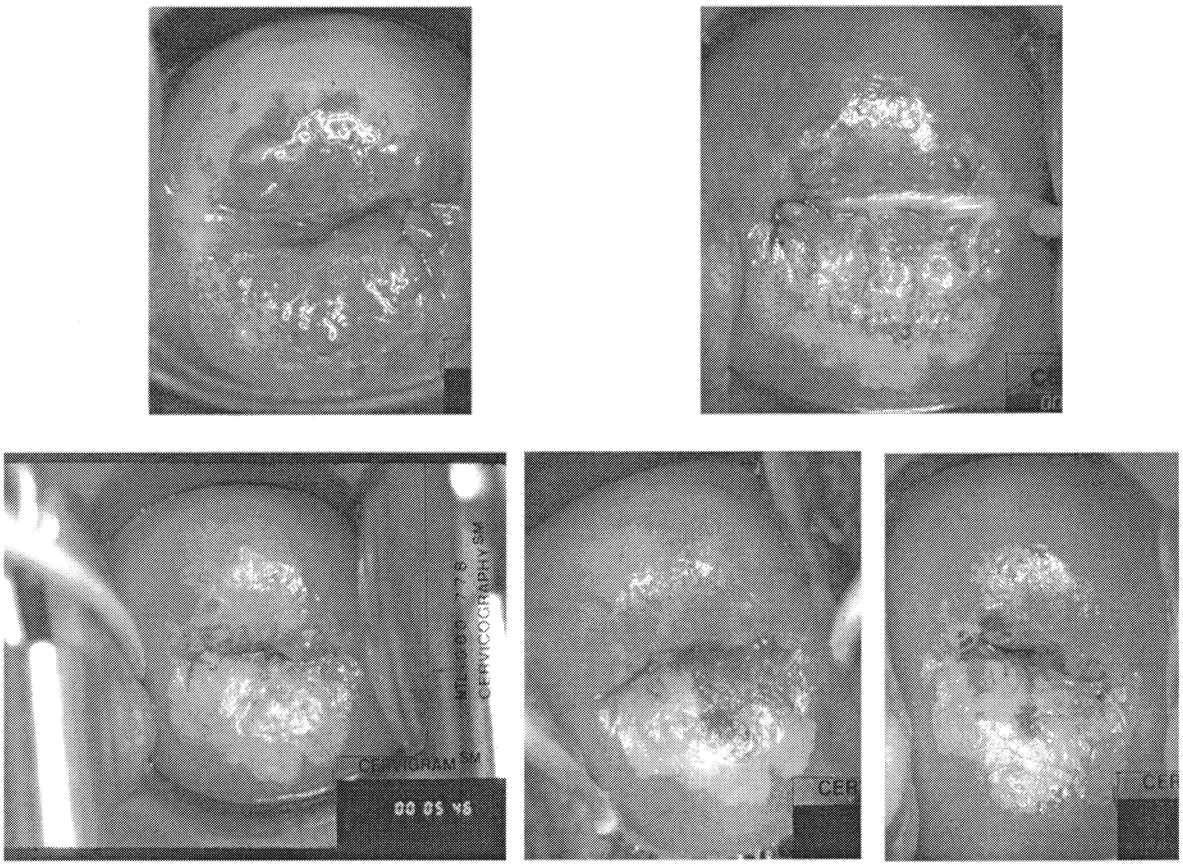



Figure 4. Serial cervical images from a 22 to 25 year old woman in the Guanacaste NCI study. The cervix changes from normal to cervical intraepithelial neoplasia during this time. Registration is necessary to align these images in order to assess changing lesion surface area.

**Cervigram Registration Technique:** Overview

Cervigram images are not easy to register as they tend to vary substantially in multiple degrees of linear and nonlinear transformation. Furthermore, the appearance of the cervix itself tends to significantly change with each patient visit. As there is no requirement placed upon the physician to provide constrained movement so as to facilitate simple registration, a simple registration scheme will probably not suffice in most cases. A segmentation-based registration algorithm, based on k-means clustering, is implemented here. The technique shows promising results as a crude first step registration and precursor to more advanced registration techniques. It may also be used alone to provide an automated registration or cropping mechanism for those applications not requiring very precise alignments.

**RGB to YCbCr Conversion**

Color of the cervix is one of the characteristics that best distinguishes it from the rest of the image. The cervix has a pink color whereas the rest of the image varies from a brown to black or white. Therefore, a color transform is first performed on the image so that the color can be more easily represented. The YCbCr transform separates the luminance from the color components of the image.

**Discarding the Luminance**

The luminance plane was observed to be less effective than the color in separating the cervix from the background of the image. Therefore, the luminance was discarded and no longer taken into consideration in subsequent steps. Only the color information is used for the segmentation and registration.

**K-Means Clustering into Three Clusters**

The images will be considered to exist as three distinct regions.

1. Cervical Region
2. Surrounding Cervical Region
3. Darker film Region

Therefore, the K-means clustering algorithm was implemented to separate the image into three distinct regions using the Euclidean distance as the separation metric. Furthermore, the clustering was repeated three times using randomly generated centroid starting locations so as to ensure that the segmentation was consistent. The features used for the clustering involved the two color components of the image that remained once the luminance values were discarded. Namely, the Cb and Cr components were used for classification.

**Choose Cluster According To Centroid**

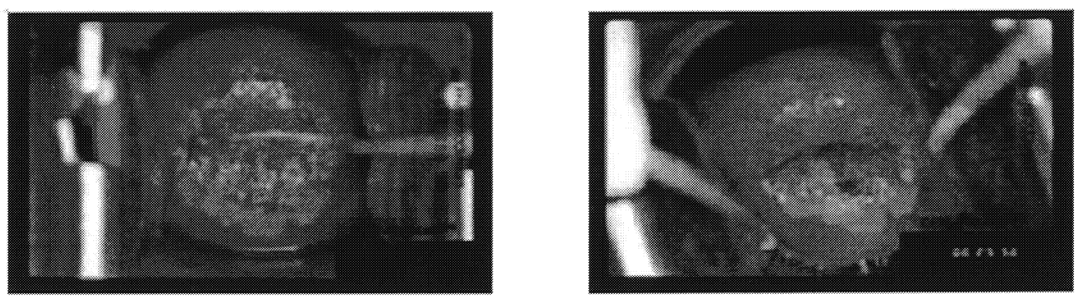
After dividing an image into multiple regions through clustering, one still is required to pick the correct region of interest. For this implementation, choosing the correct segmentation region simply involved choosing the region related to the cluster having the largest centroid component in the Cr color channel or feature space. As the cervix varied from its surroundings mostly through the Cr color component, this feature was most useful in choosing the correct cluster.

## Spatial Filtering

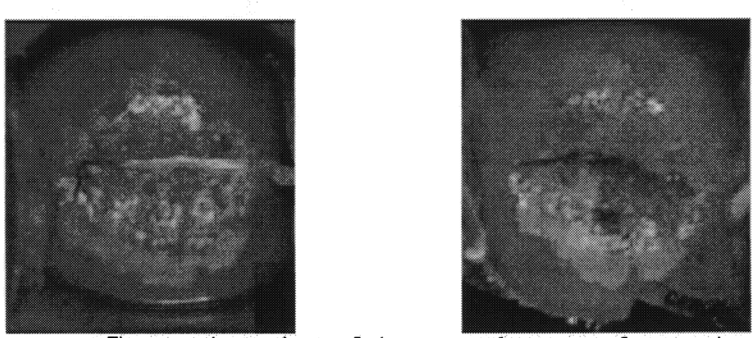
After the correct region was chosen, spatial filtering was used in order to improve the segmentation. Since it is known that the cervix is a connected object, only the largest cluster in the binary image was retained and all smaller noise clusters were discarded. Furthermore, all holes were filled in the segmented region. The end result is a disc-shaped region that corresponds to the cervical regions.

## Registration and Results

Once the segmentation is retrieved, it can be used to help align multiple Cervigram images together. From the segmentation disks, one can derive the center of mass, orientation, and scales along the major and minor axes. Therefore, it is easy to make crude registrations through the use of these values. The segmentation and registration results can be viewed below. Notice that in each case, the algorithm is able to perform the translational and scaling relatively well. However, the rotation is still crude at best. The method still suffices for correcting gross misalignments. The next set of figures (Figure 5) each show two unregistered and two registered images.



Misaligned sequence of cervigrams taken from the same patient at different times



Cropped version of the same images after registration

Figure 5. An example of misalignment and registered image sequences.

### 2.2.3 Boundary marking and image segmentation

A common clinical practice to detect early changes in cervical color is to apply acetic acid, then to visually observe the acetowhite regions and changes in boundaries of the regions during follow-up visits. The Boundary Marking Tool (BMT) developed by NLM and NCI allows expert colposcopists to visually evaluate cervical neoplasias (figure 6) and then compare these optical findings with histologic, cytologic, immunologic and results from large clinical trials (figure 7).

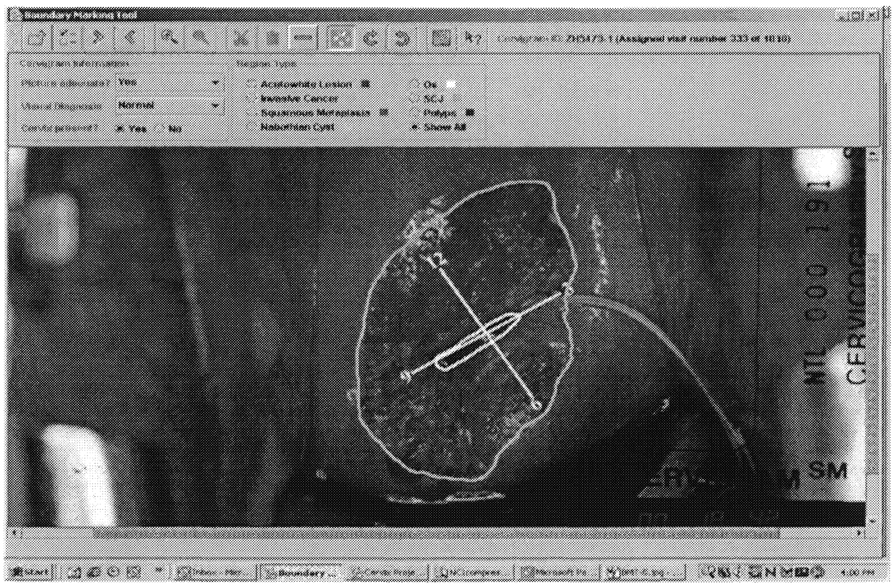


Figure 6. The boundary marking tool (BMT) developed by the National Library of Medicine and the National Cancer Institute used to study cervical neoplasia.

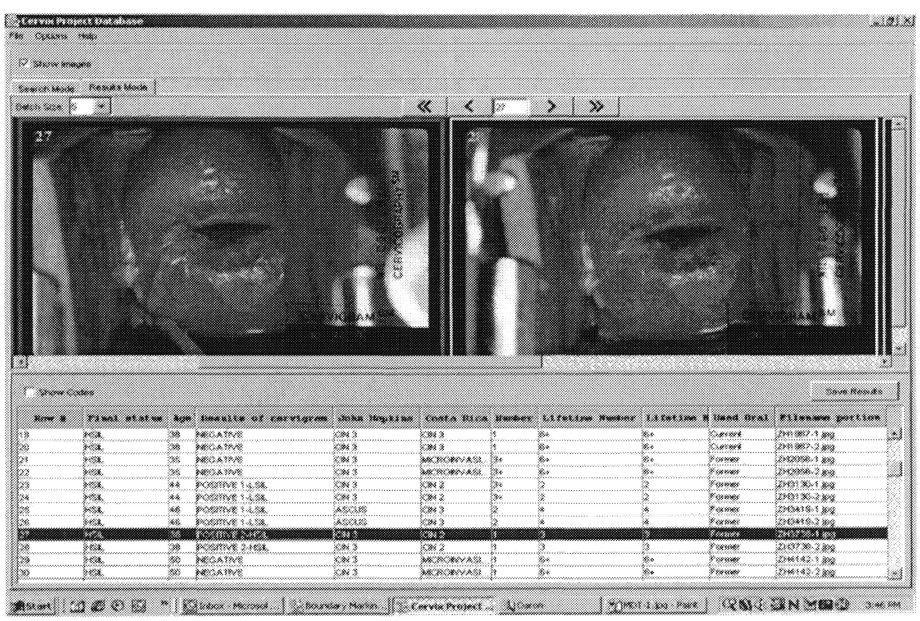
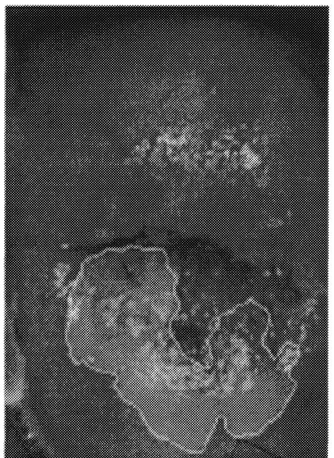
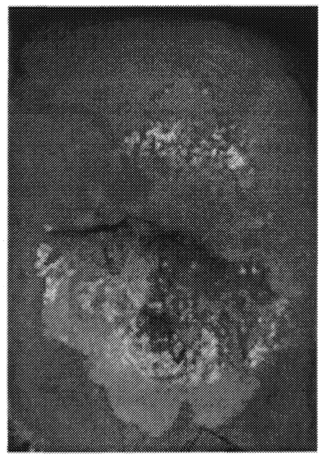


Figure 7. The Multimedia Database Tool that links trial data with cervical images.

Automated segmentation techniques will be quite useful to analyze cervical lesions. The acetowhite lesion in figure 8 (a), marked by a trained physician, serves as a reference to the region in figure 8 (b) obtained by an automated segmentation algorithm. This type of cervical image is traditionally taken with a regular high resolution color camera, thus the segmentation of the acetowhite lesion area from the rest is affected by the glare and non-uniform illumination which need to be removed for more accurate interpretation. Figure 8(b) shows the segmentation result without illumination correction.





Figures 8 a and b. Acetowhite lesions marked manually by an experienced physician 6 (a) and the corresponding automated segmentation of the affected region (b).

Advanced clustering techniques can provide general solutions for effective segmentation of a broad range of medical images. The segmentation examples presented here use image intensity as the single feature to clustering algorithms to demonstrate the efficiency of the algorithms. In real applications, local property or connectivity of adjacent pixel can be embedded into segmentation to achieve more accurate segmentation.

## 3. Automated analysis of cervix images

In order to evaluate the changes in affected regions in a precise quantitative and efficient manner, specifically-designed image analysis algorithms for registration, segmentation, automated pattern recognition and classification of cervical images are needed.[17-20] Disadvantages of current imaging-based diagnostic tools include subjective variability in interpretation of pathology, lack of quantitative documentation, lack of standardization, time-consuming manual segmentation of regions of interest and absence of medical specialists in all locations. An automated system for identification and classification of cervical neoplasia has clinical utility. Figure 9 shows a schematic diagram of the design modules of such an automated system that may be appropriate for use as a screening tool. As the diagram indicates, the system includes a number of challenging image analysis tasks.

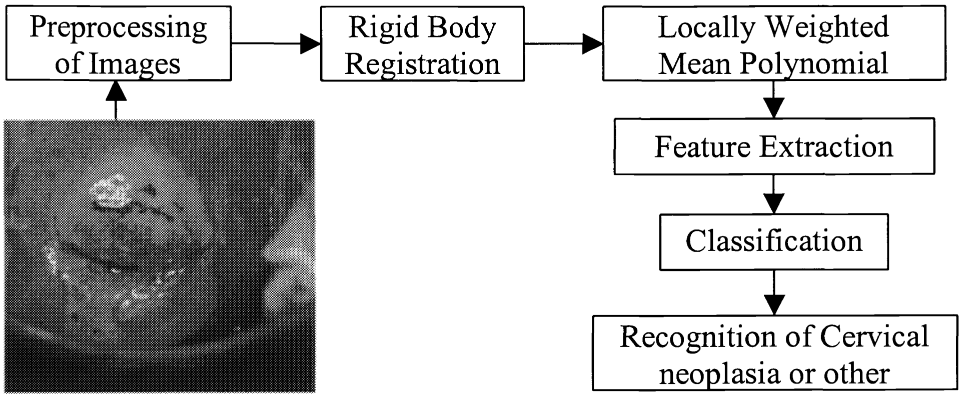



Figure 9. The entire process of digital image analysis for classification and recognition of a multi-spectral image input is shown schematically.

## 4. Steganography

Finally, the use of Steganography, a technique to hide secret messages in seemingly innocuous carriers can be considered to hide confidential patient information in digital cervix images [28]. Digital images are particularly interesting as carriers as they are extremely portable. However, they have a limited capacity when compared to audio and video streams. The Bit Plane Complexity Segmentation ( BPCS ) technique works to alleviate this problem and allows embedding data up to 70% the size of the image in which the data is being embedded. An application of the BPCS steganography technique for cervical image and patient information has been recently developed [29].

## 5. Conclusions

The public use and analysis of this data set for recognition and classification of cervical neoplasia has the ultimate benefit of improving management and reducing healthcare costs for women with cervical neoplasia, a condition associated with high morbidity and mortality risk worldwide. Our alliance (NCI, MCG, NLM, TTU) has been formed to address the optimal management and early detection of cervical cancer utilizing this cervical data set. The long-term objective of the proposed project is to facilitate the development of a unique Web-based database of digitized cervical images for investigating the role of human papillomavirus (HPV) in the development of cervical cancer and its intraepithelial precursor lesions in women. The NCI, in collaboration with the alliance formed, intends to make this unique data set available to worldwide researchers. We welcome helpful advice and collaboration with other scientists.

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