A STUDY TO DETECT CERVICAL CANCER BY USING ELECTRICAL IMPEDANCE

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A STUDY TO DETECT CERVICAL CANCER BY USING ELECTRICAL IMPEDANCE

APICHADA SILLAPARAYA

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A STUDY TO DETECT CERVICAL CANCER BY USING ELECTRICAL IMPEDANCE

BY

APICHADA SILLAPARAYA

HAS BEEN APPROVED BY THE GRADUATE SCHOOL IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE MASTER OF ENGINEERING
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Early screening for cervical cancer, especially screening for the first grade of cervical intraepithelial neoplasia (CIN) can reduce risk and improve the effectiveness of timely treatment. Current screening techniques, such as Pap smear and liquid base cytology require many laboratory processes and time. Electrical impedance of tissue is recently used to screening the CIN and more likely to well identify the presence of precancer cells. The measurement for the impedance is based on the four-electrode technique that requires at least eight measurements on the tissue. The global impedance is calculated and used for determining CIN. However, this current technique is unable to precisely identify the location of the anomaly, as well as the shape and size of the CIN. Therefore, this study proposed to use a 16-electrode array in a planar plate for locating CIN in a tissue sample. Three electrode layouts were proposed: star layout, circular layout version1, and circular layout version2. Based on the 16-electrode configuration, all measurements throughout the sample can be collects at the same time, and then we used this measurement data for reconstructing the image of conductivity distribution of the measured sample based on Electrical Impedance Tomography (EIT) technique. With this image, the locations of abnormal cells can be visualized, and this can reduce substantial investigation time. The simulation result shows that all three layouts can locate simulated Grade3-CIN objects in cervical tissue in most of the simulation cases. The amplitudes of the reconstructed CIN were smaller than the true amplitude approximately by 10 times in almost all cases. When the CIN was put in the outer edge of the cervix model, the amplitudes of the reconstructed CIN were smaller than the true amplitude approximately by 100 times. The overall localization error of the star layout where the electrode array was denser than the others was smaller than the others by approximately 2 times. The average localization errors of the star layout, the circular layout version 1 and version 2 were 0.6351 mm and 1.2859 mm and 1.3639 mm, respectively. This is because the sensitivity of the star layout is higher due to the smaller area of the electrode array. Nevertheless, for the star layout, when CIN was situated at the outer edge of the cervix model, it cannot be reconstructed. In the case of the circular layout version1, the artifact at the orifice region was larger because there was a large electrode in the center. Therefore, we recommend to use the circular layout version 2 for locating cervical cancer.

Keyword : Bioelectrical Impedance, Cervical Cancer, Electrical Impedance Tomography (EIT)

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CHAPTER 1
INTRODUCTION

1.1 Background

In 2018, cervical cancer is the eighth most common cancer of all cancer occurring in the world and the fourth most common women cancer representing 6.6% of all gynecological cancer with over 570,000 new cases in this year(1, 2). Women are recommended to have regular checks to reduce the risk of death to have late treatment. There are many techniques to detect cervical cancer e.g. Pap smear test, Pelvic examination, Colposcopy(3). Pap smear is the most common and widely used method to detect it but this technique has certain limitations since it is low in sensitivity to detect cervical cancer precursors. The accuracy of this method is less than 50%(3). Liquid based cytology technique is many times applied for improving the sensitivity of Pap smear. However, using this technique is costly and required extensive processing time(4). To determine the cancer by using the electrical characterization of cervical tissue is also a potential method. Differences in electrical impedance between normal and abnormal tissue due to the change of physiological structure of the tissue cells can be used to identify the presence of cancer or even precancerous cells(5). This technique performs by injecting electrical current into tissue and then measuring boundary voltage. Given the injected current, the measured voltages can be used to get information on the bioimpedance. Electrical impedance of tissues is a parameter can be used to distinguish cancer, and it has been used in several applications for example, brain function monitoring(6), bladder volume estimation(7), fat mass estimation(8), and including cervical cancer detection(9-15). The impedance of different types of tissues could be different due to the difference in cell arrangement or layering, shape, and size of the nuclei. Therefore, using tissue impedance is a possible way to classify the normal and the precancerous cervical tissue in the cervical application(9-14). Most of the previous studies performed measurement in eight positions of bulk tissue samples with a 5.5 mm-diameter and four-electrode (in square arrangement) probe. The diameter of the electrodes was 1mm. The bulk (overall) conductivity of the tissue was estimated by

averaging the impedances obtained from eight locations of each tissue(9-14). (9, 11)experimented on 87-124 subjects and used frequency up to 614 kHz. Cell equivalent circuit was referred to in these studies. Extracellular and intracellular resistance and cell capacitance were used to determine the presence of the abnormal cells based on Cole-Cole equation. (10, 12) carried out the experiments in a similar way and equipment to (9, 11) on 176 subjects. However, the used frequency was expanded to 1200 kHz. (13, 14) performed in the experiment on 56 subjects with the same equipment and with frequency up to 614 kHz. However, (13) and (14) used derived parameters based on an alternative form of the Cole-Cole equation and Generalized Effective-Medium Theory of Induced Polarization, respectively. These studies found that the impedance of the normal part of tissue was higher by four times than the precancerous part and can be used to identify the presence of cancer. However, there are some limitations since the calculations were based on averaging the eight impedance values of measurement. This could be not inaccurate since the spread of CIN could be various in size. Mixing grades of CIN could also be possible. Furthermore, the abnormal cells could be situated in the region where the measurement was not measured. Recently, (15) proposed a different way by using a planar electrode plate on cervical smear in the suspension of 500 microliters on 150 samples. The impedances of 100 Hz-1 MHz current excitation were used to classify the normal and the abnormal sample. This method has benefit from using smear which is less invasive than using bulk tissue.

Unfortunately, the standard impedance values of normal and precancerous cervical tissue are still lacking. This method is considered as an optional method to pre-investigate the cancer or as an additional tool in laboratories to examine for the cancer. The conventional method like Pap smear test, worked in laboratories, is then still necessary at the time of writing.

In clinical, the Gross specimens also require sampling so that the experience of pathologists to address the cancer cells is usually crucial. Good sampling could indicate the spread of cancers towards neighbor tissues. The bioimpedance

measurement technique could benefit to locate the rough location of the cancer cells, and this is one of the objects of this research.

In this study, instead of using a few values of impedance values to determine the presence of abnormal cells on bulk tissue according to the four-electrode method, we propose to reconstruct images of impedance distribution by using measurement voltage information (over 200 measurement voltages). Three electrode layouts for locating historical abnormality i.e. Star layout, Circular layout version 1, and Circular layout version 2 were investigated by simulation. These layouts are consisting of 16 electrodes locating in positions consistent with the shape of cervical tissue (which are suitable for electrode array plates). With the proposed method, abnormal cells can be located with the image of conductivity distribution reconstructed from voltage information.

1.2 Objectives

1.2.1 To study the possibility to locate cervical cancer by using the electrical impedance of tissues.

1.2.2 To determine the most efficient electrode layout for locating cancer.

1.3 Scope

1.3.1 This study is a simulation study.

1.3.2 The model was based on the geometry of a cervical tissue taken from Loop Electrosurgical Excision Procedure (LEEP) method.

1.3.3 The model considered only normal and cervical intraepithelial neoplasia (CIN) grade 3 (CIN3).

1.3.4 The amplitudes and the frequencies of the excitation current were 10μA at 100Hz.

1.3.5 Only three configurations of electrodes i.e. Star layout, Circular layout version 1, and Circular layout version2 were investigated by simulation. The number of electrodes was 16.

1.3.6 Used Netgen or NGSolve software for the simulation models.

1.3.7 Used electrical impedance and diffuse optical reconstruction (EIDORS) software for forward modeling and reconstruction method.

1.3.8 The reconstruction was used codes developed by the author and Assist, Prof. Dr.Taweechai Ouypornkochagorn.

CHAPTER 2
THEORY AND LITERATURE REVIEW

2.1 Cervical cancer

Cancer is one of a large group of diseases that can grow in almost any tissue and organ of the human body and can spread to other organs. Cervical cancer is the one of most types of woman cancer in the world, a major public health burden to women in many low- and middle-income countries. It develops in the woman's cervix, at the innermost part of the vagina where is the connection point between the vagina and the uterus. In 2018, cervical cancer is the eighth most common of all cancer and the fourth most common women cancer in representing 6.6% of all gynecological cancer with over 570,000 new cases and 311,000 cases deaths from the disease(1, 2). Approximately 6,000 Thai women are diagnosed of having cervical cancer each year, or it is approximately 7 Thai women die from cervical cancer each day(16).

Cervical cancer can be prevented and curable if it is detected early or in preinvasive stages. Human papillomavirus (HPV) is the organism that is the essential cause of almost all cases of cervical cancer(17). There are many types of HPV but it has been identified that the main cause of cervical cancer developed by approximately 15 carcinogenic HPV genotypes. There are four stages in the development process of cervical cancer including HPV acquisition, HPV persistence (V/s. clearance), progression of a persistent infection to cervical pre-cancer, and invasion. The etiology of cervical cancer is related to many factors, HPV infection alone is not an adequate cause of cervical cancer. Cofactors factors affecting the development of cervical cancer such as tobacco smoking, sexual and reproductive factors, early age at onset of sexual activity, long-term oral contraceptive use, multiple pregnancies, HIV and other sexually transmitted diseases, genetic susceptibility, certain micronutrient deficiencies, and low socioeconomic status etc. Additionally, in low- and middle-income countries (LMICs), cervical cancer is 18 times more occurrent than in high-income countries because of ill-equipped health systems. The poor screening and the poor treatment limit in both availability and accessibility.

Cervical cancer in its early stages usually has asymptomatic, but it shows symptoms when the disease develops and results in symptoms for example abnormal vaginal bleeding, pain in the pelvic, coitus, and dyspareunia, etc. The three essential histological types including adenocarcinoma, adenosquamous carcinoma, and squamous cell carcinoma, this cancer develops slowly and locally. The way of treatment depends on the stage and type of cancer. The surgery or radiation is used in combination with chemotherapy is the way of treatment for the earliest stages of cervical cancer. The later stage was treated with radiation therapy in combination with chemotherapy. Prophylactic HPV vaccination, use prevention equipment in intercourse, and regular screening tests are important strategies to prevent cervical cancer.

2.1.1 Etiology

Almost all cases of cervical cancer or accounted for 99.7% of cervical cancers are the result of ongoing high-risk HPV infection(17). There are more than 100 virus types, including infect the human genital tract approximately 30 to 40 strains. Of these, cancer-causing or high-risk types, such as 16^{th}, 18^{th}, 31^{th}, 33^{th}, 35^{th}, 39^{th}, 45^{th}, 51^{th}, 52^{th}, and 58^{th} were associated with cervical, vulvar, vaginal, and rectal cancers. But non-carcinogenic or low-risk types, including 6^{th}, 11^{th}, 40^{th}, 42^{th}, 43^{th}, 44^{th}, and 54^{th}, which were associated with genital warts. A higher incidence of HPV infection and intraepithelial neoplasia progression was seen in immunosuppressed patients. This includes people with HIV, people who receiving organ transplants, people with chronic renal failure, people with a history of Hodgkin lymphoma or receiving immunosuppressive therapy. For other reasons, women who have many sexual partners, cigarette smoking or the onset of sexual activity at early age may increase the risk of developing cervical neoplasia in women since during adolescence will occur the high rate of metaplasia and higher proportion of immature or new cervical cells in this region(17, 18).

2.1.2 Pathophysiology

The human papillomavirus (HPV) is the essential cause of cervical neoplasms, accounted for 99.7% of cervical cancers. There are more than 40 types of genital HPV, and approximately 15 types are oncogenic HPV. Over 70% of cervical cancers are found to be HPV subtypes 16th and 18th(18). In people with HPV, approximately 75-80% of people are of reproductive age. If exposed to genital HPV before 50 years old, most HPV infection is temporary. But if the infection is long-lasting It will be able to develop and cause cervical cancer. By the time since initial infection, it took about 15 years to develop high grade squamous intraepithelial lesion (HSIL) to become invasive cancer. Most invasive cervical cancers are caused by intraepithelial neoplasm that forms in the tissue of cervical ectopy. Therefore, in younger women, cancer tends to lie on the ectocervix and lie on the endocervical canal in older women. The tumors may have an exophytic or endophytic growth pattern, in exophytic tumors on the ectocervix are less likely to expand and spread into nearby tissues and organs than similarly sized endophytic tumors. HPV-induced pre-cancer can develop within 2 years after the initial infection of the unstable endocervix's squamous epithelium. However, it takes over the 10-15 year to developed the pre-cancer to invasive cervical cancer. Over time, uninfected metaplastic squamous epithelium grows and appears to be more susceptible to no-risk or low-risk viruses, such as subtypes 6th and 11th that have a tropism for the mature squamous epithelium of the mucosal surfaces(17, 18).

The abnormal precancerous cells are called Cervical Interepithelial Neoplasia (CIN) or Squamous Intraepithelial Lesions (SIL). Cervical Intraepithelial Neoplasia (CIN) is a precancerous condition, the term used to define the abnormal changes that occur in the squamous cervical epithelium, a precursor to invasive carcinoma. The cervical dysplasia can develop to invasive carcinoma if not early detected and not properly treated. The CIN progression is categorized according to the affect level of the epithelium and the severity of the dysplasia(17), divided into three stages i.e. CIN 1, CIN 2, and CIN 3 (Figure 1). Generally, the proportion of the total thickness of epithelial affected by dysplasia correlates with the stage of CIN. The case

of CIN 1, the poor maturation and enlarged nuclei known as the dysplastic cells present in 1/3 on the bottom of epithelium and the normal tissue will be throughout 2/3 of its thickness on upper. The case of CIN 2, the dysplastic cells present in 2/3 on the bottom of epithelium. And the case of CIN 3, abnormal cell structures and enlarged nuclei may be throughout of total epithelial thickness(19).

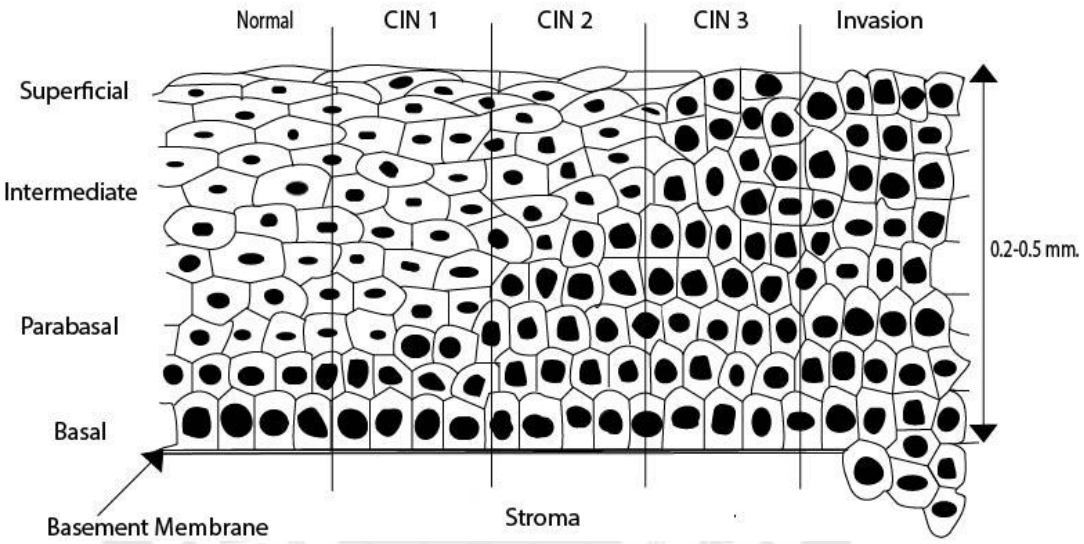


Figure 1 The cervical intraepithelial neoplasia (CIN) progression in the squamous epithelium of cervix.

Cervical cancer staging is performed by clinical examination called clinical staging, according to the FIGO system and the TNM system, which are standards and applicable to all types of cancer cells(17, 20). The criteria of TNM and FIGO classification for cervical cancer as shown in Figure 2 and 3(20).

Criteria	TNM Stage	FIGO Stage
Primary Tumor Case (T)		
Unassessable	TX	-
No evidence	T0	-
Carcinoma in situ	Tis	
Carcinoma confined to the uterus	T1 (Substages: T1A, T1A1, T1B, T1B1, T1B2, from less severe to much severe)	I (Substages: IA1, IA2, IB, IB1, IB2, from less severe to much severe)
Tumor expands to the outer region of the uterus, but not to the lower 1/3 of the vagina and the pelvic wall	T2 (Substages: T2A, T2B, from less severe to much severe)	II (Substages: IIA, IIB, from less severe to much severe)
Tumor expands to the lower 1/3 of the vagina and the pelvic wall	T3 (Substages: T3A, T3B, from less severe to much severe)	III (Substages: IIIA, IIIB, from less severe to much severe)
Tumor found in the mucosa of bladder and/or the pelvis	T4	IVA
Regional Lymph Nodes Case (N)		
Unassessable	NX	-
No metastasis	N0	-
Metastasis	N1	-
Distant Metastasis Case (M)		
Unassessable	MX	-
No metastasis	M0	-
Metastasis	M1	IVB

Figure 2 The criteria for classification staging of cervical cancer according to TNM and FIGO system part 1.

FIGO Stage	Primary Tumor Case (T)	Regional Lymph Nodes Case (N)	Distant Metastasis Case (M)
Stage Grouping			
0	Tis	N0	M0
I (Subgroups: IA, IA1, IA2, IB, IB1, IB2, from less severe to much severe)	T1	N0	M0
II (Subgroups: IIA, IIB, from less severe to much severe)	T2	N0	M0
III (Subgroups: IIIA, IIIB, from less severe to much severe)	T3	N0	M0
IIIB	T1, T2	N1	M0
IIIB	T3	NX, N0, N1	M0
IVA	T4	NX, N0, N1	M0
IVB	T1, T2, T3, T4	NX, N0, N1	M1

Figure 3 The criteria for classification staging of cervical cancer according to TNM and FIGO system part 2.

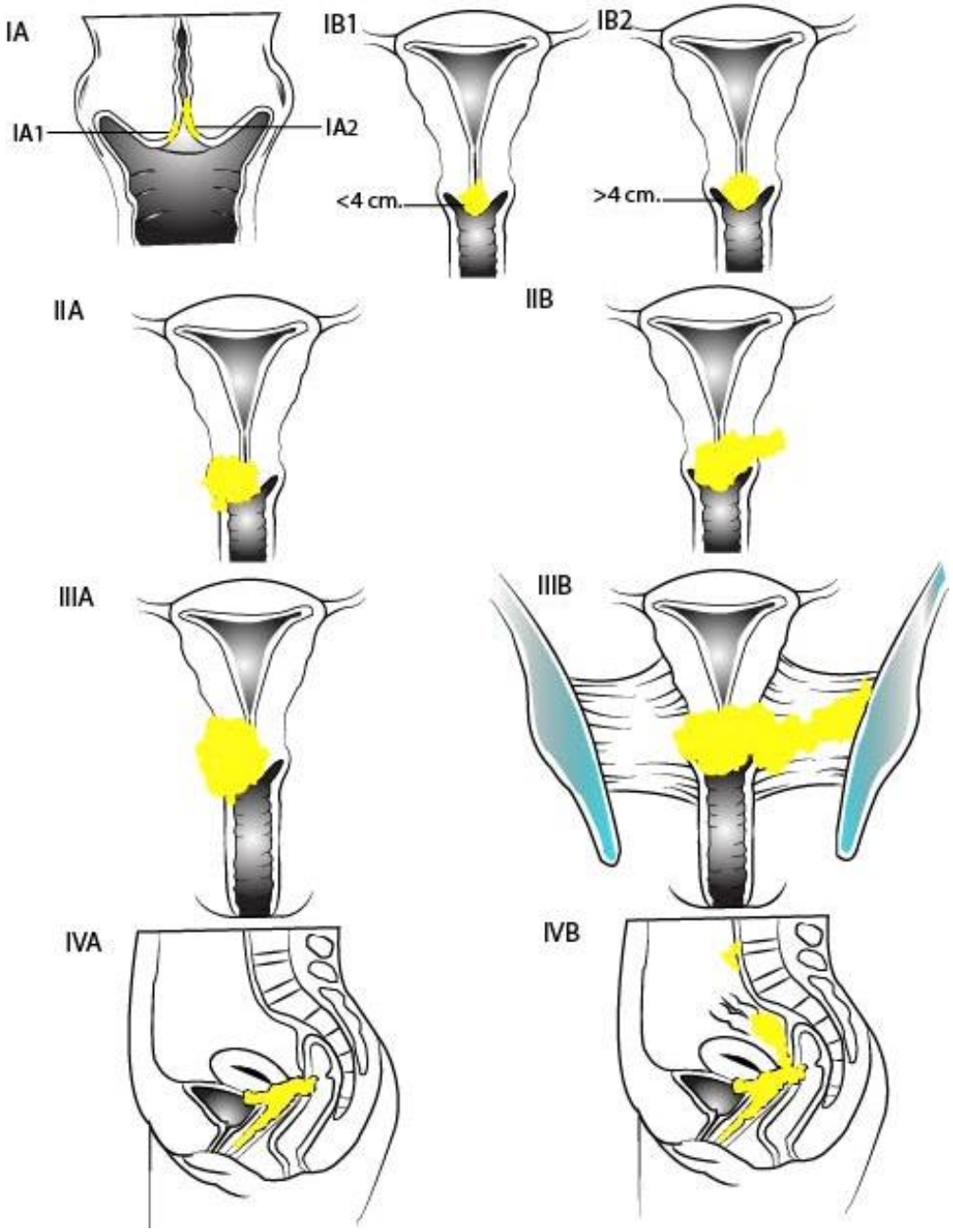


Figure 4 Staging of cervical cancer according to FIGO system.

2.1.3 Methods for screening cervical cancer

The period from the commencement of the infection to the spread of cervical cancer may take 10-15 years. Therefore, women should check the cervical screening regularly according to the doctor's advice. There are several methods for screening cervical cancer, including physical examination i.e. palpable lymph node, the vagina, and bimanual rectovaginal examination. Radiologic studies are the one choice to use for screening cervical cancer i.e. intravenous pelogram, barium enema. It is also used procedures for cervical cancer screening as well i.e. Pap smear, Pelvic examination, Colposcopy (18, 21).

Papanicolaou (Pap) smear test

Papanicolaou smear or Pap smear test is the most common test used in cervical cancer screening. This test helps to detect early abnormalities of tissues in the cervix, resulting in the early detection of cancer although it may not be 100% accurate. This test is painless, normally requires only 1-2 minutes to complete and it can be performed in a doctor´s office without the need to go to a hospital. Women who are 18-year-old or older or 3 years after having the first sexual activity are recommended to screen with Pap smear tests every 1-2 years(3, 22).

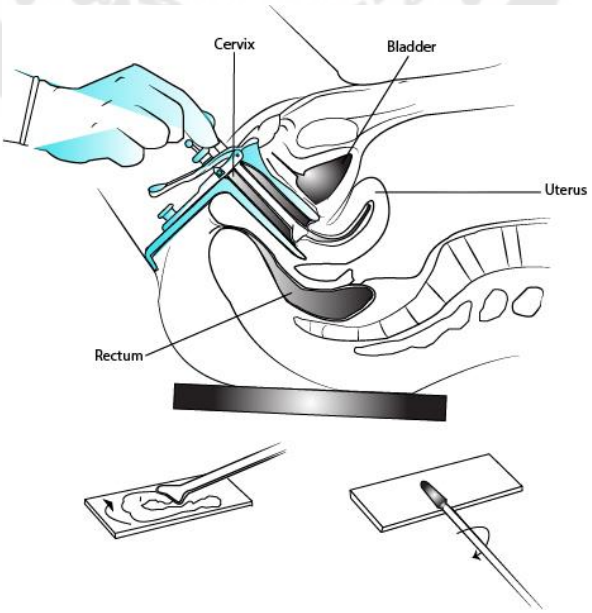


Figure 5 The process of Pap smear test.

Pap smear test is performed while a woman is lying on her back on a table. A doctor will insert a speculum into the vagina to widen it and collect epithelial cells from the area of the cervix. Some sample cells from the cervix are taken using a cotton swab or small brush (Figure 5). The sample cell will be kept onto a glass slide and will be delivered to a laboratory for cancer examination. At the laboratory, the cells in the slide is dyed using specific methods and then is investigated by a specialist pathologist for finding abnormal cells through the microscope.

Generally, Pap smear test is performed combined with the pelvic examination because the first step to examination is very similar that is a woman will lie on her back while a doctor inserts a speculum into her vagina.

Pelvic examination

Pelvic examination is the examination of reproductive organs and nearby organs in the pelvis of women (vagina, uterus, and ovaries) by an obstetrician. The procedure starts by that a doctor inserts a speculum into the vagina and visually inspects abnormalities of the shape and size of organs in the vagina and cervix. Which, if abnormal, would indicate that a disease has already occurred. After bringing the speculum off, the doctor inserts fingers into the vagina and uses the other hand presses gently at the patient's abdomen to assess the size and location of the uterus or observe pain and the abnormalities of the pelvic organs(3, 22) as show in Figure 6.

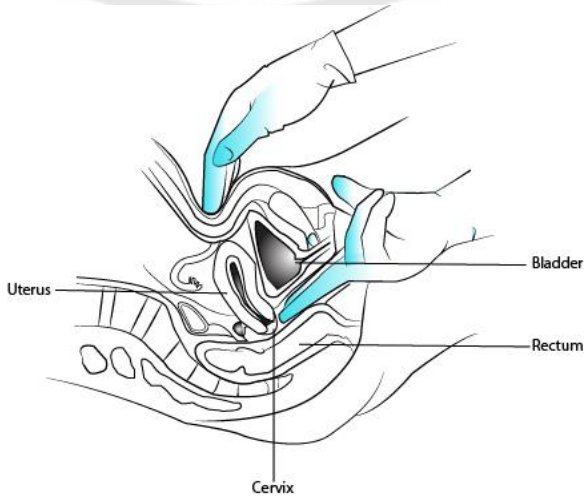


Figure 6 The process of pelvic examination.

Colposcopy

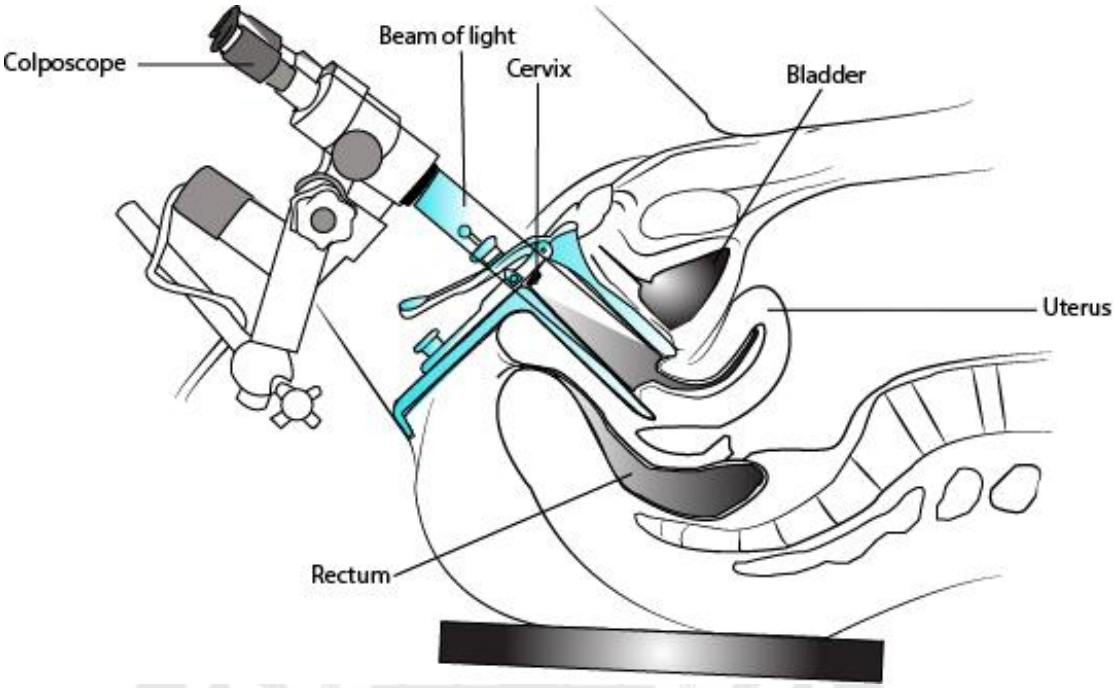


Figure 7 Investigation for cancer spreading by Colposcopy.

Colposcopy is a technique to determine abnormalities of cervix tissues by using an endoscope (Figure 7)(23). Generally, colposcopy is required when abnormality has been found by Pap smear test. It is not used as a screening test but as a diagnostic test. A colposcopy camera is a specially designed microscope that can magnify the tissue of the cervix. There is a light source that provides enough brightness to distinguish the abnormal from normal tissue by visualization very well. The examination is performed while a woman is lying on her back on a table similar to Pelvic examination but colposcopy seeing an abnormality from the endoscopy. To use colposcopy, the doctor inserts a speculum into the vagina, washes inside of the vagina with acetic acid solution which turning only the abnormal tissues to be white. The doctor is then able to identify the abnormal cells, whereas the abnormal cells may be collected for further precise pathological examination through the removed surgically tissue(3).

2.1.4 Management and treatment

Treatment depends on various factors such as the severity of the disease, stage of precancerous and stage of cancer, the health condition and age of patient including the preferences of patient and doctor. The patient who will be treated should study and discuss the treatment option and guidelines with the medical professional since the treatment methods and procedures may affect to the ability to have children.

In general, treatment is not required when in the case of CIN1 or low-grade CIN since most of these cases, the symptoms will resolve themselves. It has only approximately 1% chance of developing cervical cancer. But experts also recommend that screening should be checked periodically to monitor abnormal cell changes. While the way of treatment in the case of moderate CIN (CIN 2) and severe CIN (CIN 3) focuses on eliminating abnormal cells that may develop to be cancer. There are various removal or surgery CIN methods that are commonly used, including Loop electrosurgical excision procedure (LEEP), Cold knife cone biopsy (conization), and Hysterectomy(17, 18, 21).

Loop electrosurgical excision procedure (LEEP)

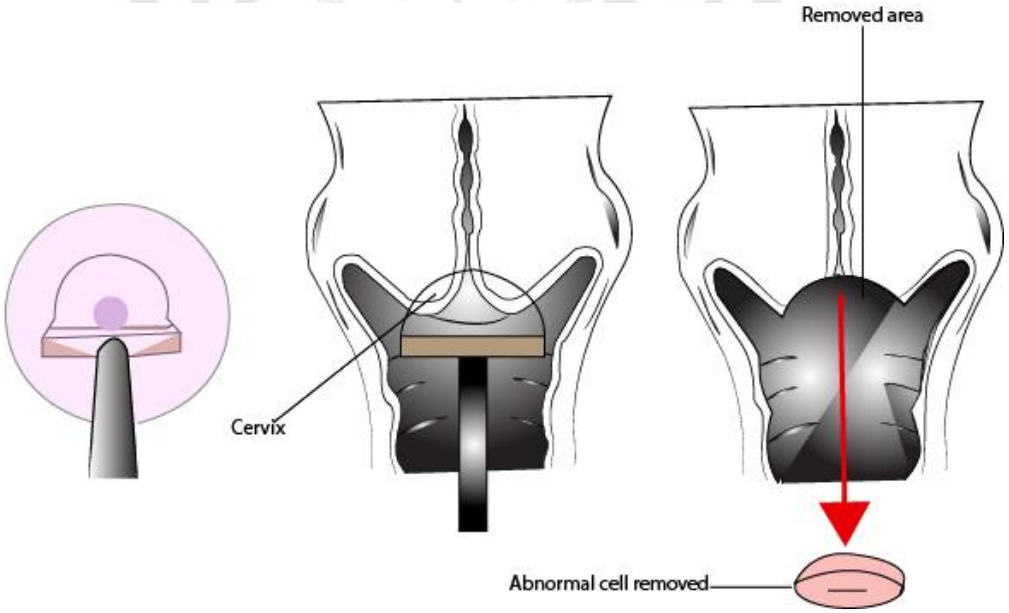


Figure 8 The removed abnormal cervical tissue with loop electrosurgical excision procedure (LEEP).

Loop electrosurgical excision procedure (LEEP) is the medical technique that use of an electrical wire loop to remove lower genital tract cells and tissue in woman. The tissue is in a cone shape and then is used for cervical biopsy to determine the presence of abnormal cells or the cancerous conditions (Figure 8). The LEEP method is wildly use method to treatment the cervical cancer. In addition, the LEEP method are also used to screening the cervical cancer(24).

Cold knife cone biopsy (conization)

Cold knife cone biopsy (conization) is one surgical method in medical, the removed abnormal tissue is in a cone shaped or wedge shaped as show in Figure 9. This procedure captures a larger tissue sample compared to those obtained from the LEEP method. Therefore, the require size of sample tissue is a deciding factor in selecting the treatment between a cervical cone biopsy versus a LEEP(25) as show in Figure 10.

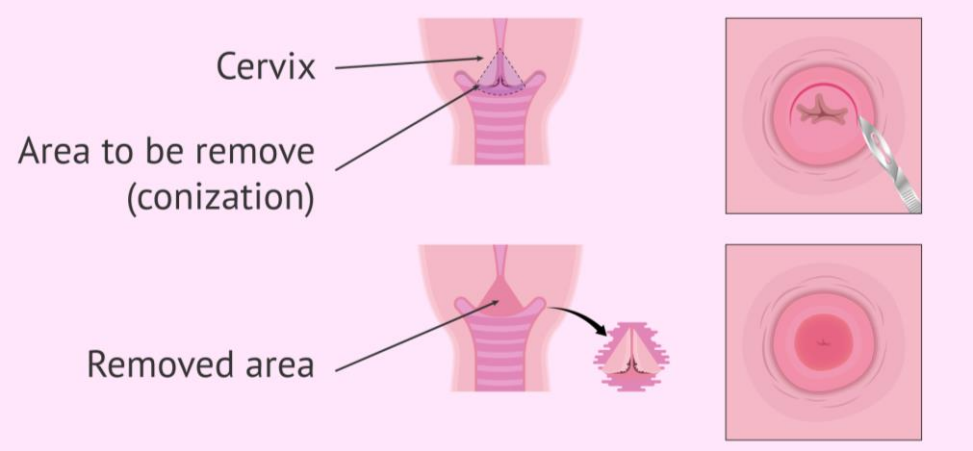


Figure 9 Cold knife cone biopsy (conization) to remove abnormal cervical tissue. (The use of this figure complies with the copyright agreement of https://www.invitra.com/.)

Source: (25)Dr.Daniel Sosa (gynecologist), Marta Barranquero Gómez (embryologist), Romina Packan (invitra staff). Cervix conization Available from: https://www.invitra.com/en/cervical-conization/cervix-conization/.

Figure 10 Different proceeding in conization between Cold knife cone biopsy and LEEP. (The use of this figure complies with the copyright agreement of https://www.invitra.com/.)

Source: (25)Dr.Daniel Sosa (gynecologist), Marta Barranquero Gómez (embryologist), Romina Packan (invitra staff). Cervix conization Available from: https://www.invitra.com/en/cervical-conization/cervix-conization/.

Hysterectomy

Hysterectomy is a surgical procedure, a method of removing the uterus. It is the way of treatment after other procedures are used but the CIN persists or does not improve. It is also used to remove the uterus in the cancer stage. The hysterectomy divided into 3 types: Extra-fascial hysterectomy or Total hysterectomy (Type A), Modified radical hysterectomy or Partial hysterectomy (Type B), and Radical hysterectomy (Type C)(21, 26).

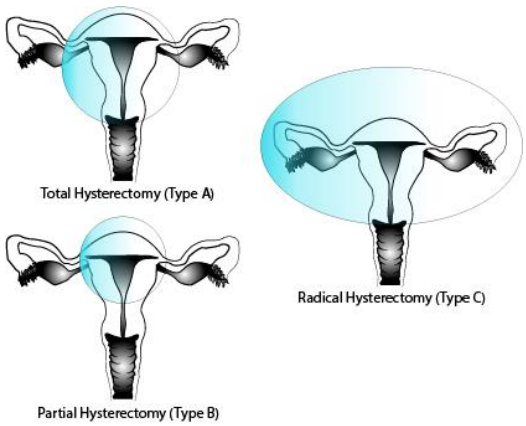


Figure 11 The three type of hysterectomy.

2.2 Pathology examination

Generally, pathology examination is the diagnosis of disease through the examination of organs or tissue that has been surgically removed, and fluids of body in a live patient or deceased body. Pathology examination uses gross examination and microscopic examination, and it also includes other techniques such as molecular pathology examination and immunohistochemistry examination. Pathology examination consists of surgical examination, cytology examination, and autopsy examination. Surgical pathology is one field of pathology, the most important and time-consuming. The primary objective of this field is to examine the removed organs or tissues with naked eye or under a microscope for definitive diagnosis of disease.

The specimens may be either small biopsies or large organs that are removed from body such as cone biopsies for the diagnosis of cancer, small biopsies of skin, or tumor and organ that is removed at the operating room. The workflow of surgical pathology examination is shown in Figure 12.

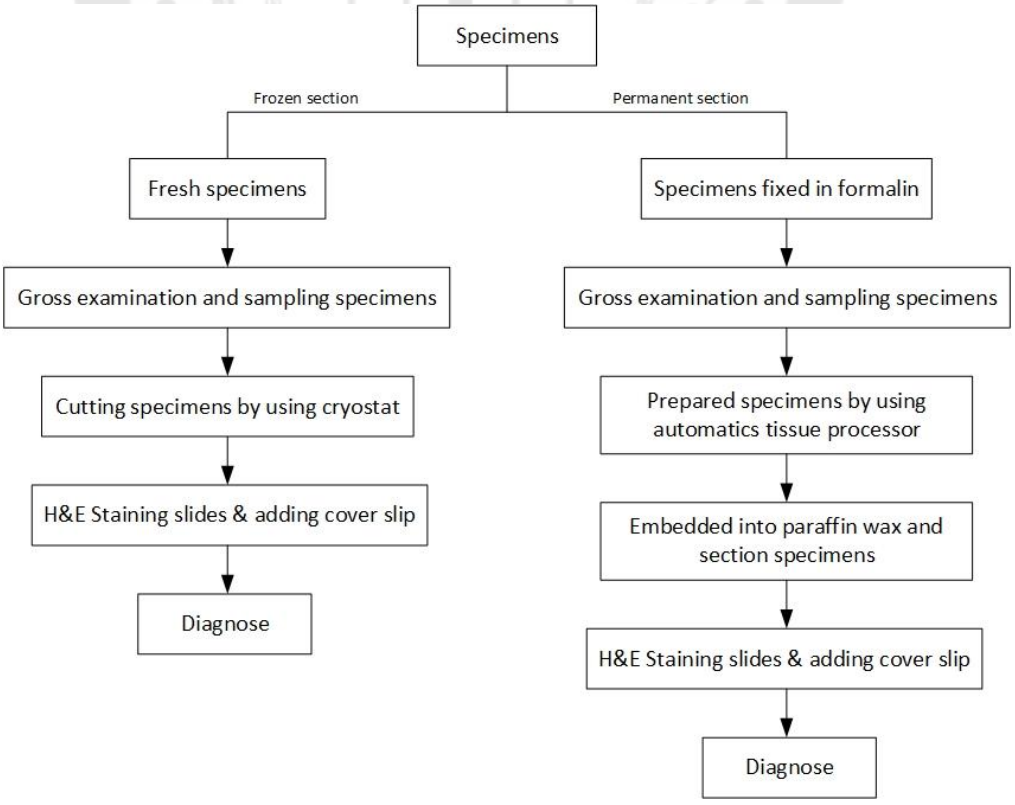


Figure 12 The workflow of surgical pathology examination.

According to Figure 12, There are many states in the workflow of surgical pathology examination such as gross examination and sampling specimens, Prepared specimens by using automatics tissue processor, embedded into paraffin wax and section specimens, H&E staining slides & adding cover slip and microscopic examination to diagnose of disease. The gross examination and sampling specimens state is important state to help the pathologist easier diagnose the abnormality condition.

Gross examination and sampling specimens

The Objective of the gross examination in pathology examination is to sample the mark of disease to put in the slides for diagnosis. The clinical information, the information of preliminary diagnosis can help pathologists very well. The pattern of the sampling specimens will vary depending on organs and the purpose of diagnosis.

The general physical investigations of the gross examination are shape, color, size, and weight of specimens. This includes the mark of disease such as size, color, distance from the edge of the specimen. In the cancer case, the pathologist will sample the normal tissue out of the tumor and the lymph nodes of the specimens. The sampling specimens are then packed into a box for the next stage of diagnosis.

2.3 Bioelectrical impedance

2.3.1 Biological tissue and bioelectrical impedance

All living object such as plant and animal made up with three dimensional (3D) arrays arrangement of cells and tissue(5). Human is animal, which a kind of living object. Human tissue made up with the 3D array of human cells. The biological cells consist of three main composition including intracellular fluids (ICF), extracellular fluids (ECF), and cell membrane (CM). These are responds differently to an alternating current (AC) electrical signal, produce a complex bioelectrical impedance as show in Figure 13. ICF, ECF, and CM consist of various materials with electrical characteristic differently. Therefore, each cell and each tissue could be responds differently to the alternating current (AC) electrical signal.

The intracellular fluids (ICF) consist of the nucleus and the cytoplasm that mostly made up of different chemicals, solution of proteins, salt and water. All of these materials are highly conduct electricity. The extracellular fluids (ECF) consist of highly conduct electricity material similar to intracellular fluids (ICF). But, the cell membrane (CM) consist of lipid bilayer that electrically nonconducting. Lipid bilayer are sandwiched between two protein layer that electrically conducting in from protein-lipid-protein call P-L-P structure as show in Figure 14.

Electrical impedance of tissues is an electrical characterization to conduct electrical current where the value depends on the tissue composition (both on the physiological and physicochemical status of tissue). It also depends on the frequency of the used the alternating current (AC) electrical signal. The complex electrical impedance of tissue changes depending on variations in structure of tissue, composition of tissue, and health status. Therefore, study of the biological impedance analysis of tissue can be used to analyze tissue anatomy and tissue physiology(5). Moreover, it was found that the complex bioelectrical impedance analysis of tissues is an effective non-invasive tool for pathological, physiological or, physicochemical status monitoring.

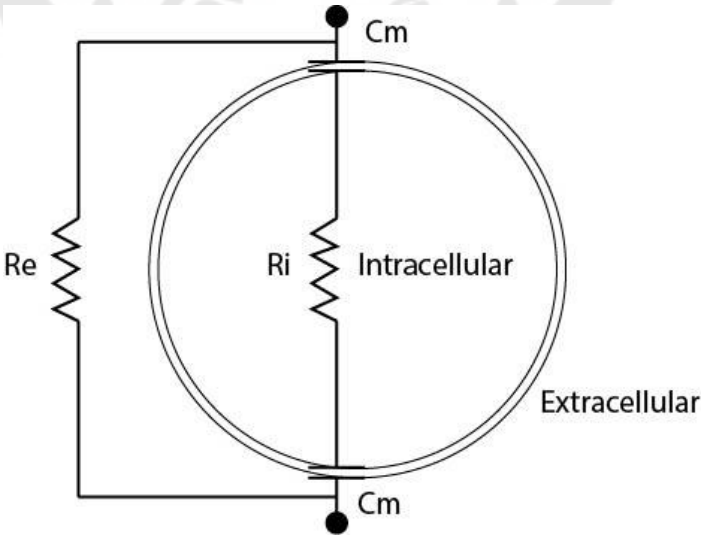


Figure 13 The electrical circuit to describes the components of the bioelectrical in a human cell.

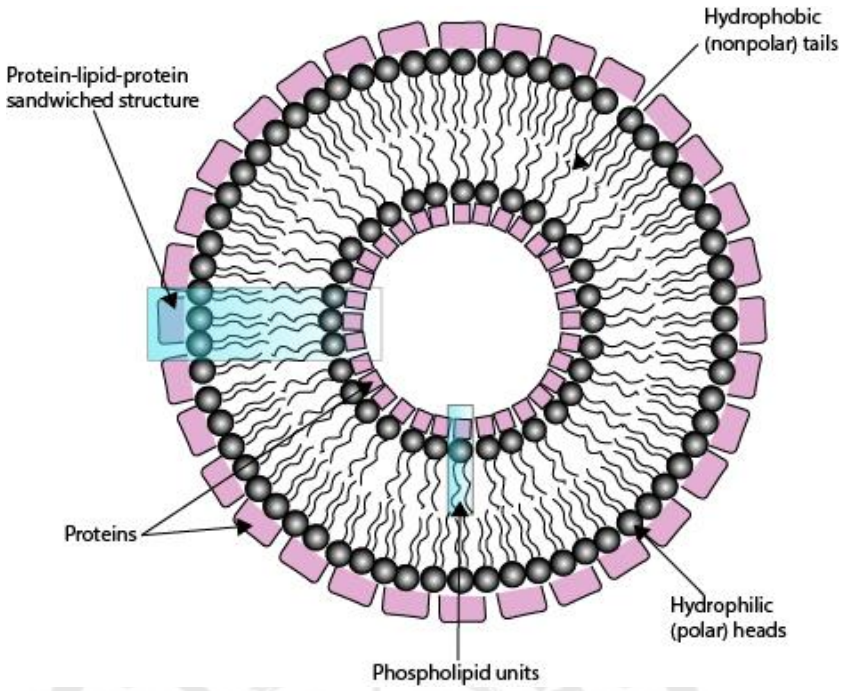


Figure 14 The P-L-P structure in cell membrane.

2.3.2 Electrical impedance for detect cervical cancer

Most of the previous studies performed measurement in eight positions of bulk tissue samples with four-electrode in 5.5 mm-diameter and (in square arrangement) probe. The diameter of each electrodes was 1mm call Mark III bioimpedanciometer as show in Figure 15. The bulk (overall) conductivity of the tissue was estimated by averaging the impedances obtained from eight locations of each tissue as show in Figure16 (9-14). (9, 11) experimented on 87-124 women subjects and used frequency between4.8-614 kHz. Cell equivalent circuit was referred to in these studies. Extracellular resistant (R) placed in parallel with intracellular resistance (S) and cell capacitance (C) were used to determine the presence of the abnormal cells based on Cole-Cole equation form equation 1(9, 11).

$$Z = R_{\infty} + \frac{\left(R_0 - R_{\infty}\right)}{\left(1 + \left[jF/F_c\right]\right)^{1-\alpha}} \qquad (1)$$

where

$$R_0 = R \qquad (1.1)$$

$$R_{\infty} = \frac{RS}{R+S} \qquad (1.2)$$

$$F_c = \frac{1}{2\pi C(R+S)} \qquad (1.3)$$

When

Z is bioimpedance.

R_0 is the impedance in real part at very low frequencies.

R_{∞} is the impedance in real part at very high frequencies.

F_c is the frequency.

α is the constant that increases according to the inhomogeneity of tissue (α = 0).

(10, 12) a similar the experiments way was performed and the equipment to (9, 11) on 124-176 subjects. However, the used frequency was expanded to between 2-1200 kHz. Finally, (13, 14) experimented on 56 subjects with the same equipment (impedance probe) but the used frequency between 9.6-614 kHz. And in addition, (13, 14)used derived parameters based on an alternative form of the Cole-Cole equation and Generalized Effective-Medium Theory of Induced Polarization (GEMTIP), respectively. All of These studies found that the impedance of the normal part of tissue was higher by four times than the abnormal part and can be used to identify the presence of cancer. However, there are some limitations since the results are obtained from averaging the eight impedance values of measurement. This could be not accurate since CIN could be spread in various size. Moreover, mixing grades of CIN could also be possible or the abnormal cells could be situated in the region where the measurement was not measured. Recently, (15) proposed a different way by using a planar electrode plate call Specialized 8-well ECIS device (Figure 17) to detect cervical cancer on cervical smear in polysol solution of 500 microliters on 150 samples. The used frequency was expanded to between 100 Hz-1 MHz current excitation were used to classify the normal and the abnormal sample. This method has benefit from using smear which is less invasive than using bulk tissue. However, All of these studies could not be identify the location of CIN or abnormal cell.

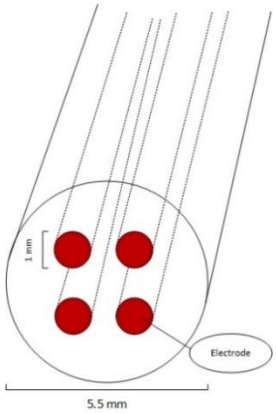


Figure 15 Cervical measurement probe.

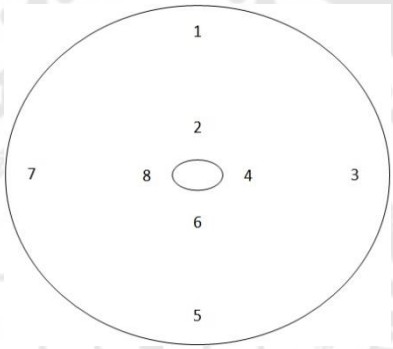


Figure 16 The eight position in cervix were measured with electrical impedance probe.

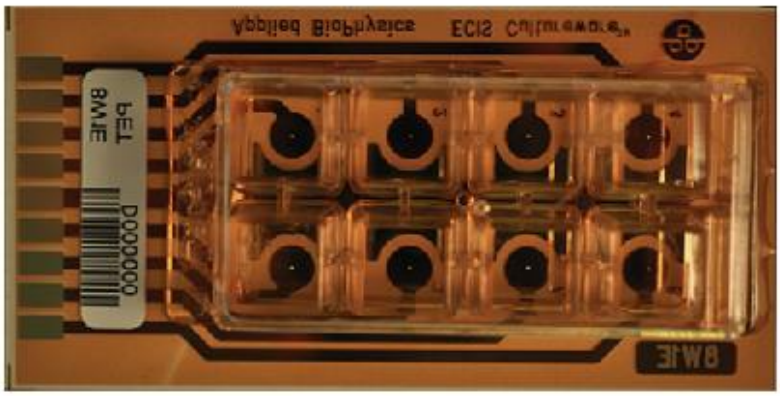


Figure 17 Specialized 8-well ECIS device. (The commercial model 8W1E PET)

Source: (27)Applied Biophysics. ECIS Cultureware. Available from: https://www.biophysics.com/cultureware.php.

2.3.3 Electrical impedance tomography (EIT)

The electrical impedance tomography (EIT) is a computed tomography image reconstruction technique with electrical impedance within tissue by using electrical stimulation and measurement with electrode on the tissue surface. This Tanique is a nonlinear inverse problem, it is a reconstruction of the electrical conductivity or resistance in the interior of an object (Ω) through injected constant electric current signal at the boundary of the object ($\partial\Omega$) as show in Figure 18(5). The image inside the conductor object will be taken after injecting the constant electric current to the boundary of the object ($\partial\Omega$) of the object (Ω) by using the electrode on the object's surface and measure the voltage information by using an electronic instrument. The injection of the constant electric current signal to the boundary of the object under test is injected through the pair of electrodes (driving electrodes), and that the other electrode pairs (measurement electrodes) are used to noninvasively collect the voltage information. After finishing measurements, the current will be reapplied to a different pair of electrodes, and the measurements will be repeated. After that, the voltage information is sent to the computer to reconstruct the new image of conductivity distribution of the object under test by using image reconstruction algorithm.

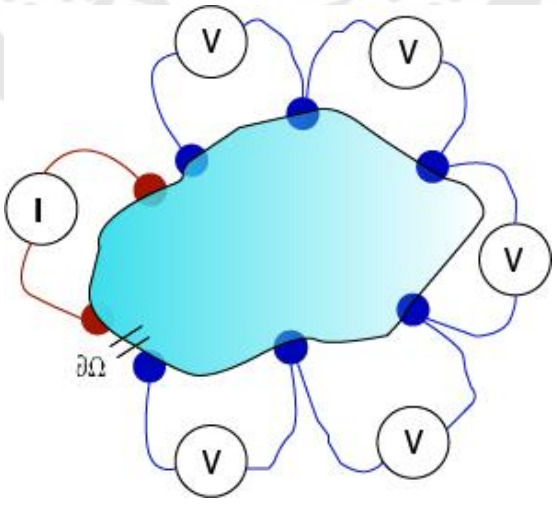


Figure 18 EIT system model on the boundary of the object under test. The constant electric current is injected through driving electrodes and the voltage information is measured with measurement electrodes.

The electrical impedance tomography (EIT) system consist of three important parts including EIT instrumentation, EIT image reconstruction algorithm on computer, and electrode array on surface of the object under test.

Constant current injector (CCI), signal conditioner block (SCB), electrode switching module (ESM), and data acquisition system (DAS) are the four main parts of EIT instrumentation. The driving electrodes are intermediate to inject a constant electric current signal to the object's boundary which the constant electric current signal is injected by a constant current injector (CCI). The voltage signal developed on measurement electrodes are processed by signal conditioner block (SCB). The electrode switching module (ESM) used to switch the driving electrode and measurement electrode in a specific fashion to collect the voltage information in a specific electric current pattern. After complete EIT scanning process of the object, the collected voltage information are then sent to the data acquisition system (DAS) on the computer for data acquisition and image reconstruction.

One of the important parts of electrical impedance tomography (EIT) technique is EIT image reconstruction algorithm on computer since the new image reconstruction of the electrical impedance tomography (EIT) technique developed by the algorithm. The collected voltage information forms the object are sent to the computer for new image reconstruction by using EIT image reconstruction algorithm. Forward solver (FS) and inverse solver (IS) are two important parts of EIT image reconstruction algorithm. The forward solver solves the voltage information called calculated real information (V_c) when known constant electric current (I) that injected to the object. And then the calculated real information are compared with measurement information (V_m) in inverse solver that different between V_c and V_m ($\Delta V = V_m - V_c$) is minimized before the conductivity distribution of object is reconstructed.

Electrode array on surface of the subject under test (SUT) is one of the most part of the EIT system since the quality of the voltage information including the quality of new image from the reconstruction depends on the pattern of electrode array. The electrodes of the EIT technique consist of two part including the pair of electrodes used

to inject the constant electric current to the object and other pair of electrodes used to collect the voltage information. Therefore, the electrode is one parameter that crucial in EIT imaging. Good electrode array designing is one of important consideration in the EIT technique. The caution to select the electrodes parameter such as the material of electrode, the geometry of electrode or shape and size, the pattern or layout of electrode array and electrode type (noncompound or compound).

EIT is a technique used for imaging purposes, similar to computed tomography techniques such as X-ray, CT scan, X-ray mammography, SPECT, MRI, PET, ultrasound, etc. This technique has many advantages over other medical imaging technique including a low cost, portable and easy to use, fast data acquisition, non-invasive, non-ionizing method, radiation-free technique, suitable for bedside monitoring or in intensive care unit (ICU) room and convenient for monitoring in ambulatory. Therefore, EIT technique has been applied in many areas of medical applications for clinical diagnosis ex. brain function monitoring, bladder volume estimation, fat mass estimation, and including cervical cancer detection.

CHAPTER 3
RESEARCH METHODOLOGY

3.1 Three dimensional (3D) modeling of the cervix with Netgen or NGSolve software

A model of the cervix was constructed with Netgen or NGSolve (http://ngsolve.org/), consisting of 59,559 tetrahedral elements. The model was based on the geometry of a cervical tissue taken from Loop Electrosurgical Excision Procedure (LEEP) method. The model was in a cone shape of 22-mm-top diameter and 25-mm-bottom diameter with a height of 3 mm. The cervix orifice was an elliptic cylinder having the size of 5-mm-major diameter and 3-mm-minor diameter. The bottom surface of the model represented the cervical epithelium as shown in Figure 19.

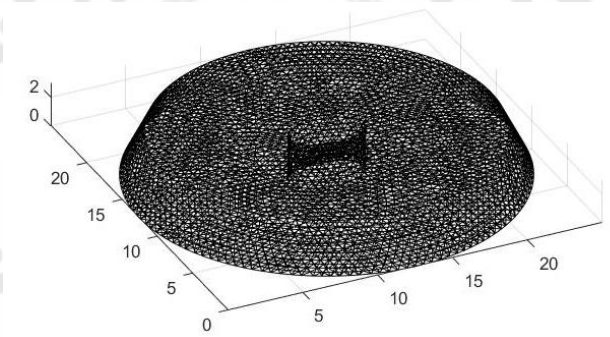


Figure 19 The LEEP cervix model with no CIN objects.

Histological abnormality associated with the third-grade progression of cervical intraepithelial neoplasia (CIN) in the cervical squamous epithelium was simulated by adding an object, a cylinder of 1 mm diameter with a height of 0.5 mm at the bottom surface of the model as shown in Figure 20.

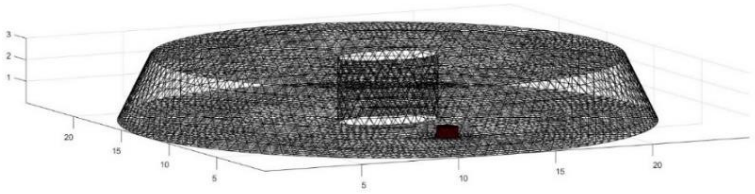
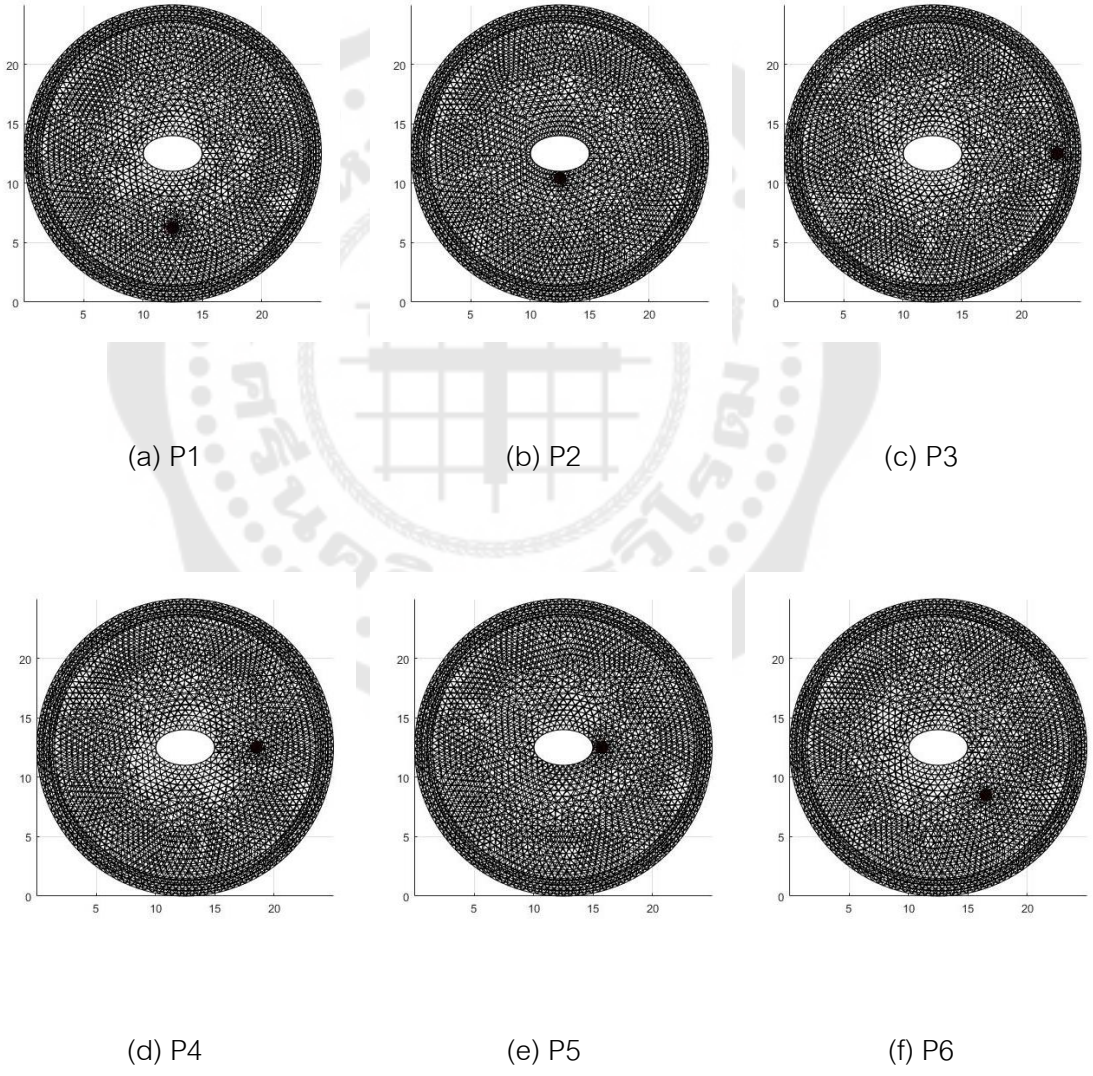


Figure 20 CIN objects in LEEP cervix model.

3.2 Forward modeling and reconstruction method by EIDORS software

The current of 10 μA was simulated with a frequency of 100 Hz. With respect to the used frequency, the conductivity of normal cells was set to 0.05264 S/m and that of grade-3 CIN (CIN3) was set to 0.25975 S/m, respectively. At the beginning, the cervical model was assumed to be homogeneous with the conductivity of the normal cervical tissue and then a simulated CIN3 object was put in six positions i.e. P1-P6 as shown in Figure 21.



(a) P1 (b) P2 (c) P3

(d) P4 (e) P5 (f) P6

Figure 21 Positions of the simulated CIN object: (a) position1 (P1), (b) position2 (P2), (c) position3 (P3), (d) position4 (P4), (e) position5 (P5), (f) position6 (P6).

The voltage information of all cases, i.e. the model with/ without precancerous cells in various sizes, was generated (the forward problem) by EIDORS software (http://eidors3d.sourceforge.net/). The voltage information was used for reconstruction which is based on the iterative Singular Value Decomposition (SVD) method (developed by authors). The regularization parameter was set to $1x10^{-4}$. The number of iterations was 10. All estimates were converged.

3.3 Electrode layout, current injection and voltage measurement patterns

Since the electrical current cannot pass through the orifice but the abnormality usually begins near the orifice, electrodes should be placed where the current pathway is near the orifice but it must not cross the orifice. The three designs of 16-electrodes layouts are proposed, and all are based on the opposite current driving pattern. Star layout (Figure 22) contained dense 12 1-mm diameter electrodes in the middle where four electrodes were located near the boundary of the cervix in order to be a source or a sink electrode. The electrodes in the circular layout version 1 (Figure 23) circularly arranged in two rings with a large electrode in the center. The diameter of the electrodes was 1 mm, except for the center one that was 5.2 mm. The center electrode was larger than the size of the orifice therefore the current will not flow across this area. Circular layout version 2 (Figure 24) contained 12 1-mm diameter electrodes, circularly arranged in two-ring layout where six electrodes. There were 10 and 6 electrodes for the outer and the inner ring respectively. There was no large electrode in the middle, since it may not be necessary. The current injection schemes of star layout, circular layout version1 and circular layout version 2 are shown in Figure 22, 23 and 24 respectively. The current was injected with a pair of electrodes and the measurement voltages were obtained from the other electrodes. The total number of current patterns was 20. The measurement schemes were in a sequential order of the electrode index number, for example, E1-E2, E2-E3, and E3-E4. Therefore, there were 11-13 measurements in the star layout and circular layout version 1, and 11-12 measurements in circular layout version 2. The total number of measurements was 228, 231, and 224 for the star layout, the circular layout version 1 and version 2, respectively.

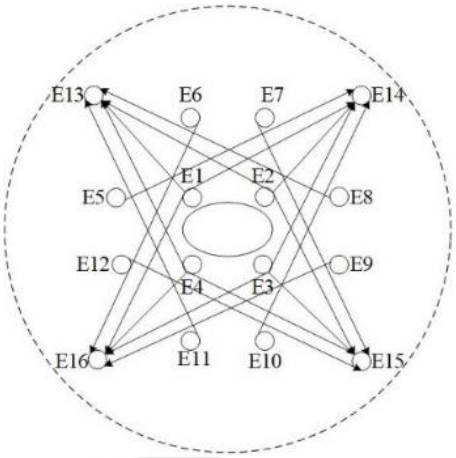


Figure 22 Planar electrode with the star layout.

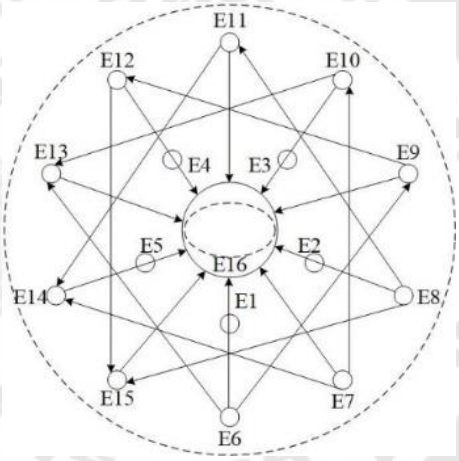


Figure 23 Planar electrode with the circular layout version 1.

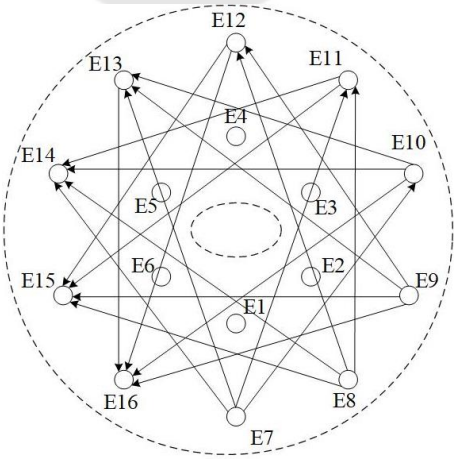


Figure 24 Planar electrode with the circular layout version 2.

3.4 Calculated the localization errors between the center of the simulated CIN objects and the center of the reconstructed objects

The localization error between the center of the simulated CIN objects and the center of reconstructed objects calculated by Euclidean distances equation given by equation 2.

Geometrically, the Euclidean distance is the distance between two points is equal to the magnitude of the vector that connecting one point to the other point in Euclidean space. The Euclidean distance can be calculated from the coordinates of the point with Pythagorean theorem. Therefore, sometime it is be called Pythagorean distance(28).

$$L = \left\| S - R \right\|$$

$$L = \sqrt{\left(S_x - R_x\right)^2 + \left(S_y - R_y\right)^2 + \left(S_z - R_z\right)^2} \quad (2)$$

When

L is localization error.

S is the center of the simulated CIN objects in x, y and z axis.

R is the center of reconstructed objects in x, y and z axis.

CHAPTER 4
RESULT

4.1 Voltage response to the presence of a CIN object

In general, the measurement voltages were between 7.25 μV and 30 mV for the star layout (see Figure 25), between 174 μV and 25mV for the circular layout version 1 (see Figure 26) and between 346 μV and 27mV for the circular layout version 2 (see Figure 27). After adding a CIN object, it resulted in voltage change up to 0.54 mV (1.8% change from the baseline) for the star layout (see Figure 28), and up to 0.37 mV (1.48% change from the baseline (see Figure 29) and up to 0.34 mV (1.26% change from the baseline) (see Figure 30) for the circular layout version 1 and 2 respectively.

The voltage change of all layouts was large when the object was situated at the high sensitivity regions i.e. especially near the orifice (P2 and P5.) The voltage change was low when the object was situated at the low sensitivity regions. This voltage change was extremely small (less than 70 μV) when the object was situated at the outer edge of the tissue (P3) of the star layout.

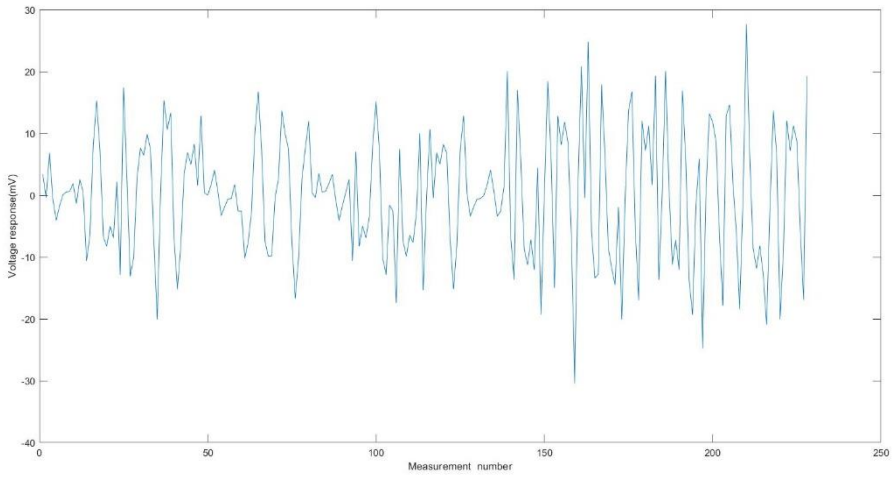


Figure 25 The voltage information in the case of the star layout without precancerous.

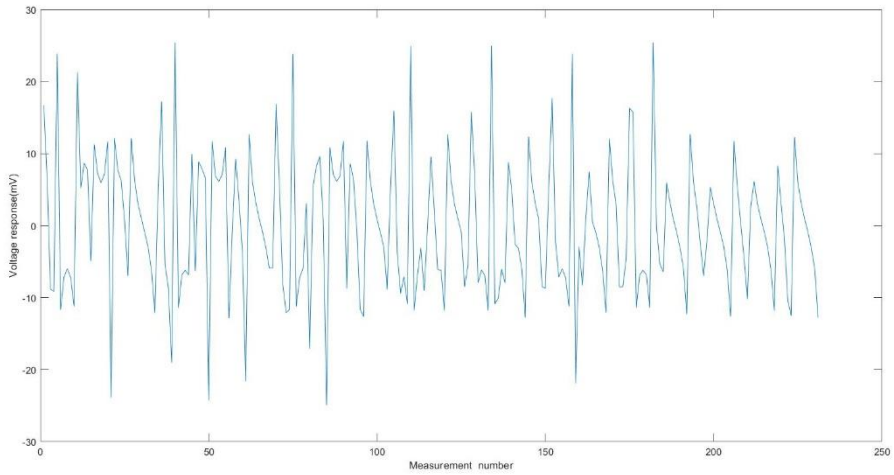


Figure 26 The voltage information in the case of the circular layout version one without precancerous.

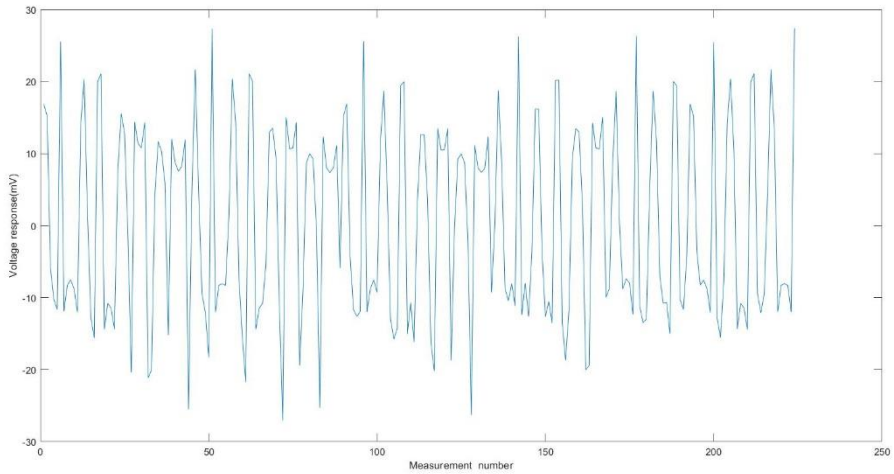


Figure 27 The voltage information in the case of the circular layout version2 without precancerous.

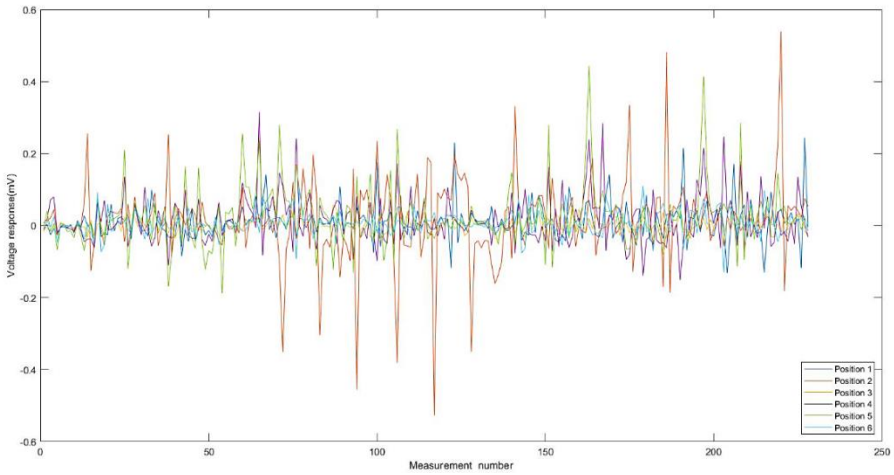


Figure 28 Voltage response to the presence of a CIN object in the case of the star layout.

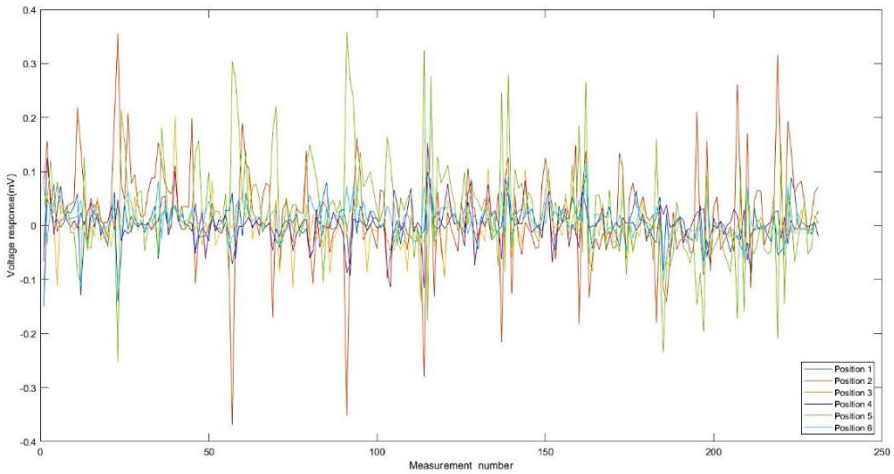


Figure 29 Voltage response to the presence of a CIN object in the case of the circular layout version 1.

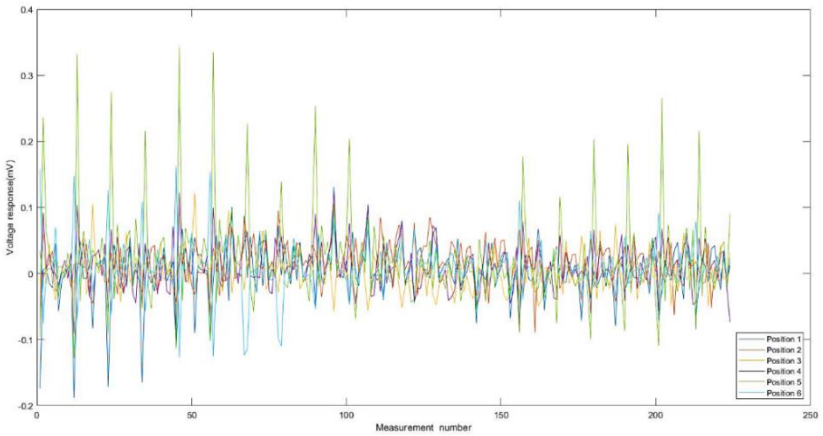


Figure 30 Voltage response to the presence of a CIN object in the case of the circular layout version 2.

4.2 Reconstruction images of CIN objects

The reconstruction images of the cases using the star layout and both circular layouts are shown in Figure 31, Figure 32, and Figure 33. In the case of the star layout, the reconstructed images can efficiently locate the simulated historical abnormalities situated in the area of the dense electrode array (P1-P2 and P4-P6). However, these images cannot locate the CIN object situated in the outer region of the electrode array (P3) (see Figure 31 (c)). On another hand, in the case of the circular layout version 1, the reconstructed images can be used to locate the historical abnormalities in all cases (see Figure 32). Artifacts tended to occur near electrodes. In the case of the circular layout version 1 where the middle electrode was extraordinarily large, the artifact was also large. With the circular layout version 2, the reconstructed images can also be used to locate the historical abnormalities in all cases and the artifacts were smaller in size than the circular layout version 1 (see Figure 33). It could be noticeable that the amplitude of the reconstructed CIN objects was much smaller than that of the true amplitude for all layouts (the true chaining amplitude was approximately 0.2 S/m.). The changing amplitude of the star layout, the circular layout version 1 and 2 were approximately 0.02 S/m - 0.03 S/m (by visualization) in almost all cases, except the case of putting the object at the outer edge of the tissue (P3). At this P3 position, it was even much smaller to between 0.003 S/m - 0.004 S/m.

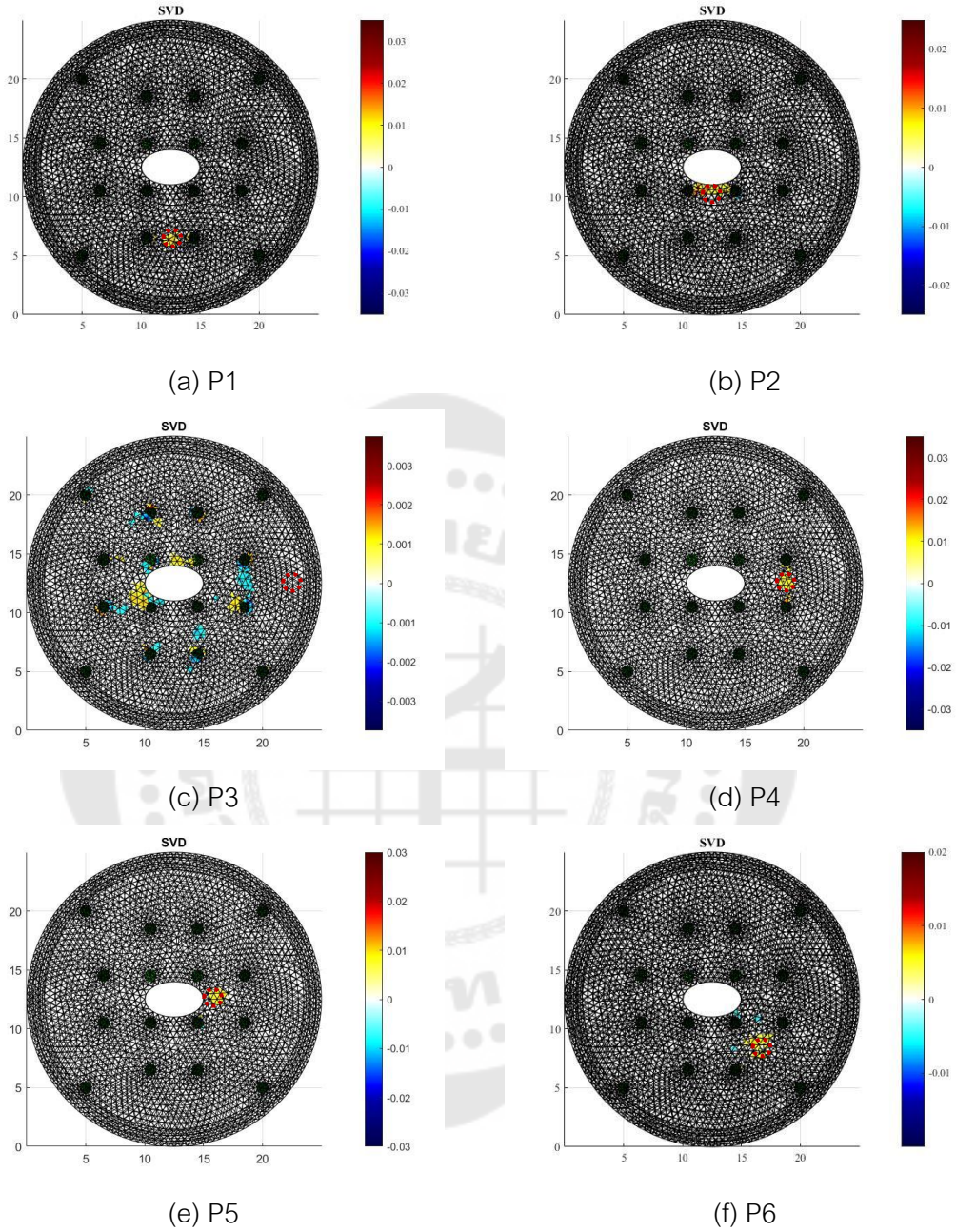
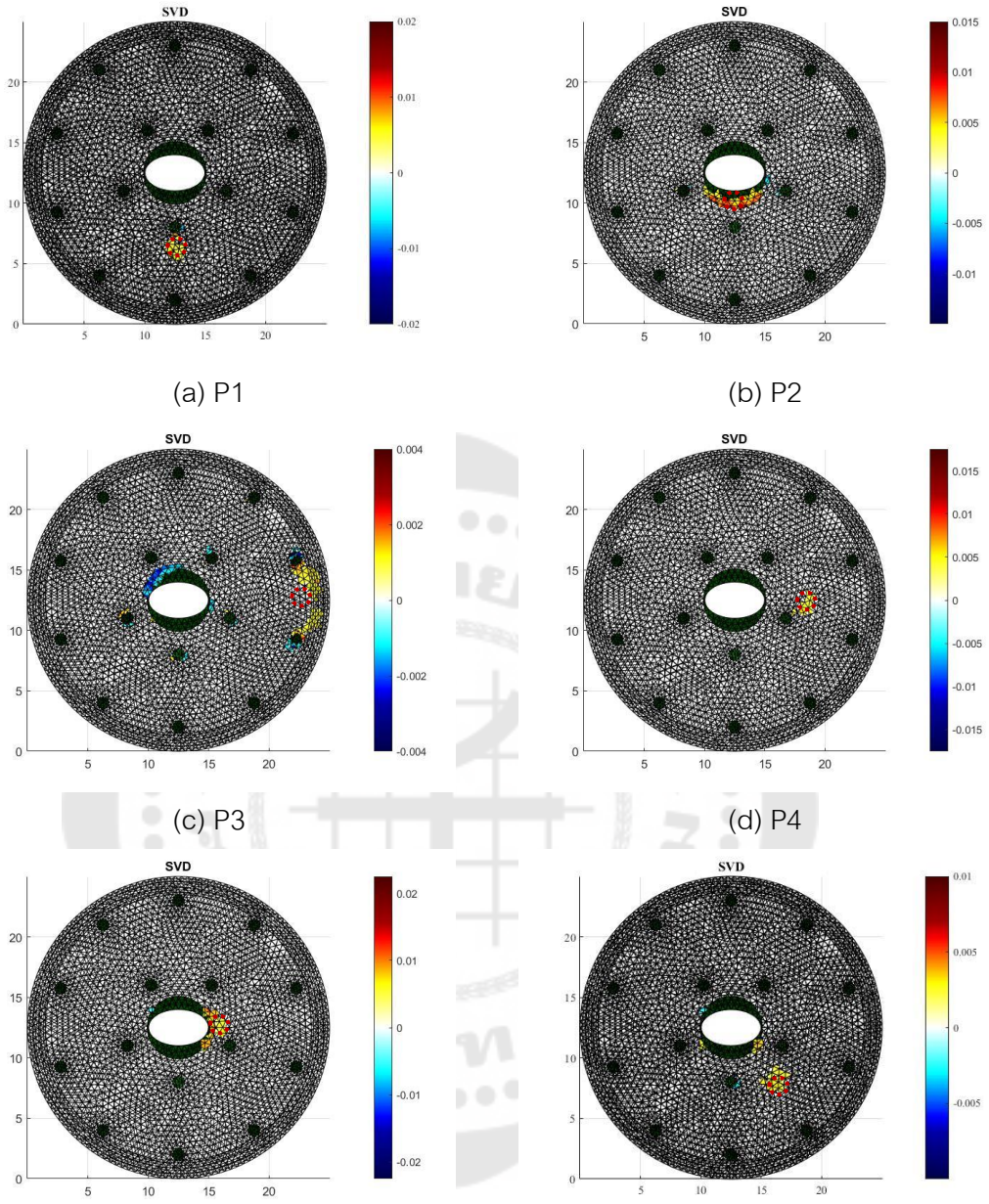


Figure 31 Reconstructed images obtained from the star layout. The dash circles represent the target location of the objects.



(a) P1 (b) P2

(c) P3 (d) P4

(e) P5 (f) P6

Figure 32 Reconstructed images obtained from the circular layout version 1. The dash circles represent the target location of the objects.

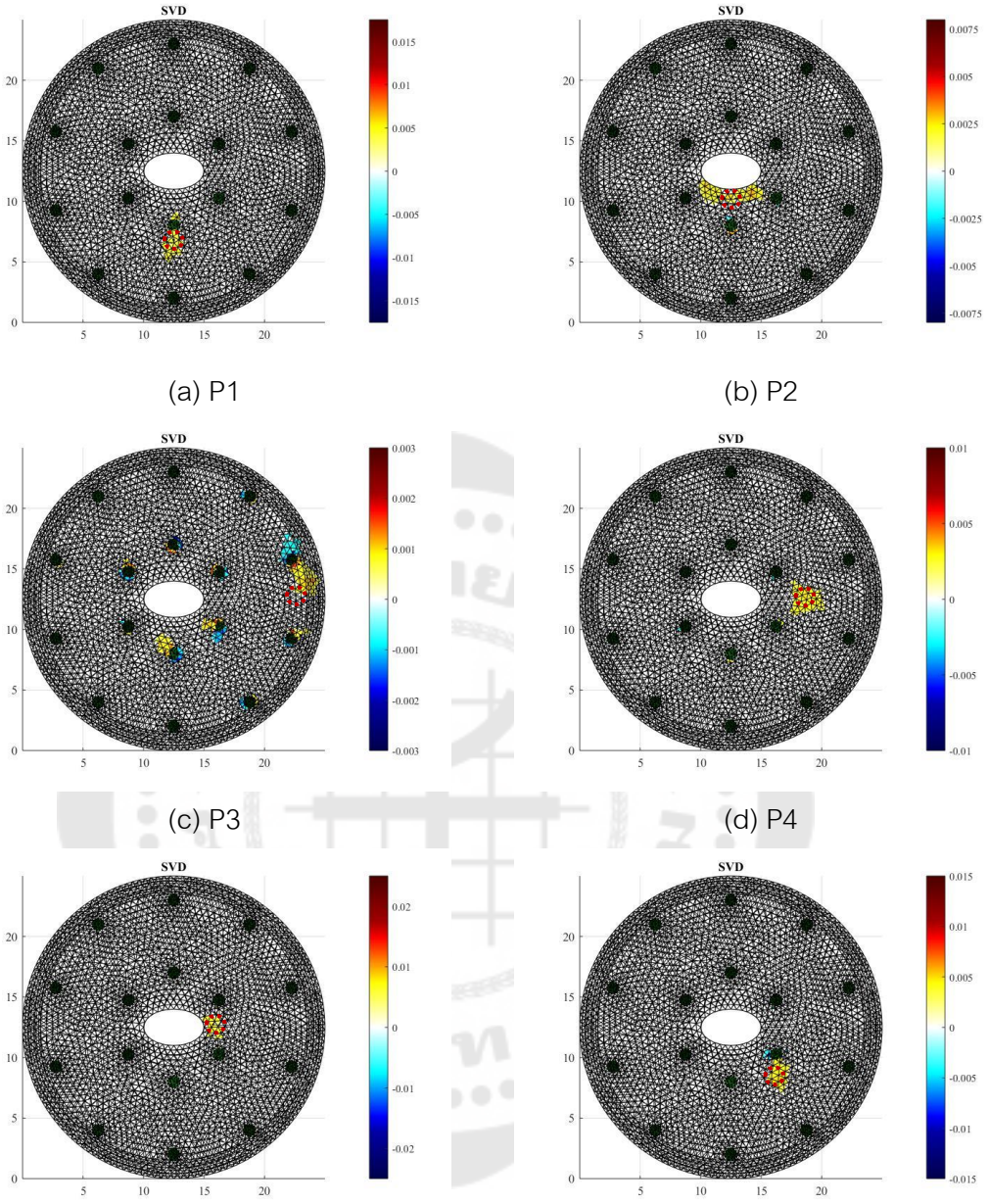


Figure 33 Reconstructed images obtained from the circular layout version 2. The dash circles represent the target location of the objects.

The localization errors between the center of the simulated CIN objects and the center of the reconstructed objects of the star layout, both circular layouts are summarized in Table 1. The localization error of the star layout was generally smaller than that of both circular layouts. Only the case of position 2 (P2), the error of the star

layout was larger than those of both circular layouts. In the case of P1-P3, the localization error of the circular layout version 1 was smaller than that of the circular layout version 2, but in the case of P4-P6, the localization error of version 1 layout was larger than that of the version 2 layout. The average errors of the star layout and the circular layout version 1 and 2 were 0.6351 mm, 1.2859 mm, and 1.3639 mm, respectively.

Table 1 The localization errors of the star and both the circular layouts.

Location of CIN object	Localization error (mm)		
	Star layout	Circular layout version 1	Circular layout version 2
Position1	0.1434	0.2550	0.4595
Position2	1.4597	0.7488	2.8437
Position3	Undetectable	2.1544	2.3379
Position4	0.4375	1.7037	1.0621
Position5	0.6964	1.2021	0.8465
Position6	0.4387	1.6512	0.6344

CHAPTER 5
SUMMARY DISCUSSION AND CONCLUSION

In this study, three layouts of planar electrodes for locating historical abnormalities were investigated by simulation i.e. the star layout, the circular layout version 1, and the circular layout version 2. The simulation result shown that the voltage information obtained from 16 electrodes of all layouts can be used to locate precancerous cell objects by reconstructing the image of conductivity distribution. The higher grade of CIN introduced the higher voltage response. The amplitude of the voltage change of the star layout was more profound. The use of star layout can effectively sense the presence of CIN situated in only the area of the dense electrode array i.e. near the orifice, generally better than both circular layouts. However, this layout cannot sense the presence of CIN at the outer region of the electrode array i.e. at the tissue outer edge. The use of the circular layout version 1 and the circular layout version 2 can sense the presence of CIN in the whole region of the cervix. But the localization error of the star layout generally was smaller than that of the circular layout version 1 by 2-4 times and smaller than that of the circular layout version 2 by 1.2-2 times. This is because the sensitivity of the star layout is higher (in the region near the orifice) due to the closer distance among electrodes. The average localization errors of the star layout and the circular layout were 0.6351 mm and 1.2859 mm and 1.3639 mm., respectively. Even though the localization error of the star layout was significantly smaller than that of both circular layouts when the simulated object was located near the orifice, the star layout cannot locate the historical abnormality at the outer edge region. This is possibly due to the lower sensitivity in this region of the star layout. Both circular layouts can locate historical abnormalities in the whole region of tissue, but the artifacts were large at the region near the middle electrode. Additionally, the amplitudes of the reconstructed CINs were all much smaller than the true amplitude by approximately 10 times.

In summary, all layouts can locate the simulated CIN objects, but the star layout can provide better images and higher voltage responses than both circular layouts.

However, the star layout has a limitation, it cannot locate the historical abnormality at the outer edge region, while both circular layouts can locate. However, larger artifact in size particularly in the orifice region is a vital issue to concern. Since CIN cells tend to appear near the orifice, the presence of artifacts could lead to a wrong diagnosis. Therefore, we prefer to propose the circular electrode layout version 2 for cervical cancer localization.

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