Effect of Foot Massage on Nausea, Vomiting and Retching in Women With Cervical Cancer Undergoing Chemotherapy, in Bali, Indonesia

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A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

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ABSTRACT

Foot massage therapy is a non-pharmacological nursing intervention that can be used complementarily in care of patients with cervical cancer receiving chemotherapy. Foot massage is one way to convey feelings of care that nurses can deliver independently. This study aimed to compare the effects of foot massage therapy on nausea, vomiting and retching (NVR) in Indonesian women with cervical cancer undergoing chemotherapy in the gynecological ward of the Sanglah Hospital Centre in Bali, Indonesia.

It is a randomized controlled study, using a two-group pre-test/post-test design. Sixty-six subjects were assigned into either the experimental group or the control group (33 subjects per group) by tossing a coin. The NVR scores were collected three times; before starting the massage therapy as the baseline data (T1), at the sixth hour after administering chemotherapy (T2) and at the twelfth hour after administering chemotherapy (T3). Data analysis was conducted by using the Chi-square test, Fisher's exact test, paired sample *t*-test, repeated measures ANOVA and independent *t*-test.

The findings showed that the subjects who received the foot massage intervention had significantly lower of the NVR scores at the two-time period (T2 and T3, t = 11.09, p = .00 and t = 9.67, p = .00, respectively). The subjects in the experimental group demonstrated a statistically significant greater reduction in NVR scores, particularly at the first sixth hour after the intervention (T2). The findings also showed that the NVR score of the experimental group was significantly different at the three time periods (T1, T2 and T3) ($F_{(2, 64)}$ = 90.16, p < .001) and the lowest NVR score was at T2. For between-groups effect, the mean difference scores were constructed and used to adjust for the effect of the baseline scores. The mean difference scores at T2 ($\bar{d}1$) and T3 ($\bar{d}2$) of the subjects in the experimental group were significantly lower than those of the control group (t = -7.04, p = .00 and t = -5.41, p = .00, respectively). These findings support the use of the foot massage intervention in reducing the NVR in patients with cervical cancer receiving chemotherapy.

Keywords: Foot massage, Chemotherapy, and Nausea, Vomiting, and Retching

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CHAPTER 1

INTRODUCTION

This chapter describes the significance of the problem, the objectives of the study, and research questions. It also describes the theoretical framework and research framework of the study, hypotheses, definition of terms, and the significance of the study.

Background and Significance of the Problem

Cancer is a leading cause of death worldwide. In 2002, there were 10.9 million new cases, 6.7 million deaths, and 24.6 million persons living with cancer (Parkin, Bray, Ferlay & Pisani, 2002). In 2007, it accounted for 7.9 million deaths (around 13% of all deaths) all over the world. Mortality due to cancer is predicted to continue rising, with an estimated 12 million deaths in 2030. Lung cancer, stomach, liver, colorectal, esophagus and prostate cancer are the most frequent types of cancer worldwide for men. Meanwhile, the most frequent types of cancer in women are breast, lung, stomach, colon and cervix (World Health Organization [WHO], 2009). In addition, cervical cancer is still a major cause of death in developing countries, with nearly 500,000 new cases still being diagnosed worldwide every year (Parkin, Bray, Ferlay & Pisani, 2005), with the estimated mortality rate up to 66,000 per year (WHO, 2008).

Cervical cancer is one of the diseases that occurs very often in women, and is the second type of cancer that kills women after breast cancer (Domingo et al., 2008; The Hospital Information Systems [SIRS], 2007). In 2004, approximately 10,520 new cases of cervical cancer in the United States were diagnosed and it has

become the third most common malignancy of the female genital tract (American Cancer Society, 2004).

The incidence of cervical cancer in Indonesia may be under reported. Little data is available describing the prevalence of cervical cancer. It has been estimated that there are 180,000 new cancer cases annually with gynecological cancer in the top spot (WHO, 2009) and approximately three-quarters of this was cervical cancer (Iswara, Suwiyoga, Mayura & Artha, 2004). Domingo et al. (2008) found that the incidence of cervical cancer in Indonesia (age-standardized rate (ART) 15,7 per 100,000) is similar to the incidence in Southeast Asia. Statistics in the Hospital Information System (SIRS) in 2006 showed that the percentage of cervical cancer in Indonesia was 11.1% (Health Department Republic of Indonesia, 2009). While the Anatomical Pathology Laboratory data (as cited in Aziz, 2001) show that the frequency of cervical cancer is the highest among the cancers that exist in Indonesia, its visible spread has accumulated at 92.4% in Java and Bali. These high rates were expected, as the known incidence numbers are believed to be an underestimation as a lot of women do not seek medical care.

Bali Health Profile 2010 states that an indicator of cervical cancer is 19.70 percent per one hundred thousand of the population. Cases of cancer have been found as much as 29,696 in all cases and 55 percent of it is cervical cancer (Bali Provincial Health Office, 2005). From the registration book at the Sanglah Hospital, it is known that the number of patients with cervical cancer has increased from year to year. There were 804 cases of cervical cancer in 2005, there were 1,554 cases in 2006, and the highest rate was 2,026 which occurred in 2007. Furthermore, more than half

of the total number of patients with cervical cancer reach stage IIb-IVb, thus they require special facilities and high cost for treatment (Sjamsuddin, 2001).

Chemotherapy is one of cancer treatments that can destroy cancerous cells and prevent metastasis. Medications commonly used in chemotherapy are Cisplatin, Cycloposphamide, Dacarbazine, and Doxorubicin. These medications have various side effects, but the common severe effects are nausea, vomiting and retching (NVR). These side effects are distressing symptoms for patients with cancer, especially those who are receiving chemotherapy (Bender et al., 2002; Rhodes & McDaniel, 2001) and can potentially lead to a patient's refusal to continue with the most effective chemotherapy treatment (Hesketh, 2000). Ritter et al. (as cited in Schnell, 2003) stated that failure to control these side effects of chemotherapy could lead to 25 – 50 percent of patients delaying or refusing possible lifesaving anti-neoplastic therapy. Moreover, high doses of these medications cause increased severity and volume of NVR by 90 percent (Miaskowski & Viele, 2000).

NVR has an impact on psychological depression and can lead to increasing anxiety and dissatisfaction with the hospital experience that contributes to anticipatory nausea in the future (Cohen, de Moor, Eisenberg, Ming & Hu, 2007; Garrett Tsuruta, Walker, Jackson & Sweat, 2003). Cohen, de Moor, Eisenberg, Ming & Hu (2007) stated that 38 percent of patients who received a new chemotherapy regimen developed acute nausea and vomiting, and 64 percent had delayed nausea and vomiting that related highly to having the previous cycle. Clinical consequences of NVR can lead to nutritional deficiencies, dehydration, and electrolytes imbalance (Ballatori & Roila, 2003). Those consequences impair patients' daily function, role, length of survival and quality of life (Ashing-Giwa & Lim, 2010) and have an impact

on daily activities (Ballatori & Roila, 2003), particularly nausea and vomiting in the late phase (Roscoe, Morrow, Aapro, Molassiotis & Oler, 2010). It means that the appropriate management of nausea, vomiting and retching related to chemotherapy at the initial treatment is important to prevent the development of delayed nausea, vomiting and retching.

Despite the development of anti-emetic therapy, nausea and vomiting are commonly seen in clinical practice. 40–60 percent of the patients receiving cisplatin still suffer from nausea and vomiting even after taking corticosteroid combined with a 5-HT3- or a dopamine-receptor antagonist as the best available treatment (Roila, Donati, Tamberi & Margutti, 2002). Since the anti-emetic drugs can not totally relieve the symptoms of chemotherapy-induced nausea and vomiting, several techniques have been used in combination with medications to reduce the symptoms (Rose et al., 1999).

Nursing intervention is needed as an additional treatment to improve the effectiveness of antiemetic drugs. Nurses can play a significant role to help the patients to cope with these symptoms through non-pharmacological therapy such as massage, aromatherapy, reflexology, guided imagery, etc. Massage has already been recommended as an aid in reducing the side effects of treatment with cancer (Reaves & McManis, 2010), and has shown to relieve nausea and relax hospitalized patients with cancer (Grealish, Lomasney & Whiteman, 2000).

A foot massage can be defined as a technique by which both the feet of the recipient are held at various positions, stroked gently and rhythmically to attain a relaxation response (Puthusseril, 2006). Meanwhile, reflexology is a specialized-foot-massage targeting specific areas of the foot that represent other parts of the body. It is

believed that the whole body is represented on the foot (mostly on the soles of the feet), and the internal organs can be stimulated by pressing particular areas of the foot (Gravett as cited in Erns, 2009). Thus, points of reflexology are used to determine the area of massage on the foot.

Many studies have found that a foot massage can contribute to better quality of life in patients including cancer patients. Sturgeon, Wetta-Hall, Hart, Good and Dakhil (2009) found that massage has shown potential benefits to improve perceived quality of life and overall functioning among cancer patients. Specifically, Grealish et al. (2000) found that foot massage had a significant immediate effect on the perceptions of nausea and relaxation, and is recommended as a relatively simple nursing intervention for patients experiencing nausea related to their cancer experience.

Various mechanisms of massage in cancer patients have been reported. Breast cancer patients who received massages regularly experienced better psychological outlooks which corresponded to an increase in vigor, dopamine, serotonin level, NK cell numbers, and lymphocytes (Sturgeon et al., 2009). Moreover, Hayes and Cox (1999) also found that a significant decrease in heart rate, blood pressure, and respirations was observed during a foot massage intervention. In relation to reducing nausea and vomiting, Lund et al. (as cited in Holst, Lund, Petersson & Uvnäs-Moberg, 2005) hypothesized that massage may influence vagal nerve activity via oxytocin that causes relaxation.

Considering the nurse's role, a foot massage is a complementary therapy that nurses can deliver independently. The essence of foot massage therapy involves touch and manipulation of the soft tissues in non-disturbing and non-

threatening ways (Puthusseril, 2006), and has effects of calming or invigorating the patient to assist relaxation (Cassileth & Vickers, 2004; Reaves & McManis, 2010). In addition, the foot is easily accessible and acceptable in different cultures. Reviews from several studies found that most studies used Swedish massage with different sessions from one to five sessions and performed over varying durations from 10 up to 90 minutes. A massage can be performed on various body areas (arm, leg or full body).

Various explanations for the effectiveness of massage have been proposed including a reduction in muscle tension, improved circulation, general relaxation, and the nurturing effects of touching. Several studies have supported the efficacy of massage in producing reductions in pain (Post-White et al., 2003), nausea (Billhult, Bergbom & Stener-Victorin, 2007; Grealish et al., 2000), depression and anxiety (Cassileth & Vickers, 2004; Hernandez-Reif et al., 2004), and the enhancement of immune functioning in a variety of populations including cancer patients (Billhult, Lindholm, Gunnarsson & Stener-Victorin, 2009). However, theoretical and empirical support in utilizing massage as a nursing intervention is limited (Ferrel-Torry & Glick as cited in Quattrin, 2006) and its benefits continue to be debatable (Reaves & McManis, 2010).

Although massage therapy is widely used on cancer patients, its benefit is still debatable. There are a few rigorous, randomized, controlled trials (RCTs) on the efficacy of massage in cancer patients. Some experts promote massage therapy while others consider it to be contraindicative (Corbin, 2005). Even if national guidelines for the use of complementary therapies recommend that massaging might be an acceptable intervention for cancer patients, it has been acknowledged that there

is a need for more evidence to support the safety and efficacy of massage therapy (Tavares, 2003). It would appear that using massage as a complementary therapy to reduce NVR has been based on limited information as to the safety and efficacy of massage therapy, therefore further exploration of the study is needed.

Massage therapy has actually been applied in Indonesia. However, the result of this massage therapy is limited to pain reduction. Evidence related to the kind of massages in Indonesia has not been provided yet. Although several previous western studies have showed that massage can relieve nausea significantly (Ernst, 2009), it was noted that the external generalized ability of those studies was often limited because of the lack of study design, control for medications and poorly described massage protocols. Therefore, this current study assesses the effect of a foot massage on reducing NVR in cervical cancer patients undergoing chemotherapy with consideration to the limitations of a previous study. This study is designed as an RCT with a control group and integrates points of reflexology to determine the areas on the foot that are to be manipulated. Considering bias on the result, some extraneous variables were controlled and a protocol of foot massage with pictures at every step of the massage was provided.

Currently, evidence-based nursing has been emphasized in the nursing profession. There is a necessity to investigate whether a massage should be recommended for reducing nausea, vomiting and retching in patients with cervical cancer undergoing chemotherapy. Thus, the foot massage was used in this study to examine its effect in relieving NVR in women with cervical cancer undergoing chemotherapy.

Objectives

1. To describe the nausea, vomiting and retching levels of patients with cervical cancer undergoing chemotherapy.
2. To compare the nausea, vomiting and retching scores of the experimental group before and after receiving foot massage therapy.
3. To compare the changing nausea, vomiting and retching scores of the experimental group over time.
4. To compare the nausea, vomiting and retching scores of the experimental group and the control group after receiving foot massage therapy.

Research Questions

1. What is the level of nausea, vomiting and retching of patients with cervical cancer undergoing chemotherapy?
2. Are the nausea, vomiting and retching scores of the experimental group after receiving foot massage therapy lower than before receiving foot massage therapy?
3. Are there any changes in the nausea, vomiting and retching scores of the experimental group after receiving foot massage therapy over time?
4. Is the nausea, vomiting and retching scores of the experimental group after receiving foot massage therapy lower than that of the control group?

Conceptual Framework of the Study

Psychoneuroimmunology (PNI) concept was used in this study as a conceptual framework that explains the process of NVR existing in women with cervical cancer undergoing chemotherapy (Figure 1). PNI is derived from the work of Ader and Cohen in 1970. It was accepted as a new hybrid discipline and a vital field of interdisciplinary research (Ader & Kelley, 2007). Specifically, PNI is the study of the intricate interaction of consciousness (psycho), central nervous system (neuro), and the body's defense against external infection and aberrant cell division (immunology) (Ader & Cohen, 1975). This theory investigated the interaction between psychological and physiological processes.

The psychological and physiological mechanisms are involved in the occurrence of nausea, vomiting and retching in cancer patients receiving chemotherapy. The psychological mechanisms include various psychological states or emotions that can be broadly classified as a negative effect, or psychological distress. These factors include the perception of information related to chemotherapy such as smell, light, sound, pain, stress, worries and the perception of subsequent physical outcomes such as the side effects of chemotherapy. The mechanism is stimulated via the cerebral cortex and the limbic system. The information related to chemotherapy is collected and interpreted in the limbic system, causing a negative emotion that will directly stimulate the vomiting centre. As a consequence, the nausea, vomiting and retching symptoms significantly increase (Garrett et al., 2003; Morrow, Roscoe, Kirshner, Hynes & Rosenbluth, 1998).

Physiological mechanisms start at the stimulation of the chemoreceptor trigger zone (CTZ). When chemotherapy substances enter the blood circulation or

spinal fluid, it will stimulate the CTZ in the fourth ventricle of the brain. In response, the CTZ releases neurotransmitters to activate the vomiting center at the reticular formation in the medulla oblongata, causing nausea, vomiting and retching. In another way, chemotherapeutic agents also stimulate enterochromaffin cells in the gastrointestinal tract to release serotonin, which activates the serotonin receptors. Activation of the receptor activates the vagal afferent pathway that activates the vomiting center causing an emetic response (Bajetta, Pusceddu, Guadalupi, Ducceschi & Celio, 2009; Garrett et al., 2003; Hesketh, 2008).

Chemotherapy is a strong psychological stressor that indirectly affects the immune and endocrine systems. Stress decreases the effectiveness of the natural killer cells (NK-cell) whose job is to detect and destroy cancer cells. Chronic stress elevated cortical levels decreases many immune functions, making it difficult for the body to fight invaders from the outside and mutant cells from the inside. Furthermore, negative psychological states, such as stress, anxiety, and depression, may alter the immune system regulation and modulation of peripheral cytokines (Ventura, 2009). Chemotherapy further compromises the immune system. Therefore, the body cannot optimally eliminate cancer cells resulting in a decreased cure rate (Bauer, 1994; Kiecolt-Glaser & Glaser, 1999).

Foot massage therapy is one modality that can be used to represent caring. The use of touch is an inherent component of the provision of nursing care (Kutner et al., 2008). Massage therapy is a methodical form of touch that provides comfort and promotes well-being by applying moving or fixed pressure and movement of the body (Greene, 2000; Uvnas-Moberg & Petersson, 2004), and induces relaxation (Pruthi, Degnim, Bauer, DePompolo & Nayar, 2009). Touch can

enhance verbal communications and facilitate social interaction including information giving and the expression of feelings (Cronfalk, Strang & Ternestedt, 2008).

Foot massage stimulates the neurotransmission when pressure is applied to particular area of the foot and the nerve impulse is transmitted along the dorsal columns pathway to the thalamus for further interpretation in the cerebral cortex and the limbic system. The interpretation of a nerve impulse will result in the perception of positive feelings and emotion, inducing endorphin release, and the patients consequently feel calm, relaxed and happy in response (Hawthorn, 1995). Foot massage stimulates blood circulation to the whole body, increases skin temperature, decreases heart rate and relaxes the mind and body (Hernandez-Reif et al., 2004), as well as increasing circulating NK cells and lymphocytes (Corbin, 2005). Underlying mechanisms of action have been hypothesized, including a reduced lactic acid build-up in muscles, a stimulation of healing of the connective tissues, and an increase in lymphatic and venous circulation (Field as cited in Corbin, 2005).

The effect of foot massage is mediated via the activation of mechanoreceptors in the skin and deeper tissue innervating A-beta fibres, which activates the information to the central nervous system including limbic structures and the pituitary gland. This process can result in the modulation of the release of adrencortiocotropin releasing hormone (ACTH) and the secretion of cortisol from the adrenal glands as well as inducing relaxation. It is known that increased levels of cortisol inversely act as an immunosuppressive (O'Leary, 1990), and decreased secretion of cortisol may thereby result in an enhanced immune function. Massage increases relaxation. The more relaxed we are the less stress we experience and the better the immune system functions (Walker & Walker, 2003).

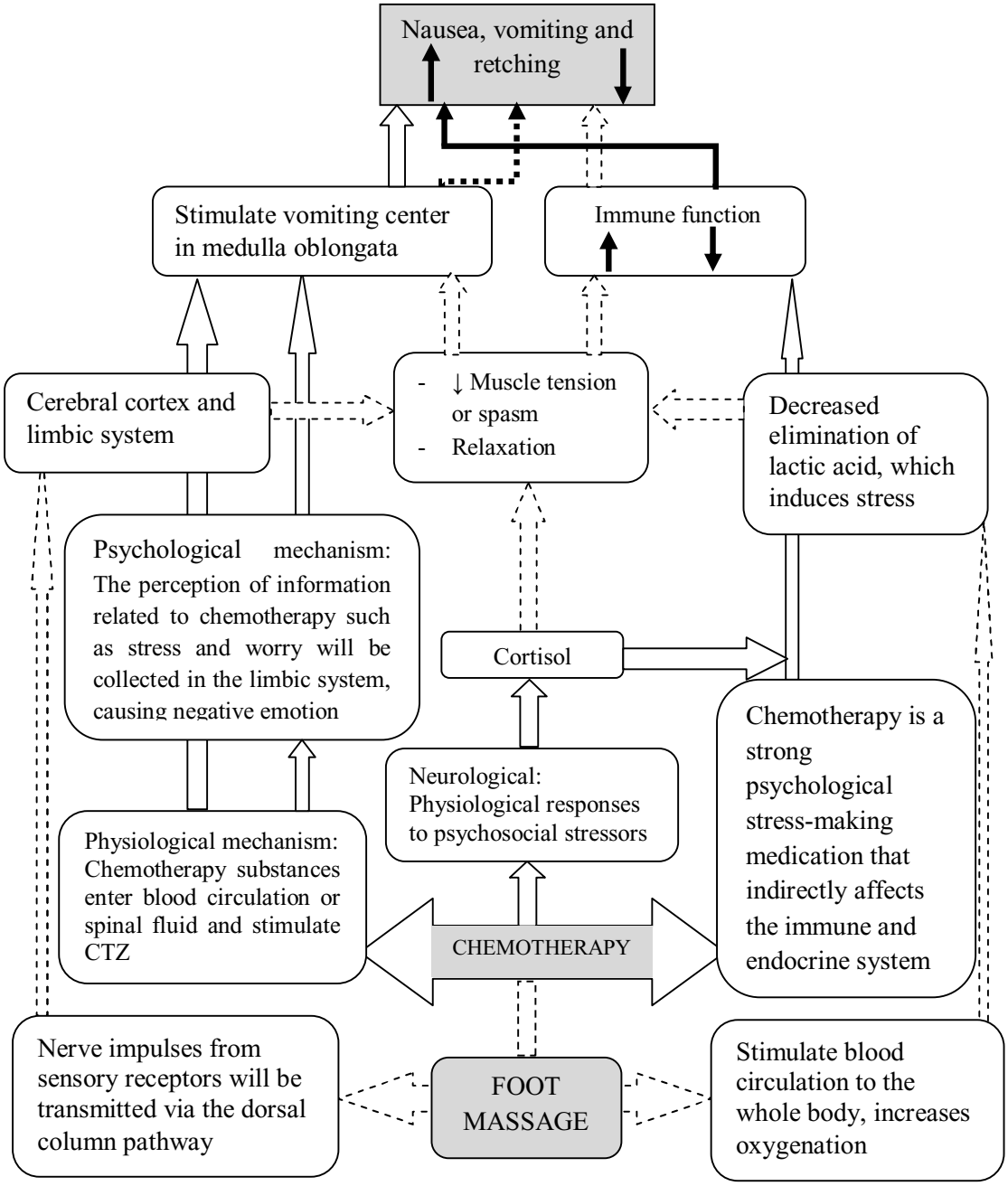


Figure 1. Conceptual framework effect of foot massage on nausea, vomiting and retching in cervical cancer patients undergoing chemotherapy.

Note: Solid arrows represent impact of chemotherapy; Dash arrows represent impact of foot massage.

Research Framework

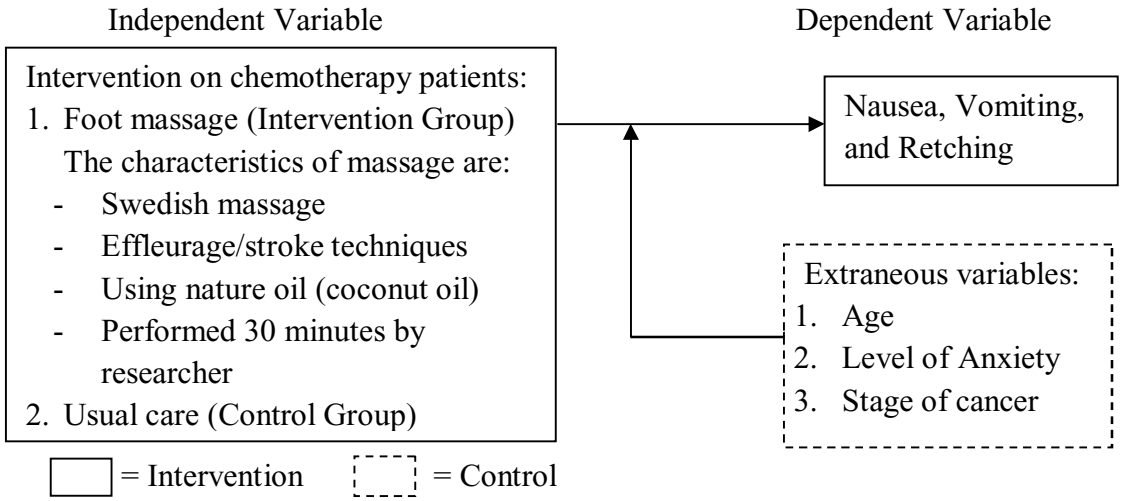


Figure 2. Research framework.

Hypotheses

The hypotheses of the study were working hypotheses that are stated as follows:

1. The scores of nausea, vomiting, and retching of the experimental group after receiving foot massage therapy (T2 and T3) are lower than that of before receiving foot massage (T1).
2. At least one time the scores of nausea, vomiting and retching of the experimental group after receiving foot massage therapy is lower than others.
3. The mean scores of nausea, vomiting and retching of the experimental group after receiving foot massage therapy (T2 and T3) are lower than those of the control group.

Definition of Terms

Foot massage is the manipulation of soft tissue on the foot using a series of techniques/basic hand movements stimulating the reflex zones on the foot using a natural oil (coconut oil) as a lubricant. The points of reflexology were used in order to determine the site of the area on the foot to manipulate.

Nausea is the unpleasant sensation in the throat and stomach reported by individuals and usually occurs before the urge to vomit. Vomiting is expelling strong stomach contents through the mouth. Meanwhile, retching is the attempt to remove the contents of the stomach to spit without expelling anything.

Scores of nausea, vomiting and retching are measured by using the Index of Nausea, Vomiting and Retching (INVR). A numeric value to each response ranged from 0, the least amount of distress, to 4, the most/worst distress. Total symptoms experienced from nausea, vomiting and retching were calculated by summing the patient's responses to each of the 8 items on the INVR (Rhodes & McDaniel, 1999).

Significance of the Study

The findings of this study provided empirical evidence regarding the use of a foot massage as a nursing intervention, and adds new knowledge to the topic of nausea, vomiting, and retching reduction through the psychoneuroimmunology concept. Moreover, the intervention of the present study can be used to guide nurses and other health care professionals to facilitate the patients to improve the quality of care to cancer patients receiving chemotherapy. The results of this study also provided

information about the effectiveness of foot massage therapy for the development of further research especially in cancer patients undergoing chemotherapy in Indonesia.

CHAPTER 2

LITERATURE REVIEW

In this chapter, several aspects of relevance to the study are explored and reviewed. This research will test the effect of foot massage on nausea, vomiting and retching in patients with cervical cancer undergoing chemotherapy. Information from related literature reviews are presented as follows:

1. Overview of cervical cancer
2. Overview of chemotherapy
3. Chemotherapy-induced nausea, vomiting and retching
4. Assessment of nausea, vomiting and retching
5. Interventions for nausea, vomiting and retching
6. Overview of foot massage therapy
7. Effectiveness of massage for the intervention of nausea, vomiting and retching
8. Safety and contraindications of massage therapy
9. Foot Massage Mechanisms to Relieve Nausea, Vomiting and Retching
10. Overview of foot reflexology

Overview of Cervical Cancer

Cervical cancer is a malignant tumor in the tissues of the cervix. Cervical cancer can metastasis to other parts of the body through the lymphatic system, which is a network of tissues, capillaries, vessels, ducts and nodes that pump

lymph fluid through the body. Most cervical cancers are preceded by precancerous changes that remain noninvasive for as long as 20 years. The progression of these cellular alterations to cancer does not always occur; however, the risk of progression increases with the degree of cellular dysplasia. Squamous cell carcinoma usually arises from cells at the transition zone between squamous and columnar ephitelium near the external cervix (Hansen, 1998). There are two main types of cervical cancer that are named after the type of cells from which they originate (The Cancer Council New South Wales, 2008):

1. Squamous cell carcinoma: This is the most common type of cervical cancer, accounting for about 80% of all cases. It starts in the skin-like squamous cells of the cervix.
2. Adenocarcinoma: This is a less common type of cervical cancer, which develops from the glandular cells.

A specific agent likely to be responsible for cervical cancer is human papilloma virus (HPV), the cause of most venereal warts. HPV of genotypes 16 and 18 shows a significant presence in women with cervical cancer (Brown, 1998). HPV is believed to be the etiological agent responsible for approximately 99% of all cervical cancers. HPV-16, -18, -31, and -45 are the most common high-risk types associated with cervical cancer; HPV-16 accounts for 60% of all cervical cancers and HPV-18 accounts for 10–20% of these cancers (Mahdavi & Monk, 2005).

Staging of cervical cancer

The clinical stage is the process to determine the spread of cancer. Clinical staging is important because it is a key factor in choosing the appropriate

therapy. In 1991 a cytology reporting system known as Bethesda was introduced. Pre-invasive lesions are classified as cervical intraepithelial neoplasia (CIN), or dysplasia. Analysis of cervical dysplasia and pre-invasive cancer can be described using the Bethesda system as follows:

1. CIN 1 corresponds to a low-grade squamous intraepithelial lesion usually confined to the lower one-third of the basal epithelium.
2. CIN 2 corresponds to a high-grade squamous intraepithelial lesion confined to the basal two-thirds of the epithelium.
3. CIN 3 corresponds to a high-grade squamous intraepithelial lesion that involves more than two-third of the epithelium, and up to the full thickness of the lesion. This lesion may also be referred to as cervical carcinoma in situ.

The Bethesda system is constantly updated however many oncologists especially those in Indonesia do not keep up to date with the new developments in the system especially in Indonesia. This leds to unification constraints in patient management (Andrijono, 2007).

Cervical cancer staging is often based on the FIGO (International Federation of Gynecology and Obstetrics) system. An extensive staging system for cervical cancer has been developed based on several criteria, including the extent of the primary lesion, lymphatic involvement and distant metastatic spread. FIGO system classifies the disease ranging from stage I to IV (Table 1) (Eifel, Berek, & Markman, 2005; Leaver & Labonte, 2010; Martin & Temple in Yarbro, Wujcik & Gobel, 2011).

Table 1

International Federation of Gynecology and Obstetrics (FIGO) Staging for Carcinoma of the Cervix 2009

FIGO	Description
0	Carcinoma in situ, intraepithelial carcinoma.
I	The carcinoma is strictly confined to the cervix.
IA	Invasive cancer identified only microscopically. All gross lesions even with superficial invasion are stage IB cancers. Invasion is limited to measured stromal invasion with maximum depth of 5 mm and no wider than 7 mm.
IA1	Measured invasion of stromal no greater than 3 mm in depth and no wider than 7 mm.
IA2	Measured invasion of stromal greater than 3 mm and no greater than 5 mm in depth and no wider than 7 mm.
IB	Clinical lesions confined to the cervix or preclinical lesions greater than stage IA
IB1	Clinical lesion no greater than 4 cm in size.
IB2	Clinical lesion greater than 4 cm in size.
II	The carcinoma extends beyond the cervix but has not extended to the pelvic wall. The carcinoma involves the vagina but not as far as the lower third.
IIA1	Tumor size of less than or equal to 4 cm. with involvement of less than the upper two-thirds of the vagina.
IIB2	Tumor size of more than 4 cm. with involvement of less than the upper two-thirds of the vagina.
III	The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with hydronephrosis or nonfunctioning kidney are included unless they are known to be due to other causes.
IIIA	No extension to the pelvic wall.
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney.
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. A bullous edema as such does not permit a case to be allotted to stage IV.
IVA	Spread of the growth to adjacent organs.
IVB	Spread to distance organs.

Note: Adapted from "Cervical Cancer: Principles and Practice" by Martin & Temple in Yarbro, Wujcik & Gobel (2011). Massachusetts: Jones and Bartlett.

Common stage of cervical cancer

In the early stages of cervical cancer, there are rarely any symptoms. Although cervical cancer can be diagnosed in its early stages by a routine Pap smear, usually no apparent symptoms would indicate cancer is present. This is why having a regular Pap smear is vital to early detection (Kooyman, 2006). In the United States, the majority of cervical carcinoma patients were diagnosed in the early stages of the disease. The incidence of squamous cell carcinomas is significantly reduced since the introduction of pap smear screening (Monk, 2004).

Unlike developed countries, the majority of cervical carcinoma patients in Indonesia were found in the advanced stages of the disease. A study by Aziz, (2001) reported that of 469 patients, 66% were stage IIB-IVB and more than one-third of the cases were in stage IIIB. Similar to other studies, Kusuma (2009) reported that cervical cancer is found in stage IIB and IIIB only and the majority of patients were in stage IIIB (62%). This data demonstrates that many patients delay seeking treatment and only come after complications occur. It might be related to a low socioeconomical and educational level of the people.

In Indonesia, a lot of effort has been done to introduce the same screening programs in developing countries but, unfortunately, it often fails to be established. The reasons are the lack of funds to provide Pap smear screening nationwide, the lack of professional human resources and qualified laboratory services and the high numbers of patients lost to follow up (Kooyman, 2006). Therefore, the majority of cervical cancer in Indonesia was found in the advanced stage.

Similar to other countries, about 75% of women in the Philippines were diagnosed in late stages of the disease. More than 70% of cases were presented at stage IIB or greater, with 40–45% in stage IIIB (Domingo et al, 2005). In Thailand it has also been found that most cases were diagnosed in the advanced stages of the disease with 51% in the International Federation of Gynecology and Obstetrics (FIGO) stage II and 31% in stage III.

As cervical cancer progresses onto more advanced stages, symptoms begin to appear. The most common symptom is abnormal vaginal bleeding, often presenting as postcoital bleeding. Women with cervical cancer also frequently complain of a watery and malodorous discharge (Yarbro, Wujcik & Gobel, 2011). As cervical cancer becomes more progressive, patients may note urinary frequency, bladder pressure, or back pain. In the most advanced cases, patients can present with inguinal lymph node metastasis, lower extremity edema secondary to pelvic sidewall invasion or a tumor replacing the pelvic lymph nodes, or in stage IV cases vesicovaginal or rectovaginal fistula (Schink in Chang et al., 2006, p 875).

Treatment for cervical cancer

Determining treatment of cervical cancer is performed after the cancer diagnosis is confirmed. Several interventions are used to treat cervical cancer, including surgery, radiation therapy, chemotherapy and combinations of these treatments. The treatments are usually based on the stage of the disease and not on cell type (Wang, 2007). Squamous and non-squamous (Adenocarcinomas) tumors are generally treated similarly although some physicians feel that non-squamous tumors have a worse prognosis when compared stage for stage (duPont & Monk, 2006).

Generally, the treatment type given depends on age, the patient's general condition, the spread of the cancer, and complications of the disease (Andrijono, 2007). In the early stages, surgery or radiation may be selected (Wang, 2007). While in the advanced stage (IIB, III, and IV), intracavity radiation (brachiradiation) or external radiation is an option. The use of chemotherapy is given to patients with locally advanced or recurrent cases which is not possible to treat by surgery or radiation (WHO, 2008).

Surgery remains the mainstay of treatment for women with micro invasive (FIGO stages IA1–IA2) and early-stage (FIGO stages IB1–IIA) cervical cancer (Tables 2) (NCCN, 2004). Cisplatin-based concurrent chemo-radiation is the current standard therapy for locally advanced disease (Peters et al., 2000). For patients with advanced, recurrent, or persistent disease, chemotherapy is often the only remaining treatment option (duPont & Monk, 2006). Radiation therapy might be prescribed for early-stage disease in patients who are medically inoperable because of morbid obesity, cardiopulmonary disease or contraindications to anesthesia (Leaver & Labonte, 2010).

Table 2

Primary Treatment Options for Cervical Cancer based on Clinical Stage

Stage	Primary Treatment
0/IA1	Extrafascial hysterectomy or Observation if cone biopsy has negative margins and patient desires future fertility
IA2	Radical hysterectomy, pelvic lymph node dissection ± para-aortic lymph node sampling or brachytherapy and pelvic radiation (point A dose: 75–80 Gy)

(table continues)

Table 2 (*continued*)

IB1 and IIA (<4 cm)	Radical hysterectomy, pelvic lymph node dissection + para-aortic lymph node sampling + tailored postoperative adjuvant therapy or
	Concurrent cisplatin-based chemotherapy* + pelvic radiation + brachytherapy (point A dose: 80–85 Gy)
IB2, IIA (>4 cm) and IIB–IVA	Concurrent cisplatin-based chemotherapy* + pelvic radiation + brachytherapy (point A dose:
IVB	Chemotherapy; palliative radiotherapy

Note: Adapted from "Chemotherapy in the management of cervical carcinoma" by DuPont, N. C., & Monk, B. J. (2006). *Clinical Advances in Hematology & Oncology*.

According to the Technical Guidelines and Protocol of Department Obstetrics and Gynecology Sanglah Hospital Denpasar-Bali, Indonesia (2003), the treatment strategy of invasive cervical carcinoma starts with staging. If carcinoma in situ is found in patients who desire future fertility, then conization is the elected treatment, while a hysterectomy is performed on patients who have no desire for future fertility. Patients with stage I-IIA can have a radical hysterectomy, and adjuvant therapy is given if malignancy is evident. Neo-adjuvant chemotherapy or internal chemo-radiation is given in stage IIB. Then, the patients who are considered operable, a radical hysterectomy is an option, while, external radiation is an option for those who are non-operable. In an advanced stage, external radiation therapy or palliative treatment will be chosen. The treatment scheme of cervical cancer at Sanglah Hospital in Indonesia is illustrated in figure 7 (Appendix I).

To prevent recurrence, patients usually will undergo a routine examination, including enlarged lymph nodes palpability supra-clavicula, recto-vaginal examination, and cytology every 3-4 months in the first two years. After two years, the examination can be conducted every six months for five years post-therapy, and then once a year.

Overview of Chemotherapy

Chemotherapy for cancer treatment

Chemotherapy for cancer treatment is the use of chemical agents to destroy or control cancer cells. The agent will inhibit cell growth and spreading. In chemotherapy, antineoplastic agents are used in an attempt to destroy tumor cells by interfering with cellular functions and reproduction. Chemotherapy is used primarily to treat systemic disease rather than lesions that are localized and amenable to surgery or radiation. The goals of chemotherapy (cure, control, palliation) must be realistic because they will define the medications to be used and the aggressiveness of the treatment plan (Smeltzer & Bare, 2008; Yarbro, Wujcik & Gobel, 2011).

Chemotherapy may consist of only one drug or may be a combination of several types of drugs to induce the best response to the treatment. Each time a tumor is exposed to a chemotherapeutic agent, a percentage of tumor cells (20% to 99%, depending on dosage) is destroyed. Repeated doses of chemotherapy are necessary over a prolonged period to achieve regression of the tumor. Eradication of 100% of the tumor is nearly impossible, but the goal of the treatment is to eradicate enough of the tumor so that the remaining tumor cells can be destroyed by the body's immune system. Actively proliferating cells within a tumor (growth fraction) are the most sensitive to chemotherapeutic agents. Non-dividing cells capable of future proliferation are the least sensitive to antineoplastic medications and consequently are potentially dangerous. The non-dividing cells must be destroyed; however, to eradicate a cancer completely repeated cycles of chemotherapy are used to kill more tumor cells by destroying these non-dividing cells as they begin to be active in cell division (Wilkes & Barton-Burke, 2009).

Research continues to develop new drugs that act to destroy cancer cells by different methods. Many drugs act against cancer cells by interacting with DNA or RNA from cancer cells. This will damage the interaction of DNA, causing cancer cells to be destroyed or prevented from growing and reproducing. Four types of chemotherapy drugs that act directly to damage the DNA in cancer cells are: DNA-damaging agents (also known as antineoplastics), antitumor antibiotics, antimetabolites, and DNA-repair enzyme inhibitors.

Chemotherapy does not only destroy cancer cells but also destroys normal fast-growing cells, such as bone marrow cells, the gastro-intestinal membrane, skin and hair cells. Chemotherapy can destroy some cancer cells or control the metastasizing of some types of cancer. However, chemotherapy has non-specific side effects on the normal cells. As a result, patients with cancer receiving chemotherapy suffer from the side effect of symptoms, such as nausea, retching, vomiting, loss of appetite, and low immunity. Nausea, vomiting and retching are the symptoms that the patients are mostly concerned with because they cause substantial physical and psychological distress. These symptoms induce fear of chemotherapy that may finally lead to death (Hernandez- Reif et al., 2005; Hughes, Ladas, Rooney & Kelly, 2008; The Cancer Council New South Wales, 2008).

Pattern of chemotherapy regimens

Chemotherapy is used with patients who are pathologically diagnosed with cancer or those whose cytological study confirms a diagnosis of cancer. The treatment strategies are based on difference purposes and difference techniques, with

the terminology of each treatment regiment listed below (Miaskowski & Viele, 2000; Yarbro, 1996).

1. Induction: Chemotherapy is given to induce complete remission. The patients may receive a high dose of one chemotherapeutic drug or combination therapy.
2. Consolidation: Repetition of the induction regiments. The chemotherapeutic agents will be given for a longer period to improve the cure rate and to increase the remission duration.
3. Intensification: Chemotherapy after complete remission, use high doses of the same agents or different agents with the intent of increasing the cure rate and remission duration.
4. Maintenance: Long-term, low-dose of chemotherapy, either single or combination therapy which is given to the patients who have achieved complete remission with an aim to delay the re-growth of cancerous cells.
5. Adjuvant: A short course of high-dose chemotherapy that is given to the patients after surgery or radiotherapy with the intent of destroying a small number of residual cancerous cells to prevent recurrent cancer.
6. Primary treatment (Neo-adjuvant chemotherapy): Chemotherapy that is given before surgery or radiotherapy. Although the treatment is inferior to surgery or radiotherapy, it can save body organs.

7. Palliative: Chemotherapy given to control symptoms or prolong life in a patient whose cancer is unlike to be cured.
8. Salvage: A potentially curative, high-dose, usually combination, regimen given in a patient who has failed treatment or cancer has recurred following a different curative regimen

Types of chemotherapy

Chemical agents used in chemotherapy are different in chemical structures and properties. Chemotherapy can be classified into two types; classified by the phase of action in the cell life cycle and classified by chemical properties (Dy & Adjei in Chang et al., 2006; Smeltzer, Bare, Hinkle & Cheever, 2008; Wilkes & Barton-Burke, 2009).

1. Classified by the phase of action in cell life-cycle

1.1. Phase nonspecific chemotherapy

Chemotherapeutic agents that act independently of the cell cycle phases are termed cell cycle–nonspecific agents. These agents usually have a prolonged effect on cells, leading to cellular damage or death. Many treatment plans combine cell cycle–specific and cell cycle–nonspecific agents to increase the number of vulnerable tumor cells killed during a treatment period.

1.1.1. Cycle specific, phase nonspecific, having an effect on the cells that are in the life cycle phase only. The drugs in this group are Alkylating agents and Dacarbazine

1.1.2. Cycle nonspecific drugs, these drugs effect the cells in the G_0 phase or the cells that have not spread yet to other

organs. The drugs in this group are steroid hormones and all antitumor antibiotics can destroy cells except Bleomycin.

1.2. Cycle specific; Phase specific chemotherapy

Certain chemotherapeutic agents (cell cycle–specific drugs) destroy cells actively reproducing by means of the cell cycle. Many of these agents are specific to certain phases of the cell cycle. Most affect cells in the S phase by interfering with DNA and RNA synthesis. Others, such as the vinca or plant alkaloids, are specific to the M phase, where they halt mitotic spindle formation.

1.2.1. G_1 phase (Gap 1 phase). In this phase, the cells produce RND and enzymes essential for DNA production. Drugs specific to this phase include L-asparaginase.

1.2.2. S phase. This is the DNA production phase. The drugs in this group include anti-metabolites and antitumor antibiotics.

2. Classified by chemical properties

Chemotherapeutic agents are also classified according to various chemical groups, each with a different mechanism of action. These include the alkylating agents, nitrosureas, antimetabolites, antitumor antibiotics, plant alkaloids, hormonal agents, and miscellaneous agents.

2.1. Alkylating agents. These drugs in this group disturb cell spreading and cause chromosome damage, leading to mutation. For example: busulfan, carboplatin, chlorambucil, cisplatin,

cyclophosphamide, dacarbazine, hexamethyl melamine, ifosfamide, melphalan, nitrogen mustard, thiotepa.

2.2. Antimetabolites. These drugs disturb DNA production and stop cells from growing and multiplying. Drugs in this group include metathotrexate, 5-fluororacil.

2.3. Antitumor antibiotics. Drugs in this group disturb cell production of DNA and RNA, inducing oncolitic toxicity and inhibiting cell growth. These drugs include anthracyclines, dactinomycin, bleomycin.

2.4. Plant alkaloids-Mitotic inhibitor. These drugs interfere with cell dividing and inhibit RNA and protein production, thus stopping cell growth. The drugs in this group include; vinblastin, vincristin, vindesine, etoposide, and teniposide.

2.5. Hormonal agents. Drugs in this group change cell growth in the target organ or inhibit the other hormones released. Hormones in this group include androgens and antiandrogens, estrogens and antiestrogens, progestins and antiprogestins, aromatase inhibitors, luteinizing hormone–releasing hormone analogs, and steroids.

2.6. Miscellaneous agents. There are several drugs of which the mechanism of action is yet unknown. They disturb protein production and inhibit metabolism in cells. These drugs include asparaginase, procarbazine hydrochloride, hydroxyurea, interferons, and aldesleukin.

Chemotherapeutic agents from each category may be used to enhance the killing of tumor cells during therapy by creating multiple cellular lesions. Combined medication therapy relies on medications of differing toxicities and with synergistic actions. Using a combination drug therapy also prevents the development of drug resistant mechanisms.

Combining older medications with other agents, such as levamisole, leucovorin, hormones, or interferons (IFN), has shown some benefit in combating the resistance of cells to chemotherapeutic agents. Newer investigational agents are being studied for their effectiveness in resistant tumor lines.

Chemotherapy for cervical cancer

Chemotherapy is used to shrink cervical cancer and decrease tumor growth. Chemotherapy may be used to treat the later stages (stages II, III, and IV) of cervical cancer. It may be used alone or in combination with radiation (chemo-radiation). Extensive research and clinical trials have studied the different chemotherapy medicines used to treat cervical cancer. Some medicines are used routinely, and some are used in combination with others for greater effectiveness.

The most common chemotherapy medicines used for initial treatment or with radiation treatment in stage IIA, IIB, IIIA, IIIB, and IVA include Cisplatin and Fluorouracil (5-FU). For advanced stage (stage IVB) cervical cancer or recurrent cervical cancer, the most common chemotherapy medicines used are Mitomycin, Paclitaxel and Ifosfamide. Some of the chemotherapy drugs including their mechanism of action are described as follows.

1. Cisplatin

The generic name is Cisplatin and the brand names are Abiplatin or Platinol. Cisplatin works by binding to the DNA affecting DNA replication, forming DNA protein cross-link, and interacting with cellular glutathione. Cisplatin's metabolism is 90% bound to plasma protein, 20%-45% eliminated unchanged via the kidneys, and 10% eliminated in bile with t1/2 (half-life) = 60-90 minute.

2. Paclitaxel

The generic name is Paclitaxel and the brand name is Taxol. Paclitaxel promotes the assembly of microtubules and stabilizes them, thereby blocking mitosis. Paclitaxel also prevents the transition of the cell from G0 phase to the S phase by blocking cellular response to growth factors. The majority of paclitaxel is protein bound. Elimination is primarily through the hepatic system and minimal through renal excretion with t1/2 (half-life) = 1.3-8.0 hours.

3. Bleomycin

The generic name is Bleomycin and the brand name is Bleonoxane. Bleomycin is a cell cycle phase specific for G2 and M phase. Bleomycin works by binding to DNA. Inhibiting cell progression out of G, results in cellular synchronization for subsequent drug therapy. Elimination through the renal system with t1/2 (half-life) = 20 minute.

4. Mitomycin

The generic name is Mitomycin and the brand names are Mutamycin or Mitomycin C. Mitomycin is an antitumor antibiotic and is cell cycle specific. Active during the G and S phase of the cell 1 cycle and works by disrupting DNA synthesis secondary to alkylation. Mitomycin is inactivated by microsomal enzymes in the liver

and is metabolized in the spleen and kidneys, 10%-30% of the drug is eliminated unchanged in the urine and t1/2 (half-life) = 0.5-1.0 hour.

The study conducted by Rose et al. (1999) found that paclitaxel-cisplatin combination seems highly active in advanced and recurrent squamous cell carcinoma of the cervix. Research conducted by the Gynecologist Oncologic Group (GOG) (as cited in Andrijono, 2007) found that cervical cancer patients who have received cisplatin-paclitaxel combination have better response rates compared with cisplatin monotherapy administration (36% vs. 19%), with numbers of progression free survival (4.8 months vs. 2.8 months). The Society of Gynecologic Oncology provides recommendations of combinations of cisplatin-paclitaxel and cisplatin ifosfamide in the treatment of cervical cancer despite the provision of such combinations accompanied by an increase in the toxicity of those drugs.

In order to evaluate the impact of this regimen on response rate, toxicity, and progression-free survival (PFS), GOG initiated a study comparing the combination of paclitaxel and cisplatin (at doses of 135 mg/m2 as a 24-hour infusion and 50 mg/m2, respectively) with cisplatin alone (at a dose of 50 mg/m2). The subject was a patient with cervical cancer stage IVB (FIGO), recurrent, or persistent disease that was not amenable to curative treatment with surgery or radiation therapy. The result found that the combination of paclitaxel-cisplatin was superior to cisplatin alone with respect to the response rate and PFS with sustained quality of life (QOL) (Moore et al., 2004). Another study evaluated the toxicity and effectiveness combination of paclitaxel-cisplatin as a neo-adjuvant therapy in patients with cervical cancer stage IB2 - IIB (FIGO) found that the combination of paclitaxel-cisplatin for

use in neo-adjuvant chemotherapy seemed to be tolerated and very active in cervical cancer (Rose et al., 1999). Thus, the combination of cisplatin-paclitaxel appears to be effective in neo-adjuvant, adjuvant and recurrent cervical cancer.

Formula used in cervical cancer

Cytostatistica drugs for cervical cancer can be either a single agent or in combination. The first choice for combination therapy is; cisplatin/paclitaxel (category 1), cisplatin/topotecan (category 1), cisplatin/gemcitabine (category 2B), carboplatin / paclitaxel (Greer, et al, 2008). For single-agent therapy, the first choice is; cisplatin, carboplatin, paclitaxel, topotecan (category 2B) (Greer, et al, 2008). Among the chemotherapy drugs used in cervical cancer, cisplatin showed the most consistent activity as single agents. Cisplatin is the single agent for cervical cancer that has been most extensively evaluated. Doses of 100 mg/m2 showed a greater response than a dose of 50 mg/m2 (31% vs 21%), but larger doses are associated with increased risk of toxicity. Taxanes were reported to have activity in cervical cancer. In the study of paclitaxel (taxol) at a dose of 170 mg/m2 over 24 hours showed objective responses were on average 17% and in other studies doses of paclitaxel 250 mg/m2 over 3 hours showed an average response of 27% (Dennis et al., 2001).

The second choice of therapy is all the agents that are included in the category 2B, docetaxel, ifosfamide, vinorelbin, irinotecan, mitomycin, 5-FU, epirubicin (Greer, 2008). Ifosfamide yield responses averaged between 33% - 50% at various doses. Doses of 1.5 g/m2 for 30 minutes to 5 days to generate a response of 40% and 20% of Kampotensin, {irinotecan (CPT-11 (Captosar)} and topotecan

(Hycamptin) results of the average objective response were 21% and 19% (Dennis, et al, 2001).

In Sanglah Hospital, two formulas have been used for chemotherapy treatment. Those are a combination of Cisplatin, Vincristine and Bleomycin (PVB) and Bleomycin, Oncovin/Vincristine, Mitomycin and Cisplatin (BOMP). Nowadays, the combination of PVB has changed to Paxus (paclitaxel)-Cisplatin, because these new combinations are more effective. BOMP has been given to the patients for seven consecutive days with an interval of 2-3 weeks; meanwhile, Paxus (paclitaxel)-cisplatin are given to the patients for two days with an interval of 21 days. The physician decides which combinations of chemotherapy to use based on the patient's condition. Based on the observations of the register book of the patients receiving chemotherapy at the gynecological ward, more than 50 percent of patients with cervical cancer undergoing chemotherapy in Sanglah hospital received combinations of paxus (paclitaxel)-cisplatin.

Side effect of chemotherapy

Chemotherapy side effects depend on the type of drugs, the amount taken, and the length of treatment. It has many side effects including decreased white blood counts and possibly reduced red blood cell and platelet counts, nausea, vomiting, and loss of appetite, hair loss, diarrhea or constipation, peripheral neuropathies, ear problems (ototoxicity), eye problems, etc (Durden & Mirmirani in Chang et al., 2006).

Every chemotherapy drug has the potential to cause myelosuppression, that is, to reduce the production of bone marrow cells. The severity of this side effect

varies widely from one drug to another. Myelosuppression can result in anemia, low white blood cell counts (leukopenia), and low platelet counts (thrombocytopenia) (Smeltzer, Bare, Hinkle & Cheever, 2008). Because chemotherapy can damage the blood-producing cells of the bone marrow, the blood cell counts may become low. This can result in an increased chance of infection (from a shortage of white blood cells), bleeding or bruising after minor cuts or injuries (because of a shortage of blood platelets), shortness of breath (due to low red blood cell counts). Fatigue is also quite common and may be caused by low red blood cell counts, by other reasons related to the chemotherapy, or by the cancer itself (Gill, Grothey & Loprinzi in Chang et al., 2006).

Nausea, vomiting and retching are the most common side effects of chemotherapy and may persist for up to 24 hours after its administration. Chemotherapy drugs can cause nausea and vomiting because they irritate the stomach lining and the duodenum. This results in activating the part of the brain that triggers vomiting. It can also be triggered through intestinal blockage and inflammation that are likely chemotherapy effects (Smeltzer, Bare, Hinkle & Cheever, 2008). Based on the National Cancer Institute, the severity of nausea and vomiting can be divided into five grades (Table 3).

Tabel 3

Grading Severity of Nausea and Vomiting

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated	Life-threatening consequences	Death

(table continues)

Table 3 (*continued)*

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
		malnutrition; IV fluids indicated <24 h			
Vomiting	1 episode in 24 hours	2–5 episodes in 24 h and IV fluids indicated <24 h	24 h, IV fluids, or TPN indicated h	Life-threatening consequences	Death

Note: IV = intravenous; N&V = nausea and vomiting (emesis); TPN = total parenteral nutrition. Adapted from "Cancer Therapy Evaluation Program" as cited in "National Cancer Institute" Available online. http://www.cancer.gov

Chemotherapy-Induced Nausea, Vomiting and Retching

Nausea is a subjective and non-observable phenomenon of an unpleasant sensation experienced in the back of the throat and the epigastria that may or may not culminate in vomiting whereas, vomiting is the forceful expulsion of the contents of the stomach through the oral or nasal cavity (Rhodes & McDaniel, 2001). The incidence and severity of nausea, vomiting and retching in patients receiving chemotherapy vary, depending on the type of chemotherapy given, dose, scheduled combination of medication, and individual characteristics. Nausea, vomiting and retching are the most common symptoms in patients with cancer and have been well-studied (Bergkvista & Wengstr m, 2006). Those occur quite frequently under various conditions and can be triggered by different inputs or combinations of input mechanisms (Shelke, Mustian & Morrow, 2004). These unpleasant sensations can appear, either as a result of treatment or a disease itself and significantly affect the quality of life of patients and compliance with therapy (Rhodes & McDaniel, 2001). Nausea, vomiting and retching symptoms are also more severe on the following

treatments, and may develop as anticipatory nausea vomiting (ANV) especially in the fourth treatment cycle (Roscoe, Morrow, Aapro, Molassiotis & Oler, 2010).

Mechanisms of chemotherapy-induced nausea and vomiting

It is believed that the chemoreceptor trigger zone (CTZ) and the vomiting centre (VC) can also be stimulated directly by toxic substances giving rise to the sensation of nausea. Receptors for these transmitters are found in high numbers in the dorsal vagal complex, area postrema, and gastrointestinal tract. Chemotherapy damages the gastrointestinal tract and activates abdominal vagal afferents. Under drug stimulus, the enterochromaffin cells of the gastrointestinal mucosa release 5-HT3, which binds its receptor on the vagal afferent neurons. The binding between 5-HT3 and its receptor stimulates two specific areas in the central nervous system both located in the medulla: the CTZ and the VC (Andrews, Nalor & Joss, 1998; Bradbury, 2004; Grunberg & Ireland, 2005). The CTZ has an important role in chemotherapy-induced vomiting because it lies outside the blood-brain barrier, which makes it accessible to circulating emetogenic substances (Miner & Sanger as cited in Grunberg). The CTZ is activated via blood or cerebrospinal fluid and invokes the release of various neurotransmitters, which stimulate the VC. Once activated, the VC modulates the efferent transmission to the respiratory, vasomotor and salivatory centers resulting in nausea (Hawthorn, 1995) as well as to the abdominal muscles, diaphragm, and esophagus, resulting in emesis (Thompson & Lummis, 2007). The mechanisms of chemotherapy-induced nausea and vomiting can be seen in the nausea and vomiting pathway (Figure 3).

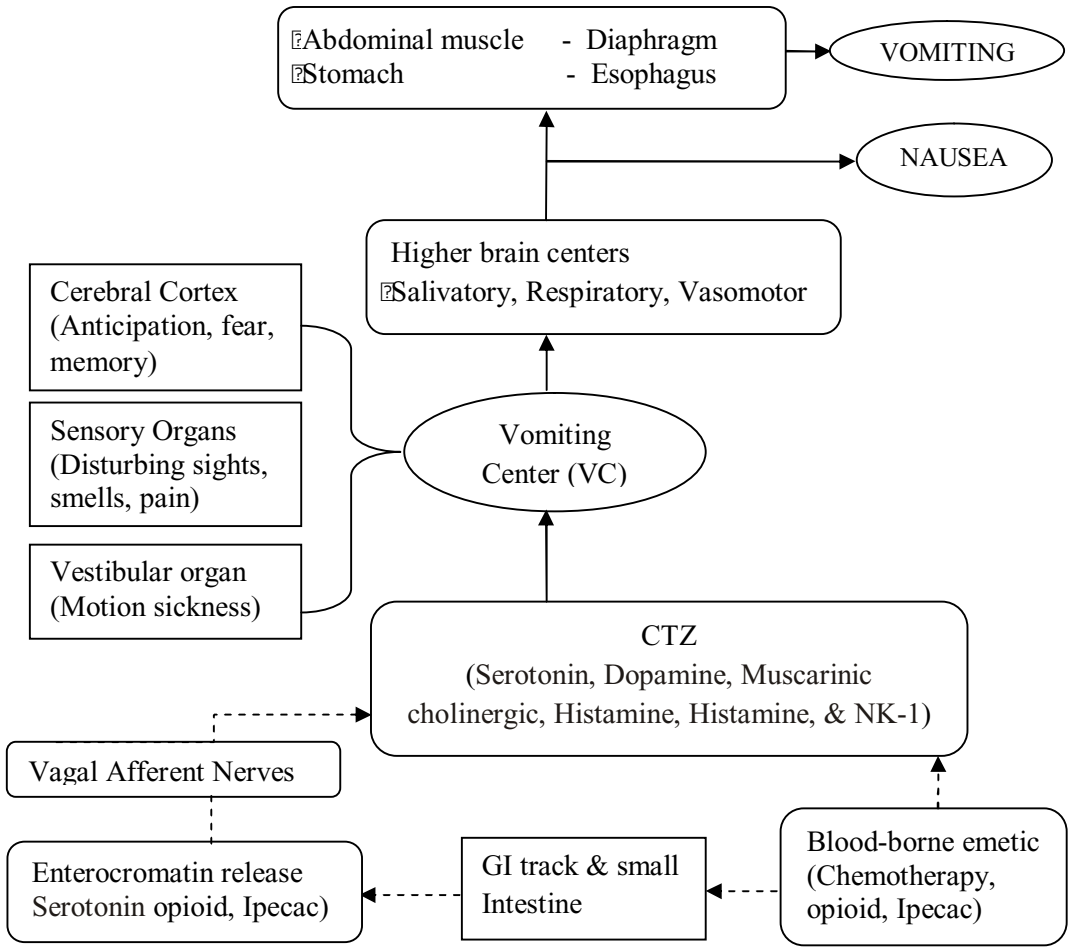


Figure 3. Nausea, Vomiting and Retching Pathway.

Solid arrows illustrate the direct mechanism; Dash arrows illustrate indirect mechanisms.

Pattern of nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is classified by the pattern and time in which it occurs. In addition, the criteria for grading the severity of nausea and vomiting is divided into five grades. The three patterns occurring in oncology patients are acute, delayed, and anticipatory nausea and vomiting (Bradbury, 2004).

Acute nausea and vomiting

The neurophysiology of acute CINV is complex. The type of chemotherapy as well as the dose and administration has an impact on the severity or risk of acute emesis (Bradbury, 2004). Acute nausea and vomiting usually occurs a few minutes to several hours after receiving the chemotherapy, goes away within the first 24 hours, and usually worsens in 5 or 6 hours after chemotherapy (National Comprehensive Cancer Network, 2007).

Many variables play an important role in predicting the risk for CINV, such as age, gender, experience to nausea and vomiting, and life style (Rhodes & McDaniel, 2001; Rosco et al., 2010). Patients who experience acute emesis with chemotherapy are significantly more likely to have delayed emesis. Evidence suggests that good control of acute CINV, particularly during the initial treatment received by chemotherapy-naïve patients, has a positive impact on the control of delayed and, by extrapolation, anticipatory symptoms, as well as of acute and delayed onset emesis associated with subsequent cycles of treatment (Liau et al., 2005). Therefore, obtaining an accurate patient history is an important component of determining the likelihood of emesis in a given patient.

Delayed nausea and vomiting

Delayed nausea and vomiting develops more than 24 hours after chemotherapy has been administered. This effect can be observed for up to as many as 5 days after treatment (Bradbury, 2004). It might occur with certain types of chemotherapy, such as cisplatin related vomiting is usually worst from 48 to 72 hours after chemotherapy and can last 6 to 7 days. It should be noted that the strongest

predictor of delayed CINV is the occurrence of symptoms in the acute phase, but delayed emesis arises in the absence of acute symptoms in 18% to 24% of patients. Moreover, delayed nausea is usually caused by the high-level emetogenic of chemotherapy (Grunberg, 2004). Delayed CINV remains a major adverse effect of cancer chemotherapy. A study conducted by Ihbe-Heffinger et al. (2004) reported that a substantial high proportion of patients continue to experience CINV, this high proportion entails not only clinical but also economic consequences.

Anticipatory nausea and vomiting (ANV)

Anticipatory nausea and vomiting (ANV) is widely believed to be a learned response as reflecting Pavlov's conditioned reflex. ANV associated with the experience of previous chemotherapy, in which the conditioned stimulus (CS) is the thought of chemotherapy or conditioning elements associated with chemotherapy. When re-exposed to the CS, some patients will then experience ANV prior to the infusion onset (Carey & Burish as cited in Aapro, Molassiotis & Olver, 2005). The authors emphasized that ANV is not only a learned response but can occur without prior exposure to chemotherapy depending on the patient's emotional distress and expectations. ANV usually develops in up to 25% of patients by the fourth treatment cycle (Morrow, Roscoe, Kirshner, Hynes & Rosenbluth, 1998).

Shelke, Mustian and Morrow (2004) confirmed that ANV occurred before treatment as a response to other triggers in the environment, such as certain objects, odors, or tastes. It is associated with poor emesis control with prior treatments. A patient who has experienced emesis from past treatments is "conditioned" to respond to the environmental stimuli (Bradbury, 2004). Therefore,

patients might experience nausea when they see the doctor, nurse, or treatment area that was associated with the past history of emesis. Aapro et al. (2005) emphasized that once ANV develops, it is difficult to control by pharmacological methods, whereas behavioral therapies involving relaxation as most notably systematic desensitization, can be used to effectively treat ANV.

Factors affecting nausea, vomiting and retching

Morrow (1984) collected data prospectively in order to evaluate risk factors. Several patient-related factors may increase the risk of CINV and have also been identified. These factors include a young age, female gender, history of low or no alcohol intake, experience of emesis during pregnancy, impaired quality of life, and previous experience with chemotherapy (Liau et al., 2005). Feyer et al. (2005) described an individual's risk profile according to patient risk factors associated with emetogenic (Table 4).

Table 4

Individual Risk Factors According to Patient-Related Emetogenic

Risk factor		Risk score
Age	> 55 years	0
	< 55 years	1
Sex	Male	1
	Female	2
Alcohol consumption	Yes (> 100 g/day)	0
	No	1
Previous N & V	Yes	1
	No	0

(table continues)

Table 4 (*continued*)

Risk factor		Risk score
Anxiety	Yes	1
	No	0
Risk profile		5-6 high risk

Note: Adapted from *"*Radiotherapy-induced nausea and vomiting (RINV): Antiemetic guidelines*"* by Feyer, P. C., Maranzano, E., Molassiotis, A., Clark-Snow, R. A., Roila, F., Warr, D. et al., 2005, *Support Care Cancer, 13*.

Not all cancer patients will experience nausea, vomiting, or both. The malignancy itself, its treatment, concurrent disorders, or nonspecific factors may contribute to additional and/or more severe nausea and vomiting (Rhodes & McDaniel, 2001). Generally, the severity of CINV is influenced by two different risk factors, individual patient characteristics and chemotherapy itself (Bajetta, Pusceddu, Guadalupi, Ducceschi & Cellio, 2009; Dodd, Onishi, Dibble & Larson as cited in Grunberg, 2005).

1. Patient factors

1.1 Age and gender

Women are more likely to experience CINV than are men (Rhodes & McDaniel, 2001; Schnell, 2003). Moreover, evidence showed that older aged patients tended to tolerate chemotherapy better than younger patients. Because younger patients are exposed to less aggressive treatment regimens than those administered to the elderly. A study conducted by Watson, Meyer, Thomson and Osofsky (as cited in Aapro et al., 2005) reported that young adult patients had greater anticipatory nausea than older adult patients, while female patients had a greater severity of anticipatory nausea than male patients.

1.2 Alcohol effect

Although nausea and vomiting are common side effects of chemotherapy, patients with a history of chronic alcohol intake experience had less severe symptoms than those who were not heavy alcohol drinkers (Olver et al. as cited in Rhodes & McDaniel, 2001; Schnell, 2003). A patient's history of low alcohol consumption may indicate increased susceptibility to chemotherapy-induced nausea and vomiting. Chronic heavy alcohol usage, which can be defined as 100 g of alcohol per day for a period a few years, has been associated with improved control of emesis. (Gralla et al. as cite in Grunberg, 2005). Even though emesis is more easily controlled in patients with chronic heavy alcohol use, these patients still require effective antiemetic regimens.

1.3 Motion sickness

The activation of a nucleus of neurons located in the medulla oblongata, known as the vomiting center, initiates the vomiting reflex. The vomiting center can be activated directly by signals from the vestibular apparatus of the inner ear (motion sickness) (Garrett, Tsuruta, Walker, Jackson & Sweat, 2003). Patients with a history of motion sickness and pregnancy-induced emesis may have a lower threshold to nausea and vomiting than the rest of the population. It can be exacerbated by patient anxiety and by a prior history of nausea and vomiting associated with chemotherapy or radiation therapy (Schnell, 2003).

1.4 Psychological factors

Seriously ill patients with cancer have a high symptom burden. NVR experience associated with the first antineoplastic treatment can have a major impact on patients who will require long-term palliative care. Unless the

symptoms of NVR have been prophylactically managed during the initial therapy (i.e., the first cycle of the first course), the actual or perceived threat of disease, treatment, and inconvenience associated with treatment, can cause a variety of emotional and physiological responses (McDaniel & Rhodes, 1998). Patients with poor control of nausea and vomiting during prior chemotherapy cycles are likely to experience nausea and in subsequent cycles (Cohen, de Moor, Eisenberg, Ming & Hu, 2007; Garrett et al., 2003).

Stress, anxiety and the patient's expectations are the psychological factors that are most widely investigated. Studies have shown that state anxiety is significantly related to both the severity and incidence of nausea (Adrykowski & Gregg as cited in Hawthorn, 1995). Another study conducted with 233 married cancer patients to examine the effects of changes in family relationships (cohesion, expression, and conflict) have shown that an increase in family conflict was associated with increased duration and severity of post treatment nausea. Psychological variables as predictors of ANV are important but the most important factor remained the previous experience with symptoms earlier (Watson, Meyer, Thomson & Osofsky cited in Aapro et al., 2005). In a current study, anxiety has a positive relationship with nausea, vomiting and retching in cervical cancer patients receiving chemotherapy. Additional analysis in this study also revealed that subjects with higher anxiety scores reported significantly higher NVR scores at the baseline.

1.5 Patient expectations

Patients are active agents who have goals and behaviors that are largely determined by their perceptions and expectations of disease. Montgomery and Bovbjerg (2003) reported that (scheme) accurate preparation and

realistic expectations could reduce the negative mood state and improve coping behaviors. These findings suggest that an appropriate pretreatment patient preparation and effective management of early symptoms can help avoid fear, uncertainty, and distress.

Expectation is another factor that contributes to ANV. Montgomery and Bovbjerg (2003) discussed that expectation was an important determinant of experiences of non-volitional outcomes (e.g. pain, nausea), but little research has explored the source. A study conducted by Hickok, Roscoe, and Morrow (2001) with 63 female cancer patients receiving their first course of chemotherapy found that anticipatory nausea and vomiting developed in 40% of patients who expected nausea, 13% were uncertain whether they would develop it, and none of them did not expect nausea and vomiting.

2. Chemotherapy factors

Patients who have experienced chemotherapy will be at risk for developing nausea, vomiting and retching. The most common causes are emetogenic chemotherapy drugs to the gastrointestinal (GI) tract, liver, or brain. Moreover, the combination of chemotherapy or the use of several chemotherapy regiments induces more severe nausea and vomiting. The primary risk factor for CINV is the intrinsic emetogenicity of the chemotherapy agent. Varying emetic risk may result because difference agents act at different sites or even multiple sites within the patient's system (Berger & Clark-Snow as cited in DeVita, Hellman & Rosenberg, 2001). Chemotherapeutic agents have been classified into four emetic risk categories according to the percentage of patients having emetic episodes when no prophylactic

antiemetic protection is provided as high (>90%), moderate (30% to 90%), low (10% to 30%), and minimal risk (<10%) as shown in Table 5 (Grunberg, 2004). In addition, high emetics risk for chemotherapy will promote acute and delayed nausea, while low emesis risk will promote acute emesis only.

Cisplatin is one of the high emetogenic chemotherapy agents. Cisplatin in doses of 50-120mg/m2 will cause emesis in the majority of patients within 24 hours of administration (Homesley et al. as cited in Bradbury, 2004). In the absence of effective antiemetic prophylaxis, virtually all patients receiving cisplatin will have nausea and vomiting 1 to 2 hours after receiving chemotherapy. Cisplatin has a peak emetogenic effect at approximately 4 hours after administration during the acute phase of nausea (Morrow, 1989). At approximately 18 to 24 hours, the emesis typically subsides, only to recur and reach a second peak at approximately 48 to 72 hours after receipt of the agent (Kris et al. as cited in Hesketh, 2008). The release of serotonin from the enterochromaffin cells has been demonstrated with the administration of cisplatin. A peak in urinary metabolites of serotonin (5-HIAA) occurs 6 hours after cisplatin administration suggesting a strong correlation of serotonin release and vomiting with this agent (Cubbeddu, as cited in Bradbury, 2004).

Tabel 5

Emetic Risk of Chemotherapy Agents

High (> 90%; Level 5)	Moderate (30%–90% Level 3 And 4)	Low (10%–30%; Level 2)	Minimal (< 10%; Level 1)
Carmustine (> 250 mg/m²)	Cyclophosphamide (< 1,500 mg/m²)	Aldesleukin (interleukin-2)	Methotrexate (< 100 mg/m²)
Cisplatin (Platinol).	Carboplatin (Paraplatin).	Mitoxantrone (Novantrone).	Vinorelbine (Navelbine).
Mechlorethamine	Cyclophosphamide (Cytoxan), less than 1,500 mg/m^2.	Paclitaxel (Taxol).	Bevacizumab (Avastin).
		Docetaxel (Taxotere).	

(table continues)

Table 5 (*continued*)

High (> 90%; Level 5)	Moderate (30%–90% Level 3 And 4)	Low (10%–30%; Level 2)	Minimal (< 10%; Level 1)
(Mustargen). Streptozotocin (Zanosar). Cyclophosphamide (Cytoxan), 1,500 mg/m^2 or more. Carmustine (BiCNU). Dacarbazine (DTIC-Dome). Dactinomycin.	Daunorubicin (DaunoXome). Doxorubicin (Adriamycin). Epirubicin (Pharmorubicin). Idarubicin (Idamycin). Oxaliplatin (Eloxatin). Cytarabine (Cytosar), more than 1 g/m^2. Ifosfamide (Ifex). Irinotecan (Camptosar).	Mitomycin (Mutamycin). Topotecan (Hycamtin). Gemcitabine (Gemzar). Etoposide (Vepesid). Pemetrexed (Alimta). Methotrexate (Rheumatrex). Cytarabine (Cytosar), less than 1,000 mg/m^2. Fluorouracil (Efudex). Bortezomib (Velcade). Cetuximab (Erbitux). Trastuzumab (Herceptin).	Rituximab (Rituxan). Bleomycin (Blenoxane). Vinblastine (Velban). Vincristine (Oncovin). Busulphan (Myleran). Fludarabine (Fludara). 2Chlorodeoxyadenosine (Leustatin).

Note: Adapted From "ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery." as cited in "Chemotherapy-Induced Nausea and Vomiting: Prevention, detection, and treatment-how are we doing?" by Grunberg, S. M., 2004, The journal of supportive oncology, 2 (1).

3. Non–chemotherapy-related causes of emesis

Non-chemotherapy factors must be considered in patients who experience nausea, vomiting and retching while receiving an antineoplastic drug. These include bowel obstruction, renal insufficiency, brain metastases, or other medications (e.g., narcotic analgesics).

3.1 Concomitant symptoms

Constipation (with resultant colonic stretch) or increased intra-abdominal pressure may stimulate the mechanoreceptor pathways to the emetic center thus triggering vomiting (Mercadante, Casuccio & Fulfaro as cited in Rhodes & McDaniel, 2001).

3.2 Tumor burden

Tumor enlargement that impinges on adjacent anatomical structures in the gut may cause severe NVR by activating mechanoreceptors in the bowel wall. Some common conditions caused by the enlargement of a tumor that contribute to NVR include delayed gastric emptying, gastric outlet or indigestion, ulcers, liver or kidney failure, hypercalcemia, hyponatremia, and increased intracranial pressure. Delayed gastric emptying may be due to physiological problems, e.g., anticholinergic effects of drugs including opioids, or to mechanical resistance (partial or complete) to emptying. Ascites, hepatomegaly and duodenal or pancreatic tumors are some of the causes of such mechanical resistance (Rhodes & McDaniel, 2001).

Impact of nausea, vomiting and retching

Nausea, vomiting and retching have a wider impact on people, especially hospitalized patients who are already weak. NVR symptoms can be debilitating if prolonged and it will impact on emotional and physical stress. Another impact is the interference with nutritional, fluid and electrolyte imbalance as well as psychosocial impact. Maintaining adequate nutritional intake may be difficult for patients who experience nausea and vomiting (Balatori, & Roila, 2003). Functional

ability and relationships are psychosocial consequences of nausea and vomiting (Noonan, 2005). Aside from these consequences, nausea and vomiting have a considerable economic impact. Direct costs include acquisition cost of antiemetic drugs and administration devices, additional patient care, such as nursing and physician time, and in some cases, extended hospitalization or readmission (Ihbe-Heffinger et al., 2004).

Nausea, vomiting and retching are frequently reported and troublesome adverse effects of chemotherapy for cancer. Moreover, the most common concern of nausea, vomiting and retching in cancer patients was a negative impact on overall quality of life (QOL). Antiemetic research have been enhanced with the introduction of 5-hydroxytryptamine 3 (5-HT3) and Neurokinin1-receptor (NK1) antagonists as the best choice for chemotherapy-induced nausea and vomiting (CINV). Despite progress in the antiemetic field CINV continues to be a significant problem for patients. CINV can cause decreasing patient QOL and negatively affect the treatment experience of the patient, and impact on physical, cognitive, social, emotional and role functioning. In addition, CINV and its impact on a patient's daily life have received little attention (Deuson et al., 2004).

Assessment of Nausea, Vomiting and Retching

Several instruments are available for the assessment of nausea, vomiting and retching. Most instruments are self-report and usually assess frequency, severity, duration, and volume of the symptoms. Psychological assessment involves the anxiety or distress from nausea, vomiting and retching. Examples of these instruments are Morrow Assessment of Nausea and Emesis (MANE), Visual Analog

Scale (VAS), the MASCC Antiemesis Tool (MAT) developed by the Multinational Association of Supportive Care in Cancer (MASCC), and Index of Nausea, vomiting and retching (INVR) developed by Rhodes.

Morrow Assessment of Nausea and Emesis (MANE)

The MANE scale is a retrospective tool, which asks separate questions in the areas of anticipatory nausea, anticipatory vomiting, post-treatment nausea and post-treatment vomiting (Morrow, 1992). Content validity is examined through a series of 36 pair wise correlations among the frequency, duration and severity of the four dimensions of CINV. It found that there is no correlation exceeding 0.50; none of the dimensions shared more than 25% variance (Brearley, Clements & Molassiotis, 2008). Emphasized by Carnrike et al. (as cited in Brearley et al., 2008), the concurrent validity and the test– retest reliability of the MANE demonstrates a moderate degree of test–retest reliability, with the instrument appears to be more reliable in the measurement of nausea rather than vomiting. Concurrent validity between the MANE and continuous self-reporting was also found to be moderate.

The MANE is designed to focus on up to 24 hours post-treatment, and effectively limits the scope of assessment to the acute phase of nausea and vomiting. The MANE assesses two phases of CINV (anticipatory and acute), two domains (nausea and vomiting) and the aspects of occurrence, frequency, duration and severity. However, no attention is given to functional impact. The scale defines vomiting as “actually throwing up”, which excludes any assessment of retching. Therefore, the MANE will not be used in this study.

Visual Analog Scale (VAS)

The VAS was developed about 60 years ago. It is used to measure many types of subjective phenomena, such as pain, anxiety, nausea and vomiting, and mood states. The analog scale consists of a 0 - 100 mm line drawn on paper with negative and positive statements about nausea. The left side indicates no nausea et al or zero nausea, and the right side points to the highest level of nausea or worst possible nausea. The patients are asked to show how much nausea they felt by marking the analogue scale (Bilhult et al., 2007).

VAS can be used to measure nausea in patients with cancer undergoing chemotherapy (Bilhult et al., 2007; Grealish et al., 2000). One study found that the VAS was sensitive to detecting early changes in patient-reported nausea (Jaeschke et al. as cited in Wood, 2011), however, it can be difficult to explain to the patients. The VAS requires patients to convert a subjective sensation to a mark on a straight line provided on the assessment tool.

The VAS are often selected because of their ease and speed of completion, moreover, it can be used regardless of language. However, patients can often require lengthy instructions from trained staff before completion, potentially leading to investigator bias, and there are differing opinions regarding the facility of interpreting results. The VAS is also limited to the measurement of one component (usually intensity) of such multi-dimensional symptoms as nausea (Brearley et al., 2008). Therefore, the VAS will not be used in this study to assess the level of nausea, vomiting and retching.

The MASCC Antiemesis Tool (MAT)

The MASCC Antiemesis Tool (MAT) was developed by the Multinational Association of Supportive Care in Cancer (MASCC) through a literature review on chemotherapy-related nausea and vomiting, interviews with clinicians, and a multidisciplinary working group of expert clinicians in nausea and vomiting. Dichotomous items are scored ‘‘0’’ (‘‘No’’) or ‘‘1’’ (‘‘Yes’’) and continuous variables as marked on the 0 - 10 scale. There is no summing of items; instead, items are evaluated on their own in clinical practice. Detailed explanations are provided to the patients through an instruction sheet, and the person who gives the scale to the patients ensures that patients understand the instructions through the use of an unrelated example, and a simple definition of nausea (‘‘the feeling that you might vomit’’) and vomiting (‘‘the bringing up of stomach contents’’) is provided.

The MAT is the most concise tool, it is easy to use, easy to understand the questions, and has a short completion time (average time = 4 minutes). However, the MAT just assesses the domains of nausea and vomiting through the acute and delayed phases of CINV, and treating each as distinct phenomena. Each phase is assessed by four items that measure the occurrence of CINV, the duration of nausea (10-point scale), and the frequency of vomiting. The MAT also assesses the quantity occurrence, frequency, and duration of nausea and vomiting. However, no evidence of its use in research or practice could be found. Since this study assesses nausea, vomiting and retching and the MAT does not cover all three, it will not be used as a tool.

Index of Nausea, Vomiting and Retching (INVR)

The Index of Nausea, Vomiting and Retching (INVR) is a patient self-report instrument to assess the objective and subjective factors of nausea and vomiting developed by Rhodes. The INVR consists of 8-items, 5 point Likert-type self-report pencil and paper instrument that measures the patient's perceived (a) duration of nausea, (b) frequency of nausea, (c) distress from nausea, (d) frequency of vomiting, (e) amount of vomiting, (f) distress from vomiting, (g) frequency of dry heaves, and (h) distress from dry heaves (Rhodes & McDaniel, 1999). This instrument measures nausea, vomiting, and retching as separate dimensions. INVR measures the perceived frequency of and distress caused by all three dimensions (symptom experience, symptom occurrence and symptom distress) using five response options (0 to 4) reported over the past 12 hours. A prior study has demonstrated excellent internal consistency reliability of the INVR, with a Cronbach's alpha of .98, and good concurrent validity with the INV-2 form (the original form of the scale), with a correlation coefficient of .87 (Rhodes & McDaniel).

The INVR has been used in clinical trials (Dibble, Israel, Nussey, Casey & Luce, 2003; Martin et al., 2003) and has been translated into Korean (Kobayashi et al as cite in Brearly, Mollassiotis & Clements, 2008) and Chinese (Fu, Rhodes & Xu, 2002). Testing for validity and reliability of the Korean translation

ement between INVR and INV-2=83%

and the correlation coefficient = .91. Construct validity was indicated by the difference in the scores of patients with and without nausea, vomiting and retching. The Chinese translation, tested for use in the oncology and obstetric patients, had a

–retest reliability coefficient = .97. As with the INV-2 the

the translated instrument were estimated by an expert panel and a representative patient, respectively (Fu et al., 2002).

A study by Wood et al. (2011) has found INVR to be clinically useful and easy for patients to understand. It is interesting that distress, not severity, is assessed in real-time symptom management. It could be viewed as unusual to ask a vomiting patient to rate the distress of vomiting as it is occurring. Severity questions may be better received, and the distress lessened by adequate, timely interventions. The INVR are accurate and effective research-based instruments assessing nausea, vomiting, and retching; hence, they are the better choice of instruments to be translated for cross-cultural/cross-national research (Fu et al., 2002). Based on the above reasons, the researcher used the Index of Nausea, Vomiting and Retching (INVR) tool in this study.

Interventions for Nausea, Vomiting and Retching

Nausea, vomiting and retching (NVR) are unpleasant sensations, and can cause prolonged recovery times, and increased costs. NVR can be treated through pharmacology and non-pharmacology intervention. Pharmacology/medication is the first-line intervention for nausea, vomiting and retching. In addition, the use of alternative or complementary intervention measures as adjuncts may improve patients' outcomes and help reduce costs.

Pharmacological intervention

Varieties of antiemetic agents are available, including antihistamines, dopamine-receptor antagonists, serotonin-receptor antagonists, and neurokinin-

receptor antagonists (Bremerkamp, 2000). To ensure the optimal symptom control for each patient without unnecessarily prolonging treatment, patients and treatment-specific risk factors must be considered. Historically, antiemetic treatment has been improved first by the introduction in 1981 of high-dose metoclopramide which reduced the amount of emesis (Gralla et al. as cited in Said, 2009), second by the development of serotonin (5-HT3) antagonist in the early 1990s, potentiated by concomitant use of corticosteroids which further improved the control of emesis (Grunberg & Kesketh, 1993). Recently a new drug, the neurokinin NK (1) receptor antagonist has been shown to have a better effect on preventing both acute and delayed CINV for patients treated with highly emetogenic chemotherapy (Dando & Perry, 2004; Dewit et al., 2004). In addition, modern classes of anti-emetic commonly used include 5HT3 antagonists, substance P neurokinin 1-receptor antagonists, motility agents, phenothiazine, benzodiazepines, and corticosteroids, as explained in Table 6.

For recommending anti-emetic regimens, most guidelines take into account the emetogenicity of the antineoplastic agent being used, as well as the type of nausea and vomiting being treated. Three commonly referenced guidelines have been published by the Multinational Association of Supportive Care in Cancer (MASCC), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN). The American Society of Clinical Oncology (ASCO) recommendations include giving potential 5-HT3 receptor antagonists plus corticosteroids before chemotherapy to patients receiving chemotherapy that are at high risk of emesis. It is well known that dexamethasone is highly effective in managing delayed nausea and vomiting (Roila, 2006), although

many clinicians are sceptical of the use of steroids for prolonged periods. Hence, the use of dexamethasone may have contributed to the better control of NV in the study by Roscoe et al. (2003).

Table 6

Common Antiemetic Agents

Anti-emetic	Trade Name	Adverse Effect	Adverse Effect Management
Substance P Antagonist			
Aprepitant	Emend	Fatigue	
Serotonin Antagonists			
Dolasetron	Anzemet	Constipation	Prophylactic laxatives
Granisetron	Kytril	Constipation	Prophylactic laxatives
Ondansetron	Zofan	Constipation	Prophylactic laxatives
Palonosetron	Aloxi	Constipation	Prophylactic laxatives
Dopamine Antagonists			
Metoclopramide	Reglan	EPS, Akathesia	Diphenhydramine, lorazepam, benztropine
Prochlorperazine	Compazine	EPS	Diphenhydramine, lorazepam, benztropine
Haloperidol	Haldol	EPS	Diphenhydramine, lorazepam, benztropine
Antihistamine			
Promethazine	Phenergan		
Diphenhydramine	Benadryl		
Corticosteroids			
Dexamethasone	Decadron	Delirium, anxiety, insomnia	Re-evaluate dose/usage
Methylprednisolone	Solumedrol	Delirium, anxiety, insomnia	Re-evaluate dose/usage
Anxiolytics			
Lorazepam	Ativan	Confusion, sedation,	Re-evaluate dose/usage

*Note: "*EPS = extrapyramidal symptoms; qhs = every bedtime. Adapted from "Chemotherapy-induced Nausea and Vomiting" by Nevadunsky, N. S., & Matulonis, U. A., 2009, *Supportive Oncology,* 10-15.

Non-pharmacological intervention

Although an effective antiemetic for preventing CINV has been available, nearly 60% of patients still experience nausea and 30% experience vomiting in the days after their first course of cancer chemotherapy (Morrow et al.,

1998). The most important risk factor for delayed nausea and vomiting is the presence of acute nausea and vomiting (Grunberg, 2004). Since pharmacological treatments have failed to manage nausea and vomiting completely, combining anti-emetics with other non-pharmacological treatments may prove more effective (Molassiotis, Helin, Dabbour & Hummerston, 2006).

Studies have confirmed that the key to the successful management of CINV is to prevent symptoms before they occur (Bajetta, Pusceddu, Guadalupi, Ducceschi & Celio, 2009; Morrow et al., 1998). Controlling CINV in many patients continues to be a challenge for the practitioner. Beside pharmacologic interventions, non-pharmacologic intervention may be used with the intent to focus the patient's attention on outside stimuli rather than the sensation of nausea. In addition, combining anti emetics with other non-pharmacological treatments may prove more effective in decreasing nausea than anti emetics alone (Molassiotis et al., 2006).

Randomized trials have attempted to explore non-pharmacological interventions for CINV. Yoga, music, acupressure (Dibbel et al., 2000), progressive muscle relaxation (Molassiotis et al., 2002), hypnosis, acupressure, acupuncture-point stimulation, and massage therapy have been shown to have some benefit (Nevadunsky & Matulonis, 2009). Among several non-pharmacologic interventions, massage has been used for many years and has been shown to relieve nausea and relax hospitalized patients with cancer (Grealish et al., 2000).

Physicians remain the central figure in the treatment of cancer patients and the study related to treatment/medication for cancer patients has rapidly developed. Several studies have been conducted in the field of pharmacological therapy, either for chemotherapy or antiemetic therapy in order to prevent side effects

of intervention. Non-pharmacological intervention is the nurse's field. Therefore, nurses should be more proactive and innovative in their patient care, education, and counseling to maximize the use of non-pharmacological interventions that may be helpful in symptom management. Further research evaluating the use and effectiveness of non-pharmacological interventions on symptom management in cancer patients is needed.

Overview of Foot Massage Therapy

General information related to foot massage therapy explained in appendix B. Massage therapy may be defined as the manipulation of the soft tissue using a hand which involves systematic, manual manipulations, such as rubbing, kneading, or rolling soft tissue (i.e., muscles, tendons, ligaments, and fascia) aimed to influence the desired changes in an individual (Tuchtan et al. as cited in Smith, 2010). Massage improves patients' range of motion, decreases the pain threshold, relaxes muscles, and improves circulation and lymphatic drainage (Cassileth & Vickers, 2004). It also has biochemical effects which increases dopamine levels and lymphocytes and natural killer cell production (Calenda, 2006; Corbin, 2005).

Massage is one way to convey feelings of care and comfort through a touch method as well as allow nurses at the bedside of the patient. Many studies have found that massage therapy contributes to a better quality of life in cancer patients. The essence of massage therapy involves touch and manipulation of the soft tissues that has effects on calming or invigorating to assist relaxation (Cassileth & Vickers, 2004; Reaves & McManis, 2010).

Type of massage

Various types of massage have been used worldwide (e.g. Swedish, sports, deep tissue, neuromuscular, shiatsu, and soon). Each one is based on different techniques, level of pressure and force applied, and some include a spiritual component.

1. Swedish massage

Swedish massage has been popular since the 19th and 20th century and is familiar to the public. Swedish massage, developed Swedish physician Per Henrik Ling in the early 1800s is currently one of the most commonly used forms of massage (Seers, 2010). Swedish massage is usually a full body massage, unless specifically requested. Swedish massage aims to relax muscles by applying pressure on deeper muscles and bones, especially rubbing in the same direction as the return of blood flow to the heart (Swedish massage). The therapist uses hands, arms and elbows to apply pressure with five basic techniques such as effleurage, kneading, deep circular movements, vibration, and tapping. Swedish massage is the most widely used type of massage in the Western world and is also known as classic massage (Donkin, 2009; Massage Therapy, 2007; Natural Standard, 2005).

Swedish massage consists of continuous systematic effleurage/strokes and deep kneading and stretching to loosen tight muscles and to reduce stress. The manual techniques specifically include effleurage/stroke (smooth gliding movements intended to evoke the relaxation response), petrissage/kneading (lifting, squeezing and wringing of soft tissues to stimulate deep muscle and to increase circulation), friction/ rubbing (penetrating pressure with fingertips to reduce muscle spasm), vibration/ shaking (move back and forth on the body without leaving

contact) and tapotement/ percussion (rapid striking to stimulate tissues) (Sagar, Dryden & Wong, 2005).

2. Sports massage

Sports massage is similar to Swedish massage, adapted specifically to the needs of athletes. Sports massage is a special form of massage and is typically used before, during, and after athletic events. The purpose of the massage is to prepare the athlete for peak performance, to drain away fatigue, to relieve swelling, to reduce muscle tension, to promote flexibility and to prevent injuries. Obviously, the main purpose of sports massage therapy is to help alleviate the stress and tension, which builds up in the body's soft tissues during physical activity (Massage Therapy, 2007; Natural Standard, 2005). Sports massage is commonly recommended to help athletes prepare both physically and mentally for a forthcoming event. In addition, sports massage is believed to decrease injury-potential factors (Weerapong, 2006), is acceptable to the community and is in accordance with the principles of managing musculoskeletal conditions (Vindigni, 2005).

3. Deep tissue massage and trigger point massage

Deep tissue massage is a massage technique that focuses on the deeper layers of muscle tissue on myofascial trigger points muscle "knots" that are painful when pressed and can cause symptoms elsewhere in the body. This massage is used to release chronic muscle tension through slower strokes and more direct deep pressure, or friction applied across the grain of the muscles and not with the grain (Massage Therapy, 2007; Natural Standard, 2005). Benefits of deep tissue massage

are; loosens tight muscles, increases the range of motion, breaks down scar tissue and adhesions, and reduces pain (Donkin, 2009).

Techniques of massage

A variety of massage techniques have been used to achieve some benefit including calming of the patients and promoting generalized well-being. Massage therapy can be administered in various ways or techniques, such as petrissage or kneading, and effleurage (Taylor as cited in Bilhult et al., 2007), friction, tapotement and vibration (Hoyme, 2006; Seers, 2010; Ostrom, 2000). These can be applied to the whole of the body, such as at the feet, the arms, the chest, the abdomen, the back, the head or the face. In general, massage therapy involves the application of combinations of specialized strokes, rubs, and pressures applied in varying intensity to the soft tissues of the body, and are tailored to the patient's particular situation (Corbin, 2005). Based on the purpose of massage and considering the clinical advantages of massage techniques, effleurage or soft stroking will be used in this study. A previous study also reported that patients with cancer feel more comfortable receiving this technique compared with other techniques (Bilhult et al., 2007). A summary of classical massage techniques can be seen in table 7.

Table 7

Summary of Classical Massage Techniques

Technique	Definition	Application	Suggested clinical advantage
Effleurage / Gliding /Stroking	Light friction. Gliding or sliding movement over the skin with a smooth continuous motion (1, 2)	Beginning of a session, during a break after applying a specific technique, and the end of each session (3) The main technique is for spreading oil (1) Performed in four different ways; with the palm of one hand, with the palms of both hands, with the thumb, with the tips of the fingers (2)	Stimulate the parasympathetic nervous system and evoke the relaxation response (3) Enhances venous return (3)
Petrissag/ Kneading/ Milking	Lifting, wringing, or squeezing of soft tissues in a kneading motion, or pressing or rolling of the tissues under or between the hands to enhance deeper circulation (1, 3)	Following effleurage (3) Different kinds of Petrissage; with the two thumbs, with the thumb and fingers, and with the two hands (2) A compression movement using kneading, pressing, twisting, and squeezing muscle tissue (1)	Mobilize deep muscle tissue or the skin and subcutaneous tissue. Assists venous return Increases circulation with clearing out toxins from muscle and nerve tissue (1, 3)
Friction/ Rubbing	Deep form of effleurage applied through the fingertips (1, 3)	The motion is circular, applying direct pressure, a fast back and forth movement or slow or deep gliding over muscles (1) Given in three different ways; with the thumb, with the tips of the fingers, with the one hand (2)	Assists in realigning scar tissue Relaxes muscles by stimulating Golgi tendon reflex Treats muscle spasm or breaks up adhesions from old injuries

(*table continues*)

Table 7 (*continued*)

Technique	Definition	Application	Suggested clinical advantage
		Used for a specific purpose such as to reduce muscle spasm (3)	
Vibration/ Shaking/ Jostling	Vibration of the skin (4)	Hands move back and forth on the body without breaking contact. A continuous trembling, pressing movement made with the hands or fingers (1)	Boosts circulation and increases the power of the muscles to contract (1)
Tapotement/ Percussion	Various parts of the hand striking the tissues at a fairly rapid rate (3)	Make a loose fist, keep wrists relaxed, and uses quick movements, alternating hands (1) Finishing a section of the body (3)	Stimulates the tissues either by direct mechanical force or by reflex action (3) Relaxation of hypertonic muscles and loosens mucus in thoracic cavity (1)

Note: Numbering refers to the statement of researcher (s) to the classical massage techniques (definition, application and suggested clinical advantage) "(1)= Hoyme, R. J., 2006; (2) = Ostrom, K. W., 2000; (3) = Weerapong, P., Hume, P. A., Kolt, G. S., 2006; (4) = Seers, H., & CAM-Cancer Consortium., 2010".

Massage lubrication

Many type of lubrication are used in massage therapy, including lotion, oils etc. Natural oil is one type of oil that can be used as a lubrication for massage therapy. There are many types of natural oils that can be used as a lubricant for massaging including fractionated coconut oil, grape seed oil, olive oil, almond oil, macadamia oil, sesame oil, pecan oil, and mustard oil (Reilly, 2002). In addition, each oil has different properties and purposes.

1. Olive oil

Olive Oil (olea europeaea), native to the Mediterranean, has been used for centuries for cooking and skincare. Considering olive oil has a natural fragrance and is described as a heaviness oil, it is better diluting it with a lighter oil. Olive oil is great, however, as a first massage oil for newborns and infants (Reilly, 2002).

2. Coconut oil

Coconut oil is a colorless to pale brownish yellow oil and has a natural fragrance with a melting point ranging from 23^0 to 26^0 C (Krishna, Raj, Bhatnagar, Kumar & Chandrashekar, 2010). Coconut oil is expeller pressed from the fleshy part of the coconut. It often comes 'refined' meaning that it has been further processed to remove impurities (Reilly, 2002). Coconut oil has been used for centuries to help heal and protect the skin (Rethinam; Krishna et al., 2010).

Ayurvedic medicine states that coconut oil could nourish the body and increase strength, while the application of coconut oil on the skin can help the fixation of vitamin D in the body. Different preparations of coconut oil are also used to protect the skin from bacterial, protozoa and other infections in the body (Rethinam). Coconut oil has a natural creamy texture, comes from a vegetable source and can be applied topically or internally. Virgin coconut oil is fractionated coconut oil that can be used to protect the skin from bacterial and viral infections (Reilly, 2002; Krishna et al., 2010).

Coconut oil is an excellent massage oil for the skin as well. It acts as an effective moisturizer on all types of skins including dry skin. The benefit of

coconut oil on the skin is comparable to that of mineral oil. Furthermore, unlike mineral oil, there is no chance of having any adverse side effects on the skin with the application of coconut oil. Coconut oil, therefore, is a safe solution for preventing dryness and flaking of the skin (Rethinam). As cited in Hawthorn (1995), essential oils with different fragrances may be pleasant or they could worsen the nausea. Considering this problem, then, virgin coconut oil will be used in this study, since it is safe and odor free. In addition, this oil is safe to use on patients with sensitive skin (Reilly, 2002).

Balinese massage and tradition

Western society tends to think of healing in terms of medical, surgical, and other technological interventions. However, in many other cultures both past and present healing has been promoted by faith, magic, rituals, and other nonmedical approaches. It is important to remember that what is considered "alternative" to one culture may be viewed as "traditional" in another, for example, Traditional Chinese medicine and Ayurvedic medicine (DeLaune & Ladner, 2002).

Balinese medicine is a unique tradition whose origins stem from many Asian countries and has been uniquely integrated by the Balinese. It has strong parallels with African medicine, Tibetan medicine and Chinese medicine, as well as the Ayurvedic medicine of India. In Bali, many factors are thought to contribute to disease. In addition to emotional and physical disorders, Balinese medicine addresses attention to the invisible realms around us to deal with complex spiritual and psychological disorders (Arriaga, 2010).

A Balinese massage is a form of deep massage, and is designed to work almost every muscle in the body. A variety of techniques are used, including acupressure movements, such as press points and palm pressure, and standard massage techniques like sliding, long exploration, short exploration, and kneading. This style of massage combines influences from a number of different cultures, including China and India. In particular, it is often linked to Ayurveda, an Indian holistic medical system which emphasizes bringing the body into balance. One of the main goals of the Balinese massage is a relaxed state of mind; to accomplish this, the technique used is to knead or fold the skin to promote the flow of blood, oxygen, and energy throughout the body (BaliSpirit.com. 2010).

Massage is regarded as an important healing art on the island of Bali. Almost every family has one member who practices this art, and there are many professionals on the island. Many of them have received their knowledge from a parent or grandparent, while others have acquired their skills directly from the Hindu deities (Reynold, Balinese Massage). Passed down from mother to daughter for generations, Balinese massage has been a vital part of everyday life on the island for centuries. Women mix natural herbs and plants, incorporating them into massages in order to maintain the health of their families. Even babies receive daily massages after their baths to aid in muscle and bone formation, keep their skin supple, and induce sleep (BaliSpirit.com. 2010).

Modern medicine may prove through science to have better results in the treatment and diagnosis of illness. However, approaches of traditional healers and methods of healing within Bali are necessary in order to maintain the Balinese traditional concepts of self and being, and are therefore valuable regardless of

scientific evidence. Massage has been applied by Balinese people and used to enhance their own health based on experiences from their family. No research has been conducted related to the benefits of massages to reduce the symptoms from disease or treatment.

Effectiveness of Massage Therapy on Nausea, Vomiting, and Retching in Cancer Patients

Massage therapy is aligned with the wellness paradigm, and places importance on addressing the client's physical, psychological and emotional needs to maximize the patient's capacity to achieve mental and physical balance (Andersen, 2006). An essential element of massage therapy is an interactive and relatively egalitarian therapeutic relationship and the health outcomes are more closely associated with the wellness paradigm of complementary and alternative medicine (Andersen) rather than those associated with biomedicine (Smith, 2010).

Several reviews and overviews of scientific literature have attributed important benefits of massage including enhanced relaxation. Grealish et al. (2000) conducted the quasi-experimental study with 87 participants to examine the effectiveness of foot massage in cancer patients. Foot massage consists of slow, firm, or gentle strokes toward the heart from the base of the toes up the foot and lower leg to the knee. The result found that foot massage had a significant direct effect on the perception of nausea and an increase in relaxation when measured by a visual analogue scale. In one study, 39 women with breast cancer undergoing chemotherapy receiving a 20 minute massage on the foot/lower leg or hand/lower arm for five sessions, showed results that the massage significantly reduced nausea (Bilhult et al.,

2007). Another study that looked at patients receiving autologous bone marrow transplantation found that patients receiving one session of massage therapy on the shoulders, neck and head for 20 minutes had significant effects on relieving nausea (Ahles et al., 1999).

Foot massage has a powerful impact on the immune function. A recent Swedish study examined the immune function of a group of 30 middle-aged women with breast malignancies. They were undergoing radiation therapy at the time of the experiment. Half of the group began a complementary course of "light pressure" massage while the remainder acted as the control group. Blood and saliva samples, blood pressure and heart rates were measured before and after each massage session. The researchers discovered that the massage group maintained better immune function (natural killer cell activity) and showed a reduction in heart rate and systolic blood pressure (Billhult, Lindholm, Gunnarsson & Stener-Victorin, 2009). Several trials suggested that massage could reduce nausea in cancer patients at varying stages of the disease (Bilhult et al., 2007).

Contrary to other studies, Sturgeon et al. (2009) found that full body massage for 30 minutes per week for three consecutive weeks, has no significant reduction in nausea and vomiting. This may be caused by many factors, such as the use of antiemetic drugs for the treatment of breast cancer, introductory acupressure technique, or an adjustment for the treatment of breast cancer. NVR assessment should be considered as an ongoing process in breast cancer treatment. Thus, an additional exploration of the effects of massage therapy in NVR is needed.

Massage can be performed on various sites of the body with many kinds of techniques. Therapists can focus on just one body area (e.g. hand, foot or

back) or the full body using oil, lotion, or powder depending on the type of massage and personal preference (University of Texas MD Anderson Cancer Center, as cited in Reaves & McManis, 2010). For the techniques of a massage, the Swedish massage has been widely used with five basic movements or techniques including effleurage, petrissage, friction, tapotement and vibration. Based on voluntary testing in patients with cancer using effleurage massage, petrissage or kneading techniques, it was reported that many patients experienced petrissage or kneading as uncomfortable and heavy handed (Billhult et al., 2007). Therefore, they suggested that effleurage seems to be the best method and suitable for patients with cancer.

Foot massage has a significant effect on nausea and vomiting regardless whether it is conducted in different durations. There is no study explaining the ideal duration of massage therapy. In most studies, a massage was performed no longer than one hour. Grealish et al. (2000) stated that 10 minutes of a foot massage as a simple nursing intervention has remarkable effects on subjective symptoms such as nausea. Studies conducted on women with breast cancer undergoing chemotherapy (Billhult et al., 2007), and patients receiving autologous bone marrow transplantation (Ahles et al., 1999), found that 20 minutes of massage significantly reduced nausea. In another study, approximately 20 minutes in length for inpatients and 60 minutes for outpatients was reported to have decreased nausea by an average of 50% (Cassileth & Vickers, 2004). In a randomized control trial study of 120 patients with postoperative cancer who received a 10 - 30 minute massage, the massage had a significant effect on nausea with an improved score by 4.5 (SD ± 3.1) as compared to 2.1 (SD ± 3.1) in those without the intervention.

Some randomized studies among patients with cancer have been conducted by the University of Texas MD Anderson Cancer Center (2008). It was found that massage induced relaxation, reduced nausea, reduced pain and improved quality of life. A massage can vary from five minutes up to 45, 60 or 90 minutes. Finally, a massage can be conducted over various durations of time, ranging from ten minutes to 20, 30, 45, 60 and 90 minutes.

Another concern of massage therapy is about the session of the massage. A study found that patients receiving approximately three times of massage-per week reported a decrease of nausea (Cassileth & Vickers, 2004). Another investigator explained that massage significantly reduced nausea and vomiting, when it was conducted for five sessions (Billhult et al., 2007). Meanwhile, Ahles et al., (1999) suggested that one session of massage therapy had a significant effect on nausea and vomiting. Nevertheless, there are not enough research studies to support whether five sessions of massage is better than three sessions or one session.

The ideal duration and session of massage therapy is not known. Therefore, further investigation is needed to determine the appropriate frequency and length of the intervention in order to guide nurses in implementing massage therapy for patients with cervical cancer undergoing chemotherapy. In this study, the researcher will allot one session of foot massage therapy for 30 minutes in women with cervical cancer undergoing chemotherapy to assess acute nausea, vomiting and retching.

Safety and Contraindications of Massage Therapy

Although a massage can be provided for a number of reasons, some contraindications for massage therapy exist, such as, deep vein thrombosis or localised conditions such as skin injuries or burns (Sherman et al., 2005). However, many conditions previously considered contraindications (e.g., metastatic cancer) are no longer considered as such (Batavia, 2004), therefore, the common forms of massage, tailored appropriately, are considered very low risk (Ezzo et al., 2007: Lafferty, Downey, Mc- Carty, Standish & Patrick, 2006; Sherman et al., 2005).

A systematic review of the safety of massage therapy concluded that although massage is not entirely free of risk, serious adverse events are rare (Corbin, 2005; Ernst, 2003). The majority of adverse effects are associated with exotic types of manual massage or a massage delivered by a layperson. Thus, therapeutic massage should be performed by a licensed massage therapist or certified reflexologist. The patients who have undergone lymph node dissection, have metastatic disease in the lymph nodes, or have thromboses or emboli in the legs should not receive massage therapy in those areas (Lafferty et al., 2006). A concern that has been raised is the theory that massage may induce the spreading of cancer cells and the development of metastasis. However, there is no evidence to support that therapeutic massage interventions may have such effects, but direct pressure on a tumor site is usually discouraged in massage practice (Corbin, 2005).

To perform the massage therapy, there are two things that should be considered by the therapist. First, the massage should be used with caution for people with heart disease, diabetes, hypertension, or kidney disease because increased circulation in these conditions may be harmful. Conducting a massage for this patient

must be in consultation with a physician. Secondly, a massage should never be attempted in areas of circulatory abnormalities such as an aneurysm, varicose veins, necrosis, phlebitis, or thrombus or in areas of soft-tissue injury, open wounds, inflammation, joint or bone injury, dermatitis, recent surgery, or sciatica (DeLaune & Ladner, 2002).

Foot Massage Mechanisms to Relieve Nausea, Vomiting and Retching

The possible hypotheses relationships of massage and its effect on nausea, vomiting and retching are explained (Figure 4). This involves the mechanism of the autonomic nervous system (ANS). The ANS is comprised of two parts namely the parasympathetic and sympathetic. When a massage is performed, the parasympathetic part is activated, thus allowing the body to relax. However, when stressed, the sympathetic is activated, and the consequences are that the body will feel the urge to fight or flight. Massage therapy can result in blood vessel dilatation, an increase in skin temperature, and a decrease in heart rate and relaxation of mind and body. Underlying mechanisms of action have been hypothesized, including a reduced lactic acid build-up in muscles, a stimulation of healing of connective tissues, and an increase in lymphatic and venous circulation, but there is a lack of good research to support these ideas (Field as cited in Corbin, 2005).

Non-noxious somatosensory stimulation including massage-like stroking causes a release of oxytocin not only into the circulation but also into various brain areas, possibly including the vagal nerve and the nucleus of the solitary tract via oxytocinergic nerves emanating in the paraventricular nucleus (PVN) (Lund et al. as cited in Holst, Lund, Petersson & Uvnäs-Moberg, 2005). Therefore, the massage-like

stroking may influence vagal nerve activity via oxytocin, which has been shown to influence the release of gastrointestinal hormones and insulin by actions in the vagal nerve and the nucleus of the solitary tract. Oxytocin seems to have anxiolytic effects, causing relaxation, which in turn reduces the nausea. Massage-like stroking, in part via vagal activation of the endocrine system of the gut, may induce an optimised digestive process, promote nutrient assimilation, and anabolic metabolism. (Holst et al., 2005). Also in adults, gentle massage has been shown to decrease gastrin and cholecystokinin levels (Uvnäs-Moberg as cited in Holst et al., 2005).

Hernandez-Reif et al. (2000) stated that common physiologic effects of massage are decreased blood pressure, heart rate, and increased skin temperature. Relaxation can explain the effect of massage on nausea. Benson et al. (as cited in Billhult et al., 2007) described this phenomenon as a decrease in activity of the sympathetic nervous system in relaxed states. Central endocrine and neuroendocrine effects such as the increased release of oxytocin and decreased blood pressure can also account for the positive effects of massage (Hernandez-Reif et al., 2004).

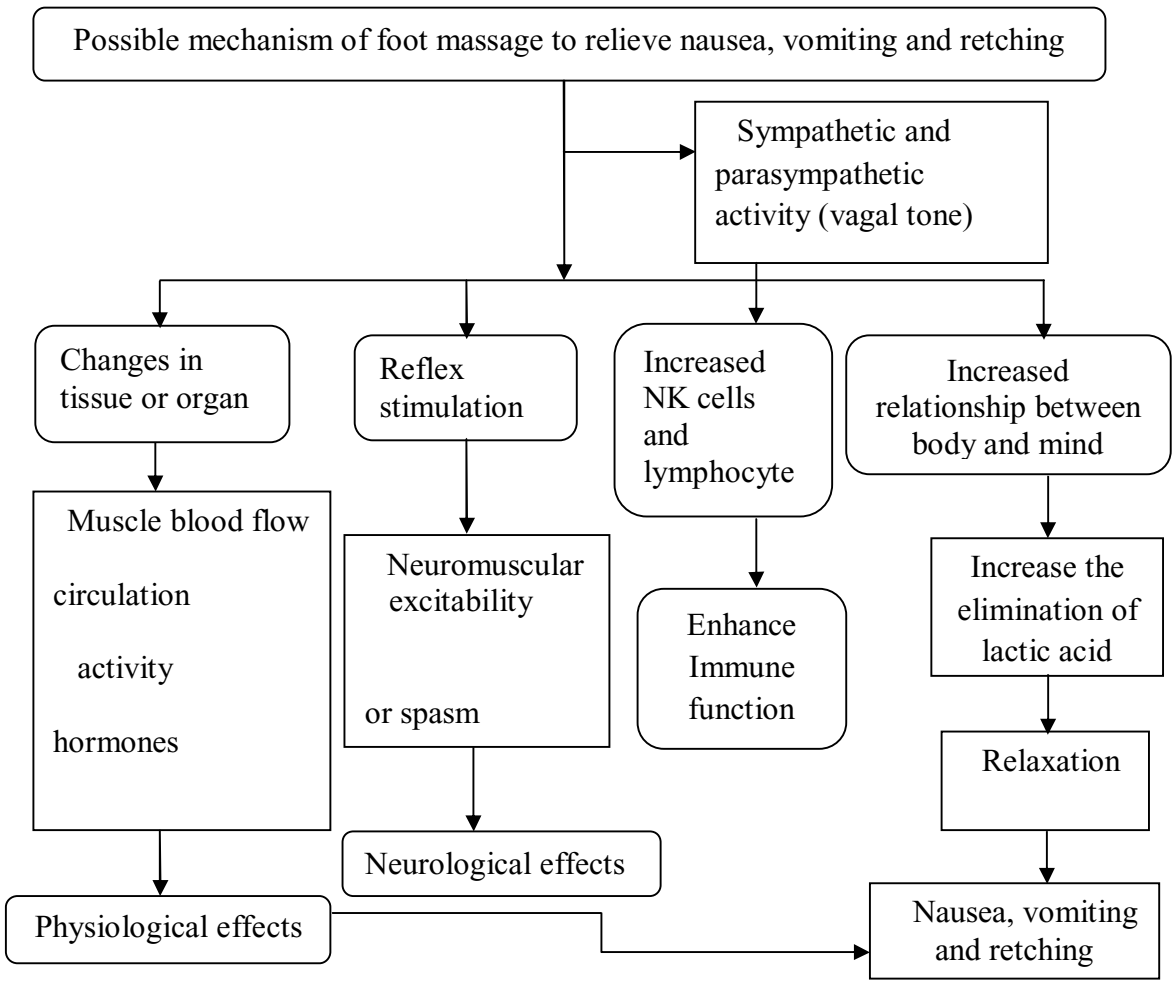


Figure 4. Possible Mechanism of Foot Massage Relieving Nausea, Vomiting and Retching

Overview of Foot Reflexology

Reflexology originated from ancient Chinese medical practice. It utilizes pressure points primarily on the soles of the feet to change the flow of energy or "chi" in the body (Arnold, 1998). Reflexology has been defined as “a Chinese and Indian system of diagnosis and treatment based on the belief that the whole body is represented on the foot (mostly on the soles of the feet), and that the internal organs can be stimulated by pressing particular areas of the foot (Gravett as cited in Ernst, 2010). Many ancient Chinese books reported the use of foot reflexology to treat

various bodily ailments. Dr. William Fitzgerald was appreciated to be the first western physician to investigate the reflex effects of pressure on the feet and hands after being taught the technique by native Americans in 1913 (Issel ac cited in Mak et al., 2007). He stated that in zone therapy, the body is divided into 10 longitudinal areas (zones). Stimulating one area in any particular zone would have an effect on other body parts within the same zone. However, although reflexology is primarily applied to the feet, it can also be applied to the hands and the ears (Botting, 1997).

Reflexology can identify the energy imbalances in the body through massage on reflexology points or 'terminals' in specific areas of the feet or the hands. It is performed using the thumb and the forefinger to apply pressure to the specific areas on the foot that are claimed to correspond to the internal organs, the glands and parts of the body (Botting, 1997). Reflexology aims to promote health and works by stimulating nerve endings in the feet, sending impulses via the spinal cord to other parts of the body. It promotes relaxation, improves circulation and may help with the disposal of waste products of tissue metabolism, particularly lactic acid (Lakasing & Lawrence, 2010).

Many practitioners of reflexology believe that medical conditions and disease arises from imbalances in energy. By correcting the energy balance through reflexology, practitioners believe it will improve the innate healing ability of the body (Wang et al., 2008). Some practitioners also believe that reflexology stimulates blood flow resulting in improved tissue perfusion and an improved sense of well-being. Other practitioners believe that reflexology stimulates the lymphatic system to release toxins or it stimulates the nervous system to improve energy (Mak et al., 2007). It has

also been suggested that reflexology may help release stress and tension, improve blood flow of the body and promote homeostasis (Botting, 1997).

A small RCT is demonstrated as a benefit for chemotherapy-related anxiety (Quattrin et al., 2006). Any beneficial effects of reflexology could be due to the purported effects on energy imbalances in the body or alternatively, they could be because reflexology enhances the relaxation response (Benson as cited in Sharp, 2010). It has been claimed that localized finger pressure on reflex points on the foot can influence the function of corresponding target organs to promote homeostasis, relaxation, and the healing response (Wang, 2008). Reflexology has been offered to patients with cancer in an attempt to improve the adverse physical and psychological symptoms associated with the illness or its treatments (Hodgson, 2000; Quattrin et al., 2006; Ross et al., 2002; Stephenson et al., 2000; Wright et al., 2002,). In addition, the human touch accompanied by reflexology offers care and attention for patients, and this psychological comforting has been reported as a primary benefit of reflexology (Gambles et al. as cited in Wang., 2008).

In conclusion, reflexology is a specialized type of foot massage, targeting specific areas of the foot that represent other parts of the body. It is believed that reflexology works by a combination of biomechanical and spiritual factors. Other effects of reflexology could be due to the additional social and physical contact the intervention entails (Frank et al. as cited in Sharp, 2010). Thus, integrating reflexology points with foot massage would enhance the result, as well as it involves an amount of physical and social contact.

Reflexology on foot massage

Massage and reflexology are often confused as similar modalities. There are several key differences between these modalities. Both involve the use of the hands to apply their techniques. However, reflexology uses small muscle movements applied to specific areas of the body (feet and hands), whereas massage uses large muscle movements and is often applied to the whole body (Hodson & Andersen, 2008). In reflexology, the pressure applied to the reflex points stimulates blood flow and nerve impulses, releases toxins and endorphins, and harmonizes physiologic function (Lakasing & Lawrence, 2010; Wang et al., 2008).

Foot reflexology is a form of foot massage that targets points on the foot believed to correspond to parts of the body. The principle of mapping zones of the feet was used in order to determine the area organs that are manipulated. Both feet represent the whole body. Before performing the massage, the mechanisms of nausea and vomiting should be known including the organ involved. By knowing the organ involved, the manipulation of reflex points to produce a desired effect can be determined. For example, if nausea was a problem, areas of the feet corresponding to the gastrointestinal are manipulated. Nausea is also reduced if the patients feel relaxed. Thus, the area corresponding to the solar plexus is manipulated as part of the relaxing techniques. Relaxation techniques can be provided through a massage technique that consists of a soft stroke or effleurage technique with back-and-forth movements of the palms on the patient's foot.

Summary

The literature review begins with the overview of cervical cancer. Cervical cancer is an important public health problem. It is a leading cause of death in Indonesia, even though current available treatments are effective, fast, and up to date. Cervical cancer can be treated with surgery, radiation therapy, chemotherapy and combinations of these treatments. However, these treatments have side effects, especially for chemotherapy that is widely used. Chemotherapy induces nausea, vomiting and retching depending on several factors. Two of these factors are gender and age, with female patients and younger patients being at greater risk. In addition, patients who have a high pretreatment expectation of nausea are more likely to have nausea after chemotherapy. Conversely, patients with a history of high alcohol consumption have a lower risk of chemotherapy-induced nausea and vomiting. In addition, treatment-related factors such as chemotherapy dose and emetogenicity are also relevant.

Although modern anti-emetic therapy have been developed, nausea, vomiting and retching (NVR) remains a significant problem in clinical practice, especially in patients on high levels of emetogenic. Chemotherapy-induced side effects disturb the treatment and substantially affect the patients' quality of life. The side effects includes bone marrow suppression, impaired nervous system function, increased susceptibility to infection, nephrotoxicity, mouth ulcers, hair loss, nausea, vomiting and retching. In addition, NVR is a physical and psychological distressing symptom for the patients receiving chemotherapy. These symptoms make the patients feel stressed, frustrated, and can disrupt the activities of daily living, it causes loss of time to work, increases anxiety and depression. Beyond their distressing effects,

severe NVR can lead to nutritional deficiencies, dehydration and electrolyte imbalance and fatigue. These consequences can interfere with adherence and continuity to the treatment regimens, as well as the patient's survival rate.

On the other hand, current recommendations for treatment of NVR also includes non-pharmacological interventions such as acupuncture, reflexology, massage, relaxation, etc. Use of non-pharmacological therapy should be determined by the patients' characteristics, clinical condition and considerations related to the interventions. Thus, the researcher reviews the complementary and alternative therapies in order to adjunct the pharmacological therapy. Among several non-pharmacological interventions, massage has been used for many years and has been shown to relieve nausea and relax hospitalized cancer patients.

Massage can activate the parasympathetic that results in blood vessel dilatation, an increase in skin temperature, decrease in heart rate and relaxation of the mind and body as well. Foot massage is a complementary therapy, given in addition to antiemetic drugs. Reflexology is a specialized foot massage, targeting specific areas of the foot that represent other parts of the body. Thus, the points of reflexology can be used to determine the area of massage. Foot massage is one way to convey feelings of care and comfort through the touch method as well as to allow nurses at the bedside to touch the patient in a not disturbing and non-threatening way. Touching, stroking and gentle massage may be a soothing and enjoyable experience. It is a therapeutic method that nurses can perform independently. This intervention is safe, simple and convenient. In addition, the foot is easily accessible and acceptable in different cultures.

The use of foot massage as a complementary method is recommended as a relatively simple nursing intervention for patients experiencing NVR or pain associated with cancer experience. A foot massage can promote body balance, increases circulating NK cells and lymphocytes, increases blood flow, and stimulates endorphin release. As a result, the patient will experience a positive emotion, which can reduce the factors causing nausea, vomiting and retching. Thus, the researcher is interested to integrate the reflex points of reflexology with foot massage in order to assess its effect on NVR in cervical cancer patients undergoing chemotherapy. Moreover, nurses play an important role in assessing the patients' problems, exploring patients' use of or interest in non-pharmacological interventions, educating patients, and advising patients to use evidence-based interventions rather than unproven interventions.

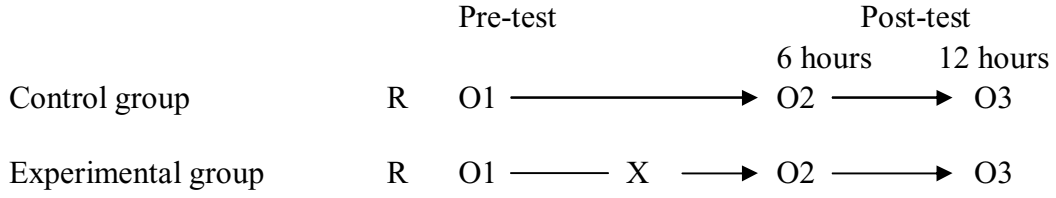
CHAPTER 3

RESEARCH METHODOLOGY

This chapter describes the design, variables, setting, population, and sample size estimation, inclusion criteria, sampling procedure, instrumentation, study protocol, ethical considerations and data analysis of the study.

Study Design

This research was a randomized controlled study using two-group and pre-test/post-test design. This study aimed to examine the effect of foot massage on scores of nausea, vomiting and retching in patients with cervical cancer undergoing chemotherapy. The research design is as follows:



R refers to randomization.

O1 refers to baseline data (pre-test score/T1) on nausea, vomiting and retching in women with cervical cancer prior to the treatment of chemotherapy.

X refers to foot massage intervention for reducing nausea, vomiting and retching in women with cervical cancer at two hours after chemotherapy.

O2 refers to the data on nausea, vomiting and retching at the sixth hour after the foot massage intervention (post-test score/T2).

O3 refers to the data on nausea, vomiting and retching at the twelfth hour after the foot massage intervention (post-test score/T3).

Variables

The independent variable in this study was the foot massage intervention and the dependent variables were nausea, vomiting and retching in women with cervical cancer undergoing chemotherapy. Some confounding variables which include age, stage of cancer and level of anxiety were controlled through the inclusion criteria. The researcher used a simple randomization by tossing a coin to assign the subject into the experimental group or the control group to control other factors that may occur unexpectedly.

Setting

The study was conducted in a gynecology ward, of a tertiary and referral hospital in the eastern part of Indonesia. This hospital is also an educational hospital, which enables multidisciplinary students to practice in the hospital. It has received a number of cancer patients undergoing chemotherapy in Bali, East Nusa Tenggara and West Nusa Tenggara. From June until December 2010, the number of gynecological cancer patients undergoing chemotherapy ranged from 26-35 patients for one month, both for new cases and repeated cases.

The gynecological ward is one of the wards in Sanglah Hospital which treats patients with gynecological problems. The gynecological ward is third class care that consists of 6-8 beds, separated by a curtain from each other. This ward

facilitates the poor patients, in order to obtain health care at a low cost or the patients who use health insurance for poor people (*ASKESKIN*).

General information of chemotherapy procedures

The patients usually start their follow-up treatment by having a blood examination and meeting with their doctors at the out patients department. After being confirmed for chemotherapy treatment, patients are admitted to the gynecological ward and prescribed the medication. The eligible patients for undergoing chemotherapy are directly started on their medication. Meanwhile, patients in a poor general condition must be hospitalized in order to improve their general condition for the requirement of chemotherapy. Generally, chemotherapy is started in the morning.

The eligible patients receive chemotherapy specially prepared by the doctor on duty on the gynecological ward. They receive antiemetic drugs 30 minutes before having chemotherapy and the administration of chemotherapy drugs takes about three hours. Each patient receives the treatment in their bed. Vital signs and abnormal symptoms are monitored before, during and after chemotherapy. After completing the chemotherapy treatment, if no abnormal symptoms are present, the doctor allows the patients to be discharged. Meanwhile, the patients who show abnormal symptoms are given an extended hospital stay to receive further treatment.

Information for chemotherapy treatment

In this study setting, two combinations of chemotherapy are given to the patients with cervical cancer, namely Paxus (Paclitaxel)-Cisplatin and BOMP (Bleomycin-Oncovin/Vincristine-Mitomycin-Cisplatin) (Table 8). The drug

combinations are determined by the examination and consideration of the patient's condition. In the gynecology ward, chemotherapy is given pursuant to the technical guidelines and procedure that has been standardized at this hospital.

Table 8

Chemotherapy Protocol

Paxus (Paclitaxel) - Cisplatin (4-5 series interval 21 days)	
Day 1	Premedication • Dexamethasone 20mg IV, 30 minutes before Paxus • DHBP (Dehidrobenzoperidol) 50mg IV, 30-60 minutes before Paxus • Cimetidine 300mg IV 30-60 minutes before Paxus • Paxus 30mg/100ml NaCl 0,5% (finished in 3 hours)
Day 2	Continued with Cisplatin • Rehydration 1000cc D5% in 5 hours • Furosemide 1 ampoule IV • B6 (Pyridoxin HCl) 200mg (2 ampoule) in 20cc aqua, IV slowly • Cisplatin 60mg/500cc D5% in 2-3 hours • Hydration 1000cc D5%
BOMP (4-5 series, @ 7 days interval 2-3 weeks)	
Day 1	• B6 (Pyridoxin HCl) 200mg (diluted with 20cc aqua, IV slowly) • Metoclopramide (Primperan) 1 ampoule IV • Dexamethason 1 ampoule IV • Oncovin/vincristine 2mg IV (dilute with 200cc aqua)→three hours • Bleomycin 15mg/D5% 500cc using micro drip IV: 12 drop per minute (for 12 hours)
Day 2	• B6 (Pyridoxin HCl) 200mg (diluted with 20cc aqua, IV slowly) • Metoclopramide (Primperan) 1 ampoule IV • Dexamethason 1 ampoule IV • Bleomycin 15mg/D5% 500cc using micro drip IV: 12 drop per minute (for 12 hours)

(table continues)

Table 8 (*continued*)

Day 3	• B6 (Pyridoxin HCl) 200mg (diluted with 20cc aqua, IV slowly) • Mitomycin 10mg in 20cc aqua IV
Day 4	• Rehydration 1000cc NaCl 0,9% → (rest 100cc + Vomceran/Cedantron 1 ampoule) • Furusemid 1 ampoule IV • D5% + 50 mg Cisplatin → drip three hours (Dose cisplatin in accordance with BW/BH) • Rehydration 500cc NaCl 0, 9% then, 500cc rest just dripping.

Note: IV = Intravenous; NaCl = Sodium Chloride; D5% = Dextrose 5%; BW = Body Weight; BH = Body Height. Adapted from "Technical guidelines and procedures of division/SMF Obstetrics and Gynecology (2003), Faculty of Medicine, Udayana University / Sanglah Hospital in Denpasar, Bali."

Population and Sample

The patients who have been diagnosed with cervical cancer and have received chemotherapy were included as the population in this study. Finally, sixty six women with cervical cancer undergoing chemotherapy that meet the inclusion criteria and agreed to participate were recruited as subjects in this study.

Sample size estimation

A previous study by Billhult, Bergbom and Stener-Victorin (2007) used massage to reduce nausea and anxiety in breast cancer patients with 30 subjects. According to Cohen's (1988) Table 2.4.2 on page 56, the necessary sample size value for significant criteria of a_1=.05 with power = .80 and effect size (*d*) = .73 was determined to be a minimum of 33 subjects per group.

Inclusion criteria

The patients who participated in this study meet with the inclusion criteria as follows:

1. 30 years old or above
2. In cycle 2 and 3 of chemotherapy treatment
3. Patients with cervical cancer stage II and III receiving chemotherapy Paxus-Cisplatin only
4. Having nausea/vomiting in their previous cycle
5. Levels of anxiety is mild to moderate
6. No evidence of Deep Vein Thrombosis diagnosed by the primary physician
7. No uncontrolled hypertension
8. Willing to participate in the study
9. No current chronic psychiatric condition.

Exclusion criteria

The subjects excluded from this study were those who were having contraindications to foot massage therapy particularly active skin rash.

Sampling technique

The nurse in the study setting approached the potential subjects who met the inclusion criteria to ascertain their interest in the study and introduce the researcher to them. Next, the researcher gave an explanation of the purpose of the study and all information related to the procedures including informed consent (Appendix A). Subjects who agreed to participate and signed an informed consent form were assigned to either the experimental group or the control group using simple random sampling by tossing a coin.

Experimentation

Foot massage was used in this study. The foot massage protocol was developed from a review of related literature. The protocol of foot massage contains information regarding foot massage therapy including a brief definition, the benefit and contraindication of massage, continued to the preparation phase, and the procedure in giving a foot massage (Appendix B). The foot massage protocol was evaluated and confirmed by an expert prior to its implementation. The evaluation of the foot massage protocol consists of the technique of foot massage, reflex points that are manipulated, and the skill of the researcher.

The foot massage was conducted at the patient's bed on the second day of chemotherapy and was performed two (2) hours after chemotherapy administration. Prior to the massage, the foot was soaked for five (5) minutes in warm water. Effleurage/ soft stroke techniques were used for 30 minutes (15 minutes for each foot), using natural oil (coconut oil). The foot was wrapped after all steps of the foot massage were completely performed. The foot massage ended with some stretching techniques and cleaning off the excessive oil.

Instrumentation

The instruments used in this study consist of the instrument for collecting background data and the instrument for assessing nausea, vomiting and retching. The instruments for collecting background data were the Personal Related Characteristic Questionnaire (PRCQ) and the Visual Analogue Scale (VAS). The instrument for assessing nausea, vomiting and retching was the Index Nausea

Vomiting and Retching (INVR). The descriptions of each instrument and the validity and reliability of the instruments are presented as follows.

Instruments for collecting background data

The Personal Health Related Characteristic Questionnaire (PHRCQ). The Personal Health Related Characteristic Questionnaire comprises of thirteen questions related to demographic information and health related information developed by the researcher. This questionnaire consists of dichotomous (yes/no) statements, multiple-choice questions, and the short answer questions (Appendix D). This questionnaire comprises of two sections. The first section consists of questions on general demographic characteristics which include age, marital status, religion, level of education, and occupation. The second section contains questions on general health including experience in motion sickness, experience of alcohol consumption, expectation of nausea, experience of receiving foot massage therapy, experience of receiving complementary therapy, serial of chemotherapy treatment, co-morbid diseases and level of anxiety. These data were collected by the researcher or an assistant from the patients' medical record or by interview.

Instrument for assessing level of anxiety: Visual Analogue Scale (VAS). The researcher used the Visual Analog Scale (VAS) in order to assess the level of anxiety. VAS is a horizontal line, 100 mm in length and patients mark on the line the point that represents their current anxiety (Appendix E). The VAS score was determined by measuring in millimeters from the left hand end of the line to the point that the patient marks. The result is reported on the Personal Health Related

Characteristic Questionnaire as a five-point Likert scale, where "0" refers to no anxiety, "1-25" refers to mild anxiety, "26-50" refers to moderate anxiety, "51-75" refers to severe anxiety, and "76-100" refers to worst level of anxiety (Billhult, Bergbom & Stener-Victorin, 2007). In addition, in order to avoid visual disabilities accompanying a patient's condition, VAS was presented in a larger format. However, the result of this symptom is not the main purposes of this study.

*Instrument for assessing nausea, vomiting and retching: the Index of Nausea, Vomiting and Retching (INVR)***.**

The Index of Nausea, Vomiting and Retching (INVR) is a new version of INV-2 developed by Rhodes that was revised in 1996. A prior study has demonstrated excellent internal consistency reliability of the INVR, with a Cronbach's alpha of .98, and good concurrent validity with the INV-2 form (the original form of the scale), with a correlation coefficient of .87 (Rhodes & McDaniel, 1999).

In the original INVR, nausea, vomiting and retching were stated as "nauseated or sickness at stomach", "threw up or vomiting", and "retching or dry heaves", respectively. Kim et al. (2007) replaced these phrases with nausea, vomiting and retching. They defined nausea as the desire to vomit without indulging in expulsive muscular movements. Vomiting was defined as the oral expulsion of gastrointestinal contents, while retching was defined as the attempt to vomit without expelling any material. In this study, the researcher used the phrases nausea, vomiting and retching, because it was a simpler explaination.

The INVR is an eight-item scale measuring nausea, vomiting and retching (NVR) experience. Each item was measured on a five-point Likert scale, and subjects were asked to report their symptoms over the past 12 hours (Appendix F). Positive events of NVR within 6 hours after chemotherapy were designated as early NVR, while positive events of NVR between 6 and 24 hours after chemotherapy were designated as late NVR (Kim et al., 2007). In order to score the INVR, each item was assigned a number based on a predefined scoring algorithm. A numeric value to each response ranged from 0, the least amount of distress, to 4, the most/worst distress. The total symptom experience from nausea, vomiting and retching was calculated by summing the patient's responses to each of the 8 items on the INVR. The potential range of scores was from a low of 0 to a maximum score of 32. The score of 0 indicated none NVR, 1-8 indicated mild NVR, 9-16 indicated moderate NVR, 17-24 indicated severe NVR, and 24-32 indicated the worst levels of NVR (Rhodhes & McDaniel, 2001).

Validity and reliability of the instrument

Validity

Back translation activities were done by three expert bilingual translators. After the back translation, the Indonesian version of the INVR was tested for face validity with 20 patients undergoing chemotherapy in the pilot study.

Two experts from the Faculty of Nursing and one expert from the Faculty of Medicine, Prince of Songkla University examined the protocol of foot massage including the reflex points on the foot, the technique of foot massage and the skill of the researcher. The protocol of massage was tested with three cancer patients

undergoing chemotherapy at the Songklanagarind Hospital under the supervision of three experts.

Reliability

The INVR was tested for the internal consistency reliability and stability. Twenty patients with cancer undergoing chemotherapy were recruited for assessing the internal consistency and stability of INVR in the pilot study. The result of Cronbach's alpha of the INVR was .79. Meanwhile, the acceptable/reliable coefficient alpha for existing tool is .80 (Polit & Back, 2008). Since the INVR was translated into the Indonesian version, thus the internal consistency with Cronbach's alpha of .79 was reliable.

To determine the stability of the INVR, the test retest procedure was used. The second measurement of the INVR was done two hours after the first. The test-retest reliability was evaluated by using intraclass correlation coefficients (ICC) between the scores that were obtained twice. Finally, from the pilot testing (N = 20) the stability of INVR was proved with an ICC value of .82.

Translation of instrument

The instrument including the PRCQ and INVR were initially developed in English. In order to ensure equivalent versions of these instruments in the Indonesian language, the researcher used the back-translation technique. The first bilingual expert (English-Indonesian) translated the original English version to Indonesian language. The second bilingual expert (Indonesian-English) translated the Indonesian version to English language. Then, the third bilingual expert compared both the English and Indonesian versions (original and back translation) to identify if there were any discrepancies, and discussed further with the researcher and the

previous two bilingual experts to solve any discrepancies. There was no any discrepancy in meaning in the INVR after being back translated, however, there were two items of INVR translated by the translators that differed in meaning.

In the discussion with the translators, it was identified that there were discrepancies related to translating of the word “threw up and vomiting” and “distress”. In Indonesian language, there is no different word used for threw up and vomiting. In fact, Indonesian speaking people often use the word “*muntah*” for these two words. For the word “distress” the two translators used the word “*stres*”. The Indonesian word "*stres*" mostly refers to psychological or psychiatric problems, therefore the third translator considered using another word. After discussing, the two translators and the researcher agreed to use the word “muntah” for the word “threw up and vomiting” and “menderita or tertekan” for the word “distress”.

Pilot Study

A pilot study is the best way to assess the feasibility of a large study. Pilot studies should be well designed with clear feasibility objectives, clear analytic plans, and explicit criteria for determining success of feasibility (Thabane et al., 2010). Conducting a pilot study prior to a large study can increase the likelihood of success of the main study and potentially help to avoid any failure in the large study. A pilot study was conducted in the gynecological ward at Sanglah Central Hospital. The number of subjects in the pilot study was three subjects. The patients recruited in the pilot study were excluded from the sample of the main study.

Data Collection Procedures

Data collection was conducted on the gynecological ward of Sanglah Hospital Centre in Bali, Indonesia. The steps taken in the data collection methods and procedures are as follows:

Preparation phase

The preparation phase consisted of the following steps: (1) Training program of massage for the researcher, (2) obtaining study approval from the Ethics Committee Faculty of Nursing, Prince of Songkla University, (3) acquiring official permission for data collection from the director of the hospital, (4) informing the head of nurse and staff in the gynecological ward about the objective of the study (5) recruiting and training one research assistant, (6) preparing data collection package including consent form, (7) conducting a pilot project and instrument testing.

Researcher preparation

For the preparation of this study, the researcher attended an 18-hour training program of foot massage, which includes both theory and practice lessons at the Thai Traditional Medicine of Songkhla School at 161/1 Ramwithee Road, Amphur Muang, Songkhla Thailand, under the supervision of Ajarn Lim Ruckthong who has been certified as a foot massager. At the end, the researcher received a certificate of completion of the program. To enhance the skills learned, the researcher practiced foot massage therapy under the supervision of a co-advisor, Assoc. Prof. Dr. Wimonrat Chongcharoen**,** who is an expert on massage and reflexology from the Faculty of Nursing, Prince of Songkla University, Thailand.

Research assistant

The researcher selected a research assistant under the following criteria: (1) has completed at least a bachelor degree in nursing, (2) has experience in caring for patients with chemotherapy and (3) has not been working at the same ward. In the training session, the research assistant received the information related to the process of this study, including detailed information about data collection, and the assessment of nausea, vomiting and retching. The researcher discussed the definitions of nausea, vomiting and retching and trained the assistant in how to use index nausea, vomiting and retching including using the visual analog scale in assessing levels of anxiety. The researcher also provided a case to make clear the terms of nausea and retching. The research assistant collected the data through interviews and the patient's medical records for both groups. The research assistant was blinded for the subjects being in either the experimental or the control group to prevent bias during data collection.

The research assistant read each item verbatim to the patient who had vision problems, or was not able to read and write. Furthermore, the patient was the one who provided the answers when the assistant researcher read the questionnaire. There was no “coercion” to force the answers.

Implementation phase

Every day, the researcher and the research assistant arrived at the hospital and obtained permission from the head nurse. Then, the potential patients who met the inclusion criteria were firstly approached by their nurse and were ascertained for their interest to participate. The nurse left the patients in order to

provide the opportunity for them to think about this study for at least 30 minutes. After obtaining informed consent, the researcher explained the purpose of the study to each potential subject. The details of the information of the research information sheet can be seen in appendix A. Next, the researcher assigned the subject randomly either to the experimental group or to the control group by tossing a coin.

The research assistant collected the data form in several steps in both groups. The illustration of the data collections is as follows; on the second day of chemotherapy, the Personal Health Related Characteristic Questionnaire including anxiety levels were assessed 15 minutes prior to the intervention. Subjects also completed the INVR questionnaire as a baseline data of nausea, vomiting and retching (T1). For the post-test data, nausea, vomiting and retching were observed at two-time periods in both groups, at the sixth hour after administering chemotherapy (T2) and at the twelfth hour after administering chemotherapy (T3) by using INVR. The detailed information of the data collection procedure can be seen in Figure 5.

For the experimental group, each subject was instructed to soak her feet for five minutes and lie down on the bed while the foot massage procedure was conducted. The environment was modified to enhance the study, by closing the curtains and providing a comfortable position for the subject. The foot massage was provided for 30 minutes (15 minutes for each foot), two hours after administering chemotherapy. For the control group, the foot massage intervention was not provided to the subjects, but they were provided the usual activities without the intervention or environment manipulation. For the subjects in the control group who were interested in a foot massage, a foot massage was provided after the completion of the study. In

addition, all subjects in the control group received the brochure of the foot massage protocol.

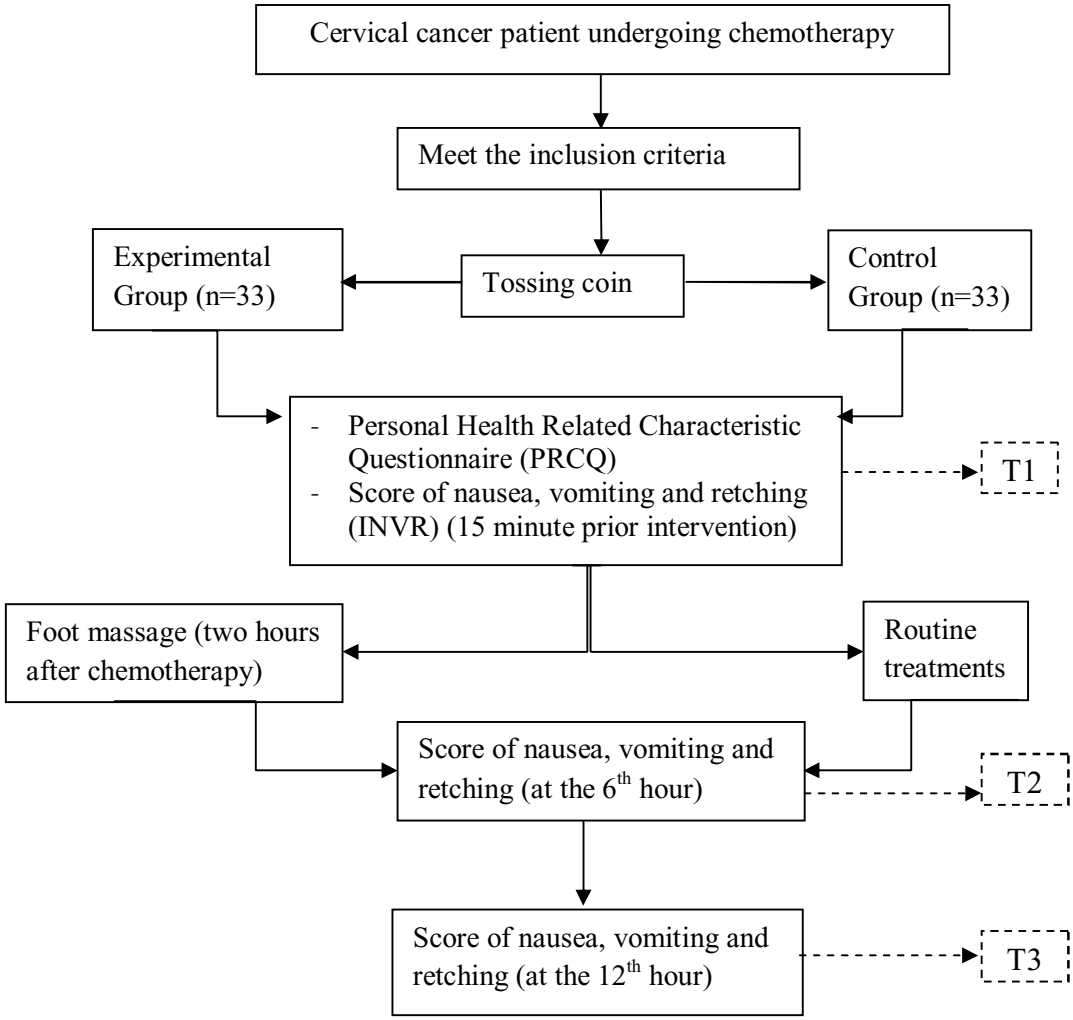


Figure 5. Foot massage procedure in cervical cancer patients undergoing chemotherapy.

T1 = Score of nausea, vomiting and retching prior intervention; T2 = Score of nausea, vomiting and retching 6 hours after intervention; T3 = Score of nausea, vomiting and retching 12 hours after intervention

Data Analysis

The descriptive analysis was used to analyze personal data using frequency, percentage, mean and standard deviation. The mean and standard deviation was used to analyze the mean score of nausea, vomiting and retching before and after the intervention for both the experimental group and the control group. The following data was calculated using descriptive statistics; age, marital status, religion, educational level, occupation, stage of cancer, serial of chemotherapy treatment, expectation of nausea, experience of receiving foot massage therapy, and co-morbidity disease. The Chi-square test was used to determine the significance of the demographic information and health related information of the subjects in the experimental and the control group. In addition, Fisher's exact test and Continuity correction were used as alternative statistics to undertake the analysis of two-by-two contingency tables when expected frequencies were too small.

The assumptions of normality and homogeneity of variance for inferential statistic variables were checked before the appropriate statistical analysis was performed. The researcher used the Independent *t*-test to detect the significant differences at the baseline data for nausea, vomiting and retching (NVR). In addition, Independent *t*-test was also used for the hypothesis testing of the NVR score differences between the experimental and the control group. For the hypothesis testing of NVR score differences within the group before and after receiving the intervention, the researcher used the dependent *t*-test (paired *t*-test). Meanwhile, repeated measures ANOVA was used to detect the significant difference of nausea, vomiting and retching scores within the group at three time periods. The level of significance was set at $p < .05$ for NVR score comparison.

Ethical Consideration

This study was approved by the Ethics Committee of Faculty of Nursing, Prince of Songkla University, Thailand and was also granted for ethical clearance by the Research and Development Division, Sanglah Hospital Centre, Bali - Indonesia. Furthermore, the researcher met the head nurse of the study setting and staff to explain the purpose of the study.

Patients who agreed to participate in this research were informed that they would be assigned into either the experimental group or the control group. The subjects received all information relating to the procedures for this research. They were told that their identities would be kept secret. All the data were stored in a confidential manner and destroyed after the completion of the study. They can ask questions about this study and have the right to withdraw from the study at any time. The subject could communicate with the researcher when the researcher gave the explanation about informed consent. They were told that there is minimal risk involved. For maintaining ethical issues regarding equity, the control group was given massage instructions after the completion of the study.

CHAPTER 4

RESULTS AND DISCUSSION

This experimental study aims to investigate whether or not foot massage therapy can reduce nausea, vomiting, and retching (NVR) in patients with cervical cancer undergoing chemotherapy. This chapter presents and discusses the study findings. The results are presented in three main parts:

1. The demographic and health-related characteristics of the subjects.
2. Nausea, vomiting, and retching of patients with cervical cancer undergoing chemotherapy
3. The effects of foot massage on nausea, vomiting, and retching
   - 3.1 Within-subject effects
     - 3.1.1 Comparison of the NVR scores before and after foot massage
     - 3.1.2 Comparison of the NVR scores across times within the experimental group
   - 3.2 Between-subject effect

     Comparison of the NVR scores between the experimental group and the control group before and after foot massage

Results

1. Demographic and Health-related Characteristics

Sixty-six women with cervical cancer undergoing chemotherapy were recruited from the gynecological ward, Sanglah Hospital centre. The age ranged from 32 to 65 years old with the mean of each group as shown in Table 9. The majority of the subjects were married and Hindu. Only small number of subjects had no education. Nearly half (47%) of the subjects in the experimental group were farmers, whereas 45 % of the subjects in the control group were private employees. There were no statistically significant differences in the demographic characteristics of the subjects between the experimental and the control group ($p > .05$). The details of the demographic characteristics are presented in Table 9.

Table 9

Demographic Characteristics of Subjects in the Experimental Group and the Control Group (N = 66)

Characteristics	Experimental group (n=33)		Control group (n=33)		*Test statistics*	*p value*
	N	(%)	N	(%)		
Age	M (SD) = 46.6 (9.0)		M (SD) = 47.7 (10.4)		0.63[a]	.48
Marital status					0.57[c]	.71
Married	28	84.8	30	90.9		
Widowed	5	15.2	3	9.1		
Religion					2.55[c]	.11
Hindu	24	72.2	30	90.9		
Non-Hindu (Buddhist/Muslim)	9	27.3	3	9.1		
Educational level					3.42[c]	.31
Elementary school	15	45.5	20	60.6		

[a] Independent t-test, [b] Pearson Chi Square, [c] Fisher's Exact test

Characteristics	Experimental group (n=33)		Control group (n=33)		*Test statistics*	*p value*
	N	(%)	N	(%)		
Junior high school	10	30.3	6	18.2		
High school	6	18.2	7	21.2		
No education	2	6.1	0	0		
Occupation					5.12[b]	.08
Farmer	17	47.0	14	42.2		
Private employee	7	33.3	15	45.5		
Housewife	9	19.7	4	12.1		

[a] Independent t-test, [b] Pearson Chi-Square, [c] Fisher's Exact test

For health-related characteristics, Table 10 shows that nearly two-thirds of the subjects (61%) had no experience in motion sickness. Only 1 subject in the experimental group had a history of alcohol consumption. The majority of the subjects in both groups expected that they might have nausea. The majority of subjects in both groups had moderate levels of anxiety with the mean anxiety score as presented in Table 10. Only 1 subject in the control group had an experience of a foot massage and the majority of them had no experience of complementary therapies (88% in the experimental group and 79 % in the control group). For those who used complementary therapies, they reported the use of hot blankets, giok stones, spiritual therapy, and acupuncture. Serials of chemotherapy between the experimental and the control group were not significantly different. More than half of the subjects in both groups were in cycle 2. All subjects did not have co-morbid disease.

Table 10

Health-Related Characteristics of the Experimental Group and the Control group (N=66)

Characteristics	Experimental group (n=33)		Control group (n=33)		*Test statistics*	*p value*
	N	(%)	N	(%)		
Experience in motion sickness					0.00[c]	1.00
Yes	13	39.4	13	39.4		
No	20	60.6	20	60.6		
Experience of alcohol consumption					1.02[c]	1.00
Yes	1	3.0	0	0		
No	32	97.0	33	100		
Expectation of nausea					1.16[c]	.48
Yes	30	90.9	27	81.8		
No	3	9.1	6	18.8		
Anxiety score	M (SD) = 36.8 (9.1)		M (SD) = 34.2 (11.7)		-1.01[a]	.32
Anxiety level						
Mild (10-25)	2	6.1	8	24.2		
Moderate (26-50)	31	93.9	25	75.8		
Experience of receiving foot massage therapy					1.02[c]	1.00
Yes	0	0	1	3.0		
No	33	100	32	97.0		
Experience of receiving complementary therapy					0.98[c]	.51
Yes	4	12.1	7	21.2		
No	29	87.9	26	78.8		
Hot Blanket					1.02[c]	1.00
Yes	0	0	1	3.0		
No	33	100	32	97.0		
Giok stone therapy					0.22[c]	1.00

[a] Independent t-test, [b] Pearson Chi Square, [c] Fisher's Exact test

(table continues)

Table 10 *(continued)*

Characteristics	Experimental group (n=33)		Control group (n=33)		*Test statistics*	*p value*
	N	(%)	N	(%)		
Yes	2	6.1	3	9.1		
No	31	93.9	30	90.9		
Spiritual therapy					0.35[c]	1.00
Yes	2	6.1	1	3.0		
No	31	93.9	32	97.0		
Acupuncture					2.06[c]	.49
Yes	0	0	2	6.1		
No	33	100	31	93.9		
Cycle of Chemotherapy					0.00[c]	1.00
II	17	51.5	18	54.5		
III	16	48.5	15	45.5		

[a] Independent t-test, [b] Pearson Chi Square, [c] Fisher's Exact test

2. Nausea, Vomiting, and Retching of Patients with Cervical Cancer Undergoing Chemotherapy

Nausea, vomiting and retching of patients with cervical cancer undergoing chemotherapy can be explained through three dimensions; symptom experience, symptom occurrence and symptom distress.

The findings revealed that the total experience and total occurrence of NVR scores of the experimental group were at a moderate level with the mean scores of each group as shown in Table 11. Similarly, the total experience and total occurrence of NVR scores of the control group were also at a moderate level. Meanwhile, the total distress scores of NVR of the experimental group and the control group was at a mild level. However, this current study focused on the symptom experience of NVR only.

Table 11

Mean, Standard Deviation and Level of Symptom Experience, Symptom Occurrence and Symptom Distress of NVR of the Experimental Group and the Control Group (N = 66)

Subscales	Items on Scale	Potential Range of Scores	Experimental Group (n = 33)				Control Group (n = 33)			
			Min-Max scores	Mean	SD	Level	Min-Max scores	Mean	SD	Level
Symptom Experience										
Nausea experience	4, 5, 7	0-12	4-10	8.09	1.44		5-9	7.24	1.39	
Vomiting experience	1, 3, 6	0-12	0-6	2.94	2.42		0-6	1.94	2.33	
Retching experience	2, 8	0-8	0-3	.36	.82		0-3	.61	.93	
Total Experience Score		0-32	4-16	11.39	3.23	Moderate	5-16	9.79	0.07	Moderate
Symptom Occurrence										
Nausea occurrence	4, 7	0-8	4-8	6.33	1.08		4-7	5.73	1.13	
Vomiting occurrence	1, 6	0-8	0-4	2.12	1.73		0-4	1.33	1.56	
Retching occurrence	8	0-4	0-2	.18	.47		0-2	.36	.65	
Total Occurrence Score		0-20	4-12	8.64	2.15	Moderate	4-11	7.42	1.96	Moderate
Symptom Distress										
Nausea distress	5	0-4	0-2	1.76	.56		0-2	1.52	.62	
Vomiting distress	3	0-4	0-2	.82	.92		0-2	.61	.86	
Retching distress	2	0-4	0-2	.18	.53		0-2	.24	.56	
Total Distress Score		0-12	0-4	2.76	1.28	Mild	0-6	2.36	1.46	Mild

3. The Effects of Foot Massage on Nausea, Vomiting, and Retching

A foot massage was performed at two hours after chemotherapy administration. Data was collected three times; at the baseline: before starting the massage therapy (T1), at the sixth hour after chemotherapy (T2) and at the twelfth hour after chemotherapy (T3).

3.1 Within-subject effects

3.1.1 Comparison of the NVR scores before and after the foot massage

Hypothesis 1: The scores of nausea, vomiting, and retching of the experimental group after receiving foot massage therapy (T2 and T3) are lower than that of before receiving foot massage (T1).

Paired sample t-test was performed to detect the differences in the mean NVR scores between T1 and T2 (T1-T2), and between T1 and T3 (T1-T3) (Table 12). The findings revealed that the NVR score of the experimental group at T2 (M = 5.85, SD = 1.64) was significantly lower than that of T1 (M = 11.39, SD = 3.23) (t = 11.09, $p < .001$). Similarly, it was found that the NVR score at T3 (M = 7.48, SD = 1.82) was significantly lower than that of T1 (t = 9.67, $p < .001$). Therefore, hypothesis 1 was supported.

In addition, the NVR scores at T1, T2, and T3 of the control group were also compared. It was found that at the sixth hour (T2) and the twelfth hour (T3) of chemotherapy, subjects in the control group also had the NVR scores

significantly lower than that of T1 but the magnitude of the differences was smaller than that of the experimental group ($t = 2.47$, $p = .02$) (Table 12).

3.1.2 Comparison of the NVR scores across times within the experimental group

Hypothesis 2: At least one time, the scores of nausea, vomiting and retching of the experimental group after receiving foot massage therapy is lower than others.

The repeated measures ANOVA were performed to detect the differences of the mean scores at T1, T2 and T3 within the experimental and the control group (Table 13). The result indicated that the NVR scores of the experimental group were significantly different at three points of time (T1, T2 and T3) ($F_{(2, 64)} = 90.16$, $p < .001$). The lowest score of NVR was observed at T2. Not surprisingly, the within subject difference of the control group was also observed ($F_{(2, 64)} = 4.68$, $p = .02$).

Table 12

Comparison of the Mean Scores of Nausea, Vomiting, and Retching between T1-T2 and T1-T3 Using Paired t-Test (N = 66)

Variable	T1	T2	*t*	*p* value	T1	T3	*t*	*p* value
	M(SD)	M(SD)			M(SD)	M(SD)		
Experimental Group (n=33)	11.39(3.23)	5.83(1.64)	11.09	.00	11.39(3.23)	7.48(1.82)	9.67	.000
Control Group (n=33)	9.79(3.07)	8.85(2.93)	2.23	.03	9.79(3.07)	8.88(2.60)	2.47	.023

Table 13

Comparison of the Mean NVR Scores at T1, T2 and T3 Using Repeated Measures ANOVA

Within Group	Sum of Squares	df	Mean Square	F	*p*	Partial Eta Squared	Observed power
Experimental group (n=33)	535.82	2	267.91	90.16	.000	.74	1.00
Error	190.18	64					
Control group (n=33)	18.81	2	12.87	4.68[a]	.023	.13	.67
Error	128.53	64	2.75				

[a] Greenhouse-Geisser

3.2 Between-subject effect

Comparison of the NVR scores between the experimental group and the control group before and after foot massage

Hypothesis 3: The mean scores of nausea, vomiting and retching of the experimental group after receiving foot massage therapy (T2 and T3) are lower than those of the control group.

The result revealed that the NVR scores of the experimental group at T2 (M = 5.85, SD = 1.64) and T3 (M = 7.48, SD = 1.82) were significantly lower than those of the control group (t = 5.14, $p < .001$ and t = 2.32, p = .014, respectively). Evidently, it was found that the NVR score at T1 (M = 11.39, SD = 3.23) was significantly higher than that of the control group (t = -2,07, $p < .05$) (Table 14 and Figure 6). Since the baseline NVR scores between the groups were significantly different, the effect of foot massage therapy on NVR was examined by comparing the mean difference of the NVR scores of T1 to T2 and T1 to T3 for adjusting the effect of the baseline scores. In other words, the variables, $\bar{d}1$ and $\bar{d}2$, representing mean difference of T1-T2 and T1-T3, respectively, were constructed.

After controlling for the effect of the baseline NVR scores, the independent t-test was used to compare the difference of between the groups at T2 ($\bar{d}1$) and T3 ($\bar{d}2$). The results revealed that the mean difference scores at T2 and T3 of the subjects in the experimental group were significantly lower than those of the control group ($t = -7.04$, $p < .001$ and $t = -5.41$, $p < .001$), respectively (Table 15).

Table 14

The Mean and Standard Deviations between the Experimental Group and the Control on NVR Scores at Each Time Point (N=66)

NVR score	Experimental Group (n=33)	Control Group (n=33)	*t*	*p value*
	M (SD)	M (SD)		
Baseline (T1)	11.39 (3.23)	9.79 (3.07)	-2.07	.042
At 6th hour (T2)	5.85 (1.64)	8.85 (2.93)	5.14	.000
At 12th hour (T3)	7.48 (1.82)	8.88 (2.60)	2.32	.014

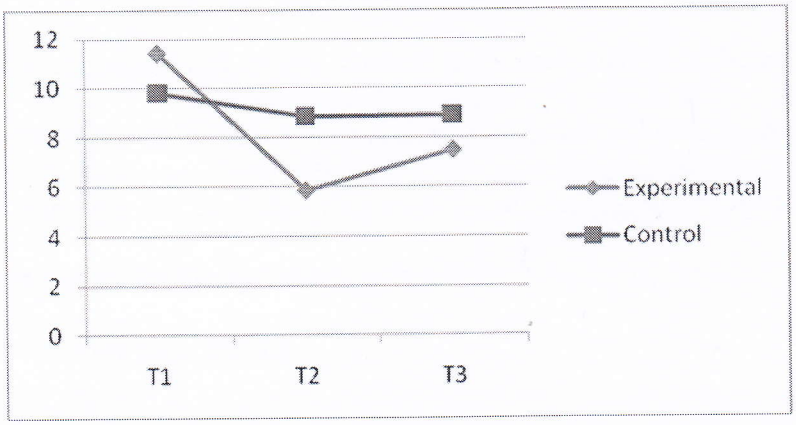


Figure 6. *Graph Depicting the NVR Scores of the Experimental Group and the Control Group at Baseline (T1), Sixth Hour after Chemotherapy (T2), and Twelfth Hour after Chemotherapy (T3)*

Table 15

Comparison of Mean Difference of NVR Scores at T2 ($\bar{d}1$) and T3 ($\bar{d}2$) between the Experimental Group and the Control Group Using Independent t-test (N=66)

Time	Experimental Group (n=33)	Control Group (n=33)	*t*	*p value*
	M (SD)	M (SD)		
T2 ($\bar{d}1$)	5.55 (2.87)	0.94 (2.42)	-7.04	.000
T3 ($\bar{d}2$)	3.91 (2.32)	0.91 (2.11)	-5.41	.000

Discussion

The findings are discussed and presented in three parts. The first part is about the characteristics of the subjects and individual risk factors that contribute to nausea, vomiting and retching. The second part is focused on the symptom experience of nausea, vomiting and retching of cervical cancer patients undergoing chemotherapy. The third part deals with the hypothesis of hypothesis testing of the effects of foot massage on nausea, vomiting and retching.

Characteristics of the subjects

The demographic characteristics of the subjects in this study are summarized in Table 9. All subjects met the inclusion criteria and were assigned to the experimental group and the control group by using coin tossing. Using coin tossing is the simplest way of randomization. Theoretically, a 50-percent chance was expected for each

individual subject to be selected in either the experimental group or the control group. Practically, this was not the case in this study. The first 61 subjects had an equal opportunity to be assigned to either group as planned. But for the last five cases, since the number of cases in the control group was already reached, the researcher decided to assign them into the experimental group without tossing the coin. This manner may induce bias unintentionally. Taking this into account all baseline characteristics of both groups were compared and revealed no significant differences. However, it is possible that there may be other unfold confounders. In addition, the chemotherapy regimen and antiemetic drugs were controlled for all subjects. Further discussion focused on individual risk factors that contribute to nausea, vomiting and retching.

In the current study, from 66 patients in the experimental group and the control group, a normal distribution of age was found with the mean age of 46.6 years old and 47.7 years old, respectively. The majority of subjects were in the young adult group (age 32-50). This is consistent with a previous study that mentions the increased incidence of cervical cancer is in the age range from 25 - 34 years old and showed a peak at age 45 - 54 years old in Indonesia (Aziz, 2001). As seen in many other countries, the age-specific prevalence of cervical cancer in Indonesia has two peaks, in the 40-49 year age group and in the group of women older than 60 years (Kooyman, 2006). There is no study found regarding the factors that contribute to age and the incident of cervical cancer. It might be related to hormonal levels, in which the rate of cell proliferation is influenced by hormones, such as estrogen and progesterone are higher in the reproductive

age and affects the persistence and prognosis of cervical cancer (DeLaune & Ladner, 2002).

The majority of the subjects in this study had low levels of education. Although there are difficulties in assessing socio-economical situations, knowing the education level of the patients can give some indication of their socio-economical status. Moreover, this study was conducted in lower class which is representative of a low economic level. From Aziz's study (2001) known that majority subjects had low education levels, either when viewed on whole stadium or on a particular stage of cervical cancer. The socio-economic and education factors may influence the delivery of vital cervical cancer prevention campaigns (Kooyman et al., 2006).

Meanwhile, in developed countries, the predicted incidence of cervical cancer has decreased because of the utilization of cervical cancer screening programs, but this is not the case in developing countries (Parkin et al., 2005). A lot of effort has been put into introducing the same screening programs in developing countries but, unfortunately, it often fails to be established. The reasons are the lack of funds to provide Pap smear screening nationwide, the lack of professional human resources and qualified laboratory services and the high numbers of patients lost to follow up (Kooyman et al., 2006).

Besides demographic characteristics, the risk for chemotherapy-induced nausea, vomiting and retching is affected by the chemotherapy agent's emetogenicity and individual characteristics (Grunberg & Ireland, 2005). Considering this effect, selecting one cancer type, cervical cancer in particular and that all subjects in the study had

received the same chemotherapy regimen have been controlled in this study. For individual characteristics, Feyer et al. (2005) proposed that the individual risk profiles according to patient-related emetogenic risk factors are gender, age, alcohol consumption, anxiety and previous experience of nausea, vomiting and retching. These factors were examined as follows.

This current study focused on female patients only. The mean age of the experimental group and the control group were 46.6 years (SD = 9.0) and 47.7 years (SD = 10.4), respectively, ranging from 32 to 65 years old in both groups. Additional analysis revealed that there was a negative relationship between age and NVR scores (r = -.33, p < .05, Appendix H1). It means that younger subjects (age 32-50 years old) reported significantly higher NVR scores at the baseline than that of older subjects (age 51-65 years old) (t = 2.76, p = .007, Appendix H2). This is similar to Watson et al.'s study (as cited in Aapro, Molassiotis & Olver, 2005). They found that young adult patients (< 50 years old) had higher NVR scores than older adult patients.

Patient factors are known to influence the risk of NVR in cancer patients. Experience of alcohol consumption also contributed to the occurrence of NVR. However, in this study, all subjects, except one (99%) had no experience in alcohol consumption. Therefore, it was not possible to further examine its relationship with the development of nausea, vomiting, and retching.

In addition, anxiety is a significant psychological predictor of chemotherapy-induced nausea, vomiting and retching. In the current study, the mean score of anxiety in the experimental group and the control group were 36.8 (SD = 9.1)

and 34.2 (SD = 11.7), respectively. The levels of anxiety of patients in both groups were at a moderate level (26-50). Additional analysis in this study also revealed that there was a positive relationship between anxiety and the NVR score ($r = .27$, $p < .05$, Appendix H1), subjects with higher anxiety scores reported significantly higher NVR scores at the baseline ($t = -2.41$, $p = .019$). Similar to Adrykowski & Gregg's study (as cited in Hawthorn, 1995), they found the state of anxiety is significantly related to both the severity and incident of nausea. Furthermore, anxiety can be exacerbated by a prior history of NVR associated with chemotherapy (Schnell, 2003).

Regarding the prior history of NVR, all subjects had experienced NVR on their previous cycle of chemotherapy in this study. Several studies proposed that previous chemotherapy-induced nausea and vomiting is a significant prognostic factor for developing nausea and vomiting (Feyer et al., 2005; Grunberg, 2004; Liau et al., 2005; Nevadunsky & Matulonis, 2009). Patients probably use their past experiences with NVR to form a prediction or response expectancy of nausea from their own upcoming chemotherapy (Roscoe et al., 2004). Thus, the findings indicated that the subjects in this study were at high risk in developing NVR.

Besides, the expectation was an important determinant of non-volitional outcomes (e.g. nausea) (Montgomery & Bovbjerg, 2003). In this study, the majority of the subjects in the experimental group (91%) had an expectation of nausea, vomiting and retching. Several researchers have reported that patients' expectations could influence the occurrence of NVR (Hickok, Roscoe & Morrow, 2001; Roscoe, Hickok & Morrow, 2000). Roscoe et al.'s study (2004) assessed the expectancy of nausea in 194 female

breast cancer patients before they received their first doxorubicin-based chemotherapy cycle and reported that expectancy was a strong predictor of subsequent nausea severity. They also found that women who have a higher expectation of chemotherapy-induced nausea, vomiting and retching were five times more likely to experience severe nausea than the patients who have no expectation of nausea, vomiting and retching.

In this study, additional analysis was conducted to examine whether the expectation of NVR may contribute to NVR scores. Contrariety to previous findings, the current study revealed that no significant relationship was reported between the subjects who reported their expectation to have NVR and those who did not (t = 0.08, p = .94, Appendix H2). The discrepancies found between the expectation of NVR and NVR scores suggest that patients did not have accurate pretreatment expectations. A similar result as a previous study that investigated the effect of an expectancy manipulation designed to reduce nausea expectancy on chemotherapy-induced nausea (Shelke, 2008). They found that changing nausea expectancies possibility does not change the occurrence of nausea. Interestingly, education levels appear to influence the expectation of NVR. In this current study the majority of subjects had low education levels. A study conducted by Hofman et al. (2004) found that patients who had some college education expected more side effects than patients who were high school graduates or those who had not completed high school.

Regarding the experience of motion sickness, the result of additional analysis revealed that subjects who had experience in motion sickness had significantly higher NVR scores than the subjects who did not have any experience (t = -4.98, p < .01,

Appendix H2). The finding of this current study is consistent with a study from Schnell, (2003). They found that patients with a history of motion sickness may have a lower threshold to nausea, vomiting and retching than the rest of the population.

In addition, the use of complementary treatments was also documented in this study. More than three-quarters of the subjects in both groups had no experience in receiving other complementary therapy (88% in the experimental group and 79%, in the control group). As known, the use of complementary therapy can improve the outcomes and help reduce the cost. The findings of the current study indicate that most patients prefer to use pharmacological therapies alone rather than combined with non-pharmacological therapies. This condition may be due to a lack of information regarding the use of complementary therapies in order to alleviate the symptoms of chemotherapy side effects.

Meanwhile, an additional analysis of the current study revealed that there was no significant difference between the subjects who reported their experience of receiving other complementary therapy than those who did not (t = -1.60, p = .114, Appendix H2). The fact that no significant difference was found may be due to unsustainable complementary therapies use or the complementary therapies used were without strong evidence in reducing symptoms. Moreover, studies on complementary therapies in Indonesia, particularly Bali, are limited.

Nausea, vomiting and retching of patients with cervical cancer undergoing chemotherapy

Nausea, vomiting, and retching, although related, are actually 3 distinct symptoms (Rhodes & McDaniel, 2001). In this study, each symptom was measured independently to address the patient's experience with these symptoms. The severity of the symptom is often measured as the intensity of the experience. It is typically measured by duration, frequency, severity and associated distress.

Generally, the results of this study showed that the symptom experience and symptom occurrence of NVR among cervical cancer patients undergoing chemotherapy in Bali, Indonesia were at a moderate level, whereas at a mild level for the distress of NVR. There are several factors identified that may contribute to these results. The cycle of chemotherapy might contribute to the severity of NVR symptoms. This current study involves the patients receiving chemotherapy on the second cycle and the third cycle and assessing the experience of NVR in previous chemotherapy cycles. This means that the experience of NVR in this study was the patients' experience in the first cycle and in the second cycle of chemotherapy. The NVR symptoms were usually more severe on the following cycle and anticipatory nausea and vomiting (ANV) may develop (McRonald & Fleisher, 2005), particularly in the fourth cycle (Roscoe, Morrow, Aapro, Molassiotis & Oler, 2010), and was a significant predictor by cycle five (Watson et al. as cited in Hickok et al., 2001). A possible explanation for the moderate level of the NVR scores could be the relatively higher number of patients with cycle 2 of chemotherapy. Thus, the NVR scores might be less severe.

Regarding the treatment type, a previous study found that in the combination therapy (radiation and chemotherapy) there was reported more symptoms of distress than simple chemotherapy (Oh, 2004). Patients receiving a combined therapy of radiation therapy and chemotherapy experienced significantly higher levels of symptom occurrence than those receiving chemotherapy only (Hur et al., 2002). This may suggest that the treatment type is an important factor contributing to the symptoms, especially in the early stages of cervical cancer. The present study uses one regiment of chemotherapy that might contribute to the severity of NVR symptoms.

Considering the disease severity, the stage of cancer might be another factor that relates to NVR. Cancer patients suffer from the occurrence of symptoms as a result of their disease or the side effects of treatments for their disease. The potential causes of NVR in cancer patients are numerous, especially in those with advanced or metastatic disease (Rhodes & McDaniel, 2001). A study conducted by Oh (2004) found that symptoms of distress were significantly higher in patients with advanced stage (Stages III and IV) than patients in the early stage group. Moreover, late stages of the disease were predictors of acute nausea and vomiting (Molassiotis, Yung, Yam, Chan & Mok, 2002). It is suspected that the stage of the disease has contributed to the moderate levels of NVR severity symptoms in this study.

Another factor could be related to beliefs and custom. The Balinese believe that all illnesses, either physical or mental have specific causes. They believe western concepts to be true within the context of certain illnesses. They also believe that illness and misfortune may result from laws of karmic cause and effect (Hobart, as cited

in Arriaga, 2010). Therefore, in seeking treatment for disease, they combine the medical treatment and ritual prayers that they believe in. It makes them believe that the god will give whatever is the best for their family or the ill person resulting in lower perceived distress.

Furthermore, Balinese people reported less the symptoms associated with disease or treatment, especially the rural communities and poor people. They tend to be more resistant to perceived symptoms and rarely complain about the disease or symptom that they experienced. When suffering from disease, they strongly believe and feel secure when they were in health services or are handled by health professionals. This study was conducted with third class citizens in that the majority of them use health insurance for poor people from the government. Usually, they would accept whatever was offered in an effort to cure the disease without complaining about the symptoms they experienced.

Symptom distress is addressed by how patients perceive the symptom's impact on their daily/ social functioning or quality of life (Wood, Chapman & Eilers, 2011). When patients receive the circumstances of their disease, distress symptoms perceived will be lower. Other factors also influence the severity of symptoms and the patient's perceived distress, including the meaning of the illness and other life events. People's ability to perceive the degree of physical or mental distress is thought to be influenced by various factors, including culture (Rhodes & McDaniel, 1999). Certain ethnic groups or cultures, for example, tend to be more susceptible to certain conditions including nausea, vomiting and retching. People of different cultures tend to respond to

symptoms differently (DeLaune & Ladner, 2002). However, there is no study found that compares the cultural or ethnic groups in Indonesia, particularly Bali.

The effects of foot massage on nausea, vomiting and retching

The results supported the hypothesis 1 and 3. The subjects in the experimental group showed statistically significant differences in NVR scores before and after foot massage therapy at two time periods, T2 (the sixth hour) and T3 (the twelfth hour). In addition, the mean difference of scores at T2 (đ1) and T3 (đ2) of the subjects in the experimental group were significantly lower than that of the control group. The results are similar to the previous studies (Ahles et al., 1999; Bilhult, Bergbom & Stener-Victorin, 2007; Grealish, Lomasney & Whiteman, 2000). This may be due to the relaxation process that contributes to NVR among cancer patients on chemotherapy.

Several reasons can explain the reduction of NVR scores of the subjects in the experimental group. Firstly, the subjects in the experimental group mostly felt relaxed when the researcher performed a foot massage and could sleep well after having received the massage. Foot massage therapy is an adjunctive human touch therapy that refers to the nursing care about caring. Massage therapy is a methodical form of touch that provides comfort and promotes well-being by applying moving or fixed pressure and movement of the body (Kolcaba, Schirm & Steiner, 2006), and induces relaxation (Aghabati, Mohammadi & Esmaiel, 2008; Grealish, et al., 2000). Touch is a vital and basic form of communication, conveying nuances of feeling more expressively and effectively than verbal communication. In depressive states, the caring touch can increase

self esteem and encourage the verbalization of feelings (Puthusseril, 2006). Moreover, foot massage can promote comfort and facilitate complete body relaxation and sleep. The result was consistent with a previous study that massage improves the patients' range of motion, relaxes muscles, and improves circulation and lymphatic drainage (Cassileth & Vickers, 2004).

Secondly, the subjects in the experimental group also mostly reported that massage encouraged their feelings of being acknowledged and cared for. This study used foot massage and integrated the reflexology points to determine the area of massage. It is believed that reflexology works by a combination of biomechanical and spiritual factors. Besides addressing the physical concerns of the body, all levels of our being can be addressed through reflexology; because we are spiritual beings having a human experience. The spiritual factor of reflexology refers to the spiritual gifts of the body. Each gland, organ and body part offers a spiritual gift, by focusing our attention on the other bodies; emotional, mental, moral, and energetic and spiritual we can bring about change on all levels (Hill, 2006). Massage was also described to facilitate their senses of inner power (Cronfalk, Strang & Ternestedt, 2008).

Others effects of reflexology could be due to the additional social and physical contact the intervention entails (Frank et al. as cited in Sharp et al., 2010). As cited in Wang, Tsai, Lee, Chang and Yang (2008), Gambles et al. stated that the human touch accompanied by reflexology offers care and attention for patients, and psychological comforting has been reported as primary benefits of reflexology. Results of a previous study describe a decrease in emotional stress among relatives in caring for

seriously ill and dying patients after receiving soft tissue massage (Cronfalk et al., 2008). Meanwhile, it is not surprising that the results of the current study, combining foot massage with reflexology, had better outcomes.

In addition, foot massage stimulates the neurotransmission when pressure is applied to particular areas of the foot and the nerve impulse is transmitted along the dorsal columns pathway to the thalamus for further interpretation in the cerebral cortex and the limbic system. The interpretation of the nerve impulse will result in the perception of positive feelings and emotion, inducing endorphin release, and the patients consequently feel calm, relaxed and happy in response (Hawthorn, 1995). Furthermore, foot massage therapy can also result in blood vessel dilatation, increase of skin temperature, decrease of heart rate, and relaxation of mind and body. This intervention may enhance the physiological response changes such as blood pressure, respiratory rate, and heart rate.

Foot massage could increase heart rate and relaxation, possibly mediated by increased parasympathetic and decreased sympathetic activity. Massage has an influence on vagal nerve activity via oxytocin, which has been shown to influence the release of gastrointestinal hormones by actions in the vagal nerve and the nucleus of the solitary tract (Lund et al. as cited in Holst, Lund, Petersson & Uvnäs-Moberg, 2005). Massage causes a release of oxytocin not only into the circulation but also into various brain areas. Holst et al. (2005) stated that oxytocin seems to have anxiolytic effects and induces relaxation, which in turn reduces the nausea. A previous study reported that massage-like stroking, in part via vagal activation of the endocrine system of the gut, may

induce an optimised digestive process, promote nutrient assimilation, and anabolic metabolism (Holst et al., 2005). Also in adults, gentle massage has been shown to decrease gastrin and cholecystokinin levels (Uvnäs-Moberg as cited in Holst et al., 2005). It is suspected that performing a foot massage will activate the parasympathetic nerve, thus allowing the body to relax.

Besides, massage can have an effect on better functioning of the immune system (Bilhult, Lindholm, Gunnarsson & Stener-Victorin, 2008; Walker & Walker, 2003), therefore the body can fight invaders from the outside and mutant cells from the inside (Bauer, 1994; Kiecolt-Glaser & Glaser, 1999). Massage has reported to have an effect on increasing circulating Natural Killer cells (NK cells) and lymphocytes (Hernandez-Reif et al., 2004). The stimulation of pressure receptors via massage therapy might be the underlying mechanism for the increased NK cells and lymphocytes. Stimulation of pressure receptors, such as in friction and stroking from massage, may decrease sympathetic and increase parasympathetic activity (vagal tone), leading to enhanced immune function (Billhult et al., 2009).

Reduction of NVR scores in the experimental group may be caused not only by the intervention but also other factors may contribute such as anxiety and the experience of NVR in previous cycles. Anxiety is a significant psychological predictor of chemotherapy-induced nausea, vomiting and retching. It has been found that anxiety predisposes some individuals to learn quickly the association between certain stimuli and the drug induced side effects of post-treatment nausea, therefore contributing to the conditioned response of anticipatory nausea (Morrow, Roscoe, Kirshner, Hynes &

Rosenbluth, 1998). Another study has shown that a state of anxiety is significantly related to both the severity and incident of nausea (Adrykowski & Gregg as cited in Hawthorn, 1995). In the current study, additional analysis revealed that subjects with higher anxiety scores had significantly higher NVR score at the baseline. Furthermore, no significant difference was found on the level of anxiety between the experimental group and the control group. Thus, the level of anxiety is not a confounder in this result.

The subjects in this study had moderate levels of anxiety. Previous studies have shown evidence of a decrease in anxiety immediately after a massage (Ahles et al., 1999; Cassileth & Vickers, 2004). Contrary to these previous studies, Billhult et al., (2007) found that massage did not affect anxiety. A possible explanation for the different findings may be that the baseline values for anxiety sum scores were low; therefore it leaves little room for improvement. The finding of the current study was similar to Billhult et al. (2007), in that the baseline of the anxiety score was low. In addition, as subjects were asked to recall their experience of NVR in the previous chemotherapy cycle, the effect of anxiety on the NVR was inaccurate.

Additionally, the family environment also influences the level of anxiety that contributed to the severity of nausea, vomiting and retching. Kim and Morrow (2007) examined the effects of family support and anxiety on the development of a patient's anticipatory nausea during chemotherapy treatment. They found that the family environment is associated with the severity of anticipatory nausea being mediated by lower levels of patient anxiety and the severity of post-treatment nausea. However, the family environment was not assessed in this study.

Another caution with respect to the interpretation of this study is the cycle of chemotherapy. Roscoe et al. (2010) stated that the NVR can be more severe in the following treatments and may develop as anticipatory nausea and vomiting (ANV), especially in the fourth cycle. Concerning the cycle of chemotherapy in this study, mostly subjects were in the second cycle, which might potentially better control the NVR symptoms.

For between-subjects effects, even though the effects of the intervention at T1 between subjects were controlled, it showed that the subjects in the experimental group also had lower scores of NVR. Subjects in the experimental group had significantly greater reduction in NVR scores compared to those in the control group. This study was consistent with a previous study (Ahles et al., 1999; Bilhult et al., 2007; Grealish et al., 2000). They found that the NVR score of subjects in the experimental group had statistically significant larger reductions compared to the subjects in the control group ($p < .01$). Foot massage therapy is a non-invasive modality and an effective adjunction to reduce nausea, vomiting and retching in cancer patients receiving chemotherapy.

An unexpected finding was the mean difference of the NVR scores of the control group having a significant difference at the two time periods, T2 (the sixth hour) and T3 (the twelfth hour). However, the subjects in the experimental group had a greater reduction of NVR scores than those in the control group. Subjects in the control group showed decreased NVR scores although they did not receive the foot massage intervention, but they showed no significantly lower score as the subjects in the experimental group did. The decreased NVR score of the subjects in the control group

can be caused by feelings of being acknowledged and cared for. This may relate to the Balinese culture. For people in Bali who have no education or are less educated and have an economic status of lower classes, they would feel respected if someone came to them and asked about their condition, even for a while it is still meaningful to them. Involving them in research study could have an effect on their psychological status. This condition may make the patients feel comfortable, being acknowledged and cared for, then, they felt relaxed, which contributes to NVR.

Another reason may be caused by the communication among the researcher, the assistant researcher, and the subjects. The nurses at the ward were overloaded with work, therefore they had no time to communicate properly and pay attention to the patient's complaints. Farrell, Heaven, Beaver and Maguire (2005) conducted a study to assess whether ward nurses could identify patients' concerns in regards to receiving chemotherapy. They found that the nurse made assumptions about the problems patients had without individually seeking to identify what the patients' specific concerns were. Furthermore, one factor that contributes is nurses' communication skills. Thus, communication is an important aspect that focuses on psychosocial concerns which touch on aspects of care.

Furthermore, the findings of this study also supported hypothesis 2. The NVR scores of the experimental group were significantly different at three time periods (T1, T2 and T3), the lowest score of NVR was observed at T2. These findings demonstrated that the efficacy of foot massage in the first sixth hour after the intervention, and also explains the decreased efficacy after the initial 6 hours. The peak

effect of foot massage was at the first sixth hour after the (T2). Similar to a previous study, the use of foot massage as an intervention for healing can provide therapeutic psycho-physiologic effects in a relatively short period of time (Grealish et al., 2000; Wilkinson, Barnes & Storey, 2008). Foot massage works through the relaxation process. However, how long the effect of relaxation lasted is unknown exactly, because there is a fairly wide variation on individual characteristics that contribute to relaxation. Whether these are reasonable explanations for the results found in the current study remain an open question for further study.

The current study proposes foot massage and integrated points of reflexology to determine the area to massage on the foot. The calculation results of the effect size in the current study was d= 1.73. Based on Cohen's table (1992) it is considered to be a large effect size. The effect size result of the current study can be used for other similar studies.

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

This chapter presents the conclusions of the study that are based on the research findings and include the strengths and limitations. Implications and recommendations are presented to suggest several further studies.

Summary of the Study Findings

This randomized controlled study was designed to examine the effect of foot massaging on nausea, vomiting and retching in cervical cancer patients undergoing chemotherapy. This study was conducted at Sanglah Hospital Centre, Bali, Indonesia from October 2011 to February 2012. Sixty-six subjects were recruited for this study. Extraneous variables such as the chemotherapy agent, antiemetic used, and the cycle of chemotherapy were controlled. There were no significant differences between the experimental group and the control group in terms of demographic characteristics and health-related characteristics. Their age ranged from 32 to 65 years old in both groups and most were married and Hindus. Only a small number of the subjects had no education and worked as a farmer or private employee. Most of subjects had no experience of motion sickness. The majority of the subjects in both groups had moderate levels of anxiety and had expected that they might have nausea. Only one subject in the control group had experience of a foot massage and the majority of them had no experience of complementary therapies. In regards to experience of NVR among cervical

cancer patients receiving chemotherapy in this study it was found to be at a moderate level. Additional analysis also found that age, anxiety and experience of motion sickness were individual risk factors that contributed to NVR experience.

The principal conclusions of this study were that the subjects in the experimental group were significantly lower in the NVR scores after receiving foot massage intervention at each time period ($p < .01$). Meanwhile, the NVR score of the experimental group was significantly different at three periods of time (T1, T2 and T3) ($p < .001$) and the lowest score of NVR was observed at T2. For between groups effects, the NVR scores at T1 were significantly different between the experimental and the control group, therefore the mean difference scores were constructed to balance the effect of T1 in all cases. After controlling the effects of T1, the mean difference scores at T2 (đ1) and T3 (đ2) of the subjects in the experimental group were significantly lower than that of the control group at each time period ($p < .01$).

Strengths and Limitations

The strengths of this study were also identified. The present study was a randomized controlled study, using control group, pre-test/post-test design. Tossing a coin technique was used to assign the subjects to either the experimental group or the control group. There was no significant difference in the demographic characteristics between the experimental and the control group. Before the experiment started, the identification and examination of various extraneous variables such as the chemotherapy regiment, antiemetic used, cycle of chemotherapy and level of anxiety, which could have

a weighty effect on the findings, was carried out. This study used foot massage therapy integrated with reflex points of reflexology to determine the area of massage. Integrating points of foot reflexology to determine the areas of the organ that are manipulated may offer better outcomes. In addition, a foot massage protocol is provided, complete with explanations and pictures for each step to make it easier to understand. Besides, the current study measured nausea, vomiting and retching at two time points to see the accumulation effect of the foot massage intervention.

In spite of these strengths, several limitations of this study were also noted. The environment in which the massage takes place is important. All subjects (the intervention group and the control group) were in the same room. It is possible that they shared among themselves about the intervention which -they received, and this can affect the internal validity of the findings. However, the researcher tried to reduce the threat by providing the information prior to the intervention. All subjects were given an explanation that they were involved in the study. They were expected not to share whatever they received related to the intervention and that the researcher would provide all information about the intervention after the completion of the study. Furthermore, the generalization of this study is limited because the data was collected in one hospital and one ward only. Therefore, the conclusion and generalizations reached may be applicable only to this particular population.

When planning a study, as many as possible confounding factors need to be eliminated, while trying to minimize the effect of the remaining confounding factors. In this study, one factor to consider is the conversation between the researcher, the

research assistant and the patient. It is possible that the conversation of the research assistant in the control group is broader instead of simply asking about the NVR symptoms, this can affect the internal validity of the findings. The possibility is to restrict the research assistant's conversation with both groups. However, we estimated this restriction would bear negative consequences for the study. Another confounding factor to consider is the feeling of being observed. As the subjects knew they were in observation, the possibility of the 'Hawthorne effect" was involved, which may affect the reliability of the result. Moreover, the NVR symptoms were subjective feelings and may be influenced by many factors, such as age, cultural origins, previous experience of nausea and vomiting and emotional state. Meanwhile, the objective data such as physiological responses (blood pressure, heart rate and respiration rate) were not documented to control personal bias.

Implications and Recommendations

The findings in this study provide important implications and insights for nursing education, practice and research.

Nursing education

The nurses should be aware and recognize the patients' problem in receiving chemotherapy for effective management. Complementary therapy such as foot massaging should be included in the nursing curriculum in order to teach nursing students how to use it to reduce nausea and vomiting in cancer patients receiving chemotherapy. Thus, it can be one of the non-pharmacological strategies and can be combined with a

pharmacological strategy to have a more positive effect on reducing nausea, vomiting and retching induced-chemotherapy and also this therapy does not have any side effects or harm patients.

Nursing practice

The research findings have clearly provided support for the use of a foot massage intervention as an effective intervention on reducing NVR in cervical cancer patients receiving chemotherapy. Nurses are responsible for providing and managing the care of cancer patients undergoing chemotherapy in many settings such as long-term care, adult day care, assisted living and at home. At a time when cost containment is a consideration in health care, foot massaging is a modality that is non-invasive, readily learned, and can provide a non-pharmacological intervention for nausea and vomiting induced-chemotherapy of the cancer patients. Foot massaging can be applied in many different settings such as home or day care, and requires no specialized equipment.

Nursing research

The positive findings of this study support a growing body of evidence that non-invasive, non-pharmacological interventions such as foot massage therapy is effective for decreasing nausea, vomiting and retching of the cancer patients undergoing chemotherapy with no adverse side effects. It is also provides a knowledge research base for nurses or other health care professionals for further research development or for replicating a similar study in a different setting. The use of foot massage therapy can advance cancer practice, enhance the care provided to cancer patients and help cancer

patients to achieve the most in controlling the undesired side effects of chemotherapy. Future studies should also include long term follow-up measures to evaluate the persisting effects of foot massaging as well as the interval between foot massages, the duration of the foot massage duration and dose.

Recommendations for Future Research

Firstly, considering the limitations in this study, future studies are needed to determine whether the results can be generalized to the cervical cancer patients in the Indonesian population. Since an unequal change of the last five cases was observed during the simple randomization of the subjects using coin tossing, applying other techniques can lessen unintentional bias. For future study, it is recommended to use other techniques such as block randomization, sealed opaque envelopes, a table of random numbers, etc. Secondly, the gender, food consumption and family support on experience of NVR may need to be explored in a further study. Thirdly, in this study the foot massage intervention was conducted one time for 30 minutes, future studies should be conducted to test varying lengths of time of a foot massage intervention for optimal effect. Considering the culture differences, replication studies in other cultures is also recommended. Finally, studies on the effect of foot massaging therapy on NVR by measuring other accurate parameters are also recommended.

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APPENDICES

Appendix A

Informed Consent

My name is Ni Ketut Guru Prapti. I am a lecturer at Study Program of Nursing Science, Faculty of Medicine, Udayana University, Indonesia, who is doing my Master Degree of Nursing at Faculty of Nursing, Prince of Songkla University, Thailand. I am conducting a research study with title "Effect Foot Massage on Nausea, Vomiting and Retching in Indonesian Women with Cervical Cancer Undergoing Chemotherapy". This is to fulfill the requirement of my study in Thailand. In addition, the findings of this study are expected will contribute to improve the quality of care to cancer patients receiving chemotherapy.

This study and its procedures have been approved by the Institutional Review Board (IRB) of Prince of Songkla University, Thailand and also have been granted permission by Sanglah General Hospital, Bali, Indonesia. You are asked to participate in this research study. Since you are currently undergoing chemotherapy under diagnose of cervical cancer, you are invited to participate in this study. Your participation will be beneficial to improve the quality of nursing care provided for cervical cancer patients who undergoing chemotherapy like you in the future.

If you decide to participate in this study voluntarily, I will initiate the following procedure:

Explanation Procedures

a. Grouping

1. You will be assigned to either the intervention group or the control group by using coin-tossing technique.
2. If you are in the experimental group, you will be given foot massage therapy two hours after chemotherapy started. In addition, you still receive routine care from your nurse, doctors, and other providers according to standard nursing care for cervical cancer patients undergoing chemotherapy in this hospital.

3. If you are in the control group, you will be given routine nursing care as a standard care in this hospital similar to what you usually have received. However, if you are interest in foot massage, you will be given after completion of the study.

b. Evaluation and Forms

1. You will be asked to fill up the forms about your personal information and health related problem one time prior to the study. This will take time around 10 minutes.
2. You also will be asked to fill eight-item scale measuring nausea, vomiting, and retching experience undergoing chemotherapy before and twice after completion of foot massage therapy (6 hours and 12 hours after administering chemotherapy). This activity will take time another 10 minutes.

Risks and Comfort

They were told that there is minimal risk involved. There is no cost or payment for your participation in this study. Researcher gives freedom to the patients in choosing the position when foot massage performed, whether they would like to lie down or in semi fowler position.

Benefits

This study will be benefit for you in order to enhance relaxation. The result of this study can be used as a protocol for nurses and health care providers to provide the foot massage therapy in order to prevent of nausea, vomiting and retching in cervical cancer patient undergoing chemotherapy. The data from this research will be used to write a research paper. It also will provide useful information for future research related to this area.

Confidentiality

All information and your responses in this study will remain confidential and will be destroyed after completion of the study. Only the researcher, researcher assistant, and the research advisors are eligible to access the data. Neither your name nor identifying personal information will be used in the report of the study. Further, the data on the report will be presented as a group rather than individual, you will be identified by a number only and it will not be possible for the reviewer to know specifically who did or did not participate in this study.

Participation and Withdrawal from Participation

Your participation in this study is voluntary. Signing the informed consent or agreeing verbally to participate and returning the form given indicate that you understand what is involved and you consent to participate in this study project. At any time of this study, you also have right to withdraw from your participation. No penalty will be incurred if you decide to withdraw and no any influence to your medical service or medical treatment.

If you have any question, suggestion or cannot participate in this study, you can directly contact the researcher (me) at mobile phone (+62 8174741810). Finally, if you agree to participate in this research study, please kindly sign your name on the consent form or verbally state your agreement to participate in the study.

Thank you for your kind cooperation

(Ni Ketut Guru Prapti)

Researcher

Research Information Sheet
Effect of Foot Massage on Nausea, Vomiting and Retching in Indonesian Women with Cervical Cancer Undergoing Chemotherapy (Experimental Group)

During this intervention, you will receive following procedure:

1. At the beginning of the study, you will be asked to fill the form of the personal health-related characteristic questionnaire and eight-item scale measuring nausea, vomiting, and retching experience in previous chemotherapy. Totally, this activity will take time around 20 minutes. The research assistant will help you to complete the form.
2. You will receive foot massage therapy two hours after administering chemotherapy.
3. Foot massage will be conducted around 30 minutes session (5 minute for each foot) with the following steps:
   a. Soak for five minute
   b. Sweeping & Rubbing (Warm-Up)
   c. Massage procedure step by step using soft stroke effleurage massage. Natural oil (coconut oil) will be used and wrapped using towel.
   d. Finish foot massage with some stretching techniques and then clean the excessive oil.
4. Within 12 hours of chemotherapy, the researcher assistant will ask you to fill eight-item scale measuring nausea, vomiting and retching experience and will be given twice, 6 hours and 12 hours after chemotherapy. This activity will take time around 10 minutes. The research assistant will help you to complete the form.
5. Beside the foot massage therapy, you also receive routine care as your usual care.
6. You have right to withdraw from the intervention without any consequences or penalty.

Risk and Comfort

There is no risk or harm that would be endangering you to join this study whether physically or psychologically.

Informed Consent Form

Study Title : Effect of Foot Massage on Nausea, Vomiting and Retching in Indonesian Women with Cervical Cancer Undergoing Chemotherapy

Researcher : Ni Ketut Guru Prapti (Master Student, Faculty of Nursing, Prince of Songkla University, Hatyai, Thailand)

Patient's Name :_____Age:_____

Patient's Consent

I,_____, was informed of the detail of the research entitled "Effect of Foot Massage on Nausea, Vomiting and Retching in Indonesian Women with Cervical Cancer Undergoing Chemotherapy." I was assured that no part of my personal information and research result should be individually revealed to the public. I would discuss with the researcher if any problem or issues arise. I have the right to withdraw from this study at any time without any effect on the nursing/medical services and treatment. I understand the intent, benefits, duration, and procedures of this study. I am willing to participate in this study without any threat and force. Hereby, I endorse my signature.

Given by:_____(Consenter) Date:_____

Researcher's note

I had given the detailed information of the research entitled "Effect of Foot Massage on Nausea, Vomiting and Retching in Indonesian Women with Cervical Cancer Undergoing Chemotherapy." The signature and return of the form indicate that the patients understand what is involved and agree to participate in this study voluntarily. I provide the opportunity to the patients to ask any question and provide the require answer.

Signature:_____(Researcher) Date:_____

Appendix B

Foot Massage Protocol

What is foot massage

Foot massage is a technique by which both feet of the recipient are held at various positions, stroked gently and rhythmically to attain relaxation response (Puthusseril, 2006). Massage employs soft tissue manipulation to influence the whole person, improving circulation, relaxing muscular and nervous tissue and speeding up the elimination of waste products (Maxwell-Hudson, 1996). All this special attention helps to detoxify and balance the body's energies, leaving one feeling refreshed and relaxed.

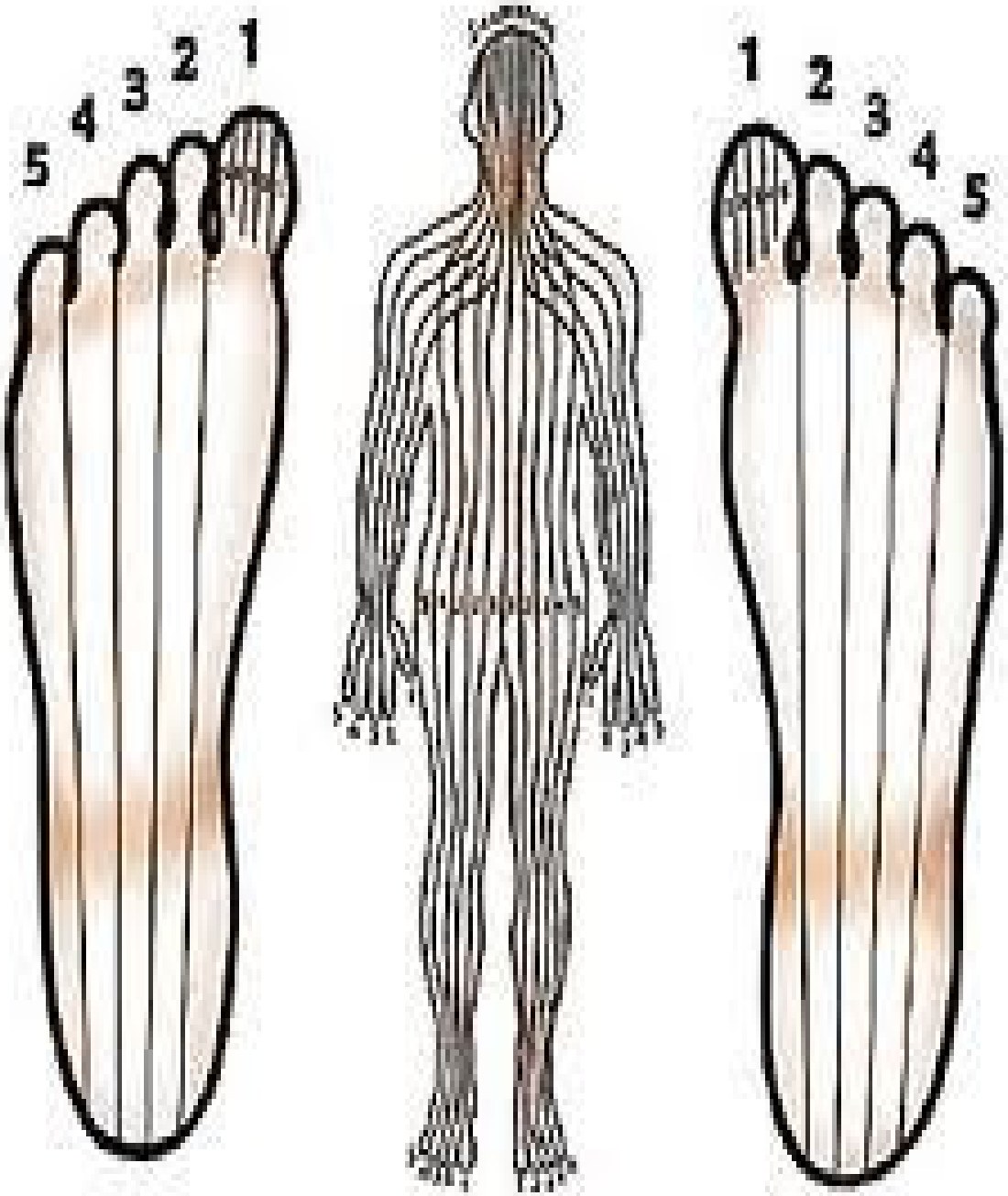
Benefit of foot massage

Physical Benefits may include; relaxes tired feet, improves circulation and enhances joint mobility, relief from headaches and eyestrain, and helps to detoxify the internal organs. Other benefits may include; improve sleep quality, helps in the reduction of stress and anxiety, and restores and balances the body's energy.

Contraindication

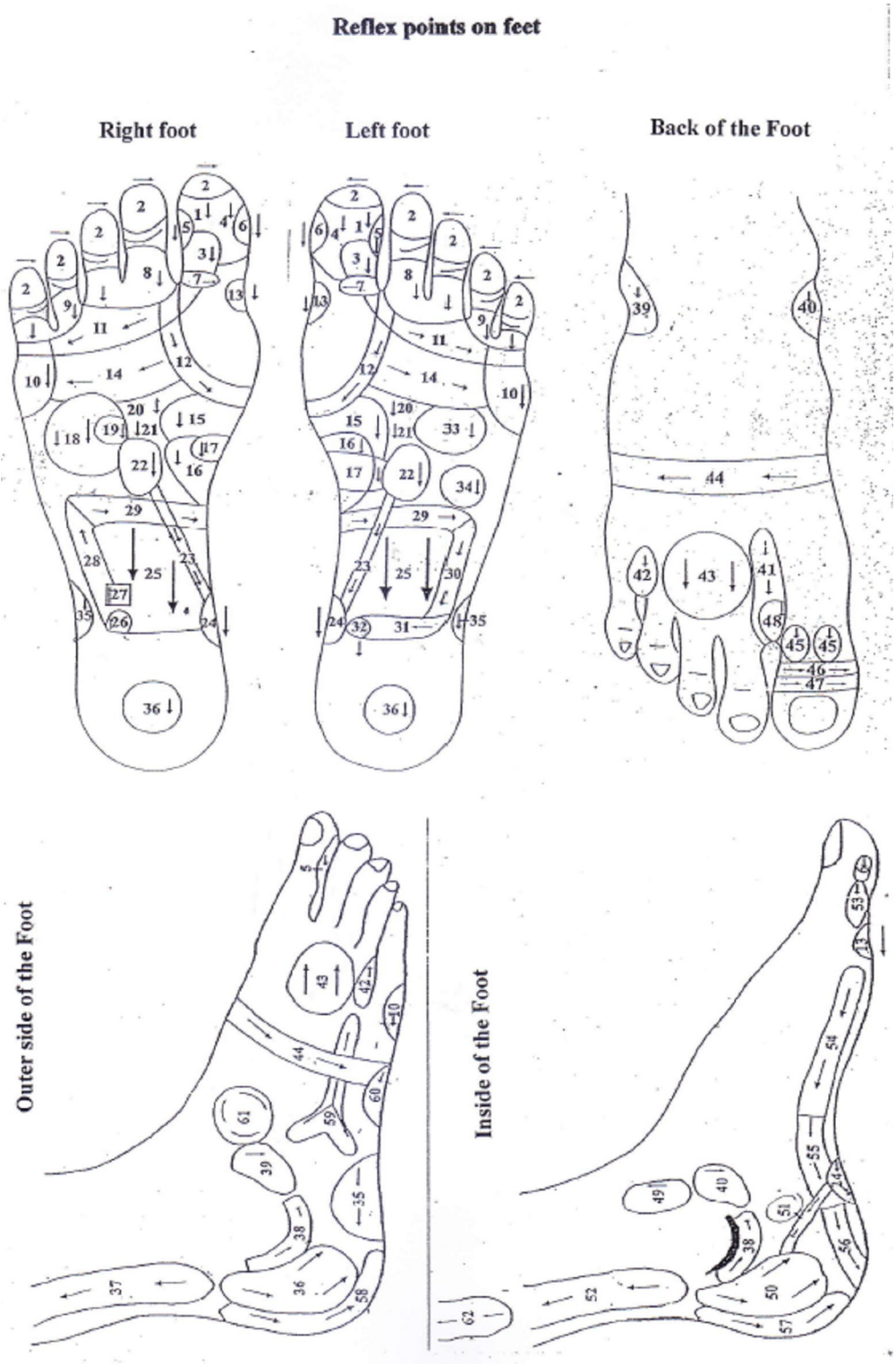
There are certain medical conditions that should not be massaged; fractures, sprains and dislocations, rheumatoid arthritis, severe neuropathy, and numbness or tingling, cuts/wounds, ulcerations, and swelling, and tender toe nail infections.

Body zone



Ten corresponding body zones can be mapped on the feet

by Dr. William Fitzgerald


Reflex points on feet
Right foot
Left foot
Back of the Foot
Outer side of the Foot
Inside of the Foot

Specification numbe

1. Heac
2. Frontal sinus
3. Cerebellum
4. Pituitary
5. ……
6. ……
7. ……
61. Relaxation abdomen
62. Hip joint

Note:

Massage will not be performed at the reflex poi that may be harmful for patients with cervical cancer and can spread the cancer such ge genital organ, uterus and lymph nodes.

Preparations of foot massage

1. Set the environment.
2. ……
3. ……
4. Warm the feet by soaking in warm water about 5 minu and drain.

5. Adjust the patient's position in lying down and com fortable.

Warming up for foot massage

1. Starting gently, working slowly and rhythmically, compress the ankle and the toes, then release, repeat 3-5 times/action.

2. Push the toes forwards, then release, repeat 3-5 times/action.

3. Cross the feet, compress the ankle and the toes, then release, repeat 3-5 times/action.

4. ……..
5. ……..
6. ……..
9. Cover the left foot with towel and do the similar steps of warming up for the right foot, continue to step massage procedure.

Massage Procedure

Note: Every step contain of pressure and effleurage/gliding /stroking massage ……..

Start massage …… that mentioned below:

1. Press on the heart area (count 10 times and then release it slowly). Repeat three to five times.

2. Using two thumbs press the area of adrenal gland and solar plexus (count 10 times and then release it slowly) (see picture). ……

3. Using both thumbs press on the midline of the foot (picture 1), ……
4. ……..
5. ……..
6. ……..

17. When finished, cover the foot with towels……

18. The foot massage is ended with some stretching techniques and cleaning the excessive oil.

Appendix C

Calculation of sample size estimation

The calculation of effect size (*d*) in this study based on previous study by Billhult, Bergbom and Stener-Victorin (2007) as follows:

$d = M1\text{-}M2/SD_{pooled}$,

$SD_{pooled} = \sqrt{[(SD1^2 + SD2^2)/2}$

Where M1: Mean of the experimental group, M2: Mean of the control group

SD_{pooled}: Standard deviation of the group and the experimental group

$SD_{pooled} = \sqrt{[(32.3^2 + 32.3^2)/2]} = \sqrt{1043} = 32.3$

$d = M1\text{-}M2/SD_{pooled} = \frac{73.2 - 49.5}{32.3} \rightarrow d = .73$

The calculation of effect size (*d*) based on results of this study as follows:

$d = M1\text{-}M2/SD_{pooled}$,

$SD_{pooled} = \sqrt{[(SD1^2 + SD2^2)/2}$

Where M1: Mean of the experimental group, M2: Mean of the control group

SD_{pooled}: Standard deviation of the group and the experimental group

$SD_{pooled} = \sqrt{[(2.87^2 + 2.42^2)/2]}$

$= \sqrt{8.2369 + 5.8564/2} = \sqrt{7.04665} = 2.66$

$d = M1\text{-}M2/SD_{pooled} = \frac{5.55 - 0.94}{2.66}$

$d = 1.73$

Appendix D

Personal Health Related Characteristic Questionnaire (PHRCQ)

Below is the form to acquire information about your current demographic data and health related problems information.

No subject :……

Demographic data

1. Age :…….. years
2. Marital status □ Single □ Married □ Widowed
3. ……..
4. ……..
5. Occupation □ Government employee □ Farmer □ Private employee □ Retired □ Housewife

Health Related Problems:

6. Experience in motion sickness □ No □ Yes
7. Experience of alcohol consumption □ No □ Yes
8. ……..
9. ……..
13. Co-morbidity disease □ No □ Yes, what is/are the co-morbid disease(s):

Date of data collection:……

Code of patient:……

Appendix E

Visual Analogue Scale (VAS)

How severe is your anxiety today? Place mark on the line below to indicate how bad you feel your anxiety is today.

No anxiety |_____| **Worst anxiety**

Interpretation:

0 = No

10 – 25 = Mild

26 – 50 = Moderate

51 - 75 = Severe

76 - 100 = Worst

Appendix F

Rhodes Index Nausea Vomiting and Retching (INVR)

Year Month Day A.M/P.M Hour Minute

Rhodes index cnausea, vomiting anretching										
1. In the last 6 hour, threw up ( ) times	7 or more		5-6 times		3-4 times		1-2 times		I did not throw up	
2. In the last 6 hours ……	……		……		……		……		……	
3. In the last 6 hours ……	……		……		……		……		……	
4. ……...	……		……		……		……		……	
5. ……...	……		……		……		……		……	
6. ……...	……		……		……		……		……	
7. ……...	……		……		……		……		……	
8. In the last 6 hours, have had period of retching ……	No		1-2 times		……		……		……	

Appendix G

List of Expert Participants

Three experts in examining the protocol of foot massage protocol:

1. Ajarn Kanit Kemapanmanus

   Faculty of Medicine, Prince of Songkla University, Thailand.

2. Assoc. Prof. Wimonrat Chongcharoen

   Faculty of Nursing, Prince of Songkla University, Thailand.

3. Assist. Prof. Sirirat Kosalwat

   Faculty of Nursing, Prince of Songkla University, Thailand.

Suggestions on the foot massage protocol:

1. Do not manipulate/massage at the reflex points that may be harmful for patients with cervical cancer and can spread the cancer such as the genital organ, uterus and lymph nodes.
2. Encourage the patients to drink a glass of mineral water directly after massage and do not wash the feet the least 30 minutes after foot massage.

Appendix H
Additional Analysis

Appendix H1

Table 16

Correlation between Individual Risk Factors and NVR Scores at T1using Pearson's Product Moment Correlation (N = 66)

Variable	Nausea, Vomiting and Retching
Age	-.33**
Anxiety	.27*
Experience of motion sickne	.53**

*p< .05, **p< .01

Appendix H2

Table 17

Comparison of Individual Risk Factors and NVR Score at T1 using Independent t-test (N = 66)

Variables	N	%	M	SD	*t*	*p value*
Age					2.76	.007
Young ag (32-50 yr)	39	59%	11.46	3.08		
Old ag (51-65)	27	41%	9.33	3.08		
Anxiety					-2.41	.019
Mild (1 - 25)	10	15%	8.4(	2.98		
Moderate (2(- 50)	56	85%	10.9	3.13(		
Expectation of naus					0.0	.940
Yes	57	86%	10.5	3.31		
No	9	14%	10.67	2.87		
Experience of motio sickness					-4.9	.000
Yes	26	39%	12.6	2.6(		
No	40	61%	9.23	2.8(		
Experence of receivin other complementary therapy					-1.6(	.114
Yes	11	17%	12.0(	3.63		
No	55	83%	10.31	3.1(		

Appendix I

Cervical Cancer Treatment Scheme

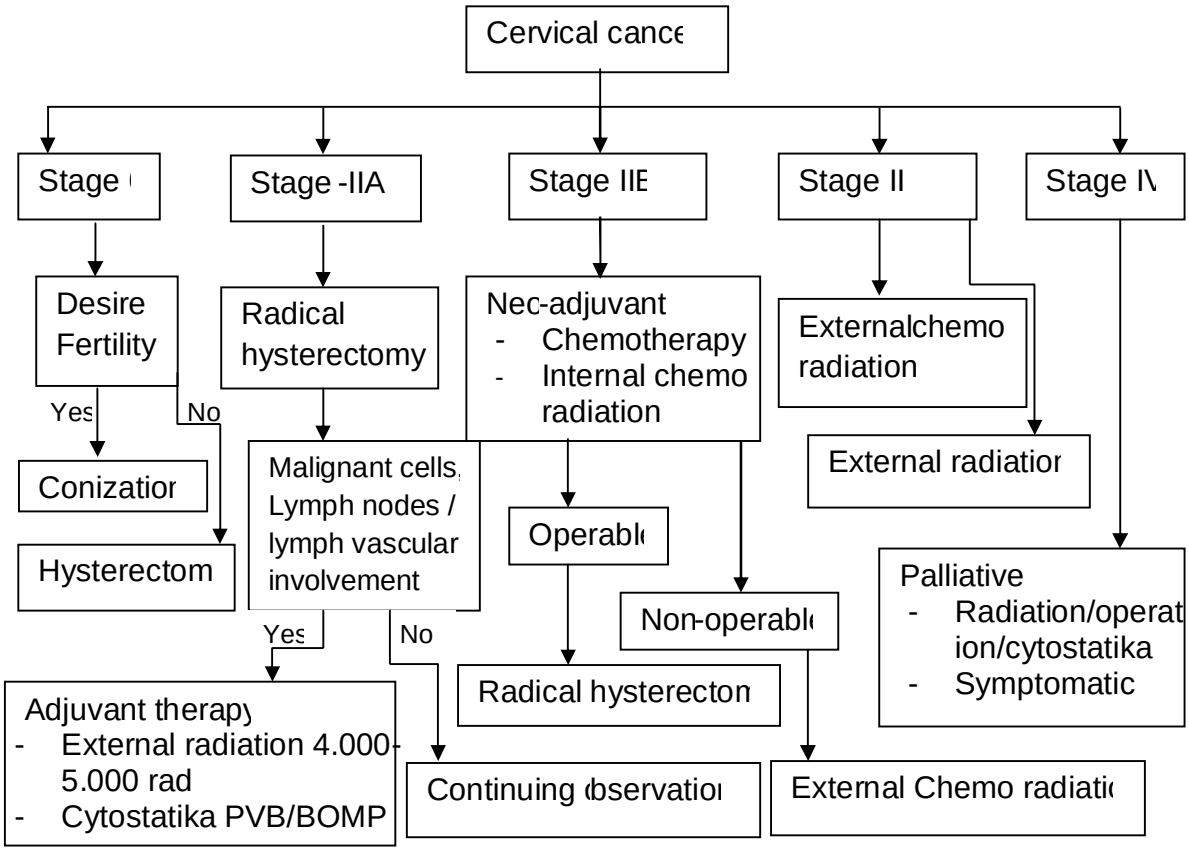


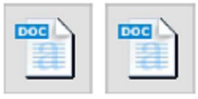
Figure 7. Cervical Cancer Treatment Scheme.
PVB = Cisplatin-Vincristine-Bleomycin; BOMP = Bleomycin-Oncovin/Vincristine-Mitomycin-Cisplatin. Adapted from "Technical guidelines and procedures of division/SMF Obstetrics and Gynecology," by Faculty of Medicine Udayana University/Sanglah Hospitalm, Denpasar – Bali, 2003

Letter of Permission using INVR Tool

YAHOO! MAIL Classic

RE: Asking information Thursday, August 11, 2011 12:23 PM

From: "McDaniel, Roxanne W." <McDaniel@missouri.edu>
To: "guruprapti Ketut" <kguruprapti@yahoo.com>
2 Files (69KB)



INVR Instruc INVR Scale.c

Dear Prapti,
Verna and I are pleased for you to use the Index of Nausea, Vomiting, and Retching (INVR) in your master's study of study of these symptoms in patients with cervical cancer undergoing chemotherapy. While there are no costs for the use of the instrument, all publications and talks from you study are to credit the instruments authorship. I am attaching the English version of the INVR and the instructions for administering.

Your intervention study should be a great contribution to the care of these patients. Don't hesitate to email me if you have further questions.

Best Wishes,

Dr. Roxanne W. McDaniel
Associate Dean for Academics
S410 School of Nursing
Columbia, MO 65211-4120
Phone: 573-882-0228
FAX: 573-884-4544
Web: nursing.missouri.edu

From: guruprapti Ketut [mailto:kguruprapti@yahoo.com]
Sent: Wednesday, August 10, 2011 9:26 PM
To: McDaniel, Roxanne W.
Subject: Asking information

Dear Dr McDaniel,

I am sorry disturb you with my e-mail. Firstly, I would like to introduce myself. My name is Prapti, from Udayana University, Bali-Indonesia. I am taking master of nursing science at Prince of Songkhla University, Thailand. Currently I am preparing the thesis proposal and interest in study of nausea, vomiting and retching in patients with cervical cancer undergoing chemotherapy. I would like to use the INVR instrument developed by Rhodes and ask permission from her. However, I could not found her e-mail address.

I read her articles, but did not provide the e-mail address (both of you). I tried to search in Sinclair School of Nursing, University of Missouri, and I found your e-mail address.
I am writing this to ask for help and seek advice from you, what can I do to get her e-mail address. And what should I do to get permission using her instrument for my study?

Thank you for your kindness and your attention. I am waiting for further good news.

Your sincerely,
Prapti