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Nausea and vomiting in patients receiving acupuncture, sham acupuncture or standard care during radiotherapy

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To Lasse, in memory, who suffered from nausea during the end of his life

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ABSTRACT

Background and aim: Many patients with cancer experience emesis (nausea and vomiting) during radiotherapy. The overall aim of this thesis was to improve the situation for patients with risk for emesis during radiotherapy, by evaluating emesis in patients receiving verum (genuine) acupuncture, sham (simulated) acupuncture or standard care during radiotherapy. **Methods:** In study I, a cross-sectional sample (n=368) treated with radiotherapy over various fields answered a study-specific questionnaire. In study II, 80 healthy volunteers were randomized to receive needling with verum acupuncture or non-penetrating telescopic sham needles by one of four physiotherapists. In study III, 215 patients were randomly allocated to verum (n=109) or non-penetrating telescopic sham (n=106) acupuncture during their entire radiotherapy period over abdominal or pelvic fields. The same 215 patients were also included in study IV. They were compared to 62 patients irradiated over abdominal or pelvic fields, selected from study I. **Results:** In study I, the weekly prevalence of nausea was 39 % in all radiotherapy-treated patients and 63 % in abdominal or pelvic irradiated patients. Age younger than 40 years and previous experience of nausea in other situations were characteristics associated with an increased risk for nausea. Of the 145 nauseous patients, 34 % considered their antiemetic treatment as insufficient. Patients with nausea reported lower level of quality of life compared to patients free from nausea. In study II, most individuals needled with verum (68 %) or sham (68 %) acupuncture could not identify needling type, and that blinding result varied from 55 to 80 % between the four therapists. In study III, nausea was experienced by 70 % (mean number of days=10.1) and 25 % vomited during the radiotherapy period. In the sham group 62 % experienced nausea (mean number of days=8.7) and 28 % vomited. Ninety five percent in the verum and 96 % in the sham group believed that the treatment had been effective for nausea. In both groups, 67 % experienced other positive effects, on relaxation, mood, sleep or pain-reduction, and 89 % were interested in receiving the treatment again. In study IV, the weekly prevalence of nausea and vomiting was 38 and 8 % in the verum group, 37 and 7 % in the sham group and 63 and 15 % in the standard care group. The nausea difference between the acupuncture and the standard care cohort was statistically significant, also after overall adjustments for potential confounding factors. The nausea intensity in the acupuncture cohort was lower compared to the standard care cohort (p=0.002). Patients who expected nausea had

increased risk for nausea compared to patients who expected low risk for nausea (Relative risk 1.6). **Conclusions and implications:** Nausea was common during abdominal or pelvic field irradiation in patients receiving standard care. Verum acupuncture did not reduce emesis compared to sham acupuncture while reduced emesis was seen in both patients treated with verum or sham acupuncture. Health-care professionals may consider identifying and treating patients with increased risk for nausea in advance. The telescopic sham needle was credible. Researchers may thus use and standardize the sham procedure in acupuncture control groups. The choice of performing acupuncture during radiotherapy cannot be based on arguments that the specific characters of verum acupuncture have effects on nausea. It is important to further study what components in the acupuncture procedures that produce the dramatic positive but yet not fully understood antiemetic effect, making it possible to use those components to further increase quality of care during radiotherapy.

Key words: *Acupuncture, Cancer, Emesis, Placebo, Radiotherapy*

TERMS

Acupuncture	To puncture the skin at different points. Can be divided into verum (genuine skin penetrating) acupuncture and sham (simulated skin penetration) acupuncture.
Acupuncture therapy	Different techniques to stimulate acupuncture points by needles or by pressure: manually, by electricity or by using a tool, for example a seaband.
Acupressure	To pressure the skin at different points.
Antiemetics	Medications for reducing nausea or vomiting, irrespectively of medication type.
Antiemetic effects	Emesis reducing effects, irrespectively of treatment type (pharmacological or non-pharmacological).
Blinding success	The individual does not know or answers incorrectly the question about which needle type was used.
Cun	The width of the treated individual's thumb, used as a distance measure for location of needling points.
Credibility	Trustworthy; ability to mask if treatment had been performed with penetrating or not-penetrating needles.
Deqi	The specific sensation that occurs when stimulating penetrating acupuncture needles, including a dull, radiating sensation and a minimal muscular contraction local to the needle.
Emesis	Nausea and vomiting. See the terms "nausea" and "vomiting".
Gray	The unit of radiotherapy dose (Gy)
Nausea	An unpleasant nauseating sensation in the gastrointestinal tract that may or may not lead to vomiting when the sensation increases.
Non-acupuncture point	A point used for acupuncture therapy outside the acupuncture medians, according to traditional Chinese medicine.
Radiotherapy field	The body-area being irradiated.

Sham-acupuncture	A procedure that simulates verum acupuncture treatment, without skin penetration and “deqi”-stimulation.
Side-effect	Effect separated from the intended or required effect. A side-effect may be negative or positive.
Specific acupuncture effects	Effects due to skin penetration and “deqi” stimulation of traditional acupuncture points
Unspecific acupuncture mechanisms	Other mechanisms than the specific characters of verum acupuncture treatment.
Verum acupuncture	Genuine acupuncture including the specific characters penetration of the skin with needles placed at traditional acupuncture points, stimulated until “deqi” occurs.
Vomiting	Throwing up stomach contents.

LIST OF PAPERS

This thesis for the doctoral degree is based on the following studies, referred to in the text by their Roman numerals:

I. Enblom Anna, Bergius Beata, Steineck Gunnar, Hammar Mats, Börjeson Sussanne. One third of patients with radiotherapy induced nausea consider their antiemetic treatment insufficient. Supportive Care in Cancer. 2008; Jun 5. (Epub ahead of print)

II. Enblom Anna, Hammar Mats, Steineck Gunnar, Börjeson Sussanne. Can individuals identify if needling was performed with an acupuncture needle or a non-penetrating sham needle? Complementary Therapies in Medicine. 2008; 16:288-294.

III. Enblom Anna, Johnsson Anna, Hammar Mats, Onelöv Erik, Steineck Gunnar, Börjeson Sussanne. Acupuncture compared to placebo acupuncture in radiotherapy-induced nausea –a randomised controlled study. Submitted for publication.

IV. Enblom Anna, Lekander Mats, Hammar Mats, Onelöv Erik, Johnsson Anna, Ingvar Martin, Steineck Gunnar, Börjeson Sussanne. Radiotherapy-therapy induced emesis in patients treated with acupuncture, sham acupuncture or no needling: effects of unspecific acupuncture mechanisms. Submitted for publication.

INTRODUCTION

Approximately one third of the Swedish population is diagnosed with a cancer disease at some time during their life (Socialstyrelsen 2007). Common treatments are surgery, chemotherapy and radiotherapy, used alone or in combination. The therapies may all induce emesis (nausea and vomiting), as a side-effect (Henry et al 2008). There are effective pharmacological therapies for treatment-induced emesis (Feyer et al 2005, Maranzano et al 2005, Kris et al 2006) but some patients ask for non-pharmacological complements (Lu 2005, Richardsson et al 2004). Acupuncture is a treatment form suggested to reduce emesis during, for example, pregnancy (Jewell & Young 2003) or after surgery (Ezzo et al 2006a) or chemotherapy (Ezzo et al 2006b). It is not known if acupuncture is effective for radiotherapy-induced emesis.

Emesis during treatment for cancer

With cancer, emesis may be caused by the tumour *per se*, through mechanical influence on vital organs, or release of emetogenic substances. An indirect role may also be played by conditions that result from the tumour, such as subileus or brain oedema (Miller 1999). However, it is more common that emesis is induced as a result of cancer treatment, occurring after surgery, opioid therapy, chemotherapy or radiotherapy (Abdelsayed 2007).

During radiotherapy an Italian observational study (IGARR 1999) found that 39 % of the patients irrespective of radiated body region and 71 % of patients radiated over abdominal fields experienced nausea or vomiting during the radiotherapy period. Radiotherapy over abdominal or pelvic fields induces cellular damages in the gastrointestinal tract, which leads to release of serotonin. The serotonin activates serotonin-receptors on closely associated vagal afferents fibers resulting in transmitter release at the level of the dorsal vagal complex, also known as the vomiting centre. The activity in the vomiting centre, located in the medulla of the brain stem close to the area postrema, causes the sensation of nausea. If the activity is strong enough, vomiting occurs (Abdelsayed 2007).

The chemoreceptor trigger zone, located within the area postrema also activates the vomiting centre. The area postrema comprises opioid, dopamine, histamine and serotonin-receptors and may thereby

react to toxic agents in the circulating blood and cerebrospinal fluid (Miller 1999), for example as a result of opioids or cytotoxic chemotherapy agents (Abdelsayed 2007), or the stress hormone cortisol (Otto et al 2006).

Stimulus from the central nervous system may also activate the vomiting centre by afferents from the visual, vestibular or limbic structures (Abdelsayed 2007). Distressing emotions (Zachariae et al 2007) or an expectation that nausea is going to occur (anticipatory nausea) (Horiot & Aapro 2004) may thus induce nausea.

Serotonin-receptor antagonists reduce nausea related to high concentrations of serotonin in the gastrointestinal tract as well as in the area postrema. Traditional antiemetics, for example dopamine-receptor antagonists, corticosteroids and antihistamines, reduce nausea related to toxic reactions in the area postrema (Abdelsayed 2007). Serotonin-receptor antagonists, possibly combined with corticosteroids, have been recommended as the most effective antiemetics for radiotherapy-induced emesis (Feyer et al 2005, Maranzano et al 2005, Kris et al 2006). Serotonin-receptor antagonists are optimized for short time use (Horiot & Aapro 2004) since they may produce side-effects, for example headache and constipation (Herrstedt 2004) during long-term use. Radiotherapy often continues for several weeks (Feyer et al 2005). A wish to use less toxic alternatives leads some patients to ask for non-pharmacological complements or alternatives (Richardson et al 2000), for example acupuncture (Lu 2005, Swarup et al 2006).

Quality of life in patients with nausea

Nausea is ranked among the most incapacitating side-effects experienced during cancer treatment (Griffin et al 1996, de Boer-Dennert et al 1997, Sun et al 2002, Henry et al 2008). Previous studies have shown that nausea induced by chemotherapy decreases quality of life (Roscoe et al 2000, Martin et al 2003a, Lachaine et al 2005, Ballatory et al 2007). Nausea during radiotherapy is often milder in intensity compared to chemotherapy-induced nausea but usually has a longer duration (Feyer et al 2005). Only a few studies (Sykes et al 1997, SC19 2006, Shun et al 2008) have described quality of life in relation to nausea during radiotherapy.

Quality of life is a widely used concept and there are several definitions. The World Health Organization (WHO 1996) describes

quality of life as “the individuals’ perception of their position in life in the context of the culture and value system and in the relation to their goals, expectations, standards and concerns”. Nordenfeldt (2004) describes quality of life in terms of well-being with the ability to reach the individual’s personal goals in life. A person’s sense of well-being may stem from a subjective satisfaction or dissatisfaction with the areas that are important for oneself (Ferrans & Powers 1992). Dimenäs and co-workers (1990) describe quality of life as covering three main factors: subjective well-being (referring to the individual's perception of his life situation), health (a subjective as well as objective evaluation of physical and mental status) and welfare (reflects the objective environmental factors). Both the individual’s "Subjective well-being" and the perception of health are seen as central components in the evaluation of quality of life according to the definition of Dimenäs and co-workers (1990), the definition used in this thesis. Welfare is considered as secondary, and environmental factors may be seen as factors hindering or stimulating an individual’s satisfactory with quality of life. Individuals may, according to that definition, rate their subjective satisfaction within different areas of the life situation (Wiklund et al 1990).

Acupuncture

Patients with cancer experience a variety of symptoms caused by the cancer illness and/or their cancer treatment, for example pain, fatigue, anxiety, low mood and nausea (Naughton & Homsí 2002, Chang & Ingham 2003, Henry et al 2008). Pharmacological treatment for those symptoms may sometimes not have satisfactory effects or may cause negative side-effects (Naughton & Homsí 2002). Many patients are interested in non-pharmacological complements or alternatives to treat different symptoms during their overall cancer treatment (Richardson et al 2000, Lafferty et al 2004, Molassiotis et al 2005), including in radiotherapy (Swarup et al 2006). Molassiotis and co-workers (2005) studied 956 patients with cancer from 14 European countries. Acupuncture was the second most commonly used “complementary therapy” (including for example herbal medications, homeopathy, acupuncture or spiritual techniques), after homeopathy. Of the Swedish patients, 30 % had ever used complementary methods. In a study including over 300 000 of the American general population, higher proportions of individuals with cancer underwent acupuncture

treatments, compared to individuals with other diagnoses (Lafferty et al 2004).

In Sweden, acupuncture therapy is incorporated within health care. The therapy has been allowed as part of approved health care for treatment of pain since 1984 and since 1993 also for other conditions, if the effect has been scientifically and clinically proven (Socialstyrelsen 1993). Acupuncture is offered in many Scandinavian oncology departments (Kolstad et al 2004) and physiotherapists are the most common acupuncture providers within the Swedish health care system (Carlsson 2001). The increasing use of acupuncture for different conditions requires scientific evaluation of effects and side-effects in each condition (MacPherson et al 2001).

Mechanisms of acupuncture

Stimulation of penetrating needles stimulates the ergo-receptor and induce a specific needle sensation; called “deqi” according to traditional Chinese medicine (Park et al 2002a, Hui et al 2007, Mao et al 2007). This sensation does not appear if blunt needles are used (Hui et al 2007). Volunteers have described “deqi” sensation as “aching, soreness, pressure” (Hui et al 2007), “aching, spreading, radiating” (Park et al 2002), “distended, sore, electric and numb” (Mao et al 2007). Penetration and “deqi” have been considered to be the effective elements of acupuncture (Kong et al 2007, Hui et al 2007). In a Chinese study, patients believed that a stronger “deqi” sensation was associated with a better effect (Mao et al 2007). Regarding emesis, researchers have suggested an antiemetic effect of different kinds of acupuncture therapy performed at the traditional acupuncture point Pericardium 6, PC6, located near the ventral side of the wrist (Ezzo et al 2006a).

Several physiological mechanisms of verum acupuncture in general have been suggested (Carlsson et al 2002, Lewith et al 2005, Lundeberg et al 2007), and it is not clear-cut which of the mechanisms might explain plausible antiemetic effects (Streitberger et al 2006). Acupuncture induces a peripheral release of substance P, vasoactive intestinal peptide and calcitonin gene-related peptide (Carlsson et al 2002). The local blood flow close to the inserted needle increases (Sandberg et al 2004). On the spinal level, acupuncture may result in a short-time spinal gate-control mechanism (the needle-induced sensory afferents blocks other sensations) (Carlsson et al 2002). On the central

level, acupuncture activates a variety of brain structures (Lewith et al 2005, Dhond et al 2007), for example the periaqueductal grey (Yoo et al 2004) and the limbic system (Hui et al 2000, Hui et al 2005), which may produce plausible antiemetic effects (Lundeberg et al 2007). A release of endorphins noradrenalin and cortisol has been suggested (Carlsson et al 2002), but results from studies on humans are contradictory (Harbach et al 2007). If acupuncture stimulates the hypothalamus-pituitary-adrenal axis to produce more cortisol (Cho et al 2006), that mechanism may hypothetically reduce emesis. So also may the release of oxytocin, associated with non painful sensory stimulations (Uvnäs-Moberg et al 1993).

Local anaesthetics blocked acupuncture effects on vomiting (Dundee & Ghaly 1991). Naloxone (blocks opioid receptors) blocked acupuncture effects on gastric peristaltic movements in dogs (Tatewaki et al 2005), but did not block acupuncture effects on the esophageal sphincter (Zou et al 2005) in humans. Thus, both peripheral neural, central opioid and autonomic neural mechanisms may be involved during acupuncture for emesis (Streitberger et al 2006).

Acupuncture for nausea during cancer treatment

A data-base search in PubMed, AMED and CINAHL (20th October 2008) resulted in no published studies regarding the effect of acupuncture on radiotherapy-induced nausea, but did reveal several studies of chemotherapy-induced nausea. Patients reported that acupuncture (Nyström et al 2008), acupressure (Gardini et al 2007, Wright 2005) or a combination (Dundee & Yang 1990, Dong 1998, Johnstone et al 2002) reduced chemotherapy-induced nausea in uncontrolled studies. Acupuncture (Aglietti et al 1990), acupressure (Dibble et al 2000, Roscoe et al 2003, Shin et al 2004, Molassiotis et al 2007) or a combination (Xia et al 2000) reduced nausea more than standard care, including antiemetics, in randomised studies.

Dundee and co-workers (1989, n=10) reported that the patients experienced less nausea and vomiting when they received electro-acupuncture in PC6 compared to a “sham” point in the elbow. Electro-acupuncture (penetrating needles stimulated with electricity) reduced vomiting more than either simulated electro-acupuncture provided with superficially inserted needles, or standard care (Shen et al 2000, n=104). Patients receiving acupressure of PC6 experienced less nausea and

vomiting compared to control groups receiving acupressure on a point on the ulna side of the hand, or standard care (Dibble et al 2007, n=160). However, compared to other sham (simulated) techniques, verum acupuncture (Streitberger et al 2003, n=80), acupressure (Roscoe et al 2005, n=96) or a combination (Melchart et al 2006, n=27) was not more effective.

Sham acupuncture

While pharmacological studies often use “placebo pills” for treatment of the control groups, it has been more problematic to find a credible but still inert sham technique in acupuncture studies. Different techniques have been used: deeply inserted needles placed at non-acupuncture points, superficially inserted needles placed at acupuncture points or non-acupuncture points, or ordinary but blunt needles (Trinh 2003, Dincer & Linde 2003). Penetrating sham techniques cause a greater activation in sensory areas in the midbrain compared to non-penetrating needles (Pariante et al 2005) and increase the peripheral blood flow, whether the needle is inserted deeply or superficially (Sandberg et al 2004). When using an ordinary but blunt acupuncture needle (Fink et al 2001), the patient may be able to see clearly that the needle does not enter into the tissue.

A blunt sham needle with a telescopic design needle was therefore developed by Streitberger and Kleinhenz (1998) and modified by Park and co-workers (1999). When the blunt sham needle touches the surface of the skin, it gives a sensation of penetration and then glides upwards in its handle. The needle is therefore shortened, which gives an illusion that it has entered into the tissue. For evaluation of whether or not acupuncture has specific effects, related to penetration and “deqi” stimulation, the telescopic sham needle has been suggested to be the most appropriate method of controlling for needle penetration (White et al 2001a).

The credibility of the sham needles has been tested (Streitberger & Kleinhenz 1998, Park et al 2002, White et al 2003, Tsukayama et al 2006, Mc Manus et al 2007) and those studies suggest that individuals cannot determine if treatment has been conducted with the verum or the sham needles. However, there are indications that the therapist may influence the credibility results (White et al 2003). Therefore it may be valuable to test the credibility in the same therapists

that are going to treat patients before conducting a study of acupuncture effects. Bang and co-workers (2004) presented a method for calculating the level of blinding success, irrespective of research area, which may be applicable in acupuncture studies (Park et al 2005).

Problem areas needing more studies

Few studies have observed the prevalence of nausea and the satisfaction with antiemetic treatment in an ordinary routine clinical setting (IGARR 1999, Hickok et al 2005) since most studies focus on patients receiving a specific antiemetic agent or include only patients receiving radiotherapy over a specific body region (Feyer et al 2005). Few studies (Sykes et al 1997, SC19 2006, Shun et al 2008) have described if patients who experience nausea during radiotherapy differ in rating the quality of life compared to patients free from nausea. Since acupuncture is increasingly used within cancer care (Lafferty et al 2004), studies of the potential effects of acupuncture need to be conducted for each separate condition using a stringent scientific design (MacPherson et al 2001). That requires a sham-controlled design with successfully blinded patients (White et al 2001a), independent of the therapists performing the treatment. Previous studies of acupuncture for chemotherapy-induced nausea suffer from methodological problems and present conflicting results (Ezzo et al 2006b). Results regarding chemotherapy-induced nausea cannot be generalized to radiotherapy-induced nausea. Therefore it became evident that it was important to study the effects of acupuncture on radiotherapy-induced nausea.

AIMS

General aim

The overall aim of this thesis was to improve the situation for patients with risk for emesis during radiotherapy, by evaluating emesis in patients receiving verum acupuncture, sham acupuncture or standard care during radiotherapy.

Specific aims

1. To describe the prevalence of nausea and vomiting, the use of and satisfaction with treatment against nausea (study I) and to identify risk factors for nausea during radiotherapy (study I and IV).
2. To compare quality of life and psychological and functional condition reported by patients experiencing nausea and by those not experiencing nausea during radiotherapy (study I).
3. To investigate whether individuals could identify if treatment had been given with an invasive needle or a sham needle (study II and III) and if different therapists influenced the degree to which individuals remained blinded to treatment allocation (study II).
4. To evaluate whether or not verum acupuncture prevented or reduced nausea or vomiting compared to sham acupuncture (study III), and compared to standard care (study IV) during radiotherapy.

PARTICIPANTS AND METHODS

Design

The studies in the thesis used a cross-sectional observational design (study I), a randomised design in an experimental setting (study II), a randomised sham-controlled prospective design in a clinical setting (study III) and an observational design in terms of a non-randomised comparison between a cohort of verum or sham treated patients (an acupuncture cohort) and a reference group (a standard care cohort) (study IV) (table 1).

Ethics

Study I, III and IV were approved by the Regional Ethics Committees (Dnr 98-301, Dnr 02-420 and M167-04). Study II included healthy volunteers giving informed consent and, according to the ethics law [2003:460] and advice from the Regional Ethics Committee, no ethics approval was needed.

Populations

Totally, 663 individuals participated in the four studies: 368 in study I, 80 in study II and 215 in study III. Study IV included no new participants (figure 1. For detailed information, see figure 1 within paper III and IV). The criteria for participating in the studies are shown in table 1. All participants received oral and written information and gave their written informed consent.

In study I a cross-sectional selection was made on four days at the Radiotherapy Departments of two Swedish University Hospitals; two days at each hospital. A research nurse at each department identified potential participants following the study criteria. The patients were informed: "To additionally increase the care, we want to evaluate how many patients experience nausea and other symptoms during the radiotherapy". If the patients were willing to take part, they were included (n=396).

In study II, the therapists consecutively invited healthy volunteers (mainly friends, for example colleagues or other acquaintances). They were informed "To conduct studies of the effect of acupuncture the needles need to be tested in healthy individuals, which provides an opportunity for the therapists to practise the techniques and needling point chosen for the prospect study". The first 80 volunteers who fulfilled the study criteria and wanted to participate were included.

In study III, all patients who had a planned radiotherapy at one of two Swedish University Hospitals and fulfilled the inclusion criteria during January 2004 to December 2006 consecutively received an information letter and a telephone call: "If you would like to participate, you will receive an ordinary acupuncture treatment with needles penetrating the skin or another treatment with needles placed just against the skin". Patients who wanted to participate and fulfilled the study criteria were included (n=237).

In study IV patients from three Swedish University Hospitals were included: the same 215 patients that participated in study III, the acupuncture cohort, were compared to the reference group of 62 patients who in study I received radiotherapy over abdominal or pelvic fields; the standard care cohort (Fig 1).

Randomization and blinding

The volunteers in study II and the patients in study III and IV were randomized to verum acupuncture or sham acupuncture - without being told which (blinded) - by drawing a "lot" that came from a random table.

In study III and IV, all health-care professionals, other than the physiotherapists performing acupuncture and the nurses performing the randomization, were blinded. The randomizing nurses were not involved in the acupuncture treatment or data collection. The evaluator was blinded to treatment allocation by use of coded questionnaires until breaking the code, which was done after analysis of the primary endpoint measured in study II and III.

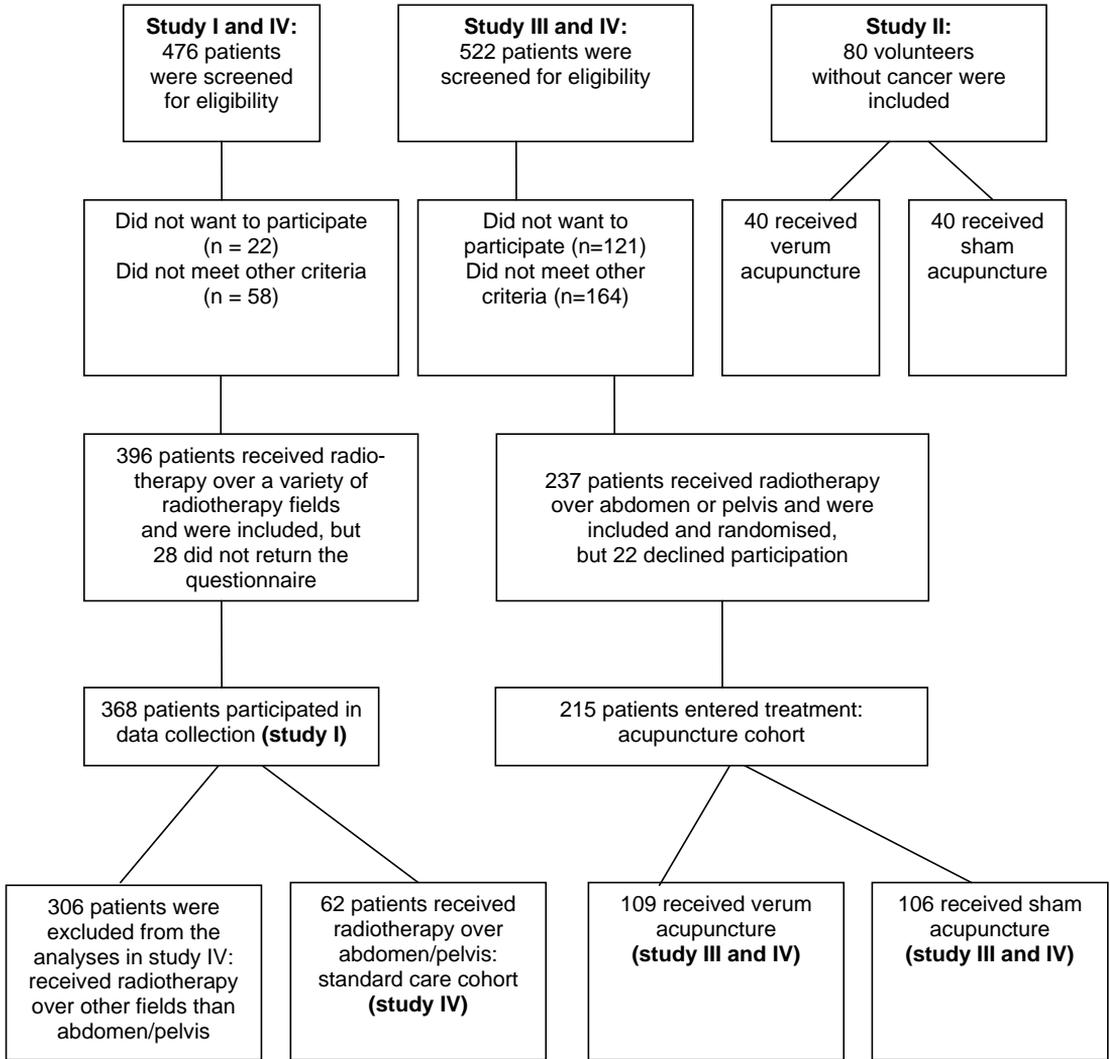


Figure 1. Flow chart of the cohorts in study I – IV.

Table 1. Overview of the designs, populations and data collection used in the studies

	Study I	Study II	Study III	Study IV
Design	Cross-sectional	Randomised experimental	Randomised sham-controlled prospective	Observational comparative study
Cohort	A cross-sectional sample of patients undergoing radiotherapy, irrespectively of radiotherapy-field (n = 368)	Healthy volunteers (n = 80)	A consecutive sample of patients undergoing radiotherapy over abdominal or pelvic fields (n = 215)	A consecutive sample of patients (n = 215) and a cross-sectional sample of patients receiving standard care (n = 62), all undergoing radiotherapy over abdominal or pelvic fields
Inclusion criteria	≥ 18 years old, radiotherapy, irrespectively of cancer diagnosis, ability to communicate in Swedish and to understand the study procedure	≥ 15 years old	Radiotherapy over an abdominal or pelvic field of ≥ 800 cm ³ volume and ≥ 25 Gray dose, ability to take part in the entire treatment and data collection procedure	For the acupuncture cohort see study III, for the standard care cohort see study I, with the addition of the criterion: abdominal or pelvic radiotherapy field
Exclusion criteria	Any kind of illness of such severity as to hinder participation	Pregnancy, education in or previous personal experience of acupuncture	Antiemetic treatment or persistent nausea within 24 hours prior to the start of radiotherapy, acupuncture treatment during the preceding year for any indication or ever for nausea	For the acupuncture cohort see study III, for the standard care cohort see study I
Data collection				
Emesis	Yes		Yes	Yes
Quality of life	Yes			
Patient satisfaction	Yes		Yes	Yes
Blinding test		Yes	Yes	
Acupuncture treatment	No acupuncture	Verum acupuncture (n = 40) or sham acupuncture (n = 40) once.	Verum acupuncture (n = 109) or sham acupuncture (n = 106) 2-3 times/week, md 5 weeks.	Verum acupuncture (n = 109) or sham acupuncture 2-3 times/week, md 5 weeks (n = 106) or no acupuncture (n = 62).
Primary outcome	Proportion of patients experiencing nausea within one week of radiotherapy	Proportion of individuals who did not know or gave wrong answer regarding needle type	Proportion of patients experiencing nausea at least once within the radiotherapy period	Proportion of patients experiencing nausea at least once within one week of radiotherapy

N=number, md=median, ≥ =at least

Treatments for nausea

Standard care

The patients in study I, III and IV received radiotherapy daily (Mondays through Fridays). All patients were, except for participation in the study, treated according to ordinary clinical routines, which included rescue antiemetics. The oncologists at the Oncology Departments, who were not involved in the study, prescribed antiemetics according to the normal clinical routines, at doses according to The Swedish Medicine Information Engine (www.fass.se). The standard care cohort received no acupuncture therapy at all.

Verum and sham acupuncture

In study III and IV, one physiotherapist at each hospital with total of five participating physiotherapists performed both verum and sham acupuncture. They started verum and sham treatments within the first day of radiotherapy and repeated treatments for 30 minutes three times per week the first two weeks, followed by twice per week during the remaining individual length of the patient's radiotherapy period. The therapists performed verum acupuncture with sharp needles inserted bilaterally in the traditional antiemetic point PC6 (Ezzo et al 2006a) and sham acupuncture bilaterally to a non-acupuncture point with Park's sham device (Park et al 1999), placed at a non-acupuncture point (picture 1).



Picture 1. The sham needle (left) was placed at double distance from the wrist compared to the verum needle. The marking tube hold the sham needles in place.

The physiotherapists stimulated the verum and sham needles three times per session, until “deqi” occurred in the verum acupuncture group and for a couple of seconds per stimulation in the sham group. The therapists followed a standardised treatment protocol covering routines for treatment and conversation with the patients (allowing everyday conversations, but avoiding the subject nausea).

In study II, four of the seven physiotherapists involved in study III and IV each provided one single needling to 20 of the 80 participating volunteers. A needling session was conducted identical as the above described procedure with the exceptions: The Streitberger’s telescopic, blunt sham needle (Streitberger & Kleinhenz 1998) was used in the sham group. Plastic rings covered with an adhesive patch marked the needle points in both groups, holding the sham needles in place.

Data collection

In summary, the patients in study I answered a study-specific questionnaire once that included questions regarding emesis, satisfaction with antiemetic treatment, interest in future acupuncture and single-item questions regarding quality of life, physical and physiological condition and satisfaction with the daily living situation (Wiklund et al 1990). Study II used a treatment protocol covering credibility testing (Bang et al 2004), pain (Briggs & Closs 1999) and side-effects induced by the needling. The patients in study III answered questions regarding emesis and satisfaction with the acupuncture, questions repeated during the radiotherapy period. A treatment protocol covering credibility testing (Bang et al 2004), pain (Briggs & Closs 1999) and side-effects during needling was used. Study IV used emesis data regarding one week of radiotherapy, collected in study I and III, and questions on expectations of nausea and of acupuncture effects, collected in study III.

Background and clinical data

Clinical data, for example diagnoses and dose of radiotherapy, were collected from the patients’ medical records. Patients added information on other background variables, for example experiences of previous nausea in other situations, in a written study specific questionnaire (study I, III and IV).

Emesis questionnaire

Study I, III and IV used a study-specific emesis questionnaire measuring the occurrence of nausea and the occurrence and intensity of nausea using category and visual analogue scales (table 2), which are established methods for measuring emesis (Börjeson et al 1997, Boogaerts et al 2000, Rhodes & McDaniels 2001). Within the emesis-questionnaire, nausea was defined as: "An unpleasant nauseating sensation in the gastrointestinal tract that may or may not lead to vomiting when the sensation increases" and vomiting as: "Throwing up stomach contents", in concordance with Rhodes & Watson (1984).

The emesis questionnaire was tested for face-to-face validity in 20 and nine radiotherapy patients before study I and III, respectively. Construct validity has been shown in terms of a correlation coefficient >0.90 between ratings with the nausea category intensity scale and the visual analogue scale, dividing the visual analogue scale in four parts in post operative (Boogaerts et al 2000) and chemotherapy-induced (Börjeson et al 1997) nausea. A pilot study showed a Spearman's correlation coefficient (r_s) of 1.0 between the nausea occurrence category scale and the nausea intensity category scale categorized into two categories (first category: No nausea, second category: Little, Moderately, Much or Very much nausea) in 456 paired observations from ten radiotherapy patients. Test-retest reliability in a total of 36 radiotherapy and chemotherapy patients ranged from $r_s = 0.98$ to 1.0 (table 2) (Enblom et al 2008).

In study I, the patients answered the emesis questionnaire once on their own. The time frame was the preceding 24-hours and the preceding week. In study III the patients answered the emesis questionnaire every morning on their own during the whole radiotherapy period, two weeks afterwards, as well as once four weeks after end of radiotherapy. The time frame was the preceding 24 hours.

In study IV, emesis questionnaire data from one single week of radiotherapy (after a mean dose of 27 Gray of radiotherapy in both cohorts) were used. The standard care cohort answered the questionnaire with the time frames the preceding 24 hours and the preceding week. The acupuncture cohort answered the questions every day with the time frame the preceding 24 hours. Patients who had experienced nausea or vomiting within the preceding seven days were assigned to one of the two groups "Experiencing nausea the preceding week" or "Experiencing vomiting the preceding week".

Table 2. The emesis-questionnaire and questions related to quality of life

Questions	Categories	Spearman's correlation coefficient
The study-specific emesis questionnaire		Test retest reliability⁴
<i>Nausea parameters</i> Have you experienced nausea? If you experienced nausea, how intensive was the nausea? Please also mark the intensity of experienced nausea by providing a mark on the scale below ²	"No", "Yes" "No", "Little", "Moderate", "Much" ¹ A 100 mm visual analogue scale with the anchors marked "No nausea" to "Worst possible nausea"	1.0 1.0 0.98
<i>Vomiting parameters</i> Have you vomited?	"No", "Yes, five ³ times or less", "Yes, five ³ times or more"	1.0
<i>Treatment against nausea</i> Have you taken any medication for nausea (as prescribed, without prescription or complimentary medication)? If you have taken any medication against nausea (as prescribed, without prescription or complimentary medication), which medicine and how often?	"No", "Yes" Type and dose of medicine were stated.	0.527
Single item questions (Wiklund et al 1990)		Construct validity; correlation to...⁵
<i>Physical and psychological condition</i> How would you describe your psychological well-being? What do you estimate your physical capacity to have been? How would you describe your totally capacity? Have you felt anxiety? Have you felt depressed or in a depressed mood?	8-graded scale, with the anchors marked 0="Very poor" and 7="Excellent" 8-graded scale, with the anchors marked 0="Never" and 7="All the time"	
<i>Satisfaction in daily living situations</i> Grade how satisfied you are in situations regarding... <ul style="list-style-type: none"> • ... home and family? • ...working? • ...leisure time? • ...health? • ...condition? • ... sleep? • ...appetite? 	8-graded scale, with the anchors marked 0="Not satisfied at all" and 7="Completely satisfied"	
<i>Quality of life</i> How would you describe your total quality of life?	8-graded scale, with the anchors marked 0="Very poor" and 7="Excellent"	... "Health" = 0.617 ... "Well-being" = 0.776

¹In study III, the question also had the answering category "very much". ²The visual analogue scale was not included in study I. ³In study III, the categorizing point was less/more than 3 vomiting episodes. ⁴Results from 36 patients receiving radiotherapy, chemotherapy or both therapies answering the questions two times. ⁵Results from the 368 patients included in study I, regarding the questions on well-being and health shown in the table.

Self-estimated risk for nausea

Before treatment started, the acupuncture cohort in study IV answered the written question: "In relation to others, how do you estimate your own risk for becoming nauseous during the radiotherapy period?" ("Much lower", "Lower", "Similar", "Higher", "Much higher" risk). The scale was before analysis categorized to "Lower", "Similar" and "Higher" risk, according to another study (Colagiuri et al 2008).

Interest in acupuncture

In study I, the patients answered the question: "If it were possible in the future to choose acupuncture for treatment of nausea, would you like to try acupuncture?" ("Yes, without any pharmacological antiemetics", "Yes, as a complement to antiemetics", "I am not sure, I would like to receive more information", "No, probably not"). The patients stated the actual use of non-pharmacological treatments for nausea. In study III, the patients four weeks after the end of radiotherapy answered the written question: "If you in the future would need a similar radiotherapy, would you then be interested in receiving acupuncture against nausea?" ("No, I am not", "Yes, a little", "Moderately", "Much" interested).

Satisfaction with antiemetic effects

The patients in study I were asked the two questions: "If you received antiemetic treatment during the preceding week, have you been helped by the treatment?" ("Not relevant, I have not experienced nausea", "Yes, I have been much", "Moderately", "A little" helped, "No, not at all helped", "No, I did not receive any antiemetics at all") and "Would you like to receive additional antiemetic treatment?" ("No, nausea is not a problem", "No, I have chosen not to take antiemetics", "Yes, I would like to have additional treatment" and "Yes, I have not received any antiemetic treatment at all").

In study III and IV, the physiotherapist at the end of the first, sixth and last acupuncture treatment asked the patients: "Do you think that the treatment that you just received is effective in preventing and reducing nausea?" ("No, I do not think the treatment is effective", "Yes, I believe a little", "Moderately", "Much" that the treatment is effective).

Measuring quality of life

In study I, the patients with the time frame the preceding week answered single item questions regarding quality of life and dimensions related to quality of life (Wiklund et al 1990): physical and physiological condition (for example well being) and satisfaction with different aspects of the daily living situation (for example health), seen in table 2. The items were developed for the general Swedish population, and have been used by others (Rådestad et al 1997).

The items were validated according to the three steps suggested by Whalen & Ferrans (2001). As a first step, the items were tested for face-to-face validity in 20 radiotherapy patients before study I; patients were asked about their understanding and meaning of the questions. In the second step the results from the patients in study I regarding the item "quality of life" were compared to results regarding the items "health" and "well-being", suggested as measures of dimensions close to quality of life: (Dimenäs et al 1990) (table 2). In the third step the predictive ability of the items were confirmed by comparing patients from study I with and without nausea. According to Whalen & Ferrans (2001) patients who are "more miserable should have different scores than patients who are fine".

Credibility testing

In study II, immediately after the needling the volunteers answered the written question: "What needling type do you think you received?" The needling alternatives were cited as "deep acupuncture" (i.e. invasive acupuncture) and "superficial acupuncture" (i.e. sham acupuncture).

Immediately after the last treatment in study III, the patients were asked a similar question: "Do you think you have been treated with needles that have penetrated the skin, or do you think the needles have been placed just against the surface of your skin?".

In both study II and III the participants were asked: "How sure are you of your answers?" ("Not sure at all, just guessed", "Fairly sure", "Entirely sure"). The participants who were not sure at all were, according to the method by Bang and co-workers (2004, assigned to the category: "Not sure, guessed", whether the guess was correct or not. The patients in study III motivated their answer regarding treatment type by open answers, which were afterwards categorized into categories of motives.

Treatment protocols

In study II and III the therapists during the verum and sham acupuncture treatments asked and inspected the participants regarding the potential occurrence of different negative side-effects or the occurrence of flush around the needling points. Immediately after the treatment in study II and the last treatment in study III the patients graded the overall intensity of pain induced by the needles using a four category scale (Briggs & Closs 1999) (“Not”, “Mildly”, “Moderately”, “Very” painful).

Every seventh day during the radiotherapy period the patients in study III answered the written question: “Have you within or close to the acupuncture sessions experienced any positive effects on...”. Four conditions were exemplified (relaxation, mood, sleep and pain) and each example was answered by “Yes” or “No”.

Data analysis

The statistical methods used in the different studies (table 3) were dependent on data level. For category data Fishers exact test was used comparing two groups and relative risks (RR) with 95 percent confidence intervals (CI) were calculated. For comparing three groups or more, Chi-square test was used. For ordinal data, or for continues but not normally distributed variables, Mann-Whitney U-test was used to compare two samples and Kruskal-Wallis test was used comparing three or more groups. Student’s t-test was used for continues normally distributed variables.

In study II and III, Bang’s blinding index (ranged -1 to 1) was calculated: $\text{number (n) of correct answers} / \text{total n} - \text{n of incorrect answers} / \text{total n}$. 1 indicates complete lack of blinding, -1 indicate opposite answers regarding treatment type and 0 indicate perfectly conducted blinding (Bang et al 2004).

In study IV, a multivariate logistic model was constructed to determine the relative importance of the different patient and clinical characters for explaining the variation in the main outcome; nausea occurrence preceding week (Logistic procedure, forward selection). The statistically significant characters from the logistic model were then analysed in proc Genmod, with a log link and binomial error distribution, to adjust the relative risks for nausea occurrence the preceding week.

The statistic analyses were performed using Statistical Package of Social Science (SPSS) version 11 – 15 in study I-IV, with the addition of SAS version 9.1.3. SAS. Institute inc. Cary, NC, USA in study IV. A significance

level of $p < 0.05$ was used in study II-IV, while $p < 0.03$ was used in study I, to adjust for multiple testing to avoid type 1 errors.

Sample size

In study III, a sample size of at least 100 patients in each group was estimated as being needed to detect a clinically meaningful reduction in nausea prevalence of 20 absolute percent in the verum compared to the sham acupuncture group (80 percent power, one-sided test at five percent significance level, Likelihood Square Test), from an expected nausea prevalence of 60 % in the sham group, based on IGARR (1999).

Table 3. Statistical methods used in the thesis

Method	Study			
	I	II	III	IV
Descriptive statistics				
m, SD	x	x	x	x
md, 25th, 75 th percentile	x	x	x	x
Hypothesis-testing				
Relative risk with 95 % confidence interval	x	x	x	x
Chi-square test: three groups or more			x	x
Fisher's exact test: two groups	x	x	x	x
Mann-Whitney U-test	x	x	x	x
Student's t-test for independent populations			x	x
Kruskal Wallis test		x		
Probability estimation				
Relative risk with 95 % confidence interval	x	x	x	x
Logistic regression				x
Bang's blinding index		x	x	
Calculation of effect-size				
Sample size calculation			x	
Power-calculation		x		

The methods used are marked with x. m= mean, SD = standard deviation, md = median.

Pilot study

A pilot study was conducted before study III, including 10 patients (Enblom et al 2008). The same design for treatment and data collection as in study III was used. The study design, including successfully blinded patients and high compliance with treatments and data collection, was found reliable. A pilot study, for validating the emesis questionnaire only, included 36 patients during one week of radiotherapy or chemotherapy.

RESULTS

Participation rates

In study I, 368 of the 396 included patients answered the questionnaire (93 %) while 28 did not (figure 1) (seven felt too ill/tired, one had eye problems and 20 gave no reason). In study II all 80 individuals completed study participation.

In study III 237 patients were randomised but 22 could not participate (figure 1) (17 patients regretted their consent, radiotherapy was cancelled in three patients and two patients died before the start of the study), leaving 215 patients entering the study, 109 in the verum and 106 in the sham acupuncture group. Of those, 205 provided nausea data, 103 in the verum and 102 in the sham group (95 % of the 215 participating patients). Ninety seven patients in the verum acupuncture group and 100 patients in the sham acupuncture group completed the entire therapy period (92 % of the 215 participating patients). Both the verum and the sham group received a median number of 12 acupuncture treatments.

In study IV, all 62 patients in the standard care group treated over abdominal or pelvic field provided nausea data. In the acupuncture cohort 183 (85 %) of the 215 initially participating patients (88 in the verum and 95 in the sham acupuncture group) participated in the emesis comparisons and 32 did not (17 had finished radiotherapy and 13 had interrupted acupuncture treatment before time for comparison, and two patients did not deliver data).

Characteristics of the participants

Table 4 describes the participants. In study I, the cancer tumour type varied widely. In study IV, 147 (68 %) of the patients in the acupuncture cohort had gynaecological tumours, 60 (28 %) had colon, rectal or anal tumours, 6 (3 %) had pancreas, gallbladder or stomach tumours, and 2 (1 %) had testicular tumours. Within the standard care cohort in study IV, the corresponding figures were 37 (60 %), 11 (18 %), 6 (10 %) and 8 (13 %)

Table 4. Characteristics of the volunteers and patients in the thesis

Characteristics	Study I n=368	Study II N=80	Study III n=215	Study IV n=277
Sex, n (%)				
Man	125 (34)	33 (41)	35 (16)	54 (19)
Woman	243 (66)	47 (59)	180 (84)	223 (81)
Age in years: m ± SD, n (%)	60±12,2	41 ± 12.5	63.7 ± 13.8	63 ± 14.0
15-40	23 (6)	38 (48)	13 (6)	19 (7)
41-60	165 (45)	38 (48)	68 (31)	85 (31)
61-89	180 (49)	4 (5)	132 (61)	171 (62)
Radiotherapy field, n		Not relevant		
Abdomen or pelvis	62		215	277
Breast	160		0	0
Mediastinum	25		0	0
Head and Neck	37		0	0
Prostate or bladder	55		0	0
Brain	22		0	0
Other, for example extremities	7		0	0
Total radiotherapy dose in Gray, m ± SD,	47.3 ± 10.9	Not relevant	49.1 ± 10.6	41.8 ± 10.0
Concomitant chemotherapy n (%)	n=363	Not relevant	n=199	n=260
Yes	51 (14)		57 (29)	72 (28)
At least one antiemetic drug n (%)		Not relevant	n=201	n=263
Yes	57 (15)		79 (39)	105 (40)

m=mean, SD= standard deviation. Number (n) of participants providing data is shown.

Prevalence of nausea and vomiting

Of all patients in study I, 28 (7 %) vomited and 145 (39 %) experienced nausea the preceding week of radiotherapy. The nausea intensity was graded as “little” in 104 (72 %), “moderate” in 27 (19 %) and “much” in 14 (10 %) patients.

Patients receiving radiotherapy over abdominal or pelvic fields had increased risk for nausea (63 %) compared to the reference field breast region (31 %) (RR 2.0, CI 1.5-2.7). The proportions of patients experiencing nausea when irradiated over other body regions were: head, neck and brain 46 %,

mediastinum 36 %, prostate or bladder 33 % and other, for example extremities 29 %. More of the patients radiated over abdominal or pelvic fields experienced at least moderate nausea (15 of 62; 24 %) compared to patients radiated over other fields (26 of 306; 8 %) (RR 2.8, C.I. 1.6 – 5.1).

Risk factors for nausea

As mentioned, abdominal or pelvic field radiation increased the risk for nausea compared to other fields, and some other patient characteristics were also associated with increased risk for nausea. An age younger than 40 years, previous experience of nausea in other situations (study I and IV) and concomitant chemotherapy (study IV) indicated an increased risk for nausea compared to patients with other characteristics (table 5). In study IV, the 27 patients who estimated their risk for nausea as higher than other patients during radiotherapy had an increased risk for nausea (81 % experienced nausea) compared to the 44 patients who estimated that they had a lower risk for nausea than other patients (50 % experienced nausea) (RR 1.6, CI 1.2-2.4).

Table 5. Risk factors for nausea

	Experiencing nausea in study I n=145	Free from nausea in study I n=223	Univariable relative risk for nausea (95 % confidence interval)	Experiencing nausea in study IV n=172	Free from nausea in study IV n=105	Univariable relative risk for nausea (95 % confidence interval)
Age years: m, SD n (%)	58 ± 13.7	61 ± 10.8		62 ± 14.8	65 ± 12.1	
19-40	14 (61)	9 (39)	1.9(1.3-2.7)*	17 (89)	2 (11)	1.5 (1.2-1.8)*
41-60	72 (44)	93 (56)	1.3 (1.0-1.7)	55 (67)	27 (33)	1.1 (0.9-1.4)
61-89	59 (33)	121 (67)	1.0 (Ref.)	98 (60)	66 (40)	1.0 (Ref.)
Previous nausea in any situation	n=144	n=222		n=164	n=255	
No	29 (25)	85 (75)	1.0 (Ref.)	30 (41)	44 (59)	1.0 (Ref.)
Yes	115 (46)	137 (54)	1.8 (1.3-2.5)*	134 (74)	48 (26)	1.8 (1.4-2.4)*
Concomitant chemotherapy, n (%)	n=143	n=220		n=169	n=91	
No	123 (39)	189 (61)	Ref.	112 (60)	76 (40)	1.0 (Ref.)
Yes	20 (39)	31 (61)	1.0 (0.9-0.1)	57 (79)	15 (21)	1.3 (1.1-1.6)*

m=mean, SD= standard deviation. Numbers (n) of patients answering the question are presented.*Patient characteristics that implied a statistically significant increased risk for nausea compared to the reference (ref) groups (the sub groups of patients having the lowest prevalence of nausea)

Effects of acupuncture treatments

Verum acupuncture compared to sham acupuncture

All 109 and 106 patients receiving verum and sham acupuncture in study III were included in the analysis, according to intention to treat. The six patients in the verum group and the four patients in the sham group, who did not deliver data, were classified as “experiencing nausea”. The proportion of patients experiencing at least one episode of nausea within the radiotherapy period was not statistically significant different in the verum (n=77 of 109; 70 %) compared to the sham acupuncture group (n=66 of 106; 62 %) (RR 1.1, CI 0.9-1.4, p=0.12). Secondary analyses based only on patients providing information on emesis data were similar, showing no significant differences between the verum acupuncture group in nausea (71 of 103) or vomiting (25 of 100) compared to the sham acupuncture group (nausea 62 of 102, p=0.14, and vomiting 28 of 100, p=0.63).

Thirteen patients in the verum and 25 patients in the sham acupuncture group (p=0.03) consumed corticosteroids for emesis. Did the higher consumption protect the sham group from nausea? An analysis of the 25 patients who received corticosteroids in the sham group showed that 21 (84 %) experienced nausea and 4 did not (16 %).

The mean number of days with nausea within the whole radiotherapy period was 10.1 (\pm 10.4) in the verum and 8.7 (\pm 7.9) in the sham acupuncture group (p=0.61). The mean number of nausea days (figure 2) and the proportion of patients experiencing nausea or vomiting (figure 3) varied during the radiotherapy weeks without any statistically significant differences between the groups at any week. The intensity of nausea measured on a category scale was at least moderate in 38 % and 36 % of the nausea days in the verum and the sham acupuncture group, respectively (figure 4). The intensity of nausea on the visual analogue scale ranged during the whole radiotherapy period (133 nauseous patients provided data) from 0-96 mm in the verum and from 0-94 mm in the sham acupuncture groups (absolute values). The median levels was 5 mm (25th -75th percentile 1-10) in the verum and 6 mm (25th -75th percentile 3-12) in the sham acupuncture group (p=0.61).

In the sub group of 57 patients receiving chemotherapy at least one week of the radiotherapy period 23 of 28 (82%) in the verum acupuncture group and 24 of 29 (83 %) in the sham group experienced nausea at least once during the radiotherapy period.

Number of days with nausea per week

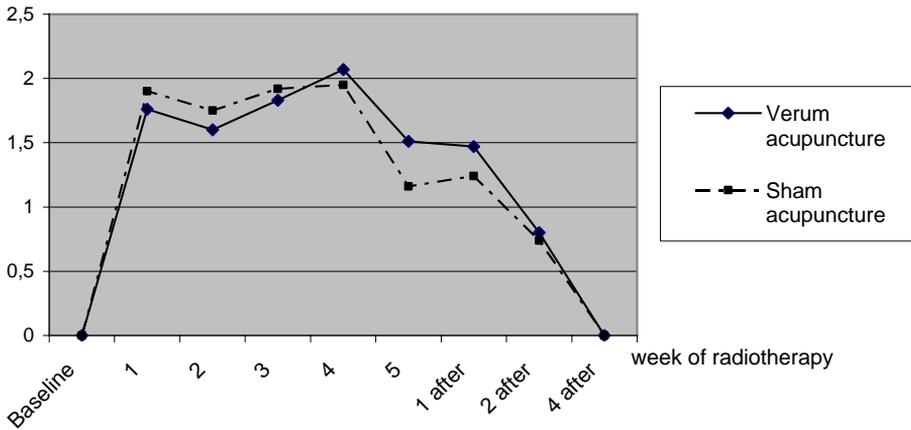


Figure 2. Mean number of nausea days per week in the patients who experienced nausea at least once within the radiotherapy period in the verum (n = 71 of 109 were nauseous) and the sham acupuncture group (n = 62 of 106 were nauseous). 103 in the verum and 102 in the sham group delivered data.

% of the patients experiencing nausea or vomiting

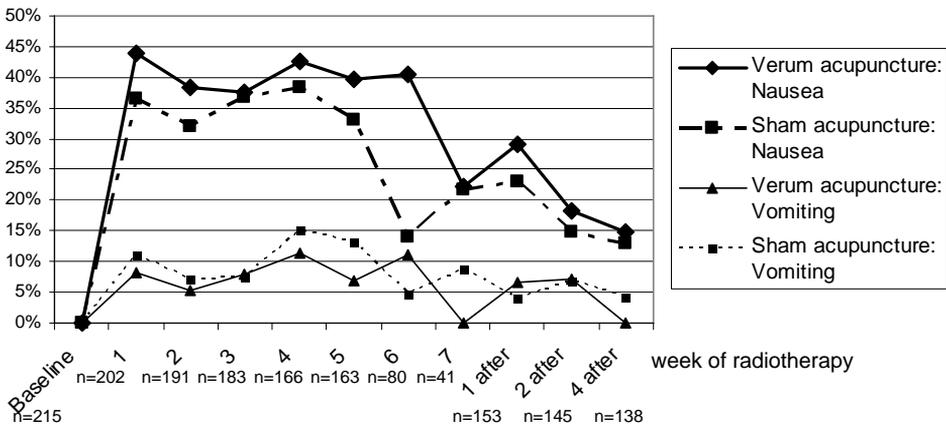


Figure 3. Percent of patients experiencing nausea and vomiting per week during and after radiotherapy. The number (n) of treated patients who provided data decreases due to the individual length of radiotherapy. Of the 197 patients fulfilling the treatment period 138 participated in the four week follow-up and 59 did not (decreased condition n=8, patient died n=2, unknown reason n=49).

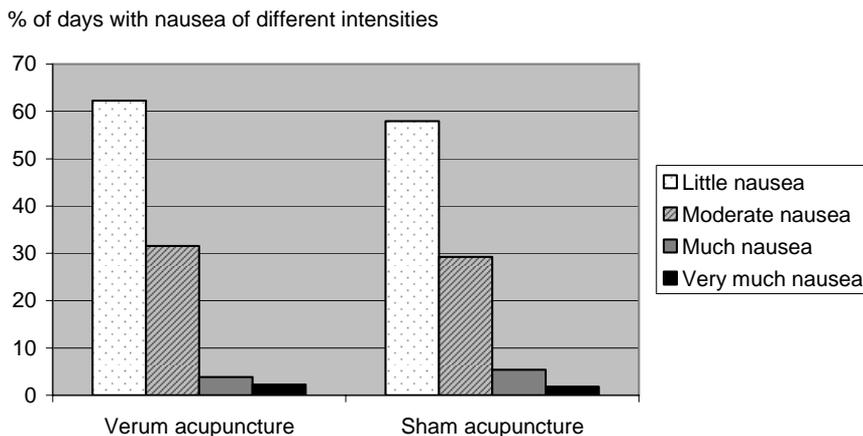


Figure 4. Percent of days (mean value) with nausea on different intensities in the patients who experienced nausea at least once within the radiotherapy period in the verum (n = 71 of 109) and the sham acupuncture group (n = 62 of 106). 103 in the verum and 102 in the sham group delivered data.

Verum and sham acupuncture compared to standard care

In study IV, statistically significant higher percentages of patients experienced nausea (63/37 %, RR 1.7, CI 1.3-2.2) and vomiting the past week and the past 24 hours in the standard care cohort compared to the acupuncture cohort, both in all patients and when patients taking serotonin-receptor antagonists and corticosteroids were excluded (figure 5). The higher prevalence of nausea in the standard care group during the preceding week remained statistically significant after adjustment for concomitant chemotherapy (RR 1.7, CI 1.3-2.2), age (RR 1.6, CI 1.2-2.1), previous nausea (RR 1.7, CI 1.3-2.2) as well as after overall adjustment (RR 1.2, CI 1.1-1.4).

The intensity of nausea was lower in the acupuncture cohort (180 provided data): 140 (78 %) experienced no nausea, 24 (13 %) a little nausea, 14 (7 %) moderate nausea and two (1 %) much nausea compared to the standard care cohort: 32 (52 %) no nausea, 20 (32 %) a little, 9 (14 %) moderate and one (2 %) much nausea (p=0.002).

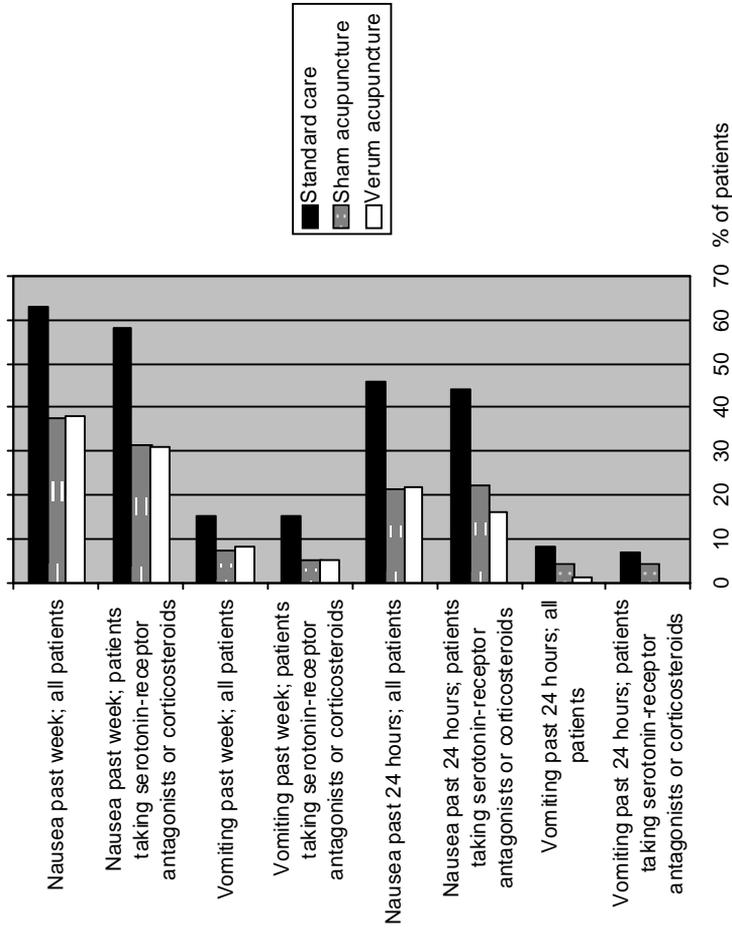


Figure 5. Nausea and vomiting within the past 24 hours and the past week, measured at that time the radiotherapy dose was 27 Gray (mean) in the verum, sham and standard care groups. Measured in all patients and in patients not receiving potent antiemetics in the verum (n=88 and n=77), sham (n=95 and n=78) and standard care group (n=62 and n=55).

Interest in acupuncture

In study I, none of the 368 patients reported use of any non-pharmacological treatment for emesis. Of the 361 patients answering the question regarding interest in acupuncture treatment for nausea; 40 % said that they would like to try acupuncture to treat nausea (19 % without any pharmacological antiemetics and 22 % as a complement to antiemetics); 38 % were not sure and asked for more information about the method and 22 % answered that they probably would not try acupuncture. In study III, equal proportions (89 %) in the verum and sham acupuncture group were moderately or much interested in receiving the same treatment again in the future (table 6).

Satisfaction with antiemetic effects

Of the 145 patients who experienced nausea in study I, 36 (25 %) stated they had received antiemetics that had helped them moderately or much. Fifty (34 %) would have liked additional treatment.

In study III, almost all patients treated with verum or sham acupuncture thought at the last treatment that the received treatment had been effective for nausea, whether the nausea had occurred within the radiotherapy period or not (table 6). Ninety-six percent of the patients in study III who had experienced nausea at some time during the radiotherapy period believed at baseline moderately or much that the treatment would be effective for nausea. Similar percentages (91 %) were seen in those who stayed free from nausea (table 6).

Quality of life in patients with and without nausea

In study I, the 145 patients who experienced nausea within the preceding week rated lower level of total quality of life, physical capacity and well-being, had more frequent anxiety and depressed mood, and were less satisfied with different aspects of daily living compared to the 223 patients who were free from nausea within the preceding week (figure 6, p-values varied <0.001 to 0.001).

Table 6. The belief in antiemetic effect and interest in receiving acupuncture again in study III

Variable	Verum acupuncture n=109	Sham acupuncture n=106	Experienced at least one episode of nausea within the radiotherapy period n=133	Free from nausea during the whole radiotherapy period n=72
Belief in antiemetic effects of the treatment stated at baseline number (%)	n=105	n=105	n=130	n=71
Do not believe	0 (0)	0 (0)	0 (0)	0 (0)
Believe little	5 (5)	6 (6)	4 (3)	6 (8)
Believe moderately	50 (46)	57 (54)	70 (54)	32 (45)
Believe much	50 (46)	42 (40)	56 (43)	33 (47)
Belief in antiemetic effects of the treatment, stated at the last treatment number (%)	n = 95	n = 95	n=120	n=70
Do not believe	0	1 (1)	1 (1)	1 (1)
Believe little	5 (5)	3 (3)	7 (5)	1 (11)
Believe moderately	30 (32)	35 (37)	47 (39)	18 (26)
Believe much	60 (63)	56 (59)	65 (54)	51 (73)
Experienced other positive effects of the received treatments at least once number/number answering the question (%)				
Relaxation	56/96 (58)	56/97 (58)		
Mood	44/94 (47)	35/95 (37)		
Sleep	36/96 (38)	36/93 (39)		
Pain-reduction in general	33/94 (35)	26/91 (29)		
Interested in receiving the same treatment again, stated at four-weeks follow-up number (%)	n = 64	n = 71	n=84	n=51
Not interested	2 (3)	5 (7)	4 (5)	3 (6)
Little interested	5 (7)	3 (4)	6 (7)	2 (4)
Moderately interested	14 (22)	15 (21)	21 (25)	8 (16)
Much interested	43 (67)	48 (68)	53 (63)	38 (75)

Numbers (n) of patients answering the questions are presented. Two of the 97 and five of the 100 patients completing the verum and sham acupuncture period could at the last treatment not be asked (radiotherapy was interrupted before the last planned verum or sham acupuncture treatment). Out of the total of 197 patients who fulfilled their individual length of therapy period, 135 answered the four-weeks follow-up question while 62 did not (reasons: did participate at the follow-up but did not answer the specific question; n=3, decreased general condition; n=8, patient died; n=2, unknown reason; n=49).

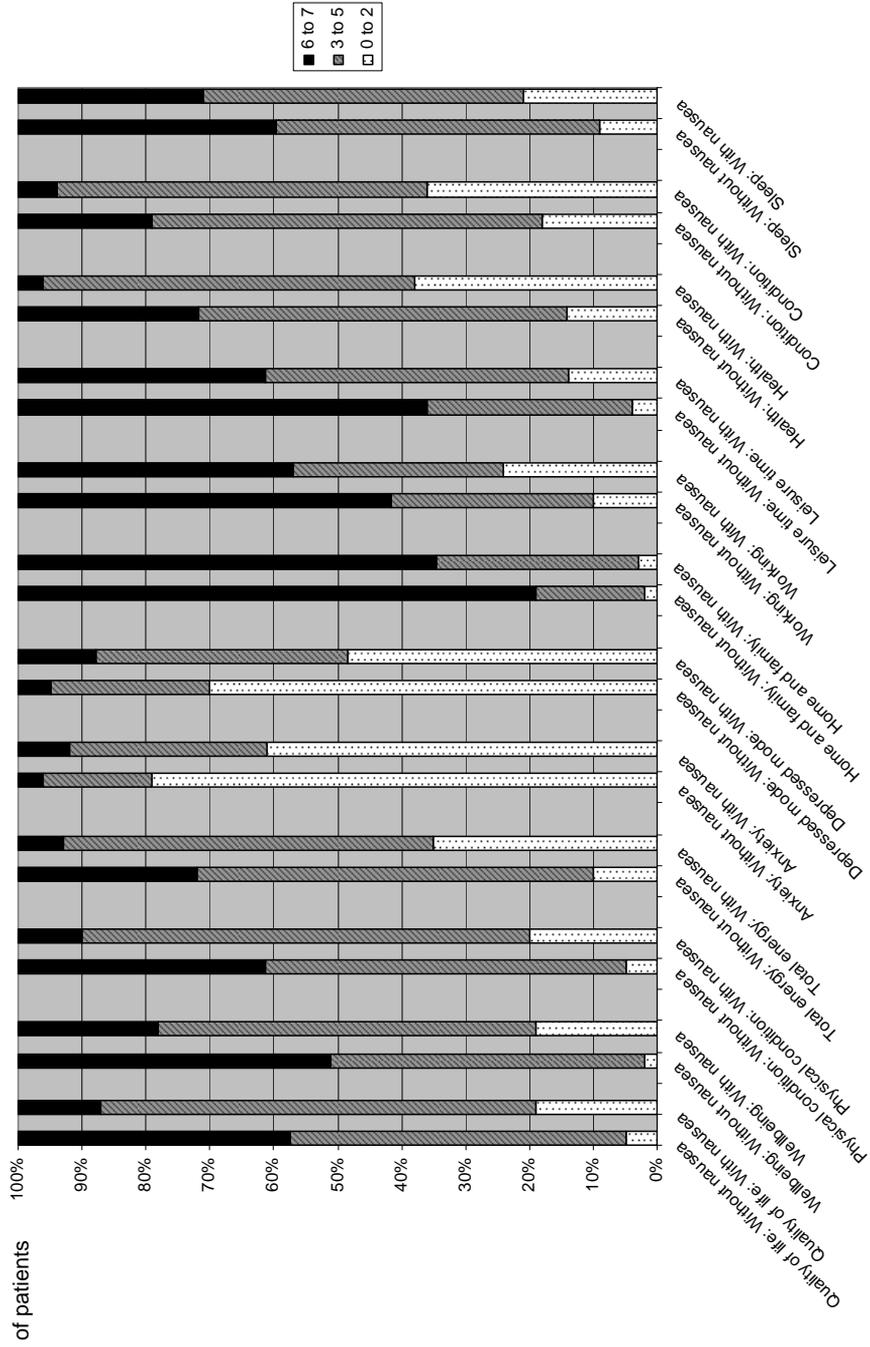


Figure 7. Self-assessed physical and psychological outcomes, global quality of life and satisfaction in daily living situations in patients with and without nausea (n = 368). Assessments on an 8-grade scale, 0 = lowest possible level and 7 = highest possible level. Percentages of patients without nausea (n = 223) and with nausea (n=145) within the preceding week.

Credibility of sham needles

In study II, 20 individuals in the verum acupuncture group answered that they thought they received verum acupuncture (i.e. stated deep acupuncture; 7 of them just guessed while 13 were fairly or entirely sure on their answer. In the sham group 27 individuals answered that they thought they received sham acupuncture (i.e. stated superficial acupuncture); 14 of them just guessed while 13 were fairly or entirely sure on their answer. Two thirds (n=27) of the individuals in each group could thus not identify needling type (answered incorrect or just guessed). The blinding index (Bang et al 2004) results (table 7) indicate that the proportion of individuals who were unblinded beyond statistical chance did not differ between the verum (20 %) and the sham (10 %) acupuncture group. The proportion of unblinded individuals did not statistically significantly differ between the therapists (p=0.397).

In study III most patients, albeit fewer in the sham (77; 81 percent) than in the verum acupuncture group (87; 92 percent), answered that they thought they were given treatment with penetrating needles (p=0.037). Of the 17 patients in the sham group who answered that they had been treated with non-penetrating needles, 15 still believed moderately or much in the antiemetic effect at the last treatment. Of the 87 patients in the verum acupuncture group in study III who answered they received verum acupuncture, 13 just guessed their answer, while 74 were fairly or entirely sure on their answer. Of the 17 patients in the sham group who answered that they had received sham acupuncture, 6 just guessed, while 11 were fairly or entirely sure on their answer. Twenty one (22 %) in the verum group and 84 (88 %) in the sham group could thus not identify needling type (answered incorrect or just guessed). The blinding index (Bang et al 2004) results (table 7) indicate that more patients in the verum acupuncture group (72 %) compared to the sham acupuncture group (16 %) identified needling type beyond statistical chance.

In the verum (n=95) and sham acupuncture (n=95) group in study III, 56 (59 %) and 41 (43%) of the patients motivated their answer regarding treatment type by that they "felt or saw signs of penetration", 4 (4 %) and 12 (13 %) by "lack of feelings or signs of penetration", 1 (1 %) and 1 (1%) by "felt effects or side-effects", 1 (1 %) and 0 by lack of effects or side-effects while 33 (35 %) and 41 (43 %) gave no motive, respectively.

Table 7. The ability to correctly identify if verum or sham acupuncture was given

Study II	Total n = 80	Stated: Deep acupuncture ¹	Stated: Superficial acupuncture (sham) ¹	Not sure, guessed	Bang's blinding index ² (95 % Confidence interval)
Verum acupuncture n (%)	n=40	13 (33)	5 (13)	22 ³ (55)	0.20 (0.03 - 0.36)
Sham acupuncture	n=40	9 (23)	13 (33)	18 ⁴ (45)	0.10 (0.09 - 0.29)
Totals n (%)	n=80	22 (28)	18 (22)	40 (50)	Not calculated
Therapist A	n=20	4 (20)	2 (10)	14 (70)	
Therapist B	n=20	9 (45)	3 (15)	8 (40)	
Therapist C	n=20	7 (35)	5 (25)	8 (40)	
Therapist D	n=20	6 (30)	4 (20)	10 (50)	
Study III	Total n=190	Stated: Penetrating the skin ¹	Stated: Placed against the skin ¹	Not sure at all, guessed n (%)	
Verum acupuncture n (%)	n=95	74 (78)	6 (6)	15 (16) ⁵	0.72 (0.68-0.86)
Sham acupuncture n (%)	n=95	68 (72)	11 (12)	16 (17) ⁶	0.16 (0.06-0.20)

The number (n) of patients is presented. In study III n=190 (two of the 97 patients who completed the verum acupuncture period and five of the 100 patients who completed the sham period could not be asked, because radiotherapy was interrupted before the last planned acupuncture treatment). ¹The individuals were fairly or entirely sure of their answer. ²Correct answers / total n - incorrect answers / total n. ³Seven guessed correct and 15 guessed incorrect. ⁴Fourteen guessed correct and four guessed incorrect. ⁵13 guessed correct, 1 incorrect and 1 stated he/she could not answer. ⁶6 guessed correct, 9 incorrect and 1 stated he/she could not answer. (Unblinded participants are marked with an ellipse.

Positive and negative side-effects of acupuncture

In study III, 67 % of 96 answering patients in the verum acupuncture group reported that they experienced some kind of positive side-effects of the acupuncture: 59 % on relaxation, 47 % on mood, 38 % on sleeping and 35 received pain-reduction in general. Corresponding figures for the 97 answering patients in the sham acupuncture group were similar: 67 %, 58 %, 37 %, 39 % and 29 %.

Negative side-effects were few and minor, both in study II and III (table 8). A minimal bleeding around the needle point was the most common negative side effect and occurred in 104 of the in total 1166 verum acupuncture treatments performed (9 %) in study III.

Both verum and sham acupuncture were mostly graded as not painful, or only a little painful in study II and III (table 8). Verum acupuncture was perceived as more painful than sham acupuncture (p<0.001) in study III, but not in study II (p=0.36). The ratings of needle-induced pain differed

between the individuals needed by the different therapists ($p=0.01$) in study II. Flush around the needling points was commonly registered in both the verum and the sham group and was more common in study II than in study III (table 8).

Table 8. Verum/sham acupuncture related variables in study II and III

Variable	Study II		Study III	
	Verum acupuncture n=40	Sham acupuncture n=40	Verum acupuncture n=109	Sham acupuncture n=106
Missed sessions within the treatment series, $m \pm SD$	0	0	0.37 ± 1.18	0.43 ± 0.82
Needle-induced pain, n (%)	30 ¹	30 ¹	n=95	n=95
Not painful	13 (43)	17 (57)	42 (44)	74 (78)
Mildly painful	15 (50)	11 (37)	37 (39)	19 (20)
Moderately painful	2 (7)	1 (3)	14 (15)	1 (1)
Very painful	0	1 (3)	1 (1)	0
Flush around needle points, n (%)	15 (38)	22 (55)	32 (29)	25 (24)
Negative side-effects within/close to the treatment/s, n (%)				
Bleeding around needle points	6 (15)	0 (0)	51 (47)	0 (0)
Tiredness	5 (13)	3 (8)	15 (14)	15 (14)
Dizziness	4 (10)	2 (5)	8 (7)	5 (5)
Needle scratched the skin	0 (0)	2 (5)	0 (0)	10 (9)

The numbers (n) of patients providing data are presented. Out of the 97 and 100 patients who completed the verum and sham acupuncture period in study III, two and five patients, respectively, could not be asked because radiotherapy was interrupted before the last planned acupuncture treatment. ¹Only the 30 last included volunteers in each group were asked to rate needle-induced pain.

DISCUSSION

Main findings

The main findings of the thesis were that verum acupuncture was not more effective than sham acupuncture in reducing nausea or vomiting during radiotherapy over pelvic or abdominal fields, but nearly all patients in both the verum and the sham group experienced that the treatment was effective for nausea. Patients treated with penetrating manual “deqi”-creating verum acupuncture or sham acupuncture experienced reduced nausea and vomiting compared to patients receiving standard care. The telescopic sham needle was credible for use in control groups to simulate acupuncture but there was a tendency that the therapist influenced level of blinding.

In an ordinary standard care setting, 39 % of radiotherapy patients in general and 63 % of patients receiving radiotherapy over abdominal or pelvic fields experienced nausea during an ordinary week of radiotherapy. Abdominal or pelvic radiotherapy field, age younger than 40 years, prior experience of nausea, concomitant chemotherapy or a self-estimated risk for nausea as higher than other patients indicated an increased risk for nausea during radiotherapy. Only one fourth of the patients who experienced nausea after receiving standard care during radiotherapy felt that antiemetics had helped them, while a third would have liked additional antiemetic treatment. The patients who experienced nausea reported lower satisfaction with aspects of daily living, lower level of quality of life and physical condition, and experienced more anxiety and depressed mood than the patients without nausea.

Discussion of the findings

Nausea reducing effects of acupuncture

The findings that nausea and vomiting were not reduced by verum acupuncture compared to sham acupuncture indicate that the specific characters of verum acupuncture, sharp needles penetrating the skin in traditional acupuncture points and “deqi” stimulation, are not effective in reducing nausea.

Although acupuncture is used all over the world, there are few sham-controlled studies exemplifying acupuncture as preventive or reducing treatment for nausea during cancer treatment. As concerns the use of

acupuncture for chemotherapy-induced nausea, there was (according to a search in data-bases 20th October 2008 in PubMed, AMED and CINAHL), only one of the two sham-controlled studies of high methodological quality that showed reduction of vomiting, as a result of electro-acupuncture compared to superficially inserted needles with the illusion of electro stimulation (Shen et al 2000). The other study showed no reduction in nausea or vomiting as a result of verum manual acupuncture compared to sham provided with the telescopic sham needle (Streitberger et al 2003); one possible reason may be that electro-acupuncture is more effective than manual, superficial needling. However, in the study by Shen and co-workers (2000), almost 50 % fewer patients (18 %) in the superficial needling group thought they received classical acupuncture compared to the electro-acupuncture group (30 %), which may indicate blinding failure.

In study IV, emesis occurred to a lower extent in both patients treated with verum and sham acupuncture compared to patients receiving standard care, in concordance with several, not sham controlled, studies investigating verum acupuncture as a means of reducing chemotherapy-induced nausea (Ezzo et al 2006b). Acupuncture has been suggested to be a cost effective method for reducing pain (Wonderling et al 2004) and the costs for performing the acupuncture in study III were low, according to a crude calculation. Using the median number of 12 30-minute long verum or sham acupuncture treatments, treating two patients (median) at the same time, one patient consumed three therapist-hours. That results in a mean cost per patient of 408 Swedish crowns (SEK) (mean salary for a public hospital physiotherapist, according to Swedish Association of Registered Physiotherapists 2007), with the addition of the cost of 24 needles (\$ 0.06 USD/needle, according to prices on <http://www.acuprime.com>, totally less than five SEK). In comparison, the approximate costs of the recommended dose of 8 mg of a serotonin-receptor antagonists once per day (a' 16.25 SEK according to prices on <http://www.fass.se>) during the radiotherapy period is 850 SEK.

That both patients treated with verum and sham acupuncture experienced lower occurrence of emesis compared to standard care indicates that different unspecific factors, not related to penetration and "deqi" stimulation, may reduce nausea during radiotherapy. The verum and sham performing therapists avoided conversations regarding emesis but might have had a supportive attitude in general. Patients participating in supportive conversations regarding their situation during chemotherapy reported increased well-being, compared to patients receiving standard care (Arving et

al 2007, Börjeson et al 2002). An indication that it may be the extra care, not the sensory stimulation of the sham needle itself that was effective in the current study is provided by the findings by Kapthuk and co-workers (2008). Of 87 patients who received sham acupuncture from an emphatic, communicating therapist 62 % reported adequate symptom relief of irritable bowel symptoms, compared to 44 % of 88 patients receiving sham acupuncture from a non-communicating therapist, and 28 % of 87 patients on waiting list.

The extra time for rest and relaxation and the slightly more tactile stimulation from the therapists' hands and the blunt needles in the acupuncture cohort, compared to the standard care cohort, may have induced a release of oxytocin (Uvnäs-Moberg et al 1993) and a reduction of distress and emesis. Psychological distress has been seen as a predictor for emesis (Zachariae et al 2007) and studies indicate that relaxation (Luebbert et al 2001, Yoo et al 2005) as well tactile stimulation (Myers et al 2008) may reduce emesis in cancer patients. Billhult and co-workers (2007) reported that patients who received massage five times during five weeks of weekly chemotherapy experienced median 80 % reduction of nausea. Patients receiving five visits including every-day conversations experienced less nausea reduction, 45 %.

Since almost all patients in the acupuncture cohort in study IV expected positive antiemetic effects of the treatment, these expectations may be another unspecific factor that reduced nausea in the acupuncture cohort. In study IV, there were no differences in reported nausea between the patients who believed more and those who believed less in the antiemetic effects of treatment. Either expectations about the effects of treatment are not important in reducing nausea, or the category scale that was used was not sensitive enough, resulting in a "roof effect". Linde and co-workers (2007) found that patients who had high expectations of pain-reduction from acupuncture reported better effects than patients with low expectations, irrespective of the actual type of acupuncture given, verum or sham. Patients believing they were treated with verum acupuncture reported larger pain-reduction compared to patients believing they were treated with sham acupuncture, irrespective of the actual type of acupuncture given (Bausell et al 2005). Expectations may be a more important part of the effect than the sensory stimulation from the blunt sham needles itself. The telescopic sham acupuncture activated mid-brain sensory regions when the individuals were informed that the sham was effective, while a sham needle that the individuals were told was ineffective did not (Pariente et al 2005).

Credibility of the acupuncture procedures

The findings of study II and III agree with previous studies that individuals treated with the telescopic sham needle do not seem to recognize that a non-penetrating treatment was given (Streitberger & Kleinhenz 1998, Park et al 2002b, White et al 2003, Park et al 2005, Tsukayama et al 2006, McManus et al 2007). White and co-workers (2003) reported that blinding results varied between two therapists, and study II in this thesis found that the therapists influenced needle-induced pain and in some way also influenced the level of blinding. In study II and III few individuals in the sham acupuncture groups were unblinded beyond statistical chance. In study III a large majority in the verum acupuncture group recognized they had been treated by penetrating needles.

That the majority of patients, irrespective of group, believe they are treated with the “best” available option is similar what has been reported from other randomised controlled trials using the sham needle (Park et al 2005, McManus et al 2007) and using placebo pills (Desbien et al 2002). This is what Bang and co-workers (2004) called “high response bias”. Since both groups in study III believed they were treated by verum acupuncture and had high and equally positive expectations, differences in blinding did not therefore seem to affect the emesis results, in concordance with the logic by others (Bang et al 2004, Desbien et al 2002).

Satisfaction with acupuncture and standard care treatment

Almost all patients treated by verum or sham acupuncture in study III believed that the treatment was effective for reducing nausea, they were interested in receiving the same treatment again for nausea and experienced substantial positive effects regarding relaxing, mood, sleep and pain reduction in general. Those subjectively experienced positive side-effects may be very valuable since patients often experience nausea, sleeping problems, pain, fatigue, anxiety and low mood during radiotherapy (Chang & Ingham 2003, Hickok et al 2005). Odsberg and co-workers (2001) reported that positive side-effects (effects other than the intended) occurred in 27 % of 9277 verum acupuncture sessions given by 187 Swedish physiotherapists, mostly pleasant drowsiness, calmness and improved sleep. The positive side-effects that appeared in the present study III may be related to the caring situation, not to the specific characters of acupuncture.

In study II and III, few negative side-effects of the verum or sham acupuncture were seen. That is in concordance with White and co-workers’

(2001b) findings showing few negative side-effects of acupuncture in general. Flushing around the needle points was common, partly as a result of verum and sham needle stimulation. Since flushing was seen more frequently in study II compared to study III, the patch used in study II may have irritated the skin more compared to the double sticky guide-tube used in study III.

Of the patients who experienced nausea and received standard care during radiotherapy in study I, only a fourth felt that antiemetics had helped them at least moderately, while a third would have liked additional antiemetic treatment. That indicates that in daily radiotherapy practise, health care professionals may underestimate nausea, in line with several earlier studies (IGARR 1999, Foubert & Vaessen 2005, Horiot & Aapro 2004, Feyer et al 2008). Nausea is a subjective symptom that is not clearly seen by others unless the patient also vomits or complains about nausea (Jenns 1994).

The low satisfaction with antiemetic treatment in study I may be due to the low utilization of antiemetics, since 61 % of all patients with nausea did not receive any antiemetics at all and only 8 % of them received serotonin-receptor antagonists. Of patients receiving abdominal or pelvic irradiation, 11 % in study I (study period 1999 and 2003) consumed serotonin-receptor antagonists compared to 20 % in study III (study period 2004 to 2006). The change in antiemetic prescriptions may be due to the fact that the first placebo-controlled studies of serotonin-receptor antagonists were not published until the early 1990s (Cubeddu et al 1990).

It may be considered important to identify and satisfactorily treat patients with risk for emesis (Jenns 1994, Naemin et al 2008) since dissatisfaction with antiemetic treatment has been reported to reduce quality of life during chemotherapy treatment (Bosnjak et al 2000). Uncontrolled nausea may also lead to anticipatory nausea, which can continue for several years (Jenns 1994, Horiot & Aapro 2000).

Prevalence of and risk factors for nausea

In study I, 39 % of the radiotherapy patients, irrespective of radiotherapy field, and 63 % of patients irradiated over abdominal and pelvic fields experienced nausea within an ordinary week of radiotherapy. IGARR (1999) and Hickok and co-workers (2005) reported that 39% and 33 % of patients in general experienced nausea during the radiotherapy period. Of abdominal radiated patients 58 to 68 % experienced nausea in other studies (Mystakidou et al 2006, IGARR et al 1999). Findings regarding prevalence of nausea may vary greatly between different oncology departments in a national and international

perspective. Feyer and co-workers (2008) recruited 4538 patients undergoing different types of cancer treatments in 49 German oncology departments. The general prevalence of nausea varied from 33 to 73 % between the departments.

A tool for estimating risk for radiotherapy-induced nausea is the international emesis risk classification systems (Maranzano et al 2005, Kris et al 2006). According to MASCC (Multinational Association of Supportive Care in Cancer) (Maranzano et al 2005), the emetic risk is divided into four levels: high risk (>90%) in total body irradiation, moderate risk (60–90%) in upper abdomen, low risk (30–59%) in lower thoracic and pelvic region and minimal risk (<30%) in cranium, breast, extremities and head and neck field.

The classifications do not consider personal risk factors. An age younger than 40 years, prior experience of nausea and concomitant chemotherapy implied an increased risk for nausea during radiotherapy in study I and IV. One possible reason that the same patient characteristics increased the risk for nausea in study IV compared to results from study I was that 62 patients were included in both study I (out of 368 patients) and in study IV (out of 279 patients). However, lower age and previous experience of nausea are known as risk factors for chemotherapy-induced nausea (Schwartzberg 2007) and have been suggested to be valid factors affecting the incidence of radiotherapy-induced nausea (Abdelsayed 2007).

In study IV, the patients in the acupuncture cohort who expected nausea had increased risk for nausea compared to patients who expected low risk for nausea. That is in concordance with Colagiuri and co-workers (2008) who studied 671 patients receiving chemotherapy. The patients who before chemotherapy expected to experience nausea after therapy experienced doubled nausea on a 7 grade scale, compared to patients not expecting increased risk for nausea. A similar relationship was seen by Higgings and co-workers (2007).

Nauseous patients experienced lower quality of life

The intensity of nausea reported in studies I, III and IV was generally low. However, the nauseated patients in study I still reported lower level of quality of life and physical condition, more frequent anxiety and depressed mood and lower satisfaction with different aspects of daily living compared to the patients who were free from nausea. Study I was not designed to evaluate whether the differences in quality of life between the nauseated and the nausea-free patients were *consequences* of nausea, or if the differences already existed before nausea occurred. Shun and co-workers (2008) observed 99

patients with liver cancer from start to finish during six weeks of radiotherapy and nausea was one of the symptoms that most severely reduced quality of life. The usually long duration of nausea during radiotherapy (Feyer et al 2005, Shun et al 2008), may be one conceivable explanation why patients with nausea, even if of low intensity, feel poorer in so many ways compared to patients free from nausea. Longer duration of nausea decreased well-being in patients receiving chemotherapy, even when nausea intensity was controlled for (Börjeson et al 2002).

Ethical considerations

All participants gave their informed written consent and could interrupt their participation any time, without giving any reason. The patients in study I, III and IV were treated according to ordinary clinical praxis, so the verum or acupuncture treatments were given in addition to, for example, antiemetics. The standard care cohort in study IV was not excluded from any kind of treatment, because acupuncture was not routinely practised at the radiotherapy departments at that time. The sham treatment was not aimed to be an optimal antiemetic treatment; nevertheless the sham group received extra care. It was necessary in study III to randomise half of the patients to sham treatment, because the effect of the specific characters of verum acupuncture compared to sham were not previously known. The participants in study II and III reported low pain ratings and minor negative side-effects during acupuncture.

The patients in study I, III and IV could have been bothered in some way by the process of data collection. However, the high answering rates indicate that the data collection was not too particularly bothersome for these patients. The patients in the standard care cohort answered the emesis questionnaire only once. To pay extra attention to nausea through daily data collection, without performing any extra nausea-reducing treatment or care in this frail patient cohort, was estimated to be unethical.

Methodological considerations

Study I to IV followed Steineck's hierarchical model (Steineck et al 2006) to avoid bias in the design and the interpretation of data. The main steps of the model are: A large population size providing good precision, inclusion of a study population without selection errors, identification and measurement of all potential confounding factors, pilot studies to learn how to create a reliable

study design providing high patient compliance, avoiding interviewer-related bias by giving questions to be answered privately in written form and with questionnaires to be returned in secrecy to avoid conscious bias and careful attention to face-to-face validation and pilot studies to formulate well-understood questions to minimize attrition and measuring errors, and use of relevant statistical methods. If the primary findings of the thesis are not valid, for example if the specific characteristics of acupuncture are actually effective in reducing nausea, the findings could depend on methodological flaws within the steps of the hierarchical model. In summary, there do not seem to be serious problems concerning internal validity that might explain the findings of the thesis, but several methodological steps do need to be examined and discussed carefully.

Generalizability

The individuals and patients who did not want to participate in the studies do not affect the internal validity of the studies of the thesis, but they do affect the external validity, the ability to generalize the results to other cohorts. There were 121 patients who did not want to participate in study III, so the findings are only applicable to groups of patients who want to receive acupuncture treatments.

The ability to generalize the results regarding the prevalence of nausea and vomiting from study I, III and IV is limited. The radiotherapy routines and routines for pharmacological and non-pharmacological treatment may differ in a national and an international perspective, thus affecting the emesis risk. Eighteen percent of the nauseous patients in study I believed there were more factors causing them to experience nausea than the radiotherapy alone. Exclusion of those patients was considered as inappropriate, since the study was intended to reflect an ordinary clinical situation. Patients undergoing radiotherapy often are affected by several factors that might induce nausea, factors such as medications and anxiety. Approximately a fourth of the patients in study III received concomitant chemotherapy during at least one week of radiotherapy. Concomitant chemotherapy was not an exclusion criterion, since the randomized design divided the patients equally into the two randomization arms.

Study II increased the therapists' knowledge regarding standardization of verum and sham acupuncture treatments. However, the completely different blinding index results from study III compared to study II imply that blinding results from health volunteers receiving one single

needling cannot be generalized to patient cohorts receiving several treatments. It would have been more appropriate to test the blinding in patients, which was done in the performed acupuncture pilot study including a total of 101 verum or sham acupuncture treatments, given to ten patients undergoing radiotherapy (Enblom et al 2008).

Study compliance

Strengths in the thesis include the high - over ninety percent - response rates to data collection in study I to IV. In study III, very few patients in the verum and sham group interrupted study participation during the radiotherapy period. The response rate decreased in both groups after the end of therapy in study III, but the time points were not included in calculation of the primary outcome.

Except for the patients who interrupted acupuncture in study III, there also were 22 patients who were randomized, but for several reasons could not participate. Hypothetically, all 11 patients who were randomized to verum acupuncture could have stayed free from nausea, and the 11 patients who were randomized to sham acupuncture could have experienced nausea. However, it would not have changed the interpretation of the results regarding nausea occurrence (verum acupuncture group 771 of 120; 64 %, sham group 78 of 117; 67 % (RR 0.96, CI 0.8-1.2).

The 28 patients who did not answer the questionnaire in study mentioned tiredness as a common reason. Fatigue is known to correlate with emesis (Ahlberg et al 2005), so the no-answering patients in study I may have had increased risk for nausea. The failure to obtain data from those patients may therefore have affected the emesis prevalence in study I, but it is unlikely to have explained the *difference* in emesis prevalence between the standard care cohort and the acupuncture cohort in study IV. In study III only 20 of the 121 patients who did not want to participate mentioned tiredness/fatigue as reason for unwillingness to participate.

Confounding factors

To avoid an imbalance of factors causing emesis between the verum and the sham acupuncture groups in study III, the patients were randomly allocated to receive verum or sham acupuncture. Despite randomization, fewer patients in the verum compared to the sham group received corticosteroids. However, the corticosteroids did not protect the sham group from nausea; all but four

patients consuming corticosteroids experienced nausea. Since the patients in study IV were only randomised to verum or sham acupuncture, not to standard care, adjustments were made for potential confounding factors and the omission of patients taking serotonin-receptor antagonists and corticosteroids. There may be other potential confounding factors that are not known and therefore were not measured. Nevertheless, after adjustments for the measured confounding factors, the lower prevalence of nausea in the acupuncture cohort compared to the standard care cohort was still valid.

The comparisons of nausea and vomiting between the cohorts in study IV were made at the time that the mean radiotherapy dose was the same in the acupuncture and the standard care cohort, 27 Gray, because emesis occurrence is related to radiotherapy dose (IGARR 1999, Shun et al 2008). Höckerfelt and co-workers (2000) performed radiotherapy over the abdomen of rats, and in that study, doses of at least 20 Gray caused significant cellular damage, resulting in emesis. If another time for comparison between the cohorts had been chosen, it would not have changed the findings of study IV. The weekly prevalence of patients experiencing nausea was higher in the acupuncture cohort during all radiotherapy weeks (range 22 to 44 %), compared to the standard care cohort, 63 %.

Blinding

Previous studies regarding acupuncture for nausea during cancer treatment have shown methodological problems (Ezzo et al 2006b). Therefore a pilot study was performed before study III, making it possible to identify weaknesses in the design. The general methodological Jadad scale (Jadad et al 1996), used in recently conducted acupuncture Cochrane reviews (Trinh 2006, Lim et al 2006), and the acupuncture specific STRICTA checklist (Standards for Reporting Controlled Trials of Acupuncture) (MacPherson et al 2001) was used to identify weaknesses of the design when planning study III. The level of compliance with the scale and the checklist was discussed after completion of the study. Twelve of the maximum 13 points and all 34 items on the STRICTA checklist may be considered to have been accomplished. The missing point on the Jadad scale resulted because unblinded therapists performed the acupuncture treatments. Acupuncture therapists must be unblinded and skilled to optimize effects and avoid negative side-effects, such as penetration of the median nerve. Streitberger and co-workers (2007) reported that in 53 of 97 verum acupuncture treatments of PC6, the needle came in contact with the median nerve. In 14 treatments, the needle penetrated the nerve.

Takakura & Yajima (2007) developed a new kind of sham needle and suggested it could be used by blinded therapists. The therapist presses that kind of sham needle through an opaque guide tube until a stopper around the needle stops the movement. The sham needle is short enough to reach only the surface of the skin, while the verum needle is long enough to enter the tissue. However, in study III and IV the therapists manipulated the verum needles until “deqi” occurred and placed the verum and sham needles in different points. Blinded therapists cannot perform such procedures.

Strengths in study III to IV are that the therapists did not collect emesis data and a treatment protocol guided the physiotherapists to perform sham acupuncture almost identical to verum acupuncture. The patients, evaluator and the antiemetic prescribing oncologists were blinded.

Verum and sham acupuncture techniques

The sham needles used in the thesis do not penetrate the skin or induce “deqi” (Park et al 2002a, Hui et al 2007), so for evaluating the aims of the thesis the telescopic sham needle was considered to be the most appropriate sham techniques. One item on the STRICTA checklist (MacPherson et al 2001) covers the appropriateness of the control treatment: “Is the intended effect of the control intervention (acupuncture or other) and its appropriateness to the research question described?” Did the sham treatment itself, the most credible and inactive placebo treatment available today (White et al 2001, Moffet et al 2008), produce specific physiological effects, *comparable* with verum acupuncture? Probably not, since several studies found that verum acupuncture needles induced more extensive limbic and paralimbic activity than tactile stimulation, comparable with a blunt needle (Dhond et al 2007). Verum acupuncture in PC6 selectively activated sensory areas in the mid-brain in comparison to sham acupuncture placed at a non-acupuncture point, tactile stimulation of the PC6 point and tactile stimulation of the sham point (Yoo et al 2004).

Tactile stimulation, similar to the stimulation from the blunt needles, has been seen to activate the limbic system (Hui et al 2000, Hui et al 2005) and probably also activates the oxytocin system (Uvnäs-Moberg et al 1993). Those systems may hypothetically reduce emesis (Lundeberg et al 2007), probably especially the emesis related to distress (Streitberger et al 2006). It is not known if it is the tactile stimulation alone or the whole therapeutic situation that provides the activity within those systems during sham acupuncture. However, the observation that the sham needle activated

mid-brain sensory regions when the participants were informed that the sham was effective, while a blunt needle did not cause this activation when the individuals were told was in-effective (Pariente et al 2005), indicate the importance of taking the entire therapeutic situation into consideration.

The needle pressure against the skin had a lower duration (the only times the sham needles were pressed against the skin were when placing and manipulating; totally about 10 seconds per session for a median of 11 sessions; about 120 seconds) compared to the whole therapeutic situation (approximately 6 hours). That is a very low dose of pressure as compared to for example acupressure, given *continuously* for several days or even weeks (Jewell & Young 2003, Ezzo et al 2006a, Ezzo et al 2006b). If the low dose of pressure at the present non-acupuncture point performed in study III and IV caused the lower emesis prevalence compared to standard care, then the traditional antiemetic point PC6 has no part of the antiemetic effect.

It may be very important to consider if the dose of verum acupuncture performed in study III and IV was optimal (White et al 2008) for treating emesis. The dose was larger than in other antiemetic sham-controlled acupuncture studies, reporting a treatment duration of only one (Streitberger et al 2003) or five sessions (Shen et al 2000). However, the findings of study III and IV could not be generalized to daily acupuncture therapy (Shen et al 2000), to electro-acupuncture (Shen et al 2000) or to multiple acupuncture points (Xia et al 2000). Study III only evaluated the effects of verum manual acupuncture in PC6, the point used in the large majority of previous antiemetic studies irrespectively of type of nausea (Jewell & Young 2003, Ezzo et al 2006a, Ezzo et al 2006b).

Appropriateness of data collection

The verum and sham groups were compared in study IV to a reference group, which has the benefit that the impact of repeated emesis data collection per se was avoided, compared to if a three-armed randomised study had been performed. It is possible that repeated measurement of emesis may either reduce emesis by the extra attention paid to the patients' problems (through the so called Hawthorne effect), or increase emesis by steering attention to the nausea symptom. Young and co-workers (2007) studied the impact of emesis questions per se in 30 healthy volunteers, by use of a virtual environment inducing motion sickness. Half of the volunteers answered questions regarding emesis both before and after the motion sickness inducing experiment. That half of volunteers rated approximately doubled nausea

intensity after the experiment, compared to the other half, who only answered the emesis questions after the experiment.

The patients in the standard care cohort in study IV did not rate nausea daily and may therefore, in some cases, have forgotten the nausea they experienced in the beginning of the preceding week. Thus, the possible bias depending on the use of different time frames in the standard care cohort (one week) compared to the acupuncture cohort (past 24 hours, answered daily during the seven days of the cross section) would reasonably favour an under- rather than over-report of symptoms in the standard care group.

Hypothetically, the findings in study III and IV could depend on flaws in the methods for emesis data collection. Rhodes Index of Nausea, Vomiting, & Retching or Morrow Assessment of Nausea and Emesis could have been alternatives (Rhodes & McDaniel 2001). However, the high number of items (8 and 16, respectively) could have been bothering when used daily. The method for emesis measuring was pilot-tested and modified for the current studies. The method, using category and visual analogue scales, has been suggested (Jenns 1994), used (IGARR 1999, Börjeson et al 2002, Mystakidou et al 2006) and satisfactorily validated (Börjeson et al 1997, Boogaerts et al 2000) by others. Test retest reliability was measured in a pilot study (n=36) (Enblom et al 2008) providing results that may be considered as satisfactory (Bruton et al 2000). Both nausea category and visual analogue scale seem to be sensitive enough to detect a reduction of nausea over time (Boogaerts et al 2000). It seems unlikely that flaws in the method for emesis measuring would explain the lack of differences between the verum and the sham group in study III in contrast to the large differences between the acupuncture cohort and the standard care cohort in study IV.

Complements to the emesis questionnaire used in study I, III and IV could have been, for example, Osoba Nausea and Emesis module or Functional Living Index-Emesis, to detect the relevance of emesis on daily living (Martin et al 2003b). In study I, single-item questions regarding quality of life and dimensions related to quality of life were instead used (Wiklund et al 1990). Single-item questions have been suggested to be optimal in cancer patients, to minimize the patient burden, compared to the use of many different psychometric questionnaires (Sloan et al 2006). This kind of simple measurement has produced results similar to those from longer well-established questionnaires in measuring quality of life (Bernard et al 2001), well-being (Hürny et al 1996), anxiety (Davey et al 2007, Onelöv et al 2007) and mood status (Onelöv et al 2007). The format for use of single-item questions has been described in two methodological articles (Steineck et al 2002a, Onelöv

et al 2007) and has been used in several studies regarding cancer related issues (Bergmark et al 1999, Steineck et al 2002b, Kreicbergs et al 2004). The single-item questions (Wiklund et al 1990) were answered once and were therefore not tested for test retest reliability. The validation process that was followed attempted to ensure that the questions and the grading of answers were appropriate for this specific patient group.

Statistical considerations

Study II reached 74 % power to detect a difference in pain between the verum and sham group. The power to statistically detect a difference in blinding success between the four therapists probably was even lower, since the variation from 55 to 80 % successfully blinded individuals was not statistically significant.

In study III there was no statistically significant difference between the verum and the sham group in nausea occurrence, irrespective if the data were analysed according to intention to treat or per protocol, based only on patients providing nausea data. Study III met the preformed criteria for statistically power, in contrast to the negative acupuncture study by Streitberger and co-workers (2003) regarding chemotherapy-induced nausea, which only included 40 % of the planned number of patients. Nevertheless study III could not detect smaller effects than those searched for. The not statistically significant, difference in nausea occurrence of eight absolute percent between the verum and sham group in study III did, however, favour the sham group.

CONCLUSIONS

Of patients undergoing radiotherapy, irrespective of radiotherapy field, 39 % experienced nausea and 7 % vomited.

Patient characteristics associated with increased risk for nausea during radiotherapy were abdominal or pelvic radiotherapy field, age younger than 40 years, concomitant chemotherapy, prior experience of nausea and the patient's expectations on the own risk for nausea.

A fourth of nauseous patients receiving standard care thought that antiemetics had helped them while a third considered their antiemetic treatment insufficient.

Patients experiencing nausea, irrespective of radiotherapy field, reported lower quality of life, more frequent anxiety and depressed mood and lower satisfaction with aspects of daily living compared to patients free from nausea.

A telescopic sham needle was credible to use in control groups to simulate acupuncture, but there was a tendency that the therapists influenced level of blinding.

Verum manual "deqi" creating acupuncture given two to three times per week during radiotherapy over pelvic or abdominal fields is not more effective than sham acupuncture in reducing nausea or vomiting.

Almost all patients treated with verum or sham acupuncture thought that the treatment had been effective for nausea and were interested in receiving the same treatment in the future.

Reduced nausea and vomiting was seen in patients treated with verum "deqi" creating acupuncture as well as sham acupuncture compared to patients receiving standard care.

IMPLICATIONS

Health-care professionals may consider identifying and treating patients with increased risk for emesis in advance, for example those with a history of nausea.

Researchers may use the telescopic sham needles in acupuncture efficacy studies and may test the blinding success and standardize the treatment procedure between the involved therapists.

The choice of performing acupuncture during radiotherapy cannot be based on arguments that the specific characters of verum acupuncture; penetration and “deqi”-stimulation have effects on nausea.

It is important to further study what the components are in the acupuncture procedures that produce the dramatic positive but as yet not fully understood antiemetic effect, since this will make it possible to use those components to further increase quality of care during radiotherapy.

SVENSK SAMMANFATTNING

Patienter med cancer som behandlade med akupunktur under strålbehandling upplevde mindre illamående och kräkningar än patienter som enbart fick vård enligt ordinarie rutiner. Detta är en av slutsatserna i avhandlingen, som innehåller fyra studier om akupunktur och illamående under strålbehandling. I den första studien besvarade 368 patienter ett frågeformulär vid ett tillfälle under sin strålbehandling som, beroende på vilken typ av cancer patienten hade, riktades mot olika regioner av kroppen. Alla patienter fick vård enligt ordinarie rutiner, vilka innefattade medicinsk behandling, men inte akupunktur. Cirka 40 % av alla 368 patienterna och 63 % av de 62 patienter som hade behandlats över buken eller bäckenet mådde illa under en vanlig strålbehandlingsvecka. En tredjedel av de illamående patienterna efterfrågade mer behandling för sitt illamående och bara en fjärdedel upplevde att de åtminstone måttligt hade blivit hjälpta av den medicinska behandlingen mot illamående.

I studie III lottades 215 patienter till en av två typer av akupunkturbehandling under sin strålbehandling mot buk- eller bäckenregionen. Etthundranio patienter gavs traditionell akupunktur, som kännetecknas av nålar som förs ned genom huden i särskilda punkter och stimuleras genom att vrida nålen tills en särskild "nålkänsla" uppstår, enligt gammal kinesisk tradition. Etthundrasex patienter gavs simulerad akupunktur, med en särskild utvecklad teleskopisk, trubbig placebonål som inte förs ned genom huden, utan fästs mot huden i ett plaströr. Behandlingarna gavs av sjukgymnast under en halvtimme två till tre gånger i veckan under hela strålbehandlingsperioden, som oftast pågick fem veckor. Patienterna besvarade dagligen ett frågeformulär om illamående och kräkningar. Resultaten visade ingen skillnad i illamående eller kräkningar mellan patienterna som hade fått traditionell akupunktur jämfört med patienterna som hade fått simulerad akupunktur, grupperna mådde i medel illa i tio respektive nio dagar av strålbehandlingsperioden och omkring en fjärdedel av båda grupperna kräktes någon gång. Efteråt upplevde 95 % av patienterna i båda grupperna att behandlingen varit effektiv mot illamående och 89 % var intresserade av att få samma behandling igen i framtiden mot illamående. I både den traditionella och den simulerade akupunkturgruppen angav 67 % att de även hade upplevt andra positiva effekter av behandlingarna, till exempel effekter på sömn, sinnestämning, avspänning och smärtlindring.

I studie IV jämfördes hur många patienter som hade mått illa och kräkts mellan de 109 respektive 106 patienter från studie III som hade behandlats med traditionell eller simulerad akupunktur, och de 62 patienter från studie I som enbart fått vård enligt ordinarie rutiner under sin strålbehandling mot buk- eller bäckenregionen. Bara 38 respektive 37 % av patienterna som behandlats med traditionell eller simulerad akupunktur mådde illa under en vanlig vecka av strålbehandlingen, jämfört med 63 % av patienterna som fått ordinarie vård. Åtta, sju respektive 15 % av patienterna som behandlats med traditionell akupunktur, simulerad akupunktur respektive ordinarie vård kräktes under en vanlig strålbehandlingsvecka. Statistiska beräkningar utfördes för att undersöka om minskningen av illamående och kräkningar kunde förklarades av andra faktorer än de olika akupunkturbehandlingarna. Ett exempel på en sådan alternativ förklarande faktor skulle kunna vara om fler av de patienter som behandlats enligt ordinarie rutiner också fått cytostatikabehandling samtidigt, en behandling som ökar risken för illamående. Efter statistiska beräkningar av sådana faktors inverkan på resultatet så kvarstod minskningen av illamående i akupunkturgrupperna jämfört med gruppen som enbart fått ordinarie vård, så resultaten kan ses som tillförlitliga.

Eftersom det inte var någon skillnad mellan de som behandlats med traditionell eller simulerad akupunktur gällande illamående, kräkningar eller de andra positiva effekterna som de akupunkturbehandlade patienterna upplevde, tycks inte den traditionella akupunktursens särskilda kännetecken kunna förklara effekterna. Effekterna tros istället bero på den utökade omvårdnad de akupunkturbehandlade patienterna fick jämfört med den ordinarie vården. Sjukgymnasterna förde vardagliga samtal och berörde patienterna vid nålplaceringen, under akupunkturbehandlingarna gavs extra tid för vila och avslappning och uppmärksamhet riktades mot patientens problem genom de dagliga frågeformulären. Även patienternas höga förväntningar på att få effekter av akupunktursen mot illamående kan ha minskat illamåendet, över 90 % av patienterna i både traditionella- och simulerade akupunkturgruppen trodde vid behandlingsstarten att deras behandling skulle vara effektiv mot illamående.

För att kunna utvärdera effekterna av traditionell akupunktur så är det viktigt att patienten inte kan genomskåda om behandlingen skett med traditionell eller simulerad akupunktur, annars kan patienternas förväntningar påverkas och därigenom effekterna av behandlingen. Metoden för att ge simulerad akupunktur med den särskilda teleskopiska, trubbiga placebonålen testades därför innan studie III startade, på 80 friska frivilliga

personer (studie II). Försökspersonerna var lottade till en enstaka behandling med endera den traditionella, vassa akupunktur nålen, eller med den trubbiga placebo nålen. Två tredjedelar av personerna i både akupunktur- och simulerade akupunkturgruppen visste inte, eller svarade fel på frågan kring vilken typ av akupunktur de fått. Endel av den restrerande tredjedelen, som svarade rätt, kan ha genomskådat rätt nåltyp enbart på grund av slumpen. När statistiska test genomfördes för att se om så var fallet, blev resultatet att enbart 20 % i traditionella akupunkturgruppen och 10 % i simulerade akupunkturgruppen bortom slumpen hade genomskådat rätt nåltyp. Av de 215 patienter som deltog i studie III trodde 92 % av patienterna som behandlats med traditionell akupunktur och 81 % av dem som behandlats med simulerad akupunktur att de hade fått traditionell akupunktur, med nålar som förts ned genom huden. Placebonålen ansågs därför vara trovärdig.

I både studie I och IV så hade de patienter som var yngre än 40 år eller hade tidigare erfarenheter av illamående i andra situationer, till exempel vid tidigare cytostatikabehandling eller åksjuka, ökad risk att bli illamående jämfört med andra patienter. I studie IV framkom också att de patienter som själva trodde sig ha en högre risk för illamående jämfört med andra, också hade en ökad risk för illamående. De 145 patienter som i studie I mådde illa upplevde lägre livskvalitet och välbefinnande, sämre kroppsligt tillstånd, hade oftare ångest, var oftare nedstämda och var mindre tillfreds med olika vardagliga situationer, till exempel arbete och fritid, jämfört med de 223 patienter som inte mådde illa.

Eftersom illamående tycks vara vanligt förekommande hos patienter som behandlas enligt ordinarie rutiner under sin strålbehandling av buk- eller bäckenregionen och illamående patienter känner sig mindre tillfreds med vardagen, är det rimligen viktigt att identifiera och på ett adekvat sätt behandla de patienter som har ökad risk för illamående. Traditionell akupunktur kan inte ges med motiveringen att akupunktorens särskilda kännetecken har effekt på illamående och kräkningar. Det är viktigt att ytterligare studera vilka delar av proceduren kring den traditionella och den simulerade akupunkturbehandlingen som minskar illamående och kräkningar, för att göra det möjligt att använda just de delarna för att ytterligare förbättra vården under strålbehandling.

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