Low fat, low lactose diet used as prophylactic treatment of acute intestinal reactions during pelvic radiotherapy

A prospective randomised study

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URN:NBN:no-2118

URN:NBN:no-2118

Abstract

Purpose. The main aim of the present study was to evaluate the effect of a low fat, low lactose diet on acute and late gastrointestinal side effects of pelvic radiotherapy. We also wanted to evaluate if such a treatment would influence the patients health related quality of life (HRQOL) in any way.

Background. Cancer therapies and their side effects may cause nutritional problems and malnutrition. Pelvic radiotherapy, a common treatment modality for patients with carcinoma of the endometrium or cervix, is associated with both acute and late side effects that may affect nutritional status. Acute injury may lead to impaired absorption of nutrients and fluid. The patients experience diarrhoea, weight loss, nausea and vomiting. Bile salt malabsorption may be a factor in the pathogenesis of the diarrhoea. In cases of bile salt malabsorption a low fat diet will cause decreased bile salt excretion and thereby relief of symptoms. This assumption was evaluated in a small, non-randomised study in 1985. The results indicated that a low fat diet may reduce the frequency of diarrhoea and use of anti-diarrhoeal agents during radiotherapy. These findings were regarded as promising and since nutrition management guidelines for radiation enteritis were lacking in the literature, a clinical trial was planned.

Methods. The study was designed as an open randomised clinical trial and conducted at the Norwegian Radium Hospital (NRH). The intervention diet (low fat, low lactose) was to be followed during and six weeks after radiotherapy. Measurements were performed at basement, the 3rd and last week of radiotherapy, six week after and then every 8th week. The entire period was one year. In November 1993 the surviving patients were approached again and asked to complete a questionnaire package similar to the one completed during the clinical trial. The study population was recruited from the department of gynaecology at NRH. The main selection criteria were pelvic radiotherapy (dose above 40 Gy) age = 75 years and a WHO functional status = 2. Patients were consecutive included from May 1988 through May 1990 and 143 women were included. Seventy-one were assigned to the intervention diet and 72 to the control group. In November 1993, 94 women were alive without any known relapse and 79 (84%) accepted participation. The women registered use of Loperamid and the daily number and consistency of bowel movements. The data on bowel movements was categorised and used to evaluate if diarrhoea was present or not. Nutritional status was evaluated by the means of weight

URN:NBN:no-2118

development, arm muscle circumference (AMC), serum transferring (STF) and serum albumin (s-Alb). Dietary intake was assessed by 48-hour recall prior to radiotherapy, 4-days unweighed dietary record during radiotherapy and 7-days weighed dietary records during follow-up. 24-hour urinary nitrogen was used to validate the food records. HRQOL was defined as the patients' self-reported subjective physical and psychosocial situation as a consequence of disease and treatment. It was measured with the EORTC Core Quality of Life Questionnaire 36-item version (EORTC QLQ-C36).

Results. During the last week of radiotherapy 14 patients (23%) in the intervention group and 32 (48%) in the control group reported diarrhoea ($p< 0.01$). The intervention group also used less anti-diarrhoea medication than the control group, 0.6 tablets per day versus 1.1 ($p<0.01$). Six weeks after end of radiotherapy, no group differences were found with regard to bowel movements or medication. The intervention group had a lower energy intake than the control group during radiotherapy, 5.7 MJ versus 6.5 MJ ($p<0.05$). The mean daily fat intake was respectively 34.3 g and 60.1 g ($p<0.001$). The intervention group received a significant lower part of the energy from milk products, meats, fats and sugar than the control group, and consumed more energy from vegetables and fruits, cereals and fish. Weight loss was more pronounced in the intervention group (mean reduction of 2.6 kg versus 1.7 kg) than in the control group (ns) during treatment. Mean values of AMC, s-Alb and STF were within the reference range in both groups during the entire observation period. During the last week of radiotherapy six patients (9%) in the intervention group and 4 (6%) in the control group were mildly depleted (ns). At 12 weeks and after one year none of the patients could be categorised as malnourished. No major differences in HRQOL were found between the two groups during radiotherapy and one-year follow up. Within the control group an association between diarrhoea and deteriorated role functioning, physical functioning and fatigue was found during the last week of radiotherapy that was not found in the intervention group. Regarding late effects of radiotherapy (3-4 years after radiotherapy) both groups had more diarrhoea than in the general population, 23.8 versus 9.5 ($p<0.01$). There was however a tendency to more pronounced diarrhoea in the control group (29.6 (SD=27.3)) than in the intervention group (19.4 (SD=25.4)) though not statistical significant. Substantial diarrhoea was associated deteriorated SF and fatigue.

URN:NBN:no-2118

Conclusions. The intervention group had less diarrhoea and used less Loperamide during radiotherapy than the control group. This finding did not affect nutritional status since no differences in nutritional status were found between the two groups. Both groups had a reduced energy intake and weight loss during radiotherapy. In the control group diarrhoea increased fatigue and had negative effects on physical functioning and role functioning. The intervention did not lead to differences in late radiation injury and chronic diarrhoea 3-4 years after treatment but diarrhoea was most prominent in the control group. Diarrhoea as a late effect increased fatigue and had a negative influence on social well being.

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Acknowledgement

The randomised prospective clinical trial cited in this doctoral thesis was carried out at The Norwegian Radiumhospital (NRH) during the 1988-1991. It would not have been possible to perform study without the benevolent grants from the Norwegian Cancer Society. Their support of a dietary intervention study already in 1988 shows a liberal view of what is import in cancer research.

I want to thank everybody who has helped me to finally realise this thesis. First of all I want to thank Professor Stein Kaasa. When I started to work with this project my ambitions were rather low and I never thought it would end up in a doctoral thesis. Kaasa did however believe in this work and encouraged me to continue the work and even expand it with a follow up study in 1994. I am impressed and thankful that he has held out with me during the strenuous process it has been to finish this work.

The idea for this study came about through a student project done with Elisabeth Elind. Turid Ose became interested our ideas and initiated this study that started in 1988. She accepted me as a co-worker and I am very grateful for her support. Her skills, experience and our close collaboration when I was working at NRH, have been of great value to me. Without her this study would never have been possible.

The study was performed at the Department of Gynaecology at the NRH and I want to thank the clinical staff of for their co-operation. Especially I want to thank dr.med Kolbein Sundfør for his work with collecting patients and time to share his experience and knowledge with me. I also want to thank Professor Claes Tropé for his support and belief in that this work was important and the nurses at the Department of Gynaecology. I am most grateful to all the patients who devoted their time and energy to participate in this study. They responded to questionnaires and informed us about eating and toilet habits for more than a year. I really hope our work will have some value to them and the future patients.

I have worked to finish this thesis while I have been working full time at the University College of Akershus. My colleges there have been wonderful supportive and encouraging and I want to thank them all. They have given me the chance to work fulltime on my thesis in periods of time. Especially I will thank Judy Lundin who has helped me with the English language.

URN:NBN:no-2118

My excursions to the Unit for Applied Clinical Research at the Norwegian University for Science and Technology in Trondheim have been of invaluable help. Thanks to the members of the Unit, especially Helene Flottorp and Finn Guttvik. Warm thanks to dr.med Jon Håvard Loge who gave me a lot of constructive and positive criticism during my final work. I also want to thank Marianne Jensen Hjermstad who so willingly let me use her reference data.

At last but not least I will thank all my friends that never asked me how my work was proceeding and Hans Pfeffer who "kicked me" to finish.

URN:NBN:no-2118

List of papers

I. Bye A, Ose T, Kaasa S (1999): Food choice and nutrient intake among patients on a low-fat, low-lactose diet: experience from a prospective randomized study. *Journal of Human Nutrition & Dietetics. 12(4): 273-285.*

II. Bye A, Ose T, Kaasa S (1999): Evaluation of the validity of the method used to assess compliance to a low fat, low lactose diet in a dietary intervention study
(submitted for publication in Clinical Nutrition)

III. Bye A, Kaasa S, Ose T, Sundfør K, Tropé C (1992): The influence of low fat, low lactose diet on diarrhoea during pelvic radiotherapy. *Clinical Nutrition 11: 147-153.*

IV. Bye A, Ose T, Kaasa S (1993): The effect of low fat, low lactose diet on nutritional status during pelvic radiotherapy. *Clinical Nutrition 12: 89-95.*

V. Bye A, Ose T, Kaasa S (1995): Quality of life during pelvic radiotherapy. *Acta Obstet Gynecol Scand 74: 147-152.*

VI. Bye A, Trope C, Loge JH, Hjermstad M, Kaasa S (2000): Health Related Quality Of Life And Occurrence Of Intestinal Side Effects After Pelvic Radiotherapy. *Evaluation Of Long Term Effects Of Diagnosis And Treatment. Acta Oncologica. 39(2): 173-180.*

URN:NBN:no-2118

1. Background, aims and research questions

1.1 Introduction

Diet and cancer have a wide interest in the public. How large this interest is may be reflected in the vast number Internet pages concerning this topic. When the two words, diet and cancer, are used to search the Internet more than one million matches may be found. A lot of this information does not distinguish between diets to prevent cancer and diets during cancer and treatment. Such a distinction is however important to make since these diets may be completely different and have different goals.

It is claimed that about one third of all cancers are related to the diet (Higginson 1993). Several dietary factors may be of importance as risk factors as well as protective agents (World Cancer Research Fund 1997). The causal relations, however, are still unclear and no final conclusions have been made. The evidence that exist indicates that diets high in vegetables and fruits are protective (World Cancer Research Fund 1997). Dietary risk factors are excessive alcohol, fat and energy intake. The recommendations made for prevention of cancer are generally consistent with the recommendations given to prevent cardiovascular disease.

While excessive energy intake might be a risk factor in development of cancer, low energy intake and inability to maintain nutritional status are common problems for patients with cancer. The disease process, its treatment and/or psychological reactions can lead to severe protein-calorie malnutrition which is a major cause of morbidity and mortality in cancer patients (Donaldson and Lenon 1979, Ottery 1995). Protein-calorie malnutrition develops when the intake of macronutrients is inadequate to meet metabolic requirements (Blackburn 1977). The results are progressive wasting, weakness, compromised immune function, potential therapy intolerance, and ultimately death. The prognostic impact of weight loss and malnutrition has been documented since the 1930s in benign disease and later in malignant disease (Blackburn 1977, Ottery 1995). It has been estimated that up to 20% of patients with cancer may die of the effects of malnutrition and starvation (Donaldson and Lenon 1979, Ottery 1995). Despite all these observation, it is not documented that any diet therapy improve survival or enhances possible success of cancer therapy.

Nutritional problems in cancer patients

Anorexia, cachexia, hypermetabolic state and negative nitrogen balance which is seen in cancer patients are all effects of the disease process (Williams 1995B). Anorexia, defined as loss of appetite or desire to eat, is the most common symptom among patients with cancer (Bruera and MacDonald 1988, Ottery 1995). Anorexia is present in 15%-25% of all cancer patients at the time of diagnosis and is almost universal among patients with widely metastatic disease (Bozzetti, Agradi and Ravera 1989, Langstein and Norton 1991). Normally a lowered energy intake will lead to a change in body size and composition that eventually results in decreased energy requirement (Shetty 1999). Cancer patients may, however, have increased metabolic rate despite low energy intake (Heber and Tchekmedyian 1999). This may bring the individuals into a wasting syndrome with symptoms such as weakness, loss of body weight, fat, and muscle volume, defined as cachexia (Donaldson and Lenon 1979, Williams 1995B). Anorexia and cachexia may occur together, but cachexia may also occur in individuals who eat enough to meet energy needs. The exact mechanisms causing cancer cachexia and anorexia are unknown. Both anorexia and cachexia may lead to negative nitrogen balance since the protein intake is decreased and the need is normal or even increased. Another reason for negative nitrogen balance may be altered protein matabolism (Tayek 1999). This may be caused by increased uptake of amino acids by the tumor cells compared with that of normal cells, decreased protein synthesis, increased protein degradation, and protein loss through fistulas or by gastrointestinal losses.

Cancer therapies and their side effects can also greatly contribute to nutritional problems and malnutrition. Surgery may lead to a wide variety of problems depending on the affected organ (Williams 1995B). Head and neck surgery may cause difficulty in chewing and swallowing, gastric surgery may cause early satiety and dumping syndrome. Pancreatic surgery may induce protein and fat malabsorption. Chemotherapy may lead to side effects like anorexia, nausea, vomiting, diarrhoea, constipation, stomatitis/mucositis, taste alterations, and infectious complications (Donaldson and Lenon 1979, Ottery 1995). The frequency and severity of these side effects depend upon the type of drugs, the dose, and whether the chemotherapy is part of a combined modality program. Radiation therapy is associated with both acute and late effects that may affect nutritional status depending on the site of irradiation (Donaldson and Lenon 1979). Irradiation of the head and neck area can be associated with anorexia, taste

alterations or aversions, dry mouth, mucositis, dysphagia, dental caries, and abscess formation. Thoracic irradiation may be associated with esophagitis, dysphagia, esophageal reflux, and nausea and vomiting. Diarrhoea, nausea and vomiting, enteritis, proctitis, or fistula formations are possible side effects caused by abdominal or pelvic irradiation.

Pelvic radiotherapy and intestinal reactions

Supportive nutritional care can be offered to relieve some of the negative effects of cancer and its treatment on nutritional status. The type of nutritional support will depend on nutritional problems and their causes. The diet that might be offered must meet the requirements of the particular condition and be based on modification of the nutritional components of a normal diet (Williams 1995A).

During the late seventies Andersson, Boseaus and Nyström (1978) showed that bile salt malabsorption possibly was an important factor in the pathogenesis of diarrhoea after pelvic radiotherapy. Based on these findings they evaluated the effect of a low fat diet in a group of patients with diarrhoea after irradiation (Bosaeus, Andersson and Nyström1979). They concluded that a low fat diet can be an appropriate therapy since decreased bile salt excretion and relief of symptoms was seen. They also pointed out that the diet might be appropriate during radiotherapy. This assumption was evaluated in a small, non-randomised study (Bye and Elind 1986). Thirteen patients from the Norwegian Radium Hospital (NRH) were included in the study and the results showed that the five patients in the intervention group had less diarrhoea and used less anti-diarrhoeal agents than the control patients used. These findings were regarded as promising and since nutrition management guidelines for radiation enteritis were lacking in the literature, a clinical trial was planned. The purpose was to evaluate the effects of the diet before it was recommended as standard therapy.

1.2 Low fat, low lactose diet – theoretical and clinical background

Pelvic radiotherapy is a common treatment modality for patients with carcinoma of the endometrium or cervix in addition to surgical treatment. Since parts of the intestine will be located in the field of irradiation, radiotherapy induces risk of injuries to the small intestine (Donaldson 1984, Yeoh and Horowitz 1987). Acute injury during radiotherapy is primarily demonstrated in the epithelial stem cells of the intestinal mucosa and leads to loss of absorbing surface area and impaired absorption of nutrients and fluid (Coia, Myerson and Tepper 1995, Letschert 1995). The patients may experience weight loss and symptoms like nausea, vomiting and diarrhoea (Thiel, Fietkau and Sauer 1988).

Principles of radiotherapy and effects on healthy tissue

Radiotherapy implies treatment via administration of various forms of radiant energy. This energy is transferred to the biological material and causes cell death (Rassekh and Kennedy 1997, Pachigolla and Pou 2000). The energy is deposited in atoms or molecules within the cells and this may result in displacement of an orbital electron or ionisation that may interact with cellular components. If the interaction is with a critical target within a cell, irreparable damage occurs (Rassekh and Kennedy 1997). Such a critical target is most likely DNA. Presumably because radiotherapy impairs DNA synthesis and interferes with cell replication, rapidly dividing cells are generally more radiosensitive than slowly dividing cells. The radiosensitivity of cells varies as a function of the phase of the cell cycle. The mitotic phase of the cell cycle when DNA is being replicated is considered relatively more radiosensitive (Pachigolla and Pou 2000). The shorter time between mitosis the greater is the radiosensitivity. Acute reactions in healthy tissue during radiotherapy are therefore typically seen in tissues with high cell turnover rates.

The biologic effects of radiation correlate with the given dose. A bigger dose leads to a bigger biologic effect and more cell death (Rubin 1989, Pachigolla and Pou 2000). It is however shown that the therapeutic effects of radiotherapy are improved if the total dose is administrated in smaller fractions instead of being given as one single dose (Pachigolla and Pou 2000). During the time intervals between each fraction the tumor cells are allowed to redistribute into more sensitive phases of the cell cycle which leads to increased tumor killing. A reoxygenation of the tumor cells also occurs during these time intervals (Rassekh and Kennedy 1997). This is

important since presence of oxygen results in increased tumor cell senistivity. Fractionated radiotherapy is also applied in order to minimise complications from healthy tissue (Rubin 1989, Rassekh and Kennedy 1997, Pachigolla and Pou 2000). During the time intervals between each fraction the normal cells have a possibility to repair injury and regenerate.

The volume irradiated and the localisation of the tumor are of importance for the reactions to radiation in normal tissue and organs (Thiel, Fietkau and Sauer 1988, Rubin 1989, Letschert et al 1994). Volume effects are important in radiotherapy, with the whole organ versus a portion of the organ being irradiated and with large versus small tumors being irradiated. Other variables that may affect an organ's response to radiation are individual patient factors such as diabetes and hypertension, surgery, trauma, chemotherapy, hyperthermia, and biological response modifiers (Rubin 1989). The individual patient variables can decrease vascular flow and increase the chance of radiation injury.

The radiosensitivity of the small intestine and acute radiation injury

The small intestine has a rapidly reproducing cell population and is therefore very radiosensitive (Vander, Sherman and Luciano 1994). Normally the epithelial cells of the small intestine are completely replaced in 3-6 days. The intestinal mucosa is highly folded and the surface of these folds has microscopic finger-like projections of the mucosal lining known as villi. Each villi is about 0.5 to 1.5 mm in length and covered with a single layer of epithelial cells whose surface membranes form small projections known as microvilli. The villi are responsible for absorption of nutrients and greatly increase the effective absorptive surface area of the small intestine. Every 24-hour there is a cell division in the base of villi (the crypt of Lieberkühn) (Vander, Sherman and Luciano 1994). The crypt is the site of stem cell proliferation. The differentiated cells move upwards and are shed 3-5 days later at the tips of the villi. In a steady state, cell extrusion from the tips of the villi equals the cell replication rate in the crypt. During the course of radiotherapy a progressive shortening of villi is seen and the total epithelial surface and the thickness of mucosa decreases (Trier and Browning 1966, Berthrong and Fajardo 1981, Yeoh and Horowitz 1987). The reason for these effects seems to be interference with and reduction of the cell replication in the crypts of Lieberkühn. Despite this interference the migration of cells from the crypt to the villi does not stop (Thiel, Fietkau and Sauer 1988). This leads to loss of cells and

impaired replacement of epithelial cells. The loss of tissue function is thought to occur as a function of the total number of cells lost.

Important in determining the effects of abdominal radiation on the small intestine is the mobility of the small intestine, which may protect any one area from receiving a critically high dose. The intestine is mobile except the entire duodenum, upper jejunum and terminal ileum. Therefore terminal ileum is the portions of the small intestine most often at risk of injury from pelvic radiotherapy together with parts of colon like rectum and sigmoid colon (Berthrong and Fajardo 1981, Yeoh et al 1993A).

Symptoms of acute radiation enteritis are reported to occur in 50% to 80% of patients undergoing pelvic radiation (Yeoh and Horowitz 1987, Resbeut et al 1997). It is indicated that acute reactions from the small intestine are frequent at total doses above 45 Gy but uncommon below 40 Gy (Letschert et al 1994) and that the intensity of reactions varies with number of fractions and dose per fraction. The acute effects are generally reversible and the symptoms are usually of limited duration and cease within six weeks after completion of treatment (Yeoh and Horowitz 1987).

Late effects of radiotherapy

Acute radiation reactions may recur as late radiation enteritis clinically characterised by diarrhoea and abdominal cramps (Danielsson et al 1991, Coia, Myerson and Tepper 1995). Late radiation complications usually appear six to 24 months after treatment, but can also occur at any time during the lifetime of the patient (Kinsella and Bloomer 1980, Berthrong and Fajardo 1981, Yeoh and Horowitz 1987, Danielsson et al 1991, Coia, Myerson and Tepper 1995). In contrast to acute injury that primarily is demonstrated in the mucosa, late effects seem to be associated with effect throughout the bowel wall (Danielsson et al 1991, Coia, Myerson and Tepper 1995, Letschert 1995). Retrospective studies suggest an incidence of severe complications in 5-15% of the patients (Yeoh and Horowitz 1987, Letschert 1995,). Common symptoms are intestinal obstruction, mucosal ulceration, perforation, chronic blood loss and severe inflammation of the rectum and colon. The late effects are often irreversible and impaired intestinal absorption of nutrients is common. For this reason the late effects tend to interfere with the nutritional status to a higher extent than the acute ones. Obstruction, fistula formation, or strictures may further contribute to the general malabsorption (Coia, Myerson and Tepper 1995).

The relationship between occurrence of an early effect and likelihood of developing a late effect is not well understood. With high doses or in locally attached immobile intestinal loops, recovery after radiation may be incomplete with persistence of villi atrophy and abnormal, stunted or cystic crypts (Berthrong and Fajardo 1981). It seems like the risk of developing significant chronic radiation enteritis increases with the severity of acute radiation syndrome. On the other hand, absence of acute enteritis does not seem to exclude late injuries (Bourne et al 1983). Previous abdominal surgery, concurrent chemotherapy and pelvic inflammatory disease may be risk factors in the development of severe chronic radiation injury possibly because of adhesions (Yeoh and Horowitz 1987, Coia, Myerson and Tepper 1995).

Impaired absorption and diarrhoea

Clinical studies conducted to evaluate the effect of radiotherapy on absorption are presented in table 1-1. Impaired absorption of bile acids, fat and lactose are most frequently reported, but also impaired absorption of proteins is seen.

Impaired absorption of bile acid and fats

Impaired bile acid absorption is demonstrated in the majority of studies evaluating intestinal absorption during radiotherapy (Jackson and Entenman 1959, Sullivan 1962, Sullivan 1965, Morgenstern and Hiatt 1967, Stryker, Hepner and Mortel 1977, Stryker and Demers 1979, Yeoh, Lui and Lee 1984, Ruppin et al 1987, Fernandez-Banares et al 1991, Yeoh et al 1993A). Impairment of bile acid absorption seems to drop gradually during radiotherapy reaching the lowest level the last week of treatment which is the period of worst diarrhoea (Stryker, Hepner and Mortel 1977, Stryker andDemers 1979, Ruppin 1987). A net loss of bile acids may occur and gradually lead to fat malabsorption (Merrick 1988). A high faecal fat has been shown to correlate with diarrhoea during radiotherapy (Reeves et al 1965).

Table 1-1 Prospective studies conducted to evaluate the effect of radiotherapy on intestinal absorption

Author, Year and Place	No. of patients	Comp. group	Treatment	Time for measuring	Assessment	Conclusion
Yeoh et al 1993, USA	23 women 4 men	Yes	Pelvic and abdominal radiotherapy	Before, during and after completion of radiotherapy	Gastrointestinal symptoms, absorption of bile acid, vitamin B12, lactose and fat, gastric emptying, transit, stool weight, intestinal permeability	Increased stool frequency was associated with decreased bile acid and vitamin B12 absorption, increased faecal fat excretion and lactose malabsorption and more rapid transit.
Fernandez-Banares et al 1991	25	No	Pelvic and abdominal radiotherapy	Before, during and at the end of radiotherapy	Gastrointestinal symptoms, absorption of bile acid and lactose, transit	More rapid transit when diarrhoea. 44% developed lactose and 57% bile acid malabsorption. Transit time may be a major factor in radiation-induced diarrhoea. Lactose malabsorption may contribute to the severity.
Ruppin et al 1987, Germany	20	No	Abdominal radiotherapy	At the beginning, at the end and 6 to 12 months following radiotherapy	Absorption of bile acid, vitamin B12, lactose and intestinal permeability	Correlation between degree of bile acid malabsorption and severity of diarrhoea. One patient developed lactose malabsorption.
Yeoh et al 1984	10	No	Pelvic and abdominal radiotherapy	During radiotherapy	Absorption of bile acid and vitamin B12	Nine of 10 had diarrhoea. Diarrhoea was associated with malabsorption of Vitamin B12. Severe diarrhoea (4 patients) associated with bile acid malabsorption.
Weiss & Stryker 1982	30	No	Pelvic and abdominal radiotherapy	First and fifth weeks of radiotherapy	Absorption of lactose	Lactose malabsorption is a factor in the aetiology of diarrhoea and the amount of bowel included in the treatment volume influences the degree of malabsorption.
Stryker et al 1977	33	No	Pelvic radiotherapy	First and fifth weeks of radiotherapy	Ileal function, bile acid absorption	Bile acid malabsorption due to ileal dysfunction may be a factor in radiation induced diarrhoea.
Reeves et al 1965	38	No	Pelvic radiotherapy	Second and third week of radiotherapy	Fat absorption	Impaired fat absorption 77% of the patients. High faecal fat correlated with diarrhoea

Most of the fat found in food is in form of triacylglycerol, which are insoluble in water (Vander, Sherman and Luciano 1994). The function of bile salts is to break up large fat droplets and form water-soluble particles, which makes it possible for the enzyme lipase to break down triacylglycerols. The result is free fatty acids, mono- and diglycerides, which form micelles together with cholesterol, bile acids and fat soluble vitamins. Fatty acids, monoglycerides, cholesterol and vitamins are absorbed across the cell membrane by simple diffusion. Short and medium chain fatty acids are more water soluble and not dependent on bile to be absorbed.

Normally 95 % or more of secreted bile salts are reabsorbed by the ileum to be used again in digestion (Merrick 1988). The body has a pool of 2-3 g of bile salts (Eusufzai 1995). A fat intake of about 100-g induces an excretion of 30-g bile salts per day. This is much more than the liver is able to produce but because of reabsorption of bile salts this is possible. It is generally accepted that bile salts are actively absorbed from the terminal ileum, and that the absorption from jejunum and colon is by means of passive diffusion (Merrick 1988, Eusufzai 1995).

The reason for impaired absorption of bile acids during radiotherapy may be damage to the terminal ileum. If intestinal mucosa is injured or inflamed bile acids are not reabsorebed adequately and a break in the enterohepatic circulation occurs (Merrick 1988). Because of its location and immobility the terminal ileum is the portions of the small intestine most often at risk of injury from pelvic radiotherapy (Berthrong and Fajardo 1981, Yeoh et al 1993A). Impaired bile acid absorption may also occur as a result of increased transit through the gut (Eusufzai 1995). Increased transit through the intestine has been demonstrated in several studies (Yeoh, Lui and Lee 1984, Fernandez-Banares et al 1991, Yeoh et al 1993A). The small intestine heals rapidly after radiotherapy and after two to three weeks mucosa appears normal. It may however last longer before the absorption of bile acid normalise. Studies have indicated about three months (Stryker, Hepner and Mortel 1977).

Diarrhoea caused by impaired bile acid absorption

Any diarrhoea is characterised by increased water content in faeces, which is caused either by decreased fluid absorption or increased fluid secretion (Vander, Sherman and Luciano 1994). The presence of unabsorbed solutes

in the lumen, as a result of decreased digestion or absorption, also results in retained fluid and diarrhoea.

The membranes of the epithelial cells are very permeable to water (Vander, Sherman and Luciano 1994). Therefore a net diffusion of water (osmosis) occurs across the epithelium whenever a water concentration gradient is established as a result of differences in the total solute concentration (osmolarity) on the two sides. Active solute transport establishes the osmotic gradient leading to a net movement of water. The net absorption of water has an important effect upon the absorption of other substances which cross the epithelium by simple diffusion. As water is absorbed the volume of the luminal contents decreases, thereby concentrating any solutes not absorbed at the same rate. This rise in concentration secondary to water reabsorption provides the concentration gradient for the net diffusion of these substances across the intestinal wall. If the necessary concentration gradient is not established, water remains in the gut and the loose bowel movement occur. Diarrhoea is normally accompanied by an increased frequency of bowel movements because of increased motility in the colon (Vander, Sherman and Luciano 1994). Diarrhoea without an increase in bowel movements is also seen (Sölvell 1981).

A break in the enterohepatic circulation may lead to excess bile salts in the colon (Arlow 1987). Dihydroxy bile salts have a direct effect on the rate of sodium absorption and colonic secretion and cause diarrhoea when they are present in the colon in abnormally high concentrations (Merrick 1988). Deficiency of dihydroxy bile salts on the other hand results in constipation. The diarrhoea is typically most severe in the morning, painless or accompanied by discomfort relieved by evacuation, watery and commonly provoked by eating (Merrick 1988).

Steatorrhoea

Increased faecal loss of bile salts is normally balanced by increased synthesis of bile salts from cholesterol in the liver (Merrick 1988, Mekhjian et al 1971). If the losses are small it is possible to maintain the body pool. A further decrease in reabsorption will make it difficult for the liver to replace the losses through increased production (Eusufzai 1995). After a while a total loss of bile acids may occur which affect the micelle formation and thereby the fat digestion, and steatorrhoea may develop (Andersson et al 1986). Unabsorbed fatty acids have no osmotic effect on the intestine but

bacterial organisms in the colon transform them to compounds that reduce salt and water absorption (Andersson et al 1986, Hessov and Ovesen 1995). Steatorrhoea is characterised by large amounts of unabsorbed dietary fat and increased faecal volume (Dotevall and Gillberg 1981). The bowel movements are greasy, light in colour and may be difficult to flush (Rönnlund, Sandahl and Hardell 1985).

Steatorrhoea may lead to decreased absorption of fat-soluble vitamins (Hessov and Ovesen 1995). Fat-soluble vitamins form micelles together with free fatty acids and bile acids. Any interference with the secretion of bile or action of bile salts in the intestine will therefore also affect the absorption of fat-soluble vitamins. The amount of fat-soluble vitamins stored in the body is however quite big and it will take a while before symptoms of depletion develop. Vitamin K is excepted from this because the stores are emptied 2-3 after the onset of decreased absorption.

Magnesium and calcium may form complexes with free fatty acids that are not absorbable (Andersson et al 1986, Hessov and Ovesen 1995). Deficiency of magnesium may develop as a result of diarrhoea. Among patients with steatorrhoea it is seen an increased excretion of magnesium when the intake of fat increases. The extent of magnesium deficiency seems to be associated with the extent of fat malabsorption and volume of bowel movements. It is also shown that patients with steatorrhoea excrete high amount of oxalate in the urine. If the diet is high in oxalate these patients have a tendency to develop renal stones (Eusufzai 1995). Normally the dietary oxalate reacts with calcium in the intestine. Calcium oxalate is formed and excreted with the stools. Steatorrhoea may cause the calcium to react with free fatty acids instead and oxalate is absorbed to a greater extent. In the kidneys the increased oxalate may lead to formation of renal stones. A low fat diet seems to increase the absorption of calcium and magnesium among patients with steatorrhoea and may prevent the formation of stones and magnesium deficiency (Andersson et al 1986).

Impaired absorption of lactose

Disaccharides like sucrose and lactose have to be split in two monosaccharides before absorption (Vander, Sherman and Luciano 1994). The enzymes are located in the plasma membranes of the epithelial cells. Reductions in the activity of disaccharidases have been demonstrated during radiotherapy (Stryker, Mortel and Hepner 1978, Beer, Fan and

Halsted 1985). The ability to digest lactose seems to be especially affected. In one study conducted to evaluate the function of intestine during radiotherapy it was found that six out of eight patients had low lactase activity while three had low sucrase activity (Beer, Fan and Halsted 1985). Stryker, Mortel and Hepner (1978) suggested that radiotherapy to pelvis and abdomen lead to a significant reduction in the ability to absorb lactose. They found that 12 of 24 patients had abnormal 14C lactose breath tests during the fifth week of radiotherapy. There was a significant correlation between bowel movements and the degree of impaired lactose absorption and between nausea and impaired lactose absorption.

Diarrhoea caused by impaired lactose absorption

The diarrhoea associated with lactase deficiency is a consequence of diminished fluid absorption in small intestine and fluid secretion into colon (Dotevall and Gillberg 1981). When the enzyme lactase is absent in the intestinal epithelium, lactose can not be absorbed. Lactose remains in the lumen of small intestine where it prevents water absorption (Vander, Sherman and Luciano 1994). The unabsorbed lactose containing fluid is passed on to the large intestine. Here bacteria, which do have the enzymes capable of metabolising lactose, produce large quantities of gas and organic products, which inhibits active-transport processes and increase osmolarity. The result is an accumulation of fluid in the lumen of large intestine.

Possible symptoms of lactose intolerance include abdominal pain, bloating, gas/flatulence, and diarrhoea (McBean and Miller 1998). The severity of symptoms varies with the amount of lactose and conditions under which lactose is consumed and the ability of the patient to tolerate the lactose load (Vander, Sherman and Luciano 1994). In general the symptoms and tolerance to lactose are highly individual. It is shown that lactose maldigesters may tolerate up to 6-g lactose when consumed in water after an overnight fast (Hertzler, Huynh and Savaiano 1996). Greater amounts may however, induce severe symptoms. However, it is suggested that lactose doses of 12 g or more may be well tolerated if consumed with other foods. Onset of symptoms is anywhere between 30 minutes and several hours after consuming lactose-containing foods and beverages
(McBean and Miller 1998).

Symptomatic treatment of radiation induced diarrhoea

Randomised clinical trials conducted to evaluate effect of bile acid binding drugs or diet on diarrhoea during radiotherapy are shown in table 1-2.

Bile acid sequestering resins

In small, not controlled studies, bile acid sequestering resins have been effective in the treatment of bile salt malabsorption (Heusinkveld, Manning and Aristizbal 1978, Condon et al 1978). Cholestyramine is an anion exchange resin that forms insoluble complexes with bile acids (Heusinkveld, Manning and Aristizbal 1978). By sequestering bile acids through binding, the effect of excess bile salts on the colonic mucosa may be prevented and thereby the diarrhoea. Clinical trials have shown that Cholestyramine may induce side effects like nausea and abdominal cramps (Chary and Thomson 1984). By many of the patients Cholestyramine was considered to be unpalatable and they were reluctant to eat it. Despite this the effect on diarrhoea was good. But because of the side effects, cholestyramine was not recommended for all patients undergoing radiotherapy (Chary and Thomson 1984). Both study groups were receiving a low fat diet from start of radiotherapy. The diet seemed to prevent diarrhoea and the patients had no problems to eat it. The authors recommended that the low fat diet should be used as a routine during radiotherapy. Cholestyramine could be offered to those patients not obtaining a control of the diarrhoea with the diet. One other problem with Cholestyramine may be that it frequently is not possible to maintain a comfortable balance between diarrhoea and constipation (Merrick 1988).

Table 1-2 Randomised clinical trials conducted to evaluate effect of diet or bile acid binding drugs on diarrhoea during radiotherapy

Author, Year and Place	**No. of patients**	**Group**	**Type of intervention**	**Assessment**	**Conclusion**
Stryker and Bartholomew, 1986, USA	64	Pelvic radiotherapy	Lactose restricted diet or 480 cc of milk with lactase enzyme added per day	Bowel movements and number of antidiarrheal tablets	No statistically significant differences between the groups
Chary and Thomson, 1984,	35	Pelvic radiotherapy	Cholestyramine Both groups received a low fat diet, 40 g	Diarrhoea	Statistically significant differences Adverse effects of cholestyramine
Stryker et al, 1983, USA	33	Pelvic radiotherapy	Colestipol hydrochloride	Diarrhoea	No statistically significant differences. Adverse effects of colestipol hydrochloride

Colestipol hydrochloride is another bile acid sequestering agent. This drug is not shown to bee as effective as cholestyramine (Stryker, Chung and Layser 1983). Colestipol was not well accepted by the patients since it was associated with considerable side effects like nausea, vomiting and abdominal cramps. There was no difference in weekly bowel movement frequency between the colestipol and the control group but the colestipol patients who took at least 50% of the prescribed dose required less antidiarrhoeal medication. It was concluded that colestipol hydrochloride is not of value in preventing radiation-induced diarrhoea because of its side effects but the theory on which the use of bile acid sequestering agents is based may be correct.

Low fat diet

In patients with impaired fat absorption a low fat diet (maximum 40-g of fat per day) seems to reduce the faecal bile salt excretion and thus the diarrhoea (Small, Dowling and Redinger 1972, Andersson et al 1973, Andersson, Isaksson and Sjögren 1974, Andersson 1976). When the fat content in the diet decreases, the amount of bile salts needed to emulgate the fat also decreases. The exact amount of fat that can be tolerated per day in the case of fat malabsorption is not clear. It is claimed that it is enough to reduce the intake of fat to 25% of the total energy content, which corresponds to 50-60 g of fat per day (Hessov and Ovesen 1995). The tolerance seems to depend on the degree of bile salt/fat malabsorption. It is presumed that less fat in the diet reduce emptying of the gall bladder. Patients who have a normally functioning gall bladder therefor have the best effect of a low fat diet (Andersson et al 1986). A higher net absorption of calcium, magnesium and zinc might be another positive effect of a low fat diet in patients with impaired fat absorption (Hessov, Andersson and Isaksson 1983).

Patients with diarrhoea and impaired bile acid absorption after pelvic radiotherapy have been treated with a low fat diet (40 g of fat per day) for 3 to 6 months (Bosaeus, Andersson and Nyström 1979). In eight of nine patients the faecal excretion of bile salts decreased concomitant with relief of symptoms. The 9th patient had no gall bladder but the diarrhoea ceased after treatment with cholestyramine.

Low lactose diet

Impaired lactose absorption is best corrected by removing the disaccharide from the diet by restricting the intake of milk (Hertzler, Huynh and Savaiano 1996). It is not shown that a lactose-restricted diet can prevent radiation-induced diarrhoea. In one study 64 patients were randomised prior to pelvic radiotherapy into one of three groups: lactose-restricted diet, hydrolysed lactose and control (Stryker and Bartholomew 1986). No statistically significant differences between the three groups were found. The group receiving hydrolysed lactose even seemed to have some more diarrhoea than the control group. They explained this finding by claiming that the low values of 14 CO_2 earlier found in breath tests (Stryker, Mortel and Hepner 1978) were misinterpreted. Delayed emptying of the stomach because of nausea and medication may have lead to the same result on the breath tests, as impaired lactose absorption would have done (Stryker and Bartholomew 1986). However, impaired lactose absorption was not excluded as a possibility for the diarrhoea, but they concluded that this could not be the most important cause of diarrhoea during radiotherapy. In addition it is known that impaired lactose absorption may come secondary to all diarrhoea (Statens ernæringsråd 1995).

Terminal ileum is the part of small intestine that receives the highest dose during pelvic radiotherapy (Wellwood and Jackson 1973, Stryker and Demers 1979). Lactose, however, seem to be absorbed during the first 20% of the intestine (Vander, Sherman and Luciano 1994). When the intestinal content reaches the terminal ileum almost all the lactose is absorbed in most patients. It is shown that the amount of small intestine included in the treatment volume influence the degree of impaired lactose absorption (Weiss and Stryker 1982). 14C lactose breath tests were performed on two groups where the amount of small intestine included in the treatment volume differed. The results showed a higher degree of impaired lactose absorption when a significant portion of the intestine was included in the treatment volume.

Dietary management of acute radiation enteritis

Several studies have demonstrated that impaired bile salt absorption is a factor in the aetiology of acute radiation diarrhoea during pelvic radiotherapy. Impaired lactose absorption also seems to be a factor, but the volume of small intestine included in the treatment field seems to influence the degree of impairment. A low fat diet, 40 g of fat, is indicated to prevent

diarrhoea caused by impaired bile salt absorption (Bosaeus, Andersson and Nyström 1979). Lactose maldigesters may tolerate up to 6-g lactose in one meal without having diarrhoea (Hertzler, Huynh and Savaiano 1996). This indicates that a low fat, low lactose diet could prevent diarrhoea during pelvic radiotherapy. The diet should be used from the first day of radiotherapy since cell-replication in the intestinal mucosa is affected from the start of treatment (Berthrong and Fajardo 1981). It is reported that the intestinal mucosa is normally healed two to three weeks after end of radiotherapy (Trier and Browning 1966, Berthrong and Fajardo 1981). Also during the healing process the diet should be low in fat and lactose.

1.3 Nutritional support and health related quality of life

Like in all other medical research it has been common to consider the effect of nutritional support on a narrow set of outcome variables like improvement of nutritional status or survival. Efforts to treat malnutrition or to improve survival or treatment toxicity with nutritional support in cancer patients, have mostly failed (Cella et al 1993). Such studies might have been be enriched if improvement in mobility, work function, mood state or social relationships had been used as outcome measures (Cella et al 1993). These additional benefits can be included in the concept health related quality of life (HRQOL).

Diet and HRQOL in cancer patients

Observations of improved well-being and symptom control have been made in connection with nutritional support and one may easily imagine that nutritional problems and deteriorated nutritional status may affect HRQOL negatively. Anorexia and weight loss may lead to depletion of energy stores as well as a catabolic state that results in fatigue and bodily discomfort (Tchekmedyian, Cella and Heber 1999). Anorexia may also have social implications since meals are important opportunities for the family to be together.

Most studies on diet and HRQOL have focused on how malnutrion in cancer patients may affect quality of life domains like psychological distress or depression (Bruera et al 1984, Westin et al 1988, Ovesen, Hannibal and Mortensen 1993). Most of these studies show an association, but it has not been possible to determine whether depression causes

malnutrition or develops as a consequence of it (Bruera et al 1984). Bruning et al (1985) showed no association between, what they called mental fitness, and dietary intake. They did however find that malaise had a clear inverse relationship with food intake, but again it was not possible to determine what came first, diminished intake or malaise. Others have found that loss of appetite may be an important determinant in the general well being aspect of HRQOL during treatment (Coates et al 1983, Macuart-Moulin et al 1999).

The instruments used to measure psychological distress in these studies vary. The investigators have often used small sets of questions developed for the given study without any systematic approach. This makes it difficult to make a direct comparison between the studies. In a study from Hammerlid et al (1998) a more systematic approach was chosen as they used a cancer specific instrument that was validated and used in several other studies (Aaronson et al 1993). The study from Hammerlid et al (1998) focused on how malnutrition affected physical functioning and symptoms. In a group of head and neck cancer they found no strong association between malnutrition and functioning or symptoms. The malnourished patients scored lower than the patients with normal nutritional status on most symptoms/functions, but the differences were not statistically significant. At the 2-year follow-up the survivors scored significant better than the deceased for appetite loss, swallowing difficulties and global quality of life. Although the groups were small, the authors concluded that measurement of HRQOL might be of prognostic value.

Despite these results showing that malnutrition might affect well being and functioning negatively, we have been able to find only one dietary intervention study in cancer patients that have used HRQOL as a primary outcome measure. Nutritional counselling was given to a group of patients undergoing chemotherapy for various cancers (Ovesen et al 1993). The counselled group increased the energy and protein intake but no statistical differences were found between the two groups after two months with respect to weight gain. Clinical benefits could not be demonstrated on survival, tumor response or measurement of QOL. The Quality of Life index (QL-index) (Spitzer et al 1981) which was rated by the patients was used to assess QOL. This index has been criticised for not capturing information about the different dimensions of QOL and the fact that each question asks about more than one aspect (Maguire and Selby 1989).

Measurement of HRQOL

In the present study we did not expect that nutritional support during radiotherapy would improve survival, but we assumed that absence or presence of diarrhoea could influence the patients' physical symptoms and functional status. To assess such outcomes of the diet intervention a questionnaire developed by the European Organisation for Research and Treatment of Cancer (EORTC) was used (Aaronson et al 1991). The term HRQOL was defined as the patients' self-reported subjective physical and psychosocial situation as a consequence of disease and treatment. When the present study started one of the first randomised trials including HRQOL-measurements in oncology was already performed at NRH by Kaasa, Mastekaasa and Naess (1988).

In 1980, a study group on Quality of Life was created within the EORTC with the long-term goal of developing a brief standardised QoL measure to be used internationally in cancer trials. The multinational effort resulted in a self-assessment core questionnaire that is multidimensional, cancer specific and cross-culturally validated (Aaronson, Bullinger and Ahmedzai 1988, Aaronson et al 1991, Aaronson et al 1993). In this approach a core of general items are given to all patients. This provides standardised assessment for comparison across disease, symptoms and treatments or with normal population (Kaasa 1992).

HRQOL is not used as a single entity but defined as a multidimensional health related construct including physical, social and mental dimensions (Aaronson, Bullinger and Ahmedzai 1988). The dimensions in HRQOL are further divided into sub-dimensions such as physical functioning, role functioning, emotional functioning, well being, fatigue etc. The core questionnaire is supplemented with illness- and treatment specific items. The general items are developed and standardised prior to the study and the investigators develop the specific items. These specific items are based on particular areas of interest implicated by the new intervention tested. This approach provides specific information about problems unique to the patient group under study.

The original questionnaire contained 42 items, which were subsequently reduced to 36. The 36-item version was widely tested and validated (Aaronson et al 1991). These 36 items have been shortened down to 30 (QLQ-C30) which is the current recommended version (Aaronson et al 1993). There are also 13 supplementary disease-specific modules, for

example for lung cancer, breast cancer and head and neck cancer (Aaronson, Bullinger and Ahmedzai 1988, Bjordal and Kaasa 1992). The questionnaire is under constant development. As an example is a work in progress were the aim is to reduce the QLQ-C30 from 30 to approximately 20 items to make it more suitable for palliative care patients (Groenvold, Petersen and Bjorner 2000). The shortened version will be comparable with the original version and is expected to ready by the end of year 2001.

1.4 Aims and research questions

The aim of the present study was to evaluate the effect of a low fat, low lactose diet on acute and late gastrointestinal side effects of pelvic radiotherapy.

The following study questions were formulated:

- Does a low fat diet affect the intake of vitamins?
- Does the study groups comply with their diets?
- Does a low fat, low lactose diet during pelvic radiotherapy reduce acute diarrhoea?
- Does low fat diet lead to reduced energy intake?
- Does diet interventions during pelvic radiotherapy influence the patients health related quality of life?
- Does a low fat, low lactose diet during pelvic radiotherapy reduce late radiation injury and chronic diarrhoea?

The study hypothesises were as follows:

- Patients, who restrict the fat intake to 40 g per day (intervention group) have a lower intake of fat-soluble vitamins and a higher intake of water-soluble vitamins as compared to patients receiving regular hospital diet (control group). (Paper I)
- Dietary counselling leads to a lower intake of fat in the intervention group as compared with the control group during radiotherapy and six weeks after end of therapy. (Paper II)
- Patients, who restrict the fat intake to 40 g per day and the lactose intake to 5 g per meal (intervention group) during pelvic radiotherapy, have less diarrhoea during treatment than patients receiving regular hospital diet (control group). (Paper III)
- Low fat, low lactose diet during radiotherapy will contribute to maintenance of good nutritional status. (Paper IV)
- Presence of diarrhoea during radiotherapy reduce patients self-reported health-related quality of life. (Paper V)
- Patients, who eat a low fat, low lactose diet during pelvic radiotherapy (intervention group), are less likely to develop late radiation injury and chronic diarrhoea as compared to patients receiving regular hospital diet. (control group). (Paper VI)

2. Material and methods

Table 2-1 gives an overview of the methods used in the papers.

Table 2-1 Overview of the methods used in the study

	Paper I	**Paper II**	**Paper III**	**Paper IV**	**Paper V**	**Paper VI**
Frequency of bowel movements			**X**	**X**	**X**	**X**
Nutritional status						
- weight		**X**	**X**	**X**		
- body mass index						**X**
- arm circumference			**X**	**X**		
- biochemical indicators			**X**	**X**		
Health related QoL					**X**	**X**
Dietary intake						
- 48-hour recall	**X**		**X**	**X**		
- 4-days food record	**X**	**X**	**X**	**X**		
by household measures						
- 7-days weighed food record				**X**		
Validation of diatary intake						
- 24-hour urinary nitrogen		**X**				
- physical activity level		**X**				
- weight development		**X**				

2.1 Design and study population

The study was designed as an open randomised clinical trial and conducted at NRH. Inclusion and randomisation were performed 1-2 days prior to radiotherapy. After the decision on treatment by the oncologists the eligible women were approached and asked to participate. AB (main author) did all contacts. If the patients accepted to participate they were immediately randomised to intervention or control group. Dietary treatment and radiotherapy started simultaneously. The diet was to be followed during radiotherapy and six weeks after the end of radiotherapy. Measurements were performed prior to radiotherapy, the 3rd and last week of radiotherapy, 6 weeks after end of radiotherapy and then every eight-week. The follow up period was one year (figure 2-1). In November 1993 the surviving patients were approached once more and asked to complete a questionnaire package similar to the one completed during the clinical trial. The response rates (respondents in percent of total eligible patients) are described in 3333 2-2.

Table 2-2 Response rates (respondents in percent of total eligible patients)

	Eligible	Declined to participate	Respondents	Response rate %
Clinical study	183	40	143	78
Survivors	94[1]	15	79	84

[1] Those who declined participation were not included among those regarded as eligible in the follow-up study

The study population was recruited from the department of gynaecology at NRH. Criteria for selection and exclusion are described in detail in paper III. The main selection criteria were external pelvic radiotherapy to a total dose above 40 Gy, age equal to or less then 75 years and a WHO functional status (WHO 1979) better than or equal to 2. The women were not considered eligible if they previously had received chemotherapy or if

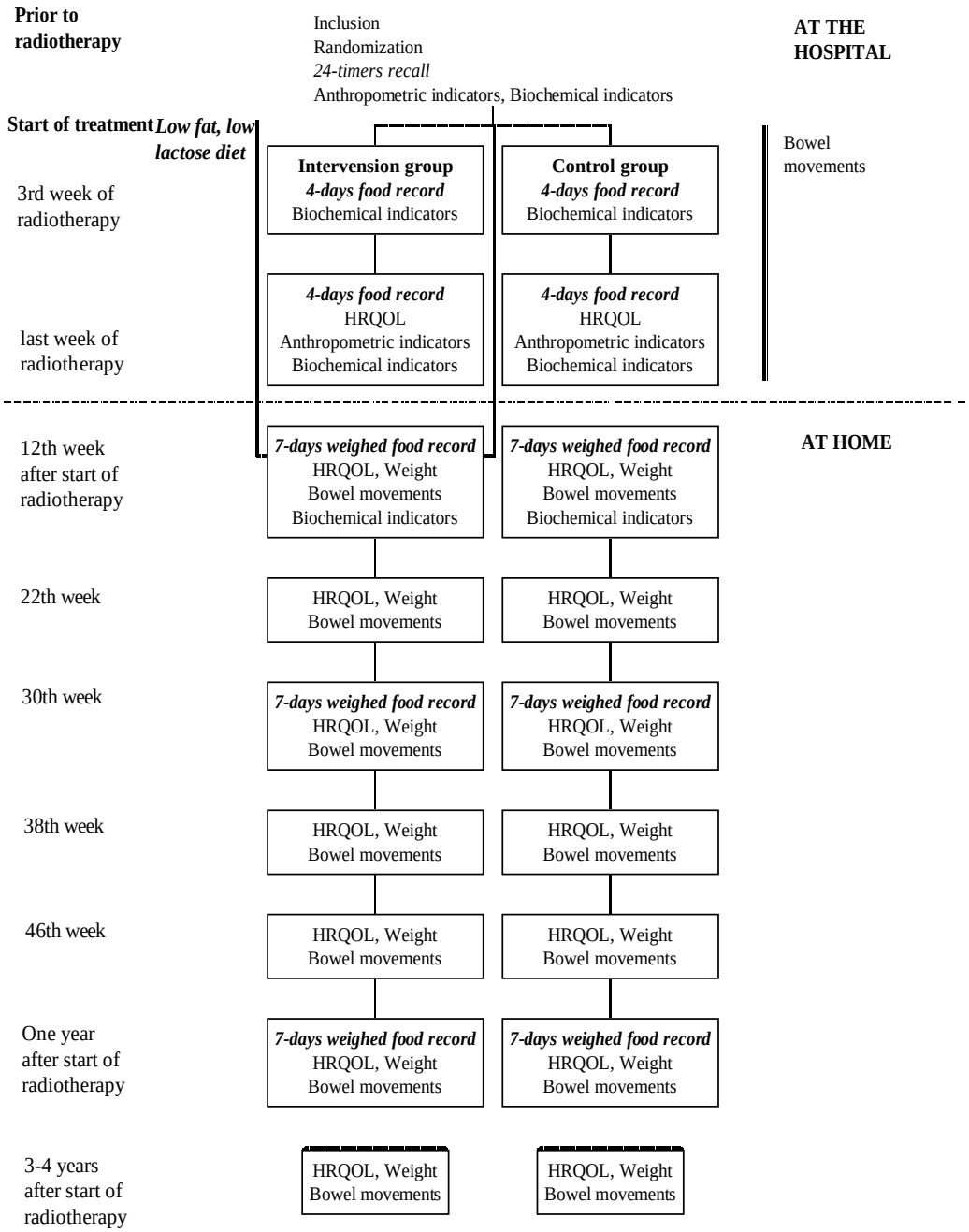

Figure 2-1 Study design

surgery were planned after radiotherapy. Women with a diagnosed inflammatory bowel disease or resection of the intestine were also excluded.

Patients were consecutive included from May 1988 through May 1990. During this period a total of 183 women were eligible and invited to participate, 143 (78%) accepted. Seventy-one were assigned to the intervention diet and 72 to the control group. In November 1993 the women, who did not withdraw during the first year of follow-up, were alive and without known relapse were approached. According to the Population Register of Norway and the hospital files 94 women were alive and without known relapse; 79 (84%) accepted participation. Drop-off in participation from inclusion and during follows up is shown in figure 2-2 and 2-3. Details about the patients' age, social status and treatment regimens are reported in paper III, IV, V and VI.

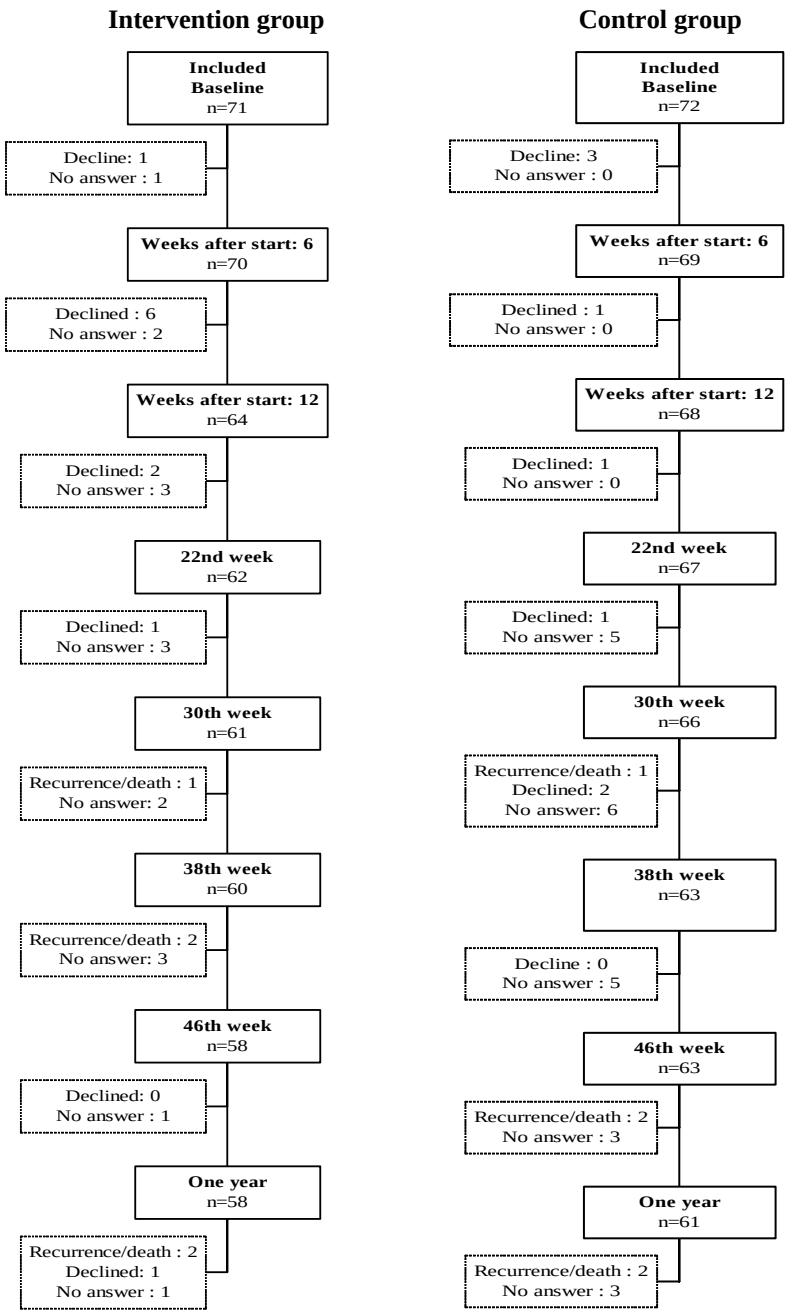

Figure 2-2. Drop-off in participation during the clinical study

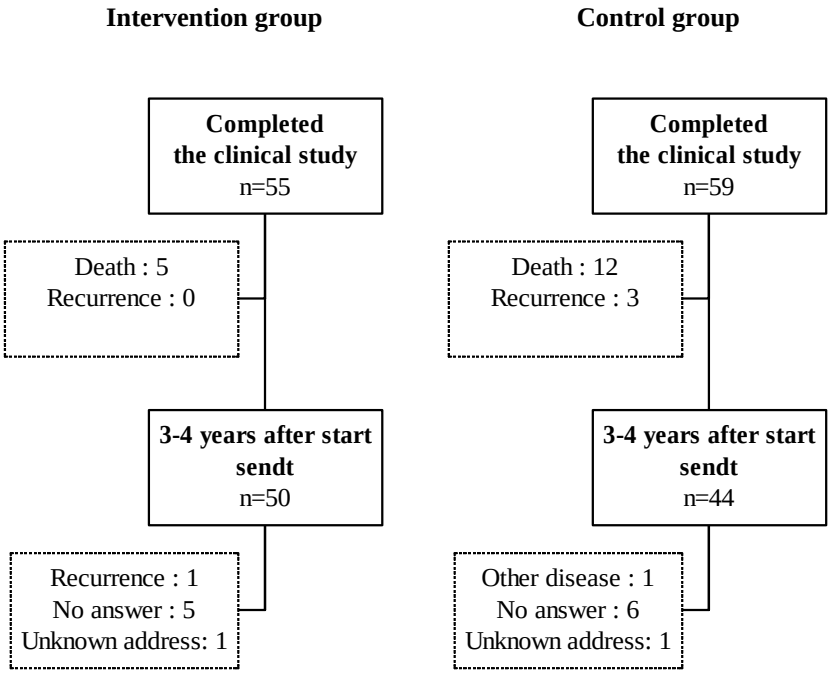

Figure 2-3 Drop-off in participation at 3-4 years follow-up

2.2 The intervention diet

The intervention diet is described in paper I and III. The average fat content in the regular hospital diet was 80 g (44% of energy from fat). To obtain the intervention diet with maximum 40 g fat per day, low fat milk products, lean meat and fish were used. The energy lost by reducing the fat was about 1.5 MJ and it was important to replace this energy to prevent weight reduction. The energy was replaced by increasing the amounts of foods with carbohydrates (bread, vegetables, and fruit). As a consequence of this the volume of the diet increased. Four slices of bread equals about 1.5 MJ. Patients in both groups were advised to eat enough to maintain weight during radiotherapy and to use nutritional supplements if necessary.

The hospital kitchen planned the intervention diet in co-operation with the dietician. Both the intervention diet and the regular diet were composed to match the recommendations for daily intake of nutrients and produced in accordance with the Norwegian Guidelines for Hospital Diets (Statens ernæringsråd 1985).

2.3 Dietary advises – intervention group

In order to secure the patients compliance to the diet individual advice on the type and quantity of foods to eat were given. Initially the women were asked what they usually ate. Based on this information the individual advises were formulated. Women reporting use of margarine or butter on the bread were advised to replace this with low fat alternatives or to stop using it. If milk intake was reported they were advised to restrict the intake of milk to the meals, no more than one glass (150-ml) at the time and not exceed three glasses of milk daily. Folders with information about low fat cooking and foods were produced and handed out to the women.

The counselling made it possible for the patients to keep the diet when they had food in addition to the hospital meals or were outside the hospital. It was also necessary for the outpatients who had to prepare the low fat, low lactose diet themselves. Thorough knowledge of low fat foods and cooking methods was considered important for compliance. Dietary habits are closely linked to the culture and changes in dietary intake may have consequences for the normal daily living. It may especially be difficult to keep to a diet at social gatherings. It was therefore reckoned important not to make more changes to

the women's diet than necessary and the intervention diet was planned as similar to the regular diet as possible.

During the hospital stay (approximately six weeks), AB had daily contact with the women. They were asked about their satisfaction with the diet and the dietary advises were repeated when necessary. Before they left the hospital the dietary advises were repeated and further information was given if necessary. During the next six weeks the women followed the diet at home. No systematic dietary follow-up was scheduled but the women were free to call (AB) if they had any questions.

2.4 Effect variables

Frequency of bowel movements

The women registered the daily number and consistency of bowel movements. The data was categorised according to table 2-3 and used to evaluate if diarrhoea was present or not. The method is described in detail in paper III and VI.

Table 2-3 Categorisation of diarrhoea

0 - no change in bowel movements
1 - increase of 1-3 bowel movements a day, normal or soft
2 - increase of 4-6 bowel movements a day, all watery bowel movements
3 - increase of > 6 bowel movements a day

Loperamide was used as standard treatment of radiation induced diarrhoea. This medicament is an opiate agonist precursor, which seem to slow down small intestine transit and increase bile acid absorption (Yeoh et al 1993B). Patients in both groups were instructed to take the medicataion when they felt it was necessary and to register the number of tablets taken.

Nutritional status

Nutritional assessment may be performed longitudinally by measuring changes in response to dietary interventions. The basic methods used in clinical practise to evaluate nutritional status may be grouped into four types of activities; anthropometrics, biochemical tests, clinical observations and dietary and personal histories (Williams 1995A). Assessment of nutritional status can be defined as the interpretation of this information and the evaluation is usually performed by a combination of the different methods. Because no single parameter alone directly measures nutritional status each part of this approach is important.

In this study it was chosen to evaluate nutritional status according to a protocol by Blackburn (Blackburn et al 1977). Table 2-4 gives a description of different parameters used in evaluation of nutritional status. The following anthropometric measures were used:

- height and weight
- body mass index, i.e. weight/ $(\text{height})^2$
- triceps skinfold thickness
- arm circumference

Biochemical indicators of nutritional status were serum transferrin and serum albumin. Assessment of dietary intake was evaluated by the means of:

- 48-hour recall prior to radiotherapy
- 4-days unweighed dietary record during radiotherapy
- 7-days weighed dietary records during follow-up

Table 2-4 Parameters used to evaluate nutritional status

Parameters	**How to measure poor nutrition**
Anthropometrics	
- Weight	Note weight loss
- Body Mass Index (BMI)	Compute BMI=kg/m^2 , < 20 indicate poor nutrition
- Mid-Upper-Arm Circumference (MAC)	Compare with previous measurements to note change
- Triceps Skinfold Thickness (TSF)	Compare with previous measurements to note change
- Mid-Upper-Arm Muscle Circumference (AMC)	Compute AMC (cm)=MAC (cm) - [3.14xTSF(cm)] and compare with reference data
Biochemical Tests	
Measures of Plasma Protein Compartment	
- Serum albumin	Compare with normal range
- Serum transferrin	Compare with normal range
Measures of Protein Metabolism:	
24-Hour Urine Tests - Urinary urea nitrogen	Compare with calculated dietary nitrogen intake to determine the nitrogen balance
Dietary assessment methods	
- 24-Hour Food record	Calculate nutrient intake
- Food records	
4-days unweighed dietary record	Calculate nutrient intake
7-days weighed dietary records	Calculate nutrient intake

Health related Quality of Life (HRQOL)

HRQOL was defined as the patients' self-reported subjective physical and psychosocial situation as a consequence of disease and treatment. It was measured with the EORTC Core Quality of Life Questionnaire 36-item version (EORTC QLQ-C36) (Aaronson et al 1991) and a module designed for gynaecological cancer. The physicians and researchers at the NRH constructed this ad hoc module for the present study. The EORTC QLQ-C36 version was a result of work in the study group of quality of life of the EORTC. The first generation core questionnaire was developed in 1987. The goal of this work was to construct a cancer specific, multidimensional, self-administered instrument responsive to clinical changes to be used in clinical trials. The study group evaluated validity and statistical properties. Since the QLQ-C36 version the questionnaire has been validated and cross-culturally tested in various cancer populations and translated into 27 languages (Bjordal and Kaasa 1992, Aaronson et al 1993, Osoba et al 1994, Kaasa et al 1995, Bjordal et al 2000). The EORTC QLQ-C30 version 1, existed when the follow up study was conducted, but it was decided to use the C-36 version to be able to compare the data longitudinally.

The questionnaire consists of 36 items with dichotomous, four or seven response categories. Multi-item scales for:

- physical functioning
- fatigue/malaise
- nausea/vomiting
- role functioning
- social functioning
- emotional functioning
- global health/quality of life

Other general cancer symptoms are covered by single items.
The additional gynaecological cancer module consists of 17 questions. This module focus on diagnosis specific symptoms, pain and treatment side effects.

In the later versions of the questionnaire the scores are linearly transformed to a 0 to 100 scale. This was done with the data collected by the QLQ-C36 version in paper IV in order to compare our data with population-based norms.

2.5 Control of the intervention

Compliance with the diet was evaluated by the means of dietary assessments methods (table 2-4). Detailed description of the methods are given in paper I, V and VI.

Three methods were applied and the choice of methods was partly dictated of practical conditions and the study design. Since the study design was prospective, use of food records was preferred (prospective methods). Dietary treatment started the very same day or the day after inclusion. It was also possible that the patients had been fasting during the 24 hours prior to inclusion. These facts made it impossible use prospective methods to obtain baseline information and instead a retrospective method (*48-hour recall)* was used (Callmer et al 1986).

During radiotherapy a *4-days food record by household measures* was used to assess dietary intake (Kuskowska-Wolk 1990). Most of the patients got the diet from the hospital kitchen and it was standardised with respect to portion sizes and composition. Because of this it was assumed that it was not necessary for the patients to weigh everything they ate. To provide weights for calculation of dietary intake extra portions of the low fat, low lactose diet and of the regular hospital diet were ordered from the kitchen to a non-existing patient. AB weighed these portions.

During the follow-up a 7-*days weighed food record* was used because day-to-day variation in the intake of fat was expected when the patients stayed at home (Kuskowska-Wolk 1990). Furthermore an increased number of measurement days and use of scales was supposed to improve reliability.

2.6 Validation of the dietary intake

The use of dietary assessment methods to evaluate compliance may be problematic since all these methods have their limitations (Crumb-Johnson et al 1993). The major disadvantages with retrospective methods are memory lapses and inadequate knowledge of food portions (Barret-Connor 1991). Prospective food records are assumed to influence the respondent's dietary behaviour and underreporting seems to be normal especially among women (Block 1982). Because of the known limitations, dietary assessment instruments should always be validated (Howat 1994). An absolute validation of dietary intake is difficult to perform since it requires knowledge about the true intake. Instead most scientists measure the relative validity by use of biochemical markers. Another way to validate dietary intake is by means of external independent markers relating reported energy intake to estimates of basal metabolic rate, physical activity level and body weight (Sandström 1993, Black et al 1995).

The following three methods were used in the validation procedure. They are described in paper V:
- 24-hour urinary nitrogen
- physical activity level
- weight development

3. Results and summary of papers

The papers are summarised as follows:

Paper I Nutrient intake and food choice among patients on a low fat, low lactose diet

Non-compliance in a dietary intervention study may cause inaccurate results and weaken the reliability of study outcomes. Dilution of effect by control subjects who decide on their own to adopt the dietary behaviour of the treatment group is one other problem. This paper describes dietary intake in the two groups in order to evaluate compliance. The foods eaten in order to achieve a reduction in dietary fat to 40g per day are presented and the nutrient intake is compared with Norwegian dietary guidelines.

Dietary intake pre-treatment was measured by a 48-hour recall method. During radiotherapy a 4-day food record method was used. Data was collected during two periods, three weeks after start of radiotherapy and during the last week of radiotherapy. The quantities eaten were estimated by the patient and described in household measures as the number of units consumed (cups, glasses, spoons, number of slices, pieces, decilitres). This was translated to weights. The volume content in the hospital cups, glasses, spoons etc. were measured. Slices of bread, cheese and other spreads prepared by the kitchen were weighed. In addition, to get an impression of the serving sizes an extra portion of food was ordered from the kitchen to a non-existing patient. This was control weighed by the dietician on a dietetic scale. To translate household measures used by the outpatients, tables of food portion sizes were used. The total intake of energy, energy yielding compounds, dietary fibre, calcium, iron, retinol, ascorbic acid, vitamin D, thiamine, riboflavin and niacin were calculated by means of the FIBER software package that is based on Norwegian food composition tables.

No significant differences were found in energy intake, contribution of macronutrients to the energy intake and nutrient intake before radiotherapy. During radiotherapy the intervention group received a significant lower part of the energy from milk products, meats, fats and sugar than the control group, and consumed more energy from vegetables and fruits, cereals and

fish. The intervention group had a higher intake of dietary fibre than the control group (11.3 (4.1) g versus 9.0 (3.3) g per day, p=0.000). The low fat, low lactose diet had an overall higher nutrient density than the ordinary diet, however, not with respect to the fat-soluble vitamins.

The intervention group had a qualitative different diet than the control group during radiotherapy. The low fat, low lactose diet was achieved through a reduction of milk products, fats and meats. The control group seemed to have reduced the intake of fats and milk but not enough to obtain a diet similar to the intervention group. The low fat, low lactose diet was a better diet in the sense of nutrient density.

Paper II **Evaluation of the validity of the method used to assess compliance to a low fat, low lactose diet in a dietary intervention study**

Dietary assessment instruments should always be validated because they all have their limitations. Prospective food records are assumed to influence the respondent's dietary behaviour and underreporting seems to be normal especially among women. This paper describes an attempt to measure relative validity by use of biochemical markers and to relate reported energy intake to estimates of basal metabolic rate, physical activity level and body weight.

During radiotherapy, the patients recorded their consumption of food, drink and nutritional supplements during two 4-day periods. The first period (period I) was three weeks after start of radiotherapy. The second (period II) was during the last week of radiotherapy. The food records were validated by using 24-hour urinary nitrogen and the Goldberg cut-off 2 as standards. In addition changes in body weight and energy intake (EI) were compared with estimated energy expenditure (EER).

For both periods there were no significant differences between the reported protein intake and the intake estimated from the urine sample in any of the groups. The EI in the intervention group was lower than in the control group ($p<0.01$). The EI: BMR_{est} ratio were below the cut-off limit of 1.22 in the intervention group at period I. At period II the ratio was below the cut-off limit in both groups.

A mean weight reduction was observed in both groups during radiotherapy. The observed weight reduction at period I corresponded to a mean energy contribution from weight loss (EW) of 2.1 MJ per day in the intervention group and 1.4 MJ per day in the control group. Mean total energy used (TEU), (EW+EI), was respectively 8.1 and 8.4 MJ. TEU was significant higher than estimated energy expenditure (EER) in both groups when using a PAL of 1.27 to estimate the EER. EER was however not different from TEU in any of the groups when a PAL of 1.55 was used to calculate the EER (respectively 8.7 (0.8) MJ and 8.5 (0.7) MJ).

The observed weight reduction at period II corresponded to a mean EW of respectively 1.6 MJ and 1.0 MJ per day. TEU at period II was respectiveley 7.3 MJ and 7.5 MJ. No significant differences between TEU and EER were found when using a PAL of 1.27. When using a PAL of 1.55 to calculate EER (respectively 8.6 (0.8) MJ and 8.5 (0.7) MJ) it was higher than TEU in both groups ($p<0.01$).

The method used to measure dietary intake seemed to give a valid estimate of the intake in the intervention period on which it was possible to make conclusions about compliance. Even though the EI: BMR_{est} ratios were below 1.22, a bias towards underreporting of EI it was not indicated. The reported protein intake corresponded well to the protein intake estimated from 24-hour urinary nitrogen excretion. There was also consistency between energy intake, loss of body weight and estimated energy requirement.

Paper III **The influence of low fat, low lactose diet on diarrhoea during pelvic radiotherapy**

This paper describes the ability of a low fat, low lactose diet to prevent gastrointestinal side effects during the course radiotherapy. One hundred and eighty three women with a primary diagnosis of gynaecological malignancy (carcinoma of the endometrium, ovary and cervix, stage I and II) were eligible for the study. Forty denied randomisation and 143 were included. After written consent, the women were randomised to receive either a low-fat, low-lactose diet or the regular hospital diet.

During the entire period with radiotherapy they recorded use of anti-diarrhoeal medication and daily number and consistency of bowel movements. These registrations were converted to a diarrhoea scale where a score = 2 indicated diarrhoea. Other treatment related symptoms like emesis, nausea and loss of appetite were evaluated with the EORTC Core Quality of Life Questionnaire C-36 version (EORTC QLQ-C36). The dietary intake was measured prior to radiotherapy (48- hour recall), during the third and sixth treatment week (4-days food record by household measures) and twelve weeks after the start of the treatment (7-days weighed food record).

Before the start of treatment there were no differences in bowel movements or use of anti-diarrhoeal medication between the two groups. During the last week of radiotherapy 14 patients (23%) in the intervention group reported diarrhoea compared with 32 (48%) patients in the control group ($p< 0.01$). The intervention group also used less anti-diarrhoeal medication than the control group, 0.6 tablets per day versus 1.1 ($p<0.01$). Twelve weeks after the beginning of radiotherapy, no group differences were found with regard to bowel movements or medication. Emesis and nausea were no serious problems in any of the groups. The highest incidence of nausea was found in week 6. Five patients (8%) in the intervention group and six (9%) in the control group (ns) experienced moderate to severe nausea. Twelve women in each group (18% of the intervention group and 20% of the control group (ns)) reported substantial loss of appetite during the last week of radiotherapy. During radiotherapy the intervention group had a lower energy intake than the control group, 5.7 MJ versus 6.5 MJ ($p<0.05$). The mean daily fat intake was respectively 34.3 g and 60.1 g ($p<0.001$). Weight loss was more pronounced in the intervention group (mean reduction of 2.6 kg versus 1.7 kg) than in the control group ($p=0.06$) during treatment.

The incidence rate of acute diarrhoea the control was twice as high as in the control group as in the intervention group, which indicated an effect of the intervention diet. The lower incidence of diarrhoea did not result in reduced weight loss.

Paper IV **The effect of a low fat, low lactose diet on nutritional status during pelvic radiotherapy**

Nutritional status of cancer patients can be negatively affected by cancer treatment. With a low intake of fat it may also be difficult to maintain a sufficient intake of energy. Results from the previous paper showed that more patients in the intervention group lost weight than in the control group. This paper describes the effects of the diet on the women' nutritional status during and after radiotherapy.

The following variables were used to evaluate nutritional status, weight loss, arm muscle circumference (AMC), serum albumin (s-Alb) and serum transferrin (TSF). More than 5% weight loss over one month and AMC, and TSF below 90% of the lowest reference value were considered to be pathological. Categories were assigned on the basis of two or more variables having scores within that category. The following categories were used to describe the nutritional status
1) mildly depleted, 80-90% of the reference value
2) moderately depleted, 60-80% of the reference value and
3) severely depleted, less than 60% of the reference value.
Where there was an equal choice between two categories, the most pathological one was given preference.

The mean weight loss during radiotherapy was 2.5 kg in the intervention group and 1.7 kg in the control group (ns). Six weeks after termination of radiotherapy the intervention group had gained 0.6 kg, while the control group had gained 1.1 kg (ns). Both groups had regained their initial weight one year after start of radiotherapy. Mean values of AMC, s-Alb and STF were within the reference range in both groups during the entire observation period. Only minor changes were observed within the groups during treatment. During the last week of radiotherapy six patients (9%) in the intervention group and 4 (6%) in the control group were mildly depleted (ns). At 12 weeks and after one year none of the patients could be categorised as malnourished.

The patients in the intervention group did not seem to manage to compensate for the lost energy intake due to fat reduction and the low energy intake lead to weight loss during treatment. Despite this only minor changes in nutritional

status were seen. After completion of radiotherapy the intake of fat increased and both groups gained weight.

Paper V **Quality of life during pelvic radiotherapy**

This paper describes the effect of the diet treatment on the women's HRQOL. It was expected that absence of diarrhoea could affect the women's HRQOL in a positive way. At the same time it was possible that the low fat, low lactose diet would be hard to accomplish and therefore not feasible. In such a case the diet would be unacceptable for the women and possibly affect the HRQOL in a negative way.

HRQOL was defined as a multidimensional concept consisting of physical, psychological and social variables and it was measured by using the EORTC Core Quality of life Questionnaire 36-item version (EORTC QLQ-C36). The questionnaire consisted of five functioning scales: physical functioning (7 items), role functioning (2 items), emotional functioning (8 items), social functioning (2 items) and global health status/quality of life (2 items), and two symptom scales: fatigue and malaise (5 items) and nausea and vomiting (2 items). Single items concerning appetite, diarrhoea, constipation, pain, dyspnea, sleeping disturbances, alertness behaviour and financial impact were also included. A 10-item diagnosis specific module focusing on disease and treatment related symptoms designed for the present study were used. The measurements were done before starting therapy, during the last week of treatment, six weeks after ending radiotherapy and every eighth week during one year's follow up.

The mean scores on the five functioning scales (physical functioning, role functioning, emotional functioning, social functioning and global health/quality of life) and the single item on financial impact during treatment, exposed no statistically significant differences between the two groups. At 38th, 46th and 54th week the intervention group had a statistically significant lower score on the role functioning scale than the control group ($p<0.05$), indicating a better role function in the intervention group. The responses to the two symptom scales (fatigue and malaise and nausea and vomiting) and the single items concerning appetite, diarrhoea, constipation, pain, dyspnea, sleeping disturbances and

alertness behaviour did also not expose any major differences between the two groups. During the last week of radiotherapy diarrhoea was associated with higher scores on the role functioning scale, physical functioning scale and the fatigue and malaise scale within the control group. This was not found in the intervention group.

The intervention did not interfere with the patients emotional and social well-being but it may influence the patients ability to cope with diarrhoea, as it provides the patients with more control over their own situation.

Paper VI **Health related quality of life and occurrence of intestinal side effects after pelvic radiotherapy**

The present paper assess the occurrence of late intestinal side effects in the two groups 3-4 years after treatment and evaluates if the diet intervention during radiotherapy had an impact on the occurrence of late effects. HRQOL was evaluated and compared this with data from a random sample of women of similar age, from the Norwegian population.

According to the Population Register of Norway and the hospital files, 94 of the women who completed the clinical trial, were alive and without known relapse on November 1, 1993. They were approached by mail and asked to complete a questionnaire package similar to the one they completed during the clinical trial. Seventy-nine women (84%) returned the questionnaires after one reminder. Use of anti-diarrhoeal medication, number and consistency of bowel movements and present weight was recorded. Information about significant late radiation injury (bowel complications requiring hospitalisation and/or surgery) was collected from the hospital files. The women also completed EORTC QLQ-C36. The scores on the EORTC QLQ-C36 were compared with reference data from a random sample of 949 Norwegian women aged 19-80 years. To be able to do so the scales and single items were transformed linearly to a 0 to 100 scale. High score for a functional scale represented a high/healthy level of functioning. High score for a symptom scale/item represented a high level of symptoms/problems.

No statistically significant differences between the two groups were found regarding significant late radiation injury, diarrhoea and use of antidiarrhoeal medication. The mean scores on the item measuring diarrhoea in QLQ-C36

differed between the two groups, 19.4 (SD=25.4) in the intervention group and 29.6 (SD=27.3) in the control group, though not statistically significant ($p=0.09$). Three women (7%) in the intervention group and eight (22%) in the control group scored 3 or 4 on the item concerning diarrhoea ($p=0.05$). In the intervention group there was no statistically significant connections between acute and late side effects. In the control group, however, a high score on the diarrhoea scale during radiotherapy was associated with a high score 3-4 years after radiotherapy ($p<0.05$). Both groups had more diarrhoea than in the general population, 23.8 versus 9.5 ($p<0.01$). Substantial diarrhoea was associated deteriorated SF and fatigue. The HRQOL on the group level was not much different than the population-based norms.

As a group, the women with carcinoma of the endometrium and cervix suffered from few treatment and/or disease related side effects 3-4 years after radiotherapy. However, increased frequency of bowel movement was common. Presence of substantial diarrhoea affected HRQOL negatively and might interfere with nutrient absorption. Since our data indicated that the women who had followed a low fat diet during radiotherapy had less diarrhoea, nutritional guidance may be of importance.

4. General discussion

Cancer therapies and their side effects may contribute to nutritional problems and malnutrition. Patients with carcinoma of the endometrium or cervix that receive pelvic radiotherapy may experience diarrhoea and weight loss. This prospective clinical controlled study was conducted to evaluate if a low fat, low lactose diet could be an appropriate treatment to relieve some of the negative side effects of radiotherapy.

4.1 The clinical study

The effects on acute diarrhoea - comparison with other interventions

The main hypotheses in this study was that patients, who kept to a low fat, low lactose diet during pelvic radiotherapy, would experience less diarrhoea than patients not making these restrictions. Our results confirmed this hypothesis. During the last week of radiotherapy only 14 patients (23%) in the intervention group reported diarrhoea compared with 32 (48%) patients in the control group ($p< 0.01$). Dietary treatment did not eliminate diarrhoea totally. This was however not expected since other factors than bile acid malabsorption also are involved in the pathophysiology of radiation enteritis. In a study of the intestinal function during radiotherapy only four of 11 patients had impaired bile acid absorption (Yeoh, Lui and Lee 1984). Other factors that might be involved in the pathogenesis are reduction in the activity of aminopeptidases, imbalances in local bacterial flora, changes in intestinal motility and exo- and endogenous toxins (Henriksson et al 1999). Treatments focusing on these factors have been evaluated in clinical trials but the results do not indicate that such treatments are more effective than a low fat, low lactose diet in preventing radiation induced diarrhoea.

Elemental diets (pre-digested feeding formula) may protect against radiation enteritis because they reduce pancreatico-bilary secretion (Bounous et al 1980). In clinical trials these diets have reduced diarrhoea and even reduced the severity of late effects (Bounous et al 1975, Craighead and Young 1998). One problem with elemental diets that makes difficult to recommend such treatment, is the lack of palatability and poor compliance (Bounous 1980). A more recent study did however conclude that elemental diets are well tolerated (Craighead and Young 1998). This conclusion was based on experience from a study on 17 patients. Twenty three percent of these patients

did not comply with the elemental diet. Compared to our results where about 10 % withdrew because of the diet, 23% is a considerable portion of non-compliance. Elemental diets are very different from normal food, which possibly is their main disadvantage. Even if they help against diarrhoea, a craving for normal foods and meals may lead the patients to give up on such a diet treatment.

Sucralfate, an aluminium hydroxide complex of sulfated sucrose which protect exposed mucosa, have been evaluated in a double blind and placebo-controlled study with 70 patients with carcinoma in the prostate or urinary bladder (Henriksson, Franzen and Littbrand 1992). The results showed a reduction in frequency of bowel movements and less pronounced weight loss in the sucralfate group. One year later, the patients in the sucralfate group displayed significantly fewer problems with diarrhoea than the placebo group. These results were not reproduced in a later study were sucralfate was given once daily during radiotherapy and for two weeks following radiotherapy (OBrien et al 1997). No significant differences were found between the placebo and sucralfate. Respectively 95% and 88% suffered from side effects during radiotherapy. They conclude that sucralfate can not be recommended as routine treatment.

Eicosanoids (prostaglandins, thromboxanes and leukotrienes) and free radicals release may be involved in the pathogenesis of radiation enteritis. The eicosanoids produce a wide range of biological effects and inflammatory responses. Mesalazine is a potent inhibitor of their synthesis and as such it has been evaluated in a randomised double blind study (Resbeut et al 1997). One hundred and fifty patients receiving external radiotherapy to the pelvis were included. All patients followed a low fibre and low lactose diet. The results showed that severity and duration of diarrhoea, use of antidiarrhoeal agents and body weight did not differ between groups. They concluded that Mesalazine 4 g/day did not decrease the symptoms of radiation enteritis.

The justification for using a low fat, low lactose diet was bile acid malabsorption. One could argue that instead of using a diet it would be possible to use bile acid sequestering resins like cholestyramine. Cholestyramine is however considered being unpalatable and it may be difficult to maintain a comfortable balance between diarrhoea and constipation. In the literature it is also indicated that cholestyramine should be used with caution, since an increase in pre-existing fat malabsorption may be induced and thereby worsen the diarrhoea (Danielsson et al 1991). Taking

this into consideration a low fat diet based on modification of normal foods would be preferable. Cholestyramine could be offered to patients not obtaining a control of the diarrhoea with the diet.

The effects on the appearance of late injuries

Both the uses of elemental diets and sucralfate during radiotherapy have been suggested to influence the appearance of later bowel effects (Craighead and Young 1998, Henriksson, Franzen and Littbrand 1992). We were also able to show a small influence of the diet on late effects. Diarrhoea seemed to be less frequent if the women had eaten a low fat diet during radiotherapy but the difference was not statistical significant. Such a statistically significant difference would however be difficult to detect since only a few of the women reported significant diarrhoea during follow up. Nevertheless, diarrhoea was more prevalent among the former cancer patients than in the general population. Among those women experiencing significant diarrhoea social wellbeing and fatigue were negatively affected. This finding was not surprising. During clinical practice we have met patients with late radiation diarrhoea who have described how diarrhoea influence their social life. They are afraid to go out because they have no control over their bowel movements and need to have a toilet available constantly. To learn and get familiar with low fat, low lactose diet during radiotherapy could therefore be beneficial. The literature clearly indicate that bile acid absorption may be present in patients with late effects (Yeoh et al.1993A, Danielsson et al 1991) and metabolic studies have shown that low fat diets may correct bile salt malabsorption (Andersson, Isaksson and Sjögren 1974).

Diarrhoea and HRQOL

It is assumed that maintenance of body composition and adequate nutritional status can help patients with cancer to maintain or improve functional status and to feel and look better. Because of this we expected that presence of diarrhoea would affect HRQOL negatively. Despite more diarrhoea in the control group during radiotherapy we did not detect any differences in general well being between the two groups. Cancer patients may tolerate a high level of symptoms during treatment and report good satisfaction with life anyway (Kaasa et al 1991). Satisfaction with life is a general measure that possibly does not capture moderate health-related problems. Since diarrhoea during radiotherapy might be regarded as a minor problem by the patients it will not

affect measurements of general well being significantly. Within the control group, however, we found an indication of a negative influence of diarrhoea. Patients having diarrhoea experienced more fatigue and limitations in role functioning and physical functioning than the patients not having diarrhoea. In the intervention we found no such negative influence. This is an interesting finding, which we have explained by that diet intervention during radiotherapy might influence the patients' ability to cope with diarrhoea by giving them more control over their own situation (Ganz 1988).

Three to four years after radiotherapy a low frequency of treatment and/or disease related side effects were detected. Not surprisingly all measures of general well being were good. But also here we found that high levels of symptomology were associated with fatigue and deteriorated functioning.

The Diet

The term diet is derived from the Greek word *diata* and may be translated as life pattern (Schlettwein-Gsell 1992). Diet has a meaning of ration, compulsion and control in every culture. These negative aspects of a diet may be very strong in connection with cancer because one would like the patients with cancer to enjoy their meals and eat what they like in a period that everything else seems difficult. A low fat diet, which was used in the present study, is a diet in every meaning of ration, compulsion and control. The withdrawal in the intervention group during the first six weeks (9.8%) may reflect that it was not easy to comply to the diet and that the restrictions given were rigid. After the first weeks the number of withdrawals decreased. This may indicate that when they learned about the diet and experienced how it worked it was easier to cope with it. On the other hand it may reflect that the intervention group ignored the diet when they left the hospital. However, our data on dietary intake does not support this assumption.

We did not find any differences in nutritional status between the two groups during radiotherapy. These findings indicate that our hypothesis that less diarrhoea during radiotherapy will contribute to maintenance of good nutritional status during treatment must be rejected. The main problem for the patients in both groups was to maintain energy intake during treatment. The fat reduction was mainly obtained by eating less high-fat milk-products, visual fat and meats. The problem was to increase in the intake of fruits, cereals and vegetables sufficiently. This is in accordance with findings from other studies where they have evaluated the feasibility of low fat diets (Ikkala

et al 1991, Insull et al 1990, Sheppard, Kristal and Kushi 1991, Kendall et al 1991, Prewitt et al 1991). Even young healthy men may have problems to eat enough if the fat intake is low (Sandström, Marckmann and Bindslev 1992).

In our study reduced appetite was documented in both groups, a common problems for almost all patients with cancer (Bruera and MacDonald 1988, Ottery 1995). For some of the patients it may be impossible to eat enough food to meet the metabolic needs. Medium Chain Triglycerides (MCT-fat) and/or other nutritional supplements may therefore be necessary in the diet for patients with high energy needs (Hessov and Ovesen 1995). But even if effeort is made to motivate the patients to maintain energy intake this might be difficult especially if they are women. We experienced that many of the women were very pleased to loose weight. Some of them expressed that for the first time in their life they were able to loose weight without struggle. With such opinions it might be difficult to make overweight cancer patients not loosing weight. This assumption is supported by that primarily overweight women lost weight during radiotherapy in our study. All these factors show that close follow-up and proper diet counselling are crucial to succeed when dealing with a low fat diet to cancer patients.

Counselling on the diet

A person who is going to change the diet needs information and education in how to achieve the necessary changes (Crumb-Johnson et al 1993). Strict rules and prohibition to eat certain foods may cause a diet with no variety, lack of nutrients and weight loss (Polivy 1996). People who are given advise that is difficult to keep may be irritable and very concerned about food and how to eat. Restrictions may also lead to periods of excessive eating or even compulsive overeating (bingeing). It is shown that the way the dietary counselling is performed and the relationship between counsellor and patient are of importance for compliance (Crumb-Johnson et al 1993). A study done to evaluate barriers to the adoption of low fat diets showed that reduction in taste quality of the diet seem to be the major problem (Lloyd, Paisley and Mela 1995). Dietary changes should be done gradually giving the patients a possibility to become accustomed to the different taste of the new diet. This type of strategy is however not possible when you change to a low fat diet during a limited treatment period.

A Swedish study showed that it is possible to reduce the intake of fat by individual dietary counselling by a dietician (Ikkala et al 1991). At the beginning they met often and they had contact over telephone during the follow up period. The dietician taught the women in nutrition skills such as low fat cooking methods, supplementing their meals with carbohydrate foods and best food choices while shopping. In a study where the dietary counselling aimed at reducing dietary fat intake from about 39 % of energy to 20 % it was concluded that the fat reduction was made possible through education and dietary counselling (Insull et al 1990). In the counselling it was emphasised to make plans for how to eat instead of giving the patients a prescribed diet. The plans were individualised and possible to change according to the patients' dietary habits.

For the patients it may be difficult to recognise what comprises effective dietary changes when reducing the fat (Lloyd, Paisley and Mela 1995). Subjects may believe that they have lowered their fat intake and consume the recommended amount of fat. Dietary records however indicate that they still consume a diet containing a high percentage of the energy from fat. If a patient is going to succeed in reducing the fat intake as well as the lactose intake, it is important to give feedback on progress. Counselling on fat content of foods and the total amount of fat to eat each day are other factors that can make it easier to obtain the goals (Lloyd, Paisley and Mela 1995). Low-fat recipes may also be of importance and since it may be particularly hard to comply with a low fat diet when they were dining out or with friends, this should be discussed during counselling.

All data indicate that a diet must be carefully planned in order to be acceptable for the patients. The principles are better understood and motivation is secured if practitioner and patient work closely together during the planning process (Williams 1995A). An individual tailoring of the diet to personal needs and desires seem also essential. The women in our study were given individual advice on the type and quantity of foods to eat. The dietary counselling was based on information about usual dietary intake and the diet was individually tailored. The dietician had contact with the women almost every day and the dietary advises were repeated when necessary. The efforts made to educate the patients in the diet resulted in a high degree of compliance, which was documented, by the results from the food records.

4.2 Methodological issues

Internal validity

The advantage of clinical trials is that their experimental design can provide direct evidence of a cause-and-effect relationship (Langseth 1996, Bowling 1997). In the present randomised clinical trial we were able to show a cause-effect relationship between the low fat, low lactose diet and the occurrence of diarrhoea during pelvic radiotherapy. For this conclusion to be internally valid, the experiment must be designed so that conditions other than the diet are ruled out as potential causes for the reduced diarrhoea in the intervention group (Bowling 1997).

Selection - mortality

The randomised design of our study secured that variables not observed should be distributed by chance between the groups and thereby minimising the possibilities for bias (Willett 1990). Despite the randomised design it could be a source of bias and a threat to the external validity if the people managing the study selected patients into the study. We have no reason to believe that it was the case in our study. Only two persons were responsible for enrolment and the inclusion and exclusion criteria were followed. The study population was recruited from the gynaecological department at NRH. All that patients that fulfilled the inclusion criteria during the period may 1988 trough may 1990 (183 women) were eligible and invited to participate. Seventy-eight percent were consecutively included. The included patients should therefor be representative for the gynaecological patients undergoing pelvic radiotherapy at NRH during this period.

In the course of an experiment, some subjects may drop out before it is completed. In such a case different scores between the two groups on the dependent measure, may be due to an unique characteristic of subjects able to endure a particular condition, a subject-related variable that would be disproportionately present in each group (Bowling 1997). The withdrawal in the intervention group was higher than in the control group during the six first weeks of the clinical trial. Seven withdraw in the intervention group and four in the control group, a difference that was not big enough to result in unequal distribution of subject-related variables.

After the first 12 weeks the withdrawals were mainly because of recurrence or death. This implies that the evaluation of HRQOL that is made mainly reflects the condition of the cured patients but this applies to both groups and should therefore not influence the results.

Diffusion or imitation of treatment

This occurs when a control group learns about the intervention program and decides to adopt the dietary behaviour of the treatment group (Willett 1990). This threat to validity tends to equalise the outcomes between groups, minimising the chance of seeing a program effect even if there is one. Non-compliance in the intervention group may also result in such an inaccuracy.

To inhibit diffusion or imitation of treatment intervention trials should optimally be conducted as double-blind experiments. If subjects are randomly assigned to intervention or control groups and the subjects do not know what treatment they get, one can assume that any difference that develops between the groups is directly caused by the factor under investigation (Langseth 1996, Bowling 1997). Unfortunately it is impossible to administer intervention trials based on counselling as double-blind experiments (Langseth 1996). Such a design would create a very artificial situation and limit the degree to which one could generalise the results to a real contexts (reduced the external validity). One could imagine that one could overcome the problem by recruiting the patients from separate hospital wards and randomise the wards each of the treatments. This would however imply problems since the trial no longer would be a true experiment (Bowling 1997). It would be difficult to ensure the comparability of the units.

If blinding is impossible one must rely on the subjects self reported diet compliance (Crumb-Johnson et al 1993). In this study dietary intake was measured to detect possible non-compliance in the intervention group and imitation in the control group. Our data did not indicate that the control group had managed to eat a low fat, low lactose diet. The fat intake in the control group were however low and lower than in the general population. It was not possible to conclude that this was a result of imitation. It could also simply be an effect of the low energy intake. The results from the validation study of the dietary assessment methods indicate that we can trust the dietary data. Energy intake was low but it agreed with the observed weight reduction. In addition the protein intakes measured by 4-day food records were in accordance with the intakes estimated from the urine samples.

After the 12 first weeks of the study the diet intervention ended. The women were allowed to eat, as they wanted. Data on dietary intake showed that the fat intake increased in both groups but it was still lower than in the general population. This might have influenced our results and minimised the chance of showing an effect on late side effects.

Measurements

Time for measuring

It is important to plan the timing for measurements in order to detect expected changes at appropriate time periods (Bowling 1997). We performed measurements at the 3rd and last week of radiotherapy since diarrhoea was expected to occur at these times (Yeoh and Horowitz 1987). A new measurement was performed 6 weeks after end of radiotherapy when diarrhoea was expected to cease. The patients made records over their bowel movements during the entire treatment period and the six weeks following radiotherapy. The results showed that the frequency of bowel movements increased gradually and reached a peak during the last week of treatment. After treatment a similar decrease was seen. This indicates that timing for performing measurements were appropriate to detect any effects of the dietary intervention.

We planned the follow up period to be one year to detect any long term effects of the use of a low fat, low lactose diet during pelvic radiotherapy. Our hypothesis was that the diet could reduce the risk of developing late radiation injury and chronic diarrhoea. In the literature it was indicated that late radiation complications usually appear six to 24 months after treatment (Berthrong and Fajardo 1981, Kinsella and Bloomer 1980). We did not find any signs of late complications after one year and since such complications may occur at any time during the lifetime of the patient (Coia, Myerson and Tepper 1995), we decided to make a new evaluation 3-4 years after radiotherapy. Also at this point we found few indications of late complications. A longer follow-up might have detected more complications but it would have been too expensive to conduct such a study.

Instruments

A diary card was used to measure diarrhoea. This implied that we had to rely on the patients' own registrations. This could theoretically have lead to two kinds of threats to the internal validity of the study. The patients in the control group might have felt "jealous" about the dietary program in the intervention group. This could have leaded them to decide to show how well they could do without the diet. This threat generally works to in the direction of equalising the results and makes it more difficult to detect an effect if there is one. The other threat could be that the intervention group wanted to please the people responsible for the study and therefore record less bowel movements than they actually had (Bowling 1997). This threat would go in the other direction making the diet intervention look even more effective than it actually was. We have no reason to believe that any of these threats were more prominent and if they existed they would have balanced each other.

One reason for assuming that the patients did not try to please the people responsible for the study was the finding of low correlation between the data from the diary card and the diarrhoea item in the HRQOL questionnaire in both groups. The records showed a higher frequency of bowel movements than the HRQOL item did which indicate that they were accurate in their registrations. This finding also made us conclude that the when measuring specific phenomena such as diarrhoea in a clinical trial, the EORTC questionnaire does not seem to be sensitive enough. Specific trial-related instruments are therefore recommended to use.

More objective measures of diarrhoea would exclude the threats to the internal validity of the study because of the patients' own registrations. This was not possible because of limited assets and human resources. Absorption of ^{75}SeHCAT (a synthetic bile acid analogue) and serum levels of vitamin B12 could have been such objective measures (Ludgate and Merrick 1985, Snijders-Keilholz et al 1993, Yeoh et al 1993A).

External validity and clinical implications

External validity is related to generalising and is the degree to which the conclusions in the study would hold for other persons in other places and at other times (Bowling 1997). We have already concluded that the included patients was representative for the gynaecological patients undergoing pelvic

radiotherapy at NRH during the actual period. Strictly we can not generalise the results from this study to other groups of patients. However, we believe that patients receiving pelvic radiotherapy as their only treatment may be recommended a low fat, low lactose diet in order to prevent diarrhoea. Bile acid malabsorption has also demonstrated both in patients treated for seminoma of the testis (Yeoh et al 1995) and patients treated for rectal carcinoma experience the same problems with diarrhoea (Letschert et al 1994).

Since measurements of the absorptive function of the small intestine during pelvic radiotherapy have indicated that low lactose diet is a minor problem one may question if it is necessary to reduce both fat and lactose. Our design makes it difficult to decide what was the main effect, low lactose or low fat. This implies that our guidelines strictly must include both diet modifications. Despite this it is a possibility that low fat is the most important factor. One can also argue that it might be possible to intervene for a shorter period of time since diarrhoea seems to develop gradually (Berthrong and Fajardo 1981). In this way it would also be possible to make dietary changes gradually so it would be easier to comply. Strictly we can not say that such a strategy would give the same effect on diarrhoea as the diet applied in our study. In all studies evaluating the effect of dietary changes during radiotherapy the diet have been introduced from the start of treatment. Especially in question of preventing radiation injury it is possible that the diet should be used the entire treatment period.

Cancer patients are often concerned about what to eat and they may want to intervene themselves and thereby stay in control over their own life (Schmale 1979, Tchekmedyian, Cella and Heber 1999). The diet is one of the few areas where the cancer patient has some kind of control. Studies have shown that patients who experience diarrhoea tend to change their diet (Hulshof 1987). An American study showed a wide variety of foods which women with chronic radiation enteritis reported to worsen the symptoms from the intestine (Sekhon 2000). Bran muffins, popcorn, broccoli, salad, peas, beans and fried fish are just some examples. Generally it is difficult for individuals to locate the food items that are causing the symptom on a mixed diet. This may lead to exclution of necessary foods and thereby generate a diet that is monotonous and low in nutritional value. Some may also become afraid to eat and loose weight. In such cases a low fat, low lactose diet would be an alternative. The diet has a documented effect and if the food plans are followed the diet is

fully nutritional acceptable. The low fat, low lactose diet even seemed to be a better diet in the sense of nutrient density than the normal hospital diet.

Furthermore, if cancer patients are given proper dietary counselling it might prevent them from seeking unproven diet therapies. Risberg et al (1995) found that diet was one of the most prevalent forms of non-proven therapies used among Norwegian cancer patients. One other study has showed that 12% of patients undergoing radiation therapy for prostate carcinoma used special diets as complementary treatment (Kao and Devine 2000). The patients seem to believe that such therapies might improve physical resistance and/or their general condition (Risberg et al 1997). When it comes to non-proven diet therapies they unfortunately often have the opposite effect of improving physical resistance, since they are high in volume and unbalanced they may lead to weight loss and malnutrition.

5. Conclusions

The results from this thesis can be summarised as follows:

- The patients receiving a low fat, low lactose diet (intervention group) had a higher intake of water-soluble vitamins than the patients receiving a regular hospital diet (control group). The intake of fat-soluble vitamins did not differ between the two groups.

- During radiotherapy and six weeks after end of therapy the intervention group had a lower intake of fat than the control group. The dietary counselling lead to high compliance in the intervention group and the diet was well accepted.

- The intervention group had less diarrhoea and used less Loperamide during radiotherapy than the control group.

- No differences in nutritional status were found between the two groups. The low fat diet lead to reduced energy intake because of incomplete compensation of energy loss due to fat reduction. The energy intake in the control group was also low and weight loss was found in both groups.

- In the control group diarrhoea increased fatigue and had negative effects on physical functioning and role functioning during radiotherapy. We did not find that diarrhoea influenced HRQOL in the intervention group.

- No differences in late radiation injury and chronic diarrhoea were found between the two groups one-year and 3-4 years after treatment. Compared with the general Norwegian population, frequent bowel movements and diarrhoea were more prevalent in both groups 3-4 years after radiotherapy, but most prominent in the control group. Diarrhoea as a late effect seemed to increase fatigue and have a negative influence on social well being.

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Errata

Paper I

Page 276. Table 5. The number 2 for patients declining the study during the 6th week in the control group should be replaced by 1.

Page 279. Results. First sentence. The correct sentence should be: A total of 11 women (7.7%) withdrew from the study during the course of radiotherapy, seven (10%) in the intervention group and four (5.6%) in the control group.

Paper III

Page 148. Second section, line 2 and 3 from the top. The correct mean age should be 57.1 in the intervention group and 55.5 in the control group.

Page 149. Second section, under results, first paragraph, last sentence. The correct sentence should be: Four patients who left the study did so during the first week, six during the 3rd week and one during the 6th week.

Paper IV

Page 91. First section, under results, second sentence. The correct sentence should be: A total of 114 patients (80%) completed the study (55 in the intervention group and 59 in the control group).

Page 91. Table 2. The correct mean age should be 57.1 in the intervention group and 55.5 in the control group.

Page 91. Second section, line 9-12 from top. The correct mean age should be 57.1 in the intervention group and 55.5 in the control group. The correct mean weight should be 70.6 in the intervention group and 67.0 in the control group.

Paper V

Page 149. First section, under results, 5th line. The correct sentence should be: A total of 114 patients (80%) completed the study (55 in the intervention group and 59 in the control group).

Page 149. First section, under results, line 7-10. The correct mean age should be 57.1 in the intervention group and 55.5 in the control group. The correct mean weight should be 70.6 in the intervention group and 67.0 in the control group.

Paper I

URN:NBN:no-2118

URN:NBN:no-2118

Journal of Human Nutrition and Dietetics (1999), **12**, 273–285

Food choice and nutrient intake among patients on a low-fat, low-lactose diet: experience from a prospective randomized study

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Objective: To describe the food consumed in order to achieve a low-fat, low-lactose diet, and to evaluate the effect of food choice on nutrient intake.
Method: This was an open prospective randomized study. The patients were randomly allocated either to receive a low-fat, low-lactose diet or the regular hospital diet during radiotherapy. Dietary intake pretreatment was measured by a 48-h recall method. A 4-day food record method was used to collect data 3 weeks after start of radiotherapy and during the last week of treatment.
Subjects: 143 women with gynaecological malignancies undergoing pelvic radiotherapy.
Results: At baseline there were no significant differences in energy intake, food choices and nutrient intake between the two groups. During radiotherapy, the average percentage of energy from fat was 23% in the intervention group and 35% in the control group ($P< 0.01$), energy percentage from protein was 18% and 15% ($P< 0.01$) and carbohydrate 58% and 50% ($P< 0.01$). The intervention group received less energy from milk products, meats, fats and sugar than the control group and more from vegetables and fruits, cereals and fish.
Conclusion: The intervention group had a qualitative different diet than the control group during radiotherapy. The fat reduction was achieved through a reduction of milk products, fats and meats.

Key words: adverse effects, female, genital neoplasm, low-fat diet, low-lactose diet.

Introduction

Women with gynaecological malignancies undergoing pelvic radiotherapy were included in an open prospective randomised study in order to evaluate the effect of a low-fat, low-lactose diet on intestinal side-effects (Bye *et al.*, 1992). Malabsorption of bile salts and lactose has been observed during radiotherapy and may contribute to diarrhoea (Stryker *et al.*, 1978; Stryker & Demers, 1979; Arlow *et al.*, 1987; Yeoh *et al.*, 1993). A low-fat diet, with a maximum of 40 g of fat, was used since such a diet has been successfully used in the treatment of diarrhoea due to bile salt malabsorption (Andersson *et al.*, 1974). The

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Table 1. Patient characteristics.

		Intervention $n=71$ mean (range)	Controls $n=72$ mean (range)
Age (years)		57.1 (29–74)	55.5 (34–74)
Weight (kg)		70.6 (47–119)	67.0 (46–112)
Height (cm)		164.7 (153–180)	163.5 (149–177)
		%	%
Performance status*	0	89	88
	1	9	10
	2	2	1
Diagnosis	Cervical cancer stage IA	4	0
	Cervical cancer stage IB	22	24
	Cervical cancer stage IIA	4	6
	Cervical cancer stage IIB	31	39
	Endometrial cancer stage I	25	22
	Endometrial cancer stage II	13	8
	Ovarian cancer stage IC	0	1
Treatment	Surgery	55	47
	Radium application	31	35
	Brachytherapy	13	19
Other diagnosis	Hypertension	13	14
	Diabetes Mellitus	4	4

* WHO performance status (World Health Organization, 1979).

lactose intake was restricted to 5 g lactose per meal (Hertzler *et al.*, 1996). Fourteen patients (23%) in the intervention group reported diarrhoea during radiotherapy vs. 32 (48%) in the control group ($P< 0.01$) (Bye *et al.*, 1992).

Earlier reports from the study showed that the intervention group kept to the diet with respect to intake of fat (Bye *et al.*, 1993). The mean daily intake of fat in the control group was 57 g, which was low compared with data from the general population. This observation may indicate changes in food intake also in the control group, which is a well-known problem in open dietary intervention studies (National Research Council, 1989). Another factor that may have influenced the diet in the control group was the high frequency of diarrhoea among these women (Hulshof *et al.*, 1987). A diet prepared by the hospital kitchen in accordance with official guidelines (Statens ernæringsråd, 1985) was expected to ensure compliance to some degree. But foods were available at the hospital wards at all times and the patients were free to choose foods at meals. Dietary counselling should secure that the intervention group made the right choices. The way dietary counselling is conducted may be of importance for the feasibility of dietary changes. The dietary recommendations have to be translated into a realistic diet and personal commitment to the staff may motivate to adherence (Crumb-Johnson *et al.*, 1993). It was therefore of interest to evaluate the dietary changes made and see if they were in accordance with the advice given. Since the reported energy intake was low in the present study (5.7 MJ in the intervention group and 6.5 MJ in the control group ($P< 0.05$)), one could suspect that the fat reduction was achieved simply through eating less. In other studies a prescribed fat reduction has been achieved through a reduction of high-fat milk products, fats like margarine and butter, meat, cakes and chocolate (Hjermann *et al.*, 1981; Nordevang *et al.*, 1992). The intake of vegetables, fruits, cereals, low-fat milk products and fish were increased.

Because of the low energy intake it may be questioned if the daily intake of nutrients was sufficient. A fat reduction may itself lead to low intake of fat-soluble vitamins like vitamin D and alfa-tokoferol if the intake of fat fish and

Table 2. Guidelines for preparation of a low-fat diet (40 g of fat) (Statens ernæringsråd, 1985).

Vegetables:	Any fresh, frozen or cooked without added fat.
Fruits:	Any fresh (except nuts and avocado), canned, frozen or dried fruit or juice.
Dairy products:	Skim milk or low-fat milk (0.5% fat). Cheese with fat content of 17% or less.
Meat, poultry, fish, eggs:	Lean and well-trimmed meat. All fish except eel. Egg yolks within the daily fat amount.
Bread and cereals:	All kinds. Low-fat cakes and cookies.
Fats:	Daily use of 5 g margarine or oil with a high content of polyunsaturated fats. Low-fat margarine or butter allowed in small amounts. In food preparation, boiling and grilling is preferred. Frying with fat is avoided.

Table 3. Recommendations for daily intake of micronutrients, women age 31–60 years and recommended nutrient density when planning a diet (Statens ernæringsråd, 1993)

Nutrient	Recommended daily intake	Nutrient density content per 1 MJ
Dietary fibre, g*	25–30	3
Calcium, mg	800	110
Iron, mg†	12–18	1.4–2.1
Retinol equivalents, µg‡	800	120
Ascorbic acid, mg	60	8
Vitamin D, µg	5	0.6
Thiamine, mg	1.0	0.14
Riboflavin, mg	1.2	0.17
Niacin, mg	13	1.5

*The recommendation is dependent on the energy intake. 3 g dietary fibre per MJ is recommended. †The recommended daily intake varies with menstrual loss. ‡1 µg retinol equivalents = 1 µg retinol = 6 µg beta-carotene.

vegetable oils are not sufficiently increased (Ikkala *et al.*, 1991). To compensate for the energy loss caused by the fat reduction the patients were advised to increase the carbohydrate intake and to some degree the protein intake. Because of this the low-fat diet was expected to have a higher content of water-soluble vitamins (Gorbach *et al.*, 1990; Ikkala *et al.*, 1991).

The aim of this study was to describe and compare the intake of foods in the intervention and control groups and to evaluate the effects of food choices on intake of nutrients.

In addition, the intake of nutrients was compared to Norwegian dietary guidelines.

Materials and methods

Subjects

Between May 1988 and May 1990, 143 women were included in the clinical trial to evaluate the effect of a low-fat, low-lactose diet on intestinal side-effects during radiotherapy. Patient characteristics are presented in Table 1. The two groups were well balanced with regard to age, diagnosis and treatment. More detailed information about eligibility criteria, staging and treatment regimens are presented elsewhere (Bye *et al.*, 1992, 1993). The patients signing the consent form were randomized before radiotherapy to receive either a low-fat, low-lactose diet or the regular hospital diet, during the treatment period of about 6 weeks. Seventy-one patients were assigned to the intervention diet and 72 to the control group. The majority of the patients (101 patients) were hospitalized during the 6 weeks of radiotherapy, but a few from each group (18 patients in the intervention group and 24 patients in the control group) were receiving treatment as outpatients.

Diet

The dietary intake in the intervention group was planned to have a maximum 40 g fat per

Table 4. Food group classification system used in the nutrient database

Vegetables and fruits:	Vegetables, potatoes, legumes, fruits, berries Fresh, canned, frozen or dried
Milk products:	Milk, yoghurt, cream, cheese, ice cream
Meats:	Beef, veal, lamb, game, pork, poultry, sausages, brawn
Fish:	Fish, shellfish, fish roe, caviar, pickled fish
Eggs	
Cereals:	Flour, grain, ready-to-eat cereals, rice, pasta, bread, crisp bread, cakes, biscuits
Fats:	Oils, butter, margarine, mayonnaise
Sugar:	Sugar, sweets, chocolate
Beverages:	Coffee, tea, soft drinks, juice, beer, wine, spirits
Miscellaneous:	All the food types and recipes supplementary to the food composition tables

Table 5. Withdrawals and number of patients completing food records at each time-point in the trial.

		Withdrawal		Completed food record			
Time-points Week	Patients alive	Dissatisfied with diet	Declined study	Intervention	Control	Responding patients	(%)
0	143	1	3	70	69	139	(97.2)
3rd	143	6		62	68	130	(90.9)
6th	143		2	62	67	129	(90.2)

day and 5 g lactose per meal in accordance with the Norwegian Guidelines for Hospital Diets (Statens ernæringsråd, 1985). The energy intake was planned to match the regular hospital diet at 7.0 MJ. The carbohydrate and protein intake was increased in order to compensate for the energy loss caused by the reduction in fat. The low-fat, low-lactose diet is described in detail elsewhere (Bye *et al.*, 1992) and the guidelines for food choices are presented in Table 2. Both the intervention diet and the regular diet were composed to match the recommendations for daily intake of nutrients (Table 3). The average fat content in the regular diet was 80 g (44% of energy from fat). The lactose content of the regular diet was not calculated, but the planned menu contained three glasses of milk at 150 mL each and 10 g of brown cheese daily (24.5 g of lactose). In addition, milk was used in sauces, desserts and porridges.

A weekly menu for the low-fat, low-lactose diet was composed with dishes and meals typical for Norwegian food habits. Large amounts of bread, pasta, potatoes, rice, fruit and vegetables were used. The hospital patients received three meals a day (breakfast, lunch and supper) from the hospital kitchen. Dinner was the only hot meal; the other meals consisted of bread or cereals. An additional evening meal consisting mainly of soup and bread was served and prepared by the nurses. In order to secure the patients' adherence with the diet they were given individual advice on the type and quantity of foods to eat. These made it possible for the patients to keep to the diet when they ate something in addition to the hospital meals or were outside the hospital. The dietary counselling was also necessary for the outpatients who prepared their own food. Patients in both groups were advised to eat enough to maintain weight during radiotherapy and to use nutritional supplements if necessary.

Dietary intake at baseline: 48-h recalls

Data on dietary intake at baseline were obtained the same day the patient was

Table 6. Mean contribution of macronutrients to energy in the intervention group and the control group at baseline as assessed by 48-h recall and during radiotherapy (period I and II) as assessed by 4-day records (mean value (SD))

	Baseline					Period I					Period II				
	Intervention		Control			Intervention		Control			Intervention		Control		
n	70		69			62		68			62		68		
Nutrient	mean	(SD)	mean	(SD)	*P*	mean	(SD)	mean	(SD)	*P*	mean	(SD)	mean	(SD)	*P*
Energy, MJ	6.7	(1.6)	6.9	(2.0)	ns	6.0	(1.5)	7.0	(1.6)	< 0.01	5.7	(1.3)	6.5	(1.6)	< 0.05
Fat, % MJ	33.1	(7.2)	34.7	(6.3)	ns	21.7	(4.8)	34.0	(6.9)	< 0.01	22.9	(4.9)	35.1	(5.5)	< 0.01
Protein, % MJ	17.0	(3.2)	16.0	(3.2)	ns	18.8	(3.1)	14.6	(2.4)	< 0.01	18.4	(3.6)	14.8	(2.4)	< 0.01
Carbohydrate, % MJ	48.9	(7.3)	48.7	(7.7)	ns	58.5	(6.0)	50.4	(8.2)	< 0.01	57.6	(6.8)	49.2	(7.4)	< 0.01
Alcohol, % MJ	0.9	(3.7)	0.7	(2.5)	ns	1.0	(1.9)	1.0	(2.7)	ns	1.0	(2.9)	0.8	(4.1)	ns

included and after randomization. A 48-h recall method was used. It was standardized according to Callmer *et al.* (1986) and conducted as a personal interview. The interview covered the two previous days when the patients either had been at home or at the hospital. Throughout the entire inclusion period the same dietitian performed the interview. The patients were asked to report all food and drink consumed starting with the first previous day. The information was registered on an open form, and household measures (cups, glasses, spoons, number of slices, pieces, decilitres) were used to determine the serving sizes. When the patients had problems remembering what they ate questions like 'what did you do yesterday?' and 'did you eat anything at this occasion?' were asked. The same dietitian who performed it coded the interview.

Dietary intake during radiotherapy: food record by household measures

During radiotherapy, the patients recorded their consumption of food, drink and nutritional supplements for four consecutive days (Kuskowska-Wolk, 1990). The dietary intake was assessed twice, 3 weeks after start of radiotherapy (period I) and during the last week of radiotherapy (period II). The patients received oral and written instructions in keeping an accurate record. At the end of each 4-day period, the dietitian reviewed the records to probe for items that might have been forgotten.

The record form contained space for date, day of the week, time of food consumption, type of food and household measure. The quantities eaten were estimated by the patient and described in household measures as the number of units consumed (cups, glasses, spoons, number of slices, pieces, decilitres). The dietitian translated these measures to weights. The volume content in the hospital cups, glasses, spoons, etc., was measured. Slices of bread, cheese and other spreads prepared by the kitchen were weighed. In addition, to get an impression of the serving sizes, an extra portion of food was ordered from the kitchen to a nonexisting person. This was control weighed by the dietitian on a dietetic scale. To translate household measures

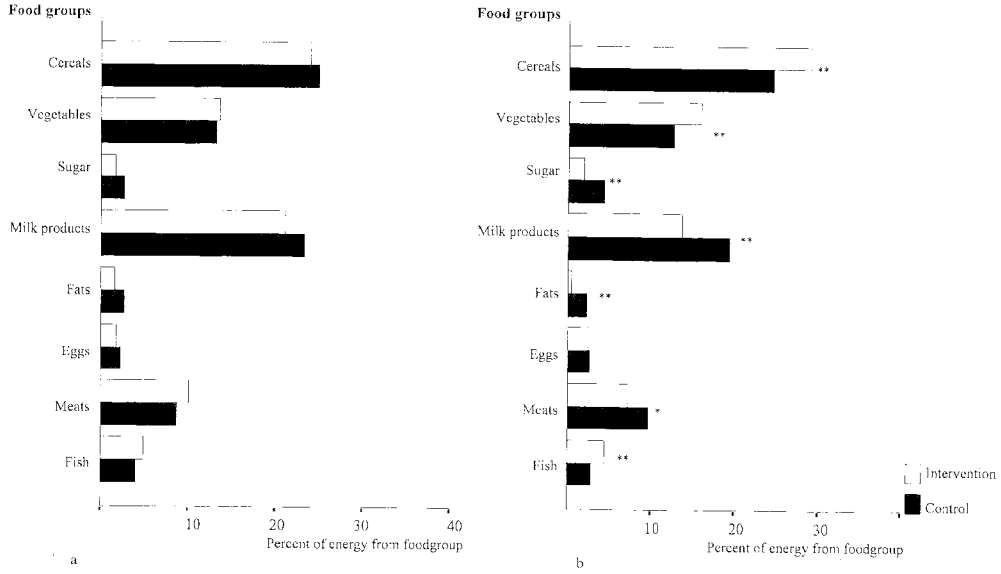

Fig. 1. (a) Mean contribution of the major food groups to energy intake in the intervention group and the control group at baseline as assessed by 48-h recall. (b) Mean contribution of the major food groups to energy intake in the intervention group and the control group during radiotherapy (period II) as assessed by 4-day records. Levels of statistical significance between groups are indicated with * ($P< 0.05$) and ** ($P< 0.01$); *t*-test.

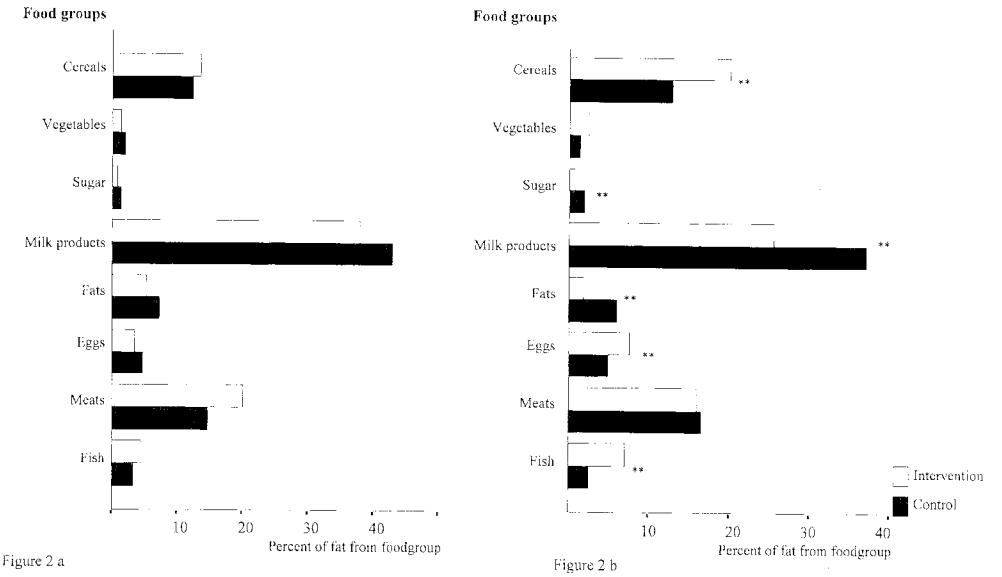

Fig. 2. (a) Mean contribution of the major food groups to fat intake in the intervention group and the control group at baseline as assessed by 48-h recall. (b) Mean contribution of the major food groups to fat intake in the intervention group and the control group during radiotherapy (period II) as assessed by 4-day records. Levels of statistical significance between groups are indicated with *($P< 0.05$) and **($P< 0.01$); *t*-test.

Table 7. Nutrient intake in the intervention and the control groups at baseline as measured by 48-h recall (mean (SD))

	Intervention		Control		
n	70		69		
Nutrient	mean	(SD)	mean	(SD)	*P*
Dietary fibre, g	13.3	(5.8)	11.8	(5.3)	ns
Calcium, mg	856	(363)	787	(318)	ns
Iron, mg	9.1	(3.0)	8.6	(2.8)	ns
Retinol equivalents, μg	1044	(840)	842	(438)	ns
Ascorbic acid, mg	73.4	(50.6)	76.6	(57.3)	ns
Vitamin D, μg	2.0	(4.1)	2.4	(1.9)	ns
Thiamine, mg	0.87	(0.35)	0.82	(0.32)	ns
Riboflavin, mg	1.4	(0.56)	1.4	(0.47)	ns
Niacin, mg	14.1	(5.1)	13.3	(7.1)	ns

used by the outpatients, tables of food portion sizes were used (Blaker & Aarsland, 1989).

Nutrient intake

The total intake of energy, energy yielding compounds, dietary fibre, calcium, iron, retinol, ascorbic acid, vitamin D, thiamine, riboflavin and niacin were calculated by means of the FIBRE software package that is based on Norwegian food composition tables (Statens ernæringsråd, 1977). The program package did not calculate the content of lactose. The Norwegian food composition tables contain mainly information about nutrients in raw and fresh foods. It was supplemented with personal recipes and information from the food industry. Means and standard deviations of energy and nutrients per group were calculated. Nutrient density defined as micronutrients per MJ was also calculated. The contributions of various food groups to energy and fat intake were obtained to learn about eating habits at each time point. The food grouping system was adopted from the FIBRE program as shown in Table 4. The following food groups were used: milk products, meats, fish, cereals, vegetables and fruits, eggs, fats, sugar and beverages. All the food types supplementary to the food composition tables were placed in a group called miscellaneous, since the FIBRE program was not able to extract these foods and place them in the proper food groups.

Ethical approval for the study was obtained from the Board of Ethics of Health Region II.

Statistical analysis

The SPSS for Windows V6.1 program was used for the statistical analysis. Student's *t*-test was used to test for mean differences between the groups.

Results

A total of 14 women (9.8%) withdrew from the study during the course of radiotherapy, nine (13%) in the intervention group and five (5.5%) in the control group (Table 5). Six from the intervention group withdrew because of the diet. They found it tasteless and lost their appetite. In the control group one declined because of the diet and preferred a low-fat diet. Other reasons for withdrawal were too much paper work, problems with alcohol or not known.

Energy intake and contribution of macronutrients to the energy intake is shown in Table 6. No significant differences were found before radiotherapy. During radiotherapy (periods I and II) the energy intake was lower in the intervention group than in the control group. The average percentage of energy from fat was lower in the intervention group than in the control group and the energy percentage from protein and carbohydrate was higher. Figure 1 shows the contribution of various food groups to the energy intake. At baseline (Fig. 1a) no significant differences were found between the two groups as measured by 48-h recalls. During period II,

Table 8. Nutrient intake in the intervention and the control groups at period I (3rd week of radiotherapy) and period II (last week of radiotherapy) as measured by 4-day records (mean (SD))

	Period I					Period II				
	Intervention		Control			Intervention		Control		
n	62		68			62		67		
Nutrient	mean	(SD)	mean	(SD)	*P*	mean	(SD)	mean	(SD)	*P*
Dietary fibre, g	12.6	(4.0)	11.0	(3.9)	< 0.05	11.3	(4.1)	9.0	(3.3)	< 0.01
Calcium, mg	769	(278)	714	(274)	ns	695	(275)	668	(272)	ns
Iron, mg	8.7	(2.5)	8.1	(2.1)	ns	8.1	(2.8)	7.4	(2.4)	ns
Retinol equivalents, μg	901	(1204)	776	(429)	ns	897	(1574)	788	(361)	ns
Ascorbic acid, mg	86.5	(51.3)	87.7	(64.2)	ns	70.2	(40.1)	70.7	(41.8)	ns
Vitamin D, μg	2.8	(3.2)	2.5	(1.7)	ns	2.3	(1.9)	2.4	(2.4)	ns
Thiamine, mg	0.94	(0.48)	0.88	(0.68)	ns	0.77	(0.24)	0.76	(0.35)	ns
Riboflavin, mg	1.4	(0.72)	1.4	(1.06)	ns	1.3	(0.53)	1.2	(0.56)	ns
Niacin, mg	14.0	(4.1)	13.4	(5.9)	ns	12.8	(4.2)	11.9	(4.7)	ns

the last week of radiotherapy (Fig. 1b), the intervention group received a significantly lower part of the energy from milk products, meats, fats and sugar than the control group as measured by 4-day records. On the other hand they consumed more energy from vegetables and fruits, cereals and fish. Figure 2 shows the contribution of various food groups to fat intake. At baseline (Fig. 2a) no significant differences were found between the two groups. During period II (Fig. 2b) milk products, fats and sweets contributed with less fat in the intervention than in the control group. Eggs, fish and cereals contributed with more fat.

The mean nutrient intake at baseline as measured by the 48-h recall method is shown in Table 7. No significant differences between the two groups were found. Compared with the recommendations (Table 3) the intakes of iron, vitamin D, thiamine and dietary fibre were low in both groups. The control group had a slightly lower intake of calcium than recommended. Nutrient intakes during radiotherapy (periods I and II) are shown in Table 8. No significant differences were found between the two groups except for intake of dietary fibre which was higher in the intervention group ($P < 0.05$) for both periods. The intake of dietary fibre, calcium, iron, vitamin D and thiamine were below the recommendations in both groups. The control group also had an insufficient intake of retinol equivalents. At period II the intake of niacin was insufficient in both groups.

Nutrient density, defined as micronutrients per MJ, is shown in Tables 9 and 10. At baseline the intervention group reported a significantly higher intake of dietary fibre and iron per MJ than the control group (Table 9). During radiotherapy the low-fat, low-lactose diet had an overall higher nutrient density than the ordinary diet (Table 10). There were significant differences between the two groups with respect to dietary fibre, calcium, iron, thiamine, riboflavin and niacin. With respect to the fat-soluble vitamins, retinol and vitamin D, there were no differences between the two groups. The nutrient density in the low-fat, low-lactose diet was in accordance with the recommendations (Table 3) except for dietary fibre and vitamin D. The regular diet, however,

Table 9. Comparison of nutrient density (micronutrients per MJ) in the intervention and the control groups at baseline as measured by 48-h recall (mean (SD))

	Intervention		Control		
n	70		69		
Nutrient	mean	(SD)	mean	(SD)	*P*
Dietary fibre, g	2.0	(0.6)	1.7	(0.7)	< 0.05
Calcium, mg	129	(46)	116	(43)	ns
Iron, mg	1.4	(0.3)	1.3	(0.3)	< 0.05
Retinol equivalents, μg	158	(120)	127	(73)	ns
Ascorbic acid, mg	11	(7.5)	11	(7.6)	ns
Vitamin D, μg	0.4	(0.6)	0.4	(0.4)	ns
Thiamine, mg	0.13	(0.03)	0.12	(0.03)	ns
Riboflavin, mg	0.22	(0.06)	0.20	(0.06)	ns
Niacin, mg	2.2	(0.7)	1.9	(0.7)	ns

had a lower nutrient density than recommended except for ascorbic acid, riboflavin and niacin for both periods and retinol for period II.

Discussion

Experimental nutritional intervention studies may be difficult to conduct since there is always a possibility that the intervention group does not keep to the diet and that the control group change their diet accordingly (National Research Council, 1989). To evaluate the success of the intervention it was therefore of interest to compare in as much detail as possible the intake of foods in the two groups.

The methods used to collect data on dietary intake in the present study have been validated by comparing reported protein intake with 24-h urinary nitrogen excretion and by comparing energy intake with presumed physical activity level and weight development (Bye, unpublished findings). Both the 48-h recall method and the 4-day records seemed to give a valid estimate for the intake of macronutrients during the registration periods. The results should, however, be interpreted with caution when using data collected by these methods to assess the vitamin and mineral intake (National Research Council, 1989). The vitamin and mineral intake may vary widely from day to day in individuals. To obtain representative data from an individual it is necessary to collect data from several days (Kuskowska-Wolk, 1990). The number of days that have to be studied and the choice of weekdays depend on the nutrients under study. The 24-h recall and the 48-h recall collect data from a short period of time and would therefore not be appropriate to use if the goal was to characterize the diet of individuals. For assessing the mean intake of a group, however, most researchers agree that these methods are valuable (National Research Council, 1989). It is also indicated that to estimate the mean intake of a group, 3-day records are adequate, provided that day-of-week variations are taken into account and that the sample size is sufficiently large.

At baseline no differences between the two groups were found with respect to intake of foods, indicating that differences in nutrient intake during treatment were a result of the intervention. The patients in the intervention group were instructed to increase their intake of vegetables, fruits and cereals. A higher percentage of the energy from these food groups in the intervention group than in the control group indicates adherence to the diet. Fish was frequently used to substitute meat at dinner and to substitute cheese as sandwich spread. The success of this advice was reflected in a higher intake of fish and less use of meats and milk products by the intervention group. One other essential advice that seems to have been adopted was to avoid butter, margarine and mayonnaise. Contribution to the energy from the food group called fats reflects the intake of these foods. The intervention group

Table 10. Comparison of nutrient density (micronutrients per MJ) in the intervention and the control groups at period I (3rd week of radiotherapy) and period II (last week of radiotherapy) as measured by 4-day records (mean (SD))

	Period I					Period II				
	Intervention		Control			Intervention		Control		
n	62		68			62		67		
Nutrient	mean	(SD)	mean	(SD)	*P*	mean	(SD)	mean	(SD)	*P*
Dietary fibre, g	2.1	(0.5)	1.6	(0.5)	< 0.01	2.0	(0.6)	1.4	(0.5)	< 0.01
Calcium, mg	131	(48)	102	(31)	< 0.01	123	(43)	103	(33)	< 0.01
Iron, mg	1.5	(0.3)	1.2	(0.2)	< 0.01	1.4	(0.3)	1.2	(0.3)	< 0.01
Retinol equivalents, μg	160	(264)	110	(52)	ns	155	(245)	125	(64)	ns
Ascorbic acid, mg	13.8	(9.3)	12.1	(6.5)	ns	12.1	(6.4)	10.7	(5.2)	ns
Vitamin D, μg	0.49	(0.7)	0.35	(0.2)	ns	0.42	(0.39)	0.37	(0.33)	ns
Thiamine, mg	0.16	(0.08)	0.12	(0.06)	< 0.01	0.14	(0.03)	0.12	(0.03)	< 0.01
Riboflavin, mg	0.24	(0.13)	0.19	(0.09)	< 0.01	0.22	(0.08)	0.18	(0.05)	< 0.01
Niacin, mg	2.4	(0.7)	1.9	(0.5)	< 0.01	2.3	(0.7)	1.8	(0.6)	< 0.01

hardly received any energy from this food group at all as compared to the control group. Compared with data describing the Norwegian diet 1989–91 (Statens ernæringsråd, 1993), the control group also had a low intake of these foods. Fats contributed with about 3% of the energy in the control group compared with about 13% in the Norwegian diet. This could indicate a change among the control patients with respect to use of fats. One should, however, be aware of differences in food grouping which make the figures not completely comparable. In the present study, the food group called miscellaneous hid oils, margarine and butter, since such foods are used in baking and other recipes.

Compared with the control group the intervention group received a higher share of the energy from proteins. The intention was to keep the energy contribution from protein at 10–15% in both groups. Other studies have shown that it may be difficult to achieve a substantial fat reduction without correspondingly increasing the protein intake (Ikkala *et al.*, 1991). The simplest way to reduce the intake of fat is to substitute high-fat milk products with low-fat alternatives (Nordevang *et al.*, 1992). This leads to an increase in the protein intake since the low-fat alternatives contain a higher share of protein. The intervention group had a higher carbohydrate intake than the control group. This led to a higher intake of dietary fibre although not in accordance with the dietary guidelines. Other studies have reported a substantial increase in dietary fibre when the fat is reduced (Ikkala *et al.*, 1991). We did not find this, probably because of an overall low food and energy intake. Lack of appetite during radiotherapy (Bye *et al.*, 1995) has most certainly influenced this. In addition, the low-fat, low-lactose diet had low energy density (energy/volume ratio) because the energy intake should be maintained by increasing the carbohydrate intake. To compensate for the low energy density the patients in the intervention group had to eat increased amounts of food. Studies have shown that even young healthy men may have problems in eating enough if the energy density is low (Sandström *et al.*, 1992).

Despite the lower energy intake in the intervention group during radiotherapy, there were no significant differences between the

two groups with respect to intake of micronutrients, and the reported intake of vitamins was mainly in accordance with the recommendations. This can be explained by the fact that the low-fat, low-lactose diet had a higher nutrient density (intake of micronutrients per MJ) than the regular diet, as expected (Gorbach *et al.*, 1990). The nutrient density in the intervention group was in accordance with the recommended nutrient density when planning a diet (Statens ernæringsråd, 1993), confirming that the meals served by the hospital kitchen were well planned.

It is reported that a reduction of fat may lead to lower intake of fat-soluble vitamins (Gorbach *et al.*, 1990; Ikkala *et al.*, 1991). In the present study no significant differences were found between the two groups with respect to intake of retinol equivalents and vitamin D. Fats usually contribute with about 23% of retinol equivalents in the Norwegian diet (Statens ernæringsråd, 1993). Despite a low intake of fats in both groups, the intake of retinol equivalents was high and highest in the intervention group. This is probably because of a higher intake of vegetables. Vegetables contribute with about 40% of retinol equivalents (Statens ernæringsråd, 1993). It is, however, indicated that 41 days is necessary to obtain reliable data on retinol equivalents on a group level because of a substantial variation in the content of retinol in foods (National Research Council, 1989). A few people eating numerous foods containing large amounts retinol equivalents during a registration period may lead to a high mean intake. Some of the women said that they had increased their intake of carrots because they had read that retinol could prevent cancer. The intake of vitamin D was lower than the recommendations in both groups. This finding is not surprising because only a few foods contain vitamin D and fats usually contribute with 56% of the vitamin (Statens ernæringsråd, 1993). When the intake of vitamin D is not lower in the intervention group, it is probably because of the higher intake of fish.

The intervention group was advised to reduce the intake of lactose. One would have expected that this would have influenced the intake of calcium in the intervention group. However, no significant difference in the mean intake of calcium was found and the nutrient density with respect to calcium was higher in the intervention group. One explanation may be that the control group also had used less milk, since a dietary change like this is easy to apply. The higher contribution to energy and fat from milk products in the control group contradicts this. However, if they had not changed to low-fat alternatives and eaten cheese as normal, they would have consumed more energy from this food group than the intervention group, even if they drank less milk.

The intake of iron is strongly correlated with the energy intake (Black *et al.*, 1991). As the energy intake was low in both groups, it was no surprise that the iron intake also was low. The mean intakes were equal in the two groups, though the control group had a higher intake of energy. The higher intake of cereals in the intervention group may explain this finding since cereals are the main source of iron in the Norwegian diet (Statens ernæringsråd, 1993). The intake of iron per MJ was also higher among the intervention patients than among the control patients pretreatment. The 48-h recalls were conducted after the randomization, and the women knew which diet they were about to receive during the interview. No dietary information was given concerning the low-fat, low-lactose diet, but it is generally accepted that cereals are healthy. It is possible that the intervention patients wanted to demonstrate that they already had a healthy diet by emphasizing their intake of whole grain cereals. This could have been avoided if the baseline data had been collected before the result of the randomization was made known. This was, however, not always possible. In quite a few cases radiotherapy started immediately after decision on treatment was made and the diet treatment was supposed to start simultaneously. To ensure that all patients were treated in the same way it was decided to allocate the patients first and then perform the 48-h recall.

There was a higher dropout rate in the intervention group than in the control group. The main reason was dissatisfaction with the diet. This indicates that the low-fat, low-lactose diet was not easy to keep to, which is not surprising. When the intake of fat is limited

to 40 g per day it causes major changes in food intake for the majority of the population.

In conclusion, the intervention group had a qualitatively different diet than the control group during radiotherapy. The low-fat, low-lactose diet was achieved through a reduction in milk products, fats and meats. The control group seemed to have reduced the intake of fats and milk but not enough to obtain a diet similar to the intervention group. The low-fat, low-lactose diet was a better diet in the sense of nutrient density.

Acknowledgments

This study was supported by grants from the Norwegian Cancer Society. We wish to thank the clinical staff of the Department of Gynaecology at the Norwegian Radiumhospital for their co-operation.

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Submitted March 1999, *Revised* April 1999, *Accepted* May 1999

URN:NBN:no-2118

Paper II

URN:NBN:no-2118

URN:NBN:no-2118

EVALUATION OF THE VALIDITY OF DIETARY INTAKE MEASURED TO ASSESS COMPLIANCE IN A DIETARY INTERVENTION STUDY

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Abstract

Background and Aims: An open prospective randomised study was conducted to evaluate the effect of low fat, low lactose diet on diarrhoea during radiotherapy. The aim of the present study was to evaluate the validity of the dietary intake, measured to assess compliance to the diet.

Methods: 143 women with gynaecological malignancies undergoing pelvic radiotherapy were included in the clinical study. Dietary intake during radiotherapy was measured by a 4-day food record method. The method was validated by 24-hour urinary collections, study specific cut-off limit for ratio between energy intake (EI) and basal metabolic rate (BMR) and comparison between EI and weight loss.

Results: The protein intakes measured by 4-day food records were in accordance with estimated protein intakes. The EI: BMR in the intervention group was below the cut-off limit at period I. At period II the ratio was below the cut-off limit in both groups. A mean weight reduction was observed in both groups during radiotherapy, and the EI agreed with the change in body weight.

Conclusion: The method used seemed to give a valid estimate of the dietary intake on which it was possible to make conclusions about compliance to the diets.

Key words: Dietary assessment, validity, diet intervention, genital neoplasm, radiotherapy

Introduction

A randomised prospective clinical trial was carried out to evaluate the effect of a low fat, low lactose diet on intestinal side effects during radiotherapy. The diet was used prophylactic and during the last week of radiotherapy 23% in the intervention group reported diarrhoea versus 48% in the control group ($p< 0.01$) (1). Dietary intervention trials should optimally be conducted as double-blind experiments to be able to conclude that any difference that develops between the groups is directly caused by the factor under investigation (2,3). Unfortunately it is not possible to administer an intervention trial based on counselling as a double-blind experiment (2). This implies a risk of adoption of the intervention program in the control group and non-compliance in the intervention group (4,5). Both adoption of the intervention program and non-compliance tend to equalise outcomes between the groups, minimising the chance of seeing an effect even if there is one. Compliance with the diet in both groups was evaluated by collecting dietary data. The mean daily fat intake was 34 g the intervention group and 60 g the control group ($p<0.001$) which indicated that the intervention group had made the necessary changes and that the control group had not adopted the diet.

During radiotherapy a prospective food record for 4-days was used to evaluate compliance (6). It is well known that all dietary assessment methods have their limitations. One must rely on information given by the subjects themselves and recording of food intake may alter the respondent's dietary behaviour (5,7). Especially among women underreporting of energy intake is a well-known problem (5). Because of the known limitations, one should try to validate the measured dietary intake (8). One way to validate is to use biochemical markers. The advantage of using a biochemical marker is that measurement errors are essentially not correlated with errors in any dietary method (9). The excretion of nitrogen in a 24-hour urine specimen, which is an estimate of dietary protein intake, is considered as one of the best biochemical markers to validate dietary surveys (10,11). Another way to validate dietary intake by means of external independent markers is to relate reported energy intake to estimates of basal metabolic rate, physical activity level and body weight (12,13,14).

In this study an attempt was done to evaluate the validity of the collected dietary data by using 24-hour urinary collections, study specific cut-off

limit for ratio between energy intake (EI) and basal metabolic rate (BMR) and comparison between EI and changes in body weight.

Materials and method

Subjects

Between May 1988 and May 1990, 183 women admitted to the Norwegian Radium Hospital were eligible for inclusion in the clinical trial. One hundred and forty-three (78%) women were included. The rest refused to participate or were lost for inclusion. The selection criteria were primary diagnosis of carcinoma of the endometrium, ovary or cervix; external pelvic radiotherapy at a minimum dose of 44 Gy or 40 Gy if combined with intracavitary treatment; age < 75 years and WHO performance status of = 2 (15). Patients with the diagnosis of inflammatory bowel disease or ulcerative colitis were not included. Other criteria for exclusion were planned surgery after completion of radiotherapy and previous treatment with chemotherapy or radiotherapy. Patient characteristics are given in Table 1. More detailed information about eligibility criteria, staging and treatment regimens are presented elsewhere (1,16). Ethical approval for the study was obtained from the Board of Ethics of Health Region II.

Experimental design

The patients signing the consent form, were randomised before radiotherapy to receive either a low fat, low lactose diet (maximum of 40 g fat per day and maximum 5 g lactose per meal) or the regular hospital diet, during the treatment period and six weeks afterwards. The regular hospital diet had average fat content of 80 g at 6.9 MJ (44% of energy from fat). The content of lactose in the regular diet was not calculated, but the planned menu contained three glasses of milk at a 150-ml each and 10g of brown cheese daily (24.5g of lactose). Milk was also used in sauces, desserts and porridges.

Seventy-one patients were assigned to the intervention diet and 72 to the control group. The majority of the patients (101 patients) were hospitalised during the six weeks of radiotherapy, but a few from each group (18 patients in the intervention group and 24 patients in the control group) were receiving treatment as outpatients. The hospitalised patients received three meals a day (breakfast, dinner and supper) from the hospital kitchen. The outpatients prepared their own food. The low fat, low lactose diet was

based on the Norwegian Guidelines for Hospital Diets (17) and is described in detail elsewhere (1). The patients in the intervention group were given individual advice on the type and quantity of foods to eat. The aim of this counselling was to secure compliance if they ate something in addition to the hospital meals or were outside the hospital. The dietary counselling was also necessary for the outpatients who prepared their own food. Patients in both groups were advised to eat enough to maintain weight during radiotherapy and to use nutritional supplements if necessary.

Dietary intake: food record by household measures

During radiotherapy, the patients recorded their consumption of food, drink and nutritional supplements for four consecutive days (18,19). They received oral and written instructions in keeping an accurate record, and were asked to complete the records in two 4-day periods. The first period (period I) was three weeks after start of radiotherapy. The second (period II) was during the last week of radiotherapy. Household measures were used to describe serving sizes. The patients received a diet controlled by the hospital kitchen. As control of the serving sizes, an extra portion of food was ordered from the kitchen and weighed by the dietician on a dietetic scale. At the end of each four-day period, the dietician reviewed the records to probe for items that might have been forgotten.

The 4-day food records were validated by using 24-hour urinary nitrogen (10) and the Goldberg cut-off 2 (12) as standards. In addition changes in body weight and energy intake (EI) were compared to estimate energy expenditure (EER). The energy, fat, carbohydrate and protein intake, were calculated by means of the FIBER software package based on Norwegian food composition tables (20). This program package did not calculate the content of lactose.

Urinary nitrogen

The patients were instructed to collect one 24-hour urine specimen during each food record period. Oral and written instructions in the collection technique were given. The first morning urine passed on the collection day was discarded and the time noted. All urine passed in the next 24-hour was collected until the noted time next day. The dietician collected the urine and it was then carefully mixed, weighed and frozen. Volume was calculated from urine density and sample weight. The samples were stored at - 20° C before they were analysed for nitrogen using a model 720/771 Antek Chemiluminescent Analyser (21). No markers were given to verify the

completeness of the urine collections, but the participants were asked to record any spillage during the 24-hour period. Protein intake was estimated from the equation: 6,25 x (urine nitrogen (g) +2) (10).

Estimation of basal metabolic rate and total energy expenditure

The Harris Benedict's equation (22) was used to estimate BMR_{est}. BMR (female)=(655 + 9.6W + 1.7H) - 4.68A, where BMR is measured in kilocalories, W= weight in kilograms, H= height in centimetres and A=age in years. This equation is commonly used to estimate basal energy expenditure in hospitalised patients. Height and weight were recorded before the start of treatment. During radiotherapy the patients were weighed every week on an electronic bathroom scale. The patients were weighed on the same scale, in the morning after passing urine and faeces and with the same clothing. Weight changes between baseline and period I, and between period I and II were calculated.

Total daily energy expenditure (TEE) is the sum of BMR, thermic effect of food eaten and the energy expended in physical activity. The TEE may be expressed by multiplying BMR with a factor matching the physical activity level (PAL). PAL can be defined as the average activity ratio for different types of activities over a 24-hour period and varies with intensity of physical activity. EER was obtained by multiplying BMR_{est} with a PAL of 1.55 and 1.27 (23). Since it was assumed that most of the women had low physical activity during hospital stay a PAL of 1.55 associated with a sedentary life-style (light occupational work), was used. Previous results from the present study showed that the patients experienced increased fatigue and malaise during the last week of radiotherapy (24) and spent most of the time in bed or in a chair. Because of this a PAL of 1.27 that allows for minimal movement, was also used.

A basic premise is that if weight is stable then the TEE equals EI. Imbalance between TEE and EI will either result in weight loss or weight gain. If a weight loss of 0.5 kg per week was registered, an energy contribution from the weight change of 2.1 MJ per day was expected (25). The daily energy contribution from weight change (EW) was calculated by multiplying weight change per week with 2.1 MJ/0.5 kg. Total energy used (TEU) was calculated by adding EI and EW. Correspondence between TEU and EER was set to indicate that the calculated EI was representative for the actual intake during the observation period.

The ratio between EI and BMR_{est} was calculated. The ratio gives an impression of how much of the registered EI is available for physical activity. To evaluate the validity of the reported EI, the Goldberg cut-off 2 was calculated, using a PAL of 1.27, energy requirement for a totally sedentary lifestyle, n=130 and 8 days of records (12,26). The cut-off was calculated to 1.22. An EI: BMR_{est} ratio below 1.22 was recognised as an indication of underreporting of EI.

Statistical analysis. The SPSS for Windows V6.1 program was used for the statistical analysis. Means and standard deviations are reported for the nutrients estimated. Students' t-test was used to test for mean differences between the groups. Differences within groups were tested with a pairwise t-test. In case of missing values it were replaced with the group mean.

Results

Seven patients (9.8%) in the intervention group and 4 (5.5 %) in the control group withdrew from the study during the course of radiotherapy. In the intervention group six patients did not wish to go on with the low-fat, low-lactose diet. The reasons were the taste and worry about not managing the diet for six weeks at home. One patient had alcohol problems and did not follow the diet. One patient in the control group changed to a low-fat diet. The other reasons for withdrawal were too much paper work or not known.

Forty-nine patients in both groups collected urine during period I. Sixty-two patients in the intervention group and 68 in the control group completed the food record. During period II respectively 48 and 52 patients collected urine while 62 and 67 completed the food record.The reasons for the low number of urine collections were incomplete urine samples and problems with urine collection among some of the outpatients.

Statistical significant differences between the two groups with respect to fat intake were found during the intervention period (table 2). There were also significant differences between the two groups with respect to contribution of macronutrients to the energy intake.

Validation of the 4-day food record against the 24-hour urinary nitrogen is presented in table 3. For both periods there were no significant differences

between the reported protein intake and the intake estimated from the urine sample in any of the groups.

Validation against the Goldberg cut-off 2 and EI and weight change is presented in table 4. The EI in the intervention group was lower than in the control group ($p<0.01$). The EI: BMR_{est} ratio were below the cut-off limit of 1.22 in the intervention group at period I. At period II the ratio was below the cut-off limit in both groups. A mean weight reduction was observed in both groups during radiotherapy, more pronounced in the intervention group than in the control group but not statistically significant. The observed weight reduction at period I corresponded to a mean energy contribution from weight loss (EW) of 2.1 MJ per day in the intervention group and 1.4 MJ per day in the control group. Mean total energy used (TEU), (EW+EI), was respectively 8.1 and 8.4 MJ. TEU was significant higher than estimated energy expenditure (EER) in both groups when using a PAL of 1.27 to estimate the EER. EER was however not different from TEU in any of the groups when a PAL of 1.55 was used to calculate the EER (respectively 8.7 (0.8) MJ and 8.5 (0.7) MJ).

The observed weight reduction at period II corresponded to a mean EW of respectively 1.6 MJ and 1.0 MJ per day. TEU at period II was respectiveley 7.3 MJ and 7.5 MJ. No significant differences between TEU and EER were found when using a PAL of 1.27. When using a PAL of 1.55 to calculate EER (respectively 8.6 (0.8) MJ and 8.5 (0.7) MJ) it was higher than TEU in both groups ($p<0.01$).

Discussion

Dietary intakes were assessed before and during radiotherapy in order to measure the patients' compliance to the diet. According to the patients self-reported dietary intake the intervention group had met the outlines for the low fat, low lactose diet with respect to fat intake. However, the mean reported energy intake in both groups was so low that the validity of the dietary intake data could be questioned. The mean EI: BMR_{est} ratio was below the cut-off limit of 1.22 in the intervention group during the 48-hour recall and the food record periods. In the control group it was below the cut-off during period II of food recording. Values less than the Goldberg cut-off 2 are generally accepted to indicate underreporting since they reflect EI incompatible with habitual intake (6,27). However, the reported dietary intake can still be a valid estimate of the actual intake during the period of investigation (27). The low energy intake may have been a result of lack of appetite and low food intake due to hospitalisation, the impact of information about the disease and psychological distress. Previous results from the present study have shown that the women experienced psychological distress before radiotherapy and reduced appetite and increased fatigue during radiotherapy (24). In addition it is shown that it may be difficult to obtain sufficient energy intake on a fat reduced diet because of increased volume (13).

Validation against urinary nitrogen

During the two periods of food records a good resemblance between estimates for protein intake and recorded intake was found in both groups, which should confirm validity (9,10). The recorded protein intake during period II was more in accordance with the estimated intake than during period I. This may be explained by the fact that training seems to improve accuracy of record keeping (8).

Since the urine collections were performed according to Isaksson (10), no markers were given to verify the completeness. Others have stated that it is important to validate the urine collections (28). The fact that we did not use any markers might imply problems with interpreting our results. If incomplete collections are used, nitrogen (N) excretion will be under-estimated and comparison with N intake will give a bias to finding intakes as valid (28). The patients were however given clear instructions about how to collect the urine and the collections were mostly conducted at the hospital under supervision of nurses. Mostly free-living subjects are found to be unreliable in collecting urine (28,29). All incomplete samples were

reported and not included in the analysis. Altogether we are quite sure that the samples analysed were complete. Our study design was problem oriented rather than methodical oriented. The main goal was to evaluate the effect of a diet and we chose to be pragmatic in methodical issues. It was easier and cheaper to perform the urine collections according to Isaksson (10) than to use markers to verify the urine collections.

One other problem was the mean weight reduction observed in both groups during radiotherapy. The use of 24 -hour urine to estimate dietary protein intake depends on the assumption that subjects are in a steady state or N balance where intake equals output (9). Weight reduction lead to a negative N-balance and the subjects were therefore not in a steady state. However, some of the individuals experienced a weight reduction and some experienced a weight gain. This must be reckoned as a normal random variation and should not necessary produce a bias if the negative N-balance cancel the positive N-balance. For individuals the discrepancies between calculated and estimated protein intake may be rather great caused by changes in the urea concentration in the body fluids due to small day-to-day variations in urea retention (9,10). This is not considered a problem as long as the validation is made on a group level.

It may also be questioned if the 24-hour urine N is optimal to validate the dietary intake among a group of cancer patients since cancer is known to effect protein metabolism (30). Muscle wasting and failure in adaptation to decreased food intake with protein depletion has been shown. Such findings may be of more concern in connection with already malnourished and cachectic patients. The patients in the present study received curable treatment and the prognosis was good. Loss of intestinal mucosa due to radiotherapy may also have resulted in protein depletion. It is however shown that modern radiotherapy is no more than a modest catabolic stimulus (31).

The group that collected urine was smaller than the group that recorded dietary intake. Urine collection is demanding, and some of the patients felt that it was uncomfortable to do it and were allowed not to. One could argue that the group who had collected urine was more accurate and conscientious than those who did not, and that this may have influenced the result. Participating in a survey may always cause some individuals to eat or report less and others to eat or report more (6). The validation was made on a group level and this was therefore not considered as a major problem.

Weight development

The energy intake corresponded to the changes in body weight during the intervention period, which strengthens the assumption that the food records were valid. At period I the total energy used (TEU) was higher than estimated energy requirements (EER) when using a PAL that allow minimal movement to predict EER. A correspondence between TEU and EER was found in both groups when using a PAL of 1.55 associated with a sedentary life-style (23). At period II, however, the best correspondence between TEU and EER was found when using the lowest PAL. The women reported increased fatigue and malaise during the last week of radiotherapy (24). This indicates that they were less active during period II than during period I and therefore different PALs should be used to calculate EER at the two time points. Because estimates of energy expenditure are dependent on activity level, one should always include a questionnaire to obtain information about the subjects' activity.

The major limitation in food records is the tendency for people to eat differently when recording, and the act of record keeping may itself alter the respondents' dietary behaviour (7). This limitation is of particular concern in a diet intervention study because of the potential bias towards adherence in the low fat intervention. The participants comply when they are recording, overestimating their reduction in the fat intake to please the investigator. This assumption is however not likely in this study. The weight loss found indicates that the patients had a dietary intake between the two periods of food recording, which did not differ much from the recorded. During hospitalisation the patients received a diet controlled by the hospital kitchen. Many reported decreased appetite and it is therefore unlikely that they would have eaten a lot in addition to the food from the kitchen. Particular concern should off course be paid to the outpatients. It is, however, shown that non-compliance to the diet among outpatients may be of a minor problem (5). It is also found that personal commitment to the staff seems to motivate subjects to adhere to the diet regimen (5). In the present study there was often and good contact between staff and the patients.

In conclusion, both methods used seemed to give a valid estimate of the dietary intake in the intervention period on which it was possible to make conclusions about compliance. Even though the EI: BMR_{est} ratios were below 1.22, a bias towards underreporting of EI it was not indicated. The reported protein intake corresponded well to the protein intake estimated

from 24-hour urinary nitrogen excretion. There was also consistency between energy intake, loss of body weight and estimated energy requirement.

Acknowledgement - This study was supported by grants from the Norwegian Cancer Society. The authors wish to thank the clinical staff of the Department of Gynaecology at the Norwegian Radiumhospital for their co-operation.

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Table 1 Patient characteristics.

		Intervention	Controls
n		71	72
		mean (range)	mean (range)
Age (yr)		57.1 (29-74)	55.5 (34-74)
Weight (kg)		70.6 (47-119)	67.0 (46-112)
Height (cm)		164.7 (153-180)	163.5 (149-177)
		%	%
Performance status (WHO)	0	89	88
	1	9	10
	2	2	1
Diagnosis	Cervical cancer stage IA	4	0
	Cervical cancer stage IB	22	24
	Cervical cancer stage IIA	4	6
	Cervical cancer stage IIB	31	39
	Endometrial cancer stage I	25	22
	Endometrial cancer stage II	13	8
	Ovarian cancer stage IC	0	1
Treatment	Surgery	55	47
	Radium application	31	35
	Brachytherapy	13	19
Other diagnosis	Hypertension	13	14
	Diabetes Mellitus	4	4

Table 2 Recorded daily fat intake and contribution of macronutrients to energy intake, mean (SD), obtained from two periods of 4 day estimated food records. Significant differences between the two groups (t-tests) are indicated with p values.

					Contribution of macronutrients to energy intake					
					% of energy from,					
		n=	Fat intake (g)	p	fat	p	carbohydrate	p	protein	p
Period I [1]	Intervention	62	34.3 (9.2)		21 (4.8)		59 (6.1)		19 (3.1)	
	Control	68	63.1 (19.7)	<0.01	33 (6.8)	<0.01	51 (8.3)	<0.01	15 (2.4)	<0.01
Period II[2]	Intervention	62	33.9 (7.5)		22 (4.8)		58 (6.8)		19 (3.7)	
	Control	67	60.1 (17.2)	<0.01	34 (5.4)	<0.01	50 (7.5)	<0.01	15 (2.5)	<0.01

[1] three weeks after start of radiotherapy

[2] the last week of radiotherapy.

Table 3 Evaluation of the validity of the 4-day estimated food records by estimated protein intake. Period I was three weeks after start of radiotherapy and Period II the last week of radiotherapy. Significant differences between the two groups are indicated with * ($p<0.05$) or ** ($p<0.01$); t-test. Significant differences within the two groups are indicated with p values; pairwise t-test.

	Period I		*Period II*	
	Intervention mean (SD)	Control mean (SD)	Intervention mean (SD)	Control mean (SD)
Protein intake (g)				
- Calculated	n=62	n=68	n=62	n=67
	66.4 (16.2)	60.7 (16.9)	61.7 (16.4)	56.9 (15.5)
- Estimated[1]	n=49	n=49	n=48	n=52
	63.9 (15.4)	59.7 (14.5)	61.3 (17.4)	57.9 (17.5)
P	*ns*	*ns*	*ns*	*ns*

[1]Protein intake estimated from the equation: 6,25 x (urine nitrogen (g) +2)

Table 4 Evaluation of the validity of the 4-day estimated food records by changes in body weight and ratio between reported energy intake (EI) and etsimates of basal metabolic rate (BMR_{est}). Study specific cut-off limit was 1.22. Period I was three weeks after start of radiotherapy and Period II the last week of radiotherapy. Significant differences between the two groups are indicated with * ($p<0.05$) or ** ($p<0.01$); t-test. Significant differences within the two groups are indicated with p values; pairwise t-test.

	Period I		*Period II*	
	Intervention mean (SD) n=62	Control mean (SD) n=68	Intervention mean (SD) n=62	Control mean (SD) n=67
Energy intake and weight change				
- Reported EI (MJ)	6.0 (1.5)	7.0 (1.6) **	5.7 (1.3)	6.5 (1.6) **
- Weight loss[1] (kg)	0.5 (0.6)	0.3 (0.6)	0.4 (0.6)	0.2 (0.6)
- EW[2] (MJ)	2.1 (2.7)	1.4 (2.7)	1.6 (2.6)	1.0 (2.4)
- BMR_{est}[3] (MJ)	5.6 (0.5)	5.5 (0.4)	5.6 (0.5)	5.5 (0.5)
Energy used				
- TEU[4] (MJ)	8.1 (3.0)	8.4 (2.7)	7.3 (2.6)	7.5 (2.4)
- EER[5] (MJ)	7.1 (0.7)	6.9 (0.5)	7.1 (0.7)	7.0 (0.6)
P	*<0.05*	*<0.01*	*ns*	*ns*
Physical activity level				
- EI:BMR_{est} ratio	1.07 (0.27)	1.29 (0.30) **	1.03 (0.25)	1.19 (0.27) **

[1]Mean weight change per week [2]EW=energy contribution from weight change (kg X (2.1MJ/0.5kg))

[3] BMR_{est} =basal metabolic rate estimated from the equation: BMR (female)=(655 + 9.6W + 1.7H) - 4.68A,

[4]TEU=total energy used= EI +EW [5]EER=estimated energy expenditure=BMR_{est} X 1.27

URN:NBN:no-2118

Paper III

URN:NBN:no-2118

URN:NBN:no-2118

Clinical Nutrition (1992) **11**: 147–153

The influence of low fat, low lactose diet on diarrhoea during pelvic radiotherapy

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ABSTRACT—In a prospective clinical trial 143 women undergoing pelvic radiotherapy for gynaecological malignancies, were randomized to receive either a low-fat, low-lactose diet (intervention group) or a regular diet (control group) in order to evaluate the possible impact of diet therapy on radiation induced diarrhoea, nausea and vomiting. The daily number and consistency of stools, use of antidiarrhoeal agents, nausea and vomiting were recorded before radiotherapy was begun (week 0), in the last week of therapy (week 6) and 6 weeks after the end of therapy (week 12).

The intervention group used half the amount of antidiarrhoeal agents in week 6, than used by the control group (mean 0.6 tablets per day versus 1.1, $p < 0.01$). 14 patients (23%) in the intervention group reported diarrhoea, versus 32 (48%) in the control group ($p < 0.01$). In week 12 there were no differences in the use of antidiarrhoeal agents and the prevalence of diarrhoea between the groups.

Introduction

Diarrhoea accompanied by nausea, vomiting and loss of appetite is a well-known complication of radiotherapy to the pelvis (1, 2). Fluid loss due to the diarrhoea and reduced intake of food may lead to fatigue, loss of body weight and reduced quality of life (3). During radiotherapy for gynaecological malignancy the small intestine is often within the radiation field. Because of the rapid cell turnover, the mucosa of the small intestine is sensitive to radiation, which reduces cell replication and replacement of epithelial cells (1, 4). A progressive shortening of villi occurs. Loss of normal mucosa leads to fluid and electrolyte loss and impaired absorption. The signs are related to the total radiation dose, volume of bowel irradiated and the fractionation schedule (1).

Malabsorption of lactose and bile salts has been observed during radiotherapy and may contribute to the diarrhoea (5–10). Unhydrolysed lactose in the intestinal lumen causes fluid accumulation, abdominal cramps and watery diarrhoea (10). High concentrations of bile salts in the colon may interfere with the absorption and secretion of water and electrolytes, thereby increasing bowel motility (11, 12, 13).

Lactose malabsorption is best managed by removing the disaccharide from the diet. One study has evaluated the effect of lactose restricted diets on radiation induced diarrhoea, but no reduction in stool frequency was found (14). It was concluded that lactose malabsorption might be one factor in the mechanism of radiation induced diarrhoea, but other factors like bile acid malabsorption, are more important. Bile acid sequestering resins have been used to treat bile salt malabsorption (15), and cholestyramine and cholestipol have been shown to be effective, but the treatment may cause nausea and abdominal cramps (16–19). A low-fat diet (maximum 40g of fat (FR-40g)) seems to reduce the faecal bile salt excretion and thus the diarrhoea (20, 21).

The purpose of the prospective clinical trial reported here was to evaluate the effect of a diet low in both fat and lactose in preventing acute radiation-induced diarrhoea. Patients undergoing pelvic radiotherapy for gynaecological malignancies were randomized to receive either a regular diet or a low-fat, low-lactose diet.

Materials and methods

The subjects were women being treated at the Norwegian Radium Hospital. They had had a primary diagnosis of gynaecological malignancy and were receiving external pelvic radiotherapy at

Table 1 Patients' characteristics

	Control group No. (%)	Intervention group No. (%)
Age (years)		
<40	9 (12)	8 (11)
40–49	17 (24)	14 (20)
50–59	16 (22)	12 (17)
60–69	22 (31)	27 (38)
70–75	8 (11)	10 (14)
Total	72	71
Diagnosis		
Cancer cervix uteri		
– stage IA	0	3 (4)
– stage IB	17 (24)	16 (22)
– stage IIA	4 (6)	3 (4)
– stage IIB	28 (39)	22 (31)
Cancer corpus uteri		
– stage I	16 (22)	18 (25)
– stage II	6 (8)	9 (13)
Ovarian cancer		
– stage IC	1 (1)	0

radiotherapy at a minimum dose of 44 Gy or a minimum dose of 40 Gy combined with intracavitary treatment. In order to be included in the trial, patients had to be ≤75 years of age, and with a WHO performance status of ≤2. The patients had the following diagnoses and treatments:

1. Carcinoma of the endometrium, ovary and cervix (stage I and II), receiving post-operative external pelvic radiotherapy at a total dose of 48–52 Gy in 2 Gy per fraction, 4 fractions per week. Antero-posterior fields were used with a field diameter of 17 cm. The upper field margin was between L4 and L5, and the lower margin was along the centre of the obturator foramen.

2. Carcinoma of the cervix, stage IB and II, receiving external radiotherapy at a total dose of 40–46 Gy followed by intra-cavity treatment at a total dose of 26 Gy.

Patients were not eligible if they had undergone intestinal surgery prior to the diagnosis of malignancy because of Crohn's disease or ulcerative colitis, if they had previously been treated with chemotherapy or radiotherapy or if surgery was planned after completion of radiotherapy.

After having given their written consent, the patients were randomized before the radiotherapy started to receive either a low-fat, low lactose diet or the regular hospital diet. Dietary information was given by a trained dietician.

The patients' characteristics are given in Table 1. The mean age was 51 years (range 29–74) in the intervention group, and 56 years (range 34–74) in the control group. Hypertension was present in 18 patients, while 6 had diabetes mellitus. 2 patients had irritable bowel syndrome and 1 had gall stones. The majority of the patients (101 patients) were hospitalized during radiotherapy, but a few from each group (18 patients in the intervention group and 24 patients in the control group) were receiving treatment as outpatients. The hospital patients received 3 meals a day (breakfast, dinner and supper) from the hospital kitchen. Dinner was the only hot meal; the other meals consisted of bread or cereals. The evening meal consisted mainly of soup and bread. The outpatients prepared their own food at home. The control group received the hospital's regular diet, which has an average fat content of 80 g at 6.9 MJ (44% of energy from fat). Patients were advised to eat enough to maintain weight during radiotherapy and to use nutritional supplements if necessary.

The intervention group was prescribed a diet containing a maximum of 40 g fat per day (FR-40 g) and 5 g lactose per meal. The FR-40 g and lactose reduced diet is based on the Norwegian Guidelines for Hospital Diets (22). The patients were given individual advice on the type and quantity of foods to eat, based on individual tastes and appetites. Carbohydrates and proteins were increased in order to compensate for the energy loss caused by the reduction in fat. The patients ate relatively large amounts of bread, pasta, potatoes, rice, fruit and vegetables in so far as they tolerated them. Boiling and grilling were the recommended methods of cooking the food. Lean meat and fish were primarily recommended for dinner. 5 grams a day of margarine or oil with a high content of polyunsaturated fats was recommended in order to ensure a sufficient intake of essential fatty acids. Low-fat margarine or butter was to be used only in small amounts. The intake of milk was restricted to 1 small glass of skimmed milk for breakfast and supper. Food prepared with large quantities of milk was not allowed. Snacks consisting of sandwiches without butter, with lean meat, low-fat cheese or jam and fat-free desserts and sweets were allowed. Patients in the intervention group who could not maintain their body weight were advised to take nutritional supplements containing medium-chain triglycerides (MCT fat).

After completion of radiotherapy, the patients were given instructions on how to continue the FR-40 g diet at home. The recommendations were

Table 2 Diahrrhoea scale

0 – no change in stool frequency
1 – increase of 1–3 stools a day, normal or soft
2 – increase of 4–6 stools a day, all watery stools
3 – increase of >6 stools a day

repeated, and each patient had an individually tailored diet prescribed. The patients were encouraged to stay on their diets for at least 6 weeks after radiotherapy. The patients in both groups were instructed to ask for an antidiarrhoeal agent (Loperamid) and antiemetics as required. The dietary intake prior to radiotherapy was measured by 48 h recall (23, 24). Patients were asked to recall all food and drink consumed during the previous 48 h (25, 26). During the third and sixth weeks, the patients recorded their consumption of food, drink and nutritional supplement for 4 consecutive days. At the end of each 4 day period, the records were reviewed by the dietician to check that the nutritional data was complete. 12 weeks after the start of the treatment the total dietary intake was recorded for a 7 days period (25, 26), and an electronic dietetic scale was used to weigh the amount of food consumed. Fat, carbohydrate, protein and total intake of energy was calculated by means of the Fiber Software Package based on Norwegian Food Composition Tables (27).

The patients recorded the daily number and consistency of stools on a diary card. Stools were classified as hard, normal, loose or watery. Stool frequency was converted to a diarrhoea scale (Table 2). Patients scoring 2 or 3 on the scale were classified as having diarrhoea.

The patients' quality of life was measured by the EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30), which measures physical functioning, role functioning, emotional functioning, social functioning, global health status/QOL and financial impact (28). It also measures disease symptoms such as fatigue and malaise, nausea and vomiting (emesis), gastrointestinal symptoms, pain, dyspnoea, sleep disturbance and cognitive disturbance. The patients filled out the questionnaire before, during and after the treatment. The findings as regards emesis (three items) are described in this article. More detailed findings from the rest of the questionnaire, will be published elsewhere.

Height, weight and weight history over the previous 3 months were recorded before the start of treatment. During radiotherapy the patients were weighed every week. Triceps skin-fold thickness (TCSF) and arm muscle circumference (AMC) were measured at the mid point of the left arm (29). AMC was compared with reference measures (30). Serum albumin level (S-Alb) (reference range, 35–50 g/l) and total iron binding capacity (TIBC) was measured. Serum transferrin (TSF) (reference range, 1.6–2.7 g/l) was calculated according to the equation: $TSF = (4.47 \times TIBC - 43) \times 1/100$. Nutritional status was classified according to Blackburn (29). More than 5% weight loss and an AMC, s-Alb and TSF below 90% of the lowest reference value, were regarded as pathological. Categories were assigned on the basis of 2 or more variables having scores within that category (29). The following categories were used to describe the nutritional status –

1. midly depleted, 80–90% of the reference value
2. moderately depleted, 60–80% of the reference value
3. severely depleted, less than 60% of the reference value.

If there was an equal choice between 2 categories, the most pathological one was given preference.

Statistical analysis: Students 't' test was used to test for mean differences. Cross tabulation was used to analyse categorical variables and differences were tested by use of the Mann-Whitney U test.

Results

14 patients were excluded from the analysis. In the intervention group 1 patient had a problem with alcohol and did not follow the diet and 6 patients did not feel they could go on with the low-fat, low-lactose diet and were excluded. The reasons for not continuing the low lactose, low fat diet was the taste of it and worry about not managing to go on with it for 6 weeks at home. 1 patient in the control group changed over to a low-fat diet. 3 patients in each group left the study for personal reasons. 8 patients who left the study did so during the first week, and 6 in week 6.

The mean weight was 70.6 kg (range 47–119) in the intervention group and 67.0 kg (range 46–112) in the control group. 21 patients (15% in the intervention group and 12% in the control group) altogether had lost more than 5% of weight prior to hospitalisation. Prior to radiotherapy the intake

Table 3 Stool frequency and use of antidiarrhoeal agents (mean ± SD) at the start of radiotherapy (week 0), in the last week of radiotherapy (week 6) and 6 weeks after the end of radiotherapy (week 12)

		Control group				Intervention group				
	Week	F	(%)	Mean	SD	F	(%)	Mean	SD	p =
Stool	0	0/69	–	1.0	0.0	1/68	(2)	1.0	0.1	N.S
frequency	6	32/67	(48)	1.4	0.7	14/61	(23)	1.0	0.7	0.005
	12	2/67	(3)	1.0	0.2	1/57	(2)	1.0	0.1	N.S
Anti-	0	0/67	–	0.0	0.0	0/69	–	0.0	0.1	N.S
diarrhoeal	6	29/68	(43)	1.1	1.2	14/62	(23)	0.6	0.9	0.006
agents	12	5/67	(8)	0.1	0.4	1/59	(2)	0.1	0.3	N.S

F = fraction of patients reporting diarrhoea on the diarrhoea scale and patients using ≥1 antidiarrhoeal tablets per day.

of energy in the intervention group was 6.7 MJ and in the control group 6.9 MJ (not statistically significant). The fat intake was 57.9 g and 63.7 g (not statistically significant), respectively. During radiotherapy the intervention group had a lower intake of energy, 5.7 MJ and 6.5 MJ respectively ($p < 0.05$). The mean daily intake of fat in week 6 was 34.3 g in the intervention group and 60.1 g in the control group ($p < 0.001$). 6 weeks after the end of radiotherapy, the intervention group still had a lower intake of fat and energy than the control group (6.5 MJ versus 7.4 MJ, $p < 0.001$, and 41.0 g of fat versus 68.5 g, $p < 0.001$).

Before the start of treatment there were no differences in stool frequency or the use of antidiarrhoeal agents between the 2 groups (Table 3). 1 patient in the intervention group had 1 watery stool per day and 1 patient in each group used antidiarrhoeal agents. At week 6, the intervention group had an average of 1.1. and the control group had 1.7 loose and watery stools per day ($p < 0.01$). 6 patients (10%) in the intervention group and 20 patients (30%) in the control group had more than 1 watery stool per day. The stool pattern was converted to a diarrhoea scale (Table 2). 14 patients (23%) in the intervention group reported diarrhoea, versus 32 (48%) patients in the control group ($p < 0.01$). The intervention group took half the amount of antidiarrhoeal tablets (mean 0.6 tablets per day versus 1.1, $p < 0.01$) used by the control group during this period. 12 patients (19%) in the intervention group and 29 (43%) in the control group took 1 or more antidiarrhoeal tablets per day. 27 patients (44%) in the intervention group and 18 (27%) in the control group took no antidiarrhoeal agents at all.

12 weeks after the beginning of radiotherapy, no group differences were found with regard to stool frequency. 90% of the patients in both groups had normal stools. 2 patients in the intervention group and 5 patients in the control group took 1 or more antidiarrhoeal tablets per day. 2 of the patients in the control group, had more than 1 watery stool per day. Emesis was not a serious problem. The highest incidence of nausea was found in week 6. 5 patients (8%) in the intervention group and 6 (9%) in the control group experienced moderate to severe nausea. 12 patients in each group (18% of the intervention group and 20% of the control group) reported reduced appetite at 6 weeks. At 12 weeks 1 and 3 patients had reduced appetite respectively. Reduced body weight was more pronounced in the intervention group (mean reduction of 2.6 kg versus 1.7 kg) than in the control group ($p = 0.06$) during treatment. At week 12 the intervention group had gained on average only 0.6 kg, while the control group had gained 1.1 kg.

The results from the nutritional assessment are given in Table 4. 1 patient in each group was classified as mildly depleted at the start of treatment. 6 patients (9%) in the intervention group and 4 (6%) patients in the control group were classified as mildly depleted during radiotherapy. At week 12, none of the patients were classified as malnourished.

Discussion

A low-fat, low-lactose diet reduced the incidence of diarrhoea and the consumption of antidiarrhoeal agents during radiotherapy. The difference

Table 4 Number of patients with nutritional parameters <90% of reference values at the start of radiotherapy (week 0), in the last week of radiotherapy (week 6) and 6 weeks after end of radiotherapy (week 12). All patients are in the category, midly depleted (80–90% of the reference value)

	Control group Number of patients			Intervention group Number of patients		
week	0	6	12	0	6	12
Loss of weight >5%	9 (12)	19 (28)	0	12 (15)	22 (35)	1 (1)
AMC < 19cm	0	0	**	0	1 (2)	**
Serum albumin <31g/L	3 (3)	4 (6)	0	2 (3)	5 (7)	1 (1)
Transferrin < 1.4g/L	2 (2)	4 (6)	0	1 (1)	8 (13)	0
Number of patients with two or more subnormal nutritional parameters	1 (1)	4 (6)	0	1 (1)	6 (9)	0

AMC = Arm muscle circumference
** = not measured
% in brackets

in stool frequency between the 2 groups was small (average 0.6 loose and water stools per day), at week 6. The control group took twice as many antidiarrhoeal tablets as the intervention group, which may explain the small difference. There are few reports in the literature concerning the effect of a low-fat, low-lactose diet on radiation-induced diarrhoea. Lactose restricted diets have failed to show an effect (14). In one trial cholestyramine prophylaxis was evaluated in conjuction with a low fat diet during pelvic radiotherapy (17). The incidence of diarrhoea was reduced from 7 out of 16 patients in the control group to 1 out of 17 patients in the intervention group. In the present study, 48% of the control patients reported diarrhoea which is comparable to the numbers in other studies (31, 32, 33). The incidence rate of 23% in the intervention group is comparable to a study where bacterial preparations were administered to prevent diarrhoea (32). In this study they concluded that radiotherapy was correlated with a decrease of the majority of bacteria within the intestinal flora. 30% of patients given vital bifidus bacteria experienced diarrhoea, compared to 65% in the control group.

The small differences between groups in the present study may be explained by the low intake of fat in the control group. Metabolic studies in patients with distal small bowel resection have shown that a reduction in dietary fat from 100g to 40g per day may correct bile salt malabsorption (34). A reduction to about 60g per day may be inadequate but still effective. Bile acid malabsorption may not be present in all patients (35), and such patients would be expected to derive only marginal benefit from a low-fat diet. This may explain why 23% of the intervention group experienced diarrhoea. Stool frequency may not be the optimal indicator of diarrhoea (17, 19); measures of stool volume and water content may be better. Accurate data on stool volume would be difficult to obtain, however, in a study with outpatients.

The relatively low intake of fat in the control group may have been a result of the patients' awareness of the purpose of the study and of the general diet information given to cancer patients. It has also been reported that women undergoing pelvic radiotherapy spontaneously change their diet and decrease their intake of fat and fibre (36). Compared with the 48h recall prior to radiotherapy, our control group did not reduce their intake of fat during treatment. The 48h recall is, however, known to underestimate the usual intake compared to the record method (23, 26). It is also not clear whether the recall figures are representative of the patients usual dietary habits. It is more likely that they reflect lack of appetite and low intake of food prior to radiotherapy. The 48h recall was taken after the patients had been admitted to the hospital, which may have influenced their dietary intake.

Acute radiation enteritis is transient. 6 weeks after the end of radiotherapy 90% of all the patients had normal stools. The gastrointestinal symptoms have been found to persist longer than the period of histological recovery, which is 2–3 weeks after radiotherapy (37). This is consistent with our findings.

The pathogenesis of radiation enteritis seems to be complex. Diarrhoea associated with acute radiation enteritis is likely to reflect changes in intestinal absorptive function, as well as more

rapid small intestinal and colonic transit of nutrients (37). More rapid small intestine and colonic transit reduce the time available for absorption of nutrients and electrolytes which may lead to diarrhoea. There is also some evidence that a decrease of the majority of bacteria within the intestinal flora and release of prostaglandins from the irradiated intestine may be important factors (32, 37). It is difficult to say which of these factors is the most significant. Our data indicate that malabsorption of fat and lactose is not the only factor in the pathogenesis of diarrhoea during radiotherapy.

The lower incidence of diarrhoea in our intervention group did not result in a better nutritional status. With the low intake of fat it was difficult to maintain a sufficient intake of energy. More patients in the intervention group lost weight than in the control group.

In conclusion, patients on a low-fat, low-lactose diet were found to have statistically significant reduction in diarrhoea and consumption of anti-diarrhoeal agents. However, these patients lost more weight than patients in the control group. No final conclusion should be drawn from these findings until the data on the patients' quality of life have been analysed and taken into consideration.

Acknowledgement

This study was supported by grants from the Norwegian Cancer Society.

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Submission date: 20 November 1991; *Acceptance date:* 25 February 1992

URN:NBN:no-2118

Paper IV

URN:NBN:no-2118

URN:NBN:no-2118

Clinical Nutrition (1993) **12**: 89–95

The effect of a low fat, low lactose diet on nutritional status during pelvic radiotherapy

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ABSTRACT—The food intake and nutritional status were assessed before, during and after radiotherapy in 143 women with gynaecological malignancies randomized to either a low fat, low lactose diet or a normal diet during treatment. The patients on the low fat, low lactose diet had an intake of fat of 34 g per day during radiotherapy, 41 g per day 6 weeks after radiotherapy and 52 g per day 1 year after radiotherapy, when they were no longer on the diet. The intake in the control group was 57 g per day, 67 g per day and 66 g per day respectively. The total energy intake was reduced in both groups during radiotherapy. The reduced intake of energy resulted in weight loss, greatest in the intervention group. 1 year after radiotherapy both groups had almost regained their initial weight. No marked changes were observed in nutritional status as a result of decreased nutritional intake during radiotherapy.

Introduction

There are several factors that can induce diarrhoea during pelvic radiotherapy, among them malabsorption of lactose and bile salts (1–6). Unhydrolysed lactose in the intestinal lumen may cause fluid accumulation, followed by abdominal cramps and watery diarrhoea (1). High concentrations of bile salts in the colon may interfere with the absorption and secretion of water and electrolytes, thereby increasing bowel motility (7, 8, 9). Malabsorption of lactose is best corrected by removing the disaccharide from the diet by restricting the intake of milk (10). A low fat diet (maximum 40 g of fat (FR-40 g)) seems to reduce the faecal bile salt content and thus the diarrhoea (11, 12).

Women with gynaecological malignancies undergoing pelvic radiotherapy were included in a prospective randomized study at the Norwegian Radium Hospital (NRH) to evaluate the effect of low-fat, low-lactose diet on the occurrence of diarrhoea. The patients in the intervention group were found to have a statistically significant reduction in diarrhoea and consumption of antidiarrhoeal agents during radiotherapy (13). The intake of fat for those on the diet was not supposed to exceed 40 g per day. Because of reduced appetite during radiotherapy (14), this may be difficult to achieve without a corresponding reduction in the intake of energy, so that it was possible that the diet was leading to weight loss and malnutrition.

Reduction of fat consumption from 80 g per day to 40 g reduces the intake of energy by 1.5 MJ. To compensate for the reduced energy intake and prevent weight loss, carbohydrates and proteins must be increased and the total amount of food consumed must be higher, since these elements have a smaller proportion of energy than fat.

During periods of inadequate nutritional intake, the body's own components are used to provide energy for essential metabolic processes (15, 16). This leads to lipid depletion and loss of somatic and visceral proteins. Depletion of proteins has a significant effect because the body has no protein reserves. This may influence vital organs, have adverse effects on wound healing and lead to depressed immune competence, which leads to increased susceptibility to infections (16). The clinical characteristics of such malnutrition include weight loss, reduction in upper arm muscle circumference and skinfold measurements and low levels of viceral proteins (serum albumin (s-Alb) and serum transferrin (STF)) (15, 17). Body weight loss of 5% over 1 month, or 10% over 6 month, is usually considered to be a clinically significant sign of malnutrition (17). The present study was undertaken in order to evaluate possible side-effects of the diet on

the patients' nutritional status during radiotherapy and 6 weeks and 1 year after treatment.

Patients and methods

143 patients with a primary diagnosis of gynaecological malignancy (carcinoma of the endometrium, ovary and cervix, stage I and II), were included in the study at the NRH. They received external pelvic radiotherapy consisting of a minimum dose of 44 Gy or a minimum dose of 40 Gy combined with intracavitary treatment. The patients were ≤75 years of age and had a WHO performance status of ≤2. Patients were not eligible if they had undergone intestinal surgery prior to the diagnosis of malignancy because of Crohn's disease or ulcerative colitis, if they had previously been treated with chemotherapy or radiotherapy or if surgery was planned after completion of radiotherapy. After having given their written consent, patients were randomized before radiotherapy to receive either a low-fat, low-lactose diet or the regular hospital diet during the treatment and for 6 weeks afterwards. Dietary information was collected by a trained dietitian.

The majority of the patients (101 patients) were hospitalized during radiotherapy, but a few from each group (18 patients in the intervention group and 24 patients in the control group) were receiving treatment as out-patients. The hospital patients received 3 meals a day (breakfast, lunch and supper). Lunch was the only hot meal; the other meals consisted of bread or cereals. The evening meal consisted mainly of soup and bread. The out-patients prepared their own food at home. The intervention group was prescribed a diet containing a maximum of 40 g fat per day (FR-40 g) and was recommended to restrict their intake of milk to a maximum of 10 g lactose per day. The general guidelines for the FR-40 g diet are given in Table 1, based on the Norwegian Guidelines for Hospital Diets (18). In addition to the guidelines, the patients were given individual advice about the type and quantity of foods to eat. Carbohydrates and proteins were increased in order to compensate for the energy loss caused by the reduction in fat. The patients were told to eat large amounts of bread, pasta, potatoes, rice, fruit and vegetables in so far as they tolerated them. Patients who could not maintain their body weight were advised to take nutritional supplements containing medium-chain triglycerides (MCT fat). After completion of radiotherapy, the patients were given instructions on how to continue the FR-40 g diet at home. Each patient was given an individually tailored diet and was encouraged to stay on it for at least 6 weeks after radiotherapy. The control group received the hospital's regular diet, which has an average fat content of 80 g, representing 6.9 MJ (44% of energy from fat). Patients were advised to eat enough to maintain weight during radiotherapy and to take nutritional supplements if necessary.

Table 1 From the general guidelines for a low-fat diet (40 g of fat) for Norwegian hospitals (18).

Vegetables:	All fresh, frozen or cooked without added fat.
Fruits:	All fresh (except nuts and avocado), canned, frozen or dried fruit or juice.
Dairy products:	Skim milk or low-fat milk (0.5% fat). Cheese with fat content of 17% or less.
Meat, poultry, fish, eggs:	Lean and well-trimmed meat. All fish except eel. Egg yolks within the daily fat allowance.
Bread and cereals:	All kinds. Low-fat cakes and biscuits.
Fat:	Daily consumption of 5 g margarine or oil with a high content of polyunsaturated fats. Low-fat margarine or butter allowed in small amounts.

When preparing food, boiling and grilling should be used as much as possible. Frying in fat should be avoided.

The dietary intake prior to radiotherapy (week 0) was measured by 48-h recall (19). During radiotherapy (week 6), the patients recorded their consumption of food, drink and nutritional supplements for 4 consecutive days (20). As a control, an extra portion of food was ordered from the kitchen and weighed by the dietitian on a dietetic scale. At the end of each 4-day period, the records were reviewed by the dietitian to check that the nutritional data were complete. 3 months (week 12) and 1 year after the beginning of the study, the total dietary intake over a 7 day period (20, 21), was recorded with an electronic dietetic scale. The intake of fat, carbohydrate and protein and the total intake of energy were calculated by means of the FIBER software package based on Norwegian food composition tables (22).

The energy intake was compared with an estimate of the patients' total daily energy expenditure (TEE). TEE was calculated by multiplying Harris Benedict's equation (17) for basal energy expenditure (BEE), by an activity factor of 1.3 (15).

$$\text{BEE (female)} = (655 + 9.6\,W + 1.7\,H) - 4.68A,$$

where BEE is measured in kilocalories, W = weight in kilogrammes, H = height in centimetres and A = age in years.

Height, weight and weight history over the previous 3 months were recorded before the start of treatment. During radiotherapy the patients were weighed every week. Triceps skinfold thickness (TCSF) and

arm muscle circumference (AMC) were measured at the mid-point of the left arm (17). AMC was compared with reference measures (23). Serum albumin level (s-Alb) (reference range, 35–50 g/l) and total iron binding capacity (TIBC) were measured. Serum transferrin (TSF) (reference range, 1.6–2.7 g/l) was calculated according to the equation:

$$TSF = (4.47 \times TIBC - 43) \times 1/100.$$

Nutritional status was classified according to Blackburn (17). More than 5% weight loss over 1 month and an AMC, s-Alb and TSF below 90% of the lowest reference value were considered to be pathological. Categories were assigned on the basis of two or more variables having scores within that category (17). The following categories were used to describe the nutritional status:

1. mildly depleted, 80–90% of the reference value,
2. moderately depleted, 60–80% of the reference value and,
3. severely depleted, less than 60% of the reference value.

Where there was an equal choice between two categories, the most pathological one was given preference.

Statistical analysis

Student's t test was used to test for mean differences. Cross tabulation was used to analyse categorical variables and differences were tested by use of the Mann-Witney U test. The SPSS/PC V2.0 program was used.

Results

71 patients were randomly assigned to a low fat, low lactose diet and 72 to a normal diet (Table 2). A total of 110 patients (77%) completed the study (55 patients in each group). One patient in the intervention group and 7 in the control group died during the observation period because of relapse. The reasons for withdrawing from the study were, relapse (3 patients in the intervention group and 1 in the control), inability to follow the diet (6 and 1 patient, respectively), too much paperwork and problems at home (5 and 7 patients, respectively) and alcoholic problems (1 in each group). The mean age was 51 years (range 29–74) in the intervention group and 56 years (range 34–74) (NS) in the control group. The mean weight before treatment was 70.5 kg (range 47–119) and 66.7 kg (range 46–112) (NS) respectively. 23 patients – 13 patients (19%) in the intervention group and 10 (15%) in the control group (NS) – had lost over 5% of their body weight prior to hospitalization. The estimated total energy expenditure was 7.4 MJ in the intervention group and 7.2 MJ in the control group (NS).

Table 3 shows the mean intake of fat and energy before, during and after treatment. At baseline the intake of fat was 59 g in the intervention group and 65 g in the control group (NS). At 6 weeks the mean daily intake of fat was 34 g and 57 g respectively ($p < 0.001$). At 12 weeks, the patients in the intervention group had a intake of 41 g of fat, while the control group had increased the intake to 67 g ($p < 0.001$). At week 52, when neither group was following the diet, the figures were respectively, 52 g of fat and 66 g ($p < 0.01$). Before the start of radiotherapy the intake of energy was similar in both groups. The mean daily intake of energy dropped during radiotherapy to 5.7 MJ in the intervention group and to 6.5 MJ in the control group ($p < 0.05$), and it remained low in the intervention group during the observation period

Table 2 Patient characteristics

Mean age (range) Diagnosis	Control group 56 (34–74) Number (%)	Intervention group 51 (29–74) Number (%)
Cancer cervix uteri		
– stage IA	0	3 (4)
– stage IB	17 (24)	16 (22)
– stage IIA	4 (6)	3 (4)
– stage IIB	28 (39)	22 (31)
Cancer corpus uteri		
– stage I	16 (22)	18 (25)
– stage II	6 (8)	9 (13)
Cancer ovarii		
stage IC	1 (1)	0

Table 3 Fat and energy intake. The table shows mean intake of fat and energy before start of radiotherapy (week 0), during (week 6), 6 weeks after end of radiotherapy (week 12) and 1 year after (week 52). Total energy expenditure (TEE) was estimated over the same period.

Time from randomization (weeks)	Group	N	Intake of fat g	(SD)	Intake of energy MJ	(SD)	TEE[§] MJ	(SD)
0	Interv.	70	59	(19)	6.7	(1.6)	7.4	(0.7)
	Control	69	65	(24)	6.9	(2.0)	7.2	(0.7)
6	Interv.	63	34	(9)	5.7	(1.3)	7.2	(0.7)
	Control	66	57**	(17)	6.5**	(1.6)	7.1	(0.7)
12	Interv.	57	41	(13)	6.2	(1.3)	7.2	(0.7)
	Control	63	67**	(18)	7.4**	(1.7)	7.2	(0.7)
52	Interv.	55	52	(19)	6.3	(0.3)	7.3	(0.7)
	Control	52	66**	(40)	7.2*	(0.4)	7.1	(0.7)

[§]TEE = Total energy expenditure
*$p < 0.05$
**$p < 0.01$

Table 4 Energy consumption. Percentage of energy from fat, carbohydrates, proteins and alcohol before start of radiotherapy (week 0), during (week 6), 6 weeks after end of radiotherapy (week 12) and 1 year after (week 52).

Time from randomization (weeks)	Group	n	Percentage of energy from Fat %	Protein %	Carbohydr %	Alcohol %
0	Interv.	70	33	17	49	1
	Control	72	35	16	49	–
6	Interv.	63	23	18	57	2
	Control	68	35**	15**	49**	1
12	Interv.	57	25	18	56	1
	Control	63	35**	15**	48**	2
52	Interv.	55	31	17	51	1
	Control	52	34**	15**	50	1

*$p < 0.05$
**$p < 0.01$

(Table 3). The estimated TEE was constant in both groups during and after treatment. Prior to radiotherapy and at 6 weeks both groups had a higher estimated TEE than the reported energy intake. The intervention group had a higher estimated TEE than the reported energy intake during the entire observation period. The percentages of energy from fat, carbohydrates and proteins are given in Table 4. The women in the intervention group reduced their intake of energy from fat from 33% at baseline to 23% at week 6, 25% at week 12 and 31% after 52 weeks. The control group reported no change in the percentage of energy received from fat (35%).

The mean weight loss was 2.5 kg in the intervention group and 1.7 kg ($p = 0.06$) in the control group during radiotherapy (week 0 to week 6) (Table 5). 22 patients (35%) in the intervention group and 19 (28%) in the control group had a weight loss of 5% of their habitual weight. 5 (8%) patients in intervention group and 9 (13%) patients in the control group weighed more at the end of radiotherapy than at baseline, although the weight gain was less than 5% of the initial weight. From 6 weeks to 12 weeks the intervention group had gained on average 0.6 kg, while the control group had gained 1.1 kg. 18 patients (35%) in the intervention group and 39 (62%) in the control group gained weight during this period. At 52 weeks both groups had regained their initial weight. AMC was similar in both groups in the observation period, and only minor changes were observed within the groups during treatment (Table 5). The mean values for s-Alb and STF were within the reference range in both groups during the observation period. 2 patients in each group had s-Alb values in the range 80–90% of reference values (mildly depleted) before the start of radiotherapy. At 6 weeks, 5 patients (7%) in the intervention group and 4 patients (6%) in the control group were within this category. One patient in each group had s-Alb in the mildly depleted category at week 12. There was a tendency to raised levels of s-Alb after completion of radiotherapy in both groups.

Table 5 Nutritional status. Nutritional markers before start of radiotherapy (week 0), during (week 6), 6 weeks after end of radiotherapy (week 12) and 1 year after (week 52).

Time from randomization (weeks)	Group	n	Weight Kg	(S.D)	AMC[§] cm	(S.D)	Serum albumin g/l	(S.D)	Trans-ferrin g/l	(S.D)
0	Interv.	70	70.5	(13)	23.3	(2.4)	38.2	(4.1)	2.1	(0.5)
	Control	72	66.7	(12)	22.6	(1.9)	37.9	(4.0)	2.1	(0.5)
6	Interv.	63	68.0	(12)	23.0	(2.2)	36.7	(3.7)	1.9	(1.0)
	Control	68	65.4	(12)	22.2	(1.9)	36.7	(3.7)	2.0	(0.4)
12	Interv.	57	68.2	(12)	–		41.2	(4.3)	2.2	(0.5)
	Control	63	66.4	(12)	–		40.7	(4.2)	2.4*	(0.5)
52	Interv.	55	70.1	(12)	–		42.0	(4.0)	2.2	(0.4)
	Control	52	66.0	(12)	–		41.2	(4.8)	2.4	(0.5)

[§]AMC = arm muscle circumference
*$p < 0.05$
**$p < 0.01$

3 patients (5%) in the intervention group and 2 (3%) in the control group had STF of 80–90% of the reference value before the start of radiotherapy. At 6 weeks, 8 patients (13%) in the intervention group and 4 (6%) in the control group had STF values within this category. At 12 weeks all the patients had normal STF values. None of the patients could be categorized as malnourished before the start of radiotherapy. At week 6, however, 6 patients (9%) in the intervention group and 4 (6%) in the control group were mildly depleted. At 12 weeks and after 1 year none of the patients could be categorized as malnourished.

Discussion

The consumption of fat was reduced to a statistically significant extent, as expected, in the intervention group during and 6 weeks after treatment as a result of the diet. A minor reduction in fat intake during treatment was also seen in the control group, and reduced intake of fat during radiotherapy has also been found in a similar study (24). 1 year after the start of radiotherapy the intake of fat in the control group had increased to the initial values. The patients in the intervention group did not manage to compensate for the lost energy intake due to fat reduction by increasing the intake of carbohydrates and proteins, and the low energy intake led to weight loss during treatment. None of the other nutritional variables were altered, however, and after completion of radiotherapy the intake of fat increased in both groups. Others have also found it difficult to maintain energy intake when fat is reduced (25, 26, 27), and in two of these studies the low energy intake was accompanied by weight loss (25, 27). In the third study the weight was not measured.

The patients' self-reported energy intake was found to agree with the observed weight loss at week 6. This finding supports the validity of the information contained in the food records and indicates that it represents the actual nutrient intake of the subjects during the treatment period. At 12 weeks and after 1 year, the intervention group had a small weight gain which could not be explained by the increased energy intake. Their activity level may have been reduced during this period, but an underreporting of energy intake may also explain this result. The weight trend in the control group is in accordance with the accepted formula that a loss of 0.5 kg over 1 week requires an energy deficit of 3500 kcal per week (28).

Prior to radiotherapy both groups had a lower intake of fat and energy than the normal population (29). There was also a tendency towards a lower level of fat intake prior to the diet in the intervention group than in the control group. The fact that the percentage of energy from fat fell in the intervention group, while remaining unchanged in the control group, indicates that the former followed the diet. The reduced intake of fat in the control group seen at week 6 was therefore probably a result of reduced intake of food and not so much a result of the patients' awareness of the purpose of the study or the general diet information given to cancer patients. When the intervention group was allowed to eat normally (after 12 weeks), they increased their intake of fat and energy. However, after 1 year the intervention group was still receiving a lower percentage of energy from fat intake than the control group. The fat intake of the intervention group was also lower than in the general population (29). This may reflect permanent changes in dietary habits which may be due to the dietary intervention. It may also be due to the record-keeping, which may have reminded the patients of the intervention period and altered their eating habits. The fact that they report a low energy intake despite a weight gain suggests that the group may have under-reported their usual intake. The control group had an intake which was comparable to that of the general population throughout the study.

A 48-h recall was used to estimate dietary intake prior to radiotherapy. This method is known to result in under-estimation of the usual intake (20). The method was not used, however, to obtain information about the usual intake, but to obtain an impression of dietary intake in hospital. The recall was carried out just after the patients were admitted to hospital. The figures may be influenced by the lack of appetite and low intake of food due to hospitalization, the impact of information about the disease, and psychological distress. Prospective food records may be a better method, but this too has limitations, since it only provides an estimate of nutritional intake over a relatively short period of time (20). Continuous record-keeping over a longer period of time would be the optimal method, but it is not suitable for general application. It has been claimed that the accuracy of recording declines after a few days and that the act of record-keeping may itself alter the respondent's dietary behaviour (30). During hospitalization the patients received a diet controlled by the hospital kitchen, and were therefore only asked to record their intake for 4 days. At home they had to keep a record for 7 consecutive days, which is generally considered as a more reliable method (20), and had to be responsible for their diet on their own. It is possible that the intervention group did not keep to the diet in the period between 6 weeks and 12 weeks. If it is true that they

kept more closely to the diet when they had to register their intake, their 7 day records represent their intake at week 12 and not their usual intake during the period in between. This could explain why they gained more weight than expected from their intake of energy.

We were only able to observe minor changes in nutritional status as a result of the low food intake during radiotherapy in the present study. Serum albumin (s-Alb) and STF have been commonly used as markers of visceral protein status when evaluating nutritional status, but neither of these proteins are optimal markers for acute malnutrition. The total body pool of s-Alb is large and the half-life of albumin is long (20 days), which makes albumin a poor marker of acute malnutrition (15). The observed low intake of energy and food at 6 weeks might not have lasted long enough to have any effect on serum albumin. STF with its shorter half-life (8 days), ought to be a more sensitive marker (15). The intervention group had a lower STF level than the control group during the entire observation period, but it was not pathological. STF can also be affected by other factors such as iron deficiency and oestrogen treatment. Prealbumin and retinol-binding protein would have been better markers of acute malnutrition, since there is a smaller body pool of these proteins and they have a shorter half-life (15).

The patient compliance in this study was good. 77% of the patients (81% if deaths are excluded) completed the diaries and the various questionnaires. These findings indicate that a long term diet intervention study is feasible. The acceptance of such a stringent diet as the low fat, low lactose diet was made possible by intensive dietary counseling and support by the dietitian. Each patient was given an individually tailored diet and this was probably of importance to secure compliance.

A striking finding in this study was that 1 patient died in the intervention group versus 7 in the control group. This was probably a coincidence. To our knowledge there is no data available which indicate that a low fat, low lactose diet during radiotherapy can improve survival from gynaecological cancer. Another possibility is that the groups were not well matched despite the randomization. The baseline data on the 2 groups does not provide support for such an assumption. Patient survival will however be re-evaluated later after a longer period of follow-up.

In conclusion, the low-fat lactose intervention was successful in terms of reducing the total fat intake during radiotherapy. Studies have shown (13) that this diet is successful in reducing the occurrence of diarrhoea during radiotherapy. The diet led to minor weight reduction because of insufficient compensatory increase of protein and carbohydrate-rich foods. The decreased intake of energy returned to normal after treatment. Because of the reduced energy intake and weight reduction during radiotherapy, our data is not convincing enough to recommend the use of a low fat, low lactose diet during radiotherapy. If such a diet is going to be used, an effort has to be made to secure an adequate energy intake. No final conclusion should be drawn before data on the patients quality of life have been analysed and taken into consideration.

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Submission date: 18 September 1992; *Acceptance date*: 11 November 1992

URN:NBN:no-2118

Paper V

URN:NBN:no-2118

URN:NBN:no-2118

Acta Obstet Gynecol Scand 1995; 74: 147–152
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Acta Obstetricia et Gynecologica Scandinavica
ISSN 0001-6349

ORIGINAL ARTICLE

Quality of life during pelvic radiotherapy

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Acta Obstet Gynecol Scand 1995; 74: 147–152. © Acta Obstet Gynecol Scand 1995

Background. A randomized clinical trial was carried out to evaluate the effect of a diet low in fat and lactose to prevent acute radiation-induced diarrhea. The effect of the diet treatment on the patients' health related quality of life was studied.
Methods. 143 women with gynecological malignancies were included. The daily number and consistency of stools, use of antidiarrheal agents and quality of life measured by using the EORTC Core Quality of life Questionnaire 36 item version, were recorded before therapy, in the last week of treatment, six weeks after end of radiotherapy and every eight weeks during one year's follow up.
Results. Fourteen patients (23%) in the intervention group reported diarrhea during radiotherapy, compared to 32 (48%) in the control group ($p<0.01$). This difference was not seen with the EORTC questionnaire. The diet intervention did not interfere with emotional and social well-being. Within the control group diarrhea was associated with higher scores on the physical functioning scale ($p<0.01$), and fatigue and malaise scale ($p<0.01$) indicating more pronounced dysfunction of symptoms.
Conclusion. When measuring specific phenomena such as diarrhea in a clinical trial, the EORTC questionnaire does not seem to be as sensitive as specific trial-related instruments. Diet intervention during radiotherapy might influence the patients' ability to cope with diarrhea by giving them more control over their own situation.

Key words: diarrhea; low lactose; low-fat diet; pelvic radiotherapy; quality of life

Submitted 20 December, 1993
Accepted 29 June, 1994

During radiotherapy for gynecological malignancy the small intestine is often within the radiation field. Because of rapid cell turnover the mucosa of the small intestine is sensitive to radiation, reducing cell replication and replacement of epithelial cells (1, 2). Malabsorption of lactose and bile salts has been observed during radiotherapy and may contribute to diarrhea accompanied by nausea, vomiting and loss of appetite (1, 3, 4, 5, 6). These side effects accompanied by fluid loss and reduced intake of food may induce fatigue, loss of body weight, increased psychological distress and reduced quality of life (7, 8, 9).

At the Norwegian Radium Hospital (NRH) a randomized clinical trial was carried out to evaluate the effect of a diet low in fat and lactose to prevent acute radiation-induced diarrhea in contrast to a normal diet. The patients on the low fat, low lactose diet had reduced diarrhea and consumed fewer antidiarrheal agents (10). There was minor weight reduction because of insufficient compensatory increase of protein and carbohydrate-rich foods (11). We now report on the effects of the diet treatment on the patients' health-related quality of life.

Patients and methods

Between May 1988 and May 1990 183 women with a primary diagnosis of gynecological malignancy were eligible for the study; 143 were included and 40 denied randomization. The selection criteria for the clinical trial were: age ≤75 years, WHO performance status ≤2, a primary diagnosis of carci-

noma of the endometrium, ovary or cervix, and external pelvic radiotherapy at a minimum dose of 44 Gy or a minimum of 40 Gy combined with intracavity treatment.

In 63 women with carcinoma of the endometrium, ovary (stage I and II) or cervix (stage IA), postoperative external pelvic radiotherapy at a total dose of 48–52 Gy in 2 Gy per fraction, 4 fractions per week was given. Anterior-posterior fields were used with a field diameter of 17 cm. The upper field margin was between L4 and L5, and the lower margin along the center of the obturator foramen. In 80 women with carcinoma of the cervix, stage IB and II, external radiotherapy at a total dose of 40–60 Gy was given followed by intra-cavity treatment at a total dose of 26 Gy.

Women were not included if they had undergone intestinal surgery for Crohn's disease or ulcerative colitis prior to the diagnosis of malignancy or if they had previously been treated with chemotherapy or radiotherapy, or if surgery was planned after completion of radiotherapy. The study groups are shown in Table I. In the intervention group 22 patients (31%) received external radiotherapy in combination with radium application, and 25 patients (35%) in the control group.

Following informed consent, the women were randomized before radiotherapy to receive either a low fat, low lactose diet (maximum of 40 g fat per day and 5 g lactose per meal) or the regular hospital diet, both during the treatment period and for six weeks. A trained dietitian explained the diet regime to the patients. Block randomization was used with 20 patients in each block.

The majority of the patients (101) were hospitalized during radiotherapy, but a few (18 patients in the intervention and 24 in the control group) were treated as outpatients. The hospital patients received three meals a day (breakfast, dinner and supper) prepared in the hospital kitchen. The outpatients prepared their own food at home.

A daily diary card was used to record the number and consistency of bowel movements, and the use of antidiarrheal tablets.

The patients' health-related quality of life was defined as a multidimensional concept consisting of physical, psychological and social variables (12), measured by the EORTC Core Quality of Life Questionnaire – 36 item version (EORTC QLQ-C36) and a diagnosis-specific module before and after radiotherapy (13). The content of the questionnaire is given in Table II, and consists of five scales to assess physical (7 items), role (2 items), emotional (8 items) and social functioning (2 items), and global health status/quality of life (2 items), as well as two symptom scales for fatigue and malaise (5 items) and nausea and vomiting (2 items). Single items concerning appetite, diarrhea, constipation, pain, dyspnea, sleep disturbances, alertness behavior and financial impact are also included. A 10-item diagnosis-specific module developed by the study group focusing on disease- and treatment-related symptoms was also used. This module was based on clinical experience and interviews with clinicians and patients.

The items were scored on Likert scales, where higher scores represent more pronounced dysfunction or symptoms with the exception of the global quality of life scale where a higher score represents improved quality of life. The patients filled out the questionnaire before and in the sixth treatment week. After treatment (12th–52nd week), the questionnaires were completed every other month.

The reliability of each scale was assessed by Chronbach's Alpha coefficient (14). A value above 0.60 was considered acceptable for group comparison. Scale reliability was satisfactory (0.6 to 0.9) at

Table I. Distribution of patient material by type of disease and randomisation group

Diagnosis	Intervention N	Intervention %	Controls N	Controls %
Cervical cancer stage IA	3	4	0	
Cervical cancer stage IB	16	22	17	24
Cervical cancer stage IIA	3	4	4	6
Cervical cancer stage IIB	22	31	28	39
Endometrial cancer stage I	18	25	16	22
Endometrial cancer stage II	9	13	6	8
Ovarian cancer stage IC	0		1	1

Table II. Content of EORTC core quality of life questionnaire (C-36 version)

Quality of life domain	No of items	Score range	Chronbachs alpha[a] Int[b]	Chronbachs alpha[a] Cont[c]
Physical functioning	7	0–7	0.6	0.6
Role functioning	2	0–1	0.7	0.4
Emotional functioning	8	1–4	0.7	0.7
Social functioning	2	1–4	0.7	0.8
Financial impact	1	1–4		
Disease symptoms				
Fatigue and malaise	5	1–4	0.8	0.8
Nausea/vomiting	2	1–4	0.7	0.7
Appetite	1	1–4		
Diarrhea	1	1–4		
Constipation	1	1–4		
Pain	1	1–4		
Dyspnea	1	1–4		
Sleep disturbance	1	1–4		
Alertness behavior	1	1–4		
Global health/quality of life	2	1–7	0.8	0.8

[a] Chronbachs alpha before start of radiotherapy. [b] Intervention group. [c] Control group.

all time points for all scales, except the role functioning scale (Table II) which had low reliability in the control group (0.4). Low reliability was also found in both groups during follow up.

Student's *t*-test was used to test for mean differences in bowel movements between the groups. Differences in categorical variables were tested by use of the Mann-Whitney U test. Analysis of variance (ANOVA) was employed to test for group differences. The tests for significant differences should be interpreted with caution because of multiple tests. Differences over time were tested with repeated measure of analysis of variance (MANOVA). The ordinary Pearson product moment correlation (r) was used to assess the relationship between variables. The SPSS/PC V2.0 program was used.

Results

Seventy-one patients were randomly assigned to a low fat, low lactose diet and 72 to a normal diet. There were no statistically significant differences between the two groups with respect to diagnosis and staging. A total of 110 patients (77%) completed the study including one year follow up (55 in each group). Mean age was 51 years (range 29–74) in the intervention and 56 years (range 34–74) in the control group (NS), and mean weight before treatment was 70.5 kg (range 47–119) and 66.7 kg (range 46–112) respectively (NS). Thirteen patients (19%) in the intervention and 10 (15%) in the control group had lost over 5% of their body weight prior to hospitalization. One patient in the intervention and seven in the control group relapsed and died during the observation period. Six patients in the intervention and one in the control group dropped out because of the diet. The reasons given were the taste of the food, and concern about not managing to maintain the diet at home for six weeks. Other reasons for withdrawing were, relapse (three in the intervention and one in the control group), too much paperwork, problems at home (five and seven patients, respectively) and alcoholism (one in each group). One patient in the control group changed to a low fat diet.

The mean scores of the functioning scales and the single item on financial impact are presented in Table III. No statistically significant differences were found between the two groups during treatment. The control group had a statistically significant higher score on the role functioning scale than the intervention group at the 38th ($F=5.58$; $p<0.05$), 46th ($F=6.45$; $p<0.05$) and 52nd week ($F=5.47$; $p<0.05$), indicating reduced role functioning in the control compared with the intervention group. At the 46th week the control group had a statistically significant higher score on the social functioning scale ($F=4.27$; $p<0.05$) than the intervention group. Six weeks after radiotherapy the control group had statistically significant higher global health/quality of life score ($F=4.36$; $p<0.05$). As the differences were small, and could be a result of multiple tests, the tests must be interpreted with caution and may have arisen because of chances.

The scores were highest before radiotherapy and fell during follow up on the emotional ($F=16.96$; $p<0.01$) and social functioning scales ($F=12.04$; $p<0.01$; MANOVA), indicating an improvement in emotional and social functioning. The scores on the global health scale were 5.0 in the intervention and 4.9 in the control group before radiotherapy. After one year the scores had increased to 5.4 and 5.5 respectively ($F=6.11$; $p<0.01$; MANOVA), indicating an improvement. The scores on physical functioning increased in both groups during radiotherapy indicating more dysfunction but improved during follow up ($F=7.61$; $p<0.01$; MANOVA).

The response to the two symptom scales and the single items are given in Table IV. No statistically significant differences between the two groups were found, except at the 30th week when more reduced appetite ($F=4.29$; $p<0.05$) and at the 46th week when more constipation ($F=6.78$; $p<0.01$) was seen in the control group.

Fourteen patients (23%) in the intervention group reported diarrhea during the last week of radiotherapy, compared to 32 (48%) in the control group ($z=-2.84$; $p<0.01$; Mann-Whitney U test). The intervention group had an average of 1.1 and the control group 1.7 loose and watery bowel movements per day ($t=3.06$; $p<0.01$; Student's *t*-test). The intervention group used 50% less antidiarrheal tablets (mean 0.6 tablets/day compared to 1.1; $t=2.91$; $p<0.01$; Student's *t*-test). The correlation between the number of watery bowel movements during the last week of treatment and the corresponding EORTC score on diarrhea was low at 0.6 in the intervention and 0.5 in the control group. At the end of radiotherapy no group differences were found with regard to frequency of bowel movements or the use of antidiarrheal tablets.

The scores on the functioning scales and the symptom scales at the last week of radiotherapy were related to frequency of diarrhea (Table V). The patients in the control group having diarrhea had higher scores on the role functioning ($F=5.45$; $p<0.05$), physical functioning ($F=13.09$; $p<0.01$) and the fatigue and malaise scales ($F=10.51$; $p<0.01$) than patients not experiencing diarrhea. This was not found in the intervention group.

No systematic differences were found between the two groups on the diagnosis specific questions

Table III. Mean scores of quality of life scales and item for the intervention group (int) and the control (cont) at start of treatment and at follow up assessment (week 6–52). With the exception of the global quality of life scale, higher scores represent reduced function. Levels of statistical significance are indicated with * ($p<0.05$) or ** ($p<0.01$); ANOVA

Quality of Life domains	Weeks from treatment start															
	0		6		12		22		30		38		46		52	
	Int	cont	Int	cont	Int	cont	Int	cont	Int	cont	Int	cont	Int	cont	Int	cont
n	67	67	61	66	57	66	56	58	58	54	53	55	55	55	55	55
Physical functioning	1.9	1.5	2.3	2.1	1.4	1.4	1.3	1.2	1.5	1.5	1.6	1.4	1.3	1.5	1.0	1.3
Role functioning	0.3	0.3	0.5	0.5	0.2	0.3	0.2	0.2	0.3	0.3	0.2	0.3*	0.1	0.3**	0.1	0.3*
Emotional functioning	2.0	2.0	1.9	1.9	1.8	1.8	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
Social functioning	2.0	2.0	1.8	2.1	1.6	1.8	1.5	1.5	1.6	1.7	1.4	1.6	1.4	1.6*	1.5	1.7
Financial impact	1.3	1.5	1.3	1.4	1.4	1.5	1.3	1.7*	1.4	1.4	1.3	1.5	1.3	1.5	1.4	1.6
Global health/quality of life	5.0	4.9	4.9	5.1	5.2	5.6*	5.4	5.4	5.1	5.1	5.2	5.4	5.2	5.5	5.4	5.5

Table IV. Mean scores of disease symptoms for the intervention group (int) and the control group (cont) at start of treatment and at follow up assessment (week 6–52). Higher scores represent more higher intensity of symptoms. Levels of statistical significance are indicated with * ($p<0.05$) or ** ($p<0.01$); ANOVA

Disease symptoms	Weeks from treatment start															
	0		6		12		22		30		38		46		52	
	Int	cont	Int	cont	Int	cont	Int	cont	Int	cont	Int	cont	Int	cont	Int	cont
n	67	67	61	66	57	66	56	58	58	54	53	55	55	55	55	55
Fatigue and malaise	1.9	1.8	2.1	2.0	1.8	1.8	1.7	1.7	1.7	1.8	1.7	1.8	1.7	1.8	1.6	1.8
Nausea/vomiting	1.2	1.2	1.4	1.4	1.2	1.1	1.1	1.1	1.1	1.2	1.1	1.2	1.1	1.1	1.1	1.1
Appetite	1.5	1.5	1.9	1.9	1.3	1.2	1.1	1.2	1.2	1.5*	1.2	1.3	1.2	1.3	1.2	1.2
Diarrhea	1.3	1.3	2.5	2.6	1.8	1.7	1.7	1.7	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.7
Constipation	1.7	1.6	1.2	1.2	1.2	1.2	1.2	1.3	1.2	1.4	1.2	1.3	1.1	1.4**	1.2	1.3
Pain	1.6	1.6	1.6	1.7	1.6	1.6	1.6	1.8	1.6	1.9	1.7	1.8	1.6	1.8	1.6	1.7
Dyspnea	1.4	1.3	1.4	1.5	1.3	1.3	1.2	1.4	1.3	1.3	1.3	1.3	1.2	1.4	1.2	1.4
Sleep distubance	1.8	1.9	1.7	1.6	1.6	1.9	1.5	1.7	1.6	1.8	1.7	1.7	1.6	1.5	1.5	1.7
Alertness behavior	1.6	1.8	1.7	1.9	1.6	1.6	1.5	1.5	1.5	1.5	1.5	1.6	1.6	1.6	1.5	1.5

Table V. Relationship between diarrhea and the functioning scales (emotional functioning (EF), role functioning (RF), social functioning (SF), physical functioning (PF) and global health status/quality of life (QL)) and two symptom scales (fatigue and malaise (F) and nausea and vomiting (NV)) at the last week of radiotherapy. The following categories were used to describe diarrhea: 1=no change in stool frequency or increase of 1–3 stools per day, 2=diarrhea (increase of 4–6 stools per day and all watery stools). Analysis of variance (ANOVA) was used to test for group differences

	Intervention group					Control group				
	1		2			1		2		
n	45	s.d.	11	s.d.	*p*	34	s.d.	32	s.d.	*p*
week 6 EF	1.9	0.4	1.8	0.6	ns	1.8	0.4	1.9	0.5	ns
RF	0.5	0.4	0.5	0.4	ns	0.4	0.4	0.6	0.4	0.023
SF	1.8	0.7	1.7	0.6	ns	2.0	0.8	2.2	1.0	ns
PF	0.3	0.2	0.3	0.2	ns	0.2	0.2	0.4	0.2	0.001
QL	4.9	1.3	4.9	1.3	ns	5.3	1.4	5.0	1.3	ns
F	2.1	0.6	2.0	0.5	ns	1.8	0.4	2.2	0.6	0.002
NV	1.4	0.4	1.3	0.4	ns	1.4	0.5	1.4	0.4	ns

(Table VI). The intervention group reported more pressure on rectum before radiotherapy ($F=15.49$; $p<0.01$), six weeks after radiotherapy ($F=5.96$; $p<0.05$) and at the 22nd week ($F=7.35$; $p<0.05$). During the follow up period the intervention group had less pain in the stomach ($F=7.34$; $p<0.01$) and pressure in the pelvic area ($F=4.11$; $p<0.05$) at the 30th week and less vaginal discharge at the 12th week ($F=6.51$; $p<0.05$).

In both groups frequent urination ($F=12.27$; $p<0.01$), burning urination ($F=6.60$; $p<=0.01$) and pressure on the rectum ($F=6.45$; $p<0.01$; MANOVA) were increased at the last week of radiotherapy compared with pretreatment. The

Table VI. Mean scores of the diagnosis-specific module measuring disease and treatment related symptoms at start of treatment (week 0) and at follow up assessment (week 6–52). Higher scores represent higher intensity of symptoms. Levels of statistical significance are indicated with * ($p<0.05$) or ** ($p<0.01$); ANOVA

Disease symptoms	Weeks from treatment start															
	0		6		12		22		30		38		46		52	
n	Int 67	cont 67	Int 61	cont 66	Int 57	cont 66	Int 56	cont 58	Int 58	cont 54	Int 53	cont 55	Int 55	cont 55	Int 55	cont 55
Pain similar to menstrual pain	1.4	1.5	1.3	1.3	1.2	1.2	1.3	1.3	1.2	1.4	1.2	1.3	1.3	1.2	1.3	1.2
Vaginal discharge	1.7	1.8	1.4	1.5	1.2	1.6*	1.2	1.4	1.3	1.3	1.2	1.3	1.2	1.3	1.1	1.2
Pressure in the pelvic area	1.7	1.6	1.4	1.5	1.4	1.4	1.3	1.4	1.3	1.6*	1.3	1.4	1.4	1.4	1.3	1.3
Pressure on rectum	1.5	1.1**	1.7	1.5	1.4	1.1*	1.5	1.2*	1.3	1.3	1.3	1.3	1.4	1.2	1.3	1.3
Pain in the stomach	1.6	1.5	1.7	1.8	1.5	1.4	1.5	1.6	1.4	1.8**	1.5	1.6	1.6	1.6	1.5	1.5
Frequent urination	1.7	1.6	2.2	2.3	1.8	1.6	1.6	1.5	1.6	1.7	1.5	1.6	1.6	1.7	1.5	1.5
Burning urination	1.2	1.2	1.5	1.6	1.3	1.2	1.1	1.2	1.2	1.1	1.1	1.2	1.2	1.2	1.1	1.2

scores fell to the base line level six weeks after radiotherapy and remained so during follow up. At the last week of radiotherapy vaginal discharge ($F=11.31$; $p<0.01$) and pressure in the pelvic area ($F=4.57$; $p<=0.01$; MANOVA) was reduced compared to the base line level. Pain similar to menstrual pain was also slightly reduced ($F=2.16$; $p<0.05$; MANOVA). The scores remained at this level during follow up.

Discussion

No major differences were found between the intervention group and the control group during treatment when using the EORTC questionnaire. At follow up minor statistically significant differences were found, most frequently in the role and social functioning scales. All differences were better for the intervention group, but these were small and should be interpreted with caution.

The intervention group had better role functioning than the control group at three assessment points and better social functioning at one point during follow up. Furthermore, better global health/quality of life was found in the control group six weeks after end of treatment. When interpreting these findings it must be taken into consideration that multiple tests were performed. The statistically significant differences found might be a result of chances.

Both groups experienced emotional and social problems before beginning radiotherapy, but global health improved during radiotherapy. This has been described previously in newly diagnosed cervical, uterine and ovarian cancer (8, 15). In a group of patients with various cancers, it was found that they believed that the need for radiotherapy implied very bad news (16).

The patients studied here reported a higher score on the global QOL scale compared to a Swedish lung cancer population (17). Among the lung cancer patients the score was 4.0 before start of treatment and 4.6 after one year. The scores before start of radiotherapy among the gynecological cancer patients were, however, comparable to the pretreatment score in a group of patients with malignant melanoma (18).

Emotional and social problems were found to be lower during the last week of radiotherapy compared to pretreatment. Both the intervention and the control group had a rather intensive follow up during radiotherapy. The patients were well aware of the possible side effects of treatment and patients who are well informed about treatment do not experience the same distress during radiotherapy (16, 19). During the last week of radiotherapy, patients were examined and most of them were informed that their cancer was under control – often in complete remission. This could also explain the improved level of emotional and social functioning during the last week of treatment. Physical functioning was reduced at the end of radiotherapy, but improved during follow up.

The lower frequency of diarrhea and lowered use of antidiarrheal tablets found from the daily diary cards in the intervention group was not seen by using the EORTC questionnaire. A possible reason may have been fewer reports of bowel movements. The divergent results may also indicate that using only one question measuring bowel habits is not sensitive enough to detect group differences. Experiences from this study indicate the importance of using specific instruments to measure detailed trial-related symptoms. This issue is now incorporated in the EORTC questionnaires by designed modules that are trial and/or diagnosis-specific (12).

The group differences seem to indicate that diet intervention made the diarrhea less stressful when the patients felt that they might control the di-

arrhea by diet. This explanation fits well with classical coping theories. If the patients are to maintain control, it is important to let them be actively involved in the reduction of unpleasant symptoms. In intervention programs designed to give the patient information about disease, treatment and side effects, the intervention groups reported a more rapid decline of pretreatment anxiety and depression than control groups (19).

A drop in disease-related symptoms is comparable to general findings in gynecological patients (20) and may be explained by the success of radiotherapy. These findings support the validity of the questionnaire.

One patient died in the intervention group, whereas seven died in the control group. Whether a low fat, low lactose diet during radiotherapy improves survival of gynecological cancer patients is not known, but the groups may not have been well matched. There was, however, no difference between the two groups with respect to type of cancer and staging.

The low fat, low lactose diet intervention did reduce diarrhea and the use of antidiarrheal tablets. The intervention did not interfere with the patients emotional and social well-being. Diet intervention during radiotherapy may influence the patients' ability to cope with diarrhea, as it provides the patients with more control over their own situation.

The EORTC questionnaire assessed general health related dimensions, and did not focus on given specific symptoms. It seems evident that when measuring specific phenomena such as diarrhea in a clinical trial, specific instruments should be used to measure detailed trial related symptoms.

Acknowledgments

This study was supported by a research grant from the Norwegian Cancer Society. The authors wish to thank the clinical staff of the Department of Gynecology at The Norwegian Radiumhospital for their cooperation.

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Paper VI

URN:NBN:no-2118

URN:NBN:no-2118

Health-Related Quality of Life and Occurrence of Intestinal Side Effects After Pelvic Radiotherapy

Evaluation of Long-term Effects of Diagnosis and Treatment

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Acta Oncologica Vol. 39, No. 2, pp. 173–180, 2000

Health-related quality of life (HRQOL) and occurrence of late intestinal side effects were assessed 3–4 years after pelvic radiotherapy for carcinoma of the endometrium and cervix. During 1988–1990, 143 women were included in a clinical trial to evaluate the effect of a low fat, low lactose diet on radiation-induced diarrhoea. Of 94 survivors, 79 (84%) answered the request. HRQOL was assessed by the EORTC QLQ-C36 and compared with population-based norms. The women scored lower than the general population on role functioning (81.5 versus 90.6 ($p < 0.01$)) and higher on diarrhoea (23.8 versus 9.5 ($p < 0.01$)). Compared with pre-treatment conditions, an increase in cases with pain in the lower back, hips and thighs was seen. Substantial pain and diarrhoea were associated with deterioration in HRQOL. In conclusion, few treatment and/or disease-related effects were detected 3–4 years after radiotherapy, with the exception of increased bowel frequency and pain in the lower back, hips and thighs.

Received 19 April 1999
Accepted 9 December 1999

The majority of women with carcinoma of the endometrium or cervix are cured but the treatment may induce alterations in functional status, activity and family relationship and thereby affect health-related quality of life (HRQOL) (1). Retrospective studies have suggested high levels of psychological distress post-treatment (2, 3). Other studies have reported good quality of life in survivors of gynaecological cancer despite physical symptoms and late effects of treatment (4, 5). These contradictory results may have been influenced by factors such as selection of patients and use of different measures. Reference data from a non-selected normal population may contribute to better understanding of the clinical impact of the findings (6). To our knowledge, such a strategy has not been applied in survivors from gynaecological cancer.

Diarrhoea and abdominal cramps are the most frequently reported late side effects after radiotherapeutic treatment for carcinoma of the endometrium or cervix (7, 8). Gastrointestinal complications usually occur 6 to 24 months after termination of treatment (9, 10). The severity of problems is related to the total dose and dose per fraction, volume of intestine irradiated, the use of single-field treatment daily and previous abdominal surgery (7). Retrospective studies suggest an incidence of severe complications in 5–15% of the patients treated with a dose of 45–50 Gy in five weeks (7, 11). Up to 40% of patients are reported to experience chronic diarrhoea and the majority of patients may experience increased frequency of bowel movements (7, 11). Factors such as thin physique, hypertension and diabetes mellitus may increase the risk of developing gastrointestinal complications, but this is controversial (7, 12). It is also claimed that severe acute radiation enteritis may be a predecessor of chronic radiation injury (10, 11). However, absence of acute enteritis does not seem to exclude late injuries.

To our knowledge, most studies on the subject of HRQOL in gynaecological cancer have assessed heterogeneous groups, various modes of treatment and have had short follow-up periods (3, 4, 13, 14). This paper describes HRQOL and gastrointestinal complications in a relatively homogeneous group of women with carcinoma of the endometrium or cervix. From May 1988 to May 1990 they were included in a randomized clinical trial to evaluate the effect of a low fat, low lactose diet in order to prevent

 ISSN 0284-186X

acute radiation-induced diarrhoea. During radiotherapy 23% of the women in the intervention group reported diarrhoea compared with 48% in the control group (15). After one year's follow-up there were no signs of severe diarrhoea in any of the groups. The diet intervention did not interfere with the patients' HRQOL assessed by the EORTC Core Quality of Life Questionnaire, 36-item version (EORTC QLQ-C36) (16).

The first aim of the present paper was to assess the occurrence of late intestinal side effects in the two groups 3–4 years after treatment and to evaluate whether the diet intervention during radiotherapy had an impact on the occurrence of late effects. Late diarrhoea was expected to correlate with acute radiation-induced diarrhoea. Secondly, we wanted to evaluate the patients' HRQOL and compare this with data from a random sample of women of similar age from the Norwegian population.

MATERIAL AND METHODS

Between May 1988 and May 1990, 143 women were included in a randomized clinical trial to evaluate the effect of a low fat, low lactose diet to prevent acute radiation-induced diarrhoea. The inclusion criteria were primary diagnosis of carcinoma of the endometrium, ovary or cervix; external pelvic radiotherapy at a minimum dose of 44 Gy or 40 Gy if combined with intracavitary treatment; age ≤ 75 years and WHO performance status of ≤ 2. Patients with the diagnosis of inflammatory bowel disease or ulcerative colitis were not included.

Seventy-one women were assigned to the intervention diet and 72 to the control group, and all were followed for one year. The intervention group was on the diet during radiotherapy and 6 weeks after termination of treatment. Eleven patients died or experienced progression during the clinical trial and 17 declined the study. Patients who experienced progression or refused to participate at one time-point were not considered as eligible at later follow-up.

Fifty-two of the women included in the study had carcinoma of the endometrium and cervix (stage IA). One had ovarial cancer stage I. They all received postoperative external pelvic radiotherapy at a total dose of 48–52 Gy in 2 Gy per fraction, 4 fractions per week. Anterior–posterior fields were used with a field diameter of 17 cm. The upper field margin was between L4 and L5, and the lower margin was along the centre of the obturator foramen. Ninety of the included women had carcinoma of the cervix (stage IB–IIB). They received external radiotherapy at a total dose of 40–46 Gy in combination with either radium application (26 Gy) or high dose-rate brachytherapy. More detailed information about eligibility criteria, staging and treatment regimens is presented elsewhere (15, 16).

According to the Population Register of Norway and the hospital files, 94 of the women who completed the clinical trial were alive and without known relapse on November 1, 1993. The women were contacted by mail and asked to complete a questionnaire package similar to the one they completed during the clinical trial. Seventy-nine women (84%) returned the questionnaires after one reminder. One woman had relapsed before she received the questionnaires. Two women had moved to an unknown addresses. Three women replied that they did not wish to participate, one because of a new disease. The other reasons for non response (9 women) are not known. The characteristics of the respondents are presented in Table 1.

The women were asked to record the number and consistency of bowel movements and the use of antidiarrhoeal medication (loperamide) daily for one week. A diary card was used and bowel movements were classified as hard, normal, soft or watery. The bowel movements were scored according to Table 2. Diarrhoea was defined as a scale score ≥ 2. Significant late radiation injury was defined as bowel complications requiring hospitalization and/or surgery. Information of this kind was collected from the hospital files. The women were asked to record their present weight. Body mass index (BMI) (weight (kg)/height (metres)^2) was calculated and a BMI < 20 was used to identify thin physique (17).

EORTC QLQ-C36 (18) was used to measure the women's HRQOL, because this questionnaire was used in the clinical trial. The construction and response categories of the EORTC QLQ-C36 have been described elsewhere (18). Briefly, the questionnaire covers physical functioning (PF), role functioning (RF), fatigue (F), nausea/vomiting (NV), emotional functioning (EF), social functioning (SF), global health status (QoL) and physical symptoms. A diagnosis-specific module for gynaecological malignancies focusing on disease- and treatment-related symptoms was included. This module is presented in an earlier paper (16). The PF and RF scales have dichotomous response choices and the QoL scale has a modified visual analogue scale format. All other items have four response choices from 1 'not at all' to 4 'very much'. A high score for a symptom item represents a high level of problems. Response categories 3 and 4 on these items were regarded as indicators of clinically significant symptom levels and used to classify 'cases'. A similar definition has been suggested elsewhere (19). The item on diarrhoea was dichotomized. The response categories 1 and 2 were set to indicate no diarrhoea and the response categories 3 and 4 to indicate occurrence of diarrhoea. The scale reliability was satisfactory for most of the EORTC QLQ-C36 scales with a Cronbach's alpha ranging from 0.7 to 0.9. The lowest reliabilities were found in the RF and the NV scales.

The scores on the EORTC QLQ-C36 were compared with reference data from a random sample of 949 Norwegian women aged 19–80 years (6). The reference data were obtained by using the EORTC QLQ-C30 (+ 3) (20). The EORTC QLQ-C36 is an earlier version of the C-30 (+ 3)

Table 1

Main sociodemographic and clinical characteristics of the women in the intervention (43 women) and the control (36 women) group

		Intervention group		Control group	
		No	(%)	No	(%)
Age (yrs)	<50	4	(9)	8	(22)
	50–59	10	(23)	8	(22)
	60–69	16	(37)	7	(19)
	>70	13	(30)	13	(36)
Social status	Single	10	(23)	10	(28)
	Married, living with partner	33	(77)	26	(72)
Work	Working at a paying job	16	(37)	20	(56)
	Working at home, retired	27	(63)	16	(44)
BMI, pre-treatment	10–20	1	(2)	5	(14)
	20–30	36	(84)	26	(72)
	>30	6	(14)	5	(14)
BMI, 3–4 years after radiotherapy	10–20	–	–	2	(6)
	20–30	37	(86)	27	(75)
	>30	6	(14)	7	(19)
Diagnosis	Cervical cancer	23	(53)	22	(61)
	Endometrial cancer	20	(47)	14	(39)
Stage	I	14	(33)	9	(25)
	IA	1	(2)	1	(3)
	IB	9	(21)	7	(19)
	II	5	(12)	5	(14)
	IIA	1	(2)	3	(8)
	IIB	13	(31)	10	(28)
	Not specified	–	–	1	(3)
Cell type	Adenocarcinoma	22	(51)	16	(44)
	Adenosquamous	2	(5)	3	(8)
	Squamous cell carcinoma	18	(42)	16	(44)
	Other	1	(2)	1	(3)
Grade	Well differentiated	–	–	2	(5)
	Moderately differentiated	23	(53)	18	(50)
	Poorly differentiated	11	(26)	16	(49)
	Moderately to poorly	5	(12)	–	–
	Not specified	2	(5)	2	(6)
Treatment	Surgery prior to radiotherapy	25	(58)	20	(56)
	Radium application	11	(26)	10	(28)
	Brachytherapy	8	(19)	7	(19)
Other diagnosis	Hypertension	8	(19)	5	(14)
	Diabetes mellitus	2	(5)	3	(8)

questionnaire. Identical scales (RF, SF, QoL, NV) and symptom items were compared. The fatigue scale in the C-36 version included five items. Three of these items are included in the C-30 (+ 3) fatigue scale and they were used to calculate the scale scores. One item in C-36 measures pain. This item was compared with an identical item in the C-30 (+ 3) version. In the later versions of the QLQ-C30 (+ 3), the scales and single items have been transformed linearly to a 0 to 100 scale (20). In order to compare data such a transformation has been performed also for QLQ-C36. A high score for a functional scale represents a high/healthy level of functioning while a high score for a symptom scale/item represents a high level of symptoms/problems.

Statistical analysis

The SPSS for Windows V8.0 program was used for the statistical analyses. Internal consistency (scale reliability) was assessed by the Cronbach's alpha coefficient (21). Values exceeding 0.70 were considered as satisfactory, a value between 0.60 and 0.70 as questionable (22). T-tests

Table 2

Diarrhoea scale

0	No change in bowel movements
1	Increase of 1–3 bowel movements a day, normal or soft
2	Increase of 4–6 bowel movements a day, all watery bowel movements
3	Increase of >6 bowel movements a day

Table 3

Occurrence of diarrhoea and use of anti-diarrhoeal medication 3–4 years after radiotherapy

	Intervention group	Control group	p-value[1]
	No. (%)	No. (%)	
Diarrhoea, scale n =	43	33	
No change	27 (63)	5 (45)	
Increase in bowel movements	16 (37)	16 (48)	
Diarrhoea	0 (–)	2 (6)	0.12
Diarrhoea			
QLQ-C36 item[2] n =	43	36	
No diarrhoea	40 (93)	28 (78)	
Diarrhoea	3 (7)	8 (22)	0.05
Antidiarrhoeal medication[3]	3 (7)	4 (11)	0.43

[1] χ^2
[2] Dichotomised scale.
[3] Number of patients using antidiarrhoeal medication.

and χ^2 statistics were used to perform bivariate analyses. Univariate analyses were performed by χ^2 statistics. Multivariate analyses were performed by ANOVA with multiple classification analysis (MCA) and adjusting for age. Owing to multiple comparisons, the level of statistical significance was set at 0.01. When analysing the recorded bowel movements and use of antidiarrhoeal medication, the significance level was set at 0.05.

RESULTS

Intestinal side effects

According to the hospital files four women (5%) had experienced significant late radiation injury, two in each group. One of the women in the intervention group had experienced ileus, and one had obstructions of the small intestine. In the control group one had experienced ileus and one had complications in both the rectum (WHO grade I–II) and urinary bladder (WHO grade II). No statistically significant differences between the two groups were found regarding diarrhoea and use of antidiarrhoeal medication (Table 3). None of the women in the intervention group and two (6%) in the control group were classified to have diarrhoea when using the diarrhoea scale (ns). Both had reported diarrhoea during radiotherapy and were taking antidiarrhoeal medication. Three women (7%) in the intervention group had used antidiarrhoeal medication compared with four (12%) in the control group (ns) (Table 3). Two women in the control group had used one or more tablets per day (ns).

According to the QLQ-C36 one of the most common symptoms at 3–4 years was diarrhoea. The mean scores on diarrhoea differed between the two groups, 19.4 (SD = 25.4) in the intervention group and 29.6 (SD = 27.3) in the control group, though not statistically significant ($p = 0.09$). Three women (7%) in the intervention group and eight (22%) in the control group scored 3 or 4 on the item concerning diarrhoea ($p = 0.05$) (Table 3). In Table 4 we show the impact of acute radiation diarrhoea, as measured by the QLQ-C36, on occurrence of late intestinal symptoms. In the intervention group there was no statistically significant connections between acute and late side effects. In the control group, however, a high score on the diarrhoea scale during radiotherapy was associated with a high score 3–4 years after radiotherapy ($p < 0.05$). No statistically significant connections were found with respect to the impact of diabetes mellitus, hypertension and thin physique (BMI < 20) on occurrence of late intestinal side effects.

Two cases (2%) of significant constipation were reported in the intervention group, but none in the control group (ns). One woman (2%) in the intervention group

Table 4

Impact of diarrhoea during radiotherapy as measured by the EORTC QLQ-C36 on occurrence of diarrhoea 3–4 years after radiotherapy

		Diarrhoea during radiotherapy								
		Intervention group n = 42				p-value	Control group n = 36				p-value
		Not at all	A little	Quite a bit	Very much		Not at all	A little	Quite a bit	Very much	
		n (%)	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	n (%)	
Diarrhoea, 3–4 years after radiotherapy	Not at all	2 (100)	11 (44)	8 (62)	2 (100)		4 (100)	5 (36)	3 (21)	1 (25)	
	A little	–	13 (52)	4 (31)	–		–	8 (57)	6 (43)	1 (25)	
	Quite a bit	–	–	1 (8)	–		–	1 (7)	5 (36)	1 (25)	
	Very much	–	1 (4)	–	–	ns	–	–	–	1 (25)	<0.05
	n (%)	2 (5)	25 (59)	13 (31)	2 (5)		4 (11)	14 (39)	14 (39)	4 (11)	

Table 5

Mean scores of the EORTC Core Quality of Life Questionnaire scales and items 3–4 years after start of treatment

	Intervention group (n = 43) Mean	Control group (n = 36) Mean	p-value	Gyn. cancer (n = 79) Mean[5]	General population (n = 949) Mean[5]	p-value
Functional scales						
Physical (PF)[1]	76.9	81.5	ns	79.2	–	
Role (RF)[1]	77.4	76.5	ns	81.5	90.6	<0.01
Emotional (EF)[2]	74.9	77.2	ns	76.0	–	
Social (SF)[2]	86.8	81.4	ns	86.0	83.5	ns
Global health status (QoL)[3]	73.0	74.3	ns	75.8	71.7	ns
Symptom scales/items[4]						
Fatigue	24.5	22.8	ns	22.5	32.9	<0.01
Nausea and vomiting	4.6	5.1	ns	4.5	5.3	ns
Appetite loss	7.7	8.3	ns	7.6	9.5	ns
Diarrhoea	19.4	29.6	ns	23.8	9.5	<0.01
Constipation	11.6	10.5	ns	8.4	14.9	ns
Pain	19.4	21.3	ns	17.5	27.2	<0.01
Insomnia	17.8	29.6	ns	19.2	26.0	ns
Financial difficulties	11.6	15.7	ns	12.5	10.9	ns

[1] Score range 1–2, high scores represent a high/healthy level of functioning.
[2] Score range 1–4, high scores represent a high/healthy level of functioning.
[3] Score range 1–7, high scores represent a high/healthy level of functioning.
[4] Score range 1–4, high scores represent a high level of symptomatology/problems.
[5] Adjusted for age by MCA.

experienced substantial nausea and vomiting compared with none in the control group (ns).

Health-related quality of life

No statistically significant differences between the intervention group and control group were found with respect to HRQOL. As no differences between the two groups were found and both groups were small, they were combined when comparing with data from the general population. The means of the subscales and single items are presented in Table 5. The scores for cancer patients were lower than those for the general population on the role-functioning scale (RF). Seventeen (22%) of the cancer patients reported limitations in ability to perform work or household tasks. This was not associated with age and retirement. The former radiotherapy patients had more diarrhoea than in the general population, 23.8 versus 9.5 ($p < 0.01$). At the same time, they felt less fatigue, 22.5 versus 32.9 ($p < 0.01$), and reported less pain, 17.5 versus 27.2 ($p < 0.01$). The scores on the social functioning (SF) and the global health/quality of life (QoL) scales were similar to those in the general population.

Disease- and treatment-related symptoms

Frequent urination was reported by 8 women (19%) in the intervention group and 5 (14%) in the control group (ns). Ten (23%) women in the intervention group and 7 (19%) in the control group (ns) reported substantial pain in the lower back. This was an increase compared with pre-treatment registrations where respectively 6 (15%) and 3 (9%) women reported pain in the lower back ($p < 0.01$). Seven women in each group (16% and 19%) reported pain in other sites of the body (ns), mainly pain in the hips and the thighs. This was also an increase compared with pre-treatment ($p < 0.01$) when 3 women (7%) in the intervention group and 2 (6%) in the control group reported such pain. Eighteen patients (42%) in the intervention group and 7 (19%) in the control group were taking analgesics ($p < 0.05$). Respectively, 12 women and 4 women reported no help or little help from the medication.

In order to illustrate a possible clinical impact of frequently reported symptoms (diarrhoea, frequent urination, pain) on the functioning scales and fatigue, a comparison between scores among cases and non-cases was made (Table 6). The women who reported substantial pain in other parts of the body scored lower on the functioning scales, the global QoL scale and fatigue than the women regarded as non-cases. Substantial pain in the lower back was associated with deteriorated QoL and fatigue and substantial diarrhoea with deteriorated SF and fatigue. Frequent urination was not associated with deteriorated HRQOL.

DISCUSSION

This paper describes occurrence of late intestinal side effects and HRQOL in a relatively homogeneous group of women with carcinoma of the endometrium and cervix 3–4 years after the initial diagnosis and successful radiotherapy. The women had participated in a randomized clinical trial to evaluate the effect of a low fat, low lactose diet to prevent acute radiation-induced diarrhoea. During radiotherapy the intervention group had less diarrhoea than the control group (15). If diarrhoea during treatment should be a risk factor for late reactions, one should expect statistically significant differences between the two groups after 3–4 years.

No difference was found between the two groups with respect to occurrence of severe late complications such as intestinal obstruction and injury to the rectum. The incidence was about 5%, which is in accordance with other studies (7). In the control group there was a tendency towards more diarrhoea than in the intervention group, though not statistically significant. There was also a connection between acute and late diarrhoea in the control group, which was not found in the intervention group. This might indicate that the intervention group has benefited from the low fat diet and less diarrhoea during radiotherapy. One other possible explanation for the differences between the two groups may be that the women in the intervention group still used the low fat diet to regulate their bowel movements. Measurements of small intestine dysfunction have suggested that about 50% of former radiotherapy patients experience increased bowel frequency and have abnormal bile acid absorption (11). Metabolic studies have shown that a reduction in dietary fat from 100 g to 40 g per day may correct bile salt malabsorption (23).

Despite few symptoms of late intestinal side effects, the women had a higher level of bowel frequency than the general population. This was not reflected in deteriorated HRQOL at the group level. However, the subgroup of women with substantial diarrhoea rated their SF as low and reported more fatigue. This finding is not surprising, since persistent diarrhoea can influence the ability to maintain a normal social life, and fluid loss and malabsorption may produce fatigue. The presence of diarrhoea did not produce more emotional distress. Information may be important to reduce emotional distress (24), and the women joining this study were well informed about the possible side effects of radiotherapy.

Since the groups were small and late diarrhoea relatively rare, a statistically significant difference between the two groups would be difficult to detect. However, the tendency is interesting and may be of clinical importance. A new study with a greater statistical power could detect significant differences, if they exist.

The women seemed to have few emotional and physical problems and their HRQOL did not differ much from the population-based norms (6). This is consistent with other studies where the mental health in cancer survivors is evaluated (5, 25). The mean score on the RF scale was lower than that obtained from the general Norwegian population. Limitations in performing work and household tasks were reported by 22% of the women. This finding is consistent with others, indicating that health-related limitations in work and daily activities are common among cancer survivors (3, 25). Compared with a normal population, cancer survivors seem to experience limitation in the number of hours that they are able to work and in the ability to do strenuous activity (25). From this, one could expect a higher level of fatigue than in the general population, but this was not found.

Survivors of cervical and endometrial cancer suffer from poor partner relations and a poor body image (2). Sexual dysfunction is prevalent after gynaecological cancer (3, 26–28). Reports of overall evaluation of QoL are often good despite these losses (27). Since the scales in the EORTC-QLQ C-36 did not focus on body image and partner relations, these hypothesis were not examined.

Table 6

Relationship between treatment-related symptoms and mean score on functioning scales (emotional functioning (EF), role functioning (RF) social functioning (SF), physical functioning (PF) and global health status/quality of life (QL)) and fatigue and malaise (F)) 3–4 years after treatment. Response categories 3 and 4 on the items concerning treatment-related symptoms were used to classify cases. Levels of statistical significance between cases and non-cases are indicated with an asterisk ($p < 0.01$); t-test. Numbers in parentheses are standard deviation

	Diarrhoea		Frequent urination		Pain in the lower back		Pain in other sites of the body	
	Cases (n = 11)	Non-cases (n = 68)	Cases (n = 13)	Non-cases (n = 65)	Cases (n = 17)	Non-cases (n = 61)	Cases (n = 14)	Non-cases (n = 62)
PF	75.7 (19.1)	79.7 (22.1)	72.6 (21.5)	80.7 (21.6)	70.5 (19.8)	81.1 (21.7)	62.6 (21.5)*	83.6 (20.2)*
RF	77.3 (34.4)	76.9 (38.6)	73.1 (43.8)	78.2 (36.9)	50.0 (50.0)	84.4 (29.9)	28.6 (42.6)*	89.0 (26.4)*
EF	68.6 (19.2)	77.1 (12.9)	73.7 (19.1)	76.2 (13.1)	71.6 (15.3)	77.1 (13.8)	66.7 (19.1)*	78.2 (12.2)*
SF	62.1 (25.9)*	88.0 (19.8)*	75.6 (27.7)	87.0 (20.2)	79.4 (22.5)	86.1 (22.6)	71.4 (24.0)	87.7 (21.5)
QL	59.1 (23.4)	76.0 (25.6)	57.7 (26.0)	77.3 (24.6)	48.5 (23.6)*	80.5 (22.1)*	45.2 (27.1)*	81.7 (18.4)*
F	39.2 (16.1)*	21.2 (16.8)*	31.8 (20.0)	21.5 (16.9)	37.1 (20.7)*	19.7 (15.0)*	45.6 (22.1)*	18.6 (12.5)*

However, in forthcoming studies assessing QoL in gynaecological cancer, sexuality ought to be measured.

The women with substantial pain in the lower back and in other parts of the body rated their global QoL as low. This is in accordance with other studies showing that patients experiencing a heavier symptom burden tend to rate global QoL lower (19, 29). Presence of pain in other parts of the body, mainly the hips and thighs, was associated with more emotional distress, fatigue and deteriorated functioning. Since pain clearly was associated with deterioration in HRQOL, it was worrying that as many as 64% of the women who took analgesics reported little or no relief from pain, which indicates inadequate or inappropriate medication. However, when looking at the general pain item in the QLQ C-36, the former radiotherapy patients experienced less pain than the general population. This finding conflicts with the patients' report on the site-specific pain measured in the disease-specific module. Such a finding might be interpreted as a problem related to the measures, thereby invalidating either the general pain item or the site-specific item. However, it could also indicate that patients interpret the general pain question "Have you had pain?" differently from the site-specific question. Our clinical experience indicates that the latter is true. However, more research is necessary to investigate how pain following treatment can be optimally measured. Compared with pre-treatment, an increase in pain in the lower back and other parts of the body was seen. It is reported that radiation-induced insufficiency fractures of the female pelvis are a frequent complication of standard radiation therapy for cervical carcinoma (30). The reported localization of pain could indicate the presence of such fractures, but Norwegian population data show that low back pain and hip symptoms are common among middle-aged to elderly women (31).

In conclusion, as a group, women with carcinoma of the endometrium and cervix suffered from few treatment and/or disease-related side effects 3–4 years after radiotherapy. However, increased frequency of bowel movement was common. Presence of substantial diarrhoea affected HRQOL negatively and may interfere with nutrient absorption. Since our data indicated that the women who had followed a low fat diet during radiotherapy had less diarrhoea, nutritional guidance may be of importance. Pain in the lower back, hips and thighs was common, and a considerable proportion of these women did not seem to receive optimal pain treatment.

ACKNOWLEDGEMENTS

The authors thank the clinical staff of the Department of Gynaecology at The Norwegian Radium Hospital for their cooperation. This study was supported by a research grant from the Norwegian Cancer Society.

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Appendices

URN:NBN:no-2118

URN:NBN:no-2118

Appendices

I. EORTC Core Quality of Life Questionnaire 36 item version: EORTC QLQ-36, with the treatment specific module.

II. Form for registration of bowel movements.

URN:NBN:no-2118

Questionnaire

We are interested in some things about you and your health. Please answer all the questions yourself by circling the number that best applies to you. There are no 'right' or 'wrong' answers. The information that you provide will remain strictly confidential.

Please fill in your initials :.....

Your birthdate (Day, Month, Year) :.....

Today's date (Day, Month, Year) :.....

FOR ADMINISTRATION ONLY

1 | 1 | 5 | 8 | 6 | 1 |

6 | | | |

9 | | | | | | |

15 | | 1 | 7 | 2 | 0 | | |

	No	Yes	
1. Can you do hard activities, like moving heavy furniture?	1	2	22
2. If you wanted to, could you run a short distance?	1	2	23
3. Do you have any trouble taking a long walk?	1	2	24
4. Do you have any trouble walking a short distance?	1	2	25
5. Are you in bed or a chair for most of the day?	1	2	26
6. Do you have to stay indoors most of the day?	1	2	27
7. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	28
8. Are you limited in any way in doing your work or household jobs?	1	2	29
9. Are you completely unable to work at a job or do household jobs?	1	2	30

DURING THE PAST WEEK :

	Not at All	A Little	Quite a Bit	Very Much	
10. Were you short of breath?	1	2	3	4	31
11. Have you had pain?	1	2	3	4	32
12. Did you need to rest?	1	2	3	4	33
13. Have you felt ill?	1	2	3	4	34
14. Have you had trouble sleeping?	1	2	3	4	35
15. Have you felt weak?	1	2	3	4	36
16. Have you lacked appetite?	1	2	3	4	37
17. Have you felt nauseated?	1	2	3	4	38
18. Have you vomited?	1	2	3	4	39
19. Have you been constipated?	1	2	3	4	40
20. Have you had diarrhea?	1	2	3	4	41

Please go on to the next page.

DURING THE PAST WEEK :

	Not at All	A Little	Quite a Bit	Very Much	
21. Were you tired?	1	2	3	4	42 ☐
22. Have you had difficulty in concentrating or remembering things?	1	2	3	4	43 ☐
23. Could you sit at ease and feel relaxed?	1	2	3	4	44 ☐
24. Have you lost interest in your appearance?	1	2	3	4	45 ☐
25. Have you felt restless as if you had to be on the move?	1	2	3	4	46 ☐
26. Did you look forward with enjoyment to things?	1	2	3	4	47 ☐
27. Did you get sudden feelings of panic?	1	2	3	4	48 ☐
28. Could you enjoy a good book or radio or television program?	1	2	3	4	49 ☐
29. Have you felt tense or 'wound up'?	1	2	3	4	50 ☐
30. Could you laugh and see the funny side of things?	1	2	3	4	51 ☐
31. Were you physically well?	1	2	3	4	52 ☐
32. Has your condition interfered with your family or social life?	1	2	3	4	53 ☐
33. Has your medical treatment interfered with your family or social life?	1	2	3	4	54 ☐
34. Has your condition or treatment caused you financial difficulties?	1	2	3	4	55 ☐

FOR THE FOLLOWING QUESTIONS PLEASE CIRCLE THE NUMBER BETWEEN 1 AND 7 THAT BEST APPLIES TO YOU

35. How would you rate your overall physical condition during the past week?

1	2	3	4	5	6	7	
Very Poor						Excellent	56 ☐

36. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7	
Very Poor						Excellent	57 ☐

Please go on to the next page.

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week.

DURING THE PAST WEEK :

	Not at All	A Little	Quite A Bit	Very Much	
37. How much did you cough?	1	2	3	4	58 ☐
38. Have you had a sore mouth or tongue?	1	2	3	4	59 ☐
39. Have you had pain like during menstruation?	1	2	3	4	60 ☐
40. Have you had vaginal discharge or bleedings?	1	2	3	4	61 ☐
41. Have you felt dizzy?	1	2	3	4	62 ☐
42. Have you had pain in your back?	1	2	3	4	63 ☐
43. Have you felt preassure in the pelvic area?	1	2	3	4	64 ☐
44. Have you had headache?	1	2	3	4	65 ☐
45. Have you felt preassure on rectum?	1	2	3	4	66 ☐
46. Have you had pain in your stomach?	1	2	3	4	67 ☐
47. Were you short of breath	1	2	3	4	68 ☐
48. Have you urinated frequently?	1	2	3	4	☐
49. Have you had burning urination?	1	2	3	4	☐
50. Have you had pain in your chest?	1	2	3	4	☐
Have you had pain in other parts of your body?	1	2	3	4	☐

If yes, where? _____

Did you take any medicine for pain?

1 No
2 Yes - how much did it help? 1 2 3 4 ☐☐

PLEASE CHECK TO MAKE SURE THAT YOU HAVE ANSWERED ALL OF THE QUESTIONS ☐☐☐☐☐☐

Please use the space below for any additional comments you may have :

FOR ADMINISTRATION ONLY

1 | 1 | 5 | 8 | 6 | 1 |

6 | | | |

9 | | | | | | |

15 | | 1 | 7 | 3 | 0 | 1 | |

1. How long did it take you to complete the questionnaire?

   _____ MINUTES

22 | | | |

2. Did anyone help you to complete the questionnaire?

   NO

   YES, WHO PROVIDED YOU WITH HELP? _____

25 | |

3. Were there questions that you found confusing or difficult to answer?

   NO

26 | |

   YES (please list below the number of the question(s) that you found confusing or difficult to answer).

   question number(s) : ___, ___, ___, ___, ___, ___, ___

4. Were there questions that you found upsetting?

   NO

27 | |

   YES (please list below the number of the question(s) that you found upsetting).

   question number(s) : ___, ___, ___, ___, ___, ___, ___

5. Please use the space below if you have other comments about the questionnaire.

   _____

   _____

   _____

   _____

URN:NBN:no-2118

ID.NR _____ **Oppgi nåværnde vekt _____ kg**

REGISTRERING AV AVFØRINGSHYPPIGHET OG BRUK AV STOPPENDE MEDIKAMENTER

Registreringen skal skje over en uke.
Sett et kryss i den rubrikken som passer best hver gang du har avføring.
Noter også hvor mange stoppende tabletter du eventuelt bruker pr.dag.

	AVFØRINGSREGISTRERING						STOPPENDE MEDIKAMENTER		
DAG	**Dato**	**Ingen avføring**	**Hard**	**Normal**	**Bløt**	**Vannaktig**	**Imodium**	**Opiums-dråper**	**Annet**
MANDAG									
TIRSDAG									
ONSDAG									
TORSDAG									
FREDAG									
LØRDAG									
SØNDAG									

Kommentarer:

I tilfelle du benytter andre stoppende medikamenter, hva slags?