SMALL BOWEL AND RECTAL TOXICITY AFTER PELVIC RADIOTHERAPY

HISTOPATHOLOGICAL DEVELOPMENT, THE INFLUENCE OF AGEING AND MODULATION BY CONFORMAL TREATMENT

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SCHADE AAN DUNNE DARM EN ENDELDARM NA BESTRALING VAN HET KLEINE BEKKEN

HISTOPATHOLOGISCHE ONTWIKKELING, DE INVLOED VAN VEROUDERING EN REGULATIE DOOR MIDDEL VAN CONFORMATIE THERAPIE

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CHAPTER 1

GENERAL INTRODUCTION

1.1. Cancer incidence and the influence of ageing

Throughout history, cancer has been one of the major causes of death. It has been estimated that in the western world approximately one in three people will develop some kind of cancer during their lifetime, and one in five will die of it.

Longevity is associated with prolonged exposure of somatic cells to environmental carcinogens leading to carcinogenesis in these ageing cells [40]. Therefore, cancer is predominantly a disease related to old age. In The Netherlands, the number of persons over 85 years of age increased from 99.000 in 1976 to 203.000 in 1995 (an increase of 105 %). It is predicted that by the year 2015 the total population living in The Netherlands will have increased by 8.4%, from 15.4 million in 1994 to 16.7 million [4,34]. However the proportion of the population more than 65 years of age is expected to grow much faster (45%), although the proportion of persons of 85 years and older will remain the same. In view of the demographic developments, the number of cancer cases can be expected to increase dramatically in the near future. Compared to 1994, for 2015 an increase varying from 30-60 % for cancer of the colon, prostate and breast has been predicted [5].

1.2. Definition of senescence

The physiological age of a person is poorly reflected in the chronological age, but the chronological age may be used as a frame of reference. Two chronological landmarks, that is the ages of 70 and 85 years, seem appropriate. Seventy years may be considered as the lower boundary of senescence, because the age-related changes start increasing sharply between 70 and 75 years [1]. Eighty-five years of age may be considered borderline for the risk of frailty, because hearing and vision deterioration cause functional dependence in the majority of persons beyond this age [18] and dementia is present in more than 50% of the individuals over 85 years [8].

1.3. Treatment of cancer and the application in the older patient

Despite the significant progress in the treatment of malignant tumors in the last decennia, still 50% of the patients cannot be cured. The 3 main modalities in treatment of cancer are surgery, radiotherapy and chemotherapy. The first two are generally used alone or in combination in local or locoregional disease. Chemotherapy is applied in principle when tumor cells have metastasized from the (primary) tumor site to other parts of the body as well as in hematological malignancies. Currently, in many patients the different modalities are combined

in (neo)adjuvant settings sequentially or even concurrently in order to improve the treatment outcome.

Older patients with cancer are frequently treated less aggressively than their younger counterparts and are less likely to receive combined modality therapy [10,28]. Patients over the age of seventy-five years are often excluded from participation in clinical trials because of concerns regarding toxicity [6,11,39]. Kearney e.a. [23] evaluated in a descriptive study the oncology health care professionals' attitude towards elderly people. It appeared that, regardless of gender, specialty and clinical experience of the professionals, they had negative expectations on tolerance for cancer treatments and clinical outcome in elderly patients. Another reason for undertreating older patients is the belief that tumors are more indolent in the elderly than in younger patients and have a lesser effect on life expectancy. However, analyses of tumor stage distribution by age and of survival rates of older patients who received less aggressive therapy do not support this hypothesis [6,12,38].

1.4. Radiotherapy

Radiation therapy is used in about 50% of all cancer patients. The treatment aims include cure (curative radiotherapy), a prolongation of the progression free interval, and/or the palliation of symptoms (palliative radiotherapy). Ionizing radiation with e.g. high energy photons, electrons or protons are aimed at the tumor and the regions with subclinical disease. It causes damage to the DNA in the constituent cells of the tumor. If the DNA has been sufficiently damaged, the duplication is impeded and cell death ensues at a subsequent cell division. Normal tissues are mostly able to repair the sublethal damage inflicted to its DNA; cell division is delayed until the DNA is repaired. In general, the repair capacity of tumors is less than that of most normal tissues.

In curative radiotherapy, the total radiation dose is usually given in a so-called fractionated treatment to take advantage of the differences in repair between the tumor cells and normal tissues [13].

There are two ways the radiation can be applied: by brachytherapy or external beam therapy. In brachytherapy, small radioactive sources are placed in or close to the tumor, either by permanent inplants or by inserting catheters or applicators that temporarily hold the sources. The tight dose distributions restrict the application of brachytherapy to small primary tumors or to the booster treatment of only a part of the tumor. In the majority of cases, external beam radiotherapy is applied. With external beam radiotherapy, the dose is usually delivered by a linear accelerator.

In clinical practice, the radiation oncologist develops a treatment plan based on the characteristics of the patient, the tumor type, extend of the disease and

additional prognostic factors. The known tumor extensions and/or the tissues at risk for containing tumor cells are defined as the clinical target volume (CTV) [22]. To compensate for the effects of internal organ and external patient movement and inaccuracies in beam- and patient setup, a margin is added to the CTV. This volume is defined as the planning target volume (PTV). The radiotherapy treatment fields are planned as tightly as possible around the PTV. Computer planning systems enable three-dimensional (3D) treatment planning using a series of successive 2D images. These images are normally obtained by computed tomography (CT) or matched MRI scans. The CT images represent the patient anatomy and are used to outline the intended tumor region and critical organs. The conformation of individually shaped fields to the specific tumor volume with maximum sparing of the surrounding normal tissues in 3 dimensions is called 3D-conformal radiotherapy. After (virtual CT) simulation, the first dose (fraction) of radiation can be applied. Patient position is verified using an electronic portal imaging device (EPID).

1.5. Toxicity of radiotherapy with emphasis on small bowel and rectum

Despite modern techniques in radiotherapy (RT), irradiation of a tumor invariably involves exposure of adjacent structures and may result in significant morbidity. Normal tissue tolerance represents the main dose limiting factor. The small bowel is one of the most radiosensitive organs in the abdomen and is at risk for development of radiation injury during treatment of intra-abdominal, pelvic and retroperitoneal tumors. However, the majority of radiation injuries are seen in the rectum. Mostly, clinical presentation of late enteropathy occurs 6 months to 3 years after completion of therapy [7,16,26]. However, chronic changes occasionally develop in continuity with the acute stage of radiation injury. Presenting symptoms of late radiation enteropathy are mostly abdominal pain, intermittent diarrhea and constipation, sometimes progressing to symptoms of total or subtotal obstruction. In late radiation damage of the rectum, blood loss and mucous secretion can also be part of the symptomatology.

Histopathological examination of small bowel and rectum with radiation induced injury usually shows normal mucosal epithelium at 1-2 weeks after treatment. However, local ulceration's may persist for longer periods of time [16]. In the early stage, ulcers are usually small and shallow, but chronic ulceration's are often larger, with reactive fibrosis extending through the entire intestinal wall, causing scarring and stricture formation. Injury of small blood vessels is a prominent feature in radiation enteropathy. The morphologic changes of blood vessels have been divided into early, intermediate and late [25]. In the early phase (hours to a few days after exposure), an inflammatory

type of reaction with dilatation of the capillaries is seen [16]. The intermediate phase, beginning approximately 4 weeks after irradiation, is characterized by patchy destruction and obliteration of capillaries, destruction of endothelial cells and focal thrombosis. Plasma proteins accumulate in the blood vessel walls. This might be a possible cause of the hyalinization which is typical of late arterial lesions and which may progress to total occlusion. Whether acute and late intestinal effects are related to cell killing only [37], or that the impaired vascular function is the main cause of parenchymal atrophy [15,20,25], is still a controversial issue.

In the intestine, three different alterations result in deposition of collagen in the intestinal wall. In the subserosal layer, edema precedes deposition, suggesting that vascular injury and/or lymphatic obstruction are important pathogenetic factors [16,41]. Fibrosis of the submucosa is not preceded by visible edema and seems to be a direct effect of ionizing radiation on extracellular material and/or cells elaborating this material. Transmural fibrosis of the intestine seems to occur only secondary to chronic mucosal ulceration [17]. It is likely that loss of epithelial integrity exposes underlying stroma to the detrimental action of various intraluminal contents, eliciting a chronic inflammatory response which eventually leads to fibrosis.

1.6. The influence of ageing on radiation toxicity

One of the reasons for the obvious difference in cancer treatment of elderly and younger cancer patients is the fear that advanced age might be associated with reduced tolerance of normal tissues. Progressive reduction of functional reserve due to depletion of tissue stem-cells might enhance the damage of normal tissues and the risk of complications. Does age per se affect the sensitivity of normal tissues to radiation and lead to increased radiation reactions? So far, only limited data on this issue are available. Several clinical studies show no increased radiation toxicity of normal tissues with age. Radiotherapy of breast cancer showed no increased incidence of teleangiectasia, subcutaneous fibrosis, arm edema, or lung fibrosis in patients over the age of 60 years and no excess of other early or late skin reactions [2,3,36]. The effect of age on acute and late reactions during and after radiotherapy was reported by Pignon et al [31]. The investigators reviewed data of 1208 patients who had participated in five different studies of the European Organization for Research and Treatment of Cancer (EORTC). These patients received chest irradiation as monotherapy or in combination with surgery or chemotherapy. Acute radiation reactions (nausea, vomiting, dyspnea, esophagitis, weight loss and change in performance status) and late side effects (dysphagia, esophagitis, spinal cord damage, heart damage and radiologically detected changes) were compared in six age groups

from less than 50 years old to more than 70 years old. Acute normal tissue reactions were not higher in the older group than in the younger patients. The mean time for development of late complications, 13 months, was similar in all age groups. Forty percent of patients was free of late complications at 4 years, with no significant difference among the age groups. Two previous reports by the same authors on patients with head and neck and pelvic malignancies, treated according to several EORTC-protocols showed similar results [32,33]. The strenght of these studies is that all data were recorded prospectively and no dose adjustment was made for age. However, all patients had a good performance with little functional impairment. Other investigators have reported similar results in older patients receiving RT [9,21,35]. The available data on the sensitivity of normal tissues to RT in elderly patients strongly suggest that older patients with good functional status tolerate radiotherapy as well as younger patients, with tumor responses and survival rates quite comparable to those of younger groups. Data on older patients with considerable functional impairment are even more sparse, and no conclusions can be based on them.

1.7. Experimental data on ageing and tolerance of normal tissues

Limited experimental data are available addressing the influence of age on radiation sensitivity. Most studies concern early skin reactions in experimental animals and do not show an increase of radiosensitivity in older age [24,27,29]. Holt e.a. [19] observed a greater rate of proliferation of crypt cells in the duodenum, jejunum and ileum in senescent rats than in young mature animals. This increase in small intestinal cell production results from a combination of an increased percentage of cell cycling at any time and larger crypts. The proliferative zone appears to be much wider and extends much further up the crypt from the base in aging animals than in the young group. Hamilton [14] studied the regeneration of colon crypt cells in young and old mice after single dose and fractionated RT. The cell survival in the crypts after irradiation appeared to be identical, although the size of the regenerating crypts was larger in the old group. Most of the available data on the relation between aging and radiation tolerance of normal tissues concern acute reactions. Experimental data on the late effects of irradiation in relation to age are rare, especially for a radiosensitive organ as the intestine.

1.8. Application of conformal radiotherapy to reduce the hazards of radiation toxicity

Conformal radiotherapy enables the radiation oncologist to make an individual treatment plan, conformed to the specific tumor volume with maximal sparing of the surrounding tissues. The benefits can be used in two ways: first, reduction of the risk on normal tissue complications without reduction of the tumor control probability and, secondly, escalation of the dose to increase cure rates without increasing complication rates. Reduction of the risk on normal tissue toxicity is only possible if the mechanism of development of such toxicity as well as the different ways of healing of the the inflicted damage and the effects of an irradiated (part of the) volume of the organ are clearly understood. Understanding of the development of radiation injury makes modulation by radioprotective agents possible. In the light of the expected increase of elderly cancer patients who will need radiotherapy, more clinical and experimental data on the risk of normal tissue complication with older age are needed.

Furthermore, if we want to reduce the risk of toxicity of surrounding tissues, we can make use of all the technical improvements of the recent years for maximal sparing of the normal tissues. For 3D-conformal therapy, a definition of the CTV as precise as possible, based on all available information such as physical examination, surgical report and radiological findings, is needed. Consensus between radiation-oncologists about elective treatment of regional areas to be treated and their anatomical location, is extremely important. As is also stressed by Nowak et al. [30], a three dimensional CT-based target definition of elective regions has to be defined for each tumor site. Research on internal movement of the CTV by influence of breathing, filling of surrounding organs as well as the external positioning variation of the patient is needed to define the minimal margin for the PTV. Treatment planning techniques and linear accelerators equipped with multileaf collimators have been developed to obtain an isodose distribution as tight as possible around the PTV. Finally exact daily patient positioning, verification of patient set-up and off-line and/or on-line correction of the set-up is a prerequisite for conformal radiation treatment of cancer patients.

1.9. Purposes of this thesis

Small bowel and the rectum are two important dose limiting normal tissues in RT of frequently occurring malignancies such as cervical-, endometrial-, prostate- and bladder cancer. Especially as the incidence of these tumors increases with age and experimental data on (histopathological) effects of RT injury in relation to age are rare, histological studies on the development of

radiation induced changes in the rectum of young and old Wistar rats were performed. In Chapter 2 the early effects at 1, 2, 4, and 10 weeks after single doses of radiation are described. The late histological changes at 24 and 52 weeks after treatment are reported in Chapter 3.

The following chapters mostly concern reduction of toxicity by application of new treatment techniques which are applicable but not restricted to elderly patients. Because postoperative RT in node-positive cervical cancer is standard treatment in most oncology departments, we made an inventory of the CTV and field borders among several experienced Dutch radiation-oncologists and compared these to a reference CTV, based on lymphangiograms and CT-scans. In Chapter 4 the differences between physicians, the relationship to the reference volume and the implications for the margins between PTV and field borders are discussed. In Chapter 5 a 3D-conformal treatment technique for node-positive cervical cancer in comparison to the conventional treatment with parallel opposing fields is described. Sparing of the small bowel and to a lesser degree the rectum were the most important issues in this study.

A study on the reduction of irradiated small bowel volume using a belly board device in pelvic radiotherapy of gynecological cancer patients is described in Chapter 6 as well as the implications of this device for patient positioning. An off-line correction protocol was used in this study. In Chapter 7, the early experience regarding on-line set-up corrections in patients with gynecological tumors is reported. The general discussion (Chapter 8) summarizes the main findings of our studies and discusses the implications of these and further studies in clinical practice. Future directions of geriatric radiotherapy and application of conformal treatments in order to reduce the risk of toxicity, are discussed in relation to our observations.

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CHAPTER 2

EFFECT OF AGE ON RADIATION-INDUCED EARLY CHANGES OF RAT RECTUM. A HISTOLOGICAL TIME SEQUENCE

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Abstract.

Background and purpose: Radiation treatment of the elderly (> 75 years) is often modified due to an assumed decrease in normal tissue tolerance in this age group. Since more radiobiological data concerning normal tissue toxicity as a function of age are needed, a histological study of age related radiation changes of the rectum was performed.
Material and methods: The rectum of young and old female Wistar rats (12 and 78 weeks respectively) was irradiated with single doses of 22 Gy and 39 Gy. The field size was 1.5 × 2.0 cm. The animals were sacrified at 1, 2, 4 and 10 weeks after treatment. To evaluate radiation damage, 12 histological parameters were scored in four areas of the rectum. A total radiation injury score was calculated. The number of proliferative epithelial cells was evaluated by BrdU labeling.
Results: Some age related histological differences were observed; especially the incidence of ulceration and vascular occlusion was higher in the older group. In the low dose group of the older animals 60 % showed ulceration, which was 0 % for the young low dose animals. Severe vascular changes occurred early and were more extensive in older animals (4 weeks) than in the younger group (10 weeks). In the area adjacent to the treatment field cell proliferation increased significantly in older rats at 1 week after 22 Gy, which did not occur in the young group.
Conclusions: Discrete radiation-induced histological differences were observed between the rectum of young and old Wistar rats, especially in the development of ulceration and vascular changes. Although the survival of these Wistar rats in earlier studies was not affected by age [19], the impact of the observed histological differences for their importance in the long term is currently being investigated.

Introduction

In most radiotherapy departments, elderly patients constitute the majority of patients to be treated [1,25]. A further increase in the average age of cancer patients is expected for the next decades for demographic reasons due to improvement of general health care as well as the age-dependent incidence of most malignant tumors [11]. In the application of curative radiotherapy for elderly patients, the treatment is often modified, because of an assumed decrease in normal tissue tolerance in this age group. From clinical studies, evidence is accumulating that normal tissue toxicity of radiation therapy depends on the functional status of the normal tissues that surround the tumor and not or very little on chronological age [1,9,21,26]. Only limited radiobiological data are available regarding the influence of age on radiation sensitivity [26]. Since the rectum is an important dose-limiting organ in radiotherapy of urogenital tumors, which occur frequently in these age groups [8,10], a histopathological study was carried out. For this purpose the rectum of young and older rats was irradiated and histological changes were studied in time to obtain detailed information on the progression of rectal injury. In this study the results of the early time points (up to 10 weeks after treatment) are presented. Late changes with time points of 24 and 52 weeks are currently being investigated.

Materials and methods

Laboratory animals

Female Wistar rats, aged 12 and 78 weeks, were used (Harlam Zeist, the Netherlands). This allowed a follow up time of 52 weeks in the majority of animals.

They were housed under conventional conditions with food and water ad libitum in light controlled rooms (light on at 06.00 h, off at 18.00 h). The experimental protocol was approved by the Animal Ethical Committee of the University of Rotterdam. Upon arrival the rats continued on their previous diet and were allowed to recover fully, as judged by a return of body weight toward that on arrival. Young rats weighed approximately 220 g, whereas the older animals had an average weight of 350 g.

Experimental design

Forty female rats in each age group were irradiated with single doses, 20 with 22 Gy and 20 with 39 Gy. These doses represent the LD20 and LD80 level, respectively, for the clinical end point of a macroscopic megacolon (unpublished data). At 1, 2, 4 and 10 weeks after irradiation 5 rats of each irradiated group were

sacrified. For each time point 3 non-irradiated rats of the same age, housed under the same conditions and sacrificed simultaneously, acted as controls.

Irradiation procedures

The animals were anesthesized with Ketamine [Parke -Davis] intraperitoneal (30 mg/kg body wt. for young and 40 mg/kg body wt. for old rats) and Xylazine 2 % [Bayer AG] subcutaneous (5 mg/kg). The control animals were treated with the same anaesthesia and were sham-irradiated.

Irradiation of the rectum was performed with a Philips 250 RT Orthovolt X-ray machine, operating at 200 KV and 20 mA. The dose rate at the level of the rectum was 1.36 Gy/min for the young animals and 1.25 Gy/min for the older rats, due to the difference in skin- rectum distance as a result of overlying fat tissue. A Cu filter of 1 mm was used (HVL 1.6 mm Cu). The focus- skin distance was 30.5 cm. During irradiation, the head, thorax, upper abdomen and limbs were shielded with lead. The field size was 1.5 × 2.0 cm, with the lower border above the orifices of vagina and urethra to avoid acute epithelial toxicity of the tissues. Previous experiments with fluoroscopic evaluation of the field size have shown that the lateral borders of the field are located at the medial side of the hip joints.

Quality control was performed with thermoluminiscency dosimetry catheters (TLD) in the rectum of 50% of randomly assigned animals.

Proliferative cell labeling

To label proliferative cells, animals were given 50mg/kg body weight of 5-bromo-2'-deoxyuridine (BrdU) [Sigma], 45 minutes before sacrifice.

Histology

Following sacrifice of the animals the entire rectosigmoid (± 5 cm) was removed, examined macroscopically and fixed in 3.7 % formalin for maximal 24 hours. The specimen was sliced transversely in four pieces of 0.4 cm each. These four slices of the rectum were embedded in one block; a) between the anus and the irradiated area (0 - 0.4 cm), b) caudal part of the irradiated area (0.8 - 1.2 cm), c) cranial part of the irradiated area (1.2 - 1.6 cm) and d) above the irradiated area (3.1 - 3.5 cm). Three of these slices were marked with different colours of dye. The specimens were routinely processed and embedded in paraffin. Sections were cut 5 µm thick and stained with hematoxylin-eosin (HE), periodic acid Schiff + reagent (PAS+), Sirius red (SR) and resorcin fuchsin (RF) according to standard methods.

Immunohistochemistry

For immunohistochemical studies, antibodies recognizing the following antigens were applied: Collagen III (Coll III) [Biogenex], 5-bromo-2'-deoxyuridine (BrdU) [Becton Dickinson], neurofilaments (NF) [Dako] and S-100 protein [Dako].

Sections, 4 μm thick were reacted with appropriate dilutions of antibodies after blocking with H_2O_2 and antigen retrieval with citric acid. Antigens were visualised using a streptavidin-biotin peroxidase conjugate system [Biogenex].

Scoring system

Based on the Radiation Injury Score introduced by Hauer-Jensen and co-workers [16], a semiquantitative histopathologic radiation damage score appropriate for this experimental setting was developed and used to assess radiation injury. Parameters were chosen for the possibility to score them present or absent, for their representation of changes in the different layers of the colon wall (mucosa, submucosa, muscularis), and for their representation of acute as well as chronic injury (for instance ulceration versus squamous metaplasia). The various parameters as changes of epithelial cells, crypt distortion, discontinous muscular mucosae, mucosal ulceration, squamous metaplasia, hyperplasia, colitis glandularis cystica profunda and adenocarcinoma were scored present when observed in either part of the section (see also Figure 2-1 and 2-2). Parameters as hyalinization of blood vessel walls and occlusion of blood vessels were scored present when observed in one or more of the blood vessels of the section (see also Figure 2-3). Furthermore the lumen was scored normal if star shaped and abnormal if circular shaped. The thickness of the submucosa was scored normal or broadened in relation to the submucosa of the non-irradiated part of the rectum. For the radiation injury score (RIS) the scores of the above mentioned 12 parameters were summated.

For each animal these parameters were scored in all four pieces of the rectum. Within the treatment field, a parameter was considered to be present when observed in at least one of the two slices of the radiation field. To describe the extent of the radiation-induced changes, the presence of a parameter in both of the sections of the treatment field was evaluated separately.

All sections were evaluated by two investigators independently (M.J.J. O.-v.A. and M.L.F. v.V.) without access to the treatment code. Discrepancies were discussed and the final score was determined by consensus.

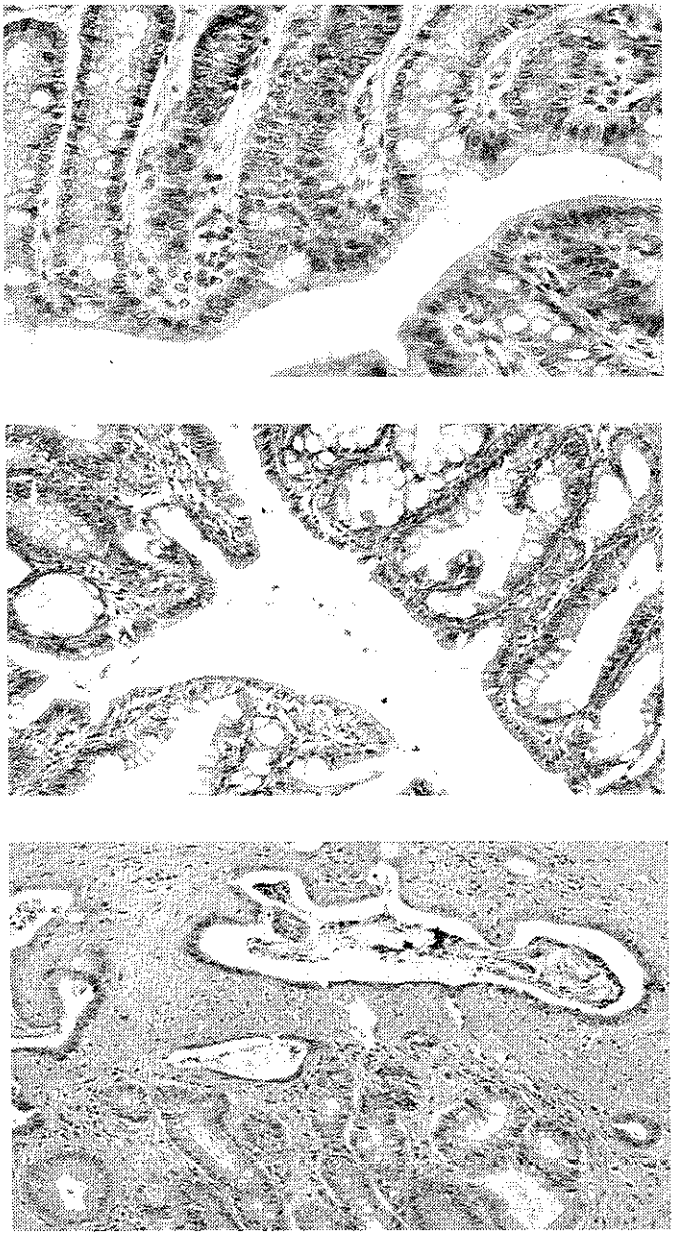
Proliferating cells were counted as the number of BrdU positive nuclei in 10 randomly selected crypts in all four sections. The cell counts obtained by the two investigators were averaged. Afterwards the mean of the two sections of the treatment field was calculated. Based on survival data of proliferating cells of large intestine after irradiation [2,3], we have analysed proliferation one week after treatment in more detail and compared these data with the control group and the later time points of 4 and 10 weeks after treatment.

Data analysis

The incidence of each histopathological parameter in all sections was calculated separately for each age group and each time point. Within the treatment field

incidences were calculated for presence in either one of the sections and separately for presence in both sections. A summation of all present parameters was calculated for each animal to obtain a quantitative injury score for the sections within the treatment field as well as for the sections above and below the field. Per group of animals the mean of the injury score (± sem) was calculated according to age, dose and time point.

Statistical comparison of data was performed with a logistic regression analysis for each histological parameter separately; for this purpose the data of all 4 time points were pooled together. The histological parameters were the dependent variables and dose and age were the independent variables in the analysis. The total injury score and the number of proliferating cells were compared by the analysis of variance test (ANOVA; single factor), using the MS Excell 97 program. In all cases, a significance level of 5 % was used.

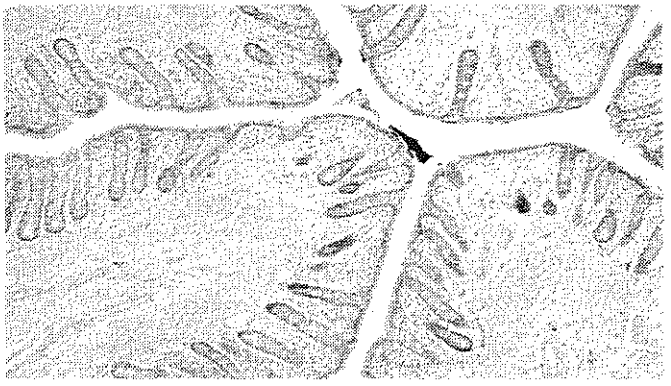


2-1A

2-1B

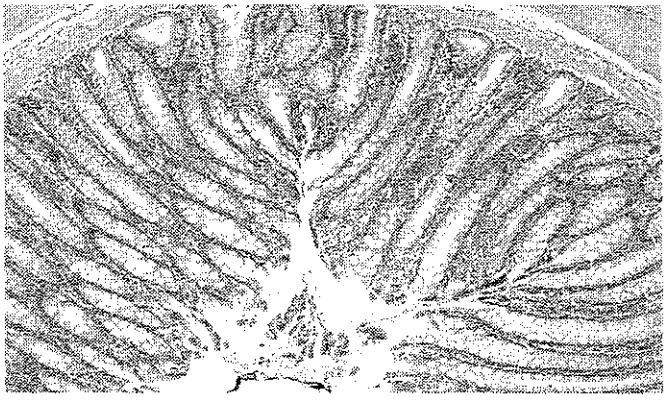
2-1C

Figure 2-1
Normal crypt architecture of the rectum of a young untreated animal (A), cryptdistorsion of a young animal after 22 Gy at 4 weeks (B) and colitis glandularis cystica profunda of a young rat after 22 Gy at 10 weeks (C). Hematoxylin-eosin staining. Magnification 100×(A), 200×(B) and 200×(C).



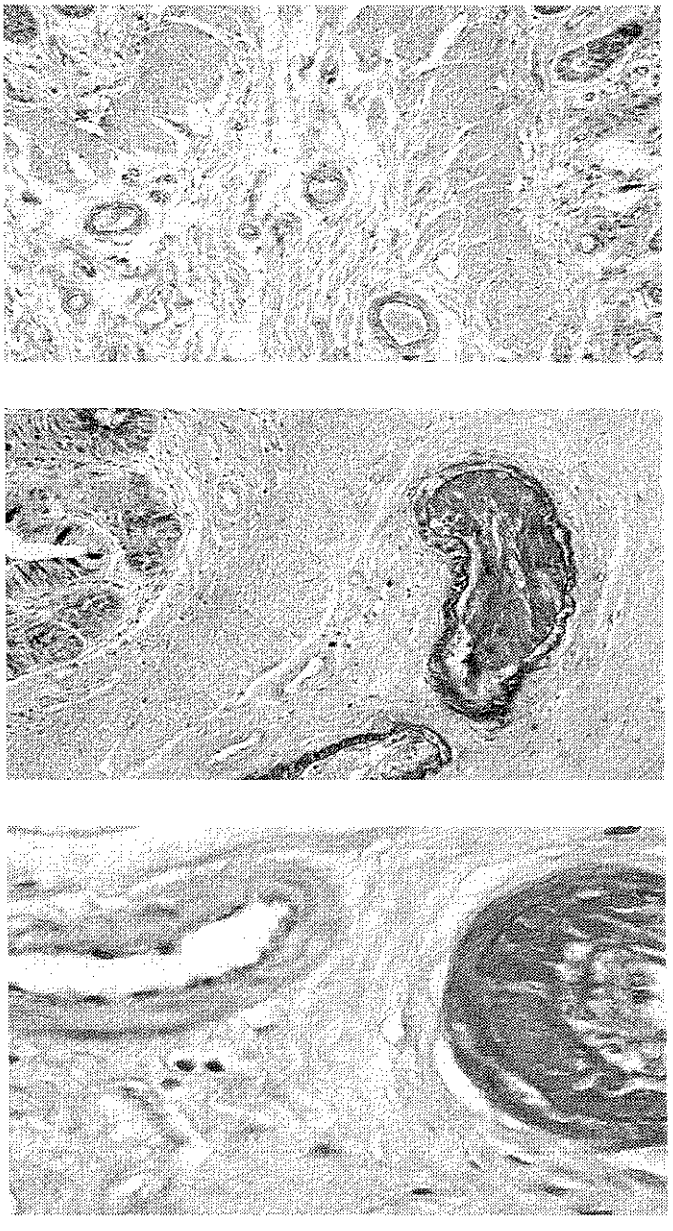
2-2A

2-2B



2-2C

Figure 2-2
Normal star shape of lumen of the rectum of a young untreated animal (A), ulceration with loss of crypts of a young animal at 4 weeks after 39 Gy (B) and hyperplasia of the section above the treatment field of the same animal (C). Hematoxylin-eosin staining, 50×.



2-3A

2-3B

2-3C

Figure 2-3
Normal blood vessels of the lamina propria of the rectum of an old untreated animal (A), occlusion and hyalinosis of the blood vessels of an old animal at 10 weeks after 22 Gy (B) and magnification of hyalinosis of one of the blood vessels of the same animal (C). Periodic acid Schiff+ staining, magnification 100×(A), 100×(B) and 400×(C).

Results

Dosimetry with TLD-measurements showed on average a small difference of minus 4.4 % (SD ±1.5) between measured and planned dose.

Control animals did not show any histopathological alterations at either of the four time points (injury score was 0), except for one animal of 78 weeks which showed an abnormal shape of the lumen and hyalinosis of the blood vessel walls.

Only one rat (of the older age group) died due to severe acute toxicity, i.e. ulceration of a major part of the mucosa within the treatment field, 3 weeks after a dose of 39 Gy. All other animals could be evaluated.

Incidences of all parameters, present at the different time points after treatment within one or more of the sections of the irradiated part of the rectum, are shown in Table 2-1.

Histopathological parameters

Below the irradiated area a normal star shaped lumen of the rectum was observed in nearly all animals (Figure 2-2A). An abnormal shape mainly concerned a circular shape of the lumen. As is shown in Table 2-1 an abnormal shape of the lumen frequently occurred after the high dose at 2 weeks and longer without significant differences between the young and old rats.

Disappearance or flattening of epithelial cells outside the irradiated area was observed in only one animal, at the anal part of the rectum at 1 week after 22 Gy. Within the irradiated area, after both doses, the incidence was maximal in both age groups at 1 and 2 weeks after treatment. These epithelial changes decreased at 4 and 10 weeks in the young rats, while the incidence of epithelial changes after a dose of 39 Gy was still maximal at 10 weeks in the older age group (difference for all time points summated was not significant).

Ulceration was observed in the irradiated area only (see Figure 2-2B). In the younger group no ulceration was observed after a dose of 22 Gy. In older rats however, ulceration was present after a dose of 22 Gy, already after 2 weeks and increased to an incidence of 60 % at 4 weeks (difference for all time points summated was not significant).

Changing of the architecture of crypts (crypt distortion) was observed in the irradiated area only (see Figure 2-1B). One week after irradiation, crypt shape was changed within the treatment field, corresponding with acute epithelial changes. These early changes of shape were not scored as crypt distorsion. At 2, 4 and 10 weeks irregular crypts were observed, repopulated with normal epithelial cells. Only these architectural changes were scored as crypt distortion. In cases with severe ulceration, no crypts were left, and distortion was not assessed.

Table 2-1.
Incidence of various histological parameters in the rectum of young and old rats within the treatment field, as well as hyperplasia in and/or rostral of the irradiated field, in relation to dose at 1, 2, 4 and 10 week(s) after treatment (RT). Total number of animals in each group was 5, except for the group of rats of 78 weeks after 39 Gy at 4 and 10 weeks; total evaluable number was 4 animals.[1]

Age (wks)/ Dose (Gy)	**12/ 22**				**78/ 22**				**12/ 39**				**78/ 39**			
Wks after RT	***1***	***2***	***4***	***10***	***1***	***2***	***4***	***10***	***1***	***2***	***4***	***10***	***1***	***2***	***4***	***10***
Abn. sh. lumen	1					1				5	3	3		3	2	1
Epith. changes	5	5	4	2	5	4	4	4	5	5	5	3	5	5	4	4
Muc. ulceration						1	3	1	1	4	4	3			4	3
Crypt distort.		5	5	5		4	5	5		3	3	1		2	4	3
Discon. musc.								2				3				2
Hyperpl.										3		3		1	1	
Hyalinosis			4	5	1		5	5			5	3			4	4
Occlusion				3			1	5				3			2	4
Incr. submuc.	1	3	4	2	5	2	5	2	5	5	5	3	5	3	4	3
Colitis gl. cyst				2			2	2								

[1] Histopathological parameters were abnormal shape of lumen, epithelial changes, mucosal ulceration, crypt distortion, discontinuous muscular mucosa, hyperplasia, hyalinization and occlusion of blood vessel walls, increase of thickness of submucosa and colitis glandularis cystica profunda. Metaplasia and carcinomas were not observed within these time points.

Crypt distorsion in one or both of the sections within the treatment field was observed in all animals after a dose of 22 Gy at 2, 4 and 10 weeks, regardless of age (Table 2-1). At 4 weeks after 39 Gy, crypt distortion was observed in 60 % of the young animals, which decreased to 20 % at 10 weeks. For the old rats this incidence was 100 % at 4 weeks, decreasing to 75 % at 10 weeks (difference for all time points summated was not significant).

A discontinuous muscularis mucosae, replaced by collagen or inflammatory infiltration, was observed in the irradiated area only, and only at 10 weeks after irradiation. In young animals this parameter was observed only after 39 Gy, while in old rats this discontinuity was observed after 22 Gy as well (difference for all time points summated was not significant).

Squamous metaplasia as replacement of columnar epithelium by squamous epithelial cells was not observed in any of the animals up to 10 weeks after irradiation.

Hyperplasia *rostral of* the irrradiation area (see Figure 2-2C) was observed in 60 % of the young animals after a dose of 39 Gy at 10 weeks after the treatment and not in the older group (difference not significant). The presence of this parameter corresponded with the macroscopic observation of a megacolon and partly with ulceration. In only two young animals ulceration was observed without adjacent hyperplasia and without macroscopic megacolon.

Thickening of the blood vessel wall by hyalinization in the lamina propria, the submucosa or the muscularis externa resulting in stenosis of the lumen was not observed outside the irradiated area. Hyalinization of the wall of blood vessels within the irradiated area (see Figure 2-3B and 2-3C) was observed after both doses, already at 4 weeks in both age groups. In the younger group a decrease to 60 % at 10 weeks was found while in the older group the incidence at 10 weeks was still maximal (difference for all time points summated was not significant).

In cases of extreme hyalinization, complete occlusion of one or more of the blood vessels in the section could occur (see Figure 2-3B). This phenomenon was not observed outside the irradiated area nor in the control animals. Occlusion of blood vessels occurred in the young animals only at 10 weeks (Table 2-1). In the older group, already after 4 weeks, occlusion occurred in 50 % of the animals after 39 Gy. Occlusion of vessels was more extensive in the older group; it was usually observed in both slices of the irradiated area. This is in contrast with the occlusion observed in the young group, which occurred mainly in only one of the sections within the treatment field ($p = 0.004$ at 10 weeks after treatment).

From 1 week after irradiation with either 22 Gy or 39 Gy, an increase in thickness of the submucosa of more than 100 % was already observed in both age groups within the irradiated part of the rectum, which decreased gradually in time. The distance between collagen fibres was enlarged, probably by edema. This occurred most frequently in both sections within the treatment field and after both dose levels.

As long as the rectum wall was not destroyed due to ulceration, ganglion cells were evenly distributed in each slide in all animals. Proliferation of neurofilaments was not observed.

There were no adenocarcinomas observed in this study. At 4 as well as 10 weeks after a dose of 22 Gy, colitis glandularis cystica profunda was found in 40% of the old animals. In the younger rats colitis glandularis cystica was observed in 40 % of the rats, after 22 Gy at 10 weeks only (see Figure 2-1C). After 39 Gy, this parameter was not observed in any of the animals.

Total radiation injury score

In Table 2-2 the mean summation of all parameters present per age group is shown for the irradiated area. The mean summation was significantly dose related for the young animals at 1, 2 and 4 weeks (p- value resp. 0.04, 0.003 and 0.03). For the young rats at 10 weeks, and for the older group as a whole, there was no significant relationship with dose.

The group of young animals at 10 weeks, treated with 39 Gy, showed a large standard deviation due to two animals with extensive damage while in the other animals of this group almost no changes were observed.

Analysis according to age groups indicated that the older group had a significantly higher total radiation score at 1 week after 22 gy ($p = 0.04$), while the younger group had a significantly higher total score at 2 weeks after 39 Gy ($p = 0.003$). At all other time points, there were no significant differences.

Number of proliferating cells

The mean number of proliferating cells per 10 crypts at one week after treatment is shown in Figure 2-4 for the different areas of the rectum. In comparison to the control animals, in the younger group a decrease of proliferating cells was observed within the treatment field, which was dose related (but not significant). In the older group however, an increase in proliferating cells was observed within the treatment field after 22 Gy (not significant). Furthermore, the number of proliferating cells in the adjacent unirradiated parts of the rectum increased significantly in the older group in comparison with the controls. Between the anus and the irradiation field this increase at 1 week was marked in the low and high dose group (p- value resp. 0.04 and 0.05). Rostral of the treatment field the proliferating cells also increased significantly in the old rats after 22 Gy and 39 Gy (p- value resp. 0.05 and 0.04). This phenomenon was not observed in the young animals.

Table 2-2.
Mean total radiation injury score (±SD) of all 12 histological parameters in the rectum of young and old rats, as assessed in the treatment field, in relation to dose and time after irradiation.

Age (wks)/ Dose (Gy)	12/ 0	78/ 0	12/ 22	78/ 22	12/ 39	78/ 39
1 week after RT	0	0	1.4 ± 0.5	2.2 ± 0.4	2.2 ± 0.4	2.0 ± 0.0
2 weeks after RT	0	0	2.6 ± 0.5	2.4 ± 1.7	4.6 ± 0.9	2.6 ± 0.5
4 weeks after RT	0	0.7 ± 1.2	3.4 ± 0.9	5.0 ± 1.4	5.0 ± 1.0	5.6 ± 1.1
10 weeks after RT	0	0	3.8 ± 1.6	5.2 ± 2.2	4.4 ± 4.0	6.0 ± 0.8

In Figure 2-5 the mean number of proliferating cells within the treatment field is shown for all time points. The control animals in the two age groups showed no differences in BrdU-positive cells. In the low dose group however the older animals not only showed an increase in proliferating cells in comparison with the young animals one week after irradiation, but also after 4 weeks (not significant). At 10 weeks no differences between young and old rats were observed anymore. The number of proliferating cells after 39 Gy was not assessed, because most of the animals developed extensive ulceration which did not permit evaluation of enough crypts.

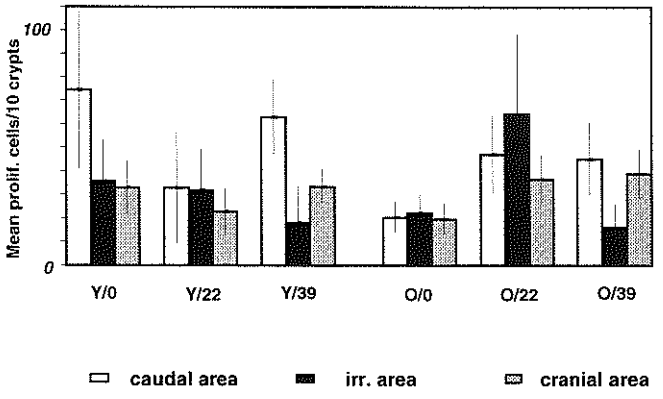


Figure 2-4
Mean number of proliferating cells per 10 crypts in the rectum of young and old rats at 1 week after treatment as a function of dose, and in relation to the position in the treatment field. Error bars indicate standard deviations.

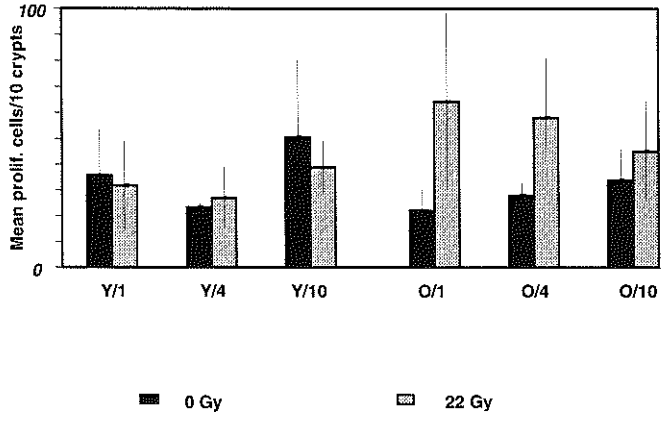


Figure 2-5
Mean number of proliferating cells per 10 crypts in the rectum of young and old control animals, as well as after 22 Gy, as a function of time after irradiation. Error bars indicate standard deviations.

Discussion

When cancer treatment of elderly patients is concerned many physicians tend to perform pretreatment selection. In radiation therapy the assumption that normal tissue tolerance decreases with increasing age is the basis for undertreatment in the elderly. Recent clinical studies on this subject strongly support the idea that tissue toxicity in patients older than 74 years is not increased compared with younger patients [9,21,22,26,30]. However only limited experimental data are available addressing the influence of age on radiation sensitivity. Studies on early reactions of normal tissues in experimental animals, usually studying skin reactions, do not indicate an increase of radiosensitivity with older age [12,17,18]. Despite the fact that the rectum is an important dose limiting organ in radiotherapy in pelvic malignancies, and radiation induced complications of the rectum can easily occur [5,13,14,15,16,20,23,24,29], studies on radiosensitivity of the rectum in relation with age are rare. In previous experiments with single doses of irradiation we demonstrated that there was no significant difference in the incidence of rectal stenosis resulting in a megacolon between young and older rats, using clinical and radiological endpoints. The latency period for development of rectal stenosis was 11.6 ± 6.2 weeks after irradiation in young rats and 15.0 ± 3.9 weeks after irradiation in older animals [19]. To study differences in reaction patterns between young and older rats and to elucidate the changes leading to this megacolon, rectal tissue was examined histologically 1, 2, 4 and 10 weeks after irradiation. Two radiation doses equivalent to the LD20 and LD80 were applied. We compared histological changes occurring after irradiation in young (12 weeks) and older (78 weeks) female Wistar rats.

Age related histological differences were observed, which were only trends and mostly not statistically significant in the analysis of the histological features separately. Probably due to the limited number of animals these trends were not significant. A different kind of reaction pattern might underlie these small differences. All young animals in the low dose group showed a continuous muscularis mucosae without ulceration, while in the low dose group of old animals both ulceration and a discontinuous muscularis mucosae was seen in up to 60 % of the rats. In contrast, in the high dose groups ulceration was observed already 1 week after irradiation in the young animals and only at 4 weeks after irradiation in the older group. Severe vascular changes (occlusion of blood vessels) occured significantly more often in both sections of the irradiated area and earlier in the older animals (4 weeks) than in the young animals (10 weeks). Dose dependency of damage was reflected in the total injury score, particularly in the young animals. The lack of dose-respons relationship in the older rats might be explained by the fact that the differences in injury score in these animals are above the discrimination threshold with doses of 22 and 39 Gy. Another explanation could be the limited number of animals, but this seems unlikely

because a significant dose-respons relationship was observed in the young groups at 1, 2 and 4 weeks after treatment. The injury score of the young animals was significantly higher than for the older rats, 2 weeks after irradiation in the high dose group ($p = 0.003$), but this tended to be lower at 4 and 10 weeks after irradiation.

The histological changes gave a few clues concerning the pathogenesis of a megacolon. A megacolon can have different etiologies: toxic, in the context of severe ulceration and bacterial infection [20], or obstructive as can be observed in innervation disorders [4]. Histologic signs of an innervation disorder were not seen in this study: ganglion cells were evenly distributed in each section as long as the rectum wall was not destroyed due to ulceration. Furthermore, neurofilament proliferation was not observed. All animals with a macroscopically observed megacolon had ulceration, but never outside the radiation area, making a toxic etiology improbable. Many animals with extensive ulceration did not develop a macroscopic megacolon within 10 weeks after treatment. According to Trott e.a. a high dose to the rectosigmoid does not inevitably lead to the fatal chronic radiation ulcer and large bowel obstruction, but several other factors, as fecal abrasion, might cause mechanical damage to the chronically atrophic mucosa, subsequently leading to ulceration and eventually to obstruction [27,28].

Ulceration is an important feature as it showed a clear dose, age and time dependency. It appeared to be reversible in some cases. We can only speculate on the factors determining the reversibility of ulceration. According to Trott e.a. [28] healing of a lesion occurs if no additional damage interferes, but healing of a manifest ulcer cannot reconstitute the original tissue structure, but leads to defective healing with scar formation, dystopic epithelial proliferation and thrombosed vessels. Vascular changes might influence the regenerative capacity of the mucosa. Especially vascular occlusion was observed more often in older rats.

Proliferation of epithelial cells is a factor of importance in wound healing. This was measured by BrDU labeling. Holt e.a. [6,7] showed that proliferative patterns in small intestine and colon have a broadened proliferative zone in senescent rats and that the small intestinal cell production can be enhanced by nutritional factors in comparison with young animals. In our study, the number of proliferative cells in the rectum adjacent to the treatment field in the older group increased one week after 22 Gy. However at 4 and 10 weeks after treatment differences in proliferating cellnumbers between young and old animals were not significant. The mucosa of young animals adjacent to the ulceration showed hyperplastic changes. Although these changes were not related to proliferation, the hyperplastic changes might reflect a regenerative proces of the mucosa in the younger animals.

Fibrosis did not occur in the course of this study. The mucosa and submucosa were thickened due to oedema but no increase in collagen fibres was seen. We did

observe the formation of fibrosis at later time points after irradiation. These later studies also elucidate whether the observed differences herald long term effects and are therefore of clinical importance, or represent only short term differences of reaction patterns.

Conclusion

In this study dose dependent radiation injury to the rectum was assessed with histopathological parameters. Several of these parameters especially ulceration, vascular occlusion and hyperplasia of the mucosa proved to be age dependent, but mostly not statistically significant. There might be a different age-related reaction pattern. Most differences between the two age groups were very subtle, supporting our hypothesis that there are no major differences in radiosensitivity with age.

The relevance of the observed histological differences should be investigated with longer follow up.

Acknowledgements

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CHAPTER 3

LATE HISTOPATHOLOGICAL CHANGES OF RAT RECTUM AFTER IRRADIATION: THE INFLUENCE OF AGEING

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Abstract

Background and purpose: Radiation treatment of the elderly (> 75 years) is often modified due to an assumed decrease in tolerance of normal tissues in these patients. There are only few radiobiological data available on radiation toxicity as a function of age. Therefore histological studies on age-related radiation changes of the rectum were performed. In our previous study on early changes, discrete histopathological differences between the rectum of young and old Wistar rats were observed [17]. To investigate whether these differences herald long term effects which could be of clinical importance, studies with longer follow up periods have been carried out.

Material and methods: The rectum of young and old female Wistar rats (12 and 78 weeks respectively) was irradiated with single doses of 22 Gy and 39 Gy with a field size of 1.5 × 2.0 cm. The animals were sacrified at 24 and 52 weeks after treatment. To evaluate radiation damage, 12 histological parameters were assessed in four areas of the rectum. A total radiation injury score was calculated. Furthermore, the number of endocrine cells in the different areas of the rectum was determined. Animals that died prematurely were also evaluated, provided autolysis did not interfer with the histology.

Results: The Radiation Injury Score (RIS) appeared to be dose related at 24 weeks but not at 52 weeks after treatment. An age related difference in the RIS was not observed. Most individual parameters did not show significant differences between young and old rats. However the incidence of mucosal ulceration and of vascular occlusion showed subtle differences, especially when the results of the previous studies with earlier time points were taken into consideration. In accordance with the previous study ulceration was not seen in the young rats after 22 Gy, while the older group occasionally showed ulceration. After 39 Gy, the incidence of ulceration was higher in the young animals. Vascular occlusion was present more often and more extensive in the older group. Moreover, the older rats showed a significant increase in the number of endocrine cells within and adjacent to the treatment field. We found a high incidence of radiation-induced tumors within the treated area (40 – 60 %), but only after a dose of 22 Gy, and which was independent of age.

Conclusions: Studies on early radiation induced changes of rat rectum showed subtle differences between young and old rats. Some of these changes were still observed at these later time points, but they did not seem to lead to significant differences in late effects.

Introduction

Elderly patients form the majority of patients to be treated in most radiotherapy departments [1,23]. A further increase in the average age of cancer patients is expected for the next decades for demographic reasons due to improvement of general health care as well as the age-dependent incidence of most malignant tumors [4]. Radiotherapy with a curative intention is often modified in elderly patients, because of an assumed decrease in normal tissue tolerance in this age group. However, from clinical studies there is evidence that toxicity of radiation therapy depends on the functional status of the normal tissues that surround the tumor and not or very little on biological age [1,21,24]. More radiobiological data are needed regarding the influence of age on radiation sensitivity of normal tissues. This applies especially for radiation changes in the long term.

Since the rectum is an important dose-limiting organ in radiotherapy of urogenital tumors, a histopathological study on rectal toxicity was carried out. For this purpose the rectum of young and older rats was irradiated and histological changes were studied in time to obtain detailed information on the progression of rectal injury. The results of the early time points (up to 10 weeks after treatment) showed subtle histological differences between the rectum of young and old rats, especially ulceration was observed in a higher incidence in the older age group [17]. Severe vascular changes occurred relatively early and were more extensive in old rats. Furthermore, in the area adjacent to the treatment field, cell proliferation increased significantly in older animals at 1 week after 22 Gy, which did not occur in the young group. In the present study the long term effects of these rectal changes at 24 and 52 weeks after irradiation, have been evaluated.

Materials and methods

Laboratory animals

Female Wistar rats, aged 12 and 78 weeks, were used (Harlam Zeist, the Netherlands). This allowed a follow up time of 52 weeks in the majority of animals.

They were housed under conventional conditions with food and water ad libitum in light controlled rooms (light on at 06.00 h, off at 18.00 h). The experimental protocol was approved by the Animal Ethical Committee of the University of Rotterdam. Upon arrival the rats continued on their normal standard diet and were allowed to recover fully, as judged by a return of body weight towards that on arrival. Young rats weighed approximately 220 g, whereas the older animals had an average weight of 350 g at the time of irradiation.

Experimental design
As described earlier, female rats of both age groups were irradiated with single doses of 22 Gy and 39 Gy [17]. These doses represent the LD20 and LD80 level, respectively. At 24 and 52 weeks after irradiation, at least 5 rats of each irradiated group were sacrified. To be able to evaluate a sufficient number of animals with complete follow up, more than 5 animals in each group were irradiated (See Table 3-1). For each time point 3 non-irradiated rats of the same age, housed under the same conditions and sacrified simultaneously, served as controls.

Irradiation procedure
The method of anesthesia as well as the irradiation procedure have been described earlier [17]. Briefly, the animals were anesthesized with Ketamine [Parke -Davis] intraperitoneally and Xylazine 2 % [Bayer AG] subcutaneously. Irradiation of the rectum was performed with a Philips 250 RT Orthovolt X-ray machine, operated at 200 KV and 20 mA. The dose rate at the level of the rectum was 1.36 Gy/min for the young animals and 1.25 Gy/min for the older rats, due to the difference in skin- rectum distance as a result of overlying fat tissue. A lead shielding for the head, thorax, upper abdomen and limbs was used during treatment. The field size was 1.5 × 2.0 cm, with the lower border above the orifices of vagina and urethra to avoid acute epithelial toxicity of these tissues.

Quality control was performed with thermoluminiscency dosimetry catheters (TLD) in the rectum of 50% of randomly assigned animals.

Histology
The method of fixation and preparation for histology was described before. In short, the entire rectosigmoid (± 5 cm) was removed after sacrificing the animal, examined macroscopically and fixed in 3.7 % formalin for a maximum of 24 hours. The specimen was sliced transversely in four pieces of 0.4 cm each, i.e. a) between the anus and the irradiated area (0 - 0.4 cm), b) caudal part of the irradiated area (0.8 - 1.2 cm), c) cranial part of the irradiated area (1.2 - 1.6 cm) and d) above the irradiated area (3.1 - 3.5 cm). Three of these slices were marked with different colours of dye for the recognition of the location of the rectum. The four slices of the rectum were embedded in one block. The specimens were routinely processed and embedded in paraffin. Sections were cut 5 µm thick and stained with hematoxylin-eosin (HE), periodic acid Schiff plus reagent (PAS+), Sirius red (SR) and resorcin fuchsin (RF) according to standard methods.

Immunohistochemistry
For immunohistochemical studies, antibodies recognizing the following antigens were applied: smooth muscle actin (SMA) [Biogenex], Collagen III (Coll III) [Biogenex], neurofilaments (NF) [Dako], S-100 protein [Dako], Cytokeratin [NeoMarkers] and serotonin [according to de Bruine e.a. [2]].

Sections, 4 µm thick were reacted with appropriate dilutions of antibodies after blocking with H_2O_2 and antigen retrieval with citric acid. Antigens were visualised using a streptavidin-biotin peroxidase conjugate system [Biogenex].

Scoring system for rectal injury

A semiquantitative histopathological radiation damage score appropriate for this experimental setting was developed, based on the Radiation Injury Score introduced by Hauer-Jensen and co-workers [10], for the assessment of radiation injury. Parameters were chosen in order to be able to score them present or absent, for their representation of changes in the different layers of the colon wall (mucosa, submucosa, muscularis), as well as for their representation of acute and chronic injury. The various parameters as changes of epithelial cells, crypt distortion, discontinous muscular mucosae, mucosal ulceration, squamous metaplasia, hyperplasia, colitis glandularis cystica profunda and carcinoma were scored present when observed in either part of the section. In cases with severe ulceration, crypts were absent and distortion was not assessed. Parameters as hyalinization of blood vessel walls and occlusion of blood vessels were scored present when observed in one or more of the blood vessels of the section. Furthermore the lumen of the rectum was scored normal if star shaped and abnormal if circular shaped. The thickness of the submucosa was scored normal or broadened in relation to the submucosa of the non-irradiated part of the rectum. For the radiation injury score (RIS) the scores of the above mentioned 12 parameters were summated.

For each animal these parameters were scored in all four pieces of the rectum. Within the treatment field, a parameter was considered to be present when observed in at least one of the two slices of the radiation field. To describe the extent of the radiation-induced changes, the presence of a parameter in both of the sections of the treatment field was evaluated separately.

All sections were evaluated by two investigators independently (M.J.J. O.-v.A. and M.L.F. v.V.) without access to the treatment code. Discrepancies were discussed and the final score was determined by consensus.

Of all animals who died prematurely, due to toxicity or other causes, the latency time was analysed. Histology was performed on the rectum of these rats, except for those with too much autolysis (see Table 3-1).

Endocrine cells were counted as the number of serotonin positive cells in 20 randomly selected crypts in each of the four sections. The cell counts obtained by the two investigators were averaged. The mean of the two sections of the treatment field was calculated.

Data analysis

The incidence of each histopathological parameter in all sections was calculated separately for each age group and for each time point. Within the treatment field

incidences were calculated for presence in either one of the sections and separately for presence in both sections. A summation of all present parameters was calculated for each animal to obtain a quantitative injury score for the sections within the treatment field as well as for the sections above and below the field. Per group of animals the mean of the injury score (± sem) was calculated according to age, dose and time point.

Statistical comparison of data was performed with a logistic regression analysis for each histological parameter separately; for this purpose the data of the 2 time points were pooled together. The histological features were the dependent variables and radiation dose and age were independent variables. The total injury score and the number of endocrine cells were compared by the analysis of variance test (ANOVA; single factor), using the MS Excell 97 program. In all cases, a significance level of 5 % (two sided) was used.

Results

Dosimetry with TLD-measurements showed on average a small difference of minus 3 % (SD ±1.0) between measured and planned dose, irrespective of dose and age group.

Control animals did not show any histopathological alteration at either of the two time points (injury score was 0), except for one animal of 78 weeks that died inexplicably after 30 weeks. Histology of this rat showed severe autolysis; the animal was excluded from analysis.

In Table 3-1 the total number of irradiated animals in each group is shown as well as the numbers with a follow up completed according to plan and those with premature death. There was no significant difference in premature death between young and old rats. Of all 46 animals that died prematurely, 21 (46 %) could not be evaluated with histology due to autolysis. Of the remaining 25 animals (54 %) with premature death, 2 rats died of urogenital complications. All the other rats died due to rectal complications and/or secundary tumors within the irradiated area. Of these 25 animals, 17 (68 %) developed a macroscopic megacolon and only 2 (8 %) of these rats had fistulas to the uterus at the time of obduction.

Table 3-1.
Total number of irradiated animals in relation to age, dose and follow up period, number of animals with complete follow up and number of animals with premature death, with or without histological evaluation of the rectum.

Age (wks)/ Dose (Gy)/ Follow up period (wks)	**Tot. num. irradiated**	**Num. With complete follow up (%)**	**Num. premature death with histol. data (%)**	**Num. premature death without histol. data (%)**
12 wks / 22 Gy/ 24 wks	6	5 (83 %)	0 (0 %)	1 (17 %)
12 wks/ 39 Gy/ 24 wks	26	9 (35 %)	9 (35 %)	8 (30 %)
12 wks/ 22 Gy/ 52 wks	6	5 (83 %)	0 (0 %)	1 (17 %)
12 wks/ 39 Gy/ 52 wks	15	6 (40 %)	4 (27 %)	5 (33 %)
78 wks/ 22 Gy/ 24 wks	6	5 (83 %)	0 (0 %)	1 (17 %)
78 wks/ 39 Gy/ 24 wks	15	9 (60 %)	3 (20 %)	3 (20 %)
78 wks/ 22 Gy/ 52 wks	9	5 (56 %)	3 (33 %)	1 (11 %)
78 wks/ 39 Gy/ 52 wks	11	4 (36 %)	6 (55 %)	1 (9 %)

The mean latency time of all animals with premature death was on average 14 weeks as is shown in Table 2, except for the older group after a dose of 22 Gy. They showed a longer latency time of 31.6 ± 12.7 weeks, probably due to the fact that in this group 80 % died of a malignant tumor within the treatment field, some with metastasis, instead of rectal complications.

Of the 48 animals with complete follow up, only 3 (6 %) had a macroscopic megacolon and 7 (15 %) rats had a fistula to the uterus at the time of obduction. Remarkably, of all animals with a fistula only one belonged to the older group. Most of the surviving animals did not show any macroscopic changes.

Table 3-2.
Mean latency time in weeks with standard deviation of the animals who died prematurely in relation to age and dose, irrespective of planned follow up period.

Age (wks)/ Dose (Gy)	Number of animals with premature death	Mean latency time ± SD (wks)
12 wks/ 22 Gy	2	16 ± 9.9
12 wks/ 39 Gy	26	11.2 ± 7.1
78 wks/ 22 Gy	5	31.6 ± 12.7
78 wks/ 39 Gy	13	15.5 ± 7.3

The incidences of all parameters, within one or more of the sections of the irradiated rectum at the different time points after treatment are shown in Table 3-3 for all animals examined histologically. All histological changes were observed within the treated area only, except for hyperplasia, which was observed proximal of the treatment field and occasionally at the cranial side within the field.

As shown in Table 3-3 an abnormal shape of the lumen of the rectum, mainly circular instead of star-shaped, frequently occurred after the high dose and in rats with premature death without significant differences between young and old rats.

After 39 Gy epithelial changes, flattening and multilayering of epithelial cells, occurred frequently in both age groups at both time points. After a dose of 22 Gy, changes of epithelial cells were observed only in the old group (this difference was not significant).

Mucosal ulceration was mainly found after 39 Gy, in both age groups at 24 weeks and in the young group also at 52 weeks after treatment, but usually not around the whole circumference and often in one of the two sections only. No significant difference between the age groups could be found. Analysis of ulceration for all time points summated, including the previously published data of 1, 2 ,4 and 10 weeks after treatment [17], also showed no significant age-related differences. As shown in Table 3-3, ulceration was observed more frequently in both age groups of those animals that died prematurely compared with the groups of surviving rats. Furthermore, in animals with premature death, it concerned ulceration of the whole circumference of both sections in 70 – 90%.

Irregular crypts repopulated with normal epithelial cells (crypt distortion) were observed very frequently at 24 as well as 52 weeks after irradiation in both

age groups, as is shown in Table 3-3. Crypt distortion in one or both of the sections within the treatment field was observed in nearly all animals after a dose of 22 Gy at both time points, regardless of age. After 39 Gy, crypt distortion was observed less frequently due to the high incidence of ulceration.

Table 3-3.
Incidence of various histological parameters (percentage) in the rectum of young and old rats within the treatment field as well as hyperplasia in and/or rostral of the irradiated field, in relation to dose at 24 and 52 weeks after treatment (RT) or at moment of premature death.
(Y = Young, O = Old, 22 = 22 Gy, 39 = 39 Gy).

Histologic parameter	Follow up 24 weeks				Follow up 52 weeks				Premature death		
	Y/22	O/22	Y/39	O/39	Y/22	O/22	Y/39	O/39	O/22	Y/39	O/39
Abn. Shape of lumen	0	0	89	89	20	60	66	75	66	92	89
Epithelial changes	0	20	66	66	0	60	50	75	66	85	67
Mucosal ulceration	0	0	56	56	0	20	50	0	66	92	78
Crypt-Distortion	100	80	78	44	100	100	66	100	66	30	33
Discont. Musc.muc.	0	0	89	67	40	40	66	75	66	85	67
Squamous metaplasia	0	0	33	11	0	0	33	0	0	15	0
Hyperpl.	0	0	0	11	0	0	17	0	0	62	44
Hyalinosis	100	80	89	100	80	100	83	100	100	92	89
Occlusion	20	60	56	78	0	40	50	75	33	77	89
Increase of collagen	100	100	44	78	80	60	17	25	66	23	33
Colitis gl. Cyst. Prof.	0	0	44	11	0	0	33	25	0	15	22
Malign. Tumors	0	0	11	11	60	40	0	0	66	0	0

A discontinuous muscularis mucosae, replaced by collagen or inflammatory infiltration occurred more frequently after 39 Gy than after a dose of 22 Gy, again without significant differences between the rats of both ages. Also in the animals with premature death, a discontinuous muscularis mucosae was observed in 67 – 85 % of the animals without significant differences between the age groups.

Squamous metaplasia of columnar epithelium was seen after a dose of 39 Gy only and more frequently in the young animals at both time points (difference for both time points summated not significant).

Hyperplasia *rostral* of the irradiation area was also observed, but only after a dose of 39 Gy. However, in the rats with premature death, the incidence of hyperplasia was significantly higher (0 –17 % vs 44 – 62 %, $p = 0.05$) (Table 3-3). The presence of this parameter frequently corresponded with the macroscopic observation of a megacolon and occasionally with ulceration. Of all the young animals with hyperplasia, 89 % developed a megacolon and in the older group, all rats with hyperplasia developed a megacolon.

Thickening of blood vessel walls by hyalinization resulting in stenosis of the lumen was observed very frequently (80 – 100 %) after both dose levels at both time points i.e. 24 and 52 weeks without significant differences between the age groups. When hyalinosis was observed at 24 weeks, it appeared to be present in both slices of the radiation field in 50 % of the animals, regardless of dose and age. At 52 weeks, in approximately all animals with hyalinosis it was observed in both slices.

In cases of extreme hyalinization, complete occlusion of one or more of the blood vessels in the section could occur. After a dose of 22 Gy occlusion of blood vessels occurred more often in the older animals (difference for both time points summated not significant). After 39 Gy, the incidence of vessel occlusion was even higher in both age groups. This also applied for the animals who died prematurely. Extensive occlusion of blood vessel walls (observed in both slices of the irradiated area) was observed in 50 – 60 % of the old animals, in contrast to the young group where extensive occlusion was observed in only 0 – 20 % (difference significant for both time points after treatment; $p = 0.05$).

An increase in thickness of the submucosa due to collagen accumulation was observed in the irradiated rectum very frequently (incidence 60 – 100 %) after 22 Gy in both age groups in comparison with unirradiated rectum and with control animals. After the higher dose, especially at 52 weeks and in animals with premature death, an increase in thickness of the collagen occurred less frequently (17 – 33 %). In these animals a change in the density of the collagen fibres of the submucosa was seen with more space between the fibres; 0 – 33 % at 52 weeks after 39 Gy, 50 – 78 % for rats who died prematurely. This change in density of the collagen fibres strongly correlated with mucosal ulceration and was independent of age.

As long as the rectum wall was not destroyed due to ulceration, ganglion cells were evenly distributed in each slide in all animals. Proliferation of neurofilaments was not observed.

At 24 as well as 52 weeks after treatment and in the animals with premature death, colitis glandularis cystica profunda was seen after a dose of 39 Gy only (11 – 44 %), without significant differences between age groups (Table 3-3).

Malignant tumors within the irradiation area most frequently occurred after a dose of 22 Gy at a follow up time of 52 weeks (40 – 60 %) and in the rats with premature death after 22 Gy (66 %). These tumors involved adenocarcinomas (85 %) and squamous cell carcinomas (15 %) (Table 3-3).

Total radiation injury score

In Table 3-4 the mean summation of all parameters for the radiation injury score (RIS) is presented for the various groups including rats with premature death. The mean summation appeared to be dose related for both young and old animals at 24 weeks (p- value 0.005 and 0.03 respectively). At 52 weeks after treatment there was no significant relationship between RIS and dose for both age groups.

For the two age groups there were no significant differences between the RIS at any time point.

Table 3-4.

Mean summation (± sem) of present parameters of radiation injury of the rectum for animals with complete follow up as well as for animals with premature death. Presented per age- and dose group.

	Young 22 Gy	**Old 22 Gy**	**Young 39 Gy**	**Old 39 Gy**
Follow up 24 wks	3.2 ± 0.2	3.4 ± 0.7	6.6 ± 0.7	6.3 ± 0.8
Follow up 52 wks	4.0 ± 0.6	5.4 ± 1.3	5.3 ± 1.5	5.5 ± 0.7
Premature death	-	6.0 ± 1.5	6.8 ± 0.5	6.1 ± 0.6

Number of endocrine cells

The mean numbers of endocrine cells per 20 crypts in the different areas of the rectum at 24 weeks after treatment are shown in Figure 3-1. In comparison with control animals, the younger group showed some increase in endocrine cells, above the treatment field, which was not significant ($p = 0.06$). In the older group however, an increase in endocrine cells was observed within the treatment field after 22 Gy as well as 39 Gy ($p = 0.008$ and $p = 0.02$ respectively). Furthermore, the number of endocrine cells in the adjacent unirradiated parts of the rectum was also increased significantly in the older group in comparison with the control animals. For the caudal area between anus and irradiation field this increase was distinct in the low and high dose group (p- value 0.06 and 0.02 respectively). Above the treatment field the endocrine cells also increased, but not significantly. This phenomenon was not observed in the young animals.

In Figure 3-2 the mean number of endocrine cells within the different parts of the rectum is shown for the follow up of 52 weeks. The control animals in the two age groups showed no differences in endocrine cells. In the younger animals no significant changes in endocrine cells were observed in comparison with control animals, irrespective of dose and location in the rectum. In the low dose group however the older animals not only showed an increase in endocrine cells within the treatment area, but also above the irradiated rectum (both p-values = 0.02). The number of endocrine cells after 39 Gy was assessed, but due to extensive ulceration which did not permit evaluation of enough crypts, these values were based on fewer data. No significant differences were seen compared with control values.

For the animals who died prematurely the mean number of endocrine cells after a dose of 39 Gy were not significantly different from control values. These data were based on few observations due to a large number of animals with severe and extensive ulceration.

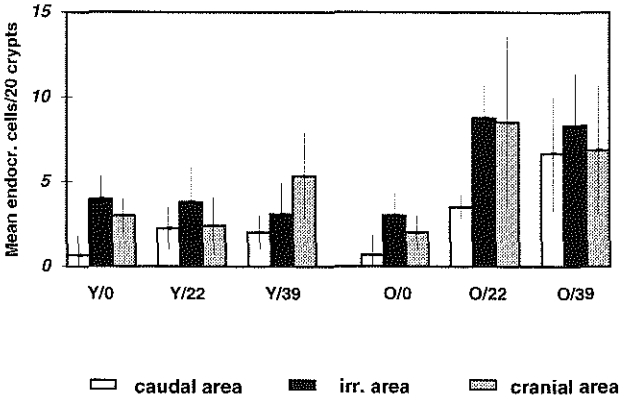

Figure 3-1
Mean number of endocrine cells per 20 crypts in the rectum of young and old rats at 24 weeks after treatment as a function of dose and in relation to the position in the treatment field. Error bars indicate standard deviations (Y = young animals, O = old animals; 0 = control group, 22 = 22 Gy, 39 = 39 Gy).

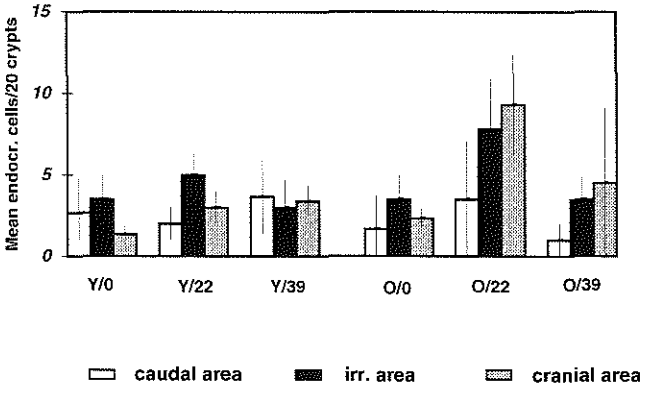

Figure 3-2
Mean number of endocrine cells per 20 crypts in the rectum of young and old animals at 52 weeks after irradiation as a function of dose and in relation to the position in the treatment field. Error bars indicate standard deviations (Y = young animals, O = old animals; 0 = control group, 22 = 22 Gy, 39 = 39 Gy)

Discussion

In cancer treatment of the elderly, many physicians tend to perform pretreatment selection. In radiation therapy the assumption that normal tissue tolerance decreases with increasing age is the basis for undertreatment in elderly patients. Recent clinical studies on this subject strongly support the idea that acute as well as late tissue toxicity in patients older than 74 years is not increased compared with younger patients [21,22,24,27]. Experimental data on this subject generally address the influence of age on acute radiation induced changes. Most of these animal studies deal with skin reactions and do not indicate an increase of radiosensitivity with older age [6,14,16]. Despite the fact that the rectum is an important dose limiting organ in radiotherapy in pelvic malignancies, and radiation induced complications of the rectum are frequently described [3,7,8,9,10,19], studies on radiosensitivity of the rectum in relation with age are rare. In previous experiments with single doses of irradiation it appeared that there was no significant difference in the incidence of rectal stenosis resulting in a megacolon between young and older rats, using clinical and radiological endpoints [18]. The latency period for the development of rectal stenosis was 11.6 ± 6.2 weeks after irradiation in young rats and 15.0 ± 3.9 weeks in older animals, which corresponds with the results of the present study. To study differences in reaction patterns between young (12 weeks) and older female Wistar rats (78 weeks) over a longer period of time, rectal tissue was examined histologically 24 and 52 weeks after irradiation. Two radiation doses equivalent to the LD20 (22 Gy) and LD80 (39 Gy) were applied. In our previous studies with follow up points of 1, 2, 4 and 10 weeks after treatment [17], some subtle age related histological differences were observed.

From our studies with early and late time points it can be deducted that ulceration apparently is reversible in some cases. The high incidences of 60 – 100 % for mucosal ulceration at 2, 4 and 10 weeks after 39 Gy and the lower incidence of 0 – 50 % observed after 52 weeks seem to indicate this. According to Trott e.a. [25,26] healing of a lesion can occur if no additional damage interferes, but healing of a manifest ulcer cannot restitute the original tissue structure, but leads to defective healing with scar formation, dystopic epithelial proliferation and thrombosed vessels. Vascular occlusions might disturb the regenerative capacity of the mucosa. If not self-limiting, chronic irradiation enteritis has been described by Oya e.a. as a slowly progressive disease [19]. Late cases of chronic irradiation enteritis showed ulcerative stricture type properties with tissue degradation, such as fistulas, perforation and dysplastic epithelia. These findings are in accordance with our studies where we found either progressive disease (ulceration, fistulas, megacolon or malignancies) or healing with scar lesions (cryptdistortion, vascular hyalinosis and occlusion of blood vessels).

In our studies with early time points severe vascular changes occurred earlier (4 weeks) and were more extensive in older animals than in the younger group (10 weeks). In the present study, again vascular occlusions were observed more often in older rats after both doses at 24 as well as 52 weeks after treatment. Despite the significant higher incidence of severe vascular changes in older rats, there was no higher incidence of premature death or severe ulceration in the older group. The significant increase in cell proliferation in the areas adjacent to the irradiated field, as was found the first week after treatment [17], might be an important factor in the healing of initial ulceration.

We found a high incidence of radiation-induced tumors within the treated area in both age groups (40 –66 %). Remarkably these tumors occurred in the group of animals after a dose of 22 Gy only. The fact that tumors were observed after the lowest dose seems in contrast with clinical literature [5,11,15]. In studies on long term effects after radiotherapy for Hodgkin's disease as well as investigations among atomic bomb survivors, the incidence of secundary tumors increased with dose. An important difference is, that the highest dose in the clinical studies was fractionated and lower in comparison with single doses used in our studies. In most clinical studies, the incidence of secundary tumors is higher for patients in their adolescence or young adulthood at the time of treatment [5,12,15]. We did not find a difference in tumor incidence between the age groups. Possibly the incidence of tumors in our young group might be higher with longer follow up periods.

Total rectal damage was expressed in the total radiation injury score (RIS). At 24 weeks after irradiation there was a clear dose dependency, but no significant difference with age. At 52 weeks this dose dependency disappeared, although the RIS remained high. This suggested that some of the parameters involved became manifest at a late stage. This is certainly true for the young rats after 22 Gy, where the RIS gradually increased from ≈ 1 (week 1) to ≈ 3 (week 10) [17], followed by a further, but small increase to 4 at week 52. After 39 Gy, already at 2 weeks, the RIS increased to 4.5, which remained ≈ 5-6 throughout the follow up period. In contrast, for the old rats the majority of parameters involved was seen already at 4 weeks after treatment with a RIS of 4-5.5, while this was ≈ 2 for week 1 and 2 [17]. This RIS remained high for the longer follow up periods, irrespective of dose. These data do support the hypothesis that late rectal damage is a consequential event of acute rectal damage.This would suggest that intervention in and amelioration of rectal damage should occur shortly after radiation for the old animals.

Hyperplasia of endocrine cells in the intestines has been noted in cases of celiac disease, chronic ulcerative colitis and chronic radiation enteritis [2,20], all characterized by chronic mucosal damage and ensuing regeneration. The cause of endocrine cell hyperplasia under the latter circumstances is not clear, but might be related to increased cell turnover or decreased maturation. De Bruine e.a. have

described the renewel and hyperplasia of endocrine cells by combination of self-replication and recruitment from primitive precursor cells [2]. There appeared to be two subpopulations of endocrine cells, a rapidly renewing fraction with a turnover time of approximately 16 days and a relatively slowly proliferating fraction which renewed in about 150 days. The slower renewing cells were evenly distributed over the crypts, were less exposed to cell loss during migration and represented therefore a more static resident population. We therefore assessed the number of endocrine cells in the crypts at these late time points in order to study radiation-related hyperplasia of these cells in the two age groups. The number of endocrine cells in the rectum of the older rats increased significantly within the treated area as well as on the caudal side at 24 weeks after both dose levels. However at 52 weeks, only the number of endocrine cells above the irradiation field of the older animals increased significantly. In our earlier studies [17], we observed an increase of proliferative cells at the first week after radiotherapy in these older rats. Therefore, the increased number of endocrine cells at the late time points might reflect this earlier proliferation activity since it has been suggested that enteroendocrine cells are a non specific result of cell proliferation [2].

Increase in thickness of the collagen of the submucosa was observed in the course of this study, especially after 22 Gy, which has also been described by others [13]. No significant differences between the age groups were found. However, after 39 Gy only a small proportion of the animals showed increased collagen thickening in the submucosa, which was evident particularly after 52 weeks (17-25 %). The fact that after 39 Gy a large number of animals did not develop collagen thickening in the submucosa coincided with the presence of mucosal ulceration. This ulceration actually masked the process of collagen thickening which gave the appearance of loose collagen fibres and hence a reduction in density.

The observed differences between the age groups for early changes of rat rectum, did not seem to lead to major differences in long term effects. Therefore, although early reaction patterns showed little differences between young and old rats, clinical outcome in the long term seemed to be similar. Based on these experimental studies, the assumption that the radiation tolerance of rectal tissue has diminished with older age cannot be justified. Since more clinical data are needed, we strongly support inclusion of older patients in clinical trials.

Conclusion

In this study dose dependent late radiation injury to the rectum was assessed with histopathological parameters. Several of these parameters especially vascular occlusion proved to be age dependent, but most of them not significantly. The significant differences between age groups were observed much earlier in the acute phase of tissue reactions. Major changes in ulceration and vasculature were not observed with longer follow up. Based on these experimental studies on radiation tolerance of rectal tissue, modifications in dose fractionation schedules for pelvic radiotherapy cannot be justified solely for reasons of old age.

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CHAPTER 4

DEFINITION AND VALIDATION OF A REFERENCE TARGET VOLUME IN EARLY STAGE NODE-POSITIVE CERVICAL CARCINOMA, BASED ON LYMPHANGIOGRAMS AND CT-SCANS

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Abstract

Purpose: To establish a reference planning target volume for postoperative radiotherapy in stage Ib and IIa N+ cervical carcinoma, based on 47 lymphangiograms and 15 CT-scans.
Methods: Radiation oncologists (n=17) from all radiotherapy institutes in The Netherlands were asked to define the clinical target volume (CTV) and planning target volume (PTV), and to delineate (on simulation films) the radiotherapy treatment portals following a radical hysterectomy with lymph node dissection for an early stage cervical carcinoma with positive iliac lymph nodes. A reference PTV was defined by using 47 normal lymphangiograms and CT-data of the pelvis from 15 patients who underwent surgery for cervical carcinoma. The simulation films were digitized and evaluated for adequacy in covering the PTV, previously individually determined by the radiation oncologists. Subsequently, the simulation films were also evaluated for adequacy in covering the reference PTV.
Results: Large variations were observed in the portals used and in treatment techniques. From the digitized films, it appeared that in 50% of the cases the defined PTV was not covered adequately. Furthermore, 71% of the treatment plans would not cover the lateral borders of the reference PTV sufficiently.
Conclusions: There appears to be no consensus on the target volumes to be irradiated in postoperative radiotherapy of early stage cervical carcinoma. When a PTV defined on the basis of lymphangiograms and CT-data is taken as a reference, 71% of the treatment plans would not cover this PTV adequately. These findings indicate the need for a consensus in the design of standardized treatment volumes.

Introduction

Patients with squamous cell carcinoma of the uterine cervix FIGO stage Ib and IIa are often treated by a radical hysterectomy and an iliac lymph node dissection. In case of histologically proven lymph node metastases it has been shown that the 5-year overall survival rate increases by adding postoperative radiotherapy to the pelvis (43%-63%) [8]. The treatment volumes vary among institutions; most agree upon including the iliac and obturator lymph nodes [1,3,7,9,14,16,21,23,24], some even add the para-aortic region to the target volume [6,15,22]. The prescribed dose to the pelvis generally varies between 45 Gy and 50 Gy [2,9].

The complication rates for small bowel or bladder are reported to range from 3% to 24%, and 3% to 8%, respectively [2]. In fact, these complications are dose limiting in this type of patients [8,17]. To reduce the volume and dose of irradiated small bowel and bladder, conformal radiation therapy has been suggested. The preamble to this high-precision radiotherapy is the need for a correct and reproducible definition of the target volume.

In this study, the variations in clinical target volumes and radiation techniques of all Dutch radiotherapy institutes were assessed [18]. All simulation films with the target volumes drawn in by the participating radiation oncologists were digitized and compared with the CT-scan of a particular patient, with the tumour region and lymph nodal chains identified. To verify the position of the target structures, a reference target volume for the primary tumour region and the involved lymph nodal chains was defined. This reference target volume was structured on 47 lymphangiograms and 15 CT-scans. Finally, the treated volumes indicated by the radiation oncologists were compared with the reference target volume.

Materials and Methods

In this study, a theoretical patient is presented with a squamous cell carcinoma of the cervix FIGO stage Ib or IIa who underwent a radical hysterectomy with an iliac lymph node dissection. Histological examination showed radical removal of the cervical tumour and parametria, with lymphatic invasion. In the specimen 34 lymph nodes were identified with two positive lymph nodes in the distal iliac region on the left and one near the common iliac artery on the right.

All Dutch radiotherapy institutes were asked to take part in the study. A case history and anterior and lateral simulation films were sent to the participating radiation oncologists. They also received four body contours (CT-slices enlarged to real size) of the 'study patient' at different levels, i.e. at the level of the parametria, the sacral promontory, the para-aortic region (level

vertebra lumbar 2) and the obturator region. Treatment portals were outlined on the anterior and lateral simulation films. The participants defined the clinical target volume (CTV) and outlined the planning target volume (PTV) on the pelvic contours. The radiation oncologists individually determined patient positioning, radiation technique and beam energy based on institutional policy (see Appendix 1).

Treatment portals and beam data of each institute were imported in a 3-D treatment planning system (CADPLAN Varian–Dosetek, Finland). Dose distributions were computed using the defined PTVs, with beam data of a 10 or 25 MV photon beam.

The calculated treatment plans and the arrived treatment volumes were compared with the PTV description of the radiation oncologists of the different institutions. A margin of at least 5 mm between PTV and field border was considered adequate.

To arrive at a correct definition of the PTV for postoperative irradiation for early stage node-positive cervical cancer, also a reference PTV was established. In this reference PTV the primary tumour region, the proximal one-third of the vagina, and the obturator, iliac and para-aortic lymph nodes were included. In this reference PTV the para-aortic region was included, although only a small part of the participants considered the para-aortic lymph nodes as part of the CTV. The precise location of the para-aortic and common iliac lymph nodal chains was defined using 47 normal lymphangiograms of females without pathological findings in the iliac and para-aortic regions. When the internal iliac lymph nodes were visible, they were identified too. The lymphangiograms were digitized on the anterior–posterior (AP) films. For comparison purpose, four bony landmarks were chosen, i.e. the upper border of the acetabulum, left and right, the upper border of vertebra lumbar 2 and the center of the symphysis. Subsequently, the digitized lymphangiograms were scaled and positioned relative to the bony structures on the AP simulation film of the study patient after being corrected for length, width and rotation of the pelvic bones (Fig. 4-1).

Computer tomography data of the pelvis from 15 female patients who had surgery for early stage cervical carcinoma were used to define the obturator lymph nodes, the internal iliac lymph nodes and the primary tumour region with the extent of the parametria to the lateral pelvic wall. The regions of interest were delineated on these CT-scan slices, i.e. the primary tumour region from the level of the diaphragm onto the vagina, and the para-aortic, iliac and obturator lymph nodes. The lateral extension of the parametria was defined by the fascia of the obturator internus muscle on the sidewall of the pelvic bones; this fascia is the surgical resection level of a Wertheim's hysterectomy. In order to obtain a contour of the defined CTVs, Beam's Eye View data were generated, digitized

and scaled to the bony structures of the study patient, in the same manner as with the lymphangiograms.

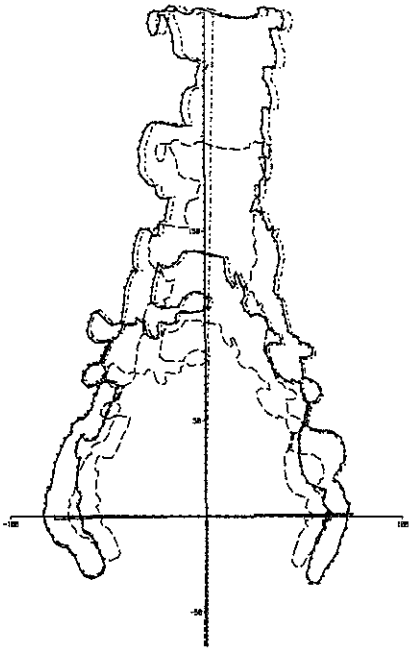

Figure 4-1
Scaling of lymphangiograms. Solid line: original contour from lymphangiogram; dashed-dotted line: rotated to get a horizontal position of the pelvis; dotted line: the axis through the spine is slanting to make the same angle with the horizontal axis as for the reference patient; dashed line: conformed to length and width of the same axis in the reference patient at isocentre level.

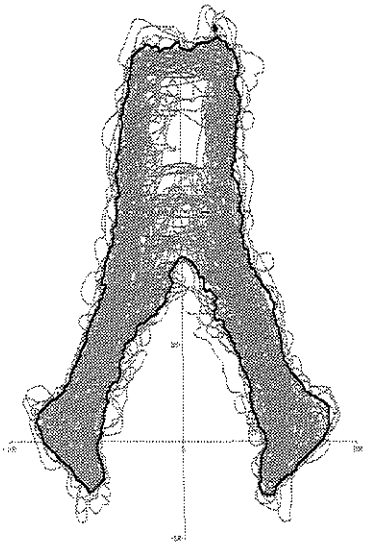

Figure 4-2
Line enclosing 90% of lymphangiograms.

We assumed the line enclosing 90% of the lymphangiograms (Fig. 4-2) and the CTVs of primary tumour and parametria based on the CT-scans to represent the reference CTV. To analyse the accuracy of this method, this procedure was also carried out with two randomly divided groups of half of the patients; the difference between these two groups appeared to be less than 3 mm. The reference PTV consisted of this reference CTV with a 10 mm margin added (Fig. 4-3).

Finally, all treatment portals defined by the participating radiation oncologists were compared with the reference PTV. The margins between PTV and field borders were measured. A margin of at least 5 mm was considered adequate.

Results

Of the 18 institutes that were asked to participate, 17 responded (94%). There seemed to be a large variation in the description of the CTV and techniques used. There appeared to be three different CTV definitions:

CTV type 1 consisted of the primary tumor, the proximal one-third part of the vagina, the obturator and iliac lymph nodes, and the para-aortic lymph node chain (5 x).

CTV type 2 was similar to CTV 1 except for the para-aortic lymph nodal chain, with the upper border at the level of the aorta bifurcation (5 x).

CTV type 3 consisted of CTV 2 with the iliac lymph nodal region ending just above the lymph nodes at the level of the common iliac artery (7 x).

Five of 17 (29%) radiation oncologists considered the para-aortic lymph nodes part of the CTV, whereas 12 out of 17 (71%) would only irradiate the pelvis. Besides the large variations in shape and size of the treatment portals used (Fig. 4-4), there were differences in the treatment technique. Seven institutes proposed to use parallel opposed anterior-posterior fields, nine institutes a four-field box technique and one institute a three-field technique (two lateral fields and a posterior field).

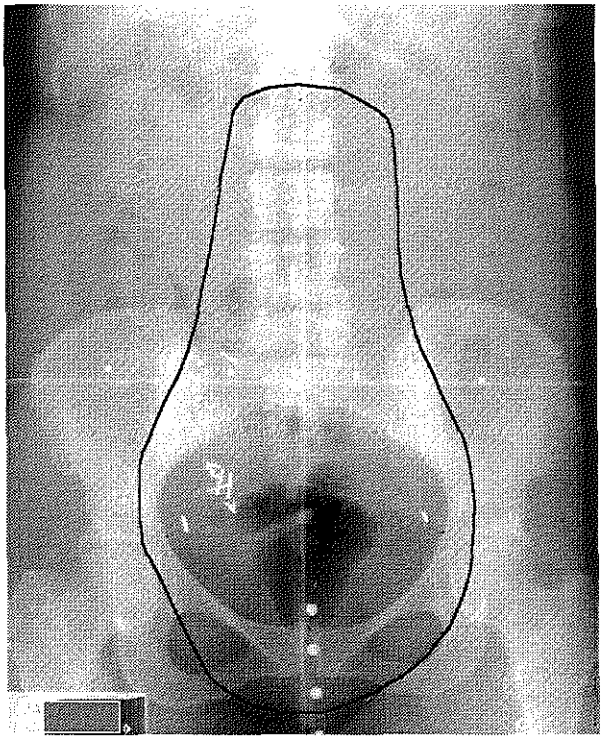

Figure 4-3
Reference PTV.

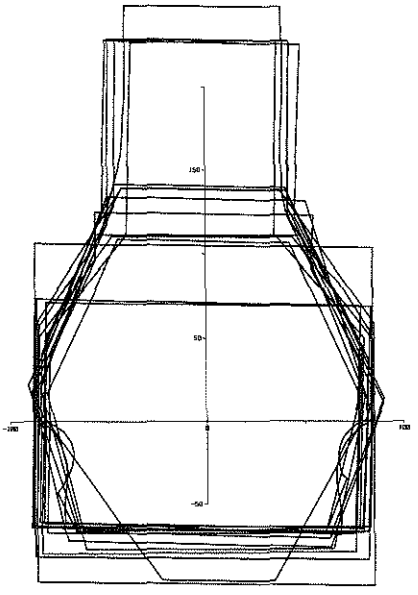

Figure 4-4
Variations in treatment portals

For all treatment plans the margins were measured between the delineated PTV in the pelvic contours and the field borders of the treatment portals used, i.e. at the level of the parametria and the para-aortic region. Results are shown in Table 4-1. At the level of the parametria 50% of all institutes had defined a margin of less than 5 mm, and 17% had defined no margin at all. At the level of the para-aortic region these percentages were 60% and 20%, respectively. The largest difference between PTV and field borders was measured at the level of the parametria: the PTV extended more than 20 mm outside the field borders.

Table 4-1.
PTV margins by the radiation oncologists to their own field borders, measured in mm

	> 5 mm	0 - 5 mm	-5 - 0 mm	< -5 mm
Parametria	6/12 (50 %)	4/12 (33 %)	0/12 (0 %)	2/12 (17 %)
Para-aortic lymph nodes	2/5 (40 %)	2/5 (40 %)	1/5 (20 %)	0/5 (0 %)

The same measurements were carried out with the defined reference PTV and the field borders (Table 4-2). That is, at the level of the parametria 71% of the institutes had defined a margin of less than 5 mm, and 59% had defined no margin. In the para-aortic region none of the institutes had defined a margin > 5 mm, particularly on the left side of the para-aortic lymph nodal chain, where the lymph nodes are located more laterally at the renal hilus, as can be seen on the lymphangiograms.

Table 4-2.
Reference PTV margins (based on lymphangiograms and CT-scans) to the field borders by the radiation oncologists.

	> 5 mm	0 - 5 mm	-5 - 0 mm	< -5 mm
Parametria	5/17 (29 %)	2/17 (12 %)	0/17 (0 %)	10/17 (59 %)
Para-aortic lymph nodes	0/5 (0 %)	2/5 (40 %)	1/5 (20 %)	2/5 (40 %)

Discussion

In this multi-institutional study a definition and validation of the CTV for postoperative radiotherapy in early stage node-positive cervical cancer was obtained. Descriptions of the CTV and treatment plans for this type of radiation treatment were obtained from all Dutch radiation oncology centres [18]. There appeared to be no uniformity in the description of the CTV, as a result of which a reference CTV and PTV were defined based on 47 lymphangiograms and 15 CT-scans. The defined reference PTV included all regions that were considered part of the PTV, as described by the participating radiation oncologists. The in this manner obtained reference PTV was compared with the description of this target volume as defined in standard textbooks. Based on these descriptions and the fact that there is a very small risk of involvement of the pre-sacral lymph nodes [4], they were not considered as part of the target volume. The reference PTV was compared with the treatment portals delineated by the radiation oncologists.

Large variations in applied treatment portals were found. Part of the differences was due to variations in the CTV definition. There appeared to be three different CTV definitions, the first consisting of the primary tumour and parametria, part of the vagina, the obturator and iliac lymph nodes and the para-aortic lymph nodal chain. The second definition was similar, except for the para-aortic lymph nodal chain, and the third comprised the smallest CTV with the iliac lymph node region ending just above the lymph nodes at the level of the common iliac artery.

Apparently, five out of 17 radiation oncologists (29%) included the para-aortic lymph nodes in the CTV. Of the remaining 12 radiation oncologists, five included the iliac lymph nodal chain up to the level of the aorta bifurcation and seven intended to irradiate the lymph nodes onto the level of the common iliac artery.

Besides three different CTV definitions, there were also major variations in the shape and size of the treatment portals used within these three groups. This is probably due to some uncertainty as to the correct location of the primary tumour and the lymph nodal chains. Furthermore, a significant number of the oncology centres have 'standard' treatment portals for this radiation technique, only based on bony structures at the simulation films. They do not use routinely CT-based planning.

Therefore, standardization of the target volume seems warranted. To design correct treatment portals for this group of patients, the American Gynecologic Oncology Group has recommended to use the bony landmarks of the pelvis [11], but this does not seem to be correct in all cases [13]. Intraoperative measurements seem to be the most accurate [10]. The precise location of the lymph nodes can be determined with a preoperative bipedal lymphangiogram

[5,19,25]. However, this procedure, being burdensome to the patient, may be unnecessary in a large number of cases. In this group of patients only a few will in fact need postoperative radiation because of positive lymph nodes [12,20].

Therefore, we have tried to define a three-dimensional reference target volume for these patients including the para-aortic region [26], using 47 lymphangiograms to locate the position of the para-aortic and iliac lymph nodes. In this reference target volume the para-aortic lymph nodes were included, although only one-third of the participants considered the para-aortic lymph node region as part of the CTV. For this group of radiation oncologist the reference PTV will be helpful in defining correct portal images, also for extended field radiation. Most of the radiation oncologists however will irradiate the pelvis only. Computer tomography data of 15 patients after surgery for cervical carcinoma, compared with anatomical encyclopaedias, were used to assess the extent of the parametria at the pelvic wall. This reference PTV appeared to be up to 1 cm wider at the site of the pelvic rim and the left para-aortic lymph nodal chain than the target volumes and treatment portals we commonly use. The reference target volume was covered by 41% of the treatment plans of the radiation oncologists at the level of the parametria and by 40% at the level of the para-aortic lymph nodes. Moreover, in the para-aortic region none of the treatment portals covered the PTV with a margin of more than 5 mm, particularly on the left side of the para-aortic lymph nodal chain, where the lymph nodes are located more laterally at the renal hilus, as seen on the lymphangiograms.

A standardization of treatment volumes based on this reference PTV and CT-data allows for a more adequate design of treatment portals. Also, when using sophisticated 3-D conformal radiotherapy, this reference CT-based PTV can provide possibilities to reduce the volume of irradiated small bowel, while maintaining a high tumour control rate.

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Appendix 1.

Questionnaire postoperative irradiation of early stage cervical carcinoma.

1. Would you advise to irradiate this patient postoperatively?
2. If not, why?
3. What techniques are used for patient positioning, do you use laser lines and/or fixation materials?
4. Describe the target volume (CTV) and delineate the Planning Target Volume (PTV) the way used in your institute, on the enclosed simulation films and contours.
5. What margin do you take between the target volume and the field borders? Draw the field borders on the simulation films.
6. What energy would you use in a "normal" patient (diameter 24 cm)?
7. Describe the radiation technique used in your institute.
8. Do you use (computer)planning and if so, how many contours do you use?
9. How do you prescribe the dose?
10. Do you take positioning inaccuracy into account and in what way?
11. What is the total dose, dose fractionation and number of fractions a week?

CHAPTER 5

THREE-DIMENSIONAL TREATMENT PLANNING FOR POSTOPERATIVE RADIOTHERAPY IN PATIENTS WITH NODE-POSITIVE CERVICAL CANCER. COMPARISON BETWEEN A CONVENTIONAL AND A CONFORMAL TECHNIQUE

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Abstract

Purpose: Reduction of irradiated small bowel volume, using a conformal three-dimensional treatment planning technique in postoperative radiotherapy of cervical cancer patients.
Methods and Materials: Large gynecological treatment fields including the para-aortic nodes were analyzed in 15 patients. A conventional treatment plan with anterior and posterior (AP-PA) parallel opposed fields and a 3D four fields conformal radiotherapy plan with a central blocking of small bowel were compared for each patient. Dose volume histograms and dose parameters were established. Because of the tolerance constraints of the small bowel, the cumulative dose applied to the target was 48.6 Gy.
Results: The mean Tumor Control Probability (TCP) values for both the conventional and the conformal technique were 0.60 and 0.61 respectively, with ranges of resp. 0.56-0.67 and 0.57-0.66. The mean volume receiving 95% or more of the prescribed dose (V95) of the small bowel was 47.6% (32.5-66.3%) in the AP-PA technique and 14.9% (7.0-22.5%) in the conformal technique [$p < 0.001$], indicating a significant reduction in irradiated volume of small bowel in the higher dose range. The mean Normal Tissue Complication Probability (NTCP) decreased from 0.11 to 0.03 with the conformal plan. In patients who received a pedicled omentoplasty during surgery, the mean V95 for small bowel could be reduced to 8.5% (7.0-9.9%).
The mean median dose to the kidneys was only slightly elevated in the conformal treatment. Especially the mean dose to the right kidney in conventional versus conformal treatment was 3.3 versus 7.9 Gy. The mean near-minimum dose (D95) to the rectosigmoid decreased from 48.4 Gy to 30.1 Gy in the conformal plan compared to the conventional plan.
Conclusion: The small bowel dose can be significantly reduced with 3D treatment planning, particularly if a pedicled omentoplasty is performed. This allows dose escalation to the tumor region without unacceptable toxicity for the small bowel.

Introduction

Patients with cervical carcinoma, FIGO stage Ib-IIa are often treated by surgery, consisting of radical hysterectomy and pelvic lymph node dissection.

In case of histologically proven lymph node metastasis, postoperative radiation is frequently instituted. The target area usually consists of the small pelvis and, in some centers, the para-aortic lymph nodal region.

Emami *et al.* [9] have reported the incidence of para-aortic nodal metastasis by stage ranging from 0-8% (stage I), 5-44% (stage II), and 10-45% for stage III.

In fact, prophylactic para-aortic irradiation is an issue which is currently unresolved. However, Rotman *et al.* [26] did demonstrate a benefit in overall and distant metastasis free survival in patients with stage Ib (bulky), IIa and IIb. Also after follow up of 5 years [7, 27] overall survival was significantly better for those treated with extended fields compared to those treated with pelvic radiation (resp. 44% vs. 55%; $p = 0.02$). It is suggested by several authors that especially patients with histologically proven lymph node metastasis in the pelvic area might have benefit of elective para-aortic irradiation [2, 23]. In this specific group of postoperative patients we therefore chose treatment with extended fields.

If patients are to receive postoperative radiation to both pelvis and the para-aortic region, a large volume is treated, encompassing the primary tumor region, the proximal part of the vagina, the parametrial region, the pelvic lymph node regions (obturator and iliacal) and the para-aortic region to the level of lumbar 1. For a total dose of 48-50 Gy, the most important dose limiting organ is the small bowel, especially after surgery when a significant part of the small bowel is located at the level of the pelvis and fixed by postoperative adhesions [10].

With a "standard" three or four-field box technique, the dose to the kidneys might exceed the tolerance dose. Therefor, most radiotherapy clinics treat this volume by AP-PA technique [9, 14, 20, 23, 24, 27].

Several authors have emphasized that CT-treatment planning is needed for patients requiring four-field pelvic radiotherapy, because of a high incidence of inadequate margins at the primary tumor region [16], as well as the lymph node regions [3]. We developed a three-dimensional (3D) treatment planning technique based on CT-planning for the larger target area, including the para-aortic region. The dose volume histograms (DVHs) [6] of target and critical organs for the 3D treatment planning technique versus the AP/PA technique were analyzed.

Methods and materials

From January 1995 until October 1996, 15 patients were referred to the University Hospital Rotterdam - Daniel den Hoed Cancer Center for postoperative radiotherapy after radical hysterectomy and lymphadenectomy. All patients had an

adenocarcinoma or squamous cell carcinoma, stage Ib-IIa, of the cervix and histologically proven lymph node metastasis in the obturator and/or iliacal region. In two out of 15 patients a pedicled omentoplasty was performed to reduce the volume of small bowel in the pelvis, draping the omentum in the left paracolic gutter covering the vaginal vault. In all patients the same target volume was irradiated, regardless of the number of positive nodes. To reduce toxicity a 3D conformal treatment planning technique was developed.

All patients had a postoperative CT-scan in supine position, which extended from the top of thoracic vertebra 8 to the introitus of the vagina in 1 cm slice increments. Small bowel contrast was given 20-30 minutes before the scanning procedure in 8 patients. To visualize the lymph node regions, intraveneus contrast was applied.

Protocol summary

The Clinical Target Volume (CTV) consisted of the proximal two third of the vagina, the primary tumor region, the parametrial region to the fascia of the obturator internus muscle and the levator ani muscle, next to the pelvic walls. The CTV also contained the obturator node area on both sides. In the iliac region the CTV consisted of the external iliacal area from the posterior part of the inguinal ligament and the whole internal nodal area as well as the region of the common iliacal node chain. The para-aortic part of the CTV contained the nodal area from the level of the common iliacal nodes to the pedicles of lumbar 1.

A computer program [29] was used to obtain a 3D margin of 10 mm around the CTV to achieve the Planning Target Volume (PTV). This margin, albeit somewhat arbitrary, was chosen to cover for inaccuracy in positioning of the patient and mobility of the target area. Creutzberg *et al.* [5] showed that overall systematic differences between simulation and treatment images for the position of the gynecological patient in the field were 4.0 mm (one standard deviation [SD]) in the lateral direction and 4.2 mm in the craniocaudal direction, using laser lines and marking of the caudal field border. Little is known about the mobility during radiotherapy of retroperitoneal structures. The retroperitoneal part of the CTV is assumed to be relatively tight to vessel and nerve structures. We estimated a margin of 10 mm as the 95% confidence interval (2 SD) for positioning and the mobility of the CTV.

The position of the vagina, especially the top, might be influenced by the filling of rectum and bladder.

The normal tissues which were considered were the kidneys, the small bowel and the rectosigmoid. The specific end points used in calculating their normal tissue complication probabilities were resp. clinical nephritis, obstruction/perforation and obstruction/proctitis [4,8]. The small bowel, including the mesenterium, was outlined on the CT-scan at the most exterior line of the bowel wall and/or mesenterium. The rectosigmoid was outlined as the exterior

wall, including any possible feces, starting at the first slice of the CT-scan which contained both sigmoid and rectum and all the way down to the anal canal.

To standardize the procedure as much as possible, the CTV was defined and contoured on each slice for all patients. All patients were planned for the conventional non CT-based AP-PA portals (which were digitized) and for the conformal technique to compare the dose volume histograms.

Dose prescription and treatment technique

The dose prescription for the whole PTV was 48.6 Gy in fractions of 1.8 Gy per day, 5 fractions per week. The dose in the conformal technique was specified according to the ICRU 50 protocol [15]. The ICRU point was chosen as the intersection point of the beam axes at the first slice of the CT-scan which was located above the femoral heads, because this slice always contained the primary tumor region, i.e. the cervical and parametrial area, and because the dose is more homogeneous in this region. The dose in the conventional technique was specified in the midline, at the beam axes.

All treatment plans were calculated with 25 MV photon beams and Multileaf Collimation (MLC) with a projected leaf width at the isocenter of 1.25 cm[1].

The conventional technique consisted of two parallel opposed AP-PA fields with blocking of small bowel, kidneys and part of the hips. The field borders were determined by bony structures. The dose was specified in the midline of the patient.

The conformal technique basically consisted of four fields, namely two parallel opposed AP-PA and two parallel opposed lateral fields. In this technique a central block for the small bowel at the level of the small pelvis is used, i.e. between the legs of the iliacal lymph nodal regions. To create the possibility of a central block with the MLC, we used one large AP-field which contained the entire PTV, except the left iliacal nodes, together with a small AP-field consisting of the left iliacal part of the PTV only. In the large PA-field, the right iliacal nodes (together with the small bowel) were blocked, followed by a small PA-field for the right iliacal region. Technique shown in Figs. 5-1 and 5-2. The exact position of the small bowel block is determined on the basis of dose distributions per CT slice. (In case of massive involvement of posterior (common iliac) nodes, the central shielding should be reduced or even omitted because of the risk of presacral involvement).

The minimal margin between PTV and field edge in lateral direction turned out to be 0.7 cm. In cranial and caudal direction these margins had to be 1.0 cm and 1.6 cm, respectively, primarily due to the narrow PTV at these sides. The field weight of the lateral and PA-fields was 1.0; the weight of the AP-field(s) was 0.75. The source-isocenter distance was 100 cm in all fields.

[1] Scanditronics MM50 Racetrack Microtron.

Three-dimensional dose distributions were calculated for each plan. The dose distributions in transverse plots at all levels of the PTV were evaluated. In case of underdosage at the caudal part of the PTV of more than 5%, the leaves were withdrawn up to 0.5 cm to dissolve the underdosage.

Cumulative dose volume histograms (DVHs) were obtained for the PTV and critical organs as small bowel, kidneys and rectosigmoid for each patient and mean DVHs for all 15 patients were plotted. Also the mean of the difference between DVH for conformal and conventional plans were plotted, together with the standard deviation (SD).

Probabilities for tumor control (TCP) [13, 23] and normal tissue complication (NTCP) [18, 22] were calculated. In the algorithm for TCP calculation, a uniform dose of 48.6 Gy was equated to a TCP of 0.6 for microscopic disease. For the NTCP calculation, the parameters from Emami et al. [8] were used.

Statistics summarizing the dose distribution in the PTV and critical normal tissues included: V95: the volume receiving 95% or more of the prescribed dose; D5: the dose equalled or exceeded in 5% of the volume (near-maximum dose); D50: the median dose (equalled or exceeded in 50% of the volume), and finally, the D95: the dose equalled or exceeded in 95% of the volume (near-minimum dose).

Plan evaluation was conducted by two clinicians and involved:

1. Reviewing the isodose curves on the monitor of the treatment planning computer to obtain an overall impression of the dose distribution achieved.
2. Reviewing the DVHs, TCPs and NTCPs and statistics for each normal tissue at risk.
3. Analyzing "hot or cold spots" in transversal dose distributions and if necessary apply corrections in leaf position.

Results

Planning target volume and tumor control probability

The mean PTV of all 15 patients had a total volume of 989 cc (range 718-1206 cc).

The mean values of TCP, V95, D5, D50 and D95 are shown in Table 5-1. There appears to be no significant difference in tumor coverage between the treatment techniques. In the conformal technique the mean V95 was slightly better for the PTV (99.1 vs 96.7%). In Fig. 5-3 the mean cumulative dose volume histograms for both techniques, averaged over all patients, are plotted with the mean difference in volume between the techniques with standard deviations. In Fig. 5-3a the mean DVH for the PTV is shown. The dose distribution in the conformal technique is somewhat more homogeneous.

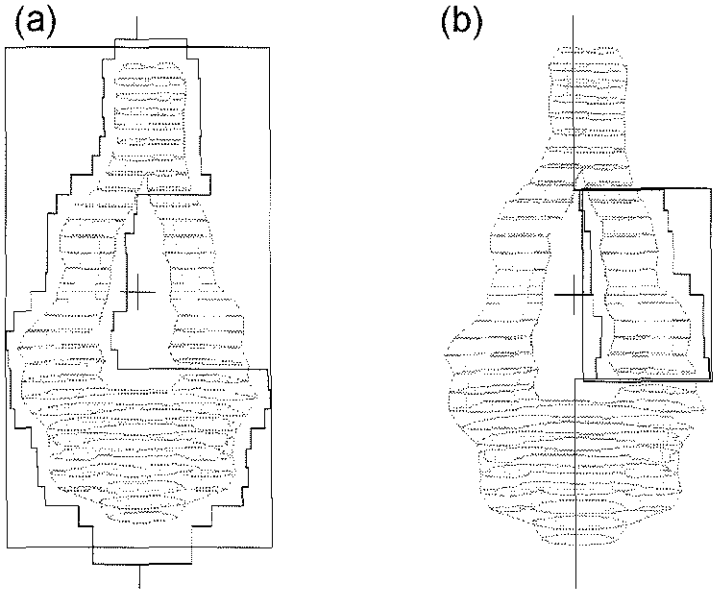

Figure 5-1a and 5-1b
Conformal therapy: CTV and PTV with leaf position in AP-direction. Blocking of the small bowel and left iliacal nodes (a); treatment of the left iliacal nodes only (b).

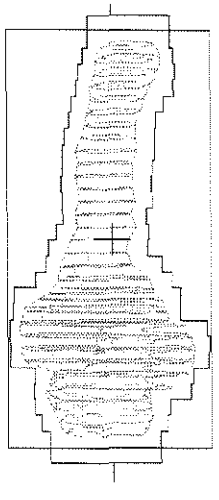

Figure 5-2
Conformal therapy: CTV and PTV with leaf position in right lateral direction.

Normal tissue coverage and complication probabilities.
Table 5-1 summarizes the mean dose statistics and NTCP values for the normal tissues studied.

Small bowel
The mean V95 was 47.6% (range 32.5-66.3) in the AP-PA technique and 14.9% (range 7.0-22.5) in the four-field technique, indicating that a significantly smaller part of the organ receives a high dose in the conformal technique [$p < 0.001$ with student T-test].

The D5 to the small bowel for the conventional plans exceeded the D5 for the conformal plans with an average of 1.8 Gy.

Figure 5-3b shows the mean cumulative DVHs of both treatment plans with the mean difference in volume for all 15 patients. Obviously, the advantages of the conformal technique versus the AP-PA portals are particularly found in the higher dose region, as in the lower dose region the small bowel in the conformal plan receives a higher dose because of the addition of the lateral portals. The significance of a low dose to a relatively larger volume of bowel is not well known.

The mean NTCP value of the small bowel for the conventional plan was 0.11 (range 0.07-0.18) and 0.03 (range 0.01-0.05) for the conformal technique, reducing the chance of severe complication significantly [$p < 0.001$ with student T-test].

In Fig. 5-4 the dose volume histogram for small bowel is shown for 1 of the 2 patients with the pedicled omentoplasty. Particularly in this group of patients, in which the small bowel is partly elevated out of the small pelvis, shielding of the central part of the bowel in the AP- and PA-fields is useful. Omentoplasty, together with the conformal technique with central blocking of the small bowel, reduced the V95 to 7.0 and 9.9% in these 2 patients.

Kidneys
As is shown in Table 5-1 the mean D50 for the right and left kidney is slightly higher in the conformal technique. The NTCPs in both treatment plans for both kidneys are 0.0. In Fig. 5-3 the mean dose volume histograms with the mean difference in volume are plotted for the left (c) and the right (d) kidney.

Rectosigmoid
The mean near-minimum dose (D95) to the rectosigmoid was 48.4 Gy (range 41.6-50.6) for the conventional plan and 30.1 Gy (range 22.1-39.3) [$p < 0.001$ with student T-test] for the conformal technique, indicating an advantage in the higher dose range. In Fig. 5-3e the mean dose volume histogram with the mean difference in volume for the rectum is shown.

Table 5-1. Comparison between conventional and conformal technique for 15 patients. Mean value with range for planning parameters for target and critical tissues.

Conventional technique

	(N)TCP(%)	V95(%)	D5(Gy)	D50(Gy)	D95(Gy)
PTV	0.60	96.7	51.0	49.8	47.2
	(0.56-0.67)	(96.2-100)	(49.4-52.9)	(48.4-51.1)	(44.6-49.0)
Small bowel	0.11	47.6	50.5	34.9	1.6
	(0.07-0.18)	(32.5-66.3)	(49.1-51.6)	(5.0-49.0)	(0.7-2.7)
Rectum	0.01	98.1	50.9	50.3	48.4
	(0.0-0.01)	(86.3-100)	(37.9-55.8)	(49.1-52.7)	(41.6-50.6)
Right kidney	0.0	0.5	17.8	3.3	1.3
	(0.0-0.07)	(0.0-6.3)	(1.9-46.5)	(1.1-15.3)	(0.4-2.5)
Left kidney	0.0	2.3	28.1	3.1	1.3
	(0.0-0.0)	(0.0-18.7)	(3.3-49.4)	(1.1-6.3)	(0.4-2.4)

Conformal technique

	(N)TCP(%)	V95(%)	D5(Gy)	D50(Gy)	D95(Gy)
PTV	0.61	99.1	50.7	49.4	47.6
	(0.57-0.66)	(98.7-100)	(49.7-51.9)	(49.1-50.7)	(46.6-48.6)
Small bowel	0.03	14.9	48.7	27.5	4.6
	(0.01-0.05)	(7.0-22.5)	(47.4-49.5)	(23.1-30.3)	(1.3-8.2)
Rectum	0.0	69.4	50.9	48.2	30.1
	(0.0-0.0)	(50.0-92.5)	(49.1-55.6)	(46.2-49.5)	(22.1-39.3)
Right kidney	0.0	0.03	25.6	7.9	1.5
	(0.0-0.0)	(0.0-0.5)	(4.1-30.5)	(1.1-25.3)	(0.4-2.6)
Left kidney	0.0	0.7	28.4	5.8	1.5
	(0.0-0.0)	(0.0-2.5)	(2.6-43.0)	(1.0-12.6)	(0.3-2.4)

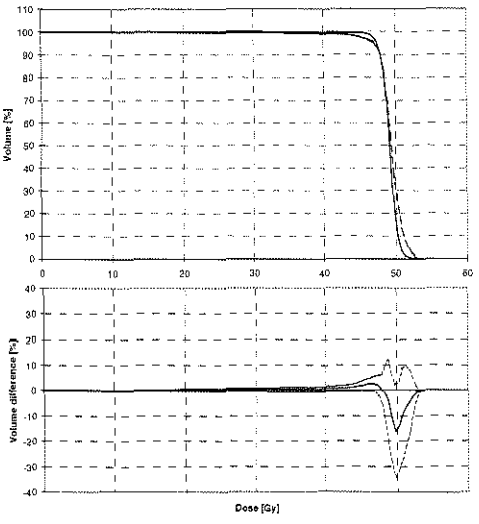

Figure 5-3a

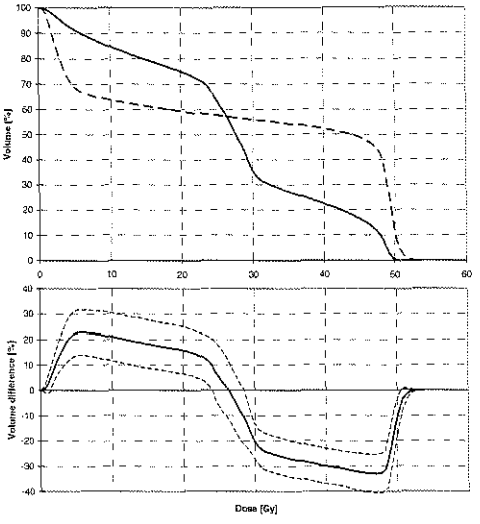

Figure 5-3b

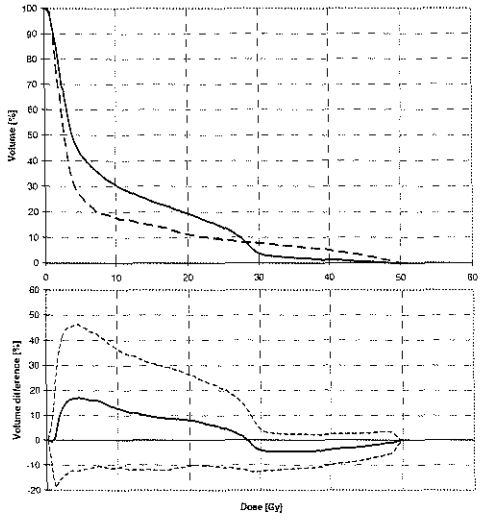

Figure 5-3c

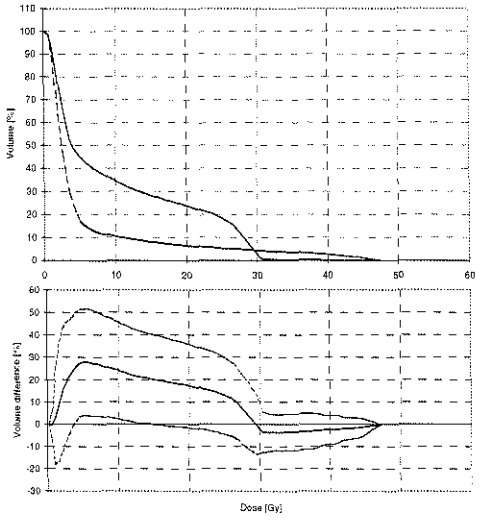

Figure 5-3d

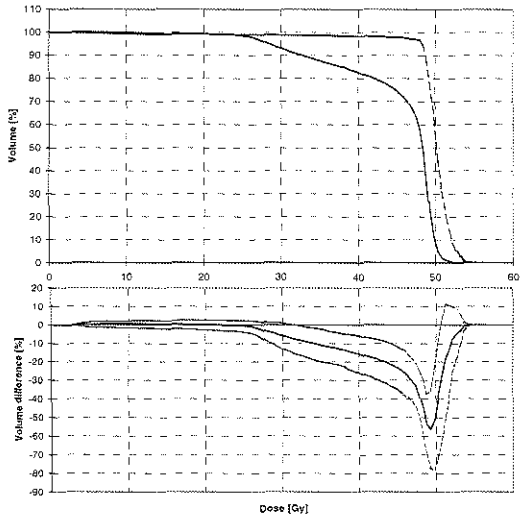

Figure 5-3e

Figure 5-3a to 5-3e
Mean cumulative dose volume histograms for all 15 patients for conventional (---) and conformal (__) technique. Underneath, the mean difference in volume for all patients (conformal minus conventional) is shown (__) with standard deviations for the differences (---). PTV (a), small bowel (b), left kidney (c), right kidney (d), and rectum (e).

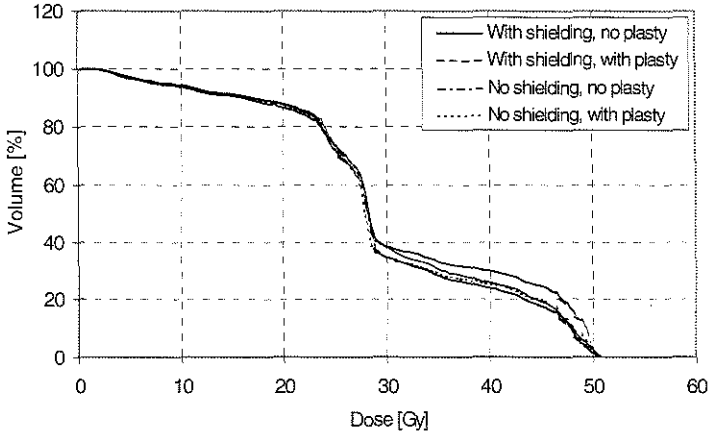

Figure 5-4
Dose volume histogram for the conformal technique for small bowel for a patient with a pedicled omentoplasty. The small bowel was contoured with omentoplasty and, based on other patient data, without omentoplasty. DVHs with and without omentoplasty and with and without central blocking of the small bowel are shown.

Discussion

In patients with cervical cancer, stage Ib-IIa with histologically proven lymph node metastasis in the obturator and/or iliacal region after surgery, postoperative radiotherapy might be of benefit for locoregional control [1, 11, 14, 17, 28].

Until recently, many radiation oncology departments were using parallel opposed fields in irradiation of the pelvis and the para-aortic nodes because of the position of the kidneys. By using a 3D four-field technique we were able to conform the dose to the prescribed target without surpassing the tolerance dose of critical normal tissues such as the kidneys.

We started a randomized toxicity study in which the conventional non CT-based AP/PA-technique is compared with the conformal radiotherapy technique, and evaluated the techniques of the first 15 patients treated to a total dose of 48.6 Gy.

The mean calculated TCP values for both techniques were almost equal. The mean V95 was slightly better in favor of the conformal technique.

Some parts of the normal organs at risk, including the small bowel and kidneys could be partly avoided in all beam directions. The separate block at the small bowel at the level of the small pelvis proved to be of additional value, reducing the mean V95 to 7.0-9.9%. An exeption for this central shielding should be made in case of massive involvement of posterior (common iliac) nodes. There could be a risk of involvement of presacral nodes which might be blocked by the central shielding.

The mean NTCP for small bowel could be significantly reduced from 0.11 to 0.03. V95 was reduced from 47.6 to 14.9%, indicating a significant reduction in irradiated volume in the higher dose range, somewhat at the cost of a higher volume of irradiated small bowel in the lower dose range.

As was demonstrated by Logmans *et al.* [21], the patients with pedicled omentoplasty had a volume reduction of the small intestine in the pelvis. In these patients, the central shielding of small bowel between the iliacal regions in the AP- and PA-fields of the conformal treatment was most beneficial.

In the conformal treatment the mean near-maximum dose to the small bowel was 48.7 Gy. Since at some levels of the para-aortic region the small bowel closely surrounded the target volume, it was inevitable that some parts of the small intestine received a dose equal or close to the target dose. In the literature, a variable increase in complications is observed in patients receiving over 50 Gy [19, 24], although in one study [26] doses ranging from 56-61 Gy were not significantly more hazardous than in case of pelvis irradiation only.

To improve local control rates in this group of patients, dose escalation studies might be performed in future. In addition to using the presented 3D conformal treatment technique, a substantial part of the small bowel will be shielded by

positioning the patient in a prone position in a belly board device [12] for the booster dose in the pelvic region.

However in pelvic radiotherapy an extensive analysis was done by Tait *et al.* to evaluate toxicity with conventional and conformal treatment [30]. No significant differences in acute toxicity could be detected. More data on late effects have to be available before dose escalation in cervical cancer can be performed, especially when the para-aortic region is included in the elective part of the treatment. In addition to potential dose escalation, we feel that the most essential part of the present CT-based technique is to define, standardize and delineate the CTV and plan the treatment fields in three dimensions as tight as possible, in contrast to the field definition with bony landmarks. The DVHs for small bowel indicate a significant reduction in the treated volume for the high dose region. Whether this contributes to a reduction of acute and late toxicity, has to be assessed from the present randomized study.

It must be emphasized that plans delivering doses appropriate for elective treatment may impact normal tissues in ways that are highly specific for the particular patient being studied. Careful analysis of dose distributions throughout the treatment volume is required before treatment is undertaken. In this study, no specific account was made for daily movement of normal tissues in and out of the fields, which might increase or decrease the dose to those organs.

Conclusion

Three-dimensional treatment planning allows careful analysis of the dose to the small bowel and kidneys which are expected to be limiting factors in radiotherapy at this site. With the described conformal technique the dose to the small bowel could be significantly reduced without exceeding the dose to other normal tissues.

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CHAPTER 6

REDUCTION OF IRRADIATED SMALL BOWEL VOLUME AND ACCURATE PATIENT POSITIONING BY USE OF A BELLY BOARD DEVICE IN PELVIC RADIOTHERAPY OF GYNECOLOGICAL CANCER PATIENTS

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Abstract.

Purpose: To reduce the volume of small bowel within pelvic treatment fields for gynecological cancer using a belly board device and to determine the accuracy of the prone treatment position.
Materials and methods: Fifteen consecutive patients with a gynecologic malignancy who were treated with postoperative pelvic radiotherapy were selected for this study. The volume of small bowel within the treatment fields was calculated for both the supine and prone treatment positions. The patients were treated in the prone position in a so-called belly board device. During treatment sessions electronic portal images were obtained. An off line setup verification and correction protocol was used and the setup accuracy of the positioning in the belly board was determined.
Results: The average volume of small bowel within the treatment fields was 229 cm^3 and 66 cm^3 in the supine and prone treatment respectively, which means an average volume reduction in the prone position of 64% (95% CI 56-72%) , as compared to the supine position.
For the position of the patient in the field, the systematic error defined by the standard deviation (SD) of the mean difference per patient between simulation and treatment images was 1.7 mm in the lateral direction, 2.1 mm in the craniocaudal direction and 1.7 mm in the ventrodorsal direction. On average, only 0.4 set-up correction per patient was required to achieve this accuracy. The random day-to-day variations were 1.9 mm **(1SD)**, 2.6 mm and 2.3 mm respectively. Standard deviations of the systematic differences between patient positioning relative to the bellyboard were 6.2 mm in lateral direction and 9.1 mm in craniocaudal direction.
Conclusions: Treatment of gynecological cancer patients in the prone position using a bellyboard reduces the volume of irradiated small bowel. An off line verification and correction protocol ensures accurate patient positioning. Daily setup variations using the bellyboard were small (1 SD < 3 mm). Therefore for pelvic radiotherapy in patients with a gynecological malignancy, the use of a belly board is recommended.

Introduction

Pelvic radiation therapy is often indicated in the treatment of patients with gynecological cancer. However pelvic radiotherapy to a dose of 45- 50 Gy causes severe late small bowel toxicity in 3 – 9 % of patients [3,15,18]. In order to decrease the volume of irradiated small bowel, various techniques have been used, e.g. surgical displacement of the small bowel out of the pelvis using mobilized omentum which is repositioned in the pelvis, or the placing of a synthetic prosthesis under the small bowel [16,17,21]. Some investigators have treated patients in the prone position with or without a bellyboard device to displace small bowel loops out of the pelvic fields. The use of an open tabletop [12], a bellyboard [20] or a small bowel displacement device [11] have been described.

Using radiation techniques with patients in the prone position, the accuracy of daily patient positioning can be an uncertain factor. There are no data available concerning the positioning accuracy in the prone position for gynecologic malignancies, in contrast to prostate cancer or rectal cancer [4,19,22,23]. This study was carried out to investigate the reduction of irradiated small bowel volume by using a bellyboard device and to study the setup accuracy in the prone position.

Patients and Methods

Fifteen patients with a gynecologic malignancy (10 endometrial cancer patients, 2 patients with sarcoma of the uterus and 3 patients with cervical cancer), who received postoperative pelvic radiotherapy, were included in this study. Patient age ranged from 49-79 years (mean 65 years). All patients were treated using a four-field box technique with shielding of parts of the small bowel, part of the rectum and the hip joints. A total dose of 46-50.4 Gy was given in 23-27 daily fractions of 1.8-2.0 Gy, using 23-25 MV photon energy in an overall treatment time of 4.5 to 5.5 weeks. The upper border of the treatment fields for cervical cancer was located between L3-L4, for sarcoma of the uterus between L4-L5 and for endometrial cancer between L5-S1.

All patients were simulated and treated in the prone position using a so-called bellyboard. This bellyboard is a device made of high impact polystyrene (HIPS)[2] with a thickness of 4 mm. The board contains 2 apertures; a large aperture in the center of the board for the belly region and caudally a smaller aperture for the pubic bone (Figure 6-1). For comfort, the lower part of the bellyboard has been adapted to support the upper legs. The bellyboard is used in

[2] Polymarin thermoforming BV.

combination with a prone pillow for head and arms and a small roll is placed under the ankles. In order to push the small bowel in cranial direction, the pubic bone must be positioned in the specially made 'pubic aperture'. This pubic aperture was marked with barium contrast to verify the position of the patient's pubic bone during simulation.
During the simulation procedure, the small bowel was visualized using bariumcontrast, administered orally 20 minutes before the simulation started. Simulation radiographs in the anterior-posterior (AP) and right lateral directions were obtained in both the supine position and in the prone position using a bellyboard in order to compare the small bowel volume in the respective radiation fields (Figure 6-2). If the volume of small bowel within the treatment fields in the prone position was reduced, the simulation procedure was completed in this position and the patient was treated using the bellyboard. The isocenter position (posterior and lateral) was visualized using laser equipment and marked on the patient's skin by small tattoos and long axial ink lines. To enable a reproducible position of the patient in the belly board, the longitudinal isocenter position was marked on the device (Figure 6-3).

For 12 of the 15 patients, the volume of small bowel within the treatment fields, in both the supine and the prone position, could be evaluated. In the AP and lateral radiographs, the areas where barium contrast was present within the fields in the supine and the prone position, were determined. In the other 3 patients the small bowel was not sufficiently visualyzed on both radiographs. Following Letschert et al. [15], these areas were divided into a grid of 1×1 cm squares. The products of the segment lengths in the two projections were summated, in order to generate a measure of the small bowel volume within the treatment fields (Figure 6-2C) [7,15]. The volumes calculated for the supine and the prone position were compared and the reduction of irradiated volume of small bowel in the prone position was calculated.

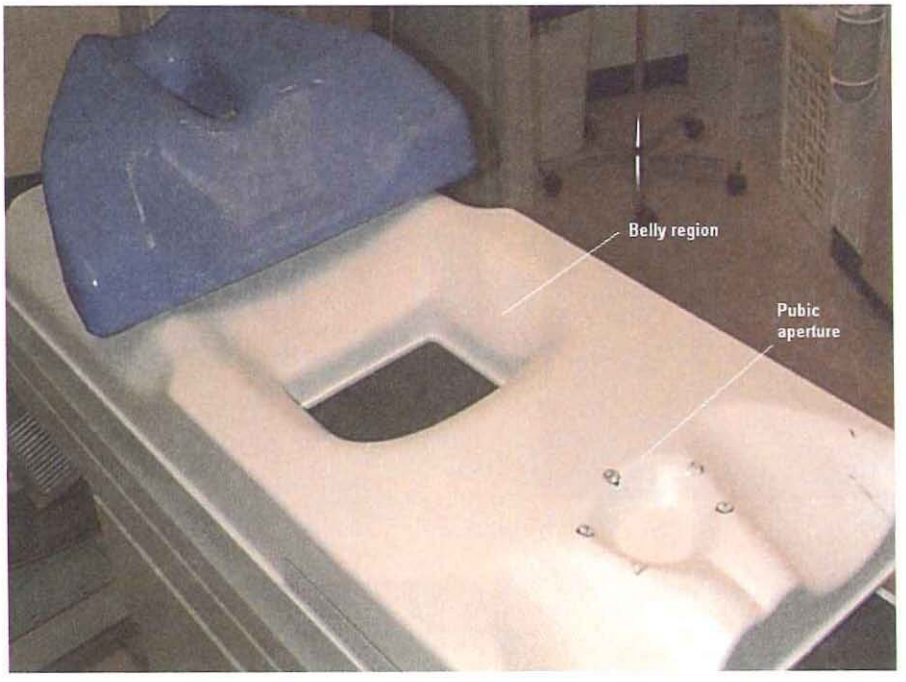


Figure 6-1
High impact polystyrene belly board for pelvic radiation treatment in prone position, used in combination with prone pillow for head and arms. The large aperture in the centre of the board is for the belly region and the small caudal aperture for the pubic bone (the pubic aperture is marked to verify the position of the patients pubic bone during simulation).

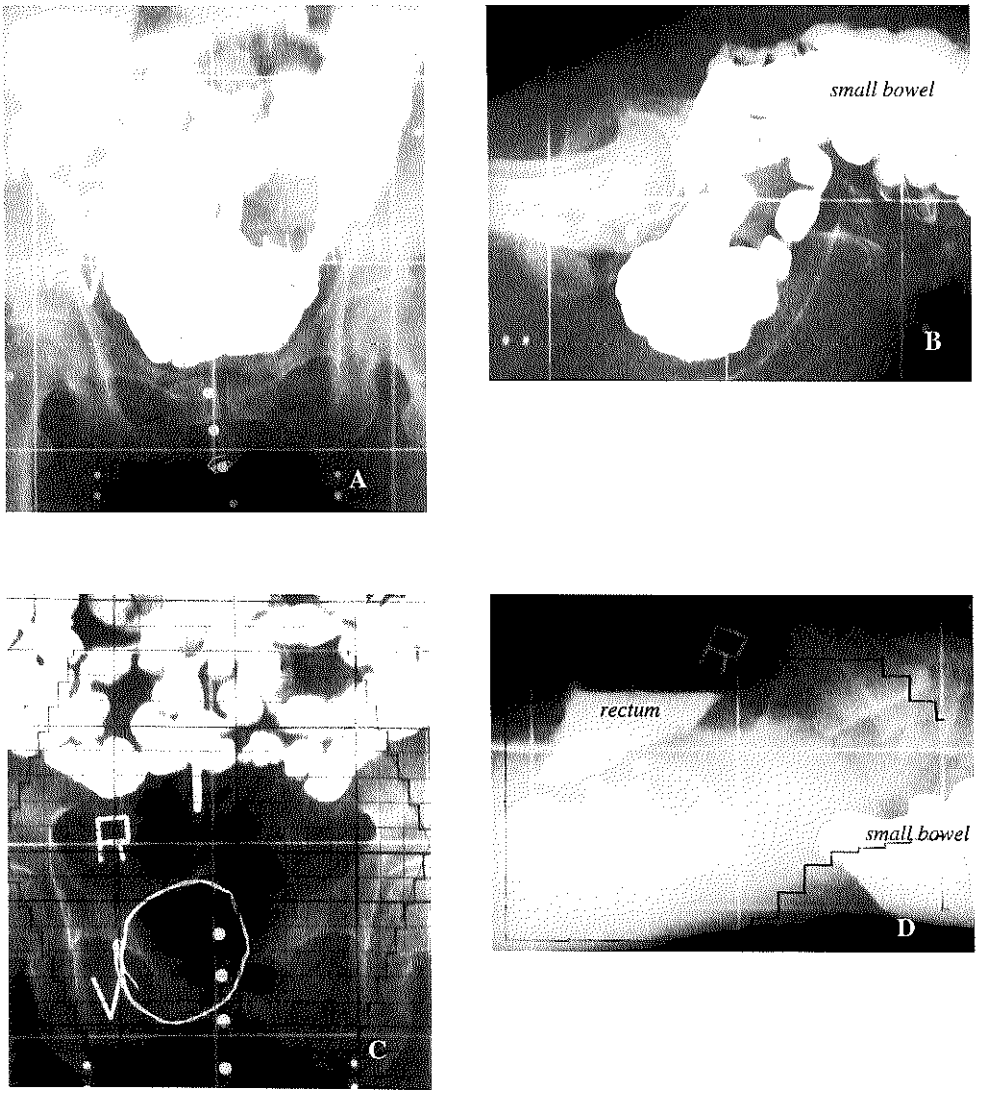


Figure 6-2
Simulation radiographs in the anterior-posterior (A) and lateral (B) direction in the supine position of a patient with an endometrial carcinoma after abdominal surgery. Radiographs in the anterior-posterior (C) and lateral (D) direction in the prone position in the belly board of the same patient. The small bowel is visualized with Barium contrast. Vaginal tube for localization of the top of the vagina inserted. Pubic aperture is marked to verify the position of the patient's pubic bone during simulation. One of the four markers in the belly board for analysis of positioning in the board is visible underneath contrast area. Radiograph C also shows the division of contrast areas into a grid of 1 × 1 cm squares (same applies for lateral direction).

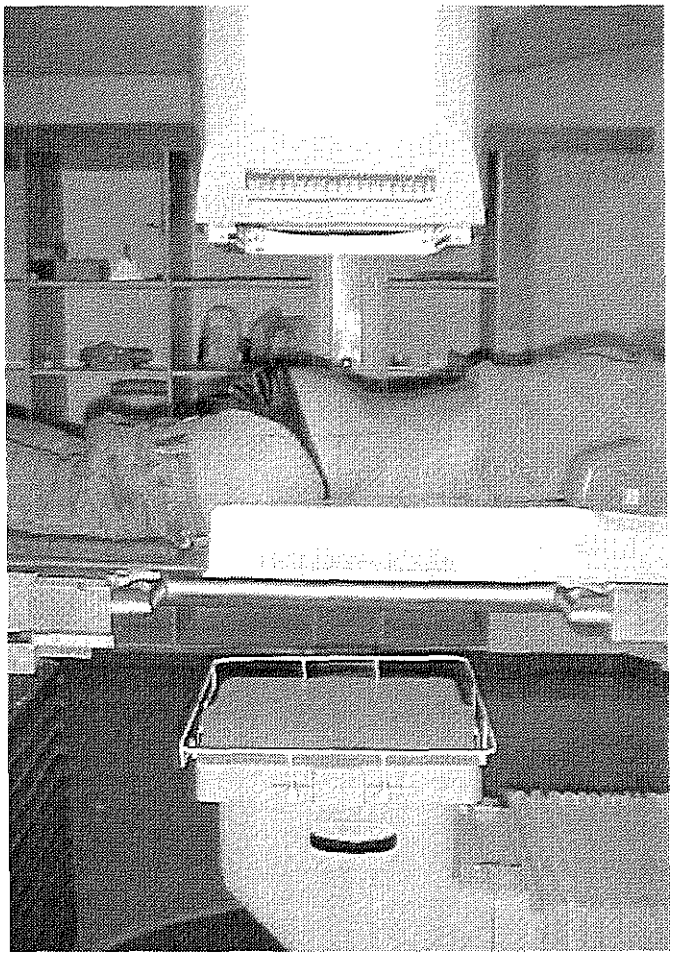


Figure 6-3
Patient positioned in the belly board with isocenter position (posteriorly and laterally) marked on the skin, using long laser lines and small tattoo points. The longitudinal isocenter position is marked on the belly board.

As the patient setup in prone position was expected to be less reproducible than in the supine position, the accuracy of daily patient positioning in the prone position in the belly board was determined using an EPID[3]. During setup the position of the bellyboard on the treatment table, and the position of the patient in relation to the bellyboard, were determined using lateral and sagittal lasers. The lateral tattoo points were the most important parameters for setup.

During the treatment sessions portal images were obtained. An off-line verification and correction protocol was used [2,10,22] to verify the position of the individual patient during four subsequent fractions in order to ascertain the systematic setup deviation for that patient. At each of these fractions, the position of the patient was calculated off-line and the three-dimensional displacement vector of the isocenter with respect to digitized simulator films was tested against a preset action level. The initial action level for correction was 12 mm, based on previous studies in gynaecological patients [4,13,22]. The action level shrunk at each subsequent fraction; after N measurements, the action level was the initial action level divided by the square root of N. The setup error which was tested against this level is the length of the mean displacement vector over N measurements. After a setup correction, again 4 measurements had to be performed. If, after 4 subsequent measurements, the action level was not exceeded, the setup accuracy was next verified (and corrected if necessary) by means of weekly measurements. During these weekly measurements the average displacement over the last 4 measurements was tested against the lowest action level. This protocol was proven to be a useful tool to reduce systematic setup errors in previous studies [2].

Bony structures (pelvic rim and sacrum) were used to determine the setup errors in the posterior and lateral fields. Differences between the simulation and treatment positions were calculated in all directions and the mean errors and the standard errors of the mean were determined. The mean (M) is the average of the mean error per patient, over all patients. The random error (σ) is the standard deviation of the day-to-day variations, averaged over all patients (i.e. the interfraction variation), whereas the systematic error (Σ) is the standard deviation of the mean error per patient (i.e. the interpatient variation). From these data, the random and systematic errors if no correction protocol was used, were derived by calculation.

The position of the bellyboard with respect to the treatment field was analysed in the PA fields by comparing the position of 4 lead markers in fixed positions within the bellyboard to their position on the simulator films. Next, the position of the markers was compared with the position of bony structures of the patient (sacrum and pelvic rim). Thus, the movement of the patient with

[3] Philips SRI 100 for 10 patients. Siemens Beam View Plus for 5 patients.

respect to the bellyboard was determined. The markers in the bellyboard were only visible in the PA direction (as they fell outside the lateral treatment fields). Therefore this analysis was limited to translations in lateral and craniocaudal directions.

Data analysis

For each of the 12 patients which could be evaluated for the volume of small bowel within the treatment field, the reduction in prone position was determined and the mean reduction was calculated.

For all 15 patients the mean setup deviation and standard deviation (SD) of the variation around that mean were determined in the medio-lateral and cranio-caudal direction. Then the mean-of-means M, the variation of means Σ (systematic error) and the mean of variations σ (random error) were calculated. Statistical correlation of data was performed with the linear correlation test, using the Stata™ program. In all cases a two sided significance level of 5 % was used and the linear correlation coefficient r was determined.

Results

Volumes

For 11 out of 12 patients, the volume of irradiated small bowel in the prone position using the bellyboard was reduced as compared to the supine position. (See Table 6-1).

The mean small bowel volume within the fields in the supine position was 229 cm^3 (range 4-529 cm^3), while in the prone position using the bellyboard this mean volume was 66 cm^3 (range 0-174 cm^3). The mean reduction of small bowel volume in the treatment fields was 163 cm^3 (64% with 95% CI 56- 72%) with a range of 0-496 cm^3 (0-100%).

Positioning

Data on the accuracy of patient positioning were available for all 15 patients. A total of 142 treatment sessions were imaged, an average of 9.5 per patient. In each treatment session 3 fields (PA, left lateral, right lateral) were imaged and analysed. Measured translations are shown in Figure 6-4. The plots show the mean translations in all three directions and standard deviations of the distribution of measurements for each patient, using the correction protocol. For all patients, the overall set-up deviations for translations in lateral, cranial-caudal, and ventral-dorsal direction are presented in Table 6-2. Using the correction protocol, the average number of corrections per patient was 0.4. The calculated systematic errors which would have occurred without using the correction protocol were about twice as high as the value of the systematic

errors with correction protocol (see also Table 6-2). These results are similar to the ones found in a multicenter study for prostate patients (systematic errors in x, y and z-direction in our institution without correction protocol were resp. 2.9, 2.1 and 3.3 mm) [2].

Table 6-1.
Comparison of small bowel volume within the treatment fields in the supine and the prone position.

Small bowel volume	Supine (cm^3)	Prone (cm^3)	Reduction (cm^3)	Reduction (%)
Patient number				
1	217	35	182	84
2	141	64	77	55
3	35	0	35	100
4	394	25	369	94
5	529	33	496	94
6	500	148	352	70
7	169	56	113	67
8	301	174	127	42
9	328	165	163	50
10	4	4	0	0
11	102	93	9	9
12	28	0	28	100
Mean (95 % CI)	229	66	163 (138- 188)	64 (56- 72)

For analysis of the position of the patient in the belly board, we have used the same definitions as for the patient set-up data, i.e. Σ is the SD of the systematic shifts relative to the simulation films and σ is the SD of the random variations. The translations were calculated in lateral and craniocaudal direction only, for reasons mentioned in the methods section. The results are shown in Table 6-3. Relatively large systematic errors in lateral (Σx) and craniocaudal (Σy) directions were found for the patient shift relative to the bellyboard markers. Especially Σy appeared to be more than 9 mm. There appeared to be no correlation between the patient variation in the bellyboard in x-direction (based on the marker analysis) and variation of the position of the patient within the treatment fields ($r=0.06$, $p=0.45$). However a larger translation between simulation and treatment in the y-direction of the patient in the belly board resulted in a significantly larger value of Σy in the patient set up ($r=0.27$, $p=0.001$). Also a correlation was found between the patient diameter (range 17 to 22 cm with a mean of 20 cm) and σy (the random patient variation in the

bellyboard in y-direction); with increasing patient diameter, the patient positioning in the craniocaudal direction was less accurate (r=0.55, p=0.05).

Table 6-2.
Accuracy of patient positioning within the treatment fields (patient setup accuracy in mm).

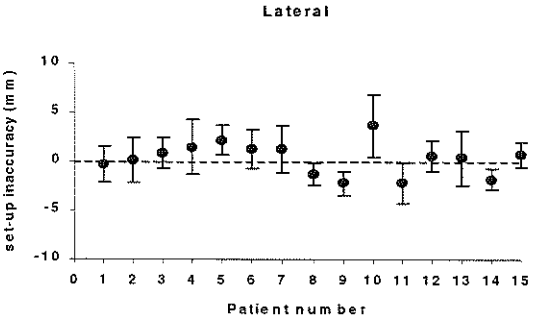
	Mx	My	Mz	σx	σy	σz	Σx	Σy	Σz
In case no correction protocol was used	0.7	-1.8	-0.9	1.9	2.6	2.3	2.5	3.7	3.6
With correction protocol	0.3	-0.8	-0.4	1.9	2.6	2.3	1.7	2.1	1.7

M = mean of means (mean error per patient, averaged over all patients)
x = patient positioning error compared to the treatment field in lateral direction
y = positioning error in cranial-caudal direction
z = positioning error in ventral-dorsal direction
σ = random error (standard deviation of the day-to-day variations, averaged over all patients)
Σ = systematic error (standard deviation of the mean error per patient)

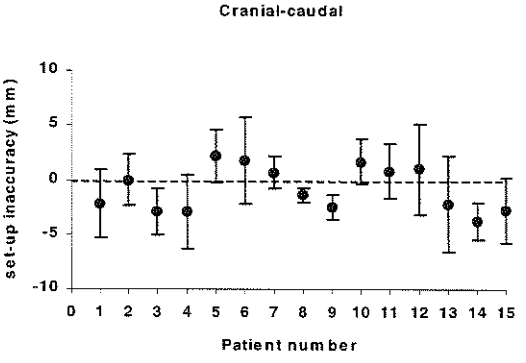
Table 6-3.
Positioning of the patient in the bellyboard; position of markers in comparison to bony structures of the patient (fiducial marker analysis in mm).

	Mx	My	σx	σy	Σx	Σy
marker	0.7	-1.3	5.5	4.8	6.2	9.1

M = mean of means
x = patient positioning error compared to bellyboard markers in lateral direction
y = positioning error in cranial-caudal direction
σ = random error
Σ = systematic error



(a)



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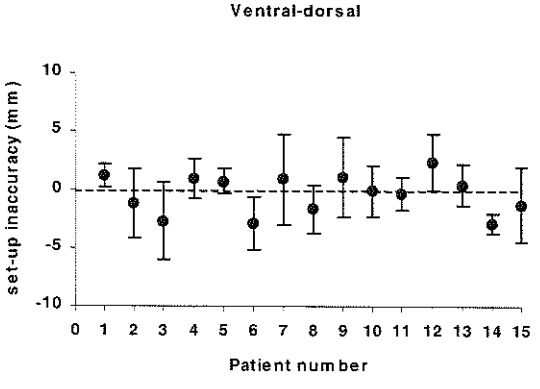

(c)

Figure 6-4
Mean translations in mm and their standard deviations for each patient in the lateral (a), cranial-caudal (b) and ventral-dorsal (c) directions.

Discussion

Small bowel toxicity is the main cause of morbidity and the dose-limiting factor during pelvic radiotherapy [3,7,9,14,20]. Prevention of radiation enteritis using special techniques and/or tools reducing the risk of acute and late complications, is therefore needed.

Surgical and non-surgical procedures to displace small bowel out of the irradiation fields have been investigated [16,17,21]. Treatment in the prone position using a bellyboard has been shown to be an effective technique to minimize the volume of irradiated small bowel in pelvic radiotherapy [3,5-7,9,14,18,20]. However when patients are treated in the prone position, the substantial setup error-rate, especially in elderly or obese patients, is of reported concern [19,20].

In this study the volumes of small bowel within the treatment fields in the supine position and the prone position were compared, yielding a mean reduction of 163 cm^3 (64% with 95% CI 56- 72%) when using the prone position in the bellyboard. In the power law model, described by Letschert e.a. [15], data on small bowel complications are related to the equivalent total doses for several small bowel volumes. The complication rate for a small bowel volume V is calculated by a logistic function, using the ratio between V and a reference small bowel volume V_{ref}. For the volume exponent n, they found a value of 0.26 ± 0.05. If we use this power law model for our data to calculate the increase of total dose to maintain the same complication rate, a mean reduction of irradiated small bowel volume of 229 to 66 cm^3 means an increase of the iso-effect dose of 38% ($(V/V_{ref})^{-0.26}$). However, the advantage strongly varies due to the great interpatient variation of small bowel volume within the treatment field. Other studies showed similar results [3,5,6,20].

Holst e.a. described a small bowel displacement device that is fixed to the treatment table [11]. A disadvantage of this method can be the difficult verification of patient positioning in relation to the device after the patient has been positioned. Moreover, lateral or longitudinal table motions will disturb the location of the device in relation to the treatment field center. Shanahan et al [20] used customized bellyboards made for each patient individually which is more expensive and time consuming.

Using a standard bellyboard, only one or two devices in a linac room are needed. No extra time is needed to position the device on the table and patients can be positioned easily. In our experience, patients seem to tolerate the device easily, in spite of previous abdominal surgery, especially if the device was used in combination with a prone pillow.

The average daily random set-up variations in our study were small (1 SD < 3 mm). The individual patient range in daily setup variation is 1 to 4 mm. These results are better than the setup variations for gynecologic pelvic fields

treating patients in the supine position [4,13]. Thus, the prone position in a bellyboard in combination with a prone pillow was proved to be reproducible for pelvic radiotherapy in gynecological patients. Perhaps positioning using skin markings on the back in stead of the abdominal skin, contributes to the reproducibility.

The patient positioning in the bellyboard showed much larger systematic errors (Σx=6.2, Σy=9.1 mm) than the treatment field analysis (Σx=1.7, Σy=2.1 mm). The largest systematic error was observed for the craniocaudal direction. We can only speculate that at the simulation procedure the patients were not yet used to the position in the pubic aperture, while during the treatment sessions this became more comfortable. Therefore, the systematic error for positioning in the bellyboard might partly be due to rotation of the pelvic rim. However from the EPID images we found that the positioning of the patients in relation to the treatment fields was accurate (Table 6-2). An alternative explanation could be that the patient positioning accuracy is more dependent on the adjustment of the laserbeams to the skin marks than on the patient positioning in the belly board. This hypothesis is supported by the observation that not only the systematic errors but also the random errors are larger in relation to the belly board than to the treatment fields.

In this study a patient positioning off-line correction protocol was used with an initial action level for correction of 12 mm. Using this protocol the resultant systematic errors in x, y, and z-direction were very small (1.7 – 2.1 mm), which is comparable with the accuracy of positioning obtained in radiation treatment of prostate cancer patients [1,2] and means a significant reduction in comparison with systematic errors in gynecological patients from previous studies without a correction protocol [4,8,10]. There was an average of only 0.4 corrections per patient due to the relatively small random deviations. For future positioning studies for gynecologic patients in our institution, a correction protocol with an initial action level of 9 mm will be used.

It is clear that the prone position with a standard bellyboard provides a significant reduction of irradiated small bowel volume in gynecologic patients (Table 6-1). Analysis of the variation of patient positioning using an off-line correction protocol showed decreased random and systematic errors in comparison with previous studies. The prone position in a bellyboard has therefore been introduced in our department as the standard positioning technique for pelvic radiotherapy in gynecological cancer patients.

Acknowledgements

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The bellyboard used in this study is a copy of the one that is used in this department. The staff of our Mouldroom is greatfully acknowledged for their support.

Information about the belly board

Information about the belly board can be obtained from Sinmed BV, Pasteurstraat 6, 2811 DX Reeuwijk, the Netherlands. Tel.: 31(0)182-394495 or www.sinmed.nl.

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CHAPTER 7

ON-LINE SET-UP CORRECTIONS DURING RADIOTHERAPY OF PATIENTS WITH GYNECOLOGICAL TUMORS

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Abstract

Purpose: Positioning of patients with gynecologic tumors for radiotherapy has proven to be relatively inaccurate. To improve the accuracy and reduce the margins from clinical target volume (CTV) to planning target volume (PTV), on-line set-up corrections were investigated.
Methods and Materials: Anterior-posterior portal images of 14 patients were acquired using the first six monitor units (MU) of each irradiation fraction. The set-up deviation was established by matching three user-defined landmarks in portal and simulator image. If the two-dimensional deviation exceeded 4 mm, the table position was corrected. A second portal image was acquired using 30 MU of the remaining dose. This image was analyzed off-line using a semi-automatic contour match to obtain the final set-up accuracy. To verify the landmark match accuracy, the contour match was retrospectively performed on the six MU images as well.
Results: The standard deviation (SD) of the distribution of systematic set-up deviations after correction was < 1 mm in left-right and cranio-caudal directions. The average random deviation was < 2 mm in these directions (1 SD). Before correction, all standard deviations were 2 to 3 mm. The landmark match procedure was sufficiently accurate and added on average 3 minutes to the treatment time. The application of on-line corrections justifies a CTV-to-PTV margin reduction to about 5 mm.
Conclusions: On-line set-up corrections significantly improve the positioning accuracy. The procedure increases treatment time but might be used effectively in combination with off-line corrections.

Introduction

Geometric uncertainties in radiotherapy

Conformal radiotherapy aims at limiting toxicity of critical organs while maximizing the tumor dose. This goal can be partly achieved by minimizing the treatment field size. The treatment field size is mainly determined by the size of the tumor including subclinical disease and by the margins applied to compensate for geometric uncertainties that occur during radiotherapy. Following the nomenclature proposed by the International Commission on Radiation Units and Measurements (ICRU), the gross tumor volume plus subclinical disease is called clinical target volume (CTV), and the CTV plus safety margins is called the planning target volume (PTV) [1]. Minimization of these so-called CTV-to-PTV margins, i.e. restraining internal tumor movement and maximizing the patient set-up accuracy, will therefore benefit conformal radiotherapy.

Set-up accuracy of patients with gynecologic tumors

Patients with gynecologic tumors seem somehow more difficult to position accurately on the treatment couch than patients with prostate cancer [2], which is treated in the same pelvic region. Rather large set-up deviations have been reported in the literature [3-5]. In recent years, several set-up techniques have been investigated in our institute as well [3,6]. However, they all yielded more or less the same distributions of random (day-to-day) set-up variations; the average standard deviations (σ) were about 3-4 mm in each of the three main directions. Since the simulator film which is used as reference image can be considered as one sample from those distributions, it is plausible that the standard deviation of the distribution of systematic (everyday) set-up deviations for the whole patient group (Σ) initially had similar values [7].

Off-line set-up corrections

The only significant improvement of the set-up accuracy was obtained by application of an off-line set-up verification and correction protocol [2,7,8]. The set-up deviations of subsequent fractions are averaged and compared with an action level that decreases with the square root of the number of measurements. If the average deviation exceeds the action level, a table correction will be applied to the following fractions and the protocol is restarted. The procedure stops if a specific number of measurements is performed without correction. Using such a protocol with about ten measurements per patient, the systematic variations for patients with gynecologic tumors were reduced by a factor two [6], as for patients with prostate cancer [2]. Random variations are not affected by the off-line protocol.

CTV-to-PTV margins
In our institute, the CTV-to-PTV margin for patients with gynecologic tumors is mainly determined by the set-up deviations; the internal CTV movement is considered to be relatively small (although this is the subject of an on-going study). Using the off-line protocol, a margin of 1 cm can be applied. This is based on previous research which concluded that the margin should be equal to at least $2\Sigma+0.7\sigma$ to guarantee an adequate tumor dose [9]. Inserting $\Sigma = 2$ mm and $\sigma = 4$ mm in this formula, results in margins of only 7 mm. However, this value is rounded up to 1 cm because of other geometric inaccuracies such as delineation uncertainty and internal organ motion.

On-line set-up corrections
To increase the cure rate, we are currently considering to raise the tumor dose for some patients with gynecologic tumors to 60 Gy. In the literature, it has been reported that maximally 30% of the small bowel volume should receive a dose of over 55 Gy [10,11]. With the current CTV-to-PTV margins, it is not always possible to fulfil this criterion for tumor doses higher than 55 Gy. Reduction of margins might be justified if an on-line instead of an off-line set-up protocol is applied. With on-line corrections, the set-up deviation is determined and corrected before the (bulk of the) daily treatment dose is given. Other groups have reported superior set-up accuracies at the cost of increased treatment time [5,12-18]. In this paper, we will discuss whether on-line set-up corrections are beneficial and clinically feasible in our institute.

Methods and materials

Treatment planning and immobilization
Fourteen patients with gynecologic tumors were included in the study. The patients were irradiated with a four-field box technique if the CTV could be restricted to the primary tumor region, the proximal two-third of the vagina, the parametria, and the obturator and iliac lymph nodes. If the CTV included para-aortic lymph nodes, anterior-posterior/posterior-anterior (AP/PA) fields were used. The CTV-to-PTV margin was 1 cm. The AP/PA patients were treated with a source-to-skin distance of 100 cm, whereas the box technique was isocentric. The total dose varied from 46 to 48.6 Gy and the number of fractions from 23 to 27. All patients were treated in supine position at the same accelerator[4] with 25 MV photons and a multileaf collimator.

[4] MM50 Racetrack Microtron, Scanditronix Medical AB, Uppsala, Sweden

For patient positioning, long lateral, sagittal and transversal laser lines were marked on the patient. The intersection points of these lines were tattooed, together with the caudal field border. A knee roll was used to decrease the pelvic rotations and a homemade foot support further secured foot and leg position. The legs were slightly exorotated to ensure decreased muscle tension in the legs and the buttocks. The arms were positioned above the head by a commercially available arm support[5]. In case of discrepancy between the skin marks in longitudinal direction, the caudal field border tattoo was the decisive parameter for set-up [3,6]. For isocentric treatments, the isocenter-to-table distances were used for table height position. The focus-to-skin distance was measured before each fraction.

On-line correction protocol

To determine the deviations in patient set-up, the position of bony structures in AP portal images were compared with corresponding positions in a reference image. The portal images were acquired with a commercially available electronic portal imaging device (EPID)[6]. The technical characteristics of this system were described in previous publications [19,20]. An on-line set-up correction procedure was developed using the high-level script language designed to operate the EPID system automatically. The procedure can be separated in four steps:

1. Before treatment, the operator selects a maximum of three anatomical landmarks in a digitized simulator radiograph (i.e. the reference image), which is displayed on a monitor. For all treatment fractions, these landmarks will reappear automatically in the reference image. Useful landmarks for AP pelvic images are the pubic symphysis and the intersections of horizontal and vertical tangents to the pelvic rim [5], as indicated in Fig. 7-1a.
2. The patient is positioned on the treatment couch and a portal image is obtained using the first 6 monitor units (MU) of the treatment dose, after which the irradiation is automatically interrupted. The image quality is improved by automatic adjustment of the display contrast. Landmarks similar to those in the reference image must be defined in the portal image. The image quality of a 6 MU image is usually sufficient to discriminate most of the bony structures, as is shown in Fig. 7-1b; however, in some cases the pubic symphysis can be less pronounced. In case of extreme set-up deviations, the pelvic rim can partially disappear behind the field defining blocks. However, normally at least two landmarks can be indicated to enable image registration.

[5] Sinmed BV, Reeuwijk, The Netherlands

[6] SRI-100, Electa Oncology, Crawley, Great Britain

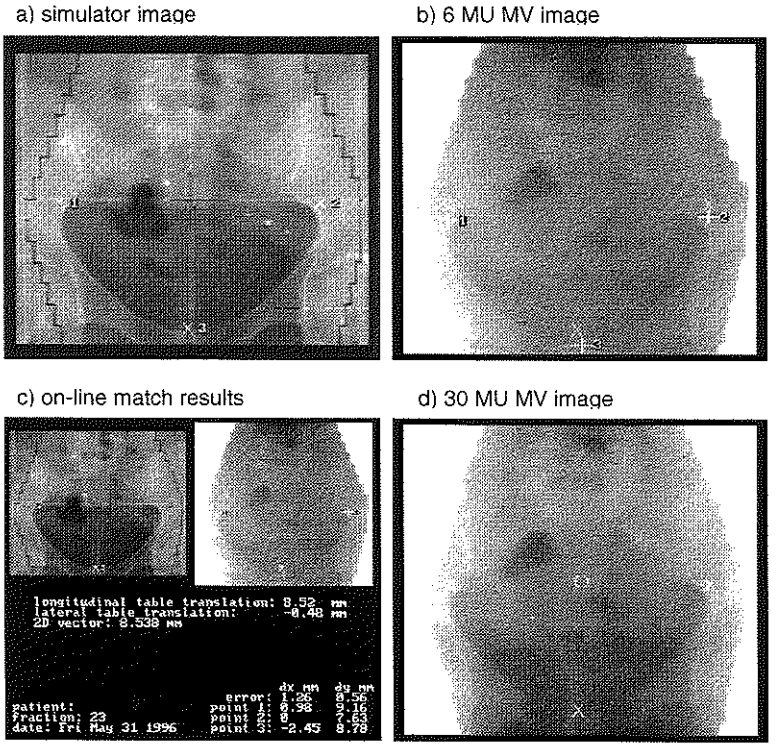

Figure 7-1
The on-line set-up correction procedure. In (a) the digitized simulator image is shown in which three reference landmarks are defined (crosses, x). Next, (b) a 6 MU EPID image is obtained in which the same landmarks are selected (numbered plusses, +). The landmarks are matched (c) and table translations are shown. A correction must be performed if the 2D vector is larger than 4 mm. Finally (d), a 30 MU EPID image is acquired of the final set-up position in which the reference landmarks are shown to verify the correction.

3. The patient position is determined by calculation of the difference between the center-of-mass of the landmarks in the portal and the reference image. If the two-dimensional (2D) set-up deviation is larger than 4 mm (i.e. about equal to one standard deviation of the expected variations), the patient couch is translated as indicated (Fig. 7-1c). Rotations can generally not be determined and corrected in a fast and reliable manner; in case of rotations, the selected landmarks are matched as well as possible by translations only. Since two landmarks are placed near the top of the pelvic rim and one at the pubic symphysis, the position of the top largely determines the outcome of the match. Once the match has been performed, the set-up position is immediately obtained; a separate field edge match is superfluous because the stiff mechanical structure of the EPID box ensures a reproducible and known isocenter position in the images.
4. With the remaining dose a 30 MU image is made, which is used for off-line determination of the final set-up position (see *contour match* section). To be able to immediately verify an applied correction, the 30 MU image is displayed on the monitor with the reference landmarks, which should be in the correct position (Fig. 7-1d).

To be effective, the on-line procedure must run at each fraction of the treatment. To estimate the extra workload involved with the on-line protocol, the time required for landmark match and table correction was monitored for some patients treated toward the end of the study. At that time, the start-up problems had been solved and the technicians were familiar with the procedure. Since lateral images were available for a limited number of patients and since the largest variations were expected to occur in the cranio-caudal direction [3,6], only AP fields were used for on-line corrections.

Contour match

To determine the accuracy of the on-line landmark match, all 6 MU images were retrospectively analyzed by contour matching as well. Contour matching was impossible with the EPID software, but is judged to be more reliable than landmark matching because a larger fraction of the anatomical structure to be matched is actually used in the calculation. To determine the accuracy of the final treatment set-up, the 30 MU images were analyzed with the contour match as well.

The contour match procedure was developed using specialized visualization software[7]. It semi-automatically registers two images, in this case an EPID image with the corresponding digitized simulator radiograph (Fig. 7-2).

[7] AVS, Advanced Visual Systems, Waltham, MA

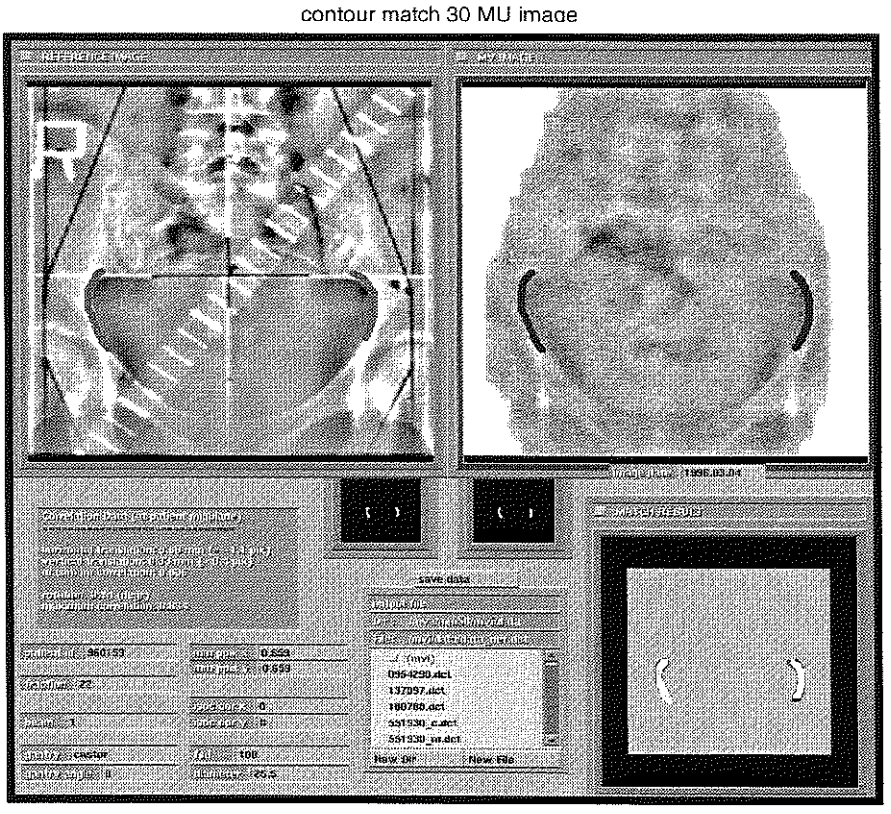

Figure 7-2
Illustration of the contour match procedure. In the upper left image the reference image is shown with a manually drawn contour (gray in this black-and-white image). In the upper right image, a 30 MU EPID image is shown in which a similar structure is contoured (black). The two small images in the middle depict the binary images used for the cross correlation match. The match result is visualized in the lower right image; where the black and gray contour overlap, the contours become light gray. Resulting translation values and patient data are shown in the bottom left.

For both images, the image quality can be improved using display equalization, which *locally* optimizes the display contrast [21]. In both images, the features to be matched must be outlined manually. The contours are subsequently converted to black-and-white binary images, the contours being white on a black background. The cross-correlation function of the two binary images is calculated using Fast Fourier Transforms. The *position* of the maximum of this function gives the translation between the two images. Jones and Boyer [22] used this method to determine the shift between two original megavoltage images directly. Since in our approach binary images are used instead of megavoltage images, the position of the maximum is more sharply defined and less dependent on gray scale variations. However, in case of rotations the delineated structures in the two images may differ in shape, which might cause a (partial) mismatch of the delineated structures if the contours are too thin. Therefore, the line thickness of the contours in the binary images can be increased and is usually about ten pixels (5 – 8 mm). The *value* of the maximum (between 0 and 1) can be considered a correlation coefficient reflecting the adequacy of the match. Values larger than 0.7 normally indicate sufficiently correct matches (accuracy < 1 mm). To obtain an estimate of the in-plane rotations, the rotation with the maximum correlation is determined for a range of rotations around the image center, using the translated images as starting point. The calculation of translations took about 20 seconds on a UNIX workstation[8], the rotations added another 10 seconds.

The structures in the MV images used for matching the AP images are also indicated in Fig. 7-2. The superior part of the pelvic rim is judged to be the best indicator of the target volume position, because it is visible in all images and near the center of the field. The inferior pelvis and symphysis are not included because they are particularly sensitive to out-of-plane rotations around the lateral axis. The contours thus defined have a center-of-mass similar to that of the landmarks used to determine the on-line corrections. The two match methods will therefore treat (out-of-plane) rotations similarly.

Statistical analysis

For each patient i the mean set-up deviation (m_i) and the standard deviation (SD) of the variation around that mean (sd_i) were determined in the left-right and cranio-caudal directions. Next, the mean-of-means M (= MEAN m_i), the variation-of-means Σ (= SD m_i), the mean-of-variations σ (= MEAN sd_i), and the variation-of-variations v (= SD sd_i) were calculated for both patient groups. M is normally close to zero; there should be no systematic difference between average set-up on the simulator and on the accelerator for a large group of patients. In that case, Σ gives an indication of the size of systematic deviations for the individual patients; therefore, Σ is called the *systematic variation*. Since σ represents an

[8] HP715/75, Hewlett Packard, Palo Alto, CA

estimate of the average random variation, it is called the *random variation.* Finally, ν indicates the degree of variation in random deviations per patient, i.e. it is a measure of the homogeneity of the mobility in the patient group.

Statistically significant differences of these four variables between the corrected and uncorrected group were investigated using the student's T-test for the mean values and an SD test as described by Hoel [23] for the standard deviations. Furthermore, a possible correlation between (uncorrected) set-up variation and patient diameter (in AP and lateral direction) was investigated. For patients treated with AP/PA fields, patient diameters were only available in the AP direction.

Results

On-line set-up correction procedure

The total number of on-line set-up measurements for the 14 patients in the study was 254 (varying from 9 to 23 per patient). In 32 measurements (13%), only two instead of three landmarks could be identified, mostly due to insufficient visibility of the pubic symphysis. In 57% of cases the initial 2D set-up deviation exceeded the 4 mm action level and a correction was applied. Set-up deviations as calculated by the contour match for all patients and all fractions before and after corrections are shown in Fig. 7-3. The 202 measurements for which the contour match results before and after correction were both available are indicated. The mean values per patient are also indicated. Both systematic and random variations are clearly reduced after the corrections. This is confirmed by the results of the statistical analysis as shown in Table 7-1. Systematic variations (Σ) and random variations (σ) which were 2 to 3 mm before corrections significantly decreased ($p < 0.01$) to < 1 mm and < 2 mm (1 SD) after corrections, respectively.

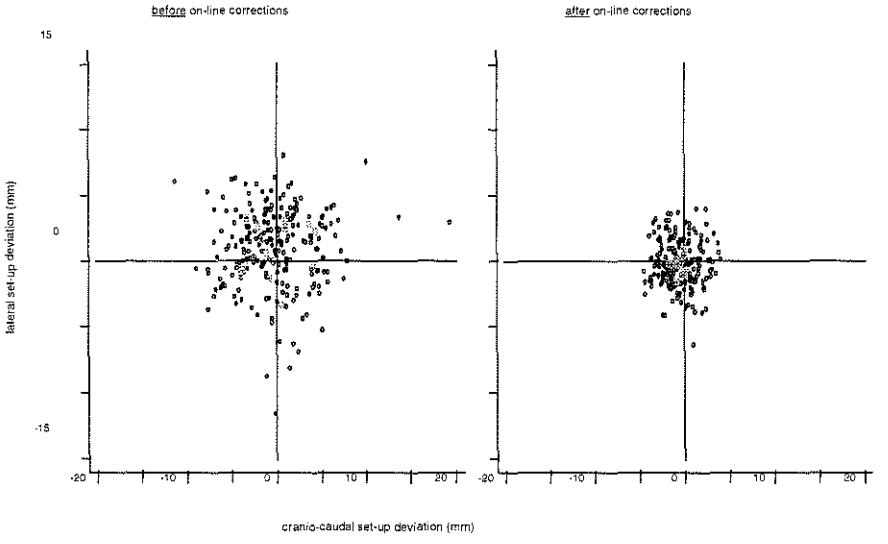

Figure 7-3
Scatter plots of the set-up deviations for each fraction before and after the on-line corrections. The gray square dots are the patient means, the black dots are the individual measurements for each fraction. The reduction of systematic as well as random set-up position variations after on-line corrections is obvious.

Rotations and correlations

The contour match yielded rather small values for in-plane rotations. The overall standard deviations were smaller than 1 degree with extremes less than 4 degrees in all cases. Although there was a relation between the patient diameter in AP direction and the standard deviations of lateral set-up inaccuracies, the correlations were not significant ($p = 0.09$, $r = 0.47$). Other correlations between diameters and set-up deviations were even less significant.

Table 7-1.
The set-up accuracies as determined by the contour matches for 14 patients with gynecological tumors. Accuracies in the left-right (Δx) and cranio-caudal (Δy) direction are indicated in mm, before and after on-line corrections. For the explanation of M, Σ, σ, and ν, see the methods section.

	M	Σ	σ	ν
Δx (before corrections)	0.9	2.0	2.3	0.7
Δy	-0.2	2.8	3.0	1.3
Δx (after corrections)	-0.2	0.7	1.6	0.5
Δy	-0.5	0.6	1.8	0.3

Comparison of match methods
For 210 measurements, both the landmark match and the contour match results of the set-up before correction were available. The same technicians (SQ and MS) performed all contour matches, whereas the on-line landmark matches were done by any technician present at the accelerator (under supervision of SQ and MS). Scatter plots of contour match versus landmark match results are shown in Fig. 7-4. The average difference between the two match procedures was 0.3 +/- 1.1 mm (1 SD) in the lateral direction, and 0.4 +/- 1.8 mm (1 SD) in the cranio-caudal direction. Both average values are significantly different from zero ($p < 0.01$), which implies that there is a small systematic difference between the two methods; this might be caused by the center-of-mass of the three landmarks, which can be slightly different from that of the contours. The variation in the lateral direction is appropriate, considering that the reproducibility of each method separately is about 0.5 - 1 mm (1 SD). The larger variation in the cranio-caudal direction is probably due to the larger pixel size in that direction (0.8 mm cranio-caudal vs. 0.5 mm lateral at isocenter), and due to the out-of-plane rotations around the left-right axis. Consequently, the match accuracy of the on-line match significantly contributes to the final set-up variation in this direction.

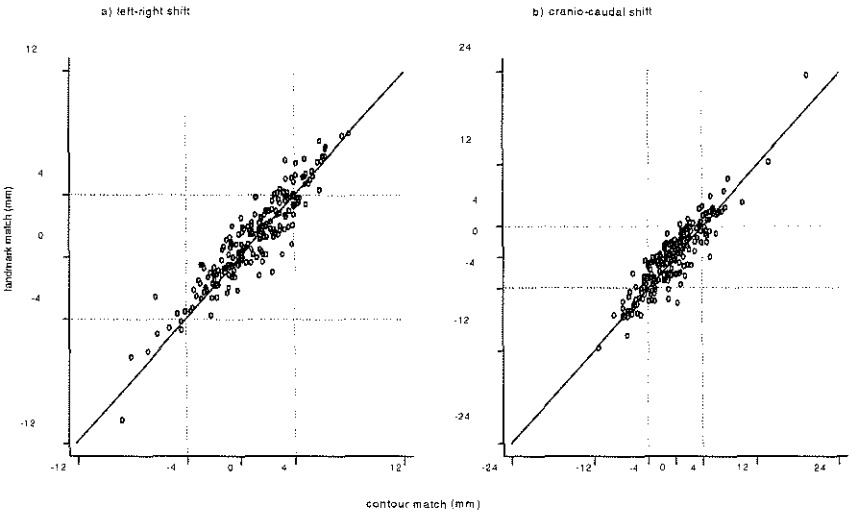

Figure 7-4
Scatter plots of the set-up deviations as measured with the contour match versus the landmark match for left-right (a) and cranio-caudal directions (b). The 4 mm lines are shown to indicate the fractions which have definitely been corrected (the 2D action level was 4 mm). The variation around the ideal one-to-one line immediately shows that there is some difference between the two match methods.

Treatment time

The extra treatment time for the on-line procedure per treatment fraction varied from 1-2 minutes if no table translation was required, to 3-5 minutes if a table correction was necessary. Considering a standard treatment time per patient of 10 minutes, this corresponds to an increase in time of 10-20% without and 30-50% with correction. The variation is due to differences in image quality and user experience. The extra treatment time was required for determination of the set-up position (1 min), restart of the accelerator (30 s), and the table correction procedure (2.5 min).

Discussion

Comparison with previous studies

The measured set-up variation before correction is largest in cranio-caudal direction, which is consistent with previous in-house studies [3,6]. However, particularly the systematic variation in the cranio-caudal direction was already significantly lower ($p = 0.02$) than for the patients in the previously reported mattress study [6], even though set-up technique and accelerator were identical. The average patient obesity was also similar. The extra attention the patients received due to the protocol might already result in better set-up accuracy before correction, especially because only one accelerator and a limited number of technicians were involved in the study. Furthermore, the match technique, e.g. the anatomical structures used for matching, has altered slightly in the course of time. In this study, extra attention has been given to consequent delineation of the same match structures, which is essential in case of out-of-plane rotations.

Although a significant correlation between patient diameter in AP direction and lateral set-up accuracy has been reported before [5], the low correlation in this study make this diameter a rather weak predictor for set-up accuracy. It is therefore impossible to individualize set-up protocols and PTV margins according to patient diameter.

Benefit of on-line set-up correction procedure

As expected, patient set-up was significantly improved using the on-line verification and correction procedure. The 4 mm action level resulted in random variations after correction of 1.5 - 2 mm. Since the systematic variations are reduced to < 1 mm and the margin to cover for geometric variation of the CTV with respect to the beam portals can be approximated by $2\Sigma+0.7\sigma$ [9], a CTV-to-PTV margin for external set-up accuracies of 3 mm will suffice. An even better set-up accuracy can be obtained by decreasing the action level. In principle, the maximum accuracy is limited by the accuracy of matching software and treatment equipment. This will off course yield more corrections and an increase in average treatment time.

Fig. 7-5 shows the dose volume histograms of a patient with a gynecologic tumor planned to a dose of over 60 Gy with two different CTV-to-PTV margins: the current clinical margin of 1 cm and a 5 mm margin for on-line corrected patients (the 3 mm is rounded up to include other uncertainties than set-up deviations). With a margin of 5 mm instead of 1 cm, the volume receiving a small bowel dose larger than 55 Gy is reduced from the critical 30% to an acceptable 15%.

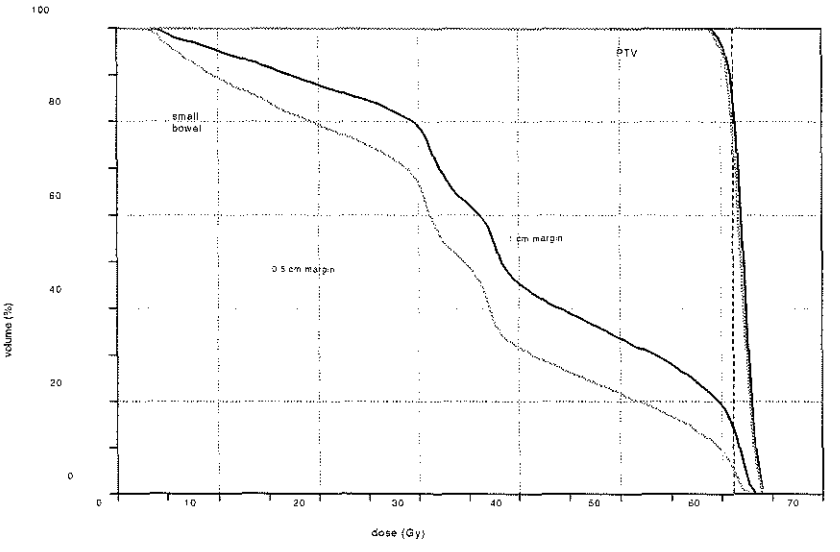

Figure 7-5
Dose volume histograms of a patient with a gynecologic tumor, which show a reduction in small bowel dosage when smaller CTV-to-PTV margins are applied. Until 48.6 Gy, the CTV consists of the primary tumor region plus the elective para-aortic lymph nodes, the boost is given on the primary tumor region only. Use of 5 mm CTV-to-PTV margins (gray lines), which is justified if on-line corrections are performed instead of the currently applied 1 cm (black lines), reduces the small bowel volume receiving 55 Gy or more, to less than 20%.

Extra treatment time

In case of a correction, the extra treatment time was 3 to 5 minutes. During the study, new table settings had to be entered at the treatment console and the patient couch had to be moved accordingly by a technician in the treatment room. However, further automation of the accelerator after the study has enabled fully automatic table corrections within 1 minute. This reduces the overall extra time in case of correction to about 2.5 minutes. Since about half the number of fields had to be corrected, the average extra time per fraction per analyzed field is now about 2 minutes. Because it takes two images to determine the 3D patient set-up, a total of 4 minutes per fraction are maximally needed, which is comparable to most other studies [12,13,15,17,18] and to the routinely used off-line protocol in our institute. Furthermore, elaborate set-up equipment such as mattresses and foot and arm supports also require extra time. One might argue that in most cases the patient set-up technique can be fast and basic as long as on-line corrections can be applied.

Recent and future developments
Since we expect that on-line correction of patient set-up (and possibly tumor position) will become an important tool for conformal radiotherapy in the future, we have developed a new portal imaging device especially equipped for on-line applications [9]. The device obtains better quality images with 1 MU than the "old" EPID system with 6 MU. Furthermore, fully automated and fast contour matching will be implemented in the software, which is expected to reduce the total time for on-line corrections to about 1 minute per field. Finally, the image resolution of the new system is significantly improved as well; radioopaque markers can now be visualized, which might be used to measure and possibly correct the internal CTV position in patients with gynecologic tumors on-line.

Combination of off-line and on-line set-up correction protocol
To minimize the current treatment time at the accelerator, a combination of an off-line and on-line protocol is applied for routine patient set-up. Table 7-1 and previous studies show that the inter-patient variation (v) was rather large for patients with gynecologic tumors. Therefore, initially all patients are treated using the off-line procedure. Only those patients with large random variations, and hence with repeated corrections in the off-line protocol, are entered in the on-line correction protocol. Furthermore, systematic variations can be determined during the course of treatment with the on-line protocol as well; instead of identical corrections each day after 6 MU, table corrections can be applied beforehand (similar to the off-line protocol), which further decreases the treatment time.

Conclusion

The on-line patient set-up correction protocol resulted in a significant improvement of set-up accuracy. This allows for the use of smaller PTVs, which might in turn allow dose escalation while maintaining acceptable complication probabilities for the small bowel. Since we believe that in the future on-line set-up corrections will be used on a more routine basis, the speed and accuracy of the procedure are being improved. Until this has been achieved, a combination of off- and on-line set-up correction protocols will yield optimal set-up accuracy with a minimal workload.

Acknowledgements

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CHAPTER 8

GENERAL DISCUSSION, FUTURE DIRECTIONS AND CONCLUSIONS

The mean age of patients with cancer submitted for radiation treatment is increasing. In the daily practice of radiation oncology departments, older cancer patients often are excluded from clinical trials and sometimes are undertreated, due to the assumption that normal tissue tolerance decreases with increasing age. However recent clinical studies have shown that normal tissue toxicity in the elderly is probably not increased compared to cancer patients of younger age groups [2,11,16,19,20,23,29,30]. This controversy needs to be resolved. Experimental data on the relation between aging and normal tissue toxicity can provide a stronger foundation for further clinical decision making on this important issue. In particular data on late effects are missing. Moreover, toxicity being a relevant issue in the young- as well as in the older patients, even to the extent that it can be dose (cure) limiting, modern treatment techniques, such as 3-D conformal radiotherapy, have created the opportunity to reduce the risk of normal tissue toxicity substantially. Both issues, that is experimental observations on the ageing effects of irradiated rectal mucosa (animal data) and the sparing capacity of 3-DCRT are reported in this thesis.

8.1. The influence of aging on the toxicity of irradiated mucosa of the rectum

Previous experiments on the development of radiation induced changes in the rectum of young- and old Wistar rats after single doses of irradiation, using clinical and radiological endpoints, showed that there were no significant differences in the incidence of rectal stenosis and the development of a megacolon [17].

The histopathological evaluation after two single radiation doses at early time points as 1, 2, 4 and 10 weeks after treatment (Chapter 2) showed small, non significant age related differences. Ulceration seemed to be an important feature as it showed a clear dose, age and time dependency. Severe vascular changes as occlusion of blood vessels occurred significantly more often in both of the sections of the irradiated area and already at 4 weeks after treatment in the old group, while in the young rats this was observed less frequently and only at 10 weeks. The regenerative capacity of the mucosa might be influenced by vascular changes after radiation.

In accordance with other investigators [9], we found a significant increase in the number of proliferative cells in the rectum adjacent to the treated area in the older group at 1 week after 22 Gy, in contrast to the young animals where only a small increase was observed. This suggests a different age-related reaction pattern.

To elucidate whether the observed (small) differences lead to long term effects, we also studied late time points as 24 and 52 weeks after irradiation (Chapter 3). In both age groups the incidence of late mucosal ulceration

appeared to be lower than in the early time points, which confirms the occurrence of regeneration. The increase in cell proliferation in the first week in the adjacent areas of the irradiated field, might be an important factor in the healing process of the initial ulceration in the older rats.

The total radiation injury score (RIS) expressed the total damage within the irradiation field of the rectum. In the young animals after a dose of 22 Gy, the RIS gradually increased with a clear dose dependency. After 39 Gy and in the older group after both doses, the RIS appeared to be high at 2-4 weeks and remained high at the longer follow up periods. There were no significant differences between the age groups, but these data do support the hypothesis that late rectal damage is a consequential effect of acute damage.

The clinical outcome with longer follow up in both age groups was similar. Obviously, these data cannot be translated to the clinical practice in a simple fashion. First of all we have limited our research to one normal tissue only; moreover, the mucosa of the rectum in Wistar rats could behave dissimilar to the rectal mucosa of humans. Secondly, the geriatric population is a highly diverse population in terms of function, co-morbidity, social support, cognitive function and emotional status. The elderly patient might suffer from more than one clinical problem, whether somatic, psychological and/or socio-economical. This multifactorial complexity can impose limitations in daily life functioning and determines the final quality of life score. However, from these animal data it seems reassuring that, at least in Wistar rats, there is no extra-morbidity to be expected due to ageing per se from radiating normal tissues such as the rectal mucosa.

8.2. Standardization of CTV

Besides collecting more experimental and clinical data on acute- and late side effects, more sparing types of cancer treatments have to be developed. In radiation oncology, the introduction of 3D conformal radiotherapy, which "tightly" conforms the radiation to the target and thereby spares the surrounding normal tissues, has provided challenging possibilities in this respect. However, a precise definition and delineation of the target volume(s) is mandatory.

In the study as outlined in Chapter 4, 17 radiation oncologists were asked to define the CTV and PTV and delineate the treatment portals on simulation films for postoperative radiotherapy in a patient with early stage cervical carcinoma with iliac node involvement. A reference PTV was defined by using data of normal lymphangiograms and CT-data of the same group of patients. There appeared to be no agreement in the description of a uniform CTV by the participating radiation oncologists. The CTV could in fact be divided into three different CTV's with the most important controversy being the "yes or no"

inclusion of the para-aortic nodes in the CTV. Besides these different CTV-definitions, there were also major variations in the shape and size of the treatment portals used within these three groups, probably due to uncertainties in the precise location of the primary tumor and the lymphnode chains. A significant number of the participating centers appeared to have 'standard' treatment portals, based on bony structures visualized on the simulation films, while the current literature on the subject has shown that this could lead to a considerable risk for a geographical miss [13,25]. Our reference CT- and lymphangiogram based PTV was covered by only 40% of the treatment plans at the level of the parametria as well as at the level of the para-aortic nodes. None of the treatment portals covered the para-aortic region with a margin of more than 5 mm (needed for set up inaccuracy).

From these observations we highly recommend (more) standardization in the definition of the CTV in cervical carcinoma, especially with regard to the elective parts. Based on these findings, the Dutch Group of Gynecological Radiation Oncology (LPRGT) is working on consensus guidelines for definition of target volumes in cervical cancer. Furthermore we think that the use of a CT-based planning is essential to prevent geographical misses and maximize sparing of normal tissues in this patient group.

8.3. Three dimensional conformal treatment planning techniques

The importance of CT-based treatment planning is also stressed in the study on cervical carcinoma, described in Chapter 5. In this study the conventional technique with AP-PA parallel opposed beams is compared to a 3D-planned technique for postoperative radiotherapy in 15 patients with early stage cervical carcinoma with histologically proven lymph node metastasis. The mean calculated values for the Tumor Control Probability (TCP) were almost similar. The mean Normal Tissue Complication Probabilities (NTCP) for the small bowel and the rectosigmoid could both be significantly reduced by the conformal technique. The volume of the small intestine which received ≥ 95 % of the prescribed dose (V95) was significantly reduced from almost 48 % to 15 %, which means a considerable reduction in the high dose range. The subsequent higher volume of irradiated small bowel volume in the lower dose ranges, due to the application of the lateral fields, could potentially lead to more low grade acute toxicity. This seems to be a frequently occurring effect of using multiple beam directions in conformal therapy. Its clinical relevance is not yet clear. Jackson e.a. [12] found in a study with conformal radiotherapy to doses of 70.2- 75.6 Gy in prostate cancer an independent association between rectal bleeding and large percentages of volume of the rectum exposed to intermediate doses ($\approx$ 46 Gy). They conclude that this could indicate that a large surrounding region of intermediate dose may interfere with the ability to repair the effects of

a central high dose region. Further studies on this aspect are necessary, but might lead to more constraints in the treatment planning process in the near future. In fact, this might make the use of intensity modulated radiation therapy, with typical constraints on particular normal tissues, mandatory.

With the reduction of dose to the small intestine, a booster dose to the pelvic region in microscopically involved areas, and therefore dose escalation, might be possible in the future, using conformal- and intensity modulated radiotherapy. In addition to using 3D treatment planning techniques, a substantial part of the small bowel can be shielded by positioning the patient in a prone position in a belly board device (Chapter 6).

8.4. Volume-effect in reduction of toxicity

The belly board device is extensively discussed in Chapter 6. In this study the reduction of irradiated small bowel volume using a belly board device in pelvic radiotherapy of gynecological cancer patients was measured. From this experience the patients seem to tolerate the device easily, in spite of previous surgery, especially if the device was used in combination with the prone pillow (Fig. 6.1). There appeared to be a mean reduction of small bowel volume within the treatment fields in the prone position compared to the supine position of 163 cm^3 (64 % with 95% CI 56-72 %). It is clear that this advantage strongly varies due to the interpatient variation of small bowel volume within the treatment field. Hopewell and Trott [10] stated that volume effects are more related to organ anatomy and organ physiology than to cell survival data. Wachter e.a. [28] performed a prospective study on the rectum of patients who were treated with conformal radiotherapy for prostate cancer. A rectosigmoidoscopy was done 20-41 months after treatment. The topographical distribution of rectoscopic changes could be matched to the dose distribution along the rectal wall. Secondly, the extent and severity of local damage appeared correlated with clinical grades of proctitis. In 3D conformal therapy with high doses of radiation, studies that determine how to decrease the amount (volume) of normal tissues (e.g. bowel), albeit by technical means (belly board) or 3D treatment planning techniques, are indispensable.

8.5. Improvement of positioning

The accuracy of patient positioning in the belly board was also studied using Electronic Portal Imaging Devices (EPID's) at the linear accelerator (Chapter 6). The average daily random setup variations in our study using an off-line setup verification and correction protocol were small (1SD < 3 mm), with an individual range of 1- 4 mm. These results appeared to be better than setup variations for gynecologic pelvic fields treating patients in supine position in our institute [4]. A possible explanation might be an increase of reproducibility by skin markings on the back instead of the abdominal skin. Therefore we introduced the prone position in a belly board as the standard positioning technique for pelvic radiotherapy in patients with gynecological cancer. In the correction protocol we used an initial action level of 12 mm. The systematic errors in x-, y- and z-directions were small (1.7 –2.1 mm), which means a significant reduction in comparison to positioning of gynecological patients of previous studies without a correction protocol [4].

In contrast to an off-line correction protocol, the set-up deviation can be determined and corrected before the bulk of the daily treatment dose is given by an on-line correction protocol. This could mean a reduction of the margin of the PTV around the CTV which covers for the set-up variation (and other geometric uncertainties as delineation uncertainty and internal organ motion). This might lead to a decrease in toxicity; a reduction in the margin for the PTV might provide the possibility of dose escalation to increase the cure rate. In Chapter 7, a study with on-line set-up corrections in gynecological patients is described. We used a 4 mm initial action level which resulted in random variations of 1.5 –2 mm. Because the systematic variations were reduced to < 1 mm, the CTV-to-PTV margin to cover for external set-up inaccuracy could be reduced from 7 mm to 3 mm. The accuracy that can be obtained by on-line verification is limited by the accuracy of the measurements and the corrections, which depend on the accuracy of the accelerator, the treatment couch and the EPID. However the most important obstacle for clinical use is the extra time that is required to measure and correct the set-up on-line. In view of the waiting period for many patients for radiation treatment at this moment, this seems unacceptable for routine clinical application. Therefore we perform on-line corrections only in patients with large random set-up variations with an off-line correction protocol. A specific threshold in these patients reduces the amount of on-line corrections, while a high accuracy is maintained.

8.6. Future directions

8.6.1. Clinical assessment of the elderly population

It is obvious that older patients need a geriatric assessment before they enter a clinical trial with aggressive therapy. The National Cancer Center Network in the USA (NCCN) has recently proposed a number of guidelines related to the management of the older cancer patient to identify frail individuals who are at excessive risk, to identify co-morbidity and lack of social support and to assess life expectancy of the older cancer patient [1]. The first priority for clinical trials in older individuals appears to create a common language to account for and report on the diversity. In randomized trials with elderly patients, survival as an endpoint of outcome may not always be appropriate. Alternative outcomes, such as progression- and disease-free survival, clinical benefits, preservation of function and quality of life may be more difficult to evaluate, but for this population more worthwhile.

8.6.2. New developments in conformal radiation treatment

Recent improvements of treatment planning and techniques have provided the possibility to reduce irradiated volumes of normal tissues. This might lead to a decrease in late toxicity. Frequent and continued assessment of toxicity will be needed to determine whether the costs and the benefits are balanced. Quality of life forms scored by the patients themselves provide us invaluable information. However, before we can draw conclusions about reduction of toxicity by conformal treatment techniques, consensus on the definition of the CTV is needed as well as uniformity in delineation of the CTV. National working groups with representation of all centers in the Netherlands are working on such definitions for a number of tumor sites at this moment. Besides consensus on the definition of the CTV, more accuracy in the determination of the CTV is also needed. There can be inter- and intraobserver variations in the delineation due to inaccurate diagnostic images on CT of the borders of the CTV and surrounding normal tissues. This variability in tumor delineation has been investigated e.g. in cancer of the prostate and lung. Differences between physicians or between the same physician at different times can exceed 1 cm. [3,7,22,27,32]. Translation from other image modalities like MRI and SPECT to CT images and generation of new software to contour the different organs automatically will be subjects for further investigation.

In the near future Intensity Modulated Radiotherapy (IMRT) as a form of conformal treatment, with dose constraints to particular normal (critical) tissues, will be applied clinically in our department on a routine basis. By varying the intensity of the beamprofiles of multiple beams, for instance by using dynamic multileaf collimation [6], surrounding tissues might be spared in a more optimal way. More research has to be focused on internal movement of surrounding organs, as well as movement of the primary tumor and the areas which have to

be treated electively. Many studies have been performed in prostate cancer, using a number of computed tomography (CT) scans for each patient [5,8,14,15,24,26,31], but data on other tumor sites of the pelvis are rare. In order to see whether we could reduce the CTV-to-PTV margin, we recently initiated a study on internal movement of the cervix and the uterus in patients with cervical carcinoma, marking the cervix with 2 to 3 surgical clips after which planning CT scans are obtained. During the radiation therapy CT-scanning evaluates the position of the cervix (clips), the movement of the uterus and the influence of the rectum- and bladder volume. Frequent portal imaging with EPID is also performed to investigate whether the cervical markers move during the treatment period of 5 weeks. It is felt that a reliable off-line or on-line verification- and correction protocol with EPID is indispensable in future radiation treatment techniques.

According to some groups [18,21], there might be a potential gain in the future from dose individualization strategies based on both normal tissue dose-volume data and radiosensitivity (assuming that reliable (molecular radiation biological) assays will become available). These new ideas might be of importance for the elderly population and provide reasons for maintaining an optimistic view.

8.7. Conclusions

In this thesis, experimental studies on the relation between age and radiation tolerance of normal tissues were combined with clinical studies on reduction of toxicity, using 3D-conformal treatment techniques.

Based on the early and late histopathological evaluations of rectal damage of young and old rats, the assumption that radiation tolerance of rectal tissue has diminished with old age cannot be justified. For the individual patient, however, more data on radiation response of normal tissues in the elderly are needed, particularly in a clinical environment. Recent progress in 3-D treatment planning-, immobilization-, and verification techniques have provided the clinicians tools to further reduce volumes and dose of the irradiated normal tissues.

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SUMMARY

Introduction

In radiation therapy of pelvic malignancies, small bowel and rectum often are the dose limiting organs due to the hazards of severe acute- and late toxicity. Especially pelvic tumors as prostate- and rectal cancer and gynecological malignancies frequently occur in the elderly. The assumption that normal tissue tolerance decreases with increasing age is often the basis for undertreatment in the elderly patient. However recent clinical studies strongly support the idea that tissue toxicity in patients older than 74 years of age is not increased compared with younger patients. Only limited experimental data are available addressing the influence of age on radiation sensitivity. Especially data with regard to the relation between ageing and late effects of radiation to normal tissues are rare.

Chapter 1 discusses the relationship between the proportional increase of the aging population and the incidence of cancer as well as the application of cancer treatments in the elderly, in particular the application of radiotherapy. The radiation toxicity of the small intestine and the rectum are described, both clinically and histopathologically. Besides experimental studies on the relation between ageing and normal tissue tolerance for radiotherapy, modern treatment techniques which provide the opportunity to modify the doses in the critical organs such as small intestine and rectum are important in order to prevent the risk on late (irreversible) toxicity.

Chapter 2: After experiments with single doses of irradiation on the rectum of young and old Wistar rats (12 and 78 weeks old respectively) with clinical and radiological endpoints, histopathological studies with two radiation doses (the LD20 and LD80, resp. 22 and 39 Gy) were performed. In this chapter early follow up time points as 1, 2, 4 and 10 weeks after treatment are described.

In **Chapter 3** the late effects of the radiation on the rectum are reported with evaluation time points of 24 and 52 weeks after treatment. At the early time points, after 22 Gy, 60 % of the old animals showed ulceration and a discontinuous muscularis mucosae in the part of the rectum within the treatment field due to severe damage , while the young rats had a continuous muscularis without ulceration. However after 39 Gy, ulceration was observed already at 1 week after irradiation in the young group and only at 4 weeks in the older animals. At the late time points, the incidence of mucosal ulceration appeared to be lower in both age groups (0 –50 % at 52 weeks), indicating the possibility of regeneration. In contrast to the early time points, there appeared to be no difference between the age groups. A significant increase in the number of proliferative cells in the rectum adjacent to the treatment field at 1 week after 22

Gy which we found in the older group only, suggests a different age related reaction pattern. This early proliferation was also reflected in a significant increase of the number of endocrine cells in the crypts adjacent to the treated area of the old rats at 52 weeks. We consider these enteroendocrine cells as a non-specific result of cell proliferation.
Severe vascular changes as occlusion of blood vessels also occurred significantly more often and earlier in the older animals, but as most of the observed (small) differences at the early time points, these differences did not lead to significant differences with longer follow up and the clinical outcome in the long term was similar. Based on these experiments, the assumption that radiation tolerance decreases with older age cannot be justified. More experimental and clinical data on radiation tolerance of normal tissues in the elderly are badly needed and clinical trials including older people may provide important answers in geriatric oncology.

Chapter 4: In radiation oncology, the development of 3D-treatment planning and new treatment techniques have provided the opportunity to conform the radiation fields as much as possible to the individual situation (tumor) of the patient. This may lead to better sparing of the critical organs and, on the other hand, to escalation of the dose in the tumor area in order to increase the cure rate. In 3D-treatment planning with CT-based delineation, a precise definition and deliniation of the tumor as well as the surrounding normal tissues is mandatory. In this chapter, a study on differences in definition of the Clinical Target Volume (CTV) and Planning Target Volume (PTV) in postoperative radiation of a patient with cervical carcinoma is described. Seventeen Dutch radiation oncologists participated and defined the volumes and delineated the treatment portals on simulation films. These volumes were compared by a reference PTV, using data of lymphangiograms and pelvic CT-scans of a large number of female patients. There appeared to be no consensus around the country about the definition of the elective parts of the CTV. The treatment portals as drawn on the films, mostly based on bony structures, did not cover the parametria of the reference PTV in 41 % and the para-aortic node region (if defined in the CTV) in 40 % of the cases. More standardization in definition of the CTV in different tumor sites is needed, especially in the elective parts of the CTV.

In **Chapter 5**, a comparison is made between a conventional and a 3D conformal treatment technique is described in postoperative radiotherapy of 15 patients with early stage cervical carcinoma and histologically proven lymph node metastasis. The mean Normal Tissue Complication Probabilities (NTCP) for the small bowel and the rectosigmoid could both be significantly reduced by

the conformal therapy technique. Further studies on the clinical outcome in reduction of toxicity are needed.

Chapter 6: In pelvic radiotherapy, a prone position of the patient in a so called belly board device might decrease the volume of small bowel within the irradiation fields. Displacement of the bowel to the region above the fields is performed by an aperture for the belly region in the device. A study on the reduction of volume of irradiated small bowel in pelvic radiotherapy of gynecologic cancer patients, using the device, is described. There appeared to be a mean reduction in the volume of small bowel within the treatment fields of 64 % (95 % CI 56 –72 %) in prone position in the belly board compared to the supine position on the treatment couch. At the same time, the accuracy of the positioning in the belly board was studied using Electronic portal imaging Devices (EPID's) using an off-line setup verification and correction protocol. The average daily random setup variations appeared to be small (1 SD < 3 mm), which means a significant improvement compared to setup variations in supine position in these patients in previous studies in our institute. The mean systematic errors in x-, y- and z- direction in prone position were also small (1.7- 2.1 mm), using an initial action level for correction of 12 mm.

Chapter 7: If the setup of a patient is verified and corrected after a small fraction of the daily treatment, before the bulk of the irradiation is given, a so called on-line correction protocol is used. This might lead to a reduction of the CTV-to-PTV margin which covers for the setup variation (among other geometric uncertainties). A significant reduction of this margin could lead to a reduction in toxicity and eventually to increasement of the dose to the primary tumor region. In Chapter 7, a study with on-line setup verification and corrections in gynecologic cancer patients is described. The initial action level for correction was 4 mm and resulted in random variations of 1.5- 2 mm. The systematic variations were reduced to < 1 mm, which lead to a reduction of CTV-to-PTV margin of 4 mm (from 7 mm to 3 mm). However, on-line verification and correction is more time consuming on the treatment machine and, because of the frequent treatment interruptions, more bothersome for the patient. On-line correction of the setup should therefore be used in cases with large random errors only.

SAMENVATTING

Introductie

Bij radiotherapie van maligniteiten in het kleine bekken, zijn zowel dunne darm als endeldarm de belangrijkste dosisbeperkende organen door het risico op ernstige acute en late bestralingsschade. In het kleine bekken gelokaliseerde tumoren zoals prostaat-, endeldarmkanker, en gynaecologische maligniteiten komen vaak voor op oudere leeftijd. Oudere patienten worden regelmatig onderbehandeld daar men van de veronderstelling uitgaat dat de tolerantie voor radiotherapie van normaal weefsel, afneemt met het stijgen van de leeftijd. Recent klinisch onderzoek heeft echter laten zien dat schade aan normaal weefsel bij patienten welke ouder waren dan 74 jaar, niet is toegenomen in vergelijking met jongere patienten. Er is slechts op zeer beperkte schaal experimenteel onderzoek verricht naar de invloed van leeftijd op radiosensitiviteit. Vooral data met betrekking tot de relatie tussen leeftijd en late effecten van bestraling op normaal weefsel zijn zeldzaam.

In **hoofdstuk 1** wordt de relatie tussen de toenemende vergrijzing en de incidentie van kanker beschreven. Tevens worden de mogelijke behandelingsvormen van kanker bij de oudere mens besproken, met name behandeling met radiotherapie. De ontwikkeling van bestralingsschade aan de dunne darm en de endeldarm, zowel klinisch als histopathologisch, wordt beschreven. Behalve experimentele studies naar de relatie tussen veroudering en tolerantie van gezond weefsel, zijn ook moderne behandelingstechnieken van belang die de mogelijkheid bieden om de doses in de kritieke organen zoals dunne darm en endeldarm, te modificeren, ten einde het risico op late (irreversibele) schade te beperken.

Hoofdstuk 2: Nadat eerst experimenten werden uitgevoerd met bestraling van de endeldarm van jonge en oude Wistar ratten (respectievelijk 12 en 78 weken oud) met enkelvoudige doses en klinische en radiologische eindpunten, werden histopathologische studies verricht met een tweetal doses (de LD20 en LD80, respectievelijk 22 en 39 Gy). In dit hoofdstuk worden de vroege tijdpunten zoals 1, 2, 4 en 10 weken na bestraling beschreven.

In **hoofdstuk 3** worden de late effecten van bestraling van de endeldarm van Wistar ratten beschreven met tijdpunten van 24 en 52 weken na bestraling. Na 22 Gy werd op de vroege evaluatie tijdstippen bij 60% van de oudere dieren ulceratie gevonden met een discontinuiteit van de muscularis mucosae in het deel van de endeldarm binnen het bestralingsveld, terwijl dit bij de jongere dieren niet of nauwelijks het geval was. Echter na een dosis van 39 Gy, werd

ulceratie bij de jonge groep al gezien na 1 week en pas na 4 weken bij de oudere ratten.
Bij de late tijdstippen bleek de incidentie van ulceratie van de mucosa lager in beide leeftijdsgroepen in vergelijking met de vroege evaluatie momenten (0–50% na 52 weken), hetgeen een indicatie is voor het vermogen tot regeneratie van de mucosa. In tegenstelling tot de vroege tijdstippen was er geen sprake van een verschil in incidentie van ulceratie tussen de beide leeftijdsgroepen. Alleen bij de oudere groep bleek sprake van een significante toename in het aantal prolifererende cellen in het aangrenzende gedeelte van het bestralingsveld, 1 week na een dosis van 22 Gy, hetgeen duidt op een verschillend reaktiemechanisme na bestraling bij jonge en oude dieren. De vroege proliferatie werd tevens teruggevonden in een significante toename van het aantal endocriene cellen in de crypten van de darm, aangrenzend aan het bestralingsveld bij de oude ratten, 52 weken na bestraling. Deze entero-endocriene celproductie wordt beschouwd als een gevolg van de celproliferatie.
De incidentie van ernstige schade aan de bloedvaten van de endeldarm, zoals occlusie, was significant hoger in de oudere groep, waarbij deze schade ook eerder optrad dan in de jongere dieren. Echter alle gevonden (kleine) verschillen tussen de beide leeftijdsgroepen tijdens de vroege tijdpunten, leiden niet tot significante verschillen op de latere tijdstippen waarbij ook de overleving van de dieren op de langere termijn vergelijkbaar was. Deze studies steunen de veronderstelling dat tolerantie voor radiotherapie op oudere leeftijd afneemt niet. Meer experimentele en klinische data met betrekking tot de relatie tussen leeftijd en tolerantie voor bestraling zijn noodzakelijk. Klinische trials waaraan ook oudere patienten mogen deelnemen, eventueel met modificatie van de eindpunten, kunnen belangrijke vraagstukken van de geriatrische oncologie oplossen.

Hoofdstuk 4: In de radiotherapie hebben de ontwikkeling van 3D-planningstechnieken en moderne lineaire versnellers de mogelijkheden geschapen om de bestralingsvelden zoveel mogelijk aan te passen aan de individuele situatie (tumor) van de patient. Dit kan enerzijds leiden tot verbeteringen in het sparen van de kritieke organen en anderzijds tot escalatie van de dosis in de tumorregio ten einde de overleving te verbeteren. Bij 3D-planning op basis van een CT is een exacte definitie en intekening van de tumor en de omgevende normale weefsels vereist. In dit hoofdstuk wordt een studie beschreven met betrekking tot de verschillen in definitie van het Clinical Target Volume (CTV) en het Planning Target Volume (PTV) bij een patient met baarmoederhalskanker waarbij een indicatie bestaat voor postoperatieve radiotherapie. Zeventien Nederlandse radiotherapeuten namen deel aan deze studie; zij definieerden bovenbeschreven volumina en tekenden de volumina en/of de bestralingsvelden aan op bijgeleverde simulatiefoto's. Deze volumina

werden vergeleken met een referentie PTV, waarvoor data van een groot aantal lymfangiogrammen en CT-scans van vrouwelijke patienten werden gebruikt. Er bleek geen consensus te bestaan met betrekking tot de definitie van het electieve deel van het CTV. De bestralingsvelden welke waren aangetekend op de simulatiefoto's, veelal gebaseerd op de anatomie van de benige structuren, waren in 41 % niet adequaat ter hoogte van de parametria in vergelijking met het referentie-PTV en in 40 % van de gevallen waarbij werd aangegeven dat de para-aortale klierketen tot het CTV behoorde, ter plaatse inadequaat. Meer standaardisatie in definitie van het CTV voor de diverse tumoren is noodzakelijk, met name voor het elektieve gedeelte van het CTV.

In **hoofdstuk 5** wordt een vergelijking gemaakt tussen een conventionele en een 3D-conformatie bestralingstechniek bij 15 patienten met baarmoederhalskanker, stadium Ib-IIa, met histologisch bewezen lymfkliermetastasen. Met behulp van de conformatie bestralingstechniek was het mogelijk de gemiddelde kans op normale weefselschade (NTCP), voor zowel de dunne darm als de endeldarm, significant te reduceren. Verder onderzoek naar de klinische relevantie van dergelijke technieken ten einde de toxiciteit te verminderen, is noodzakelijk.

Hoofdstuk 6: Bij bestraling van tumoren in het kleine bekken kan de patient in buikligging gepositioneerd worden in een zogenaamd belly board. Dit heeft als doel om (een gedeelte van) de dunne darmen te sparen doordat ze verplaatsen naar de regio boven het bestralingsveld, waar een opening in het board gemaakt is. In dit hoofdstuk wordt een studie beschreven naar de reductie van volume van dunne darm binnen de bestralingsvelden van gynaecologische patienten, gebruik makend van het belly board. Er bleek sprake van een gemiddelde reductie van het volume dunne darm binnen bestraald gebied van 64 % (95 % CI 56- 72 %) in buikligging in het board, vergeleken met positionering in rugligging op de bestralingstafel. Gelijktijdig werd de nauwkeurigheid van de positionering in het belly board onderzocht waarbij gebruik gemaakt werd van electronische megavolt afbeeldingsapparatuur en een zogenaamd off-line verificatie- en correctieprotocol. Bij een dergelijk protocol ter verificatie van de positionering wordt het megavoltbeeld na de betreffende fractie geanalyseerd en een eventuele correctie bij de volgende behandeling uitgevoerd. De gemiddelde dagelijkse random variatie in de positionering bleek klein (1 SD < 3 mm), hetgeen een significante verbetering betekende ten opzichte van de variaties in rugligging bij dezelfde patientengroep uit eerdere studies binnen ons instituut. De gemiddelde systematische fouten in x-, y-, en z-richting in buikligging in het belly board waren eveneens klein (1.7- 2.1 mm), waarbij een aktie-drempel van 12 mm werd gehanteerd voordat een correctie van de positionering werd uitgevoerd.

Hoofdstuk 7: Wanneer de positionering van een patient gecontroleerd en eventueel gecorrigeerd wordt nadat een klein gedeelte van de betreffende fractie is gegeven, waarna de rest van de fractie wordt voltooid, spreekt men van zogenaamde on-line verificatie en correctie. Dit kan leiden tot een reductie van de marge tussen CTV en PTV welke onder andere aangebracht wordt voor de onnauwkeurigheid van de positionering. Een significante reductie van deze marge zou kunnen leiden tot een reductie in toxiciteit en eventueel tot een verhoging van de dosis in de primaire tumorregio. In dit hoofdstuk wordt een studie beschreven waarbij on-line verificatie en correctie werd toegepast bij gynaecologische patienten. De initiele aktie-drempel was 4 mm; de random variaties waren 1.5- 2 mm. De systematische variaties konden worden gereduceerd tot < 1 mm, hetgeen een reductie in de marge van CTV tot PTV van 4 mm mogelijk maakte (van 7 naar 3 mm). Echter, in vergelijking met off-line correctie, kost on-line correctie meer tijd bij de lineaire versneller gedurende de behandelingen. Bovendien is het meer belastend voor de patient door de herhaaldelijke onderbrekingen van de behandeling. On-line correctie van de positionering dient derhalve gebruikt te worden in gevallen waarbij sprake is van grote random fouten.

Nawoord

Aan het einde van de rit heb ik zeker de behoefte om een aantal mensen in het bijzonder te bedanken, niet alleen omdat dat op deze plaats gebruikelijk is, maar vooral omdat zonder hen dit boekje er nooit gekomen was.

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De basis voor het belly board-onderzoek werd gelegd in de MVA-groep, waar ik eveneens per toeval ingerold ben. Met name Andries Visser, Hans de Boer en Lars Murrer hebben mij hierin wegwijs gemaakt en geholpen met zinvolle discussies. John Sörnsen de Koste heeft op zijn minst een eervolle vermelding verdiend voor alle hulp bij de analyse van en gedachtewisseling over de belly boardpatiënten.

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ook je hulp bij mijn eerste schreden op het computerpad, bij mislukte figuren en bij het scannen van suboptimale foto's, zal ik nooit vergeten. En dan zullen we het maar niet hebben over een finale versie van het proefschrift op een kapotte harde schijf gedurende de nachtelijke uurtjes. Je moet toch best wel eens getwijfeld hebben of het ooit af zou komen, maar hebt dit nooit laten blijken. Mijn dank is heel groot.

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Curriculum vitae

Manouk Olofsen- van Acht werd op 1 oktober 1960 geboren te Sittard. In mei 1979 behaalde zij het VWO diploma aan het Bisschoppelijk College Schöndeln te Roermond. Zij studeerde gedurende een tweetal jaren Biologie aan de Rijksuniversiteit Leiden, alwaar zij na inloten in 1981 ook de studie Geneeskunde kon aanvangen. Tijdens haar studietijd was zij van 1984-1985 student-assistent op de afdeling Neuroradiologie. Van 1985-1988 was zij als student-assistent op de afdeling Klinische Oncologie betrokken bij onderzoek naar het larynxcarcinoom (Dr W.V. Dolsma, Prof. dr J.W.H. Leer). In februari 1988 behaalde zij haar arts-examen. Nadien volgde zij de opleiding tot radiotherapeut-oncoloog te Leiden (Opleider: Prof. dr J.W.H. Leer).
Sinds maart 1992 is zij werkzaam als staflid op de afdeling Radiotherapie van het Academisch Ziekenhuis Rotterdam/Dr. Daniel den Hoed Kliniek. Vanaf 1994 maakt zij deel uit van de conformatie-projectgroep, in het kader waarvan enkele studies tot stand kwamen die resulteerden in dit proefschrift. Gelijktijdig deed zij radiobiologisch onderzoek naar de invloed van veroudering op tolerantie voor radiotherapie van gezond weefsel.
Zij is getrouwd met Stef Olofsen en is de trotse moeder van Juana Isabel (1998) en Iván (2000).

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