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TOWARDS BETTER QUALITY OF LIFE AFTER RADIATION THERAPY BY IMPROVED RESPONSE MODELING

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ABSTRACT

Background: To improve the quality of life of radiotherapy cancer survivors we need to improve our knowledge of the dose, volume and time-response relations of radiotherapy induced late effects.

Aims: The aim of the thesis was to investigate predictors for normal-tissue complications of head and neck, and gynecological radiotherapy using response modeling. We aimed to study this effect by using existing and new normal-tissue complication models.

Methods: In this thesis, we included 72 patients, who had received external beam radiation therapy (EBRT) for head and neck cancer in Stockholm. Of those, 33 developed esophageal stricture to the proximal esophagus. Gynecological-cancer survivors were treated with pelvic-radiation therapy only or in combination with other treatments in the Stockholm and Gothenburg regions during 1991 to 2003 were also investigated. Dose-volume histograms (DVHs) of 519 gynecological cancer survivors and 73 head and neck cancer survivors were extracted from the treatment planning systems. The dose-effect relations between the symptom ‘emptying of all stools into clothing without forewarning’ and bowel organs and the anal-sphincter were investigated, considering additional possible risk factors. The dose-volume response relations for these organs at risk (OAR) were also investigated for 77 gynecological cancer survivors, who were treated with EBRT only. Moreover, the dose, volume and time-effect of the dose to the vagina and ‘absence of vaginal elasticity’ were investigated for 78 survivors treated with EBRT only. A novel model is proposed, describing the influence of follow-up time on the dose-response relations. To explore the dose-volume effect of the late complications the Relative Seriality, the Lyman and the gEUD models were fitted to the dose volume data. To investigate the dose-effects and the dose-time effects the Probit and the proposed Probit-time models were also used.

Results: The best estimates of the dose–response parameters indicated a steep dose-response relation for the radiation induced esophageal strictures for the period of 2001–2005. Mean doses higher than 50 Gy to the anal-sphincter and bowel organs were related with the occurrence of ‘emptying all stools into clothing without forewarning’. Dose to the anal-sphincter region and sigmoid seemed to be most relevant, but all OARs were found to have steep dose-responses for this symptom. According to the estimated volume parameters the investigated OARs do not show any volume effect for this endpoint. All the studied models had the same predictive power for the symptom as a function of the dose for all investigated OARs. The Probit-time model fit our data better than the pure Probit for ‘absence of vaginal elasticity’. According to the volume parameter from the relative seriality, the vagina has shown a pronounced volume effect for this endpoint.

Findings: Dose-response relations and volume dependence were found for the radiation induced esophageal strictures. The EBRT dose to the bowel organs and the anal-sphincter were related to the occurrence of ‘emptying of all stools into clothing without forewarning’. The mean dose to the vagina was related to the occurrence of ‘absence of vaginal elasticity’. The steepness of the dose-response relation for the mean dose to the vagina and the symptom increased with time.

Implications: The risk of ‘emptying of all stools into clothing without forewarning’ might be lowered by delineating the anal-sphincter region and the sigmoid as well as the rectum and the small intestines during the treatment planning process. This thesis suggests radiobiological parameters for the proximal esophagus, the anal-sphincter region, the bowel organs and the vagina. Those parameters could be used in terms of avoiding the studied normal-tissue complications in the future. Finally, our findings suggest that the effect of time be considered at the time of treatment and communication with the patient.

List of Publications

- I. **Alevronta E**, Ahlberg A, Mavroidis P, al-Abany M, Friesland S, Tilikidis A, Laurell G, Lind BK: Dose-response relations for stricture in the proximal oesophagus from head and neck radiotherapy. *Radiother Oncol* 2010, 97(1):54-59.
- II. Lind E, **Alevronta E**, Steineck G, Waldenström A. C, Nyberg T, Olsson C, Wilderäng U, Dunberger G, Al-Abany M, Åvall-Lundqvist E: Emptying of all stools into clothing without forewarning and mean dose to bowel and anal-sphincter among gynecological cancer survivors. *Radiotherapy and Oncology (submitted)* 2013.
- III. **Alevronta E.**; Lind, H., Al-Abany M., Waldenström A. C., Olsson C., Dunberger G., Mavroidis P., Nyberg T., Johansson K. A., Avall-Lundqvist E., Steineck G., Lind B. K.: Dose-response relationships for an atomized symptom of fecal incontinence after gynecological radiotherapy. *Acta Oncol* 2013, 52(4): 719-726.
- IV. **Alevronta E**, Åvall-Lundqvist E, Al-Abany M, Nyberg T, Lind H, Waldenström A.C, Olsson C, Dunberger G, Bergmark K, Steineck G, Bengt K. Lind BK: Time-dependent dose-response relations of absence of vaginal elasticity after gynecological radiation therapy (Manuscript).

Related publications not included in the thesis:

Ahlberg A, al-Abany M, **Alevronta E**, Friesland S, Hellborg H, Mavroidis P, Lind BK, Laurell G: Esophageal stricture after radiotherapy in patients with head and neck cancer: experience of a single institution over 2 treatment periods. *Head Neck* 2010, 32(4): 452-461.

Lind H, Waldenström A. C, Dunberger G, al-Abany M., **Alevronta E**, Johansson K. A, Olsson C, Nyberg T, Wilderäng U, Steineck, G, Åvall-Lundqvist E: Late symptoms in long-term gynaecological cancer survivors after radiation therapy: a population-based cohort study. *Br J Cancer* 2011, 105 (6), 737-45.

Waldenström, A. C, Olsson, C, Wilderäng U, Dunberger G, Lind H, **Alevronta E**, al-Abany M, Tucker S, Avall-Lundqvist E, Johansson K. A, Steineck G: Relative importance of hip and sacral pain among long-term gynecological cancer survivors treated with pelvic radiotherapy and their relationships to mean absorbed doses. *Int J Radiat Oncol Biol Phys* 2012, 84 (2), 428-36.

Contribution to the papers

For Paper I, I took part in the extraction of treatment protocols from the archive together with Massoud al-Abany and I performed part of the DVHs collection from the treatment planning system at Radiumhemmet. That included loading the data in the treatment planning system, delineation of 2 cm, 5 cm and the whole esophagus and extraction of the DVHs. I did part of the reproduction of the DVHs in the computer and conducted the DVH analyses and the statistical analysis presented in table 1. Finally, I took the main responsibility for the writing of the paper and the correspondence with the journals.

For Papers II, III and IV I performed part of the DVHs collection from the treatment planning system at Radiumhemmet under the supervision of Massoud al-Abany and Helena Lind. That included loading the data in the treatment planning system, delineation of seven organs at risk and extraction of the DVHs. I also reproduced the DVHs from the files of the treatment planning system and conducted the DVH analyses.

For Paper II, I took the main responsibility for the DVH analysis. My main contribution to the writing of the paper was the DVH analyses part of the manuscript.

For Paper III, I took the major responsibility for the radiobiological analysis under the supervision of Bengt Lind using the in-house developed optimization software *bml*. I also took the major responsibility for the statistical analyses with the assistance of the statistician Tommy Nyberg. Finally I took the major responsibility for the writing of the paper and the reviewing process with the journal.

For Paper IV, I took the major responsibility for the radiobiological analysis under the supervision of Bengt Lind using the optimization software *bml*, the writing of the manuscript and the correspondence with the journal. Finally, I took the major responsibility for the statistical analyses with the assistance of the statistician Tommy Nyberg.

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LIST OF ABBREVIATIONS

AIC	Akaike information criterion
AUC	Area under the curve
BED	Biological effective dose
CI	Confidence interval
CTV	Clinical target volume
DVH	Dose volume histogram
EBRT	External beam radiation therapy
EQD	Equieffective dose
EUD	Equivalent uniform dose
FIGO	Federation Internationale de Gynecologie et d'Obstetrique
FSU	Functional subunits
gEUD	Generalized equivalent uniform dose
GTV	Gross tumor volume
HDR	High dose rate
IMRT	Intensity- modulated radiotherapy
ITV	Internal target volume
LDR	Low dose rate
LKB	Lyman Kutcher Burman
LL	Log Likelihood
LQ	Linear quadratic
MRI	Magnetic resonance imaging
NG-tube	Nasogastric tube
NTCP	Normal tissue complication probability

OAR	Organ at risk
OR	Odds ratio
PDR	Pulsed Dose Rate
PEG	Percutaneous Endoscopic Gastrostomy
RS	Relative Seriality
PTV	Planning target volume
RCR	Repairable-conditionally repairable
ROC	Receiver operating characteristic
RR	Relative risk
TCP	Planning target volume
TN	True-negative
TP	True-positive

1 INTRODUCTION

The number of long time survivors among treated cancer patients is increasing and therefore more effort should be put into improving their health-related quality of life. The main goal of radiation therapy is to eradicate the malignant disease causing the least possible side effects. The effect of radiation therapy is associated with many factors, such as the treatment technique, the quality of the radiation used, biological processes, and patients' general health condition during the treatment.

The radiotherapy-treatment techniques have been developed with the aid of new technologies. The development of conventional radiotherapy was mainly based on clinical experience and 'trial error' varying several factors like the field size, beam angles, the weights of the beam and dose per fraction [1]. The three-dimensional conformal radiotherapy was developed to reduce the dose load by adjusting the dose distribution to the planning target volume (PTV). An important and exciting advance of radiotherapy was the introduction of intensity-modulated radiotherapy (IMRT) [2-5]. The concept of IMRT was introduced by Brahme *et al.* 1982 [6], who also introduced the inverse planning some years later (Brahme 1988 [7]). Today IMRT is a widely used technique.

Dose constraints and radiobiological parameters are tools that aim to optimize the radiation therapy treatment and are based on past technologies. However, these historical data can be very useful to improve the radiation therapy outcome today.

1.1 AIM

The aim of the research on which this thesis is based was to investigate and quantify late complications of radiation therapy and as a result to help in mitigating these symptoms in the clinic. In addition, the goal was also to fit the epidemiological data to the existing normal-tissue complication (NTCP) models, to improve the NTCP models and to also introduce a new model including the effect of time to follow up on the dose-response relations. This work was empowered by linking the clinical epidemiological tradition and the normal tissue complication modeling.

The specific aims of the studies for the four papers included in the thesis were:

- I. To determine the dose-response relations for esophageal stricture after radiotherapy of the head and neck.
- II. To analyze the relationship between mean dose to the bowel and anal sphincter and the occurrence of 'emptying of all stools into clothing without forewarning'.
- III. To determine what bowel organs and doses are most relevant for the development of the symptom 'emptying of all stools into clothing without forewarning' and also to derive the corresponding dose-volume-response relations as an aid in avoiding this distressing symptom in the future.

- IV. To investigate the influence of the follow up time on the dose-response relations of the ‘absence of vaginal elasticity’ and to model these relations with respect to the follow up time.
- V. To investigate the influence of the follow up time on the dose-response relations of the ‘absence of vaginal elasticity’ and to model these relations with respect to the follow up time.

2 BACKGROUND

2.1 HEAD AND NECK CANCER

2.1.1 Treatment of head and neck cancer

The incidence rate of head and neck cancer in Sweden in 2011 is 13.2 per 100 000 men and 8.2 women [8]. Treatment options for head and neck cancer depend on the specific sub-site of the primary tumor and on tumors stage as well as on patient's physical condition and possible co-morbidities [9, 10]. During most of the twentieth century, only surgery and external radiotherapy were considered effective against head and neck cancer but at the end of the century, combined chemoradiation became more common [9, 10].

2.1.2 External beam radiation therapy techniques in Stockholm

The patients included in the study presented in Paper I, received their treatment at Radiumhemmet, Karolinska University Hospital in Stockholm and the treatments were planned according to local guidelines. Two PTV were defined, PTVA and PTVB. The PTVA, receives 46 Gy and includes the known primary tumor (GTV-T) and positive lymph nodes (GTV-N) as well as structures for elective treatment with margin for the uncertainties of microscopic spread. The PTVB included a second target volume that receives additionally, 18–22 Gy. The PTV includes the gross tumor volume (GTV) with a margin of the subclinical microscopic malignant disease [11, 12]. The total dose in PTV was 64–68 Gy.

In the end of 90s, the treatment technique changed due to change of PTV, according to new guidelines. This change results in to smaller volume and optimization of the conformal therapy. Consequently, smaller volumes received a high dose and a larger proportion of normal tissue could be spared. In addition, if the larynx was not included in the planning target volume, it was blocked from the anterior-posterior fields. The field orientation was also changed from lateral to anterior posterior. Today, other treatment modalities are also used to spare normal tissue such as proton or ion therapy, intensity-modulated radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT). At Radiumhemmet VMAT is in use.

In Paper I, the patients received EBRT for tumors at various primary sites and in different stages [13]. Diagnoses included oral, oropharyngeal, epipharyngeal and laryngeal cancers and a group of miscellaneous tumors consisting of cancers of the salivary glands, nose, sinuses and finally cervical metastasis from cutaneous tumors in the head and neck area.

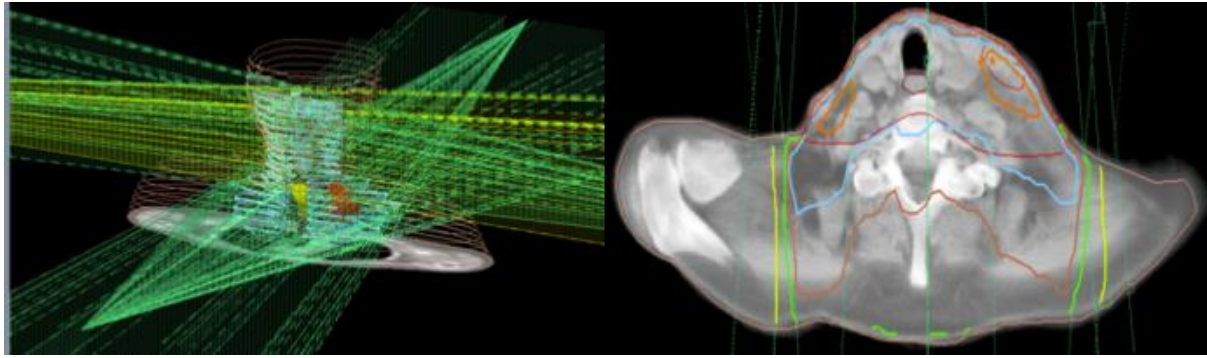


Figure 1: The left panel illustrates a 3-D reconstruction of the treatment plan of a head and neck patient included in Paper I. The PTV is denoted with blue color, the tumor with red color, the proximal esophagus with yellow color and the dose bins with green color. The right panel illustrates the esophagus with dark red color and the different isodose curves.

2.1.3 Brachytherapy techniques

Low dose rate (LDR), high dose rate (HDR) and Pulsed Dose Rate (PDR) brachytherapy techniques are often used in the treatment of head and neck squamous cell carcinoma. Brachytherapy is a highly effective technique in the treatment of limited-stage squamous cell carcinoma of the oral cavity and oropharynx [9]. However, in order to use brachytherapy the tumor has to be accessible for implantation of catheters. Some studies report that brachytherapy alone could be used for smaller tumors, while larger tumors, such as at the base of tongue, should be treated with a combination of external and internal radiotherapy [14, 15]. Brachytherapy is used at the Karolinska University Hospital.

2.1.4 Esophageal stricture

The esophagus is the upper extreme of the gastrointestinal tract and its length in an adult is about 25 cm [16]. The esophagus is reported to be fragile and radiosensitive [17]. Early and late esophageal toxicities are common after head and neck radiation therapy. The relation of esophageal stricture and EBRT dose to the proximal esophagus has been discussed in several studies [13, 17-20] and also in Paper I. The incidence of this late effect was reported in less than 5 % [13, 17, 19], while if the patients also received chemotherapy in less than 37.5 % [19].

As described by Laurell *et al.* [17], the strictures of the proximal esophagus are classified in grade I, II and III according to the findings at endoscopy for diagnosis of dysphagia or treatment of stricture. The grade I stricture could be passed using a rigid esophagoscope and dilated by placing endoscopes of different sizes, starting with a 7 mm x 10 mm endoscope and ending with a 14 mm x 16 mm endoscope. Strictures, classified as grade II, were severe and fibroses at the esophageal inlet were present. Even the smallest esophagoscope (7 mm x 10 mm), could not pass grade II strictures without dilation. In grade III strictures, total obliteration was present with no visible communication between the hypopharynx and the esophagus.

Impaired swallowing is a common problem in head and neck cancer patients [13, 17, 21] and different radiation induced factors could contribute to it, *e.g.* xerostomia, increased mucus viscosity, mucositis and edema of soft tissues. At a later stage fibrosis and rigidity in the soft tissue may result in a loss of function in muscles that are part of the swallowing process [9, 22]. A previous paper [13] of our group investigated several possible risk factors for the development of esophageal strictures. EBRT dose exceeding 45 Gy was significantly associated with the occurrence of esophageal strictures. An additional risk factor was the use of a nasogastric tube (NG-tube) or percutaneous endoscopic gastrostomy (PEG) during or immediately after EBRT, a result that was confirmed by other studies as well [13, 23, 24]. However, the enteral feeding per se may indicate patients at risk for dysphagia [9]. Other possible risk factors as reported by Lee *et al.* [25] are hypopharyngeal primary tumor, female sex, and hyperfractionated radiotherapy.

2.2 GYNECOLOGICAL CANCER

2.2.1 Treatment of gynecological cancer

The incidence rate of gynecological cancer standardized according to the Swedish population per 100 000 for 2011 was 54.8 [8]. The female genital organs consist of the ovaries, the fallopian tubes, the corpus and cervix uteri, the vagina and the vulva. The treatment of gynecological cancer consists of a combination of surgery, chemotherapy and radiation therapy (RT), depending on the tumor site and extension. Standard-of care for ovarian and fallopian tube cancer, is primary cytoreductive surgery followed by postoperative chemotherapy [26]. Whole abdominal radiation therapy is rarely used nowadays due to the risk of severe late gastrointestinal side-effects, but can be used in the palliative setting [26, 27].

Surgery and radiation therapy seem to be equally effective in International Federation of Gynecology and Obstetrics (FIGO) [28] stage IB or IIA cervical cancer [29]. Preoperative intrauterine brachytherapy was previously frequently used in Sweden for early stages of cervical cancer. [30]. Patients treated with intracavitary brachytherapy and receiving EBRT had a central shield with a width of four cm. The prescribed dose to the shielded volume was adjusted in order not to exceed a total dose of 50 Gy to the rectum and 60 Gy to the urinary bladder. An additional prophylactic paraaortic field with total dose of 40 Gy (1.6 Gy per fraction) was prescribed in some regions to patients with pelvic lymph node metastasis until 2000.

The standard treatment for endometrial cancer is primary surgery including hysterectomy and bilateral salpingo-oophorectomy. Adjuvant pelvic radiotherapy is used for patients with high risk early stage tumors [31]. For advanced stages of endometrial cancer, patients often receive a combination of surgery, pelvic EBRT and chemotherapy.

Uterine sarcoma entails a rare but aggressive form of gynecological cancer. The benefit of surgical adjuvant pelvic EBRT for uterine sarcoma is unclear although studies suggest improved local control without improvement of disease-free survival [32]. Possible options for inoperable uterine sarcoma treatment include pelvic RT and chemotherapy. For early stage stromal sarcoma, hormonal therapy and chemotherapy are applied [33].

For the treatment of vaginal cancer, a combination of EBRT and vaginal brachytherapy, with or without chemotherapy, are applied [34]. For the vulvar cancer treatment, radical vulvectomy with bilateral inguinal lymphadenectomy has so far been the predominant method [35]. Treatment for more advanced stages of disease is individualized and usually involves a combination of surgery, radiation therapy and chemotherapy.

2.2.2 External beam radiation therapy techniques

The gynecological-cancer survivors included in the study received EBRT in Radiumhemmet in Stockholm or Jubileumskliniken in Gothenburg between 1991 and 2003. The EBRT were administered according to the local treatment programs and applied study protocols at the time of treatment. The predominant radiation therapy treatment technique before 1996 was two opposing fields, while after 1996 it was more common to use a four-field box technique. The EBRT dose was prescribed either at isocenter or as mean dose to the target covering at least 95 % of the planning target volume (ICRU, 1993 [36]). Patients were treated in supine position, using linear accelerators with energy ranges between 6 and 50 MV. The dose per fraction used during the treatment period was 1.6 Gy, 1.8 Gy or 2.0 Gy. EBRT was verified by portal image films and with check-and-confirm systems [37]. The treatment planning was performed by TMS (Nucletron, Veenendaal, the Netherlands) in Stockholm and Cadplan and Eclipse (Varian Medical Systems, Palo Alto, USA) in Gothenburg. EBRT was based on computed tomography (CT) scans performed before radiation therapy. The thickness of the CT scanning was 5 to 20 mm and it was performed with the patients in treatment position on a flat table, using laser markers and conversion factors to electron density.

The prescribed dose to the gynecological malignancies was 39.6 to 46.0 Gy for endometrial cancer, 50.4 Gy for uterine sarcomas, 55.0 to 70.0 Gy for cervical cancer and for ovarian and fallopian tube the prescribed dose was 20.0 Gy to the abdomen and an additional 20.0 Gy to a volume with lowered cranial margin.

2.2.3 Brachytherapy techniques

Classical methods of brachytherapy were ^{226}Ra introduced with an applicator. After the 1950's and 1960's afterloading techniques were introduced, for which the application and the irradiation were separated. The radiation sources that used were ^{137}Cs , and ^{192}Ir . All these devices use intrauterine and intravaginal sources [26]. Several approaches have been developed over the past decades with a significant range of applicators. The classical 'Stockholm method' for brachytherapy was developed at Radiumhemmet. This method was based on a flexible intrauterine tube and a flat box (plate) in the vagina pushed by an individual packing device against the cervix. Other classical brachytherapy methods were the Paris method, which use an intrauterine catheter plus corks or ovoids and the Manchester method, which used an intrauterine catheter plus ovoids [38].

As it is reported in ICRU 38 [39], brachytherapy can be applied using different dose rates. LDR ranges between 0.4 and 2 Gy per hour. However, in routine clinical practice, LDR brachytherapy is usually delivered at dose rates between 0.3 and 1 Gy per hour. This is com-

patible with conventional manual or automatic afterloading techniques. MDR brachytherapy can be also applied and ranges between 2 Gy and 12 Gy per hour. MDR can also be delivered by manual or automatic afterloading, although the latter is far more frequent. HDR brachytherapy delivers the dose at 12 Gy per hour or more and can thus be applied only using automatic afterloading because of the high source activity. Finally, PDR brachytherapy, delivers the dose in a large number of small fractions with short intervals. This method allows only for incomplete repair, aiming at achieving a radiobiological effect similar to low dose rate over the same treatment time, typically a few days [40].

The evaluation of brachytherapy plans were traditionally based on 2D X-ray images, while the dose calculation based on sectional imaging such as CT and MRI have played a minor role in brachytherapy [41]. However, nowadays many clinics all over the world are using 3D image-guided brachytherapy. The use of sectional imaging offers the possibility to accurately delineate the GTV, define and delineate the clinical target volume (CTV) and PTV and the OAR [42]. The DVHs can also be calculated with this method for the tumor and the defined OAR.

In our study presented in Paper II, brachytherapy was applied using standardized techniques and applicator templates. The brachytherapy dose was prescribed according to local practice. Pre-treatment orthogonal X-ray images verified the position of the brachytherapy applicator [37]. HDR brachytherapy for endometrial cancer was prescribed at 5 Gy per fraction in two fractions or 3.75 Gy per fraction in three fractions. For cervical cancer LDR brachytherapy was prescribed at 10-24 Gy per fraction in one to three fractions depending on tumor size and EBRT dose or as HDR brachytherapy at 4 Gy per fraction in three fractions.

3 COLLECTION OF CLINICAL DATA IN RADIATION THERAPY

Before the modeling of responses for different normal-tissue complications takes place, the actual data have to be gathered. This data collection is a time consuming but crucial procedure. Patients receiving radiation therapy for a specific malignant disease need to go through the treatment-planning process. The treatment plan is nowadays performed using segmentation imaging techniques, such as CT and MRI. The GTV, CTV, ITV and PTV are delineated to each treatment plan, as well as the corresponding OAR. The treatment-planning system calculates the dose distributions for the delineated structures using an implemented dose-calculation algorithm. The treatment plans for each patient are archived in the treatment planning system. Patients' medical records are also archived in hospital databases. To conduct a study with the purpose to evaluate normal tissue complications among cancer survivors, one should do the follow up of survivors at one or several chosen time points. In the present work OAR were delineated as part of the project since this had not been previously done. For future studies of late effects of radiation therapy will be quicker to retrieve the dose volume histograms for the selected OAR.

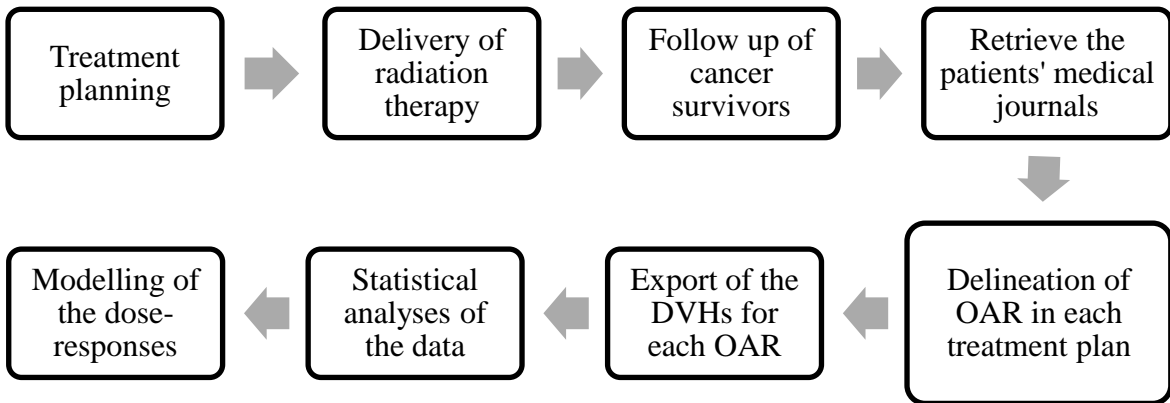


Figure 2: Flowchart that describes the steps that lead from the treatment planning to the modeling of the dose-response relationships.

3.1 STUDY DESIGN

The epidemiological design for each study is crucial for the quality of the data. For this thesis a case-control study was conducted and presented in Paper I, while papers II, III and IV were parts of a retrospective cohort study designed following the hierarchical step model [43].

Esophageal stricture

The study reported in Paper I is a case-control study in which 72 patients, who received head and neck radiotherapy were included. Of them, 33 patients developed esophageal stricture

and 39 were symptom free. All patients included in the study received radiation therapy for head and neck cancer at Karolinska University Hospital in Stockholm, Sweden. Patients included in the study received no chemotherapy and had complete medical records. Patients whose treatment planning information could not be restored in the treatment planning system and patients with swallowing problems before the diagnosis of the current tumor were excluded.

Patients with no sign of esophageal stricture and reporting no swallowing problems in a questionnaire two years after receiving full-dose EBRT including at least part of the esophagus were considered to be symptom-free. All patients had given informed consent to participate in the study.

Follow Up

After EBRT, patients had regular check-ups for 5 years every 1 to 3 months by the surgeon and oncologist respectively. A nurse controlled patients' weight, before and after treatment, every second week for 3 months. In case of 5 % of weight loss or more in comparison with the weight before radiotherapy; the patient was referred to a physician for nutritional support [13].

All 72 patients were analyzed in two subgroups due to the change of the treatment technique during the year 2000. The first subgroup included patients treated during 1992–2000 while the second one, patients treated during 2001–2005.

Late effects of gynecological radiation therapy

The study cohort of gynecological cancer survivors has been described in detail in papers from our group [37]. In this study, 1800 gynecological cancer patients were included. The patients were identified in 2005 and were treated between 1991 and 2003 with radiation therapy at Karolinska University Hospital in Stockholm or at Sahlgrenska University Hospital. Of those 1101 did not meet the inclusion criteria. For the survivors to be included in the study, they should be alive at follow up, be younger than 80 years, to understand Swedish, have a primary tumor and to have EBRT to the pelvic region. An introductory letter was sent to 789 cancer survivors, while 698 agreed to receive the questionnaire. Of them, 81 did not complete the study. Thus, with a participation rate of 78 %, we received completed questionnaires from 616 survivors.

An age-matched control group consisting of 489 women was randomly retrieved from the Swedish Population Registry [37]. To be eligible for this group, the women should be younger than 80 years, understand Swedish and to have received no prior pelvic radiation therapy. Eight of them did not meet the eligibility criteria and were thus excluded. An introductory letter was sent to 478 women and 420 of them agreed to participate in the study. Finally, 76 women did complete the study, resulting in 344 control women returning a completed questionnaire. The flowchart for the inclusion of the survivors in the study is illustrated in Figure 3.

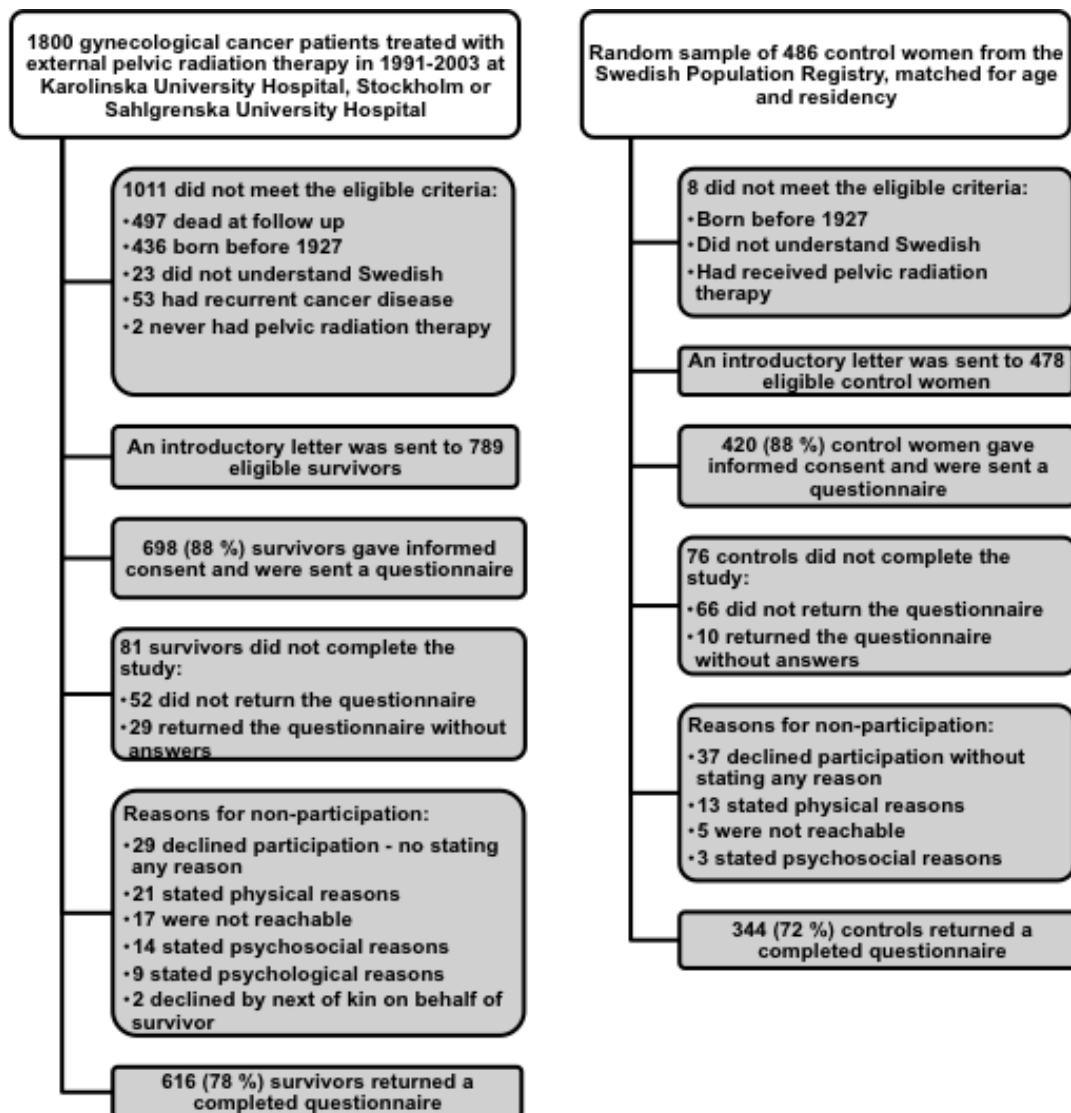


Figure 3: Flow chart describing the inclusion criteria [36].

All 519 out of total 616 survivors returning a completed questionnaire had radiotherapy treatment plans where DVHs for the OARs could be collected and were included in Paper II. In 77 out of 519 survivors, no brachytherapy was given and were described in Paper III. Survivors that experienced heart failure were excluded. Thirteen out of 77 survivors reported having ‘emptying of all stools into clothing without forewarning’. In 78 out of 519 gynecological cancer survivors, no brachytherapy was administered and were included in Paper IV. Twenty-four out of 78 survivors reported having ‘absence of vaginal elasticity’.

3.1.1 Questionnaire

A validated, postal questionnaire was constructed including 351 questions covering physical symptoms from the anal sphincter, the bowels, the urinary and genital tracts, the pelvic bones, lower abdomen and legs. In addition, there are questions about quality of life, social functioning and demographics [44]. Additional information about the incidence, prevalence, intensity and duration of the symptoms and their impact on different aspects of social functioning was asked for.

To develop the questionnaire, a qualitative preparatory study, which lasted 18 months, was conducted. For this study, 26 gynecological cancer survivors who received EBRT one to ten years earlier were interviewed. The questions asked were dealing with the survivors' present condition, symptoms, quality of life and social functioning. The symptoms and themes that the women reported during the interviews were reformulated as questions. To form the final questionnaire, additional questions were included according to the clinical experience of our group, previous questionnaires from our research unit and from available literature. The questionnaire was also validated face-to-face with the women of the study population and the non-irradiated ones to assure that the questions were clear and correctly understood. Finally, in order to test the participation rate, rate of missing values and logistics a pilot study was done.

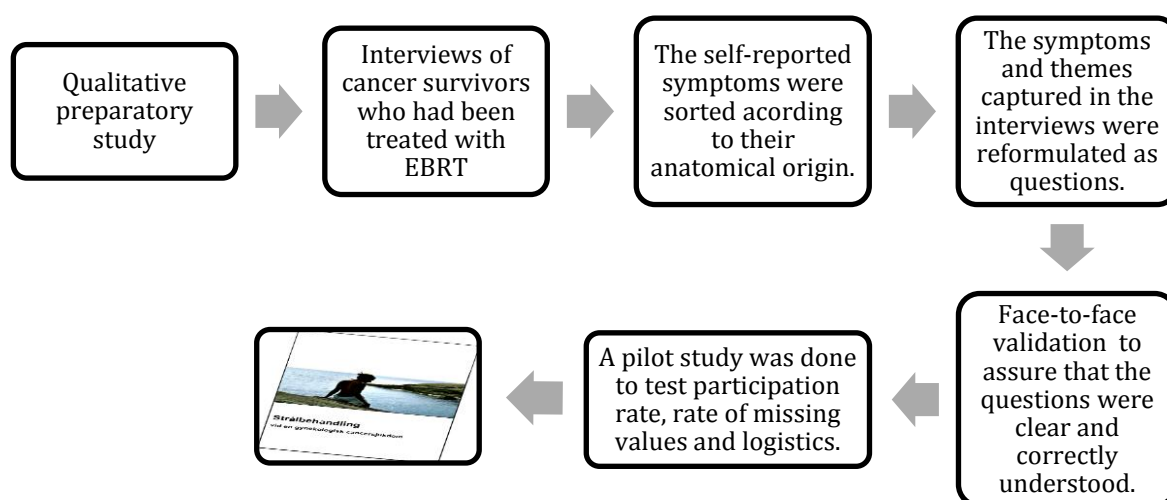


Figure 4: Flowchart for the construction of the questionnaire.

Table 1: Questions from the questionnaire used in Papers II, II and IV

Question	Answers
Have you emptied all your stools into clothing without forewarning the past six months?	<ol style="list-style-type: none"> 1. No 2. Yes, occasionally (once every six months) 3. Yes, at least once a month 4. Yes, at least once a week 5. Yes at least three times a week 6. Yes at least once every day
How was your vaginal elasticity during the last six months?	<ol style="list-style-type: none"> 1. None at all 2. Little 3. Moderate 4. Well

3.2 DELINEATION OF THE ORGANS AT RISK

To extract the DVHs for the head and neck patients, we delineated the first 5 cm of the esophagus in each CT image for every patient. The delineation was performed in the TMS (Nucletron, Veenendaal, the Netherlands) treatment planning system at Radiumhemmet, Karolinska University hospital in Stockholm, Sweden. The scan thickness of the CT slices was 5 or 10 mm. The entrance of the esophagus was defined anatomically at the level of the cricoid cartilage, which is 2 cm below the vocal cords.

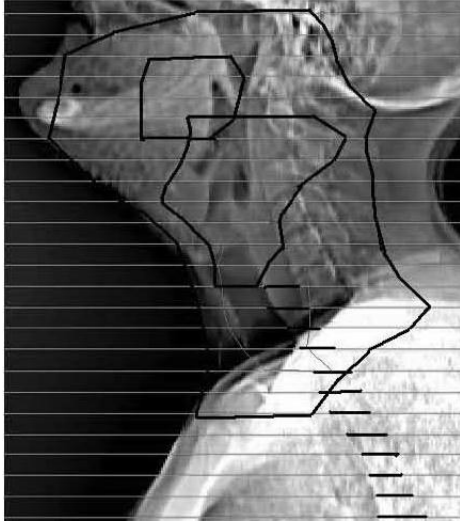


Figure 5: Delineation of the whole esophagus in the CT scan of a patient with 1 cm distance of the slices. Except from the esophagus, the PTV, the CTV and the tumor are contoured.

For the gynecological-cancer survivors, we delineated ten OARs; the anal-sphincter region, rectum, the sigmoid, the small intestines, the urinary bladder, the vagina, the pubic bone, the sacrum and finally the left and right femoral heads. We delineated the OARs in the CT scan of each survivor. The thickness of the CT scan slices was 5 to 20 mm. The delineation of the OARs was done both at Radiumhemmet, Karolinska University hospital in Stockholm and Jubileumskliniken, in Gothenburg, Sweden. The treatment planning system used in Stockholm was the TMS and Cadplan and in Gothenburg Eclipse (Varian Medical Systems, Palo Alto, USA). Two persons at each clinic performed the contouring under the supervision of a Senior Oncologist (Helena Lind. in Stockholm and Ann-Charlotte Waldenström in Gothenburg). To assure that the contouring was consistent, written guidelines including pictures were used [37] (see Paper II in the current thesis).

Table 2: Delineation of the OAR.

Organs at risk	Definition of delineation area
Anal sphincter	Inner muscle layer of the sphincter up to the anal verge.
Rectum	Depicted by its outer contour with filling extending from the anal verge to the recto sigmoid junction.
Sigmoid	Outlined from where the rectum deviated from its mid-position to where it could be located in the left part of the abdomen in at least two consecutive slices and connecting to the colon descendens.
Small intestines	All visible small bowels in the pelvic region up to the caudal part of the sacro-iliac joints.
Urinary bladder	Represented by its outer contour including filling.
Vagina	Elliptical-shaped area measuring one cm by three cm located between the urethra/urinary bladder and the rectum to cervix portio or if not present to the lower border of the pelvic cavity.
Pubic bone	Contoured using the symphysis as a starting-point reaching laterally including the anterior parts of the superior and inferior rami.
Sacrum	Defined by the body of the sacrum, excluding the dorsal spinal processes and the coccyx.
Femoral heads	Outlined separately covering the head but excluding the femoral neck

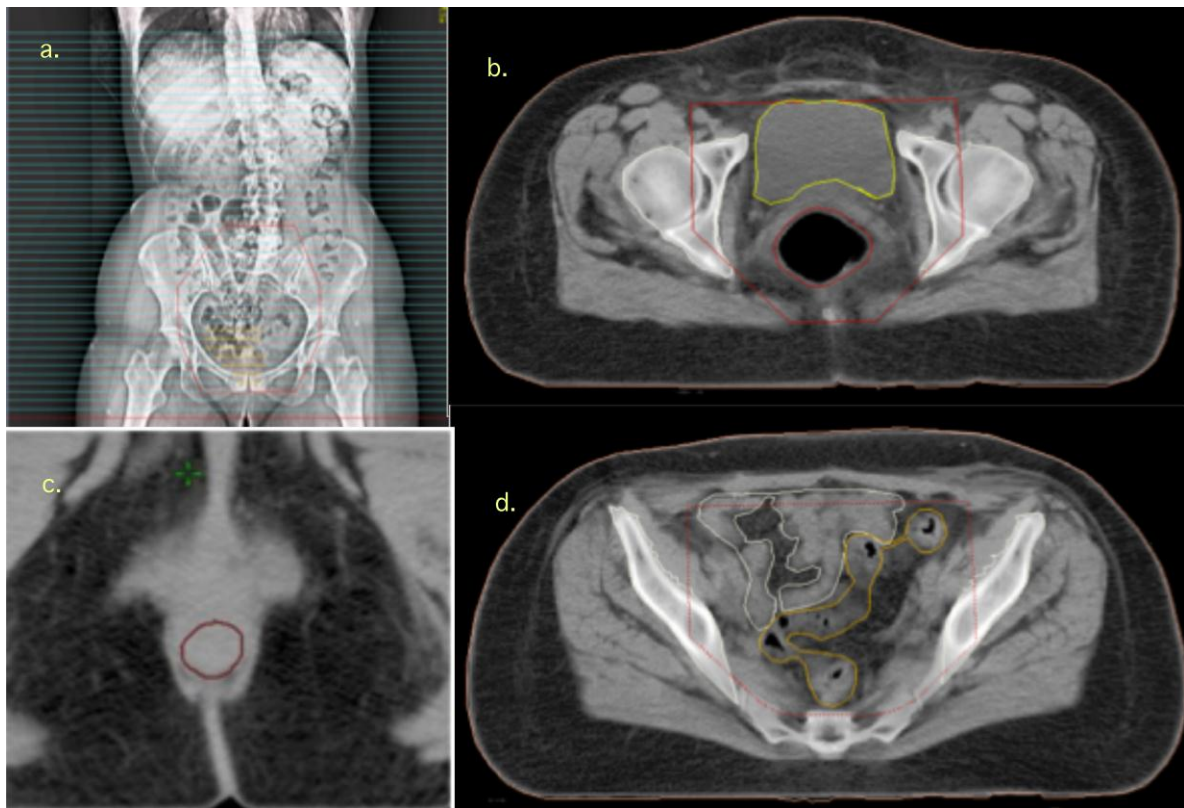


Figure 6: a. CT scan of a patient, showing the rectum outlined with yellow color contour, the pelvic field outlined with red contour. b. The PTV and the rectum are outlined with red contour and the urinary bladder with yellow. c. The anal-sphincter region outlined with red contour. d. The sigmoid outlined with orange contour and the small intestines with white.

3.3 DOSE-VOLUME HISTOGRAMS

Three-dimensional treatment planning includes a vast amount of dose-volume information, which may be difficult to interpret and evaluate [45]. To graphically summarize the dose distribution to the target or OAR they can be condensed into two-dimensional dose-volume histograms, which can graphically summarize the dose distribution to the target or OAR. The disadvantage of the DVHs is that the spatial information of the dose deposition is lost.

To calculate the DVHs the boundaries of the tumor or OAR are defined in the treatment planning system and the dose is calculated for the defined structure. The dose delivered to the voxels included in the defined anatomical area is summed. The dose in each voxel is accumulated in the corresponding dose bin of the histogram to form the DVH of the structure. The differential DVHs are plots of the accumulated volume of those elements receiving dose in a specified dose interval against a set of equally spaced dose intervals. There are also cumulative DVHs, which are used more

In most DVHs included in Papers I, II and III the volume was specified as a percentage of the total volume of the defined OAR. Using the relative volume of the OARs is a consistent way to compare volumes of organs from different patients, since each of them has different size. However the absolute volume was used for the small intestines in Papers II and III, since not the whole organ was defined. To compare DVHs from different groups of interest *i.e.* patients with a specific symptom and patients without the symptom, the DVH for each individual included in each group were summed. Thus we were able to compare the mean cumulative DVHs of each group of patients (Figure 7). We also used the DVHs in the relative seriality and Lyman models to produce values of NTCP.

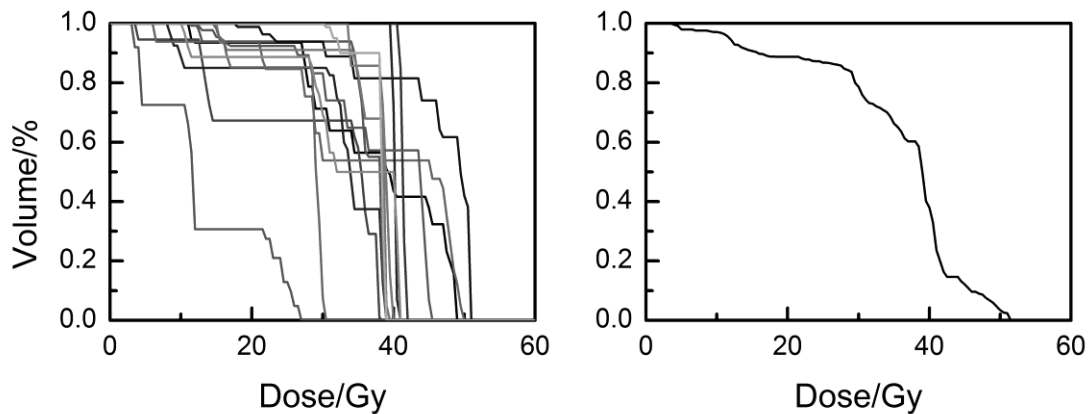


Figure 7: DVHs from the anal sphincter region of some of the gynecological cancer survivors included in Paper III. Left panel: Cumulative DVHs of individual patients for anal sphincter area. Right panel: Mean cumulative DVH of anal sphincter for that group of patients.

4 MODELING RADIOTHERAPY LATE EFFECTS

4.1 THE LINEAR QUADRATIC MODEL (LQ) MODEL

The LQ model [46, 47] is the most frequently used model to describe the clonogenic cell survival and is given by the following expression:

$$S(nd) = e^{-\alpha nd - \beta nd^2}, \quad (1)$$

where $S(n, d)$ is the fraction of cells that survives a total dose $D=nd$, where n is the number of fractions, and d is the dose per fraction.

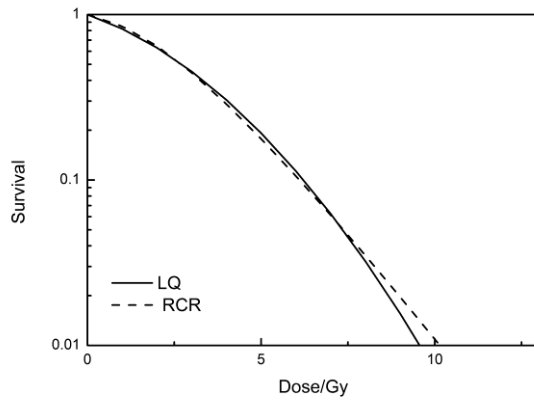


Figure 8: Typical fit of the LQ and RCR models with in vitro data [48]. LQ, solid line and RCR, dashed line.

The linear component of LQ model, αD , represents the initial linear part of the survival curve, while the quadratic component βnd^2 becomes more important at higher doses. The ratio of α over β is equal to a dose α/β , where the linear and quadratic components of cell killing are equal [46]. The LQ model suffers from two main limitations; it does not account for low dose hypersensitivity and it predicts too much damage due to the quadratic term, at high doses [49].

4.1.1 The repairable-conditionally repairable (RCR) model

In an attempt to account for the limitations of the LQ models and to describe the shoulder of the cell survival curve, Lind *et al.* proposed the RCR model in 2003 [50]. The cell survival expression of the RCR model is given by:

$$S(D) = e^{-aD} + \beta e^{-cD}. \quad (2)$$

In this equation, surviving cells that are missed or not damaged are included in the first term of the RCR model, e^{-aD} , and cells that are damaged and correctly repaired in the second term, βe^{-cD} .

4.1.2 Dose fractionation

Knowing the physical dose is not sufficient in order to determine the effect of a delivered treatment schedule because the physical dose can be delivered in different fractionation schedules. The most popular way to account for different doses per fraction is to use the biological effective dose (*BED*) [51, 52], based on the LQ model, to compare isoeffective treatment schedules:

$$BED = nd \left(1 + \frac{d}{\alpha/\beta} \right). \quad (3)$$

In a recent publication, Bentzen et al [53] suggested the use of the term equieffective dose, $EQDX_{\alpha/\beta}$, which they defined as “the total absorbed dose delivered by the reference treatment plan (fraction size X) that leads to the same biological effect as a test treatment plan that is conducted with absorbed dose per fraction d and total absorbed dose D ”. $EQDX_{\alpha/\beta}$ is given by the following relation adapted to the Wither’s formula [54]:

$$EQDX_{\alpha/\beta} = D \frac{d + \alpha/\beta}{X + \alpha/\beta}. \quad (4)$$

4.2 NORMAL-TISSUE COMPLICATION MODELS

The ultimate aim of radiation therapy is to treat the tumor while minimizing the possible complications in the normal tissues. Therefore it is important to account for inhomogeneously delivered dose outside the PTV [55]. Modeling the response of the tumor and normal tissues, the goal would be to achieve the highest possible tumor control probability (TCP), while minimizing the normal tissue complication probability (NTCP). Generally the NTCP models are single risk measures, which consist of more complicated dosimetric and anatomic information [56]. According to Yorke *et al.* perhaps an ideal NTCP model would be a statistical model based on physiology and cellular biology [55]. Most of the NTCP models used in different studies can be separated in two parts; one part that describes the dose response, which is the sigmoid shape of the response curve and one part that describes the volume effect, *i.e.* the change in dose response when only a fraction of the tissue/organ is exposed [5].

4.2.1 Dose-response models

The most common dose-response models are the Probit, Logit and Poisson. The Probit and Logit are empirical models, while the Poisson is a mechanistic model based on the cell killing process. The dose response models are conveniently parameterized with, D_{50} , the dose corresponding to a 50 % complication probability after uniform irradiation of the reference volume, and γ , the maximum normalized dose response gradient. The maximum normalized dose response gradient is at 50 % response probability, γ_{50} , for the Probit and Logit models and at 37 % response probability, γ_{37} , for the Poisson. All models presented in this chapter are parameterized in terms of D_{50} and γ_{50} .

The Probit model

The Probit model is based on the cumulative normal distribution and was *e.g.* used in [57] to derive tolerance dose data for various percentage volumes irradiated across a variety of organs and is given by the following expression:

$$P(D) = \frac{1}{2} \left(1 - \text{Erf} \left[\gamma_{50} \sqrt{\pi} \left(1 - \frac{D}{D_{50}} \right) \right] \right). \quad (5)$$

The Logit model

The Logit model [58] is an empirical model also used in radiotherapy and given by the following expression:

$$P(D) = \frac{1}{1 + \left(\frac{D_{50}}{D} \right)^{4\gamma_{50}}} . \quad (6)$$

The Poisson model

The Poisson model [59] derived from the usual statistical distribution, is a mechanistic model based on clonogenic cell survival, which is widely used in radiotherapy. The Poisson model is an approximation to the Binomial model [5] and can be defined as:

$$P(D) = 2^{-e^{\frac{2}{\ln 2} \gamma_{50} \left(1 - \frac{D}{D_{50}} \right)}} \quad (7)$$

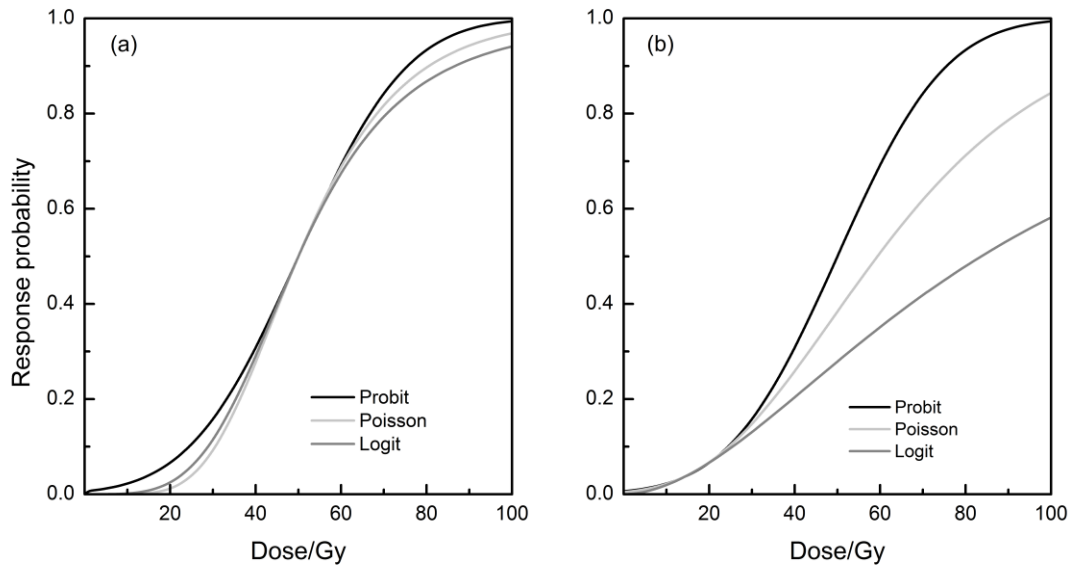


Figure 9: Dose-response curves for the Probit, Logit and Poisson models. (a) The curves are plotted with the same $D_{50}=50$ Gy and $\gamma_{50}=1$. (b) The curves are plotted with the same $D_5=17$ Gy and $\gamma_5=0.88$. In this curve we calculated the D_5 and γ_5 parameters for the Probit model and we normalized Poisson and Logit model according to those values.

Comparing the shapes of the sigmoid models Probit, Logit and Poisson (Figure 9) using the same D_{50} and γ_{50} , we observe that they agree well at intermediate doses. On the other hand the sigmoid curves that are plotted with the same D_5 and γ_5 agree well for low doses but they vary a lot for doses higher than D_5 . The above dose-response relations are examples of generalized linear models [31]. It is difficult to justify the favoring of a specific-dose response model, although there are statistical reasons for selecting among them [60]. For parameter estimation those models behave similarly. In the literature about radiobiological modeling there are no specific trends for the choice of models. However, the Poisson model is more often used in tumor-control studies, and the Logistic or Probit models in normal-tissue complications studies [60]. The use of the Probit model to model normal-tissue complications probabilities could perhaps be justified due to the central limit theorem [5]. If we intend to compare steepness estimates *e.g.* the values of γ parameter, then that would be affected from the selected model [60].

Generalization of the Probit model

The Probit model is one of the most common in the class of generalized linear models for binomial outcomes [31]. In its linear form, with y representing a binary outcome and fitted with p covariates, it is given as:

$$\begin{aligned} P(y=1|x_1, \dots, x_p) &= \Phi(\beta_0 + \beta_1 x_1 + \dots + \beta_p x_p) \\ P(y=1|x_1, \dots, x_p) &= \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\beta_0 + \beta_1 x_1 + \dots + \beta_p x_p} \exp(-t^2/2) dt, \end{aligned} \quad (8)$$

where $\Phi(x)$ is the cumulative distribution function of the standard normal distribution. To apply radiobiological modeling using one dosimetric variable $x_1 = D$ as predictor, the equation (8) reduces to:

$$P(y=1|D) = \Phi(\beta_0 + \beta_1 D). \quad (9)$$

The dose that gives 50% of response probability D_{50} is:

$$\begin{aligned} P(y=1|D_{50}) &= \Phi(\beta_0 + \beta_1 D_{50}) = \frac{1}{2} \\ \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\beta_0 + \beta_1 D_{50}} \exp(-t^2/2) dt &= \frac{1}{2}. \end{aligned} \quad (10)$$

Since the standard normal distribution is symmetric around 0:

$$\begin{aligned} \beta_0 + \beta_1 D_{50} &= 0 \\ D_{50} &= -\frac{\beta_0}{\beta_1}. \end{aligned} \quad (11)$$

The normalized dose response gradient γ_{50} is then given by:

$$\gamma_{50} = D_{50} \left. \frac{dP}{dD} \right|_{D=D_{50}}$$

$$\gamma_{50} = D_{50} \frac{1}{\sqrt{2\pi}} \frac{d}{dD} \left(\int_{-\infty}^{\beta_0 + \beta_1 D} \exp(-t^2 / 2) dt \right) \Big|_{D=D_{50}}. \quad (12)$$

$$\gamma_{50} = -\frac{\beta_0}{\sqrt{2\pi}}$$

Using equations 11 and 12 to the equation 9:

$$P(y=1|D) = \Phi\left(-\sqrt{2\pi}\gamma_{50} + \frac{\sqrt{2\pi}\gamma_{50}}{D_{50}} D\right) = \Phi\left(-\sqrt{2\pi}\gamma_{50} \left(\frac{D-D_{50}}{D_{50}}\right)\right), \quad (13)$$

and by substituting from equation 13 to the equation 8, it follows:

$$P(y=1|D) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{-\sqrt{2\pi}\gamma_{50} \left(\frac{D-D_{50}}{D_{50}}\right)} \exp(-t^2 / 2) dt, \quad (14)$$

And using the substitution: $t = -\sqrt{2\pi}\gamma_{50} \left(\frac{u-D_{50}}{D_{50}}\right)$,

the equation 14 becomes:

$$P(y=1|D) = \frac{\gamma_{50}}{D_{50}} \int_{-\infty}^D \exp\left(-\pi \left(\gamma_{50} \frac{u-D_{50}}{D_{50}}\right)^2\right) du. \quad (15)$$

If we consider the more general case when a Probit model is fitted with $x_l = D$ and $p-1$ other covariates x_2, \dots, x_p , it may be noted that γ_{50} and D_{50} will generally not be independent of the other covariates. We may rewrite the standard model of the equation 8 as:

$$P(y=1|x_1, \dots, x_p) = \Phi(\beta_0 + \beta_1 D + \dots + \beta_p x_p) = \Phi\left(\sqrt{2\pi}\gamma_{50}(\vec{x}) + \frac{\sqrt{2\pi}\gamma_{50}(\vec{x})}{D_{50}(\vec{x})} D\right), \quad (16)$$

$$D_{50}(\vec{x}) = -\frac{\beta_0 + \vec{x}\vec{\beta}}{\beta_1}$$

$$\gamma_{50}(\vec{x}) = -\frac{\beta_0 \vec{x}\vec{\beta}}{\sqrt{2\pi}}$$

$\vec{x} = [x_2, \dots, x_p]$ and $\vec{\beta} = [\beta_2, \dots, \beta_p]^T$. From this formulation however, it is simple to calculate model-estimates of γ_{50} and D_{50} for fixed levels of x (personal communication with Tommy Nyberg).

4.3 VOLUME-RESPONSE MODELS

One way to account for the volume effect is to assume that the organs are divided in identical functional subunits (FSUs), which perform the basic function of the organ [59, 61]. A tissue and a specific endpoint is assumed to behave in a serial way, when the inactivation of any

FSU by radiation leads to tissue complications *e.g.* spinal cord and paralysis. Those tissues-endpoints have a small volume effect and the maximum dose is a sufficient parameter for the description of the data. On the other hand, a tissue is assumed to behave in a parallel way if it can lose a high proportion of functional subunits and still continues to function *e.g.* lung and pneumonitis. Those tissues-endpoints have a large volume effect and the mean dose suffice to describe the data. The most common cases of tissue architecture are the cross-linked, which have combined serial and parallel organization.

Effective dose

Brahme [62, 63] first introduced the concept of the effective dose D_e , which reduces the 3-D dose distribution to a single dose, which is related to the treatment outcome. D_e is given by the following expression for tumors:

$$D_e = \bar{D} \left[1 - \frac{\gamma}{2P(\bar{D})} \left(\frac{\sigma}{\bar{D}} \right)^2 \right], \quad (17)$$

where, \bar{D} is the mean dose delivered to the tumor, γ is the steepest normalized gradient of the dose response curve, $\frac{\sigma}{\bar{D}}$ is the coefficient of variance of the delivered dose distribution and is $P(\bar{D})$ the probability of local control at the dose level \bar{D} . For normal tissue the effective dose was derived by Mavroidis [64]:

$$D_e = \bar{D} \left[1 + \frac{\gamma}{2(1-P(\bar{D}))} \left(\frac{\sigma}{\bar{D}} \right)^2 \right]. \quad (18)$$

Equivalent Uniform Dose (EUD)

Niemierko [65] introduced the equivalent uniform dose (EUD), which assumes that any two dose distributions are equivalent if they eradicate the same fraction of clonogenic cells [66-68]. The equivalent uniform dose causes the survival of the same fraction of clonogenic cells as the true delivered dose distribution:

$$S(EUD) \equiv S(D(\vec{r})). \quad (19)$$

Biologically effective uniform dose $\bar{\bar{D}}$

In order to generalize the concept of EUD and D_e and extend it for different volumes of interest the concept of biologically effective uniform dose, $\bar{\bar{D}}$, was defined. $\bar{\bar{D}}$ is defined as the uniform dose that causes exactly the same total tumor control or normal tissue complication probability as a non-uniform dose distribution [66]. The general expression of the $\bar{\bar{D}}$ is not dependent on the NTCP model used and is defined by:

$$P(\bar{\bar{D}}) \equiv P(\bar{D}). \quad (20)$$

4.3.1 DVH-reduction models

Using any DVH reduction model, each DVH, which includes various discrete volumes for each dose can be reduced to a single dose bin. All suggested models, presented below could be used as a tool for the biological optimization of a treatment plan and try to provide a common dose-scaling base for treatment plan comparison.

The generalized uniform dose (gEUD)

The gEUD [65, 69] is a way of ‘summarizing’ the whole dose distribution in a volume of interest to a single value and is the most common expression for OAR. The gEUD is the dose that supposedly, if given uniformly to the entire organ, will cause the same complication rate as the true dose distribution and is given by the following equation:

$$gEUD = \left(\frac{1}{N} \sum_{i=1}^N D_i^{1/n} \right)^n, \quad (21)$$

where N is the number of voxels of the anatomical structure of interest and d_i is the dose to the i^{th} voxel. The concept of *gEUD* did not solve the previous problems since it shares the disadvantage of D_e that two different dose distributions could have the same gEUD value but different response probabilities [63].

The reference volume V_{eff}

The reference volume V_{eff} [70] is given by:

$$V_{eff} = \sum_{i=1}^N \left(\frac{D_i}{D_{ref}} \right)^{1/n} \cdot V_i, \quad (22)$$

where D_i is the dose of each dose bin, V_i the fraction of volume, which receives each dose bin and n is the parameter, which describes the volume effect. The volume parameter n as well as the s parameter of the relative seriality model are both endpoint and tissue specific parameters.

Effective dose D_{eff}

The effective dose derived by Mohan *et al.* [71] is given by the following expression:

$$D_{eff} = \left(\sum_i D_i^{1/n} \cdot V_i \right)^n, \quad (23)$$

where, V_i is the fractional volume of a dose bin and D_i is the dose to bin i and n is the volume parameter. This effective dose provides a way to reduce the dose-volume histogram to a single parameter and should not be confused with the effective dose derived Brahme *et al.* described above. One limitation of the gEUD, the reference volume and the reference dose reduction schemes is that dose distributions that differs a lot could still give the same NTCP

[56].

4.3.2 Relative-seriality model

In the Relative Seriality (RS) model [59], the volume effect is assumed to be a combination of both serial and parallel organization of functional subunits (FSU). For a heterogeneous dose distribution the response of normal tissues is given by:

$$P(\vec{D}, \vec{V}) = \left[1 - \prod_{i=1}^M (1 - P(D_i, V_{ref})^s)^{V_i/V_{ref}} \right]^{1/s}, \quad (24)$$

where V_i is the irradiated subvolume of an organ compared to the reference volume, V_{ref} and s is the RS parameter that characterizes the structural organization of the FSUs in the organ. M is the total number of voxels in the organ and $P(D_i, V_{ref})$ is the probability of response of the organ having reference volume V_{ref} and being uniformly irradiated to dose D_i .

4.3.3 The Lyman and LKB models

In the Lyman model [57, 72], the probability of observing a specified complication after irradiation to dose D of subvolume V , expressed as a proportion of the whole organ or other reference volume, is modeled using the probit function:

$$P(D, V) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-t^2/2} dt, \quad (25)$$

where

$$t(D, V) = \frac{D - D_{50} V^n}{m D_{50} / V^n}, \quad (26)$$

where n is the volume parameter and m is inversely related to the slope of the dose–response curve or the normalized dose response gradient γ_{50} .

$$m = \frac{1}{\gamma_{50} \sqrt{\pi}}. \quad (27)$$

The Lyman model is often combined with a DVH reduction technique and is then known as the LKB model [72, 73]. The LKB model is not based on cellular radiobiology but is easy to use to compute parameters from clinical data. The gEUD model or any dose reduction model can also be used in combination with the Lyman model [74].

4.3.4 Cut-off models

In the literature the complication risks are often estimated using a single DVH point based on a statistically significant dose or volume cutoff point [56].

Cutoff-dose model

The dose–volume effects are often presented as a proportion VD_c of an organ, which receives doses higher or equal than a cutoff dose, D_x [75], *e.g.* V_{20} corresponds to the volume of the organ that receives 20 Gy. VD_c is given by the following expression:

$$VD_c = \sum_{i \in (D_i \geq D_x)} v_i . \quad (28)$$

Cutoff-volume models

In this case, we consider the minimum dose D_{V_c} , to the hottest volume V_c of an organ of size V_c , *e.g.* D_{20} is the dose corresponding to 20 % of the organ.

Correlating threshold points based on single DVH points to complication probabilities is a very simple method and those parameters can be used as constraints or objectives in the treatment planning system. A limitation of this method is that they can easily be manipulated by the treatment planner or by the optimization software [56]. An additional limitation of cutoff models is that an infinite number of various dose distributions can have the same V_x value.

4.4 TIME-EFFECT MODELS

Previous reports suggested models that describe the effect of time to the late effects of radiotherapy. Taylor *et al.* [76] discussed the proportional hazards model, which is based on the Cox model [64]. The underlying assumption for the proportional hazards approach is that all subjects will eventually get the complication with sufficiently long follow-up. In this model the covariates determine the instantaneous event rate, or hazard, through the equation:

$$h(Z, t) = h_0(t) \exp(bZ), \quad (29)$$

where t is the time of occurrence of the event, Z are the different covariates, b are the parameters, $h_0(t)$ is the baseline hazard and $h(Z, t)$ is the hazard at time t for covariate Z . The parameters b are estimated by maximizing the partial likelihood (Cox 1972) [76]. The $h_0(t)$ is non-parametric and does not need to be specified to estimate b .

In a study by Jung *et al.* 2001 [77], the authors investigated the occurrence of radiotherapy-induced late complications. The data sets used in this study were retrieved from the literature. To describe the occurrence of the late effects, three types of kinetics were identified; Type 1 kinetics, which was purely exponential. The model used to fit those data is:

$$P_{ef} = 100\exp[-k(t - t_{lag})], \quad (30)$$

where P_{cf} is probability of complication free patients, k represents the slope of the curve, t is the time after treatment, and t_{lag} is the lag time to the occurrence of the first complications. The k and t_{lag} values are estimated from the fit.

Type 2 kinetics was exponential and the slope decreased exponentially with time. The data were fitted using the following equation:

$$P_{ef} = 100\exp\left[-\frac{k_i}{b}\{1 - \exp[-b(t - t_{lag})]\}\right], \quad (31)$$

where b is a coefficient that may be expressed by the half time and indicates how long it takes for the slope of the curve to reach half its value; k_i is the initial slope of the curve at time t_{lag} . Type 3 kinetics consisted of two components, a fast initial decline followed by an exponential decrease. The study shows that for each kind of kinetics, the incidence of late effects was exponential or approximately exponential kinetics, even many years after treatment. This implies that a random process might be involved in the occurrence of late radiation sequel.

4.5 DOSE-TIME EFFECT MODELS

4.5.1 Mixture models

Bentzen *et al.* in 1989 [78] suggested that mixture models [79] could be used to describe at the same time the latency and fractionation characteristics of radiation injury in late responding tissues. The basic concept in this model is to separate out long-term incidence and conditional latency. Immediately following radiation it is assumed that there are two groups of animals, those who will eventually develop the late effect if allowed to live long enough, and those who will never develop the late effect. The probability (P) of being in the first group can be modeled using a logistic function, *i.e.*

$$\log\left(\frac{P}{1-P}\right) = Zb, \quad (32)$$

where Z are the covariates and b are the parameters to be estimated, and Zb represents a linear combination of the covariates. Link functions other than the logistic could also be used. The second half of the model is concerned with conditional latency. It specifies the distribution of times of occurrence of the late effect given that the animal is in the first group. It might be considered to be Weibull:

$$F(t) = 1 - \exp(-\alpha t^\beta). \quad (33)$$

For some data sets it may represent an accurate description of the biological mechanism generating the data. It enables one to think separately about long-term incidence and the conditional latency distribution. If there is no clear indication from the data that the observation

period adequately covers the time frame during which complications occur, then the model parameters may not be identifiable. The mixture model requires specification of a latent-time distribution.

4.5.2 Generalized Lyman model

The generalized Lyman model is a mixture of the NTCP or the incidence component and the latency component $f(\tau)$ [80]. In this model, the NTCP represent the probability that the complication would eventually occur if the patient survived and were followed for a sufficient amount of time. Using maximum likelihood method, a patient experiencing toxicity at time τ contributes to the likelihood:

$$NTCP(Def, Y_1 \dots Y_k) \cdot f(\tau), \quad (34)$$

where the variables Y_1 through Y_k represent nondosimetric risk factors. The contribution to the likelihood for a patient without experiencing toxicity at time τ is:

$$1 - NTCP(Def, Y_1 \dots Y_k) \cdot F(\tau), \quad (35)$$

where $F(\tau)$ is the cumulative distribution function corresponding to $f(\tau)$. To model the distribution of times to toxicity $f(\tau)$, the log-normal distribution could be used:

$$f(\tau) = \frac{1}{\sigma\tau\sqrt{2\pi}} e^{-(\ln\tau - \mu)^2 / 2\sigma^2}, \quad (36)$$

where μ and σ are the latency parameters. Log-logistic distribution or an empirical distribution based on the observed event-time data can be also used.

4.5.3 Probit-time model

In Paper IV the Probit-time model was suggested to describe the effect of follow up time to the dose-response relations. The model assumes that the incidence rate is constant over time and it is parameterized according to D_{50} and γ_{50} parameters:

$$P(D, t) = 1 - (1 - P_t(D))^{t/T}, \quad (37)$$

The relation between the D_{50} and the normalized dose response gradient, γ_{50} is:

$$\gamma_{50}(t) = \frac{t}{T} \frac{D_{50}(t)}{D_{50}} \gamma_{50} 2^{T/t-1}. \quad (38)$$

In this model Probit or any dose-response model can be used. The Probit-time and the dose-response models are nested.

4.5.4 Software

Two different kind of ‘in house’ software were used in this thesis for the estimation of the dose-volume response parameters. In Paper I, the best estimates were calculated using MINOS [81]. In Paper II and III the C++ software *bml* was used, which is based on the optimization software NPSOL [82]. Both optimization packages are written in standard Fortran 77. NPSOL is a package designed to solve nonlinear programming problem. Both MINOS and NPSOL are free for noncommercial use.

5 STATISTICAL METHODS

5.1.1 Maximum-likelihood method

The maximum likelihood estimation is a common way to fit NTCP model parameters [83]. The advantage of this method is that can be applied to data with any kind of distribution and handle individual data points, thus no information is lost due to averaging processes like data binning [84]. In a data set including N DVHs for each patient the corresponding NTCP values P_i are calculated for any NTCP model. Each DVH has an observed binary endpoint ep , which takes values 0 or 1. In the maximum likelihood estimation the optimal set of the model parameters is the one that maximizes the likelihood value (L). The likelihood function is given by:

$$L = \prod_{i=1}^N L_i = \prod_{i=1}^N P_i^{ep_i} (1 - P_i)^{1-ep_i}. \quad (39)$$

In practice the log likelihood (LL) value is more often used:

$$LL = \ln(L) = \ln(\prod_{i=1}^N L_i) = \sum_{i=1}^N \ln(L_i) = \sum_{i=1}^N [ep_i \ln(P_i) + (1 - ep_i) \ln(1 - P_i)]. \quad (40)$$

In the optimal set of the model parameters, in this case is the one maximizing the LL value.

5.1.2 Turnbull estimator

For the case of double censored data, Turnbull [85] suggested a modified Product-Limit or Kaplan-Maier estimator [64].

5.1.3 Goodness of fit

LL value

In order to evaluate the goodness of fit of a model the LL value is often used. The LL assesses the agreement between the measured and predicted by the model results [84].

Akaike information criterion (AIC)

In this method, the LL value is adjusted for the number of parameters of each model [75] in order to balance model fit and model complexity, by penalizing models with more parameters. The compared models should be nested. The AIC is defined as:

$$AIC = 2k - 2(LL), \quad (41)$$

where k is the number of model parameters. Comparing different models, the model that get the lower AIC value is considered to provide a better fit to the data.

Receiver Operating Characteristic (ROC) analyses

The ROC curve is a very popular visualization of the discriminative ability of a model by going through all available model-predicted probabilities [86, 87]. The ROC curve is a plot of sensitivity as a function of (1-specificity). Sensitivity is defined as the true-positive (TP) classifications among the total number of responders (N_{resp}): TP / N_{resp} . Specificity is the true-negative (TN) classifications among the total number of non-responders ($N_{\text{non resp}}$):

$$TP / N_{\text{non resp}} . \quad (42)$$

The area under the ROC curve (AUC) is the value that describes the probability that a model will correctly separate the responders from non-responders in the data set. In other words is the probability that a randomly selected responder will have higher model predicted probability than a randomly selected non-responder. Thus AUC, evaluate the model average discriminative ability. A value of 0.5 indicates the discrimination is no better discrimination than a random chance, while a value of 1 is perfect classification.

The ROC depends only on the rank order of the classifier or the model-predicted probabilities. All simple models will result of the same ROC curve, if they are monotonic function of the including variable.

6 RESULTS

6.1 CLINICAL CHARACTERISTICS

6.1.1 Esophageal stricture

The incidence of radiation induced esophageal strictures for patients treated with radiation therapy in Stockholm between 1992-2005 was 3.3 % [13, 17]. As described in Paper I, 72 patients who received radiation therapy for head and neck cancer during 1992-2005, were evaluated. Of them 33 developed the symptom of esophageal stricture. The total group of patients was analyzed in two subgroups according to the treatment period. 34 patients were treated during the first treatment period (1992-2000) and 19 of them developed esophageal stricture. During 2001-2005, 28 patients were treated and 8 of them developed the symptom. The patients were well balanced for sex and age but not for the treatment diagnoses.

6.1.2 Gynecological project

The demographic and clinical characteristics of 519 gynecological-cancer survivors are described in Paper II. Of them 63 reported emptying of all stools into clothing without forewarning occurring at least once the past six months. Survivors, who received treatment combinations including surgery, had lower risk of the development for the symptom both in the total group of 519 survivors and the subgroup of 77 survivors. Delivery of at least two children with birth weight exceeding four kg (RR=2.2, 95% CI 1.2-4.1), heart failure (RR=3.4, 95% CI 2.0-6.0), and lactose intolerance and/or gluten intolerance (RR=2.6, 95% CI 1.4-4.7) were significantly associated with a risk of having the symptom.

In all 77 out of the total 519 gynecological-cancer survivors did not have any brachytherapy and are described in Paper III. Of them 13 reported 'emptying of all stools into clothing without forewarning'. Uterine and cervical cancers were the dominant diagnoses. The tumor diagnoses of the patients were found to be associated with the symptom. It was observed that survivors not having surgery ($p=0.0038$) are more likely to develop the symptom. The survivors who had surgery received a lower average total dose (42.3 Gy, SD: 7.1 Gy) than survivors who had no surgery (66.2 Gy, SD: 2.5 Gy).

In Paper IV, the clinical characteristics of 78 cancer survivors that did not receive brachytherapy were described. Of them 24 reported 'absence of vaginal elasticity'. Mean absorbed dose to the target and survivor's age was significantly associated with the symptom's occurrence. However, no significant interaction ($p=0.5$) between the mean absorbed dose and different age groups were found. Heart failure (0.03) and estrogens (0.04) were also significantly associated with the symptom. In this group, the survivors who had surgery had also significantly lower prevalence of the symptom.

6.2 DOSE-EFFECT RELATIONS

As described in Paper I, the mean doses to the esophagus for the cases and the controls were 49.8 Gy and 33.4 Gy, respectively for treatment administered in 1992–2005. Corresponding

figures for the period 1992–2000 were 49.9 Gy and 45.9 Gy and for the period 2001–2005 were 49.8 Gy and 21.4 Gy respectively. The mean cumulative DVHs of the proximal esophagus for patients with the symptom and patients without the symptom are also described in the Paper I for all treatment periods. The DVHs for the total treatment period (1991–2000) and for (2001–2005) were well separated for cases and controls. However, for the patients treated during 1991–2000, the DVHs do not separate for cases and controls. Odds ratio was found to be (OR) = 19.0 with 95 % confidence interval (CI) of 4.2–85.6 with the cut off chosen at 50 Gy. The patients receiving doses higher than 50 Gy were 19 times more likely to develop esophageal stricture than patients who received a dose less than 50 Gy.

In the total group of the 519 cancer survivors, studied in Paper II, the averaged total EBRT dose for survivors with ‘emptying of all stools into clothing without forewarning’ was higher among survivors with the symptom than without the symptom. In all 52 % of survivors with the symptom had a total dose > 45 Gy compared to 35 % of survivors without the symptom. brachytherapy was less common among survivors with the symptom. The prevalence of the symptom was higher among survivors with mean doses > 50 Gy for all the OARs, compared to lower mean doses. In this group, the unadjusted RRs and ORs for mean doses > 50 Gy and the studied OAR were significantly increased. However, when the RRs and ORs were adjusted for risk factors, the OR for mean dose > 50 Gy to the rectum was no longer significant.

Further analyses included only survivors treated with Iridium brachytherapy dose 0–11.25 Gy. All OARs with the exception of the rectum showed significantly increased OR for mean doses > 50 Gy. Although adjusting for risk factors the significantly increased ORs remained for all OARs except for the rectum. The DVHs for the anal-sphincter region were significantly separated ($p < 0.05$) for doses in the interval of 34.5–66.5 Gy, for the rectum in 39.0–41.5 Gy and 45.0–68.0 Gy respectively, for the sigmoid in 38.0–70.0 Gy and for the small intestines in the interval of 45.5–50.5 Gy and 53.0–69.5 Gy respectively.

A multivariable analysis were performed for the 77 survivors included in Paper III using the Probit model and forward selection including mean and maximum doses, demographic, obstetrics, co-morbidities and treatment received. The maximum dose to the anal sphincter was found to be significant.

The mean absorbed dose, as calculated from the treatment planning system, to the different tumor sites were: 37.1 Gy (SD: 11.9 Gy) for endometrial cancer, 49.2 Gy (SD: 3.6 Gy) for sarcomas, 39.3 Gy (SD: 2.4 Gy) for ovarian cancer, 39.9 Gy (SD: 4.9 Gy) for vulvar cancer and 57.4 Gy (SD: 12.8 Gy) for cervical cancer. The mean doses among survivors with and without the symptom was significantly different for anal sphincter ($p = 0.011$), rectum ($p = 0.0094$), and sigmoid ($p = 0.0069$) but not for small intestines ($p = 0.17$). The DVHs (Figure 10) for the four OARs and survivors with and without the symptom were significantly separated ($p < 0.05$) for doses 15–37 Gy and 41–67 Gy for anal-sphincter region, 44–69 Gy for rectum, 43–70 Gy for the sigmoid and 47–70 Gy for small intestines.

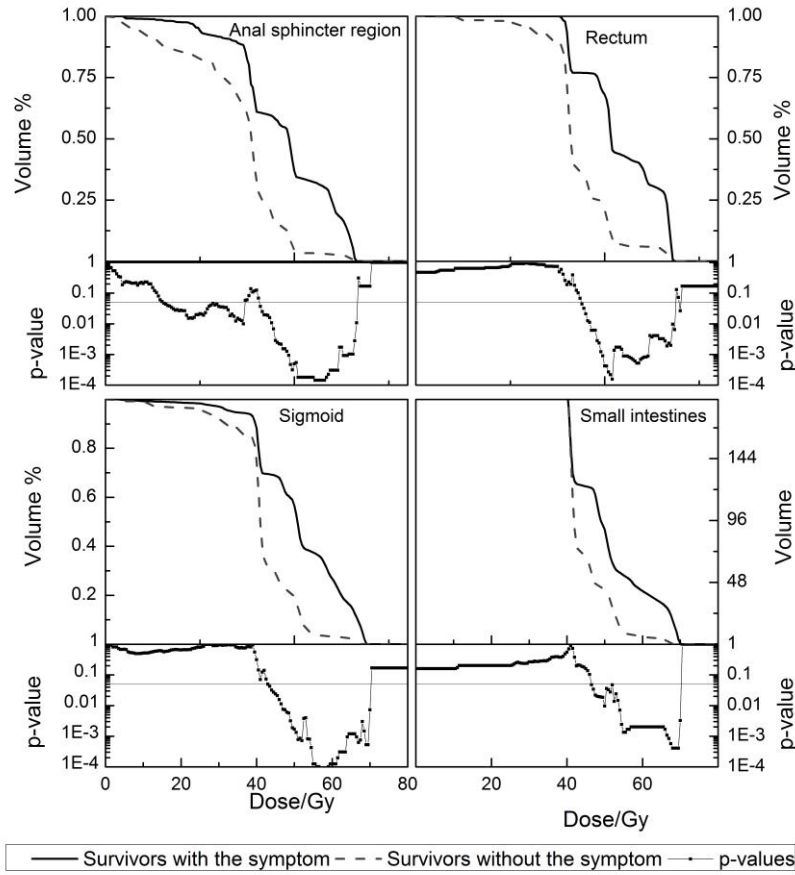


Figure 10: Dose-volume histograms and p -values for 13 survivor with the symptom ‘emptying of all stools into clothing without forewarning’ and 64 survivors without the symptom (data from Paper III).

For the group of 78 survivors studied in Paper IV, the mean absorbed doses to the vagina for the different tumor sites were 18 Gy (SD: 7 Gy) for endometrial cancer, 14 Gy (SD: 11 Gy) for cervical cancer, 18 Gy (SD: 4 Gy) for ovarian, 19 Gy (SD: 6 Gy) for vulvar, 17 Gy (SD: 15 Gy) for vaginal and 22 Gy (SD: 6 Gy) for sarcoma uteri.

6.3 NTCP MODELING

In this thesis, dose, volume and time response relations have been investigated using Probit, RS, Lyman, gEUD and Probit-time models for three different clinical endpoints. In Paper I, the relative seriality model was used to investigate the dose-volume response relations of the proximal esophagus and the symptom esophageal stricture. The sigmoid function used with the RS model was the Poisson model. Steep dose-volume response relations were assessed for the treatment period 2001-2005 ($\gamma=1.4$). The value of D_{50} was found 61.5 Gy, and the relative seriality value s was 0.1 (Table 3).

The observed prevalence of esophageal stricture was 1.2 % for biologically effective dose, \bar{D} , 24-35 Gy, 20.0% for \bar{D} 35–50 Gy and 28.6% for \bar{D} 50–65 Gy, respectively. The expected

prevalence for those dose intervals that the RS predicts are 1.6 %, 13.2 % and 40.8 %, respectively. To assess the goodness of fit, the probability of χ^2 for having a perfect agreement between the expected and the observed complication results was computed and was 0.8. This value indicates that the relative seriality model and the estimated parameters very well reproduce the pattern of the clinically recorded complications. The expected value of the log-likelihood function resulted to be -22.3 with a variance of 38.0, while the observed value of the log-likelihood function from the fit was -21.5. Assuming a Gaussian distribution of the LL, these results indicate that the probability of finding a worse fit (smaller value of LL) is 60.5 %.

The estimates of the dose-volume response parameters in Paper III were calculated using the RS, Lyman and the gEUD model for anal-sphincter region, rectum, sigmoid and small intestines (Table 3). In Figure 11 the corresponding dose-response curves are illustrated for the four OARs, using both the RS and the Lyman model, and the figure shows that the dose response curves of the two models are very similar. The figure also shows that the sigmoid has the steepest curve ($\gamma_{50}=1.60$) and thus the highest dose-response relationship. The values of the volume parameters s and a for anal-sphincter region, rectum, sigmoid and small intestines ($s=7.3, 10, 15.8, a=2.3, 83.2, 119$) were very high, which indicated that there is almost no volume effect for the studied OAR and the symptom ‘emptying of all stools into clothing without forewarning’. Therefore the maximum dose is an important parameter for the description of these data.

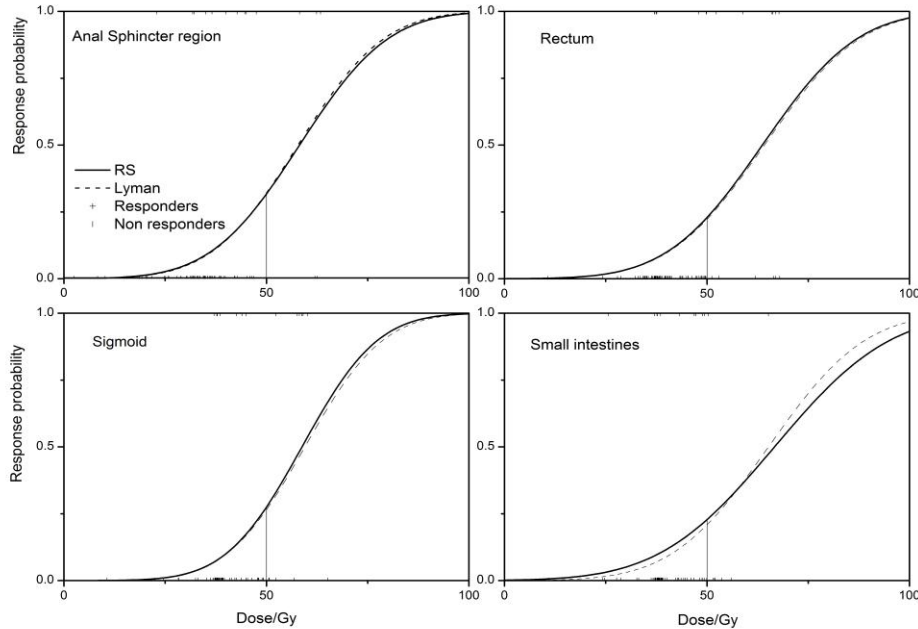


Figure 11: The figures illustrate the RS (red line) and Lyman (red line) models plotted against the mean dose for the anal sphincter, rectum, sigmoid and small intestines. The vertical line indicates the level of D_{50} value for the two models. The mean doses for the responders (vertical lines) and non-responders (crosses) are also plotted (data from Paper III).

To evaluate the goodness of fit the values of AUC were computed for the studied OAR. The AUC was highest (0.74), for anal sphincter and the sigmoid, rectum had AUC=0.73 and small intestines had the lowest AUC=0.62. To assess the fit of the RS and Lyman fitted for each OAR, the LL values were calculated. For anal sphincter region the LL values for RS and Lyman were -29.1 and -29.0, respectively; for rectum -29.5 and -29.4, respectively; for sigmoid -29.0 and -28.9, respectively and for small intestines -28.4 and -28.1, respectively.

In Paper IV the dose-volume and time response relation were calculated for the vagina and the endpoint ‘absence of vaginal elasticity’. The Probit model was used to calculate the dose-response relations, the RS-Probit for the dose-volume response relations and the Probit-time for the dose-time response relations. The maximum likelihood estimates for the dose-response model parameters for the mean dose and the symptom are presented in Table 3.

The evaluation of the goodness of fit in the studied models was done by the estimation of the AIC value. The value of AIC was the lowest (80.9) for the Probit-time model, which indicates that this model fits our data best.

To investigate the prediction of our model that D_{50} should decrease with time while γ_{50} should increase, we divided the total group of 78 survivors into two groups with shorter and longer follow up time than the median. The parameter values for the two subgroups were: $D_{50}=53.0$ Gy, $\gamma_{50}=1.54$ and $D_{50}=45.0$ Gy, $\gamma_{50}=1.66$ respectively and the dose-response curves for the Probit model and the total group, the group with the short follow up and the group with the long follow up are presented in Figure 12.

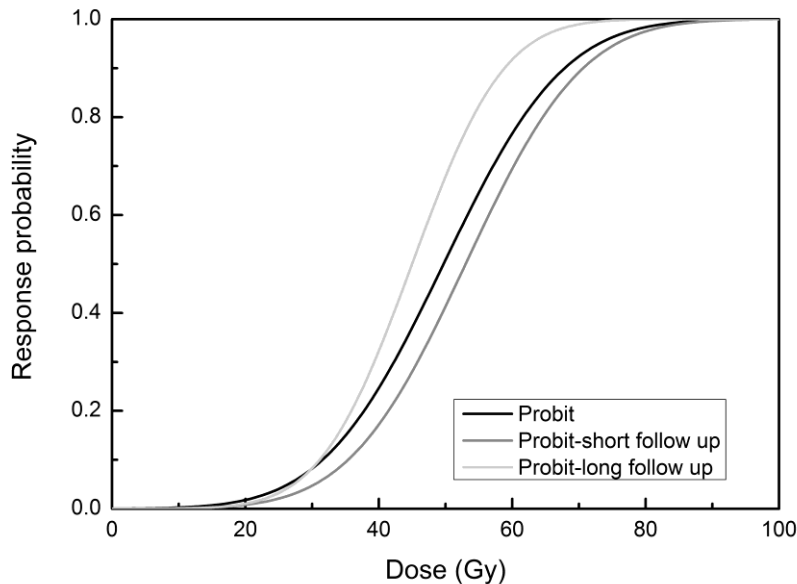


Figure 12: The figure illustrates the dose-response curves for the mean dose to the vagina and the symptom absence of vaginal elasticity, for the Probit for the total material (light grey), the Probit for the group with short (dark grey)) and long (black) time (data from Paper IV).

To study the time-effect of the symptom ‘absence of vaginal elasticity’ two subgroups with doses above and below the median dose were analyzed using the Turnbull estimator. The Turnbull plots are presented in Figure 13 and indicate that the probability of having the symptom gets higher over time for the group of higher dose than the group of lower dose.

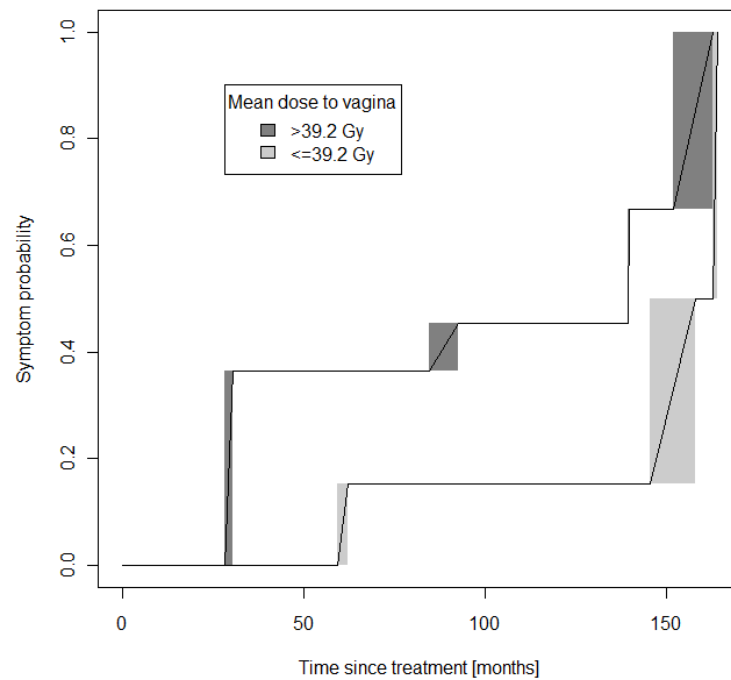


Figure 13: Turnbull graphs for a group of survivors with mean dose higher than the median dose and one group with mean dose less than the median (data from Paper IV).

Table 3: Doses in Gy, volume and time response parameters and the 68 % confidence intervals.

	RS			LKB			Probit		Probit-time	
	D_{50} (CI)	γ_{50} (CI)	s (CI)	D_{50} (CI)	m (CI)	n (CI)	D_{50} (CI)	γ_{50} (CI)	D_{50} (CI)	γ_{50} (CI)
Endpoint: Esophageal stricture										
Esophagus	61.5 (52.9–84.9)	1.4 (0.80–2.6)	0.1 (0.01–0.3)	-	-	-	-	-	-	-
Endpoint: Emptying of all stools into clothing without forewarning										
Anal-sphincter region	58.2 (54.3-62.9)	1.35 (1.11-1.63)	7.3 (1.4-19.2)	57.8 (54.0-62.2)	0.41 (0.35-0.49)	0.45 (0.09-0.17)	56.1 (51.5-61.7)	1.13 (0.94-1.34)	-	-
Rectum	63.7 (59.6-75.7)	1.38 (1.15-1.52)	10 (0.5-14)	64.2 (60.1-69.1)	0.41 (0.35-0.49)	0.012 (0.0098-0.53)	63.6 (59.4-68.7)	1.34 (1.12-1.58)	63.6 (59.4-68.7)	1.34 (1.12-1.58)
Sigmoid	58.8 (55.5-62.5)	1.60 (1.32-1.89)	1.32 (2e-08 -10.3)	59.5 (56.1-63.3)	0.36 (0.30-0.43)	0.13 (0.016-0.65)	57.2 (54.0-60.8)	1.58 (1.31-1.86)	-	-
Small intestines	66.7 (63.3-74.0)	1.19 (1.10-1.08)	15.8 (7.9-33.5)	65.2 (60.5-69.9)	0.41 (0.35-0.50)	0.0084 (0.027-0.0076)	66.9 (60.6-75.1)	1.04 (0.86-1.23)	-	-
Endpoint: absence of vaginal elasticity										
Vagina	40.5 (48.2-53.4)	1.37 (1.08-1.567)	4e-8 (0-0.7)	45.1 (42.4-48.1)	0.51 (0.36-0.71)	2.2 (0.64-7e9)	49.7 (47.2-52.4)	1.40 (1.12-1.70)	46.9 (43.5-50.9)	1.81 (1.17-2.51)

7 DISCUSSION

7.1 ESOPHAGEAL STRICTURE

For head and neck cancer patients (Paper I), dose-response relations were found for the radiation induced esophageal strictures for the treatment period 2001–2005. In contrast no dose-response relation was found for patients treated during the total treatment period or during 1992–2000. Taking into account that the treatment technique in Radiumhemmet changed around 2000, our data imply that treatment techniques could influence the development of the symptom.

Dose-response relations and volume dependence were found for the radiation induced esophageal strictures for the treatment period 2001–2005. Laurell *et al.*, [17] also found dose-response relation for the development of strictures of the proximal esophagus for patients treated with radiation therapy only. However, Kim *et al.* [88] did not find any correlation between dose and esophageal stricture, probably because the majority of the patients included in the study were treated with two-dimensional planning. In the current study and for the group of patients treated during 2001–2005 a significant risk was observed for development of strictures even at small doses of 20–40 Gy.

The esophagus was found to behave in a parallel way for the endpoint esophageal stricture and dose to the proximal esophagus. That indicates that the mean dose to the proximal esophagus can sufficiently describe our data. Mavroidis *et al.* [20] also reported that the upper esophagus has a parallel behavior ($s = 0.22$). However, Emami *et al.* and Ågren *et al.* [59, 89, 90] reported that the total volume of esophagus behaves in a serial way ($s = 3.4$). There are several reasons for the difference in the volume parameter. Firstly, that the measured dose delivered to the esophagus in current studies is more correctly estimated using 3D treatment planning systems, etc. Secondly, almost all of the previous studies investigated other parts of the esophagus whereas this study focused on the proximal esophagus. Finally the whole esophagus is used as a reference organ in the studies presented by Emami *et al.* and Ågren *et al.* [59, 89, 90]. Our data support the view that the radiosensitivity and possibly the volume dependence of the esophagus vary along its length. In a study by Mavroidis *et al.* [20], it was also suggested that to achieve higher accuracy, different radiosensitivity parameters could be used in different parts of the esophagus.

Additional to the EBRT, dose risk factors could be associated with the development of esophageal strictures of the proximal esophagus. In our previous study [91], it was found that the use of a nasogastric tube (NG-tube) or percutaneous endoscopic gastrostomy (PEG) during or immediately after EBRT, surgery combined with EBRT were significantly associated with the appearance of strictures of the proximal esophagus. Caglar *et al.* [92] has reported that a history of smoking was also correlated with the presence of stricture after therapy; however, we did not study this factor.

7.2 LATE EFFECTS OF GYNECOLOGICAL RADIOTHERAPY

In Papers II and III it was found that the dose to the anal-sphincter region, rectum, sigmoid and the small intestines is related to the symptom ‘emptying of all stools into clothing without forewarning’. In Paper II, mean doses > 50 Gy to the studied OAR were related with the occurrence of the symptom. For the study populations included in both papers, the dose distributions between survivors with the symptom and survivors without the symptom were significantly separated for intermediate and high doses. Fonteyne *et al* [93], reported that the volume of small bowel receiving doses 50-60 Gy is associated with the development of late side effects, which is in line with our results. Al-Abany *et al.* [94] also reported that for prostate cancer increasing the dose from 45–55 Gy to a large portion of the anal-sphincter increases the risk of fecal leakage. In a study by Heemsbergen *et al.* [95], the authors performed an anorectal dose-surface map analysis and found a dose-effect relation for fecal incontinence in the anal region and lower rectum.

In Papers II and III, we support that the sigmoid as well as the anal sphincter region, the rectum and the small intestines should be considered as OAR in terms of avoiding the development of ‘emptying of all stools into clothing without forewarning’. A study by Fonteyne *et al.* [93] also depicts the sigmoid colon except from anal sphincter and rectum as an OAR for the development of lower intestinal toxicity.

In our studies, we found that all studied OAR are related to the symptom ‘emptying of all stools into clothing without forewarning’. We consider this specific symptom is neither to be a fecal incontinence nor a pure urgency symptom but is mainly related to urgency. Specifically, we believe that survivors who experience this symptom have a change in their sensitivity and are not able to sense the need to go to the toilet and defecate. The symptom also includes an irritative component that is responsible for the sudden emptying of a large volume of stools. Thus we believe that this symptom is related to all bowel organs and anal-sphincter region. In a study by Andreyev *et al.*, the authors argue that symptoms that originate from the pelvic area have multiple causes and thus their anatomic origin could be questioned [96]. Some researchers hypothesize that symptoms may originate from specific anatomic regions. Smeenk *et al.* [97] reported that urgency and incontinence originate from both the anal and rectal wall, while frequency seemed mostly associated with rectal wall dysfunction. Heemsbergen *et al.* [95] also support the importance of discriminating between different symptoms and their origin in order to increase specificity.

In our study presented in Paper II, we found no statistically significant increase in risk for developing the symptom during follow up (28-170 months). Fitting the data from the sigmoid for the 77 survivors, included in Paper II, in the Probit-time model (Table 3), we observed that the fit of the model was best with the standard Probit model. That implies that the time to follow-up does not influence the normal tissue complication probabilities for ‘emptying of all stools into clothing without forewarning’ and the sigmoid. However, there are reports of rectal symptoms in prostate cancer survivors that show both increase and decrease of those symptoms with time [98].

To our knowledge there is no other study investigating the dose-volume response relations of the anal-sphincter region, the rectum, the sigmoid and the small intestines and the symptom ‘emptying of all stools into clothing without forewarning’. Steep dose-response relationships were found for anal-sphincter region, rectum, sigmoid and small intestines and ‘emptying of all stools into clothing without forewarning’. The mean doses to the OARs were however highly correlated with each other, and it is difficult to say if only one or if multiple organs are involved in the development of the symptom. The Relative Seriality, Lyman and gEUD models were found to have the same predictive power for relating this endpoint and the dose to the anal-sphincter region, rectum, sigmoid and small intestines.

In Paper III, the anal-sphincter region, rectum, sigmoid and the small intestines was found to behave in a serial way for the symptom ‘emptying of all stools into clothing without forewarning’. The maximum dose was found to be an important parameter for the description of the dose-response relations of the anal-sphincter region, rectum, sigmoid and the small intestines and ‘emptying of all stools into clothing without forewarning’. For prostate cancer survivors and the symptom fecal incontinence, Mavroidis *et al.* [99] reported an $s = 0.37$ for anal sphincter, while Peeters *et al.* [100] reported an $n = 7.5$ value for the anal wall. Those parameters’ values indicate that the anal sphincter and the anal wall behave in a parallel way for the symptom fecal incontinence.

For the 519 survivors included in Paper II, additional risk factors associated with the symptom ‘emptying of all stools into clothing without forewarning’ were deliveries with high birth weight, heart failure and lactose and/or gluten intolerance. For the subgroup of survivors that received no brachytherapy, heart failure was the only risk factor that was found to be significantly associated with the development of the symptom. The survivors that experience heart failure were excluded from the analyses in Paper III. For the symptom ‘emptying of all stools into clothing without forewarning’, Alsadius *et al.* [101] reported that current smokers among prostate cancer survivors had an increased risk (prevalence ratio of 4.7) of developing the symptom of sudden emptying of all stools into clothing without forewarning.

NTCP models offer a powerful tool for accounting for the probability that a late radiotherapy side effect will occur. As discussed in a chapter 4, the commonly used NTCP models can investigate the dose-response relationships and the dose-volume response relationships. They are flexible tools that can be modified to include other clinically important factors, in order to achieve modeling as close as possible the multiparametric and complicated reality of the response of a normal tissue to radiation. Therefore in Paper IV, we proposed a novel model that describes the effect of time that a symptom occurs to the dose-response relation. In this paper we fitted the data of the mean dose to the vagina and the symptom ‘absence of vaginal elasticity’ with the standard Probit, the new Probit-time and the Probit-RS models. The Probit-time model was found to fit our data best.

Steep dose-response relations were found for the mean dose to the vagina and the symptom ‘absence of vaginal elasticity’. That indicates that there is a strong dose-response relation of the mean dose to the vagina and the symptom. The low relative seriality parameter s , indicates that there is a volume effect of the vagina and the symptom. In addition, the mean dose

to the vagina can describe these data sufficiently. A multivariable analysis also indicated that the mean dose to the vagina is significantly correlated with the ‘absence of vaginal elasticity’. Our results from the Probit-time model shows that the steepness of the dose-response relation for the mean dose to the vagina and ‘absence of vaginal elasticity’ increases with time.

In previous studies from Jung *et al.* [77, 102], the effect of time in the occurrence of a symptom was investigated and modeled. For some late effects they found purely exponentially distributed responses that are in agreement with the model assumption in this study [95].

Many authors choose non-parametric methods to describe time to toxicity data. The most popular method is the Kaplan-Maier or product limit estimator, which estimates the survival function for time to event data. This estimator is a good choice, when the data are uncensored and right censored, which means that the future time that toxicity may occur after a specific point (follow up) is unknown. Our data, presented in Paper IV are double censored and therefore the Kaplan-Maier estimator is not applicable. A non-parametric way to describe double-censored data is a modified Kaplan-Maier estimator, the Turnbull estimator. To describe the time effect of ‘absence of vaginal elasticity’, Turnbull estimator has been applied for doses to the vagina above and below the median dose. Our results from the Turnbull plots (Figure 13) imply that the group of higher dose has higher probability to experience the symptom over time than the group of lower dose.

A limitation of the present model is the assumption that the incidence rate is constant over time, which may not be valid for every data set. In a study by Jung *et al.* [77] the authors reported constant incidence rates as well as incidence rates increasing over time or had two components, one of which remained constant over time and one component that increased with time. Our modeling methods described in Paper IV could be modified to handle other incidence distributions as well. Another limitation, in this specific study is that we do not know the exact time when the symptom occurs or whether it appears after follow up thus our data are double censored.

8 CONCLUSIONS

In the research presented in the current thesis we investigated the dose-volume response relations of the dose to the esophagus and the occurrence of esophageal strictures and also the dose to the anal-sphincter region, rectum, sigmoid and small intestines for the symptom ‘emptying of all stools into clothing without forewarning’. Moreover, we investigated the dose, volume and time response relations for the mean dose to the vagina and the symptom ‘absence of vaginal elasticity’. The most important findings were the following:

- Dose-response relations and volume dependence were found for the radiation induced esophageal strictures.
- The esophagus was found to behave in a parallel way for the endpoint esophageal stricture.
- The mean dose was found to be a sufficient parameter for the description of the dose-response relations of esophageal strictures.
- The applied treatment techniques could also influence the development of the symptom.
- Mean doses > 50 Gy to the anal-sphincter region, the rectum, the sigmoid and the small intestines were related to the occurrence of the symptom.
- Risk factors associated with the symptom ‘emptying of all stools into clothing without forewarning’ were deliveries with high birth weight, heart failure and lactose and/or gluten intolerance.
- Steep dose-response relationships were found for anal-sphincter region, rectum, sigmoid and small intestines and ‘emptying of all stools into clothing without forewarning’.
- The anal-sphincter region, rectum, sigmoid and the small intestines were found to behave in a serial way for the symptom ‘emptying of all stools into clothing without forewarning’.
- The maximum dose was found to be an important parameter for the description of the dose-response relations of the anal-sphincter region, rectum, sigmoid, small intestines and ‘emptying of all stools into clothing without forewarning’.
- The Relative Seriality, Lyman and gEUD found to have the same predictive power for the symptom ‘emptying of all stools into clothing without forewarning’ and the dose to anal-sphincter region, rectum, sigmoid and small intestines.
- Steep dose-response relations were found for the mean dose to the vagina and the symptom ‘absence of vaginal elasticity’.
- The vagina was found to behave in a parallel way for the symptom ‘absence of vaginal elasticity’.
- The mean dose to the vagina was indicated to be a parameter that describes our data sufficiently.
- A novel prediction model, which describes the influence of the time on the dose response relations, was proposed.

- The proposed Probit-time model was found to fit our data better than the pure Probit model and the relative seriality model.
- The steepness of the dose-response relation for the mean dose to the vagina and ‘absence of vaginal elasticity’ increases with time.

9 IMPLICATIONS

We believe that the outcome of this work could have important implications in the clinical practice. The mean dose to the proximal esophagus should be kept low to avoid esophageal strictures. The applied treatment technique should also be carefully chosen in order to protect the proximal esophagus.

Professionals involved in the treatment planning process may consider delineating the anal sphincter region, the rectum, the sigmoid and the small intestines to avoid ‘emptying of all stools into clothing without forewarning’. In order to minimize the risk to develop this distressing symptom, physicians and physicists may keep the mean dose below 50 Gy to the bowel organs and the anal sphincter region. Additional, non-dosimetric risk factors like delivery of at least two children with birth weight exceeding four kg, heart failure and lactose intolerance and/or gluten intolerance may also be considered.

The radiobiological parameters computed in this thesis for the esophagus and esophageal strictures; for anal sphincter region, the rectum, the sigmoid and the small intestines and ‘emptying of all stools into clothing without forewarning’; for vagina and ‘absence of vaginal elasticity’ may be used for the treatment plan optimization in terms of avoiding those distressing radiotherapy late effects in the future.

A step towards achieving a patient specific treatment plan could be accomplished by modeling the influence of time of the symptom occurrence to the dose-response relation. Patients could thus be treated according to their life expectancy and possible comorbidities. Knowing the probability of the occurrence of a symptom in any specific time point, clinicians could inform the patients better and if possible apply preventive treatments. The Probit-time model we propose in Paper IV, predicts the lifelong risk of the symptom ‘absence of vaginal elasticity’ and the mean dose to the vagina sufficiently well. However, it is important to validate the model with different data sets.

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