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Time-dependent dose–response relation for absence of vaginal elasticity after gynecological radiation therapy

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ABSTRACT

Background and purpose: To investigate the dose–response relation between the dose to the vagina and the patient-reported symptom '*absence of vaginal elasticity*' and how time to follow-up influences this relation.

Material and methods: The study included 78 long-term gynecological cancer survivors treated between 1991 and 2003 with external beam radiation therapy. Of those, 24 experienced absence of vaginal elasticity. A normal tissue complication model is introduced that takes into account the influence of time to follow-up on the dose–response relation and the patient's age. The best estimates of the dose–response parameters were calculated using Probit, Probit-Relative Seriality (RS) and Probit-time models. Log likelihood (LL) values and the Akaike Information Criterion (AIC) were used to evaluate the model fit.

Results: The dose–response parameters for 'absence of vaginal elasticity' according to the Probit and Probit-time models with the 68% Confidence Intervals (CI) were: LL = −39.8, D_{50} = 49.7 (47.2–52.4) Gy, γ_{50} = 1.40 (1.12–1.70) and LL = −37.4, D_{50} = 46.9 (43.5–50.9) Gy, γ_{50} = 1.81 (1.17–2.51) respectively.

Conclusions: The proposed model, which describes the influence of time to follow-up on the dose–response relation, fits our data best. Our data indicate that the steepness of the dose–response curve of the dose to the vagina and the symptom 'absence of vaginal elasticity' increases with time to follow-up, while D_{50} decreases.

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Sexual dysfunction after gynecological radiation therapy has an important impact on the quality of life of gynecological cancer survivors [1,2]. Most of the population-based studies focusing on the sexuality of survivors only include cervical cancer patients. In a population-based cohort study of long-term cervical cancer survivors, it was found that vaginal shortness and inelasticity due to radiation therapy-induced changes of vaginal anatomy and function causes distress to the survivors [1]. This effect of radiation therapy on sexual function of cervical cancer survivors has been confirmed in several studies [3–5]. Previously, we reported the results from a large population-based cohort study including 616 gynecological cancer survivors that received radiation therapy and 344 non-irradiated controls [6,7]. A study-specific validated questionnaire was mailed to all included women [6]. The symptom 'absence of vaginal elasticity' was reported by 34% of the survivors having received radiation therapy (RT) compared to 14% among the control women [7].

Jung et al. [8,9] investigated the effect of time to follow-up on the occurrence of different late radiation therapy effects. In these studies they suggested models for different time kinetics and they concluded that clinicians and patients should be aware that the risk for late complications might be lifelong. Based on mixture models, Tucker et al. [10] introduced a generalized Lyman model to incorporate censored time-to-toxicity data and different risk factors. This model was applied to radiation pneumonitis, which is an early radiation therapy reaction. However, the fitting of the generalized Lyman model including the time to toxicity was not significantly improved if an additional latency parameter was modeled as a linear function of normal tissue complication probability (NTCP). The influence of the time to follow-up on the

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dose–response relation has not been thoroughly described in the literature. To study this effect is of great importance in maintaining the quality of life of cancer survivors and we should consider not only the occurrence of a symptom but also the length of time between treatment and the appearance of the symptom. Thus, for every time point we could have different radiobiological parameters, resulting in different dose–response relations. The estimated life expectancy of each patient might be used to make it possible to treat various age groups differently and thus perhaps make it possible to calculate some accumulated or integrated effect on quality of life.

The aim of the present study was to investigate the dose–response relations for the symptom 'absence of vaginal elasticity' in a subset of patients from the population-based study, who underwent external beam radiation therapy without brachytherapy. In addition, a new model, which accounts for the influence of time between treatment and appearance of the symptom on the dose–response relations, is proposed. Finally the effect of time to follow up on the dose–response relations of the symptom was thoroughly investigated.

Materials and methods

Subjects

The total cohort includes 616 gynecological cancer survivors and 344 non-irradiated control women, who were matched for age and residency [6,7]. Of the 616 survivors 109 were treated with external beam radiation therapy without brachytherapy (BT) and included in the study. Treatment plans could be retrieved from 78 of the 109 gynecological cancer survivors treated with external beam radiation therapy (EBRT). Among these, 24 survivors (31%) reported experiencing 'absence of vaginal elasticity'. Of the 344 non-irradiated controls 300 had answered the specific question and were included in the study. Of them 14% had the symptom.

In our study-specific questionnaire [6], the survivors were asked: 'how was your vaginal elasticity during the last six months?' with the possible answers 'none at all', 'little', 'moderate', 'good'. Thirty-one percent of the survivors answered 'none at all', 26% 'little', 28% 'moderate and 15% 'good'. We dichotomized cancer survivors into having or not having ''absence of vaginal elasticity''. All survivors included in the study have answered that specific question. Cancer survivors were diagnosed with different gynecological malignancies and received various treatment combinations of surgery and chemotherapy [7]. The 78 survivors included in the present study were treated between 1991 and 2003. Patients were followed up during 2006. The mean time to follow up for this group of patients was 7.2 years. The time to follow up used in this study is the time after end of treatment until the time each patient filled out the questionnaire in 2006. The time of the symptom occurrence among the survivors with the symptom is unknown since the survivors were only asked if they had experienced the symptom during the last six months, but not when in relation to end of radiation therapy. This implies left censoring. The future time when the symptom may occur among survivors without the symptom at follow-up is also unknown, implying right censoring. This means that our data are double-censored. The model we propose in this paper is applicable in double censored data and thus uses the assumption that the symptom occurs at or earlier than time t.

The vagina was delineated in the treatment planning systems. The vagina was defined in the Computed tomography (CT) scans used for treatment planning as an elliptical-shaped area. The dimensions of the ellipse were one by three cm located between the urinary bladder and the rectum and extending to the portio of the cervix or if that was not present, to the lower border of the pelvic cavity (Fig. 1e) [11]. The mean volume of the vagina was 16.2 cm^3 (SD: 7.4 cm^3). The DVHs for the vagina were exported from the treatment planning systems for each patient.

The predominant RT treatment technique before 1996 was two opposing fields, while after 1996 it was more common to use a four-field box technique. The treatment planning was performed in TMS (Nucletron, Veenendaal, the Netherlands) and in Cadplan or Eclipse (Varian Medical Systems, Palo Alto, USA). The energy range was 6–50 MV according to ICRU 1993 [12]. CT scanning was made with the patients in treatment position on a flat table, using laser markers and conversion factors to electron density. The slice thickness was 0.5–2 cm (mean value was 1 cm (SD: 0.2 cm)). Only two patients were scanned with 2 cm.

The treatment technique for each diagnosis is described in detail in a previous paper [11]. The fractionation schedule for the EBRT, in the studied treatment period was 1.6, 1.8 and 2.0 Gy per fraction. The dose–response models were parameterized by D_{50}, the dose corresponding to a 50% complication probability and γ_{50} the normalized dose–response gradient at 50% complication probability. The parameter, which describes the volume effect in the RS model, is the parameter s. We used our own dose–response fitting software to do the calculations and to fit the dose–response models to the data. This software is based on the software package Nonlinear Programming, Systems Optimization Laboratory (NPSOL) [16].

Optimizing all D_{50}, γ_{50}, s and α/β for Probit-RS and D_{50}, γ_{50}, and α/β for Probit, the optimal value of the α/β for this group of cancer survivors and this endpoint were infinite. Therefore, the parameter values that have been estimated with the average dose to the vagina were not corrected for the different fractionation schedules. The dose–volume response parameters were calculated using the Probit [13], the relative seriality (RS) [14] and the new Probit-time model. The response probability $P(D)$ of the vaginal elasticity used in the RS model, were calculated using the Probit model [15]. Another method used in this study to account for the effect of the time to follow-up is to estimate the dose–response relations for two groups of patients. The groups were dichotomized according to the median time to follow-up. The first had shorter than median (2.3–6.8 years) and the second longer (7.0–14.2 years) time to follow-up.

To model the influence of time to follow-up on the dose–response we assume that $S(D, t)$ is the probability that a patient treated to dose D is complication-free at time t after treatment, *i.e.* no complication has occurred up to time t. If $\lambda(D, t)$ is the hazard function or the incidence rate of the complication then:

$$S(D,t) = e^{-\int_0^t \lambda(D,t')\mathrm{d}t'}. \quad (1)$$

We assume that the incidence rate $\lambda(D, t)$ remains constant over time. Then Eq. (1) becomes:

$$S(D,t) = e^{-\lambda(D)t}. \quad (2)$$

The probability that a patient has a given complication at an arbitrary time point T is given by a sigmoid shaped response function $P_T(D) = P(D, T)$, then:

$$1 - P_T(D) = S(D,T) = e^{-\lambda(D)T}, \quad (3)$$

$$\lambda(D) = -\frac{ln(1 - P_T(D))}{T} \quad (4)$$

The probability that a patient has a given complication at time t can now be calculated using $P(D,t) = 1 - S(D,t)$ and by inserting (4) in (2):

$$P(D,t) = 1 - (1 - P_T(D))^{t/T}. \quad (5)$$

To be able to more easily compare Probit and Probit-time model a parameter δ was introduced to make the models nested.

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