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Consolidating Risk Estimates for Radiation-Induced Complications in Individual Patient: Late Rectal Toxicity

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Summary

Much dose-response data for normal tissue toxicity exists in the literature. This study describes a model, synthesized from published data, which allows calculation of risk for individual patients based upon their planning DVH. It took late rectal toxicity after treatment for prostate cancer as an example, and developed risk estimates for Grade 1,Grade 2, and Grade 3 or greater rectal bleeding in12 test patients. This method allows for more systematic use of published dose-response data to estimate complication risks for the individual.

Purpose: To test the feasibility of a new approach to synthesize published normal tissue complication data using late rectal toxicity in prostate cancer as an example.

Methods and Materials: A data survey was performed to identify the published reports on the dose−response relationships for late rectal toxicity. The risk estimates for Grade 1 or greater, Grade 2 or greater, and Grade 3 or greater toxicity were obtained for a test cohort of patients treated at our institution. The influence of the potential factors that might have affected the reported toxicity levels was investigated. The studies that did not conform to the general data trends were excluded, and single, combined risk estimates were derived for each patient and toxicity level.

Results: A total of 21 studies of nonoverlapping patient populations were identified. Three studies provided dose−response models for more than one level of toxicity. Of these 21 studies, 6, 14, and 5 were used to derive the initial risk estimates for Grade 1, 2, and 3 or greater toxicity, respectively. A comparison of risk estimates between the studies reporting rectal bleeding and rectal toxicity (bleeding plus other symptoms) or between studies with follow-up <36 months and ≥ 36 months did not reveal significant differences ($p \geq .29$ for all comparisons). After excluding three reports that did not conform to the general data trends, the combined risk estimates were derived from 5 reports (647 patients), 11 reports (3,369 patients), and 5 reports (1,330 patients) for Grade 1, 2, and 3 or greater toxicity, respectively.

Conclusions: The proposed approach is feasible and allows for more systematic use of published dose−response data to estimate the complication risks for the individual patient.

Keywords: Normal tissue complication probability, NTCP, Meta-analysis, Late rectal toxicity, Radiotherapy, Prostate cancer

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Introduction

A vast amount of dose–response data for radiotherapy-related normal tissue complications has been accumulated in the era of computed three-dimensional dosimetry. Normal tissue complication probability (NTCP) models constructed from single-institution series are usually based on a limited number of observed complications and a narrow range of dose–volume combinations owing to the use of standardized treatment techniques. Such models can lack the predictive power when applied to data from another institution (1). The process of comparing and combining outcomes data from different published studies is challenging because of the variability in reporting standards, clinical endpoint definitions, organ-at-risk delineation, choice of predictor variables, and NTCP models (2). One solution to the problem is to pool and reanalyze the raw data from several institutions to produce a collective model (1, 3–5). However, this approach is not always feasible, because it requires large and technically difficult collaborative efforts.

An alternative strategy would involve applying dose–response models from each published report to an individual patient's dosimetric and clinical data to obtain a battery of NTCP estimates. If different studies produce concordant results, the study-specific NTCP estimates can be consolidated into a single combined NTCP estimate for that patient. Because it is generally easier to manipulate patient data to obtain the various metrics reported in the published studies than to convert one dose–response model to another, this proposed approach allows the reconciliation of the heterogeneity across a wider spectrum of the published reports.

The QUantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review (6) represents the most comprehensive attempt to date to summarize the modern dose–response data. One of the research priorities identified by QUANTEC was the "development of methods for synthesizing results across studies with appropriate estimation of prediction uncertainty" (2). In the present study, we tested the feasibility of a novel strategy for synthesizing NTCP data that meets this research priority. Using late rectal toxicity as an example, we used a cohort of patients treated at our institution to investigate the variability in NTCP estimates obtained from published dose–response relationships and to identify the models that result in concordant risk predictions.

Methods and Materials

Data search and selection criteria

A comprehensive data search was performed to identify the studies reporting an association between any level of late rectal toxicity after external beam radiotherapy and one or more predictor variables, such that an estimate of risk can be obtained, given the values of those variables. The scope was limited to studies in which three-dimensional dosimetry was performed and rectal dose–volume histograms (DVHs) or dose–wall histograms (DWHs) were generated. No distinction was made according to surgical status (intact prostate or after prostatectomy), toxicity assessment technique (physician-reported toxicity or patient-reported toxicity), treatment technique (three-dimensional conformal or intensity-modulated radiotherapy), modality (photons or protons), and fractionation. Some candidate reports were excluded for the following reasons:

1. Insufficient information to reconstruct the dose–response relationship (*i.e., p* values, correlation coefficients, odds ratios, hazard ratios, or average values of a predictor variable in patients with and without complications were reported without any information about toxicity risks associated with different values of the predictor variable).
2. Overlapping patient populations in separate publications. In such cases, a report that included a larger patient population or provided more detailed description of the dose–response relationship was used (*e.g.,* a model resulting in continuous NTCP estimates was preferred to a model predicting discrete levels of toxicity).
3. Rectal volume definition not clearly described.

Test cohort

Twelve prostate cancer patients with intact prostate gland whose treatment was previously planned using the XiO treatment-planning system, release 4.50 (Elekta CMS Software, Maryland Heights, MO) at the Medical College of Wisconsin were selected. All patients were treated with the intensity-modulated radiotherapy using the following radiation schedules: 70.2 Gy (1 patient), 72 Gy (2 patients), 73.8 Gy (3 patients), and 75.6 Gy (6 patients) at 1.8 Gy/fraction to the prostate planning target volume. In 6 patients, the proximal seminal vesicles were included in the planning target volume.

NTCP estimation

The relevant data were extracted from the tables and figures in the selected reports and, where necessary, digitized using Engauge Digitizer, version 4.1 (available at: digitizer.sourceforge.net). The extracted dose–response models were used to compute the NTCP by applying the methods originally used in the study to the treatment planning dose distributions for patients in the test cohort. If the clinical variables were included in the model, it was assumed that the corresponding factors were not present in the test cohort.

To account for the variability in rectal volume delineation methods in the craniocaudal direction among the selected reports, all encountered methods were classified into five definitions (Table 1). The outer rectal wall was contoured according to each of the five methods by 1 observer (K.D.). In addition, the cross-sectional definition of the rectum (*i.e.,* solid organ vs. hollow organ, entire rectal wall vs. anterior half of the rectal wall) was reproduced. For defining the hollow rectum, two different approaches were used. Peeters *et al.* (7) defined the rectum as a hollow organ and used a method described by Meijer *et al.* (8) to reconstruct the inner rectal wall from the outer

Table 1 Rectal volume definition methods in craniocaudal direction

Short notation	Description
M1	1 cm above and below planning target volume
M2	1 cm above seminal vesicles and 1 cm below prostate apex
M3	Superior limit of anus to 2 cm above prostate
M4	Rectosigmoid junction to 1.5 cm caudal to apex of prostate
M5	Anal verge/ischial tuberosities to rectosigmoid junction/sacroiliac joints