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Original article

Can reduction of uncertainties in cervix cancer brachytherapy potentially improve clinical outcome?

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ABSTRACT

Aim: The aim of this study was to quantify the impact of different types and magnitudes of dosimetric uncertainties in cervix cancer brachytherapy (BT) on tumour control probability (TCP) and normal tissue complication probability (NTCP) curves.

Materials and methods: A dose–response simulation study was based on systematic and random dose uncertainties and TCP/NTCP models for CTV and rectum. Large patient cohorts were simulated assuming different levels of dosimetric uncertainties. TCP and NTCP were computed, based on the planned doses, the simulated dose uncertainty, and an underlying TCP/NTCP model. Systematic uncertainties of 3–20% and random uncertainties with a 5–30% standard deviation per BT fraction were analysed.

Results: Systematic dose uncertainties of 5% lead to a 1% decrease/increase of TCP/NTCP, while random uncertainties of 10% had negligible impact on the dose–response curve at clinically relevant dose levels for target and OAR. Random OAR dose uncertainties of 30% resulted in an NTCP increase of 3–4% for planned doses of 70–80 Gy EQD2.

Conclusion: TCP is robust to dosimetric uncertainties when dose prescription is in the more flat region of the dose–response curve at doses >75 Gy. For OARs, improved clinical outcome is expected by reduction of uncertainties via sophisticated dose delivery and treatment verification.

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Knowledge of correlations between dose and clinical outcome is fundamental for dose prescription in radiotherapy. Radiotherapy dose prescription is essentially a balance between maximum tumour control and acceptable side effects. Correlations between dose and effect exist both for targets and normal tissue, and clinical evidence for specific dose–effect relationships can be used to support decisions for an individual patient treatment or to guide the developments of new radiotherapy techniques and schedules. The implementation of volumetric 3D imaging since the 1980's for dose planning in radiotherapy has significantly improved the abilities to identify target structures and organs-at-risk. Furthermore, it became possible to report dose in terms of dose and volume histogram (DVH) parameters evaluated based on 3D dose distributions. The success of DVH reporting has been demonstrated by multiple studies having shown dose–effect relationships based on tumour and organ DVH parameters and correlations with local control and side effects, respectively. E.g. during the last decade, the QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) effort has aimed to summarise current knowledge about dose–effect data for organs at risk (OAR) in order to provide recommendations – when possible – on dose–volume constraints [1]. In cervix cancer brachytherapy, 3D image guidance was rapidly disseminated after the publication of the GEC ESTRO recommendations on contouring and dose reporting [2,3]. Based on patient cohorts treated with 3D image guidance a number of dose–effect relationships have already been published for target [4–6], rectum [7–9], bladder [7,9] and vagina [10].

However, dose planning and delivery is always related with dosimetric uncertainties that may lead to a difference between prescribed and delivered dose. The sources of uncertainties can be of a technological nature (source calibration, dose calculation and dose delivery), or due to the clinical workflow and anatomy of the patient (applicator movement, delineation uncertainties, anatomical changes (inter-/intra-fraction variations) [6,11–13]. Recent reports have highlighted the magnitude of different types of uncertainties for different BT treatment sites [6,12]; and references therein).

Uncertainties are categorised as either systematic (e.g. source calibration) or random (e.g. inter-fraction variations) [12]. A recent

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multicenter comparison of dosimetric variations caused by anatomical changes, within and between different BT fractions for cervical cancer, have revealed that expected random intra- and inter-fraction uncertainties are of the order of 10% for the minimum dose to 90 percent (D_{90}) of the high risk clinical target volume (CTV_{HR}) and 20–30% for the maximally exposed 2 cm^3 (D^3_{2cm}) for organs at risk, for the physical dose of each BT fraction [13]. Systematic dosimetric uncertainties were found to be low and can in some cases be minimised with efficient organ filling protocols. Random inter-/intra-fraction variations due to fluctuations of organ shape and position can be considered as the main contributors to the total uncertainty of the delivered BT doses [6,12]. The results of the aforementioned study have triggered further investigations, considering that in a fractionated BT treatment protocol the observed uncertainties of physical absorbed dose, will lead to an accumulated uncertainty of the RT treatment dose, reported in total equivalent dose in 2 Gy fractions (EQD2) – which (including contributions from EBRT to the overall treatment) is used to analyse clinical dose–response relationships [4,7,14].

An observed dose–effect relationship from a clinical data-set is influenced by uncertainties, since the delivered doses – causing the clinical effect – are not identical to the recorded "planned doses". In this study, the impact of uncertainties on the shape and position of the dose–effect curve was investigated for different scenarios in terms of (1) target and OARs, (2) uncertainty distributions and (3) fractionation schedules. The overall purpose was to investigate the potential clinical advantage of reducing uncertainties in image guided brachytherapy in cervix cancer. The results are applicable to other sites in radiotherapy with similar dose–effect relationships and distribution of uncertainties.

Material and methods

Overview of the simulation study

In order to quantitatively study the interplay of clinical uncertainties of dose reporting vs. dose delivery and dose–response analysis, a custom Interactive Data Language, IDL (v7.0, ITT Visual Information Solutions) script was developed to simulate a large number of patients and generate a database of "modelled observations" that consists of prescribed doses, actually delivered doses and predicted events (local control/side effects).

Throughout this manuscript the terms "prescribed dose" and "delivered dose" are used to differentiate between the dose that has been prescribed and reported, and the dose that would actually be delivered to a patient under the influence of uncertainties [15].

For each simulated patient cohort, the same set of prescribed doses was assumed, and different systematic or random dosimetric uncertainties were applied to the entire cohort. In this way the prescribed doses were the same for each simulated cohort, but the delivered doses heterogeneously distributed, depending on the assumed uncertainty distribution.

Subsequently, a dose–response model for tumour control (TCP) or normal tissue complication probability (NTCP) was used to predict whether an event (side effect or local failure) occurred for each individual patient in the cohort, based on the delivered dose.

Finally the set of simulated observations, i.e. prescribed doses and events, were analysed with a commercial statistical package, SPSS (v20, IBM), using the same technique that is usually applied to derive dose–response relationships from real clinical outcome data (e.g. [7,10,18]). The resulting simulated "observed dose–response relationships" were finally compared to the underlying model of the "true dose–response relationship".

Typical dose and fractionation schedules for cervix cancer radiotherapy (combined EBRT and BT) were used, as well as published dose–effect relationships from cervix cancer.

An illustration of the overall workflow of the simulation study is shown in Fig. 1.

Detailed description of the simulation study

Simulation of delivered dose based on uncertainties

Typical total dose levels ranging from a total EBRT and BT dose of 45-180 Gy EQD2 (in 5 Gy steps) were investigated for a

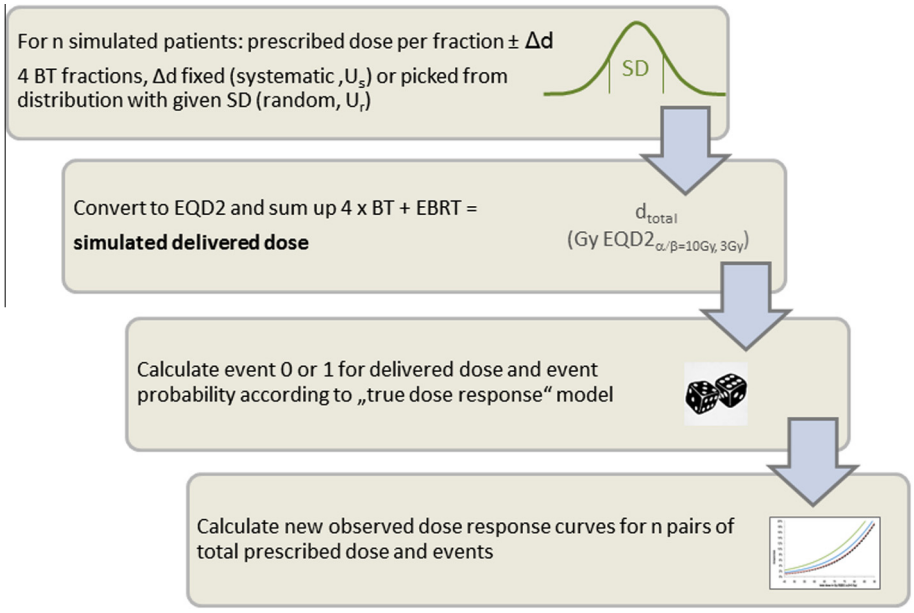

Fig. 1. Overview of the simulation workflow. (1) For *n* simulated patients, prescribed dose per fraction is converted to delivered dose per fraction, by adding a dose Δd, based on systematic or random dosimetric uncertainty. (2) For 4 BT fractions, the absorbed dose is converted to EQD2 using α/β = 3 Gy for NTCP/OARs and 10 Gy for TCP/target calculations. The BT dose is summed up with the full EBRT dose in EQD2, which results in the total simulated delivered dose for the patient. (3) Based on the assumed true dose–response model curve, for each simulated patient, "dice are rolled" with the probability for an event taken from the dose-response model. Event "1" or no event "0", are recorded. 4. For a full set of *n* simulated patients, new "observed" dose–response curves are calculated from *n* pairs of total prescribed dose (BT prescribed dose × 4 + EBRT, in Gy EQD2) and events.

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