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PHYSICS CONTRIBUTION

A STUDY OF THE EFFECT OF SETUP ERRORS AND ORGAN MOTION ON PROSTATE CANCER TREATMENT WITH IMRT

Valeria Landoni, Ph.D.,* Bianca Saracino, M.D.,† Simona Marzi, Ph.D.,* Michaele Gallucci, M.D.,‡ Maria G. Petrongari, M.D.,† Enrico Chianese, M.D.,† Michaela Benassi, M.D.,† Giuseppe Iaccarino, Ph.D.,* Antonella Soriani, Ph.D.,* and Giorgio Arcangeli, M.D.†

*Laboratorio di Fisica Medica e Sistemi Esperti, †S.C. Radioterapia, and ‡S.C. Urologia, Istituto Regina Elena, Rome, Italy

Purpose: To assess the influence of setup errors and organ motion in terms of the probability of tumor control and normal-tissue complications by tumor control probability and normal-tissue complication probability.
Methods and Materials: Twelve patients were treated for prostate cancer with intensity-modulated radiation therapy. Two orthogonal portal images were taken daily. All patients underwent three computed tomography scans during the 8-week treatment time (i.e., baseline, intermediate, and final). The original treatment plans were re-evaluated, taking into account setup errors and organ motion.
Results: The mean shifts ± standard deviation of the whole patient population in the lateral, anterior-posterior, and craniocaudal direction were 1.0 ± 1.5 mm, 0.9 ± 2.1 mm, and 1.9 ± 2.1 mm, respectively. In most of the recalculated dose–volume histograms, the coverage of clinical target volume was granted despite organ motion, whereas the rectal wall histograms were often very different from the planned ones.
Conclusion: We have studied the impact of prostate and rectum motion, as well as setup errors, on dose–volume histograms. The estimate of these effects may have implications for predictive indications when planning intensity-modulated radiation therapy treatments on prostate.

Intensity-modulated radiotherapy, Setup errors, Organ motion, Dose volume histograms.

INTRODUCTION

Radiotherapy treatment aims to kill all neoplastic cells to obtain local tumor control with acceptable normal-tissue morbidity. This goal can be achieved by avoiding as much as possible organs at risk (OARs) close to the tumor. This implies that the entire clinical target volume (CTV) receives the full planned dose and that OARs are not exposed to doses above critical levels. This procedure of dose delivery is complicated by both daily repositioning uncertainties and internal organ motion. Therefore, the probability of hitting the tumor in each fraction and, at the same time, avoiding as much as possible the involved OAR becomes in practice a question of the size of the safety margins around the CTV and OARs. This problem is particularly important in the treatment of tumor sites such as the prostate, where the internal motions of the CTV and organs at risk have to be added to the patient daily repositioning uncertainty. This problem is further complicated when the treatment is delivered by an intensity-modulated radiotherapy (IMRT) technique that provides high dose gradient distributions to tissues. Therefore, every department, particularly if it is involved in dose-escalation studies, should define the extent of its safety margins and dose–volume constraints and thereby provide a reliable prediction of normal-tissue complication probability (NTCP).

The importance of evaluating the effect of setup errors and organ motion on treatment efficacy has been recently emphasized (1–3), as has the possibility of performing dose escalation on prostate (4–6). Some authors have also introduced radiobiologic considerations in their analyses (7).

Although bone anatomy and external marks have been used to quantify setup errors, they are not able to estimate the extent of organ motion. The analysis of multiple dose–volume histograms (DVHs) obtained by multiple computed tomography (CT) scans, before and during a radiation course, could provide more accurate information to predict late complications and eventually avoid dose escalation in patients at higher risk (2). The present study aims to evaluate the effect of setup errors and organ motion on DVHs and to introduce radiobiologic considerations evaluating tumor control probability (TCP) and NTCP in a group of patients undergoing IMRT for prostate cancer. The evaluation of setup errors and organ motion was carried out by

Reprint requests to: Valeria Landoni, Laboratorio di Fisica Medica e Sistemi Esperti, Istituto Regina Elena, IFO, via Elio Chianesi 53, 00144, Rome, Italy. Tel: (+39) 06-52665411 or (+39) 06-52665613; Fax: (+39) 06-52665411; E-mail: landoni@ifo.it

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analyzing, respectively, daily portal images and multiple CT scans taken at different intervals during the radiation therapy course.

METHODS AND MATERIALS

Patient population

The study included 12 patients with prostate cancer classified as intermediate risk; i.e., one of the following parameters was present: prostate specific antigen (PSA) = 10–20 ng/mL, or Gleason ≥7, or Stage ≥T2b.

Contouring

All patients underwent a baseline CT simulation in prone position in a customized immobilization cradle including the whole trunk, from the ankles to the breast, with a wedge cushion under the ankles to prevent rotation. CT scans were acquired with a spiral CT, and slices were reconstructed with 5-mm spacing. To eliminate intraobserver variability (8), CTV and rectal wall were always contoured by the same radiation oncologist. Planning target volume (PTV) was obtained by expanding the CTV with a margin of 1 cm in each direction, only posteriorly the margin was 0.6 cm to avoid excessive rectal wall involvement. The CTV was the prostate gland and the entire seminal vesicles; the rectum was contoured from the distal ischiatic branch to the sigmoid flexure as a hollow organ (i.e., it consisted of the rectal wall). No particular instructions were given about rectal filling, whereas patients were told to have a partially filled bladder.

Treatment planning and delivery technique

Treatment plans were developed using an inverse planning system (Helios 6.3, CadPlan v 6.3.5) to deliver 80 Gy in 40 fractions to the ICRU reference point, with percent minimum and maximum PTV dose of 95% and 107%, respectively. Dose–volume constraints on rectal wall were as follows: doses ≥70 Gy (V70) and ≥50 Gy (V50) to less than 35% and 50% of rectal wall volume (9–13). When it was not possible to respect the V50 constraint on rectal wall, the coverage of PTV with minimum isodose of 95% was considered to be more important. Because a strong correlation was found between the high dose constraints and rectal bleeding (9–13), doses higher than 70 Gy to more than 35% of rectal wall volume were always avoided. Digitally reconstructed radiographs (DRR) were generated from the CT data and used as reference images. Because of the independence of their outline on the filtering technique, the pubic symphysis and the ischiatic bone on lateral DRRs and the ilium and pubis on anterior DRRs were chosen as reference regions. Treatments were delivered by 15 MV photon beams from linear accelerators (Varian 2100 C/D), all equipped with 0.5 cm leaf width multileaf collimators (MLC Millennium 120, Varian), with a 5-field sliding window technique.

Treatment verification and statistics

Two orthogonal portal images were taken daily in treatment position by a silicon electronic portal imaging device. An online matching of the anatomic structures on portal and reference DRR images allowed a daily isocenter check. Unless a systematic deviation from the planned position was detected, daily corrections on patient position were made only for deviations larger than 2 mm. To evaluate the size and the distribution of portal shift, deviations from the planned position were measured by an automatic matching method after each treatment session. Deviations from the planned position during a treatment course can be generated by systematic or random errors; the former are those affecting a measure always in the same direction, whereas the latter randomly affect measurements in all directions. For example, assuming the reference patient geometry that derived from CT scans, a systematic error can be generated by a wrong patient setup during a CT simulation, whereas random errors can be caused by wrong daily setups during the treatment procedures. Assuming that random errors in the overall treatment average to zero, the original treatment plan was recalculated to simulate the systematic error. For a patient population, the systematic and random errors can be described using standard deviations. The overall error is given as the root-sum-square of random and systematic errors (14).

Beyond the initial CT scan taken for the simulation, 2 more CT scans, 1 at the fourth and 1 at the eighth week of treatment, were taken on each patient. The volumes of interest were recontoured by the same radiation oncologist, and the new data were transferred to the planning system. In each patient, dose distribution was recalculated on the new CT data using the original beam parameters and DVHs for CTV and rectal wall, with three distributions of dose (i.e., baseline, intermediate, and final). Because all patients were irradiated at the same anatomic site, in the same position (i.e., prone), and with the same immobilization technique (i.e., cradle) as described by other authors (15–18), we considered the patients to be a representative sample of the population similarly treated. Following these considerations, we assumed that in the differential DVHs for each value of dose, the values of volumes were randomly distributed around a mean value with a standard deviation, even though this may not be the only way to represent this distribution (19). Each volume of the original DVHs was weighted for its Gaussian probability, and new DVHs, now called $(DVHs)_w$, were obtained.

Radiobiologic indicators

NTCP was calculated from normalized $(DVHs)_w$ obtained converting the total physical dose into the biologically equivalent total dose normalized to 2 Gy per fraction according to the Lyman–Burman–Kutcher model (20). An $\alpha/\beta = 3$ Gy was assumed for the rectum, and the recently fitted parameters of TD50 = 81.9 Gy, $n = 0.23$, and $m = 0.19$ were used (21). These parameters were calculated for a group of patients with a minimum follow-up of 18 months, considered as bleeders if showing Grade ≥2 late complication according to a slightly modified Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scoring system. TCP was calculated using the Poisson model from normalized $(DVHs)_w$ without taking into account tumor repopulation. Because patients recruited for this study are classified as intermediate-risk patients, we assumed $\alpha = 0.0391$ Gy^{-1} and $\alpha/\beta = 1.5$ Gy as reported by Fowler *et al.* (22) for this patient group. According to Stavrev *et al.* (23), the maximum likelihood method was used to fit the experimental data for external beam irradiation reported by Fowler *et al.* (22) for an estimation of the initial clonogenic cell number (N_0) for our patient population. An N_0 value of 253 ± 34 cells was obtained, which was used to evaluate a mean clonogenic cellular density r of 3.5 ± 1.4 cells/cm^3, for a mean prostate volume of 72.6 ± 18.9 cm^3. TCPs were calculated assuming a constant clonogenic cellular density r and taking into account each patient's CTV.