High-precision radiotherapy: where are we going and how do we get there?

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LOCK M, CATTON C. High-precision radiotherapy: where are we going and how do we get there? The Canadian Journal of Urology. 2006;13 (Supplement 2):34-36.

In January 2006, physicians with an interest in urologic cancers met to discuss patient care at the 4th Annual Current Problems in Urology Conference. A portion of the meeting was focused on technical issues in prostate cancer radiotherapy. This portion of the meeting sought to answer the questions: where are we going? And how can we get there? Work performed at the Princess Margaret Hospital (PMH) and the London Regional Cancer Program (LRCP) served as the basis for discussion and to present examples of options for implementation of new techniques. The response to the first question reviewed the issue of improved outcomes with dose escalation and the preliminary implementation of hypofractionated treatment. The impact on toxicity was reviewed in detail. The response to the second question revolved around the options available to ensure adequate tumor localization. As dose is increased, the need to localize the prostate accurately has become more important in order to ensure tumor control and to avoid toxicity. Selection of appropriate margins around the prostate is determined by a center's ability to localize the target. Options to localize organs including three-dimensional ultrasound, fiducial markers, megavoltage CT and cone beam CT were discussed. The basic research to enable selection and implementation of these options were presented.

Key Words: radiation, prostate cancer, intensity-modulated radiotherapy, hypofractionation

Introduction

The treatment of prostate cancer with external beam radiation has undergone significant development over the past half decade. At the Current Problems in Urology Conference 4th Edition, an update on current investigations and treatments was undertaken. In particular, how technical issues were practically addressed at two Canadian centers was highlighted. The value of quantifying and minimizing sources of set-up error was reviewed. Techniques to optimize patient positioning, minimization of target motion and the development of protocols to monitor organ position on-line were of particular interest. This article reviews some of the key technical radiation issues discussed.

Where are we going?

There are now two phase III trials confirming the value of dose escalation[1,2] for prostate cancer. Princess Margaret Hospital (PMH) has been escalating doses as new technology became available.[3,4] A 3D conformal technique and then an intensity modulated radiotherapy (IMRT) have been implemented with a portion of patients being treated using an on-line organ localization technique. These patients form a valuable source of information because with this large population we can address the questions of whether dose escalation results in increased toxicity and if certain dose parameters can help avoid complications. A survey of 442 patients treated with dose-escalated radiotherapy at PMH assessed the toxicities after a median follow-up of 3.5 years. Patient-reported late toxicities were low. More importantly, there was no increase in toxicity between 75.6 Gy and 79.8 Gy. In addition no significant correlation between dose to organs at risk and complications could be found.

Dose escalation often requires increased resources to ensure accurate targeting over an extended period. Radiobiologic data suggesting a low α/β ratio for prostate cancer have prompted both PMH and the LRCP to initiate hypofractionation trials. The hope is to reduce treatment time, and to dose escalate without increasing toxicity to normal tissues. PMH studied 92 low and intermediate risk prostate cancer patients treated to 60 Gy in 20 daily fractions. Image guidance

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and intensity-modulated radiotherapy (IMRT) were utilized. With a median follow-up of 28 months the 3-year biochemical recurrence-free rate is 90% and 87% according to the ASTRO and nadir+2 definition, respectively. The late toxicity is available for 87 patients beyond 12 months. Two percent of patients had grade 2 or more genitourinary and gastrointestinal toxicity, respectively. Ninety-six percent have no gastrointestinal toxicity and 92% have no genitourinary toxicity. Therefore, hypofractionation appears feasible and has a low risk of late effects. A large multicenter trial to investigate this method for intermediate prostate cancer patients is being sponsored by the Ontario Clinical Oncology Group. The trial compares 60 Gy in 4 weeks to 78 Gy in 8 weeks. The primary endpoint will be 5-year biochemical recurrence-free rate and attendees were encouraged to participate.

How can we get there?

Technological advances in planning and delivery must come with an advance in target localization. IMRT offers accuracy within 3 mm.[5] The promise of IMRT is that reduced margins may translate to reduced complications. However, the possibility of geographic miss and decreased tumor control must be addressed by accurate localization. Options available include fiducial markers, ultrasound, megavoltage-computed tomography (MVCT) and kilovoltage-computed tomography (KVCT).

Fiducial marker localization

One option for localization is the placement of fiducial markers. Chung[6] published data from the PMH image-guidance experience with fiducial markers. This study addresses the feasibility and experience of implementing an on-line protocol employing fiducial markers to reduce inter-fraction error. Seventeen patients were assessed before each fraction with a lateral amorphous silicon (aSi) portal image. The position of the fiducial markers was compared to the digitally reconstructed radiographs using chamfer matching. Couch translation was used to account for marker displacements. An action point of 3 mm was chosen. Therapists found it simple to match markers 88% of the time using this system. Treatment delivery times were 8.7 minutes for patients requiring isocenter adjustment and 6.1 minutes for those who did not. The authors found that fiducials and the correction protocol were easily included in the daily routine and provide the opportunity for margin reduction.

Work performed at the LRCP was also presented. Ten low and intermediate risk prostate cancer patients had five fiducials placed. Patients were CT scanned weekly. Based on individual and centre-of-mass assessments, this study concluded that a PTV (planning target volume) margin reduction below 10 mm could only be achieved if off-line target-based verification is implemented. A reduction below 6 mm can only be achieved if daily on-line localization was used. Without this localization, tumor control probabilities decreased by greater than 5%. Furthermore, CT localization was inferior to portal image detection as it introduced a superior-inferior error. This error is likely due to the slice thickness of the CT image versus the portal image. Therefore, portal imaging or electronic portal image devices (EPID) remain the standard for localization of fiducial markers.[7]

Ultrasound localization

Fiducial marker placement is a relatively invasive procedure requiring additional resources and increased planning time. Ultrasound localization systems are an increasingly popular alternative.[8] The role of these systems was addressed. At LRCP, two systems are currently in use, the Restitu from Resonant Medical Systems and SonArray from Varian Medical Systems. Data from the SonArray commissioning and implementation studies were presented. Patients were localized using daily EPID and compared to daily three-dimensional infrared-guided ultrasound using the SonArray system. One of the first 3D systems available, SonArray is based on a single infrared camera system. Infrared markers are placed on an ultrasound probe. The probe uses transabdominal 3D ultrasound to localize structures such as the prostate. The camera can localize the markers and, therefore, the structures within the 3D space of the room. The location of the structures relative to their location at time of simulation is compared and appropriate adjustments can be made on a daily basis. Prior to implementation, a commissioning process was performed. Data on training time, treatment delays, cost and reproducibility were assessed. This commissioning determined that the ultrasound process was an acceptable and reliable addition to the radiation therapy process though it did add approximately 5 minutes to the treatment procedure.

Data from the implementation study of 15 low and intermediate risk prostate cancer patients determined that when compared to the gold standard of fiducial markers, the SonArray system is not as accurate as fiducial markers. Specifically, in the superior-inferior dimension the difference between the localization by fiducials and ultrasound was 2.8 mm+/-6.1 mm. This is relative to other dimensions where the directed difference was less than 1 mm. A review of data from Van den Heuvel[9] and Langen[8] reveal similar results

across studies. Three-dimensional ultrasound appears a viable alternative to fiducial markers up to approximately 1 cm. Based on LRCP data,[10] 3D ultrasound localization becomes insufficient when margins are reduced below 7.5 mm. Further reductions require the use of fiducial markers and an on-line correction protocol. This conclusion was based on the tumor control probability calculations provided by van Herk's margin formulas[11] as applied to LRCP data.[10]

CT image localization

New options using MVCT and KVCT imaging are being investigated.[12] At the LRCP, the TomoTherapy Hi-Art System with daily megavoltage localization has been studied. The first step in MVCT localization is to determine whether the prostate could be consistently determined between and within observers. Seven observers contoured the prostate on five patients. This study found that the variation of inter- and intra-observers was not systematically different. However, the MVCT prostate was on average 10% larger than the planning CT contours, which reflects the poorer soft tissue discrimination of the MVCT. This data is discouraging if MVCT is to be used for daily localization.[13] Optimization of slice thickness and dose utilization is being investigated to improve the image.[14]

PMH studied the benefit of cone beam image guidance in 16 patients using fiducial markers. The KVCT images were obtained daily and reviewed retrospectively. Random and systemic errors determined from marker localization were compared to the errors determined by soft tissue localization. Formulas published by van Herk were used to determine appropriate margins for each method.[11] The lateral, anterior-posterior and superior-inferior margins would need to be 1.3 mm, 3.4 mm, and 3.4 mm, respectively using marker localization with cone beam CT. This is compared to 1.9 mm, 7.1 mm and 4.5 mm for the soft-tissue localization. Sources of difference include inter-observer variability and tissue deformation between assessments. Soft-tissue localization appears to be inferior to the localization by markers, but still provided sufficient accuracy to reduce the PTV margin in current use at PMH, and also provides the ability to directly image the normal soft-tissues at risk. The quality of images is expected to improve with additional experience.

Conclusion

The results of dose escalation have demonstrated improvement in biochemical control. Hypofractionation promises to be an efficient method to dose escalate. The goal of new technologies is to allow practical and safe dose escalation. The options to enable high precision treatment abound, but there appears to be a convergence of techniques. Image-guidance with ultrasound, fiducials, MVCT and KVCT are options currently being introduced. This meeting provided data on which options are feasible in the Canadian context, and which options are being applied in various centers. In addition, the groundwork required to select practical options and the specific considerations required to implement these options were reviewed. □

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