Medical Dosimetry ■■ (2017) ■■–■■

Medical Dosimetry

journal homepage: www.meddos.org

Dosimetry Contribution:

Evaluation of the preimplantation worksheet in determining Calypso eligibility for men prescribed postprostatectomy radiotherapy with electromagnetic transponder guidance

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ARTICLE INFO

Article history:
Received 6 January 2017
Received in revised form 26 April 2017
Accepted 17 May 2017

Keywords:
Calypso
Electromagnetic transponders
Prostatic neoplasms
Postprostatectomy radiotherapy
Radiotherapy planning

ABSTRACT

This study aimed to assess the design and performance of the preimplant suitability worksheet in determining Calypso eligibility for prostate cancer patients prescribed postprostatectomy radiotherapy with electromagnetic transponder guidance. The medical records and radiotherapy planning datasets of 75 patients prospectively recruited between June 2015 and September 2016 to a Phase 2 trial evaluating electromagnetic transponder-guided postprostatectomy radiotherapy were retrospectively examined. Correlation and differences between computed tomography (CT)-defined greater trochanter and prostatic fossa landmarks were evaluated. Receiver operating characteristic curves were also generated to assess the expected and observed accuracy of the worksheet in determining Calypso eligibility. Strong correlation was demonstrated between anterior surface to planning CT-defined greater trochanter and prostate bed center distances ($r = 0.95$, $p < 0.001$), with a mean difference between measurements of 1.1 cm (95% confidence interval [CI]: 0.9 to 1.3). A similar correlation coefficient was found for surface to greater trochanter location and posterior beacon location ($r = 0.92$, $p < 0.001$) but with a reduced mean difference of 0.4 cm (95% CI: 0.1 to 0.6). Performance of the worksheet as assessed by planning CT data demonstrated excellent accuracy as a test to determine eligibility (area under the curve: 0.97; 95% CI: 0.92 to 1.00); however, this was not replicated using the same data captured clinically (area under the curve 0.83; 95% CI: 0.68 to 0.98). Although the greater trochanter is a good surrogate for the prostate bed center, it is better associated with the posterior beacon location. As a result, the worksheet will underestimate the truly eligible population if performed accurately and according to manufacturer guidelines. Theoretically, the worksheet could be improved if a cut off of 20 cm is used and the greater trochanter is accurately identified; however, the latter appears to be difficult to achieve in practice.

Introduction

In 2012, 20,065 men in Australia were diagnosed with prostate cancer.[1] It has been reported that of the proportion managed surgically, up to 40% of all men, and just over 70%

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http://dx.doi.org/10.1016/j.meddos.2017.05.003

of those with high-risk prostate cancer, will develop biochemical recurrence on long-term follow up.[2,3] In these men, postprostatectomy radiotherapy to the prostatic fossa has been shown to improve survival.[4,5] Despite this, however, there are multiple reports that highlight ongoing underutilization of postprostatectomy radiotherapy in everyday clinical practice.[6-10] The main reasons for this are due to concerns surrounding overtreatment and the possibility of additional treatment-related toxicities that may lead to a decline in patients' quality of life.[11]

With advancements in radiotherapy delivery techniques, including intensity-modulated radiotherapy, there has been associated reductions in radiotherapy-related toxicities.[12,13] Image-guided radiotherapy (IGRT) using implanted markers or electromagnetic transponders has also been instrumental in further reducing toxicities in the intact prostate setting. Improved targeting of the prostate has allowed for tighter margins, resulting in decreased treatment volumes and hence further dose reduction to the normal tissues, which has enabled safe dose intensification.[14-16] This has led to IGRT's rapid implementation, such that it is now considered routine practice in the intact prostate setting.

IGRT in the postprostatectomy setting, however, is more complex due to the absence of the prostate. Compared with an intact prostate, the prostatic fossa is a potential space that is filled in by the bladder and rectum, making it more susceptible to shift and deform with changes in bladder and bowel filling.[17] Cone beam computed tomography has enabled soft tissue assessment and alignment, but this does not provide feedback regarding intrafractional motion of the prostate bed. Conversely, electromagnetic transponders have been approved by the US Food and Drug Administration and Australian Therapeutic Goods Administration for postprostatectomy radiotherapy treatment guidance and are being increasingly studied.[17-19] However, because of signal loss between the implanted transponders and external sensory array in larger men, their usage is reserved for men with a suitably small physical build.

Despite both transrectal and transperineal insertion of fiducials and electromagnetic transponders being a relatively safe day procedure, it is not an entirely risk-free procedure.[19-22] Additionally, the placement of electromagnetic transponders in the postprostatectomy setting is complicated by the lack of a prostate to implant into. Given the complexity, possible morbidity, and increased patient-related costs, it is therefore important to be able to accurately determine, before implantation, those patients who would likely have usable beacons and hence benefit from their implantation.

Presently, the manufacturer recommends the use of an eligibility worksheet to predict patients' suitability for implantation via evaluation of patient body habitus. As such, it is designed on the assumption that patient surface anatomy, in the form of the femoral greater trochanter, is a strong surrogate for the mid-prostate gland or prostate bed. However, given this measurement is based on clinical palpation of the greater trochanter, it is susceptible to inter- and intraobserver variability and may be difficult to execute accurately in practice.

To our knowledge, this is the first study of its kind to analyze and validate the Calypso worksheet in determining suitability of patients for implantation in the postprostatectomy setting. Therefore, the overall aim of this study was to assess the design and the expected and observed performance of the manufacturer's preimplantation eligibility worksheet in determining patients who would and would not be eligible for beacon insertion.

Methods and Materials

Patient population and eligibility criteria

Following approval by the *Epworth* Human Research Ethics Committee (EH2016-137), the medical records of 108 patients who were prospectively recruited to an active Phase 2 trial (PINPOINT; ANZCTR ID—ACTRN12615001183572) were reviewed. The aims of the PINPOINT trial are to explore the use of ^{68}Ga-prostate-specific membrane antigen positron emission tomography in staging patients with biochemically recurrent prostate cancer and to analyze treatment outcomes following electromagnetic transponder-guided (Calypso; Varian Medical Systems, Palo Alto, CA) salvage postprostatectomy radiotherapy. Patients who proceeded to postprostatectomy radiotherapy with a completed preimplantation worksheet (Fig. S1) and an empty rectum (rectal separation less than 4 cm) on their planning CT were included in this study.

Radiotherapy simulation

All patients who were recruited into PINPOINT were assessed for Calypso suitability using the preimplantation manufacturer worksheet following written informed consent. Patients were assessed in the supine position on the CT simulation tabletop (TT) either with or without a personalized vacuum cushion to immobilize the pelvis and lower extremities. The distance (cm) from the TT to the most anterior surface on maximum inhalation (*free breathing*) (length A), and the height of the leveled, palpated left and right greater trochanters (length B), were recorded and then used to calculate the worksheet score (A minus B). Following trial staging investigations, patients suitable for radiotherapy returned for CT simulation within a week of their beacon implantation or PET/CT scan (if ineligible for Calypso). Before CT simulation (free breathing) and during radiotherapy treatment, patients were instructed to have an empty bowel and