A clinical assessment of external beam focal therapy for localized prostate cancer measured by Gafchromic film.

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Abstract

Background: Traditionally, EBRT prostate treatments have been administered using three different techniques: three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), and volumetric modulated arc therapy (VMAT). These radiation therapy treatment techniques are often combined with additional options focusing on treating systemic disease and the entire volume of the prostate. A novel approach to EBRT is currently in development, a localized treatment administered to only the primary disease within the prostate volume termed 'Focal Therapy'.

Methods/Design: The proposed research study is aimed to simulate 10 random EBRT prostate focal therapy treatments replicated within two treatment planning software; Monaco treatment planning system and Eclipse treatment planning system. All ten plans will be contoured simulations of focal therapy imaging sets replicated from authentic mpMRI anatomical images of focal therapy eligible prostate cancer patients. Following the completion of the 10 clinical plans, QA plans will be generated and administered via each products current commercial linacs; the TrueBeam and the Versa. All QA plans will have their radiation doses measured with Gafchromic EBT3 radiochromic film and analyzed using the gamma analysis index (γ).

Discussion: To examine the uncertainties and limitations of an EBRT focal therapy prostate cancer treatment, it's imperative that a large study replicating many clinical cases under varying conditions should be conducted. This allows the ability for the clinician to investigate errors and uncertainties at each stage of the treatment process prior to committing to a clinical study. The experimental results can also be used as a reference for the creation of a standard guideline for the administration of focal therapy as a curative treatment for prostate cancer.

Background

With the exception of skin cancer, prostate cancer is the most commonly diagnosed cancer within the North American male. About 1 in 7 men will be diagnosed throughout their lifetimes and 1 in 39 men will die from this disease [1, 2]. Prostate cancer patients are organized into low, intermediate and high risk groups determined from clinical stage, PSA level, and Gleason score [3]. Currently, there are many different prostate cancer treatment options available. The benefits of radiation oncology consisting of external beam radiation therapy (EBRT) and brachytherapy, is to provide a highly conformal, minimally invasive, curative form of treatment. Traditionally, EBRT prostate cancer treatments

have been administered using three different techniques: three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), and volumetric modulated arc therapy (VMAT). The administration of an external beam radiotherapy treatment is often combined with an additional treatment option, with a goal to treat systemic disease delivered to the entire volume of the prostate. A novel approach to EBRT is currently in development, the localized treatment of only the primary region of disease within the entire volume of the prostate, termed 'Focal Therapy'. The capability to administer a focal therapy EBRT prostate cancer treatment has become possible due to two new scientific breakthroughs: the imaging capability of multiparametric magnetic resonance imaging (mpMRI) and the effectiveness of treating only the primary index lesion for a curative result.

The main limitation to administering a highly localized treatment to the prostate is the capability to precisely identify the areas of malignancy with high accuracy and precision. This is now possible by incorporating an MRI based imaging technique called multiparametric magnetic resonance imaging (mpMRI). MpMRI consists of complementing T1 and T2 weighted anatomic imaging with functional MR techniques including diffusion weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging [4, 5]. The imaging potential of mpMRI has undergone scrutinizing validation studies comparing mpMRI image sets directly with radical prostatectomy specimens that have been whole mounted in sections [6]. A study by Turkbey et al. concluded for a foci >0.5mL using 1.5T mpMRI that the sensitivity, specificity and positive, negative predictive values were 90%, 88%, 77% and 95%. For a foci >0.2mL the results reduced to 77%, 91%, 86% and 85% [7, 8]. For small tumors ≈ 0.2mL, the sensitivity of MRI decreased from 90 to 76%. The imaging capability to accurately delineate cancerous tissue is directly dependent on the volume of the malignant tissue. For small tumors mpMRI can only be used to exclude eligibility for focal therapy treatment [7, 8, 9].

A theoretical drawback to the proposition of prostate focal therapy is the fact that prostate cancer is largely a multifocal disease. In fact, estimates have largely determined that up to around 78% of all cases of prostate cancer are multifocal malignancies [10]. However, through various individual studies and with the assistance of whole-mounted specimens, it's been determined that it's the highest grade index lesion that drives the metastatic process of the prostate cancer [11]. For the low grade satellite lesions left behind, a study performed by Klass et al. reported of low risk prostate cancer over a sample of 1300 men in which of this group only 93 (7%) had died from their disease at a 15 year follow-up [12]. With curative treatment of the high grade index lesion, low grade satellite lesions are unlikely to metastasize or lead to death. Due to the small chance that a low grade lesion could potentially lead to mortality, post-treatment follow up in the form of PSA testing and further imaging is recommended.

As a result of these two discoveries, focal therapy and specifically external beam radiation focal therapy is now considered a possibility but, is still within early investigative stages. Currently, there are many questions to ask regarding the administration of such a highly conformal radiation therapy technique. Studies regarding the most effective method to deliver prostate cancer focal therapy are presently being investigated. For each delivery method, parameters and techniques are being explored to set the precedent for standard guidelines for future delivery. For example,

there are still questions as to what the best energy is for administering a focal therapy treatment. Experimental results are limited to only short-term outcomes [13-16]. Different interest committee groups have defined recommendations for patient eligibility to receive focal therapy as a treatment option for prostate cancer. Table 1 outlines a summary of recommendations authored by treatment related health care clinicians.

To advance the clinical directive for a standardized EBRT focal therapy prostate cancer treatment, a clinical replication with variations of different treatment parameters is proposed. A research study aimed to simulate 10 random EBRT focal therapy clinical treatments in two treatment planning software, Monaco treatment planning system and Eclipse treatment planning system is needed. All ten plans will be contoured replications of various focal therapy imaging sets provided by authentic mpMRI images of focal therapy eligible prostate cancer malignancies. The direction is to randomly select ten cases, all with variation in volume and location of localized disease. Due to a lack of EBRT focal therapy published documents, all plans will be created following established IMRT prostate treatment protocol with adjustments made to establish a more localized treatment. Following each treatment's design, all plans will be made into QA plans. The ten QA plans developed in Monaco treatment planning system will be administered on an Elekta Versa linac. The ten QA plans produced within Eclipse treatment planning system will be administered on a Varian TrueBeam linac. All QA plans will have their radiation doses measured with Gafchromic EBT3 radiochromic film and analyzed using the gamma analysis index (γ).

To provide clinical guidance on creating a standard EBRT focal therapy prostate treatment, it's important to produce investigatory replications in a clinical scenario in order to study delivered treatment metrics and discover problems in clinical administration. Through this compared product investigation, many important determinations can be made, including: recommended treatment margins, oar doses, requirements for conformal limits and a comparison between commercial vendor products.

Authorship	Life Expectancy	Stage	Gleason Score	Prostate Specific Antigen (PSA)
EAU [17]	> 10 years	T1-T2	GS ≤ 7	< 10 ng/mL
NCCN [18]	> 10 years	T1-T2, Nx-N0	NA	< 10 ng/mL
NICE [19]	≥ 10 years	T1-T2, Nx-N0	NA	< 10 ng/mL
Xavier et al. [20]	> 10 years	T1c-T2a	GS ≤ 7	< 15 ng/mL
Donaldson et al. [14]	> 10 years	NA	GS ≤ 7	NA

Table 1. Focal therapy eligibility guidelines.

Methods

a) Experimental Design

For the ten clinical plans, a standard prostate CT image series will be imported into Eclipse treatment planning software. Ten random mpMRI image sets of clinical prostate cancer eligible for focal therapy will have their primary index lesions contoured and replicated on a standard prostate CT image set. A focus will be placed on selecting ten clinical malignancies with varied region and size of clinical disease; this will be important for validating experimental results. All organs at risk will be contoured for comparison between the radiation dose administered to radiosensitive structures for each created treatment plan.

Prescription Dose (Gy)	Minimum PTV Dose ≥ 98% PTV.	Minimum CTV Dose ≥ 100% CTV.	Maximum PTV Dose ≤ 2% of PTV (No variation).	Maximum PTV Dose ≤ 2% of PTV (Minor variation).	Maximum PTV Dose ≤ 2% of PTV (Major variation).
79.2Gy: 1.8Gy in 44 fractions.	79.2 Gy	79.2 Gy	84.7 Gy	87.1 Gy	> 87.1 Gy

Table 2. Prostate cancer dose prescription [21].

b) Treatment Planning

The treatment plan design will consist of IMRT technique for all ten clinical prostate therapy plans. The dose administered will be 79.2 Gy prescribed to the PTV in 44 fractions at a dose rate of 1.8 Gy per fraction [21]. The external beam radiation therapy dose prescription goals are outlined in table 2 referenced from RTOG 0126.
Seven fields will be used to administer the radiation therapy treatment plan, each with an energy of 6 MV. The dose constraints for the organs at risk (OAR) are motivated by RTOG 0126 and QUANTEC [21, 22]. All radiation sensitive structures will receive doses respectively lower than the recommended dose constraints. A benefit to a highly conformal, focal therapy treatment is the localized delivery to the prostate but also, a much lower dose to OARs. The radiation dose administered to OARs will vary depending on the size and location of clinical disease. A 0.5cm margin will be expanded globally around the contoured CTV [21].

Within Eclipse treatment planning system, two separate plans will be generated in which one treatment plan will be calculated with the anisotropic analytics algorithm (AAA) and the other with the Acuros treatment algorithm. Within Monaco treatment planning system, the initial prostate CT images and structure sets will be transferred over from Eclipse. The same treatment plan will be replicated in Monaco treatment planning system but, the plans will be calculated using the (XVMC) X-ray Voxel Monte Carlo dose calculation, calculated with a 1% statistical

Organ Limit	No more than 15% V receives dose that exceeds.	No more than 25% V receives dose that exceeds.	No more than 35% V receives dose that exceeds.	No more than 50% V receives dose that exceeds.
Bladder Constraint	80 Gy	75 Gy	70 Gy	65 Gy
Rectum Constraint	75 Gy	70 Gy	65 Gy	60 Gy
Femoral Head	50 Gy	45 Gy	40 Gy	30 Gy
Penile Bulb	Mean dose ≤ 52.5 Gy			

Table 3. Prostate cancer radiosensitive organs [21].

uncertainty and a 1mm voxel size [23].

c) Radiation Dose Measurement

Following the completion of each focal therapy prostate plan, QA plans will be generated. Each QA plan will be calculated by the three variations of treatment planning algorithms being: AAA, Acuros and Monte Carlo. The QA plans generated will be administered on a large virtual cube like box with an electron density forced to 1. The Cube representing a QA phantom is to replicate a solid water setup with Gafchromic EBT3 radiochromic film placed at a 5cm depth. All QA plans will have the gantry and pedestal values forced to zero. The designated fields will be administered individually and from the AP gantry position. The calculated and measured fields are to be compared via the gamma analysis index (γ). The criteria used for the gamma will be 3%/3mm (percent dose difference and distance-to-agreement) and 2%/2mm. To exclude low dose regions within the measured profiles, a threshold of 10% of the maximum dose will be applied within the film analysis software. The dose will be calculated as absolute dose [24-26].

Discussion

The contemporary application of mpMRI and correlation between the primary index lesion and metastasis for prostate cancer have led to the conceived technique of administering a localized focal therapy prostate treatment for a curative result. Currently, there is a lack of investigatory studies looking into the implications of a prostate focal therapy treatment delivered by external beam radiation therapy. The design of this research experiment provides a clinical simulation of ten focal therapy prostate cancer treatments and replicates their mpMRI images into two different radiation oncology treatment planning software. The ten clinical examples are to be purposefully selected to exhibit varying size, shape, and quadrant of disease to allow the capability to pre-determine errors and uncertainties for clinical implementation. The choice to select two different treatment planning software and utilize three variations of dose calculation methods allows a direct comparison required for such a highly conformal treatment. To measure the radiation dose administered, Gafchromic EBT3 radiochromic film will be used for a 2D-plane dose distribution. Film is selected over a commercial array device due to a high spatial resolution and ability to measure steep dose gradients necessary when measuring a highly conformal modulated treatment [27]. Radiochromic film is excellent for measuring absorbed dose levels in a large variety of situations. It's ideal for the measurement of irregular fields as well as small field sizes down to a lower limit of approximately $1x1cm^2$ shaped by the multileaf collimators [28].

Lastly, the gamma analysis index (γ) is to be used to evaluate each of the treatment plan calculated fields with the fields measured by Gafchromic film. The gamma analysis index (γ) has it's own calculation sensitivities which includes regions of high dose gradients. It is important to investigate the percentage pass points over each of the treatment plans to evaluate comparable magnitudes of γ [24, 25].

To examine the uncertainties and limitations of an EBRT focal therapy prostate cancer treatment, it's imperative that a large study replicating many clinical cases under varying conditions is conducted. This allows the pre-determining of errors and uncertainties throughout the entire radiation treatment

process. The experimental results can be used as a reference for the implementation of standard guidelines for prostate cancer focal therapy.

References

1) Canadian Cancer Society. Prostate Cancer Statistics. Government of Canada. 2016 [cited 15 April 2017]. Available from: http://www.cancer.ca/en/cancer-information/cancer-type/prostate/statistics/?region=sk.
2) American Cancer Society. Statistics for Prostate Cancer. The American Cancer Society. 2017 [cited 15 April 2017]. Available from: https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html.
3) Washington CM, Leaver DT. Principles and practice of radiation therapy. Elsevier Health Sciences; 2015 Mar 10.
4) Barrett T. What is Multiparametric-MRI of the Prostate and Why Do We Need It?
5) Hoeks CM, Barentsz JO, Hambrock T, et al. Prostate cancer: multiparametric MR imaging for detection, localization, and staging. Radiology. 2011 Oct;261(1):46-66.
6) Yamamoto H, Nir D, Vyas L, et al. A workflow to improve the alignment of prostate imaging with whole-mount histopathology. Academic radiology. 2014 Aug 31;21(8):1009-19.
7) Muller BG, Fütterer JJ, Gupta RT, et al. The role of magnetic resonance imaging (MRI) in focal therapy for prostate cancer: recommendations from a consensus panel. BJU international. 2014 Feb 1;113(2):218-27.
8) Turkbey B, Mani H, Shah V, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. The Journal of urology. 2011 Nov 30;186(5):1818-24.
9) Turkbey B, Xu S, Kruecker J, et al. Documenting the location of systematic transrectal ultrasound-guided prostate biopsies: correlation with multi-parametric MRI. Cancer Imaging. 2011 Mar 29;11(1):31.
10) Karavitakis M, Winkler M, Abel P, et al. Histological characteristics of the index lesion in whole-mount radical prostatectomy specimens: implications for focal therapy. Prostate cancer and prostatic diseases. 2011 Mar 1;14(1):46-52.
11) Bass EJ, Ahmed HU. Focal therapy in prostate cancer: A review of seven common controversies. Cancer treatment reviews. 2016 Dec 31;51:27-34.
12) Klaff R, Rosell J, Varenhorst E, et al. The long-term disease-specific mortality of low-risk localized prostate cancer: a prospective population-based register study over two decades. Urology. 2016 May 31;91:77-82.
13) De la Rosette JJ, Ahmed H, Barentsz J, et al. Focal therapy in prostate cancer—report from a consensus panel. Journal of Endourology. 2010 May 1;24(5):775-80.
14) Donaldson IA, Alonzi R, Barratt D, et al. Focal therapy: patients, interventions, and outcomes—a report from a consensus meeting. European urology. 2015 Apr 30;67(4):771-7.
15) Muller BG, van den Bos W, Pinto PA, et al. Imaging Modalities in Focal Therapy: Patient Selection, Treatment Guidance and Follow-up. Current opinion in urology. 2014 May;24(3):218.
16) Linares EE, Barret E, Sivaraman A, et al. Localized prostate cancer Focal Therapy:" A la carte" Model. Archivos españoles de urología. 2016 Jul;69(6):345.

17) Mottet N, Bastian PJ, Bellmunt J, et al. Guidelines on Prostate Cancer. European Association of Urology, 2014. Available at: http://uroweb.org/ wp-content/uploads/1607-Prostate-Cancer_LRV3.pdf. Accessed March 2016.
18) Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate cancer, Version 3.2012: featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2012; 10: 1081-1087.
19) National Institute for Health and Care Excellence. Prostate Cancer: Diagnosis and Treatment. NICE clinical guideline 175, 2014.
20) Cathelineau X, Sanchez-Salas R. Focal Therapy for Prostate Cancer: Pending Questions. Current urology reports. 2016 Dec 1;17(12):86.
21) Michalski JM, Moughan J, Purdy JA, et al. Initial results of a phase III randomized study of high-dose 3DCRT/IMRT versus standard dose 3D-CRT/IMRT in patients treated for localized prostate cancer (RTOG 0126). Int J Radiat Oncol Biol Phys. 2014;90:1263.
22) Bentzen SM, Constine LS, Deasy JO, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys. 2010; 76(3):S3-9.
23) IMPAC Medical Systems Inc. Monaco Training Guide. Elekta Medical Systems. 2013;1.
24) Low DA, Harms WB, Mutic S, et al. A technique for the quantitative evaluation of dose distributions. Med Phys. 1998;25(5):656-661.
25) Low DA, Dempsey JF. Evaluation of the gamma dose distribution comparison method. Med Phys. 2003;30(9):2455-2464.
26) Ezzell GA, Burmeister JW, Dogan N, et al. IMRT commissioning: multiple institution planning and dosimetry comparisons, a report from AAPM Task Group 119. Med Phys. 2009;36(11):5359-73.
27) Schneider F, Polednik M, Wolff D, et al. Optimization of the Gafchromic™ EBT protocol for IMRT QA. Zeitschrift für Medizinische Physik. 2009 Dec 31;19(1):29-37.
28) Fuss M, Sturtewagen E, De Wagter C, et al. Dosimetric characterization of GafChromic EBT film and its implication on film dosimetry quality assurance. Physics in medicine and biology. 2007 Jun 18;52(14):4211.