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TITLE: A Phase II Randomized Study of the Use of Artificial Intelligence Generated Contours in Ultrasound-based Prostate HDR Brachytherapy

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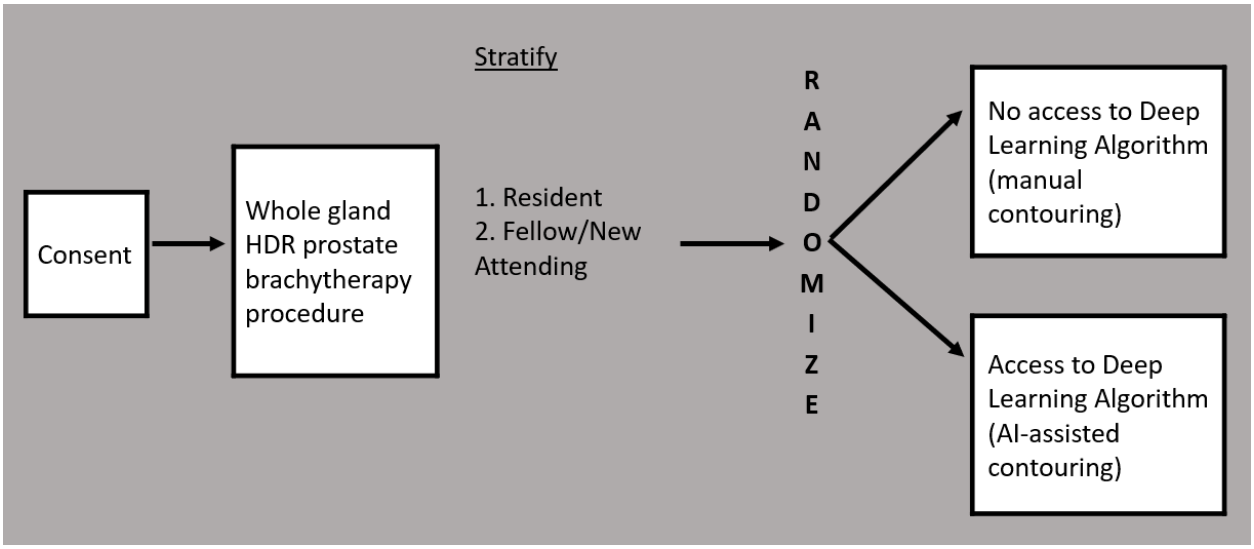

Consent
Whole gland HDR prostate brachytherapy procedure
Stratify
1. Resident
2. Fellow/New Attending
RANDOMIZE
No access to Deep Learning Algorithm (manual contouring)
Access to Deep Learning Algorithm (AI-assisted contouring)

1. INTRODUCTION

1.1 Study Disease

Prostate cancer is very common with about 1 in 8 men being diagnosed with prostate cancer during their lifetime [1]. There are different treatment options for localized prostate cancer including surgery, external beam radiotherapy (EBRT), brachytherapy and hormonal systemic treatment or multimodality approaches [2]. More recently, high dose rate (HDR) brachytherapy techniques have been developed in addition to the low dose rate (LDR) brachytherapy permanent radioactive seed implants for prostate cancer treatment. HDR brachytherapy has become a standard of care option as monotherapy or in combination with EBRT plus/minus androgen deprivation therapy as a boost [3 4]. HDR brachytherapy has also been increasingly used to treat recurrent prostate cancer with local failures in the prostate after radiotherapy [5 6].

1.2 Rationale

HDR brachytherapy in the treatment of prostate cancer is a procedure consisting of insertion of hollow needles into the prostate under transrectal ultrasound (TRUS) guidance with the patient in dorsal lithotomy position. An intraoperative radiation plan is created following acquisition of a planning image and delineation of the targets (prostate) and organs-at-risk (OARs including rectum, bladder, and urethra). The radiation plan is then delivered with an iridium-192 source using an afterloader machine. The needles are removed, and the patient is transferred to a recovery area followed by same day discharge.

A key component of radiotherapy planning, including HDR brachytherapy planning, is identifying the volumes that will be treated and OARs that will be spared to deliver a safe radiation treatment through contouring of structures. Contouring for HDR prostate brachytherapy can be done on TRUS, CT or MRI images [7 8]. TRUS is often preferred as it offers the convenience of the patient remaining in the same position throughout the entire procedure without a need to be moved for CT or MRI acquisition, which saves both time and resources. However, poor soft tissue contrast, prostate deformation and artifact on ultrasound can make prostate delineation on TRUS challenging especially with the needles in place for HDR treatment. The difficulty in contouring can be compounded for new learners developing brachytherapy expertise and working on obtaining proficiency in ultrasound-based prostate contouring.

With the advent of deep-learning artificial algorithms, auto-contouring has been continually integrated into routine clinical use in EBRT planning. Deep learning algorithms are being developed for brachytherapy planning and can be a useful tool for learning brachytherapy contouring during the implant procedure. The standard U-net algorithm being investigated in this study was assessed retrospectively in a pilot cohort of 150 patients (110 training, 20 validation and 20 testing sets) to estimate the geometric accuracy of the algorithm [9]. This was the first study to investigate auto-contouring with the needles in place in the prostate during HDR brachytherapy. The median Dice coefficient between AI and reference contours was 0.92 (IQR: 0.90 – 0.94). The current study aims to assess whether the same deep learning AI algorithm can improve the quality of prostate contours for new learners (resident or fellow/new attending)

performing prostate HDR brachytherapy.

2. OBJECTIVES

2.1 Study Design

This is a Phase II prospective study evaluating a deep learning AI algorithm for auto-contouring of the prostate during HDR prostate brachytherapy with the needles in place by new learners. The study will be conducted with a randomized design. Each patient will be assigned to a new learner and then randomized to manual versus AI-assisted contouring. The randomization will be stratified by new learner type: resident versus fellow/new attending. The hypothesis is that AI-assisted learner contours will have improved Dice coefficients with respect to clinically approved contours compared with manual learner contours. All brachytherapy contours will undergo review by the treating radiation oncologist who is the experienced clinician for clinical approval prior to patient treatment. The experienced clinician will be blinded to the randomization. Clinicians will not be registered in OnCore.

DF/HCC Office of Data Quality will perform randomization. If the new learner of a case is a resident, then the "resident" randomization tab will be used for the randomization. If the new learner of a case is a fellow/new attending, then the "fellow/new attending" tab should be used to determine which arm the case goes to.

2.2 Primary Objective

The primary objective of the study is to evaluate the Dice coefficient [0: no match, 1: complete match] between the final clinically approved brachytherapy prostate contours versus the manual and AI-assisted contours provided by the new learner.

2.3 Secondary Objectives

- To measure contouring time-to-complete needed to generate and edit manual vs AI-assisted contours for a new learner.
- To evaluate the subjective impressions of AI or manual contours by the new learner based on survey responses.
- To evaluate the subjective impressions of AI or manual contours by the experienced clinician based on survey responses.
- To calculate Dice coefficients of expert clinician contours between TRUS images with implanted needles and TRUS images after removal of bottom needle rows.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

1. 18 years of age and older
2. Deemed suitable candidates for whole gland HDR prostate brachytherapy under general anesthesia as a monotherapy, boost or salvage treatment.

3.2 Exclusion Criteria

1. Prior permanent seed LDR brachytherapy implant
2. Prior transurethral resection of the prostate (TURP)
3. Presence or insertion of a rectal spacer
4. Focal HDR brachytherapy treatment ie. not whole prostate

3.3 Inclusion of Women and Minorities

All patients with a prostate of all races and ethnic groups are eligible for this trial.

4. PRETREATMENT EVALUATIONS/MANAGEMENT

- Within 90 days prior to registration
  - Informed consent
  - Diagnosis and staging information
  - Oncologic history

5. REGISTRATION PROCEDURES

5.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

The eligibility checklist(s) and all pages of the consent form(s) will be emailed to ODQ at **ODQ@dfci.harvard.edu**. The ODQ will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant.

Randomization can only occur during ODQ business hours (8:30am - 5pm Eastern Time, Monday through Friday excluding holidays).

An email confirmation of the registration and/or randomization will be sent to the study coordinator(s) from the registering site, treating investigator and registering person immediately following the registration and/or randomization.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

5.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC Policy REGIST-101 must be followed.

5.3 General Guidelines for Other Investigative Sites

N/A

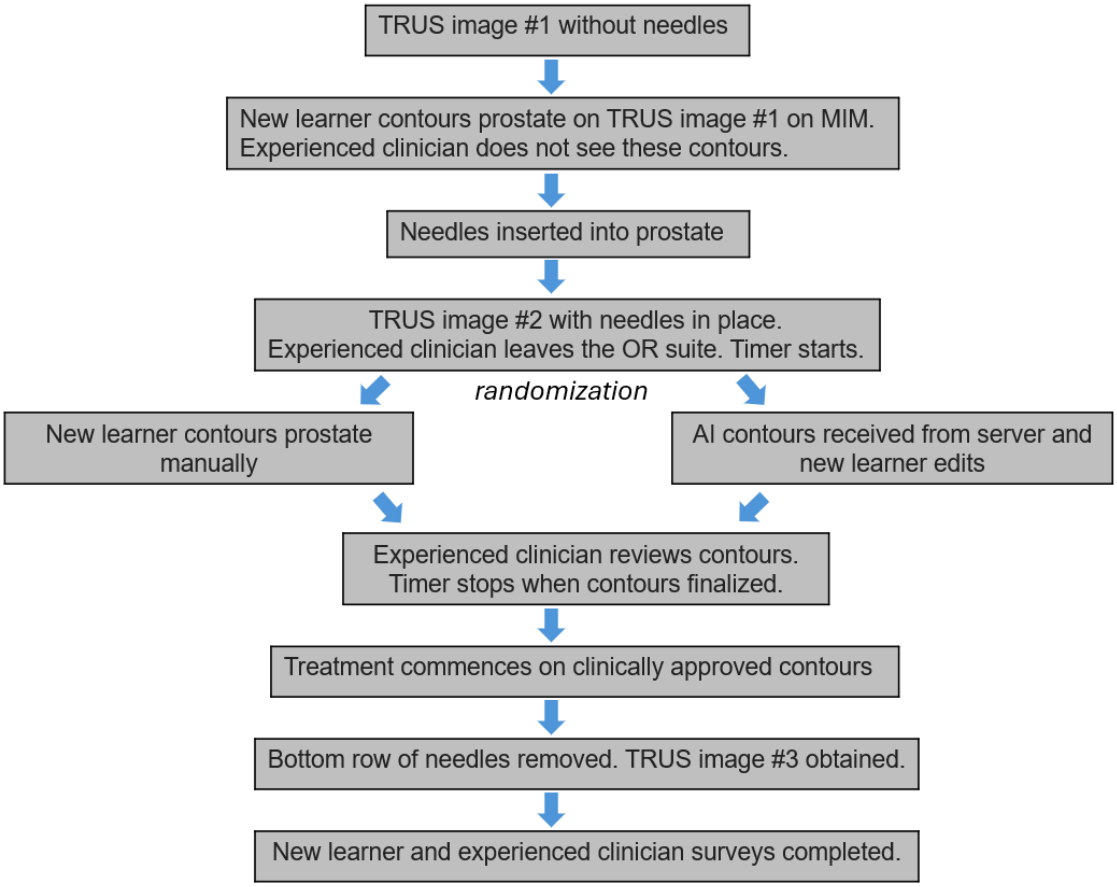
5.4 Registration Process for Other Investigative Sites

N/A

6. TREATMENT PLAN

6.1 Study contouring workflow

As mentioned above, the goal of this study is to evaluate whether artificial-intelligence can improve the quality of implanted prostate contours for new learners by comparing the dice coefficient of manual versus AI-assisted learner prostate contours to the final clinically approved prostate contours. The diagram below describes the workflow for the study.



6.2 New learner credentialing

All new learners will undergo a credentialing process prior to participation on the study. New learners must be a radiation oncology resident, fellow, or a new attending who has performed less than 20 ultrasound-based prostate HDR brachytherapy cases independently.

The credentialing procedure will take place over a 60 minute period under the direction of the principal investigator. First, the principal investigator will review a power-point presentation showing relevant anatomy of the prostate on ultrasound images with needles in-place. The principal investigator will then ask the new learner to provide contours of the prostate for 3 cases (case 1, case 2, and case 3). For each case, the principal investigator will then show the actual clinical contours utilized for treatment planning, and point out discrepancies between the new learner and clinical contours.

6.3 Dose/Fractionation

High dose rate brachytherapy will be delivered to the clinical target volumes with prescription doses at the experienced clinician discretion based on the clinical scenario. Participation in the trial does not alter the standard of care treatment.

6.4 Target and Organs-at-risk (OAR) Volumes

All contouring of prostate will be done on TRUS images which is the usual HDR brachytherapy workflow.

- Prostate_Learner_Image1 = prostate contour prior to needle insertion on TRUS images #1
- Prostate_Learner_Image2 = prostate contour generated by the new learner with or without AI assistance on TRUS images #2 with needles
- Prostate_Clinician_Image2 = prostate contour reviewed and edited by experienced clinician
- CTV = clinical target volumes contoured by experienced clinician (prostate +/- seminal vesicle target)
- Prostate_Clinician_Image3 = prostate contoured by experienced clinician on TRUS images #3 following HDR treatment delivery with the bottom half needle rows removed to better visualize the anterior border of the prostate

6.5 Contour Evaluation, Treatment Planning, and Treatment Delivery

The experienced clinician will review and edit all contours for final approval and clinical use for HDR prostate radiotherapy planning and treatment. Treatment planning will be done in the usual fashion by the brachytherapy medical physicist using Oncentra prostate treatment planning software. The experienced clinician will review and approve the HDR brachytherapy treatment plan per institutional metrics and constraints. The HDR brachytherapy plan will be delivered to the prostate using an iridium-192 afterloader per standard operating procedure.

6.6 Post-treatment TRUS

Following treatment plan delivery, the bottom half of the interstitial prostate needles will be removed. TRUS images #3 will be obtained with better visualization of the anterior border of the prostate. These TRUS images represent the “ground truth” in terms of the location and outline of the prostate.

The interstitial implant will then be completely removed, and the patient will be transferred to recovery area.

6.7 Radiation Adverse Events

It is not anticipated that auto-contouring of the prostate would increase the risk of side effects of prostate HDR brachytherapy. The procedure may take longer overall, such as to obtain the post-brachytherapy TRUS, increasing the length of general anesthesia. This is not expected to pose an increased risk to participants beyond the usual total procedure time variations which occur in the real-world setting.

7. PARTICIPANT ASSESSMENTS

Patients with prostate cancer will be assessed in clinic for suitability for HDR prostate brachytherapy as a monotherapy, boost or salvage treatment per investigator discretion. No additional assessments are required for participation in this study.

8. DATA COLLECTION

Study Evaluation	**Patient screening** Within 90 days prior to registration	**New learner prostate contouring training session**[1]	**HDR Brachytherapy**
REQUIRED PATIENT ASSESSMENTS			
Informed consent	X		
Diagnosis and staging information	X		
Oncologic history	X		
BRACHYTHERAPY			
New learner baseline contours		X	
Prostate_Learner_Image1			X
Prostate_Learner_Image2			X
Prostate_Clinician_Image2			X
Prostate_Clinician_Image3			X
Time to generate and edit contours			X
STUDY SURVEYS			
New learner baseline experience survey		X	
New learner contouring survey			X
Experienced clinician survey			X

[1]The training session will only be performed one time prior to the first case in which the new learner participates.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

The primary objective of this study is to evaluate whether AI-assisted contours perform better than manual contours as measured by the Dice coefficient between the final contours used for treatment delivery versus the contours, either manual or AI-assisted, provided by the new learners. Patients will be accrued in one stage. Each patient will be assigned to a new learner and then randomized to manual versus AI-assisted contouring. The randomization will be stratified by new learner type: resident versus fellow/new attending.

The experienced clinician will be blinded to the randomization of the contouring method by the

new learner. The prostate contour generated by the new learner will then undergo review by the experienced clinician. The dice coefficient between the new learner prostate contour and the experienced clinician contour will be calculated. The experienced clinician will approve the prostate brachytherapy contours to be used clinically for HDR prostate radiotherapy planning and treatment.

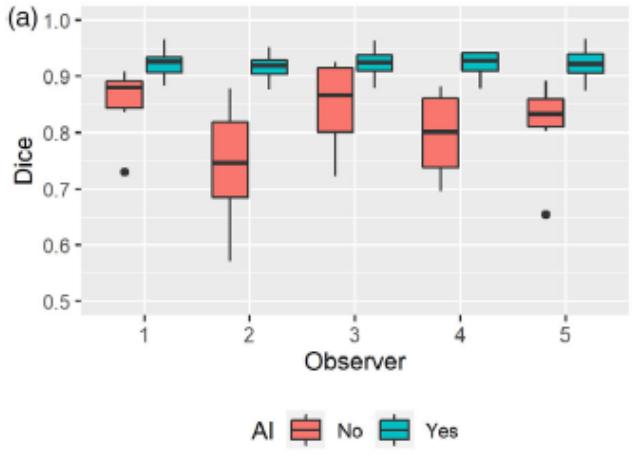
9.2 Primary Objective

The primary objective of this study is to evaluate whether the addition of artificial intelligence can improve the quality of implanted prostate contours as measured by the Dice coefficient between the final contours used for treatment delivery versus the contours, either manual or AI-assisted, provided by the new learners. The Dice coefficient ranges between 0 and 1, where 0 indicates no match, and 1indicates complete match.

9.3 Sample Size, Accrual Rate and Study Duration

The sample size of this study will be 36 patients.

Based on data from previous published work with the AI algorithm for HDR brachytherapy prostate contouring with the needles in place, we can assume a mean Dice coefficient of 0.87 for manual new learner contours (without AI) and a mean Dice coefficient of 0.92 for AI-assisted new learner contours [9]. Using a standard deviation of 0.05, a one-sided alpha of 0.1, and a power of 0.9, a total of 27 patients will be needed for this study using a t-test. As each new learner will generate prostate contours for multiple patients in this study, the correlations among patients contoured by the same new learner need to be taken into account. Assuming an intra-cluster correlation of 0.15 and an average of 3 patients to be contoured by the same new learner in a given arm, the sample size will be inflated by 30% (36 analyzable patients) in order to maintain sufficient power. The maximum number of cases that a new learner can contour would be 10.



There are approximately 75 prostate brachytherapy patients that undergo HDR treatment of the whole gland in the Department of Radiation Oncology at Brigham and Women's Hospital. If about half agree to participate, we expect the study to take about 12 months to accrue.

This study does not include follow-up after HDR brachytherapy treatment delivery and termination of accrual.

Accrual Targets								
Ethnic Category	**Sex/Gender**							
	Females			**Males**			**Total**	
Hispanic or Latino	0		+	3		=	3	
Not Hispanic or Latino	0		+	33		=	33	
Ethnic Category: Total of all subjects	0	(A1)	+	36	(B1)	=	36	(C1)
Racial Category								
American Indian or Alaskan Native	0		+	0		=	0	
Asian	0		+	3		=	3	
Black or African American	0		+	3		=	3	
Native Hawaiian or other Pacific Islander	0		+	0		=	0	
White	0		+	30		=	30	
Racial Category: Total of all subjects	0	(A2)	+	36	(B2)	=	36	(C2)
	(A1 = A2)			(B1 = B2)			(C1 = C2)	

Note that this study is limited to patients with a prostate. There may be some patients who identify as female and were assigned male at birth with a prostate eligible for this study not explicitly stated in the accrual targets.

9.4 Stratification Factors

We will introduce a stratification factor by training category of new learner: 1. resident versus 2. fellow/new attending.

9.5 Interim Monitoring Plan

This is not a therapeutic trial and the standard U-net algorithm generating a prostate auto-contour during HDR prostate brachytherapy will be used by the new learner. All brachytherapy contours will undergo review by the experienced clinician for clinical approval prior to patient treatment in the usual fashion of an academic teaching center. As such, there will not be planned interim safety monitoring.

9.6 Analysis of Primary Endpoints

The participant cohort are patients undergoing whole gland prostate HDR brachytherapy for monotherapy, boost or salvage radiation at the Brigham and Women's Hospital/Dana-Farber Cancer Institute Department of Radiation Oncology.

The primary endpoint of the study is the Dice coefficient [0: no match, 1: complete match]

between the final clinically approved prostate contours versus the manual or AI-assisted contours provided by the new learner. The primary objective is to evaluate whether the addition of artificial intelligence can improve the quality of implanted prostate contours as measured by Dice coefficient. As multiple patients will be contoured by the same new learner on this study, the Dice coefficient will be compared between the two groups using a mixed-effect model with new learner as a random effect to account for the potential variability of contouring among the new learners.

9.7 Analysis of Secondary Endpoints

- Descriptive statistics will be used to characterize measurement of contouring time-to-complete needed to generate and edit manual vs AI-assisted contours for a new learner. The contouring time will be compared between the two groups using the t-test.
- Likert scale data from the new learner and experienced clinician surveys will be reported using mean and standard deviation and compared between the two arms using a t-test [10].
- The percentage of correct predictions by the experienced clinician of whether the prostate was contoured with or without AI-assistance will be reported along with 90% exact binomial confidence interval.
- The prostate contour quality score of the new learner's prostate contour presented to the experienced clinician during radiotherapy plan development with and without AI-assistance, described using descriptive statistics and compared using the chi-squared test.

9.8 Reporting and Exclusions

9.8.1 Evaluation of Toxicity

N/A- this is not a radiotherapy treatment trial and no additional toxicity from the inclusion of AI algorithm during prostate contouring by the new learner is expected. The HDR prostate radiotherapy delivered will be as per standard of care.

9.8.2 Evaluation of the Primary Efficacy Endpoint

All patients will be analyzed for all primary and secondary endpoints listed above based on the intent-to-treat principle.

10. REGULATORY CONSIDERATIONS

10.1 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The Board is chaired by a medical oncologist from outside of DF/HCC and its membership composed of internal and external institutional representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Sponsor-Investigator, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or

not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; all adverse events and serious adverse events reported across all sites by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

11. PUBLICATION PLAN

The results of this study are anticipated to be published in a peer-review journal and made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported. The initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three (3) years after the end of the study.

REFERENCES

[1] American Cancer Society (2025). *Key Statistics for Prostate Cancer*. Retrieved https://www.cancer.org/cancer/types/prostate-cancer/about/key-statistics.html

[2] National Comprehensive Cancer Network. (2025). *Prostate cancer (version 1.2025)*. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

[3] Morton, G., McGuffin, M., Chung, H. T., Tseng, C.-L., Helou, J., Ravi, A., Cheung, P., Szumacher, E., Liu, S., Chu, W., Zhang, L., Mamedov, A., & Loblaw, A. (2020). Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Efficacy results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. *Radiotherapy and Oncology*, *146*, 90–96. https://doi.org/10.1016/j.radonc.2020.02.009

[4] Crook, J., Marbán, M., & Batchelar, D. (2020). HDR Prostate Brachytherapy. *Seminars in Radiation Oncology*, *30*(1), 49–60. https://doi.org/10.1016/j.semradonc.2019.08.003

[5] Chen, C. P., Weinberg, V., Shinohara, K., Roach, M., Nash, M., Gottschalk, A., Chang, A. J., & Hsu, I.-C. (2013). Salvage HDR Brachytherapy for Recurrent Prostate Cancer After Previous Definitive Radiation Therapy: 5-Year Outcomes. *International Journal of Radiation Oncology*Biology*Physics*, *86*(2), 324–329. https://doi.org/10.1016/j.ijrobp.2013.01.027

[6] Valle, L. F., Lehrer, E. J., Markovic, D., Elashoff, D., Levin-Epstein, R., Karnes, R. J., Reiter, R. E., Rettig, M., Calais, J., Nickols, N. G., Dess, R. T., Spratt, D. E., Steinberg, M. L., Nguyen, P. L., Davis, B. J., Zaorsky, N. G., & Kishan, A. U. (2021). A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). *European Urology*, *80*(3), 280–292. https://doi.org/10.1016/j.eururo.2020.11.010

[7] Lavoie-Gagnon, H., Martin, A.-G., Poulin, E., Archambault, L., Pilote, L., Foster, W., Vigneault, E., Carignan, D., & Lacroix, F. (2022). Advantages of TRUS-based delineation for high-dose-rate prostate brachytherapy planning. *Journal of Contemporary Brachytherapy*, *14*(1), 1–6. https://doi.org/10.5114/jcb.2022.113544

[8] Podgorsak, A. R., Venkatesulu, B. P., Abuhamad, M., Harkenrider, M. M., Solanki, A. A., Roeske, J. C., & Kang, H. (2023). Dosimetric and workflow impact of synthetic-MRI use in prostate high-dose-rate brachytherapy. *Brachytherapy*, *22*(5), 686–696. https://doi.org/10.1016/j.brachy.2023.05.005

[9] King, M. T., Kehayias, C. E., Chaunzwa, T., Rosen, D. B., Mahal, A. R., Wallburn, T. D., Milligan, M. G., Dyer, M. A., Nguyen, P. L., Orio, P. F., Harris, T. C., Buzurovic, I., & Guthier, C. V. (2023). Observer preference of artificial intelligence-generated versus clinical prostate contours for ultrasound-based high dose rate brachytherapy. *Medical Physics*, *50*(10), 5935–5943. https://doi.org/10.1002/mp.16716

[10] Sullivan, G. M., & Artino, A. R. (2013). Analyzing and Interpreting Data From Likert-Type

Scales. *Journal of Graduate Medical Education*, *5*(4), 541–542. https://doi.org/10.4300/JGME-5-4-18