Clinical impact of contouring variability for prostate cancer tumor boost

Zhong, A.Y.; Lui, A.J.; Kuznetsova, S.; Kallis, K.; Conlin, C.; , D.D. do; ... ; Seibert, T.M.

INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
www.redjournal.org

CLINICAL INVESTIGATION

Clinical Impact of Contouring Variability for Prostate Cancer Tumor Boost

Allison Y. Zhong, MD,* Asona J. Lui, MD, PhD,* Svetlana Kuznetsova, PhD,* Karoline Kallis, PhD,* Christopher Conlin, PhD,† Deondre D. Do, MS,‡ Mariluz Rojo Domingo, MS,‡ Ryan Manger, PhD,* Patricia Hua, CMD,* Roshan Karunamuni, PhD,* Joshua Kuperman, PhD,† Anders M. Dale, PhD,†,§,‖ Rebecca Rakow-Penner, MD, PhD,†,‡ Michael E. Hahn, MD, PhD,† Uulke A. van der Heide, PhD,¶ Xenia Ray, PhD,* and Tyler M. Seibert, MD, PhD*,†,‡

*Department of Radiation Medicine and Applied Sciences, UC San Diego School of Medicine, La Jolla, California; †Department of Radiology, UC San Diego School of Medicine, La Jolla, California; §Department of Neurosciences, UC San Diego School of Medicine, La Jolla, California; ‖Halıcıoğlu Data Science Institute, UC San Diego School of Medicine, La Jolla, California; ‡Department of Bioengineering, UC San Diego Jacobs School of Engineering, La Jolla, California; and ¶Department of Radiation Oncology, The Netherlands Cancer Institute (NKI-AVL), Amsterdam, The Netherlands

Received Jan 31, 2024; Accepted for publication Jun 14, 2024

Purpose: The focal radiation therapy (RT) boost technique was shown in a phase III randomized controlled trial (RCT) to improve prostate cancer outcomes without increasing toxicity. This technique relies on the accurate delineation of prostate tumors on MRI. A recent prospective study evaluated radiation oncologists' accuracy when asked to delineate prostate tumors on MRI and demonstrated high variability in tumor contours. We sought to evaluate the impact of contour variability and inaccuracy on predicted clinical outcomes. We hypothesized that radiation oncologists' contour inaccuracies would yield meaningfully worse clinical outcomes.

Methods and Materials: Forty-five radiation oncologists and 2 expert radiologists contoured prostate tumors on 30 patient cases. Of these cases, those with CT simulation or diagnostic CT available were selected for analysis. A knowledge-based planning model was developed to generate focal RT boost plans for each contour per the RCT protocol. The probability of biochemical failure (BF) was determined using a model from the RCT. The primary metric evaluated was delta BF (DBF = Participant BF − Expert BF). An absolute increase in BF ≥5% was considered clinically meaningful.

Corresponding author: Tyler M. Seibert, MD, PhD; E-mail: tseibert@ucsd.edu

Disclosures: AJ.L. reports consulting for MIM Software. A.M.D. is a Founder of and holds equity in CorTechs Labs, Inc, and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc, and receives funding through research agreements with GE Healthcare. R.R.P. has an equity interest in CorTech Labs and Curemetrix, serves on the Scientific Advisory Board of Imagine Scientific, and receives research funding from GE Healthcare. M.E.H. reports honoraria from Multimodal Imaging Services Corporation and research funding from GE Healthcare. U.A.vd.H. reports research funding from the Dutch Cancer Society and travel support from Elekta AB. X.R. reports consulting for KM Pharmaceutical Consulting LLC, receives research funding from Varian Medical Systems and Siemens Healthineers, and serves as vice chair of AAPM TG-395. T.M.S. reports honoraria from Varian Medical Systems, WebMD, GE Healthcare, and Janssen; he has an equity interest in CorTechs Labs, Inc, and serves on its Scientific Advisory Board; he receives research funding from GE Healthcare through the University of California San Diego. These companies might potentially benefit from the research results. The terms of this arrangement have been reviewed and approved by the University of California San Diego in accordance with its conflict-of-interest policies. This work was supported, in part, by the National Institutes of Health (NIH/NIBIB K08 EB026503, NIH/NCI U54CA132384, U54CA132379, UL1TR001442), the American Society for Radiation Oncology (ASTRO), the Prostate Cancer Foundation, the Radiological Society of North America (RSNA), the American College of Radiation Oncology (ACRO), the Grillo-Marxuach Family Fellowship at the Moores Cancer Center of UC San Diego, and the US Department of Defense (CDMRP PC220278).

Author Responsible for Statistical Analyses: Tyler M. Seibert, MD, PhD; Email: tseibert@ucsd.edu

Data Sharing Statement: De-identified data are available to bona fide researchers for noncommercial use on request.

Acknowledgments—We are grateful to the radiation oncologists who participated in our original study as well as our physics team for developing and validating the knowledge-based planning model implemented in our current study.

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijrobp.2024.06.007.

Int J Radiation Oncol Biol Phys, Vol. 120, No. 4, pp. 1024−1031, 2024
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2024.06.007

Results: Eight patient cases and 394 target volumes for focal RT boost planning were included in this analysis. In general, participant plans were associated with worse predicted clinical outcomes compared to the expert plan, with an average absolute increase in BF of 4.3%. Of participant plans, 37% were noted to have an absolute increase in BF of 5% or more.
Conclusions: Radiation oncologists' attempts to contour tumor targets for focal RT boost are frequently inaccurate enough to yield meaningfully inferior clinical outcomes for patients.

Introduction

In a phase III randomized controlled trial (RCT), adding a focal radiation therapy (RT) boost to prostate tumors visible on multiparametric MRI (mpMRI) improved disease-free and regional/distant metastasis-free survival for patients with intermediate- and high-risk prostate cancer, without increasing toxicity.[1,2] This trial demonstrated that the probability a patient would experience biochemical failure (BF) (cancer recurrence) was predicted by the RT dose delivered to the visible tumor. Higher tumor doses yielded better treatment outcomes, and lower tumor doses yielded more treatment failures.

The focal RT boost technique relies on the accurate delineation of prostate tumors on MRI. The recent prospective ReIGNITE study evaluated radiation oncologists' accuracy when asked to delineate prostate tumors on MRI.[3] High variability was observed in tumor contours. When using conventional MRI alone, participants completely missed the tumor (0 overlap with the true target) in a median of 13.6% of attempts (IQR, 9.1%-23.6%). The accuracy and reliability of tumor contours improved considerably when participants were given advanced diffusion MRI maps (called the restriction spectrum imaging restriction score, or RSIrs) that improved prostate cancer conspicuity. Complete misses, for example, were much more uncommon when using RSIrs (median 0.0%; IQR, 0.0%-4.3%). Nonetheless, contours still varied considerably among radiation oncologists. Given smooth radiation dose plans and RT penumbra, it is unclear how near misses and partial overlap will affect patient outcomes.

Here, we evaluate the impact of contour variability and inaccuracy on predicted clinical outcomes. We measured the RT dose delivered to the true tumor if a participant's contours were used to generate the focal RT boost plan instead of using the guidance of an expert radiologist, as was done in the aforementioned RCT. Using the model from this RCT,[2] we then calculated the probability of BF for each RT plan. We hypothesized that radiation oncologists' contour inaccuracies would yield meaningfully worse clinical outcomes.

Methods and Materials

Initial prospective ReIGNITE study

Forty-five radiation oncologists with a range of experience in treating prostate cancer were enrolled as participants (Table E1). All study recruitment materials, communications, and procedures were approved by the institutional review board. Participants were asked to contour tumors on 20 patient cases of clinically localized intermediate- or high-risk prostate cancer in each of 2 sessions at least 1 month apart. Specifically, they were instructed to target MRI-visible lesion (s) for RT boost. They were told to disregard any concerns about the impact of their volumes on meeting organ-at-risk (OAR) constraints. Additionally, they were informed that they were welcome to use outside resources to guide target delineation, although it was not necessary nor expected to do so. In each case, participants were provided either conventional MRI alone or conventional MRI with RSIrs overlay. Ten cases were repeated between the 2 sessions, with RSIrs either added or removed; the participants were not made aware of this. Provided MRI sequences included T_2-weighted, ADC, and DWI (b = 0 and b = 2000 s/mm^2). In addition, participants were given clinical information regarding each case, including the patient's age, prostate specific antigen level at the time of MRI, number of positive biopsy cores, location of positive biopsy cores, and radiologic description of the tumor. Contouring was performed on the MIM Zero Footprint^{TM} (ZFP) platform (MIM Software).

Expert-defined lesions were created by the consensus of a radiation oncologist (with 3 years of experience) and 2 board-certified, subspecialist genitourinary radiologists (with 5 years and 7 years of experience, respectively). This was done for all patient cases on conventional MRI alone (ie, the full mpMRI data set, including dynamic contrast enhancement), because the clinical standard per the RCT is to target the tumor visible on MRI.

MRI patient cases for the ReIGNITE study were selected from among patients with biopsy-confirmed intermediate- or high-risk cancer who had mpMRI with RSI prior to biopsy. The biopsy-confirmed tumor had to correspond to the lesion visible on mpMRI, defined as a PI-RADS $\geq$3 lesion identified on mpMRI by the interpreting radiologist per clinical routine. The lesions were then confirmed and contoured in consensus by 2 expert radiologists for the ReIGNITE study. Patients who had undergone any treatment for prostate cancer prior to the MRI or biopsy were excluded, as were those with locally advanced disease (eg, large, macroscopic extraprostatic extension). Patients had to be eligible for RT, but selection of cases preceded knowledge of treatment decisions. For the present study, we included all patient cases for which either a CT simulation or a diagnostic CT was available unless there was a severe artifact on CT (eg, from hip implants) that would interfere with the precision of RT planning.

OAR and target volume definitions

Where a CT simulation was available, OARs had been contoured per clinical routine. For those with only a diagnostic CT, OARs were contoured manually. T_2-weighted MRI for each case was rigidly coregistered to the CT to optimize registration specifically of the prostate, and the corresponding transformation was applied to the expert-defined tumor target, as well as to each participant's target contour.

Knowledge-based RT planning

To ensure RT planning was unbiased, we developed a knowledge-based planning (KBP) automated algorithm to generate RT plans with focal tumor boost per the RCT protocol: 77 Gy in 35 fractions to the whole prostate and an integrated boost up to 95 Gy to the focal target, provided no normal tissue constraints were violated. To facilitate the development of the KBP algorithm, we used Varian RapidPlan (Varian Medical Systems), a vendor-based solution for KBP[4] that is widely used in the field.[5-10] A total of 62 clinical plans with contoured targets (prostate and boosted lesion) and OARs (bladder, rectum, bowel, sigmoid, urethra, penile bulb, right femur, and left femur) were added to the training set for the model. RapidPlan then uses geometric features extracted among the set of targets and OARs and the OAR dose-volume histograms (DVH) to build models that can predict the achievable OAR DVHs for a new patient. Additionally, the set of OAR DVH models is linked to a template of weighted optimization metrics that use the patient-specific predicted dose values to optimize and calculate dose for new plans. This allows for fully automated, high-quality planning. The plan optimization metrics for our model (Table E2) reflect those used in the RCT as well as an additional urethra constraint proposed in a subsequent normal tissue complication probability analysis of participants.[11]

We tested the KBP model on 10 unrelated patient cases from our institution that were treated with focal RT boost. A dosimetrist manually generated optimal plans using the RCT protocol for each of the 10 cases, using the focal tumor target actually treated for that patient. KBP plans were generated for the 10 cases, and the resulting dose metrics and 3D dose distributions were compared to the clinical plan used for those patients to validate the model (Table E3). To further validate the KBP model, we confirmed that it gave expected results for focal RT plans using the expert contours (Table 1). We then applied the algorithm to each participant's tumor contour and compared dosimetric parameters to those achieved when using the expert-defined tumor.

RT plan evaluation and statistical tests

For each plan, we calculated the dose covering 98% of the expert-defined tumor (D98), which was associated with the probability of BF at 7 years in a model from the RCT (Fig. E1).[1] The primary metric we evaluated was delta BF probability (ΔBF), which was calculated as (Participant BF − Expert BF). A contour that led to a ≥5% increase in BF was considered clinically meaningful. The percentage of participants whose contours yielded a clinically meaningful BF increase was also calculated for each case. Secondary metrics included D98, BF, delta D98 (ΔD98 = Participant D98 − Expert D98), and the OAR dose metrics.

Case-wise *t* tests were performed for ΔBF and ΔD98 for all patient cases. For cases that were contoured both with and without RSIrs, paired *t* tests were performed to compare ΔBF and ΔD98 with and without RSIrs.

Effect of radiation oncologist experience

Among radiation oncologist participants in the ReIGNITE study, 57% were still in residency training. To assess the impact of oncologist experience level on contour accuracy, we performed subset analyses comparing outcomes of plans generated using targets from trainee and attending physician participants, respectively. Outcome measures were percentage overlap with expert contour, BF, ΔBF, and ΔD98. We compared the subsets with summary statistics (mean and SD), violin plots, and *t* tests. We then assessed the overall effect of experience (trainee vs nontrainee) on ΔBF using linear mixed-effects models with patient case and physician participant as random effects (to account for repeated measures in these categories).

Table 1 Results of knowledge-based planning (KBP) model on validation plans. The generated validation plans were based on expert contours. Clinical plans were generated by an experienced dosimetrist using clinical target and organ-at-risk volumes. All plans were normalized to meet the prostate V100% metric, leading to no difference between clinical and KBP plans. Other parameters were allowed to vary

Parameter	Dose constraint	Clinical mean ± SD	KBP mean ± SD	Difference (KBP − clinical)
Prostate V100%	V100% ≥ 94%-95%	95% ± 0%	95% ± 0%	0%
Rectum D_{1cc}	D_{1cc} ≤ 103%-105%	100.46% ± 1.10%	100.85% ± 0.99%	−0.39% ± 1.74%
Bladder D_{1cc}	D_{1cc} ≤ 105%	101.56% ± 0.34%	102.44% ± 0.35%	−0.88% ± 0.66%
Urethra $D_{0.1cc}$	$D_{0.1cc}$ ≤ 105%-107%	101.88% ± 0.51%	102.33% ± 0.34%	−0.50% ± 0.80%
Lesion expert D98	D98 > 120% Rx	113.90% ± 1.52% Rx	114.78% ± 7.57% Rx	−0.88% ± 6.10% Rx

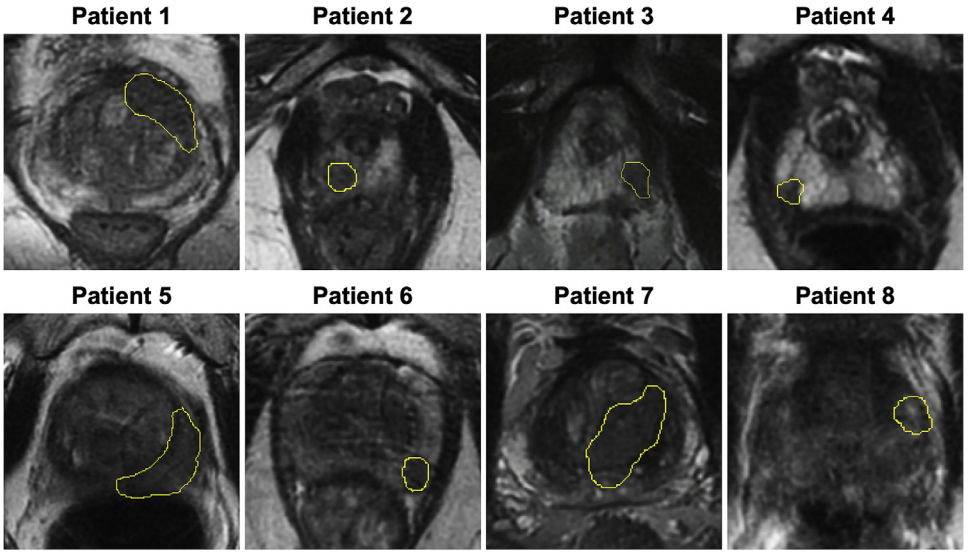

Fig. 1. T_2-weighted MRIs of 8 patient cases included in this study, with expert-defined lesions shown in yellow.

Results

Nine patient cases from the ReIGNITE study had available pelvic CT scans, but 1 had severe metal artifacts from a hip implant; hence, 8 cases were included in analyses (Fig. 1, Table 2). The rest underwent treatment at outside institutions, were lost to follow-up, or underwent radical prostatectomy without a CT scan. Two cases had CT simulation available; the time between MRI and simulation was 103 days and 155 days, respectively. The 6 remaining cases had diagnostic CT only; the time between MRI and diagnostic CT was a median of 175 days (IQR, 54-502 days). No androgen deprivation therapy was administered between MRI and CT scans. Three cases were contoured by ReIGNITE study participants on conventional MRI only; 2 cases were contoured on conventional MRI + RSIrs only; and 3 cases were contoured on both with and without RSIrs. In total, 394 participant target volumes and 8 expert target volumes were used to generate RT plans. All plans had adequate coverage of the prostate and met all key normal tissue constraints.

Table 2 Characteristics of 8 patient cases included in this study

Median age, y (IQR)		**70 (67-78)**
Median prostate specific antigen (PSA) level at time of MRI, ng/mL (IQR)		8.7 (7.7-18.8)
Clinical stage	T1c	6
	T2a	1
	T2c	1
PI-RADS v2.1 score per lesion	3	2
	4	3
	5	3
Biopsy status	Systematic	3
	Systematic and targeted	5
Worst Gleason score per lesion	3 + 4	4
	4 + 3	2
	4 + 4	1
	4 + 5	1
Underwent prostatectomy		2
Pathologic stage	T2a	1
	T3b	1

In general, using radiation oncologist participants' target volumes yielded worse BF and D98 values compared to the expert target volume (Fig. 2). Across all participants' plans, BF increased by an average of 4.3%. A clinically meaningful absolute increase in BF of ≥5% was seen in 37% of the participant plans.

Case-wise *t* tests comparing participant plans to expert plans demonstrated a statistically significant difference for ΔBF and ΔD98 in 6 of 8 patient cases ($P < .01$) (Table 3). Among the 3 cases that had contours with and without RSI (patients 6-8), paired *t* tests showed a statistically significant improvement in both ΔBF and ΔD98 with RSIrs for patients 7 and 8.

Study participants included 23 still in training at the time of participation (trainees) and 22 in independent clinical practice (nontrainees). Of the 394 total participant volumes, 200 were contoured by trainees and 194 by nontrainees. On average, trainees' contours covered more of the expert contour than nontrainees (mean 51%, SD 12% for trainees vs mean 46%, SD 13% for nontrainees, $P << .01$). There was no significant difference in BF or ΔBF between trainee and nontrainee plans (Table E4, Fig. E2). The linear mixed-effects model of ΔBF also showed no difference for trainees versus trainees (BF was 0.019% higher for nontrainees, 95% CI, 1.05-1.09%; $P = .97$). Given the surprising observation

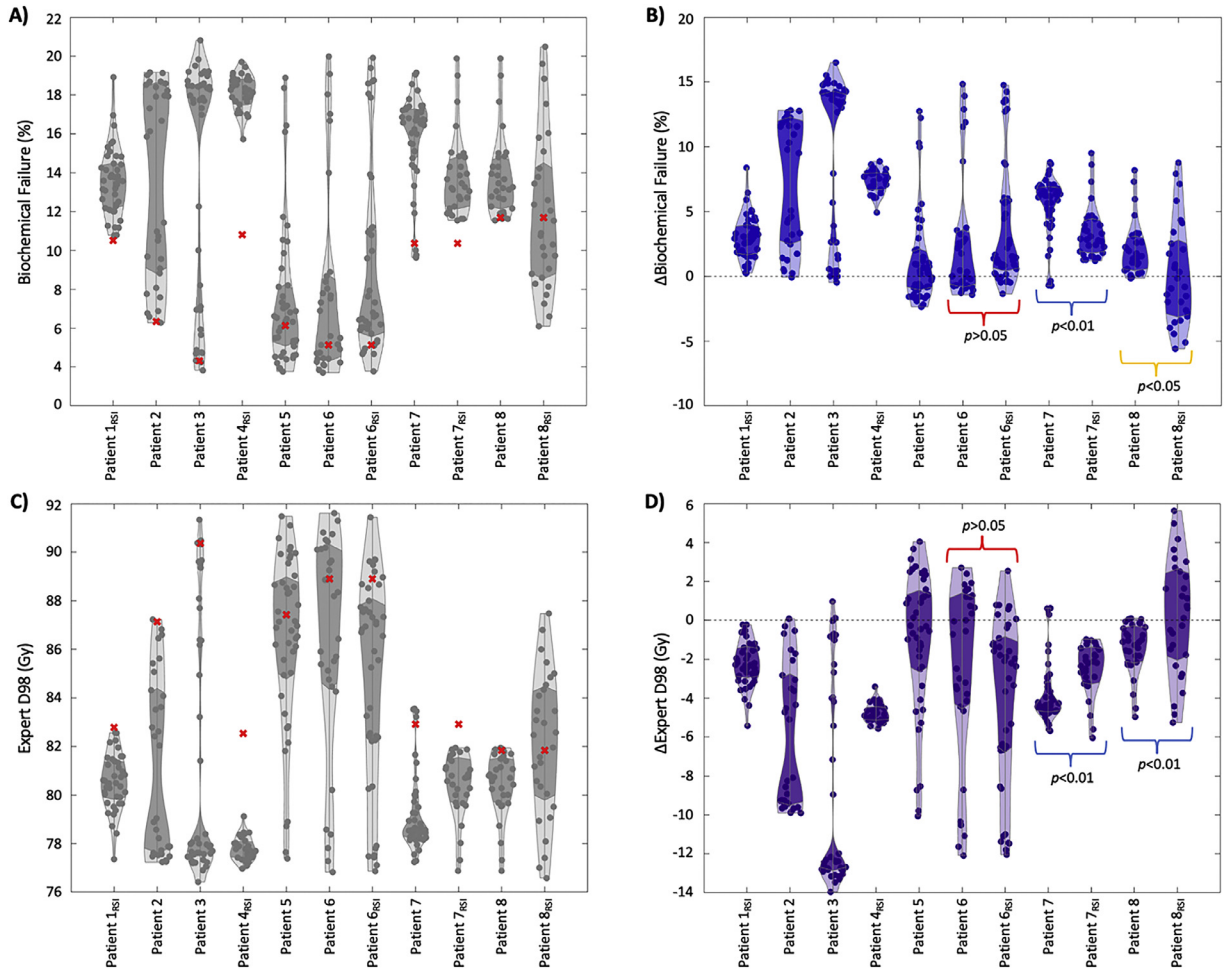

Fig. 2. Violin plots for 8 patient cases for (A) biochemical failure (BF), (B) ΔBF = Participant BF − Expert BF, (C) D98 of expert-defined tumor, and D) ΔD98 = Participant D98 − Expert D98. Predicted outcomes for the plans based on the expert contours are shown in red. *Abbreviations:* RSI = restriction spectrum imaging.

Table 3 Case-wise *t* tests of ΔD98 = Participant D98 − Expert D98 and ΔBF = Participant BF − Expert BF

Patient	Mean ± SD (ΔD98)	*P* value	Mean ± SD (ΔBF)	*P* value
Patient 1_{RSI}	−2.22 ± 1.14 Gy	<< .01*	3.05 ± 1.72%	<<.01*
Patient 2	−6.04 ± 3.64 Gy	<< .01*	7.12 ± 4.92%	<<.01*
Patient 3	−8.90 ± 5.33 Gy	<< .01*	9.51 ± 6.27%	<<.01*
Patient 4_{RSI}	−4.75 ± 0.48 Gy	< .01*	7.31 ± 0.90%	<<.01*
Patient 5	−1.02 ± 3.62 Gy	.07	1.42 ± 3.79%	<.05*
Patient 6	−2.61 ± 4.62 Gy	<< .01*	2.90 ± 5.02%	<.01*
Patient 6_{RSI}	−4.05 ± 4.24 Gy	<< .01*	4.11 ± 4.92%	<<.01*
Patient 7	−3.68 ± 1.67 Gy	<< .01*	5.38 ± 2.50%	<<.01*
Patient 7_{RSI}	−2.48 ± 1.33 Gy	<< .01*	3.43 ± 2.12%	<<.01*
Patient 8	−1.41 ± 1.33 Gy	<< .01*	2.09 ± 2.12%	<<.01*
Patient 8_{RSI}	−0.24 ± 2.97 Gy	.67	0.22 ± 3.97%	.77

Abbreviations: RSI = restriction spectrum imaging.
* Significant with $P < .05$.

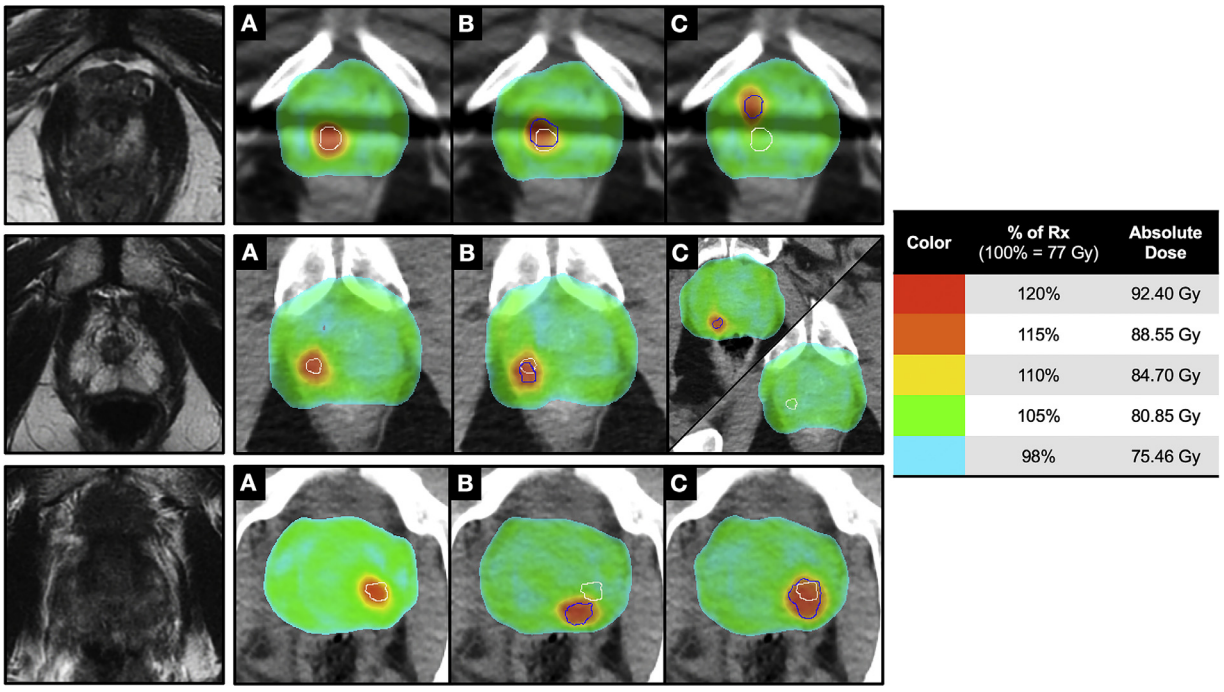

Fig. 3. Example contours with dose overlays and corresponding T_2-weighted MRI for 3 patient cases: (A) Expert, (B) and (C) Participants. Expert contours are shown in white, and participant contours are shown in blue. The greater the accuracy of the participant contour, the higher the dose delivered to the true tumor. When the participant drew the contour larger than and including the expert contour (such as in patient 8[C]), this led to a higher dose to the true tumor than that seen in the expert plan.

that trainees covered more of the expert contour than nontrainees, we performed a post hoc comparison of the size of trainee and expert contours, because larger contours could lead to more coverage of the true target. However, we found that trainee tumor contours were not larger than nontrainee contours (mean, 2.5 mL; SD, 2.8 mL for trainees vs mean 2.7 mL; SD, 2.7 mL for nontrainees; $P = .58$).

Discussion

We investigated the clinical impact of radiation oncologists' prostate tumor contour variability. Overall, we found that using radiation oncologist participants' target volumes yielded plans with worse predicted clinical outcomes compared to the expert target volume. On average, participants' target volumes led to a predicted 4.3% absolute increase in BF. In more than one-third of participant plans (37%), the absolute increase in BF exceeded our a priori threshold for clinical significance (≥5% absolute increase in BF). Thus, the high tumor contour variability demonstrated in the ReIGNITE study is expected to adversely impact clinical outcomes for patients.

Accurately delineating prostate tumors on mpMRI is a challenging task, and there are currently no established guidelines for doing so. Substantial variability in prostate tumor contours has been observed among radiation oncologists and even expert radiologists.[3,12,13] Discrepancies in contouring practices among observers and institutions may arise because of variations in the interpretation and prioritization of different MRI sequences. Although some level of variability can be reasonably expected in the RCT, boosting the expert-defined lesions nonetheless led to meaningful improvement in long-term clinical outcomes. The pathology and location of all analyzed lesions were confirmed using histopathology (biopsy and/or prostatectomy). Our emphasis in this study is on targeting the expert-defined MRI-visible lesion, which is supported by a phase III RCT.

The ReIGNITE study showed that one way to improve radiation oncologists' contouring accuracy is to provide RSIrs maps.[3] The present study was not powered for a full evaluation of the impact of RSIrs on treatment plans, with only 3 cases included. Nonetheless, of the 3 cases that allowed for comparison of contours with and without RSIrs, 2 cases showed a statistically significant improvement in ΔBF and ΔD98 with RSIrs. Other strategies to improve contouring accuracy for MRI-visible prostate tumors include the involvement of expert radiologists in target delineation and dedicated training for radiation oncologists.[14,15] Alternative imaging modalities like PSMA PET may also prove useful.[16-21] Automated target delineation using artificial intelligence has potential, though these currently still require considerable expert oversight.[22,23] For less experienced or resourced settings, one could consider adding a margin around the gross tumor volume to account for contouring uncertainties. Future studies should measure both the feasibility of these strategies and their impact on

predicted clinical outcomes of focal RT boost. Meanwhile, it is nonetheless noted that all calculated BFs in the present study were lower than that if the prostate were treated only with a uniform dose of 77 Gy, illustrating that even somewhat inaccurate contours may still benefit the patient.

It is reasonable to consider the impact of experience on contour accuracy. We found no significant difference in predicted clinical outcomes between participants in training and those in independent practice. The only statistically significant finding was that trainees' contours had a higher overlap with the expert contour. Experience treating prostate cancer, in general, may not necessarily translate to better targeting of tumors on prostate MRI (a task for which few radiation oncologists have received formal training). Though not evaluated in the present work, it stands to reason that practice in contouring prostate tumors on MRI, with feedback on accuracy, would improve physician performance.

In some instances, an imprecise contour led to a higher dose than that seen in the expert plan. This was especially prevalent for patients 5, 6, and 8_{RSI}. Upon inspection of these cases, it appeared that participants tended to draw their contours larger than the expert-defined lesion while encompassing the true target (Fig. 3), which likely spread out the high dose away from OARs. In clinical practice, a dosimetrist would recognize the potential for improving a plan with the correct target, eg, by inserting an optimization structure to better target the lesion. This indicates that the KBP model used in this study has room for further improvement to achieve more optimal planning.

The present study inherits some limitations from the ReIGNITE study that serves as the source of data. Images used in the study were from a single institution, which may limit generalizability. Radiation oncologist participants, on the other hand, were from 9 countries and many institutions. Additionally, only 8 of the 30 patient cases from the study were available for dosimetric analysis. On the other hand, we included nearly 400 individual contouring attempts and made observations that are both statistically and clinically meaningful, suggesting realistic variability in target volumes can impact patient outcomes.

Conclusion

Radiation oncologists' attempts to contour tumor targets for focal RT boost are frequently inaccurate enough to yield meaningfully inferior clinical outcomes for patients. Further studies are warranted to investigate the impact of RSIrs on predicted clinical outcomes of focal RT boost.

References

1. Kerkmeijer LGW, Groen VH, Pos FJ, et al. Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial. *J Clin Oncol* 2021;39:787-796.
2. Groen VH, Haustermans K, Pos FJ, et al. Patterns of Failure Following External Beam Radiotherapy With or Without an Additional Focal Boost in the Randomized Controlled FLAME Trial for Localized Prostate. *Cancer Eur Urol* 2021;82:252-257.
3. Lui AJ, Kallis K, Zhong AY, et al. ReIGNITE Radiation Therapy Boost: A Prospective, International Study of Radiation Oncologists' Accuracy in Contouring Prostate Tumors for Focal Radiation Therapy Boost on Conventional Magnetic Resonance Imaging Alone or With Assistance of Restriction Spectrum Imaging. *Int J Radiat Oncol* 2023;117:1145-1152.
4. Fogliata A, Belosi F, Clivio A, et al. On the pre-clinical validation of a commercial model-based optimisation engine: Application to volumetric modulated arc therapy for patients with lung or prostate cancer. *Radiother Oncol* 2014;113:385-391.
5. Ray X, Kaderka R, Hild S, Cornell M, Moore KL. Framework for evaluation of automated knowledge-based planning systems using multiple publicly available prostate routines. *Pract Radiat Oncol* 2020;10:112-124.
6. Kaderka R, Mundt RC, Li N, et al. Automated closed- and open-loop validation of knowledge-based planning routines across multiple disease sites. *Pract Radiat Oncol* 2019;9:257-265.
7. Li N, Carmona R, Sirak I, et al. Highly efficient training, refinement, and validation of a knowledge-based planning quality-control system for radiation therapy clinical trials. *Int J Radiat Oncol Biol Phys* 2017;97:164-172.
8. Hussein M, South CP, Barry MA, et al. Clinical validation and benchmarking of knowledge-based IMRT and VMAT treatment planning in pelvic anatomy. *Radiother Oncol* 2016;120:473-479.
9. Chua LMH, Pang EPP, Master Z, Sultana R, Tuan JKL, Bragg CM. Dosimetric comparison of RapidPlan and manually optimised volumetric modulated arc therapy plans in prostate cancer. *J Radiother Pract* 2021;20:257-264.
10. Scaggion A, Fusella M, Roggio A, et al. Reducing inter- and intra-planner variability in radiotherapy plan output with a commercial knowledge-based planning solution. *Phys Med* 2018;53:86-93.
11. Groen VH, van Schie M, Zuithoff NPA, et al. Urethral and bladder dose-effect relations for late genitourinary toxicity following external beam radiotherapy for prostate cancer in the FLAME trial. *Radiother Oncol* 2021;167:127-132.
12. Steenbergen P, Haustermans K, Lerut E, et al. Prostate tumor delineation using multiparametric magnetic resonance imaging: inter-observer variability and pathology validation. *Radiother Oncol* 2015;115:186-190.
13. Sonn GA, Fan RE, Ghanouni P, et al. Prostate magnetic resonance imaging interpretation varies substantially across radiologists. *Eur Urol Focus* 2019;5:592-599.
14. Zhong AY, Lui AJ, Katz MS, et al. Use of focal radiotherapy boost for prostate cancer: radiation oncologists' perspectives and perceived barriers to implementation. *Radiat Oncol* 2023;18:188.
15. Dornisch AM, Zhong AY, Poon DMC, Tree AC, Seibert TM. Focal radiotherapy boost to MR-visible tumor for prostate cancer: a systematic review. *World J Urol* 2024;42:56.
16. Zamboglou C, Spohn SKB, Ruf J, et al. PSMA-PET- and MRI-based focal dose escalated radiation therapy of primary prostate cancer: Planned safety analysis of a nonrandomized 2-armed phase 2 trial (ARO2020-01). *Int J Radiat Oncol Biol Phys* 2022;113:1025-1035.
17. Bettermann AS, Zamboglou C, Kiefer S, et al. [68Ga-] PET/CT multiparametric MRI gross tumor volume delineation in a slice by slice analysis with whole mount histopathology as a reference standard – Implications for focal radiotherapy planning in primary prostate cancer. *Radiother Oncol* 2019;141:214-219.
18. Draulans C, De Roover R, Van Der Heide UA, et al. Optimal ^{68}Ga-PSMA and ^{18}F-PSMA PET window levelling for gross tumour volume delineation in primary prostate cancer. *Eur J Nucl Med Mol Imaging* 2021;48:1211-1218.
19. Eiber M, Weirich G, Holzapfel K, et al. Simultaneous ^{68}Ga-PSMA HBED-CC PET/MRI improves the localization of primary prostate cancer. *Eur Urol* 2016;70:829-836.

20. Zamboglou C, Thomann B, Koubar K, et al. Focal dose escalation for prostate cancer using 68ga-HBED-CC PSMA PET/CT and MRI: A planning study based on histology reference. *Radiat Oncol* 2018;13:81.
21. Dhar A, Cendejas-Gomez JJ, Castro Mendez L, et al. Using multiparametric magnetic resonance imaging and prostate specific membrane antigen positron emission tomography to detect and delineate the gross tumour volume of intraprostatic lesions − A systematic review and meta-analysis. *Radiother Oncol* 2024;192 110070.
22. Tsui JMG, Kehayias CE, Leeman JE, et al. Assessing the feasibility of using artificial intelligence−segmented dominant intraprostatic lesion for focal intraprostatic boost with external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 2024;118:74-84.
23. Holzschuh JC, Mix M, Ruf J, et al. Deep learning based automated delineation of the intraprostatic gross tumour volume in PSMA-PET for patients with primary prostate cancer. *Radiother Oncol* 2023;188 109774.