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Improved MR Imaging-Pathology Correlation With Imaging-Derived, 3D-Printed, Patient-Specific Whole-Mount Molds of the Prostate

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Abstract

OBJECTIVES—To compare the anatomical registration of preoperative magnetic resonance imaging (MRI) and prostate whole-mounts obtained with 3D-printed, patient-specific, MRI-derived molds (PSM) versus conventional whole-mount sectioning (WMS).

MATERIALS AND METHODS—Based on an *a priori* power analysis, this institutional review board-approved study prospectively included 50 consecutive men who underwent 3 Tesla multiparametric prostate MRI followed by radical prostatectomy. Two blinded and independent readers (R1 and R2) outlined the contours of the prostate, tumor, peripheral and transition zones in the MR images using regions of interest (ROIs). These were compared with the corresponding ROIs from the whole-mounted histopathology, the reference standard, using PSM whole-mount results obtained in the study group (n=25) or conventional WMS in the control group (n=25). The spatial overlap across the MRI and histology data sets was calculated using the Dice similarity coefficient (DSC) for the prostate overall (DSC_{prostate}), tumor (DSC_{tumor}), peripheral (DSC_{pz}) and transition (DSC_{TZ}) zone. Results in the study and control groups were compared using Wilcoxon rank sum test.

RESULTS—The MRI-histopathology anatomical registration for the prostate gland overall, tumor, peripheral and transition zones were significantly superior with the use of PSMs (DSCs for R1: 0.95, 0.86, 0.84 and 0.89; for R2: 0.93, 0.75, 0.78 and 0.85, respectively) than with the use of standard WMS (R1: 0.85, 0.46, 0.66 and 0.69; R2: 0.85, 0.46, 0.66 and 0.69) (p<0.0001).

CONCLUSIONS—The use of PSMs for prostate specimen whole-mount sectioning provides significantly superior anatomical registration of *in vivo* multiparametric MRI and *ex vivo* prostate whole-mounts than conventional WMS.

Keywords

prostatic cancer; magnetic resonance imaging; histopathology; case-control studies

INTRODUCTION

The initial diagnosis of prostate cancer (PCa) is a multi-step process involving urologists, pathologists and, increasingly, radiologists. The growing implementation of prostate magnetic resonance imaging (MRI) programs in recent years has been propelled by a recognition of the ability to visualize and characterize cancer non-invasively. This recognition has been largely predicated on the use of histopathology after radical prostatectomy to provide a reference standard^{1–3}.

A critical requirement for MRI-pathology correlation is adequate image registration. Histopathologic analysis using standard tissue-based processes where the prostate is sectioned in multiple blocks leads to challenges in correlation between the *in vivo* MRI findings and the reference histopathologic standard. The implementation of histopathologic whole-mount sectioning (WMS) allows for a straightforward correlation between *in vivo* MRI findings and histopathologic findings^{1–3}. However, since the prostate is an easily deformable organ, with variable size and morphology, sectioning the gland in a plane similar to that used for imaging can be challenging. To improve such *in vivo* imaging and *ex vivo* histopathological image registration, three-dimensional(3D)-printed, patient-specific, MRI-derived molds (PSM) for whole-mount processing have been proposed^{4–7}. This PSM holds the prostate in place while a knife is inserted into computer generated slots for sectioning the entire gland in a manner that corresponds to the orientation and location of the MR images. While the theory behind this approach is logical, the extent to which the anatomical registration of preoperative imaging and prostate whole-mounts might be improved upon over the conventional whole-mount processing has not been previously investigated.

Hence, the goal of this study was to compare the anatomical registration of preoperative MRI and prostate whole-mounts obtained with PSM versus conventional WMS.

MATERIALS AND METHODS

This Institutional Review Board-approved and Health Insurance Portability and Accountability Act-compliant study is a prospective, non-randomized, dual-arm investigation. The requirement for informed consent was waived.

Patient cohort

All patients who underwent radical prostatectomy between December 2015 and April 2016 preceded by preoperative MRI of the prostate at our institution were reviewed for inclusion in this study. In November 2015, a whole-mount program was implemented at **BLINDED**. During the initial stage of this project, patients from a single urologist (**BLINDED**.) had

their prostatectomy specimen processed using a PSM ('study group'). The remaining eligible patients operated by other urologists followed the conventional processing technique with standard WMS ('control group'). Exclusion criteria was defined as not having an MRI-visible index lesion, non-diagnostic MRI (e.g., due to severe motion artifacts), MRI performed 12 or more months prior to surgery and previous treatment with radiation or androgen deprivation therapy (Figure 1).

Multiparametric MRI and image post-processing

All MRI studies were performed in a 3 Tesla MRI scanner (Philips; Best, The Netherlands) with an endorectal and a phased-array surface coil. Our routine, clinical imaging multiparametric protocol includes T2-weighted, diffusion-weighted, and dynamic contrast-enhanced images² (Supplemental Table 1). A commercially available workstation (VersaVue, iCAD; Nashua, NH) was used to generate volumetric reconstructions of the prostate using an automated, built-in segmentation tool based on high-resolution axial T2-weighted images of the prostate gland which were reviewed, validated – manually edited when needed – and saved as 'radiotherapy structure set' (RTSTRUCT) files.

3D Printing

A MATLAB (The MathWorks, Inc.; Natick, MA) script was used to extract the volumetric reconstruction from the RTSTRUCT and convert it to a stereo-lithography (STL) file. The STL files were imported into Netfabb (Netfabb GmbH; Parsberg, Germany) where the PSM was generated based on a generic, parametrically controlled 3-part slicing mold with holes for fixative perfusion and slots for slicing alignment created in SolidWorks (Solidworks Corporation; Waltham, MA). A boolean subtraction of the prostate model from the slicing mold was then performed in Netfabb, and the resultant PSM was imported into 3D Slicer⁸ along with the axial T2-weighted images to confirm accurate orientation and segmentation of the prostate gland. Once the PSM passed quality assurance it was 3D printed and shipped to the pathology department prior to the surgical case via internal mail for use in sectioning. In the first cases, the PSM was printed on a commercial-grade 3D printer (ProJet 3510 HD Plus, 3D Systems, Rock Hill, SC) using a ultra-violet light curable resin (Visijet Crystal, 3D Systems, Rock Hill, SC). Once the process was well-established, PSMs were produced on a consumer-grade 3D printer (Leapfrog Creatr XL, Alphen aan den Rijn, Netherlands) using a polylactic acid plastic (Figure 2).

Histopathological processing

After surgery, the fresh prostate specimen was received in the pathology department and processed following the standard procedures recommended by the International Society of Urological Pathology⁹. As part of our routine whole-mount technique, slices were processed by use of a 7-hour schedule with automatic microwave assistance (Pathos Delta; Milestone, Italy). In the study group, the specimen was placed into the PSM for initial formalin fixation and, subsequently, serial slicing (Figures 3 and 4).

Radiology-Pathology image registration

The Dice similarity coefficient (DSC) was used to quantify the correspondence of anatomical registration across data sets in each arm. This method, also known as the proportion of specific agreement, relies on a spatial overlap index with values ranging from 0 (indicating no spatial overlap between two sets of binary segmentation results) to 1 (complete overlap).¹⁰ In this study, the whole-mount slide that best depicted the index cancer lesion according to the interpretation of a specialized genitourinary pathologist who was blinded to the MRI findings, was downloaded from the Aperio eSlide Manager (Leica Biosystems; Buffalo Grove, IL) and imported to the open-source image viewer OsiriX (Pixmeo; Geneva, Switzerland) using the 'JPEG to DICOM' tool. The pathology slides contained a scale which was used to ensure the field-of-view and pixel size were comparable to those of the MR images. The existing annotations in the original slide were used by a radiologist (**BLINDED**) with 12 years of experience reading prostate MRI to manually draw a free-hand region of interest (ROI) delineating the contours of the prostate (ROI-Path_{prostate}), (ROI-Path_{tumor}), peripheral (ROI-Path_{pZ}) and transition (ROI-Path_{TZ}) zones. Since the pathology slides and the MR images did not share the same coordinate system, these were manually aligned by the radiologist to enable a direct comparison based on pixel location. Following a minimum 2-week wash-out period, this radiologist selected the axial T2-weighted image that better represented the index cancer. The radiologist did not have access to the pathology slide however was aware of the index cancer location (side and zone; e.g., right posterolateral mid gland peripheral zone). The selected axial T2-weighted mpMRI image was used to generate one ROI delineating the contours of the prostate (ROI-MRI_{prostate}), tumor (ROI-MRI_{tumor}), peripheral (ROI-MRI_{pZ}) and transition (ROI-MRI_{TZ}) zones in each patient (Figure 5) by two independent readers (**BLINDED**. and **BLINDED**) with 2 and 12 years of experience reading prostate MRI. In all these steps, readers were blinded to whether the patient belonged to the study or control group and integrated the findings in the different MR pulse sequences to determine the index tumor location. The spatial coordinates of each pixel within these ROIs were then exported as 'comma-separated values' (.csv) files using the 'ROI-Info' Osirix plug-in (available for download from <https://github.com/TimAllman/ROI-Info>) and DSCs were calculated using an R (R3.3.1, R Foundation for Statistical Computing; Vienna, Austria) script. DSC_{prostate} was calculated for each patient by comparing the degree of spatial overlap between ROI-Path_{prostate} and ROI-MRI_{prostate}. Similarly, DSC_{tumor} (comparing ROI-Path_{tumor} and ROI-MRI_{tumor}), DSC_{pZ} (ROI-Path_{pZ} and ROI-MRI_{pZ}) and DSC_{TZ} (ROI-Path_{TZ} and ROI-MRI_{TZ}) were calculated.

Statistical analysis

Results across cohorts were compared using one-sided Wilcoxon rank sum test. The alternative hypothesis was that DSC in the control group is more likely to be lower than DSC in the study group. An additional superiority by a margin test was performed with a superiority margin of 0.1 for DSC_{prostate}. The test was conducted with the same Wilcoxon rank sum test while all DSC from the PSM were replaced by DSC-0.1. Preliminary data obtained by reader 1 (**BLINDED**) from the first 10 men (5 in each cohort) were used for an *a priori* power analysis. Mean and standard deviation were 0.94 and 0.01 in the pilot study group, 0.78 and 0.09 in the pilot control group, respectively. A sample of 25 cases and 25

controls was estimated to provide 84% power of detecting superiority using a Wilcoxon rank sum test when the margin of superiority is 0.1. The results are based on 2000 Monte Carlo samples from beta distributions and were calculated in PASS 14 (NCSS Statistical Software; Kaysville, UT).

To assess for potential differences between the characteristics of men in the study and control groups, age, PSA, prostate volume as measured by MRI, greatest index tumor diameter as measured by histopathological assessment, Gleason score, T stage and time between imaging and surgery were compared. A two-sided Wilcoxon rank sum test was used for continuous variables and Fisher's exact test was used for categorical variables to test any imbalance between both cohorts. A Wilcoxon rank sum test with propensity score based stratification was used to adjust for possible confounders. SAS 9.3 (SAS Institute; Cary, NC) was used for this analysis. A significance level of 0.05 was used for statistical testing.

RESULTS

The first 50 consecutive men from 69 eligible patients were selected for this study, 25 in the case and 25 in the control groups. No significant difference in age, PSA, prostate volume, index lesion size, time between MRI and surgery, T stage and Gleason score was found across cohorts (Table 1).

The anatomical registration across the two data sets – MR imaging and whole-mount histology – for the prostate gland overall, tumor, peripheral and transition zones were significantly superior with the use of PSMs in the study group (DSCs for reader 1: 0.95, 0.86, 0.84 and 0.89; for reader 2: 0.93, 0.75, 0.78 and 0.85, respectively) than with the use of standard WMS in the control group (DSCs for reader 1: 0.85, 0.46, 0.66 and 0.69; for reader 2: 0.85, 0.46, 0.66 and 0.69, respectively) ($p < 0.0001$) (Table 2).

DISCUSSION

Interpretation of radical prostatectomy specimens by pathologists is the standard of reference for PCa diagnosis and staging. There is, however, an increasing contribution of multiparametric MRI in patients being evaluated for known or suspected PCa¹¹. In this setting, preoperative MRI localizes suspicious lesions while biopsy, commonly employing a targeted approach^{12, 13}, confirms the presence of cancer and characterizes the tumor using nomograms that combine data such as Gleason score, number of positive cores and the percentage of core length involved by tumor¹⁴. Under the current architecture of diagnostic medicine, radiologists and pathologists function as members of distinct disciplines, with no direct linkage between their workflows or reporting systems¹⁵. These separate specialties would ideally work in close collaboration to exchange information facilitating patient care and research opportunities. The results of this study, demonstrating improved registration of *in vivo* multiparametric MRI and *ex vivo* prostate whole-mounts using 3D-printed, patient-specific molds (PSMs), reflect the feasibility of such integration.

The use of MRI-derived PSMs for processing whole-mounted radical prostatectomy specimens has been reported^{4–7}. However, our study quantitatively demonstrates the improved anatomical registration provided by this technology. By improving image

registration, use of PSMs represents a significant step towards the pixel-by-pixel correlation desired for validation of quantitative imaging biomarkers with potential to distinguish aggressive and indolent forms of PCa (e.g. diffusion-weighted^{16–18} and dynamic contrast-enhanced imaging¹⁹), the correlation between cancer imaging features and gene expression (radiogenomics)²⁰, the development of computer-aided diagnosis systems²¹ and, in clinical practice, the continued evaluation and refinement of structured reporting systems (such as PI-RADS – Prostate Imaging-Reporting and Data System²²).

Our study has some limitations. First, we compared two different approaches, each of which was used in a separate patient cohort; one cannot predict to which extent and in what direction differences between the cohorts and surgeon's techniques may have played a role in our results. However, our comparison of both arms did not reveal statistically significant differences pertaining to key patients' characteristics. Secondly, we analyzed a single slice rather than the entire gland; the differences observed in that one slice may not preserve a linear relationship with the differences observed should the entire gland had been analyzed. Additionally, while PSMs pursue image registration based on direct anatomical similarity, different strategies using software-based algorithms have been proposed by other groups^{23–25} and have not been compared to the PSM approach. Although we presented an example of how the cost of the technology has been decreasing, we did not objectively perform a cost analysis of this technique. Finally, the use of an endorectal coil is expected to distort prostate anatomy which may complicate co-registration efforts; the degree to which such an effect might impact the results is unknown.

CONCLUSIONS

The use of 3D-printed, PSMs for prostate specimen whole mount sectioning provides significantly superior anatomical registration of *in vivo* multiparametric MRI acquired with an endorectal coil and *ex vivo* prostate whole-mounts compared with conventional whole-mount sectioning (WMS). Future studies should investigate the potential incremental value of combining this approach with software-based algorithms to further improve such image registration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Patient cohort

Flowchart of the criteria for eligibility and number of men enrolled. RALP, robot-assisted laparoscopic prostatectomy; mpMRI, multiparametric magnetic resonance imaging; n, number of men; XRT, radiation therapy; ADT, androgen deprivation therapy.

*No MRI-visible lesion

**Severe motion artifact

***First 25 consecutive patients of each cohort were included

Figure 2. Patient-specific, 3D-printed mold

For each patient, a custom mold is printed. The mold is composed of 3 inter-connected parts (A) which together create a single module (B). Within the mold, a cavity (*P* in A) corresponds to the three-dimensional representation of the prostate based on the MRI data and is where the specimen will be placed during the tissue fixation and cutting. The patient-specific nature of this cavity allows for placement of the prostatectomy specimen in a position less vulnerable to rotation. When assembled, the mold has an opening (*) in B) where the seminal vesicles are positioned. At the early stage of this project's development, a higher end 3D printer (3D Systems ProJet 3510 HD Plus) was used (*translucid* in A, B and C) and was later replaced by a lower cost device (Leapfrog Creatr XL) capable of creating similar molds (*green* in C) for approximately one fifth of the cost. The multi-perforated nature of the mold aimed at facilitating the contact with the fixative material and the evenly spaced gaps (*arrowheads* in A) ensured slabs with consistent thickness and oriented by a plane defined by the axial MR images).

Figure 3. Radical prostatectomy specimen handling

Whole prostate gland is received intact with urethral catheter in place (A). It is then inked, right orange, left blue, anterior green and posterior black (B). Whole prostate gland is placed into patient-specific, 3D-printed mold for fixation (C) followed by slicing using the guides present in the mold (D). In this case, the gland was sliced into six, 5.0 mm sections. Apex slab 1 section (E) is serially sectioned, right to left. Base Slab 6 section (G) is serially sectioned right to left and bilateral seminal vesicles transected (H). Body of Prostate Gland sectioned, slabs 2 through 5 (I). These are the slabs that maintain anatomical correspondence with the axial MR images.

Figure 4. Steps involved in the generation and delivery of the patient-specific, 3D-printed molds used for radical prostatectomy specimens in the study group
 RTSTRUCT, radiotherapy structure set; T2W, T2-weighted; STL, stereo-lithography; 3D, three-dimensional; MRI, magnetic resonance imaging.

Figure 5. Calculation of image spatial overlap using the Dice similarity coefficient

Magnetic resonance images were used for drawing regions of interest (ROIs) for the entire prostate ($\text{ROI-MRI}_{\text{prostate}}$), tumor ($\text{ROI-MRI}_{\text{tumor}}$), peripheral zone ($\text{ROI-MRI}_{\text{PZ}}$) and transition zone ($\text{ROI-MRI}_{\text{TZ}}$) boundaries. In parallel, whole-mount prostatectomy slides were used for drawing ROIs for the prostate ($\text{ROI-Path}_{\text{prostate}}$), tumor ($\text{ROI-Path}_{\text{tumor}}$), peripheral zone ($\text{ROI-Path}_{\text{PZ}}$) and transition zone ($\text{ROI-Path}_{\text{TZ}}$). The Dice similarity coefficient (DSC), an index of image spatial overlap, was used to compare $\text{ROI-MRI}_{\text{prostate}}$ vs. $\text{ROI-Path}_{\text{prostate}}$ ($\text{DSC}_{\text{prostate}}$), $\text{ROI-MRI}_{\text{tumor}}$ vs. $\text{ROI-Path}_{\text{tumor}}$ ($\text{DSC}_{\text{tumor}}$), $\text{ROI-MRI}_{\text{PZ}}$ vs. $\text{ROI-Path}_{\text{PZ}}$ (DSC_{PZ}), and $\text{ROI-MRI}_{\text{TZ}}$ vs. $\text{ROI-Path}_{\text{TZ}}$ (DSC_{TZ}). The DSC represents the ratio of the number of spatial elements (pixels) shared by histology and MRI divided by the total number and were calculated on a per-patient basis. The $\text{DSC}_{\text{prostate}}$ and $\text{DSC}_{\text{tumor}}$ for these two examples were, respectively, as follows: study group patient (*left*), 0.96 and 0.96 for reader 1, 0.95 and 0.92 for reader 2; control group patient (*right*), 0.87 and 0.65 for reader 1, 0.87 and 0.66 for reader 2. ROIs and DSCs for the peripheral and transition zones not presented in this figure. ROIs shown were drawn by reader 1.

Patients characteristics

Table 1

	Study group	Control group	All patients	p-value
Age (years)	64.0 ± 7.8 [65] (61–69)	63.8 ± 6.7 [67] (60–68)	63.9 ± 7.2 [65] (60–68)	0.91485
PSA (ng/mL)	7.9 ± 4.0 [7.3] (5.2–10.6)	9.1 ± 8.9 [6.0] (5.1–9.2)	8.5 ± 6.8 [6–7] (5.1–9.6)	0.87661
Prostate volume ¹ (cc)	38.1 ± 13.6 [37.0] (26.5–47.0)	39.8 ± 10.5 [36.0] (32.3–49.0)	38.9 ± 12.1 [36.5] (31.9–49.0)	0.46661
Index lesion size ² (mm)	19.2 ± 11.3 [16] (12–23)	15.8 ± 7.9 [16] (10–20)	17.5 ± 9.8 [16] (11–22)	0.37146
Time between MRI and surgery (days)	72 ± 43.6 [70] (43–89)	92.7 ± 77.4 [78] (30–115)	82.4 ± 63.1 [72.5] (38–111)	0.58693
Local stage	T2	68%; 17/25	54%; 27/50	0.0877
	T3	32%; 8/25	46%; 23/50	
Gleason score	≤3+4	52%; 13/25	58%; 29/50	0.5672
	>3+4	48%; 12/25	42%; 21/50	

Study group: whole-mounted specimen processed using patient-specific, 3D-printed mold; Control group: conventional whole-mounted specimen processing

Numbers represent mean ± standard deviation unless otherwise specified

[Median]; (Interquartile range)

* Number of men

¹ MRI-based calculation

² Largest dimension as measured by histopathological assessment PSA, prostate-specific antigen; MRI, magnetic resonance imaging p-value compares the study and control groups

Table 2

Measurement of anatomical registration for the prostate and tumor boundaries between *in vivo* preoperative MRI of the prostate and *ex vivo* whole-mount histology using the Dice similarity coefficient

		Study group	Control group	p-value
DSC _{prostate}	Reader 1	0.95 ± 0.01 [0.95] (0.94–0.96)	0.85 ± 0.06 [0.86] (0.82–0.89)	<0.0001
	Reader 2	0.93 ± 0.02 [0.93] (0.91–0.95)	0.85 ± 0.06 [0.87] (0.82–0.88)	<0.0001
DSC _{tumor}	Reader 1	0.86 ± 0.06 [0.87] (0.84–0.89)	0.46 ± 0.20 [0.44] (0.29–0.63)	<0.0001
	Reader 2	0.75 ± 0.12 [0.78] (0.68–0.84)	0.46 ± 0.20 [0.46] (0.30–0.61)	<0.0001
DSC _{PZ}	Reader 1	0.84 ± 0.06 [0.84] (0.82–0.88)	0.66 ± 0.08 [0.68] (0.63–0.72)	<0.0001
	Reader 2	0.78 ± 0.15 [0.83] (0.75–0.86)	0.66 ± 0.10 [0.67] (0.61–0.70)	<0.0001
DSC _{TZ}	Reader 1	0.89 ± 0.05 [0.88] (0.86–0.92)	0.69 ± 0.12 [0.67] (0.60–0.77)	<0.0001
	Reader 2	0.85 ± 0.20 [0.91] (0.86–0.93)	0.69 ± 0.12 [0.70] (0.60–0.76)	<0.0001

Study group: whole-mounted specimen processed using patient-specific, 3D-printed mold; Control group: Conventional whole-mounted specimen processing. Numbers represent mean ± standard deviation unless otherwise specified [Median]; (Interquartile range)

DSC, Dice similarity coefficient; PZ, peripheral zone; TZ, transition zone