Three-dimensional MRI-based Printed Models of Prostate Anatomy and Targeted Biopsy-proven Index Tumor to Facilitate Patient-tailored Radical Prostatectomy – a feasibility study

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Abbreviations:

DCE: Dynamic contrast-enhanced Imaging

DRE: Digital-rectal examination

EPE: Extraprostatic extension

ESUR: European Society of Urogenital Radiology

GGG: Gleason Grade group

IFS: Intraoperative frozen sectioning

mpMRI: multiparametric Magnetic Resonance Imaging

MRI: Magnetic Resonance Imaging

NSM: Negative surgical margins

PC: Prostate cancer

PI-RADS: Prostate Imaging - Reporting and Data System

PSA: Prostate specific antigen

PSM: Positive surgical margins

PV: Prostate volume

RP: Radical prostatectomy

SB: Systematic biopsy

sPC: Significant prostate cancer

STARD: Standards of Reporting of Diagnostic Accuracy

TRUS: Transrectal ultrasound

61 TV: Tumor volume

Abstract

In this prospective single center feasibility study, we demonstrate that the use of 3D-printed prostate-models support nerve-sparing radical prostatectomy (RP) and intraoperative frozen-sectioning (IFS) in ten men suffering from intermediate- and high-risk prostate cancer (PC), of whom seven harbored pT3-disease. Patient-specific 3D resin models were printed based on preoperative multiparametric MRI (mpMRI) to provide an exact 3D impression of significant tumor lesions. RP and IFS were planned in a patient-tailored fashion.

The 36-region PI-RADSv2.0 scheme was used to compare the MRI/3D-print with whole-mount histopathology. In all cases, the localization of the index lesion was correctly displayed by MRI and the 3D-model. Localization of significant PC lesions correlated significantly (Pearson`s correlation coefficient of 0.88 ($p<0.001$). In addition, a significant correlation of the width, length and volume of the tumor and prostate gland derived from the printed model and histopathology was found, using Pearson`s correlation analyses and Bland-Altman plots.

In conclusion, 3D-printed prostate-models correlate well with final pathology and can be used to tailor RP.

Patient summary

The use of 3D printed prostate-models based on preoperative MRI may improve prostatectomy outcome. This study confirmed accuracy of 3D printed prostates compared to pathology from RP specimens. Thus, MRI-derived 3D printed prostate-models can assist prostate cancer surgery.

Main report:

Multiparametric MRI (mpMRI) and transrectal ultrasound (TRUS)-fusion targeted biopsy detect significantly more significant prostate cancers (sPC) than standard TRUS-biopsy [1,2]. In addition, high spatial resolution of MRI facilitates precise knowledge of the localization of sPC before nerve-sparing radical prostatectomy (RP), to gain maximum security while reducing burden of erectile dysfunction after RP **[3]**. Another possible tool is intraoperative frozen sectioning (IFS).Schlomm et al. described that IFS has the potential to significantly increase nerve-sparing and to reduce positive margins (PSM) [4]. In addition, Petralia et al. combined both approaches and could demonstrate that preoperative MRI can guide IFS to significantly reduce PSM [5]. This is of specific interest, as unfavourable PSM (>3 mm and/or multifocal) confer a higher oncologic risk of developing metastasis [6]. Another promising step might be utilization of MRI-derived 3D printed prostate models **[3]**.

In our feasibility study we used customized, patient-specific 3D printed prostates. The main purpose was to evaluate the correlation of the index tumor lesion and of all sPC lesions between the 3D-prints and RP specimens. Differences in index lesion dimensions (length, width, volume) and whole gland between MRI-based print models and RP specimens were analysed, as underestimation of the lesion volume by MRI of up to 30% has been demonstrated [7]. Lastly, we investigated the role of MRI/3D-model-directed IFS to decrease the rate of PSM after RP [5].

In this feasibility study (review board-approval, 19-TEMP579281-BO, 03/2019-06/2019), ten consecutive patients with clinically localized intermediate- and high-risk PC underwent a 3-Tesla mpMRI using a Prostate Imaging-Reporting and Data System (PI-RADS)v2.0-conform protocol and subsequent MRI/TRUS-fusion biopsy. [8].

The 3D printed prostates were outlined based on the mpMRI, manually marking the boundaries of the prostate gland and seminal vesicles using the open source software 3D-Slicer (version: 4.10.2). Index lesions were defined as the lesion with the highest International Society of Urological Pathology (ISUP) Gleason grading groups (GGG) or the largest volume within a prostate. sPC was defined as ISUP ≥2. Biopsy-proven index lesions on mpMRI and all sPC lesions were contoured manually marked under supervision of a dedicated uro-radiologist with experience > 1000 image reports in prostate MRI (AW). A 3D printer (Anycubic Photon, Shenzhen, China) printed the specimens out of resin whereas the index lesion was left blank or filled with a different color.

RP was performed by one experienced surgeon (BAH, >500 cases) using a retropubic or robot-assisted technique. Based on National Comprehensive Cancer Network risk-groups (intermediate- and high-risk in the present cohort) and with aid of the 3D-printed models, a nerve-sparing approach and IFS were planned and performed. Specifically, IFS was performed for each index lesion and other sPC lesions. Pathological work-up was performed according to current clinical standards by a dedicated pathologist with 12 years of experience in genitourinary-pathology (HR). For the analysis, quarters were digitally reconstructed to whole-mounts. Tumor dimensions were measured using MITK software (Medical Imaging Interaction Toolkit, v2018.04.02). The 3D-printed prostate was sliced at the index lesion with a commercial hacksaw. The correct orientation was achieved by interdisciplinary workup between clinicians and pathologists on an individual case-basis and according to anatomical landmarks of the prostate. Histopathologic slides with the greatest cross-section of the specific lesion were used for agreement analysis of location on T2-weighted images. The slides as well as the T2-weighted images had a 90° flip-angle which was transferred accordingly to the anatomical preparation. Agreement and true positivity of the MRI lesion were

considered if there was exact agreement or a discrepancy with the pathologic lesion in up to one region in any direction [7]; correlation was assessed using Pearson`s correlation coefficient.

Correlation of the dimensions of the index lesion and the prostate volume on 3D-printed model and RP specimen was analysed by Pearson`s correlation coefficient and graphically by scatter plots and Bland-Altman plots (Figure 1). Statistical analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism (GraphPad Software, San Diego, USA).

Patients' demographic and histopathological data are given in Table 1. In all 10 cases, the index lesion of the 3D-print was correctly located considering the 36-region PI-RADS scheme compared to histopathology. 13/14 sPC lesions (93%) were also correctly located, resulting in a significant correlation with a Pearson's coefficient of 0.88 ($p<0.001$). Histopathology proved negative surgical margins (NSM) in 7 patients. PSM was found in three men suffering from locally advanced pT3 disease. These matched with the suspected extraprostatic extension (EPE) of MRI and the 3D-printed models. Out of the 3 cases with positive IFS, in two repeat resection demonstrated cancer free tissue out of which final pathology demonstrated PSM in one. In the last case a further resection was not possible due to infiltration of the urethral sphincter.

Measurements of tumor and prostate dimensions showed a significant correlation between the 3D-print and histopathology (length: $r^2=0.59$, $p=0.01$; width: $r^2=0.64$, $p=0.005$; tumor volume (TV): $r^2=0.52$, $p=0.045$; prostate volume: $r^2=0.70$, $p=0.002$). Pathology measurements were multiplied by a correction factor of 1.15 to compensate for tissue shrinkage due to formalin-fixation. Bland-Altman plots emphasize differences on TV between printed models and histopathology. Particularly, large tumors were

underestimated on MRI/3D-print as compared to pathology by up to 30%. Of note, the deviation increased with increasing TV, whereas smaller tumor dimensions had an accurate correlation. These results are in the line with findings by Baco et al., suggesting that mpMRI is able to predict the presence of extra-prostatic disease, rather than representing the EPE by means of volume [9]. Contrary the prostate volume is overrated in the MRI compared to histopathology (Figure 1).

Discrepancies of these volume measurements might be caused through different measurement types. Whereas the TV was measured using MITK software, the prostate volume was measured manually using the GE RIS/PACS software (Version 3.0, Chicago, Illinois, USA). Recent literature suggests that computer-assisted TV calculation might attenuate underestimation [10]. Comparison between the histopathologic slide and the sliced 3D-model might be influenced through marginally different heights of the MRI slide and the corresponding histopathologic slide.

Nonetheless, the visual and haptic aid of a 3D-model in an intraoperative setting can lead to more precise IFS. Pre- and intraoperative benefits of a 3D-model approach have been described, namely planning of a patient-tailored RP and training of surgeons undergoing the learning-curve [11,12]. The significant correlation of both, localization and lesion volume between histopathology and 3D-print in our study is crucial for the assumption that applying MRI-derived 3D-models might correctly guide IFS and increase the rate of NSM [6].

Chen et al. have recently shown that the use of a fused-deposition-modelling-printer is possible, resulting in much lower cost. Certainly, cost-efficient models which are printed in a short turnaround are favourable for the surgeon [13].

Some limitations of our manuscript merit discussion. Firstly, the number of patients in this feasibility study is limited. This small number of patients seems justifiable, due to

oncologic safety purposes. A strength of the study is that for the first time statistical analyses using correlation coefficients are presented to demonstrate not only feasibility, but also precision of preoperative imaging and 3D-models as compared to RP specimen. Secondly, we investigated only the PSM-rate, and not the more sophisticated surrogate of biochemical recurrence-free survival. However, for a direct analysis of an accurate application of MRI-guided IFS, the SM-status may be sufficient. We did not account for a comparison of a preoperative MRI alone versus MRI-derived 3D-models. In view of the recently updated European Association of Urology (EAU) guidelines, knowledge of the preoperative MRI results alone might be sufficient to facilitate patient-tailored RP as recently demonstrated [14,15]. For accurate prediction of EPE, standardized reading using ESUR classification is crucial, as accuracy is decreased by unstandardized MR-reading [14,16]. Lastly, the single-surgeon experience in this feasibility study limits generalizability of the results for cohorts consisting of multiple surgeons with different expertise.

Conflict of interest:

All authors of this manuscript indicate no conflicts of interest regarding the present work.

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Table legends:

Table 1:

Patient demographics and histopathologic characteristics.

Supplementary Material legends:

Supplementary Material 1:

Standards of Reporting of Diagnostic Accuracy (STARD) checklist

Figure legends:

Figure 1:

Figure 1A. Evaluation of different dimension modalities of the tumor and prostate comparing 3D-print/MRI with histopathology. For each analysis Scatter plots (left) and Bland-Altman plots have been performed. The red line shows the ideal line. The black line displays the balancing line. 1: Length of the tumor ($r^2 = 0.59$; $p = 0.01$), 2: Width of the tumor ($r^2 = 0.64$; $p = 0.005$), 3: Volume of the tumor ($r^2 = 0.52$; $p = 0.045$), 4: Volume of the prostate ($r2 = 0.70$; $p = 0.002$).

Figure 1B. All four images are taken from the same prostate. This prostate is printed out of liquid photopolymer cured through UV light, the tumor is presented in red photopolymer and more cured than the rest of the prostate. 1: mpMRI of the prostate with index lesion (caudal view), 2: 3D printed prostate with index lesion (photo is taken from caudal), 3: histopathology of the prostate with index lesion (caudal view) 4: 3D printed prostate with index lesion (cranio-dorsal view).