The Use of Augmented Reality to Guide the Intraoperative Frozen Section During Robot-assisted Radical Prostatectomy

Published Version:
Bianchi, L., Chessa, F., Angiolini, A., Cercenelli, L., Lodi, S., Bortolani, B., et al. (2021). The Use of Augmented Reality to Guide the Intraoperative Frozen Section During Robot-assisted Radical Prostatectomy. EUROPEAN UROLOGY, 80(4), 480-488 [10.1016/j.eururo.2021.06.020].

Availability:
This version is available at: https://hdl.handle.net/11585/847875 since: 2022-01-26

Published:
DOI: http://doi.org/10.1016/j.eururo.2021.06.020

Augmented Reality 3D guided intraoperative frozen section targeted to index lesion during nerve sparing RARP

Running title: *Augmented reality frozen section for robotic radical prostatectomy*

Bianchi L[1-2], Mineo Bianchi F[1], Chessa F[1-2], Angiolini A, Cercenelli L[3-4], Lodi S[5], Bortolani B[3], Casablanca C, Molinaroli E, Gaudiano C[6], Angiolini Mottaran A[1], Porreca[7], Golfieri R[6], Romagnoli D[7], Giunchi F [8], Fiorentino M [9], Diciotti S[5], Marcelli E[3], Schiavina R[1-2]*

[1] Department of Urology, University of Bologna, Bologna, Italy

[2] Department of Experimental, Diagnostic and Specialty Medicine (DIMES), Cardio-Nephro-Thoracic Sciences Doctorate, University of Bologna, Bologna, Italy

[3] Department of Experimental, Diagnostic and Specialty Medicine (DIMES), Laboratory of Bioengineering, University of Bologna, Bologna, Italy

[4]Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy

[5] Department of electrical, electronic and information engineering "Guglielmo Marconi", University of Bologna, Bologna, Italy

[6] Radiology Unit, Department of Diagnostic Medicine and Prevention, St. Orsola-Malpighi Hospital, Bologna, Italy.

[7]Department of Urology, Abano Terme Hospital, Padua, Italy.

[8] *Pathology Department* Azienda Ospedaliero-Universitaria di Bologna, Via Albertoni 15, Bologna- Italia

[9] Department of Experimental, Diagnostic and Specialty Medicine (DIMES), Pathology Department, University of Bologna, Bologna, Italy

Word count: 2689; Abstract word count: 300; Tables: 3; Figures: 4; References: 25; **Pages: 26**

Keywords: augmented reality; 3D reconstruction; real-time intraoperative frozen section; nerve sparing; robot assisted radical prostatectomy

ABSTRACT

Background: Intraoperative frozen section (IFS) can facilitate real-time surgical margins assessment during robot-assisted radical prostatectomy (RARP).

Objective: to propose a novel technique of augmented reality-3D (AR-3D) guided RARP with IFS targeted to the index lesion.

Design, Setting, and Participants: Twenty consecutive patients with index lesion detected at preoperative multiparametric Magnetic Resonance Imaging (mpMRI) underwent AR-3D guided RARP between March 2019 and July 2019 with IFS analysis directed to the index lesion projected by the 3D model (study group). Control group (n=20) consists of PCa patients with index lesion at mpMRI undergone standard RARP, 1:1 propensity-score-matched for age, clinical stage, clinical ISUP grade and PSA.

Surgical Procedure: In study group, AR-3D superimposed model was used to guide the surgical dissection. IFS analysis was performed by sampling tissue in the periprostatic area in which the index lesion is projected by AR-3D guidance.

Measurements: Chi-squared test, T-student test and Mann-Whitney U-test were used to compare proportion, means and medians between study and control group.

Results and limitations: On a patient-based analysis, patients in AR-3D guided IFS group received higher proportion of unilateral and bilateral nerve sparing (NS) compared to those in control group (25% vs. 20% and 65% vs. 45%, p=0.009. Overall, PSMs rates were comparable between the two groups (15% vs 25%, p=0.2). PSMs at level of the index lesion were significantly lower in patients referred to AR-3D guided IFS to the index lesion (5%) compared to control group (20%, p=0.02).

Conclusion: The novel technique of AR-3D guidance for IFS analysis allows to reduce the PSMs at level of the index lesion and to increase the NS approach.

Patient Summary: AR-3D guidance for IFS analysis during RARP facilitate the real-time assessment of surgical margins and allows to combine reduction of PSMs at level of the index lesion and preservation of neurovascular bundles.

Introduction

Positive surgical margins (PSMs) during radical prostatectomy (RP) are strong predictors of biochemical recurrence (BCR)[1,2,3]. Thus, different surgical techniques were introduced to reduce PSMs[1] and several methods have been proposed for "real-time" evaluation of surgical margins[4]. The cognitive guidance of multiparametric magnetic resonance imaging (mpMRI) during robot assisted RP (RARP) may improve neurovascular bundles (NVBs) preservation and avoid PSMs[5,6,7]. Intraoperative frozen section (IFS) analysis is the most commonly used technique for real-time assessment of surgical margins during RARP[4], despite some authors reported low sensitivity[8,9] . Moreover, the ways to collect samples for IFS include different techniques[10]. A systematic IFS analysis was originally proposed to monitor the safety of nerve sparing (NS), using a whole neurovascular structure–adjacent frozen section examination (NeuroSAFE)[11]: significant increase of NS and reduction in PSMs were reported, without compromising oncologic safety[11,12,13]. Alternatively, IFS can be directed to the index lesion detected by mpMRI since the larger volume index lesions are responsible for the vast majority of PSMs[5]. Indeed, Petralia et al.[14] reported that mpMRI-directed IFS was able to reduce the risk of PSMs. However, this approach is limited by a cognitive evaluation during surgery. In the era of patient-tailored surgery, the augmented reality (AR) technology by overlapping of 3D models in the robotic view could facilitate the intraoperative navigation by identifying the index lesion and guiding IFS samples. We aimed to propose a novel technique of AR-3D guided IFS for real-time assessment of surgical margins during NS RARP and to evaluate the impact of this novel approach on PSMs.

Materials and methods

Study design

This was a retrospective analysis of prospectively acquired data. We prospectively enrolled patients with diagnosis of PCa basing on positive mpMRI-targeted Fusion biopsy at the index lesion[15] and preoperative preserved erectile function (International Index of Erectile Function-5 [IIEF-5] questionnaire >21[16]) scheduled for NS RARP at single tertiary centre. The study was conducted in accordance with Good Clinical Practice after Institutional Ethics Committee (IRB approval 4325/2017) and informed consent was obtained from each patient. Exclusion criteria were absolute contraindications for robotic surgery, no index lesion at mpMRI or mpMRI not available.

Study Group

Overall, 26 consecutive PCa patients with index lesion detected at preoperative mpMRI underwent RARP between March 2019 and July 2019. Prior to the intervention, patients enrolled were addressed to undergo 3D virtual model reconstruction based on preoperative mpMRI images. Finally, the surgeon performed RARP with the help of the 3D model projected in AR inside the robotic console (AR-3D guided RARP). For the purpose of this study, we included only 20 patients underwent AR-3D guided RARP with implementation of real-time IFS analysis directed to the index lesion projected by the 3D model (study group).

Control group

Overall, 387 PCa patients with suspected index lesion at preoperative mpMRI, complete clinical, intra-operative and pathologic data underwent standard mpMRI guided NS RARP from January 2018 to July 2019 without the aid of 3D-AR technology neither IFS analysis (control group).

To reduce the inherent differences between patients undergoing mpMRI guided RARP and those referred to 3D-AR guided RARP with IFS analysis, we used a 1:1 propensity-score-matched analysis adjusted for age, clinical stage, clinical ISUP grade and preoperative PSA. The matched population (n=40) included 20 patients on study group and 20 patients in control group.

Preoperative imaging

All the mpMRI examinations in both groups were performed with a 1.5-T whole body scanner (Signa HDxt; GE Healthcare, Milwaukee, WI, USA) and a standard 8-channel pelvic phased-array surface coil combined with a disposable endorectal coil (MedRad, Indianola, Pa) as previously described[7]. All lesions were scored using the PI-RADS-v2 score[17]. The index lesion is the one with the highest PIRADS-v2 assessment category[17].

3D Model reconstruction

All 3D virtual models were based on preoperative mpMRI. Segmentation was achieved using D2P™ software ('DICOM to PRINT'; 3D Systems Inc., Rock Hill, SC); semi-automatic tools (*multi-slice interpolation* and *threshold segmentation)* of D2P™ software were adopted to segment the healthy prostatic gland, the index lesion, the urinary sphincter and the NVBs. D2P™ was also used to obtain the 3D virtual models, as previously described. (Figure 1a-b)

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Augmented Reality technology

The surgical video stream has been acquired from DaVinci video cart via a frame grabber (USB3HD, Startech, London, Ontario, Canada) and sent to an AR-dedicated PC (equipped with an Intel i7 CPU, 8 GB RAM and NVIDIA GeForce 840M video card). A 3D view of the virtual model obtained using Meshmixer software (Autodesk Inc, San Rafael, CA, US), was superimposed on the aforementioned operatory field with vMIX (StudioCoast Pty Ltd, Robina, Queensland, Australia), as previously described. The DaVinci TilePro has been activated in the console (Figure 1c) and real-time manual alignment has been carried out by a biomedical engineer using a 6 degrees of freedom (3D) mouse (SpaceMouse, 3D Connexion, Munich, Germany).

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Surgical technique

All patients underwent RARP using four-arm DaVinci Xi Surgical System (Intuitive Surgical, Sunnyvale, California, USA), as previous described[18,19]. The NS approaches were classified on patient-based level (considering 40 patients) as bilateral NS, unilateral NS, or non–NS. Indeed, the extent of NVB preservation was recorded on side-based level (considering 80 sides) as Grade 1, Grade 2, Grade 3-4 according to incremental NS classification as described by Tewari et al[20].

AR-3D guided NS RARP with real time IFS analysis

AR-3D superimposed model was used to identify the site of the mpMRI-derived 3D index lesion during RARP (Figure 2a-b) and to drive the surgical dissection of crucial steps (namely, apex, bladder neck and NS), through the TilePro visualization, as previously described. Therefore, a sample from the periprostatic tissue was taken in the periprostatic area in which the index lesion is projected by AR-3D guidance (Figure 2c-d) and sent for

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IFS (first IFS). In case tumor cells were detected in the tissue's sample (first IFS), the AR-3D model was superimposed in the surgical view to guide the resection of a second deeper and wider sample of periprostatic tissue in the area of the index lesion derived by AR-3D guidance and sent for IFS (second IFS). If tumor cells were found in the secondary resection tissue, further resections were performed. In case of apical or bladder neck location of the index lesion, a partial resection of periprostatic tissue was send for IFS analysis at apical or basal aspects, respectively. In case of postero-lateral location of the index lesion, a partial resection of the ipsilateral NVB was performed by IFS analysis in the area nearby the index lesion: in case presence of PCa cells in the second IFS, a complete resection of the ipsilateral NVB was performed.

Standard mpMRI guided NS RARP

During standard RARP, the intraoperative dissection of NVBs and the apex were guided by clinic data and cognitive evaluation of mpMRI information without the implementation of IFS analysis, as previously described[7].

Histopathological examination

All the pathological examinations including first and second IFS samples were performed by a single dedicated uro-pathologist. The whole mount histological examinations from the RARP specimens were performed following a prostate map as previously described[21]. The index lesion was identified as the lesion with the highest Gleason score; in case of more than one lesion with the highest Gleason score, the focus with larger volume was detected as the index lesion. The surgical margins were considered as positive if tumor cells are in contact with the ink on the specimen surface when cancer tissue was present on the inked

Commentato [LB4]: Cita AR RARP in press surface of the prostate specimen. The tissues for IFS analysis were prepared for staining with hematoxylin and eosin for microscopic examination: presence of PCa cells in IFS samples was considered positive, thus patients underwent secondary periprostatic tissue resection. (Figure 3a-b)

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Statistical analyses

Chi-squared test, T-student test and Mann-Whitney U-test were used to compare proportion, means and medians between the 3D-AR guided RARP with IFS and the matched population of cognitive mpMRI guided RARP. A p value of <0.05 was considered statistically significant. All statistical tests were performed using SPSS 22.0 (IBM, Harmonk, NY, US) for Mac.

Results

Patients characteristics and mpMRI parameters

After matching 1:1, there were no significant differences between the two groups concerning the covariate used for the propensity score match (all $p \geq 0.07$; Table 1). Preoperative mpMRI reported organ confined index lesion, suspected ECE and SVI in 17 (80%), 3 (20%) and 0 (0%) patients referred to AR-3D guided IFS approach and in 16 (80%), 3 (15%) and 1 (5%) patients referred to mpMRI guided approach (p=0.5).

Intraoperative outcomes and nerve-sparing approach

Mean console time and estimated blood loss were comparable between AR-3D guided IFS group (216 min and 200.2 ml) and mpMRI guided group (196 min and 191.8 ml; all $p \geq 0.4$; Table 2). On a patient-based analysis, patients in AR-3D guided IFS group received higher proportion of unilateral and bilateral NS compared to those in mpMRI guided group (25% vs. 20% and 65% vs. 45%, p=0.009); similarly, on side-based level, Grade 1, 2 and 3-4 NS have been performed in 17 (42.5%), 9 (22.5%) and 14 (35%) sides vs. 8 (20%), 12 (30%) and 20 (50%) sides in patients referred to AR-3D guided IFS RARP compared to mpMRI guided RARP (p=0.002; Table 2).

AR-3D guided IFS approach

In 4 patients the AR-3D guided IFS analysis (first sample) revealed the presence of residual PCa cells in the periprostatic tissue in contact with the index lesion (2 apical and 2 postero-lateral location). All these patients underwent a secondary resection (second sample) of periprostatic tissue, that resulted negative for the presence of PCa in all cases, contributing to conversion into negative surgical margins in 3 patients at final pathology:

only 1 out 4 patients revealed PSM outside the index lesion. In 16 patients the AR-3D guided IFS analysis (first sample) was negative for PCa and contributed to conversion into negative surgical margins in 14 patients at final pathology: 2 men revealed PSMs, including 1 PSM at level of the index lesion (Figure 4).

Positive surgical margins status

Overall, PSMs rates were comparable for AR-3D guided IFS RARP and mpMRI guided RARP (15% vs 25%, p=0.2; Table 3). Similarly, no differences were found between the two groups concerning PSMs rates after stratifying according to pathologic stage and site of PSMs. However, PSMs at level of the index lesion were significantly lower in patients referred to AR-3D guided IFS directed to the index lesion (5%) compared to men treated with mpMRI-guided approach (20%, p=0.02; Table 3).

Discussion

Different surgical techniques were introduced to reduce PSMs[1] and several methods have been proposed for "real-time" evaluation of surgical margins[4].

A systematic IFS of postero-lateral prostatic surface (NeuroSafe) showed significantly higher NS approach and lower PSMs with conversion to a definitive negative surgical margin in 86% of cases, suggesting that the benefit of increased NS was not achieved at the expense of higher rates of PSMs both with open[11] and robotic approach[13]. Recently, the diffusion of imaging-guided surgery has led to a more selective approach for IFS, despite there is no consensus regarding the appropriate sites, methods or clinical indications for IFS analysis[22]. Indeed, the accuracy of mpMRI to identify the dominant index Pca has been proposed as a promising tool for mpMRI-guided IFS. Petralia et al[14]. report a 11.3% reduction in PSM when the site submitted for IFS was selected according to the preoperative mpMRI report. The final result by combining IFS and mpMRI data lead to lower rates of overall PSMs (7.5%)[14] compared to previous report of IFS without the use of mpMRI (25%)[11]. Of note, the added value of mpMRI allows to direct IFS analysis to the areas at highest risk of PSMs.

However, it is not a "real-time" method to evaluate the surgical anatomy during RARP and main concern regards the lack of precision to localize the index lesion and the contact with the periprostatic tissue in real time manner. To note, high fidelity 3D models represent one of the most appealing method for better understanding of "in vivo" surgical anatomy and for intraoperative "real-time" navigation during RARP[23,24]. Porpiglia and co-workers[23,24] have reported their preliminary experience with the use of AR technology of 3D models, overcoming the cognitive reconstruction and improving surgical outcomes.

The approach proposed in our work is a novel strategy for the application of AR-3D technology to guide surgical dissection during RARP. Current way to use AR-3D guidance is focused to modulate the NS approach tailored to the index lesion, by resecting more

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tissue nearby the lesion and preserving more tissue outside the lesion[24]. The potential to identify in real time the location of the index lesion during RARP could be used to target the IFS analysis of periprostatic tissue in the area nearby the index lesion overlapped in the robotic view through AR-3D guidance.

Several findings are noteworthy. First, the proposed IFS analysis targeted to the index lesion with AR-3D model implementation may prevent blinded resection of functional periprostatic tissue (both nearby the urethra and the NVB). Of note, the AR-3D guidance for IFS has the advantages to resect tissue nearby the index lesion and to spare periprostatic tissue far from the tumour, with the aim to preserve functional results together with improving oncologic outcomes. Second, the proposed AR-3D guided IFS analysis allows to selectively analyse the periprostatic tissue regardless location of the index lesion. Thus, since the larger volume index lesions are responsible for almost all PSMs[5], the AR-3D guidance for IFS allows to significantly reduce PSMs at index lesion identified by 3D model compared to control group (5% vs. 20%), despite similar overall PSMs. It could be explained with the predominant role of mpMRI and cognitive information to guide NS surgery even without the implementation of AR-3D model and IFS. Third, despite higher Gleason score and pT stage in patients referred to the NeuroSAFE approach, some authors[11,12,13,25] reported higher potency rates and pad-free continence[25], due to higher NVB preservation. Similarly, in our cohort, patients underwent AR-3D guided IFS had higher rates of NS approach both on patient-based level (25% vs 20% unilateral NS and 65% vs. 45% bilateral NS) and side-based level (42.2% vs.20% Grade 1 NS) compared to control group. Fourth, our AR-3D guided IFS approach does not significantly prolong overall surgical time by using the waiting time for IFS analysis to perform hemostasis, completion of the anastomosis and lymph node dissection.

Despite several strengths, our study is not devoid of limitations. First, this study is retrospective, and it could be biased from not modifiable confounding factors. However, the adoption of propensity score match, aims to reduce the inherent differences between the two groups. Second, the first IFS analysis was targeted to a limited sample of periprostatic tissue in contact with the index lesion, limiting the accuracy of proposed IFS analysis. Indeed, major concern of IFS analysis consist in false negative results, since a wide range in sensitivity and specificity has been reported[4]. Third, we cannot separate the contribution of AR-3D guided approach and IFS analysis to reduce the PSMs rate at index lesion. Of note, the results of IFS analysis of periprostatic tissue is strongly related to the level of dissection, since IFS in case of more radical resection of NVBs nearby the index lesion had higher chance to result in a negative IFS. Fourth, the presence of PSMs outside the index lesion detected by AR-3D model and sampled with IFS analyses in 2 patients (1 pT2a and 1 pT3b) indicates a failure of the modality to identify of all significant tumour foci by mpMRI or mpMRI-derived 3D model, in case of bilateral tumour involvement or microscopic involvement of prostatic capsule. Finally, the major limitations of AR-assisted surgery consist of possible registration inaccuracy, translating into a poor navigation precision and the need of manual external adjustments, thus tissue samples for IFS analysis guided by overlapped 3D model may be objective of inaccurate due to error in registration process.

Conclusions

The proposed technique of AR-3D guidance for IFS analysis allows to reduce the PSMs at level of the index lesion regardless location within the prostate and to increase the preservation of NVBs. The AR-3D guided approach with IFS targeted to the 3D index lesion could be the evolution of NeuroSAFE technique and allows to modulate the NS surgery tailored to the index lesion with the aim to maximize both oncologic and functional outcomes.

Acknowledgment: None

Author Disclosure Statement: No competing financial interests exist

Conflict of interest

The project was supported by a Technology Research Grant by Intuitive Surgical for the development of augmented reality technology in robotic surgery.

Figure legend

Figure 1 The 3D virtual anatomical model is obtained starting from patient mpMRI (a), by the segmentation (b) of the anatomical regions of interest (prostatic gland, index lesion, urinary sphincter and neurovascular bundles) to the final 3D model (c) that is overlapped in the robotic view through the Augmented Reality technology (d)

Figure 2: Example of AR-3D guided surgical dissection for real-time assessment of the index lesion during the nerve sparing RARP through the TilePro visualization and AR-3D guided IFS analysis. A 17 mm left postero-lateral apical index lesion (a) PIRADS v.2 score 5 (yellow area) is detected by mpMRI (Gleason score 3+4 in 6 cores at fusion-targeted biopsy). The 3D model (b) is employed with reconstruction of the index lesion (yellow), prostate glands (pink), urethra (light blue) and neurovascular bundles (blue). AR-3D guided RARP with IFS analysis targeted to the projected index lesion was performed (c). A first sample of the postero-lateral periprostatic tissue is taken for IFS analysis at level of the index lesion guided by AR (d). The first frozen section resulted negative for tumoral cells, thus the surgeon performed a Grade 2 nerve sparing on the left side, modulating the dissection in real time avoiding a plane of dissection too close at level of the index lesion.

Figure 3: The whole mount prostate specimen (a) revealed a predominant left apical tumors Gs 4+3 pT3a with negative surgical margins. The index lesion is covered by thin amount of periprostatic tissue and the final pathologic reports of IFS analysis targeted to the index lesion confirmed the absence pf prostate cancer cells (b)

Figure 4: Diagram depicts the IFS analysis results and final pathologic examinations in patients who underwent AR-3D guided RARP with real time IFS directed to the index lesion. Final pathologic examinations findings in matched patients who underwent mpMRI guided RARP (control group) are shown.

Video

Example of AR-3D guided surgical dissection during RARP through the TilePro visualization and real time AR-3D driven IFS analysis of periprostatic tissue targeted to the projected index lesion.

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