GRADUATION INTERNSHIP
TECHNICAL MEDICINE

The Usability of PCaVision

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> *Usability is about people and how they understand and use things, not about technology.*

— **Steve Krug**
(Usability consultant and author of *The Do-It-Yourself Guide to Finding and Fixing Usability Problems*)

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Master thesis

Workflow and user interface optimization for three-dimensional multiparametric transrectal ultrasound in prostate cancer diagnostics

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Summary

Introduction: Multiparametric magnetic resonance imaging (mpMRI) is widely used as an imaging tool for prostate cancer (PCa), but it has varying sensitivity and specificity and relies on specialized radiologists. To address these limitations, 3-dimensional multiparametric ultrasound (3D mpUS) has been introduced to enhance US-based PCa diagnosis. Nevertheless, its lack of standardization and reliance on operator expertise hinder widespread adoption. This study evaluates operator dependency in the standardized 3D mpUS recording procedure and develops a PCaVision-based diagnostic workflow for cognitive and fusion-targeted biopsies.

Methods: This thesis comprises two studies. The first evaluates operator dependency of the 3D mpUS recording procedure and compliance with quality standards through usability tests. The second study utilizes a design study approach, collaborating with end-users and conducting formative usability testing of the PCaVision-based diagnostic workflow and graphical user interface.

Results: Usability tests showed high compliance with procedural steps and troubleshooting, with only two minor use errors. The training program effectively enhanced operator confidence, and most scans met quality standards. The second study resulted in the development of the PCaVision-based diagnostic workflow, although one design requirement was partially fulfilled. The primary workflow facilitated cognitive targeted biopsy, and the usability evaluation yielded a System Usability Score (SUS) of 60.

Discussion: Both studies contributed to establishing a standardized 3D mpUS pathway using PCaVision. The standardized recording procedure proved effective, boosting operators' confidence with minimal errors. While the training program and device's usability may be enhanced, the procedure is easy to learn and user-friendly. The prototype of the primary PCaVision-based workflow enabled cognitive biopsies, while the fusion-targeted biopsy workflow requires further validation. Enhancements in usability are required for both training and the GUI. Overall, these results suggest that PCaVision holds promise as a valuable tool, but additional trials are necessary to validate its clinical utility and role in the diagnostic workflow of prostate cancer.

Conclusion: The first study's findings highlight operators' successful training in the standardized 3D mpUS recording procedure, resulting in increased confidence and minimal errors. The primary PCaVision-based diagnostic workflow enables cognitive targeted biopsy, whereas the fusion-targeted biopsy workflow requires further validation. The standardization of the 3D mpUS pathway is an essential cornerstone for the future of accurate and effective PCa diagnostics.

Keywords: 3-dimensional multiparametric ultrasound (3D mpUS); Prostate cancer (PCa); Operator dependency; PCaVision; Cognitive and fusion-targeted biopsy; Usability testing; Standardization.

Contents

List of definitions

3D	3-dimensional
4D	4-dimensional
AA	Angiogenesis Analytics
ADC	Apparent diffusion coefficient
AOI	Area of interest
CADMUS	Cancer diagnosis by multiparametric ultrasound
CE	Conformitee Europeenne
CEUS	Contrast-enhanced ultrasound
CI	Confidence interval
csPCa	Clinically significant prostate cancer
CUDI	Contrast-US-dispersion imaging
DCE	Dynamic contrast-enhanced imaging
DP	Doppler imaging
DWI	Diffusion-weighted imaging
EAU	European Association of Urology
GG	Grade Group
IFU	Instructions for use
iPCa	Clinically insignificant prostate cancer
ISUP	International Society of Urological Pathology
MDR	Medical Device Regulations
mpMRI	Multiparametric Magnetic Resonance Imaging
mpUS	Multiparametric ultrasound
MRI	Magnetic Resonance Imaging
PB	Prostate Biopsy
PCa	Prostate cancer
PI-RADS	Prostate Imaging Reporting and Data System
PSA	Prostate-specific antigen
SBx	Systematic biopsy
SOP	Standard operating procedure
SUS	System Usability Scale
SWE	Shear wave elastography
T1W	T1-weighted imaging
T2W	T2-weighted imaging
TBx	Targeted biopsy
TRUS	Transrectal ultrasound
US	Ultrasound

Preface

This thesis reflects the culmination of my 10-month graduate internship for the master's program in *Technical Medicine - Medical Imaging Interventions*. It is the result of a collaboration between the Department of Urology at Amsterdam University Medical Centers (Amsterdam UMC) and Angiogenesis Analytics (AA). While the clinical testing was carried out at the Amsterdam UMC and Netherlands Cancer Institute, the AA product team developed the medical device PCaVision. During this project, it became clear that PCaVision had room for usability improvement while aiming for CE certification. Recognizing the chance to improve both my clinical competence and innovation skills, I dedicated my graduation internship to researching the usability of the medical device PCaVision. The goal was to become an expert clinical user of the device as a technical physician, teach other medical professionals, and test the technology in a real-world setting.

The thesis is divided into seven chapters, each addressing specific aspects of the research. The clinical background is discussed in Chapter 1, outlining the challenges faced in current clinical practice when utilizing multiparametric ultrasound. This chapter also introduces the PCaVision medical device and its proposed method for prostate cancer diagnostics. The technological foundation of several imaging pathways and the chosen approach for assessing usability are addressed in detail in Chapter 2. An overview of the studies is given in Chapter 3, outlining the specific study objectives. The usability study for the standardized 3D mpUS recording procedure is covered in Chapter 4. Chapter 5 details the design of a PCaVision-based workflow for prostate cancer diagnosis. A comprehensive discussion of the overall findings and recommendations for integrating PCaVision into the diagnostic workflow of prostate cancer is provided in Chapter 6. Finally, the thesis finished with a general discussion in Chapter 7.

Remark: The next chapters of this thesis are prepared in a way that they can be read independently. As a result, several chapters have information that is redundant. The report's structure was improved using ChatGPT for content organization and coherence.

1 Clinical background

In this first chapter, a detailed overview of prostate cancer will be presented, along with the current diagnostic approach and a novel imaging modality. Additionally, the chapter will introduce the medical device PCaVision and explore its potential to enhance prostate cancer diagnosis.

1.1 Prostate cancer

Prostate cancer (PCa, Figure 1.1) is the second most commonly diagnosed cancer in males, with a total of 107 000 deaths in 2018 in the EU, and is the fifth leading cause of cancer deaths in men [1, 2]. Developing countries have a higher prevalence, and differences in incidence rates worldwide reflect differences in diagnostic testing.

Men with increased age, black race, and a family history of the disease have a higher risk for PCa [3]. Although body fatness, adult-attained height, dairy products, a diet high in calcium, and low plasma selenium and alpha-tocopherol concentrations are sometimes associated with increasing the risk of PCa, the clinical evidence is poor [4].

In 2020, more than 14 600 men were diagnosed with PCa in the Netherlands alone. Due to the increasing elderly population, the number of PCa patients is expected to reach 18 300 in 2040 [5].

However, not all prostate cancers are clinically significant. Clinically significant prostate cancer (csPCa) is likely to cause harm if left untreated and is typically characterized by an International Society of Urological Pathology (ISUP) Grade Group (GG) of 2 or higher [6, 7]. The ISUP GG assigns a grade of 1 to 5 to prostate cancer based on its aggressiveness and assists in determining therapy options [7]. Clinically insignificant prostate cancer (iPCa) is characterized as ISUP GG 1 and is not likely to progress or cause harm.

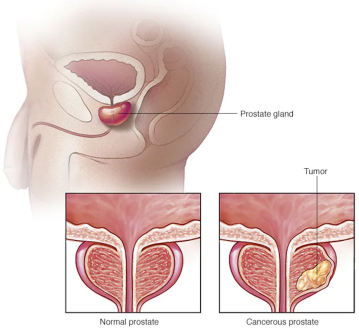


Fig. 1.1.: Prostate anatomy. Left: normal prostate. Right: cancerous prostate.

1.2 Present diagnostic pathway

To effectively manage and treat PCa, it is critical to accurately assess and characterize the presence of clinically significant tumors, the corresponding tumor grade, and the progression risk. When these criteria are accurately determined, overtreatment of individuals with minimal progression risk and undertreatment of those with clinically significant malignancy can be avoided [8, 9].

Multiparametric Magnetic Resonance Imaging (mpMRI) uses T2-weighted, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging to visualize tissue structure and vascularity. These images help the urologist to determine if a suspected lesion is csPCa. The European Association of Urology (EAU) guidelines recommend performing a mpMRI as an imaging tool in men with a clinical suspicion of PCa. This recommendation is based on three prospective multi-center trials. These studies found that MRI-guided targeted biopsy reduced the number of biopsy procedures and the detection of iPCa while maintaining the detection of csPCa (GG 2), as compared to transrectal ultrasound (TRUS) systematic biopsy [10–12]. Based on 12 studies including 3091 patients, MRI has a sensitivity of 0.91 (95% Confidence Interval, CI: 0.83-0.95) and a specificity of 0.37 (95% CI: 0.29-0.46) for detection of csPCa [13]. Due to its high sensitivity and negative predictive value, men with a negative MRI have a low risk of having csPCa. This allows men who have a negative MRI and no other high-risk factors to avoid having a biopsy.

Unfortunately, MRI-based PCa diagnosis has multiple drawbacks and limitations. MRI has a significant variation in sensitivity and specificity between individual studies [14, 15], which can be attributed to differences in MRI equipment, study design, and inter-observer variability [16–20]. In addition to its limited accessibility, MRI is a time-consuming, expensive imaging technique that is not available as a point-of-care test and requires highly qualified radiologists for interpretation. To improve the early detection of PCa, the EAU provides clear recommendations for the effective use of prostate-specific antigen (PSA) testing as a component of a risk-adapted strategy, which will increase the demand for MRI imaging [21, 22]. To summarize, MRI is a valuable diagnostic tool, but its limitations will prove challenging to meet the growing need for prebiopsy imaging using MRI alone.

1.3 Novel imaging modality

The urologist is familiar with ultrasound (US), which is widely accessible, and inexpensive to use, but only advised for prostate biopsy guidance at this time [12]. New US modalities, including contrast-enhanced US (CEUS) and shear wave elastography (SWE), have been introduced to improve US-based PCa diagnosis [23, 24]. An ultrasound contrast agent (CA) is intravenously injected during a CEUS procedure to improve cancer detection [25]. The ultrasound contrast agent's dispersion in the vascular network is measured over time, allowing visualization of angiogenesis. For PCa to develop into a clinically significant disease, angiogenesis is necessary [26]. Furthermore, it has been demonstrated that the degree of angiogenesis is correlated with PCa aggressiveness [27–29]. Contrast-US-dispersion imaging (CUDI), which focuses on the identification of angiogenetic alterations in the microvascular architecture, provides several parameters that can be used for PCa localization [30–32]. According to research by Mannaerts et al., the combination of B-mode, SWE, and CEUS has a significantly higher sensitivity of 74% (95% CI: 67-80) compared to B-mode, SWE, and CEUS alone [33]. These have an individual sensitivity of 55% (95% CI: 47-63), 55% (95% CI: 47-63), and 59% (95% CI: 51-67), respectively. In 2019

the methods were validated in a head-to-head comparison against MRI. In total, 150 biopsy-naïve men underwent mpMRI and CUDI prior to biopsies. When one or more lesions were identified on MRI and/or CUDI, the lesions were sampled separately using the relevant imaging modality for targeting the biopsies (TBx). The procedure was followed by 12-core SBx, showing a comparable PCa detection rate for the mpMRI- and CUDI-TBx strategy [34]. A similar clinical study will start in Q2-3 2023 with improved CUDI algorithms.

The CADMUS trial demonstrated that multiparametric ultrasound (mpUS) has the ability to detect csPCa at a similar rate as mpMRI. However, when used alone, more patients required a biopsy with mpUS than with mpMRI [35]. The study used a hand-held two-dimensional image acquisition, which makes it a time-consuming procedure and the quality of the image operator dependent. Mannearts et al. used 3 planes (base, mid, and apex) to sequentially scan the three imaging modalities: the interobserver agreement was 0.23 (95% CI 0.18-0.28) for B-mode, 0.36 (0.31-0.42) for SWE, 0.32 (0.26-0.37) for CEUS and 0.33 (0.28-0.38) for mpUS [33]. This demonstrates how operator-dependent present approaches are and the necessity for developing a standardized clinical workflow for mpUS [36, 37].

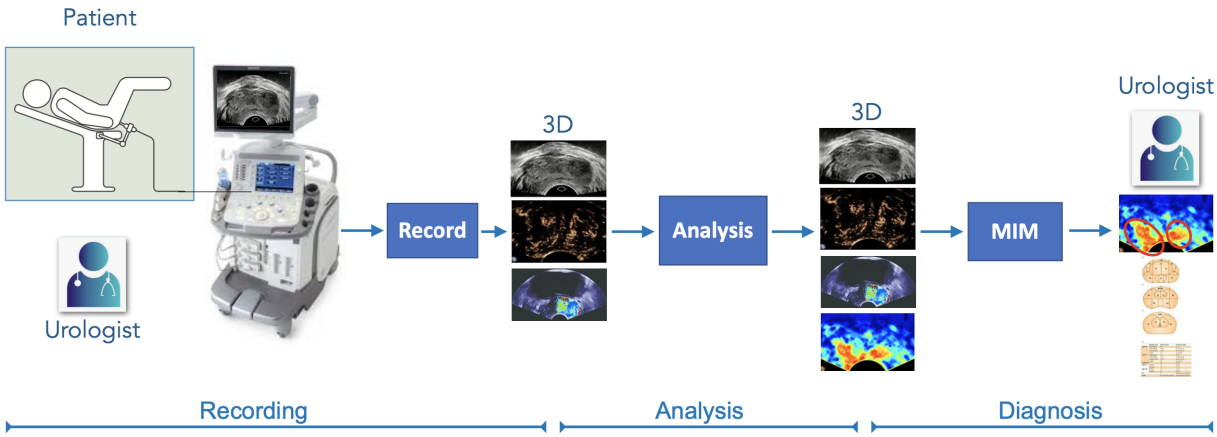


Fig. 1.2.: Workflow of PCaVision: 1) Recording, 2) Analysis, and 3) Diagnosis of PCa.

1.3.1 PCaVision

The Biomedical signal processing group at TU Eindhoven, the Urology department at the Amsterdam University Medical Centers (Amsterdam UMC), and Angiogenesis Analytics (AA) work closely together to further develop the mpUS method into a commercial medical product, named PCaVision. PCaVision is a medical diagnosis decision support system capable of supporting the detection, localization, and characterization of PCa lesions based on US images. PCaVision consists of three steps, as visualized in Figure 1.2. First, the transrectal ultrasound images will be recorded, then an artificial intelligence algorithm will analyze the images, and finally, the urologist will assess the images for suspected PCa lesions. This research is aimed at optimizing the recording and diagnosis procedure by means of a usability study.

The product's architecture is depicted in Figure 1.3. Three-dimensional (3D) mpUS will be performed using the GE LOGIQ E10 US machine (GE Healthcare, Chicago, USA). A probe fixture is required to provide fixation of the transrectal ultrasound imaging probe during the TRUS examination. A computing module (the off-the-shelf embedded computer which is enclosed in

a medical-certified housing) is attached to the ultrasound machine with a wired network cable, enabling PCaVision to communicate and acquire data.

PCaVision is intended to:

1. Provide images and analysis of the prostate to aid the physician in:
    a) Identifying the absence or presence of csPCa lesion(s);
    b) Determining the position of suspected csPCa lesion(s);
2. Enabling targeted biopsy planning and execution.

PCaVision is operated by the urologist or a specialized urology assistant in the regular clinical urology consulting room. The output of PCaVision supports the urologist in making the final diagnosis for further clinical intervention planning and facilitates targeted biopsy procedures.

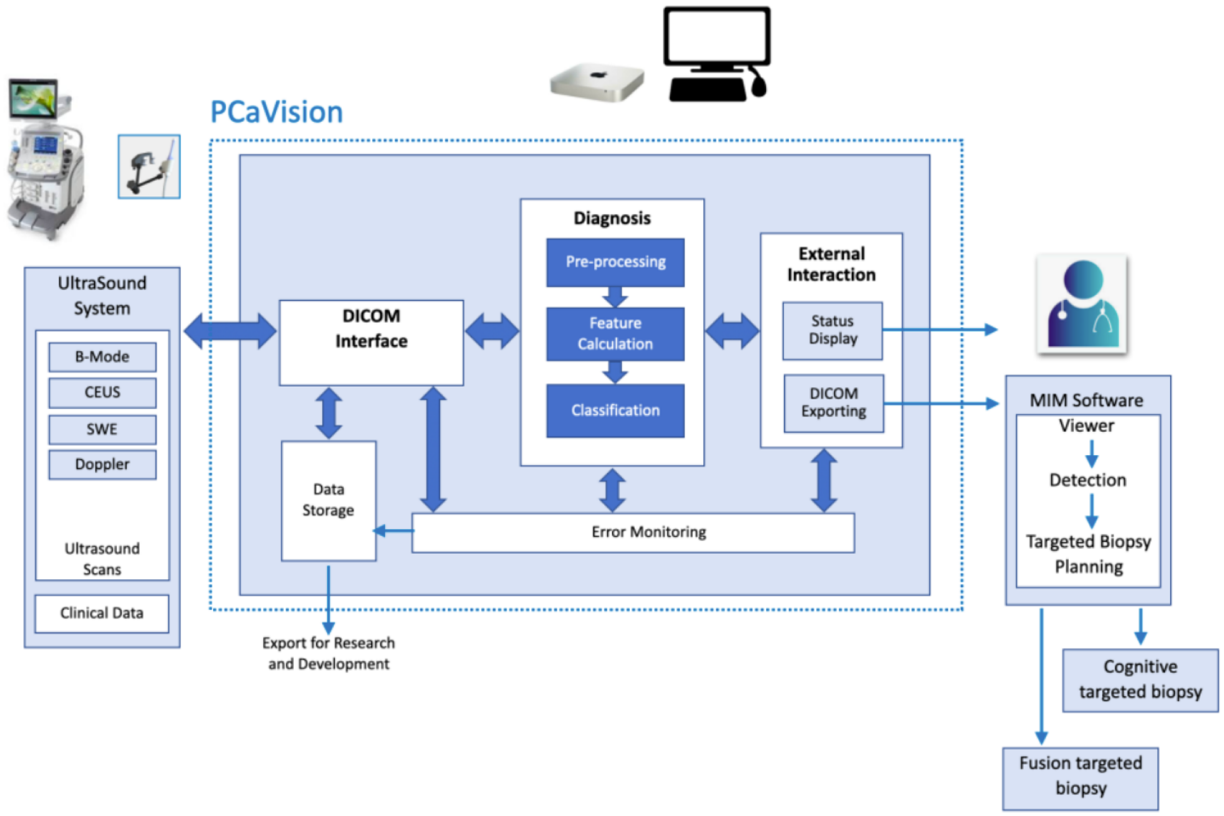


Fig. 1.3.: PCaVision software architecture. On the left: acquisition of 4 ultrasound modalities with an ultrasound machine and probe fixture. In the center: PCaVision software connection with the ultrasound machine and computing module. On the right: the output of PCaVision is provided to a urologist in MIM software for potential targeted biopsy.

1.3.2 Present and future PCa diagnosis pathways

Nowadays, the diagnostic care pathway for PCa entails the urologist referring the patient to a radiologist for an MRI, which is subsequently examined by a qualified radiologist. The urologist receives the report and decides whether prostate biopsies are indicated. The biopsy procedure results in a pathological diagnosis and determines the treatment plan. Future diagnostic pathways are envisioned using PCaVision. The urologist will not refer the patient to radiology, but instead

will perform a PCaVision scan instead. As soon as this is completed, the urologist can evaluate the US images and determine whether prostate biopsies are indicated. As a result, this care pathway may have a quicker turnaround time than we currently have. The pathways are visualized in Figure 1.4.

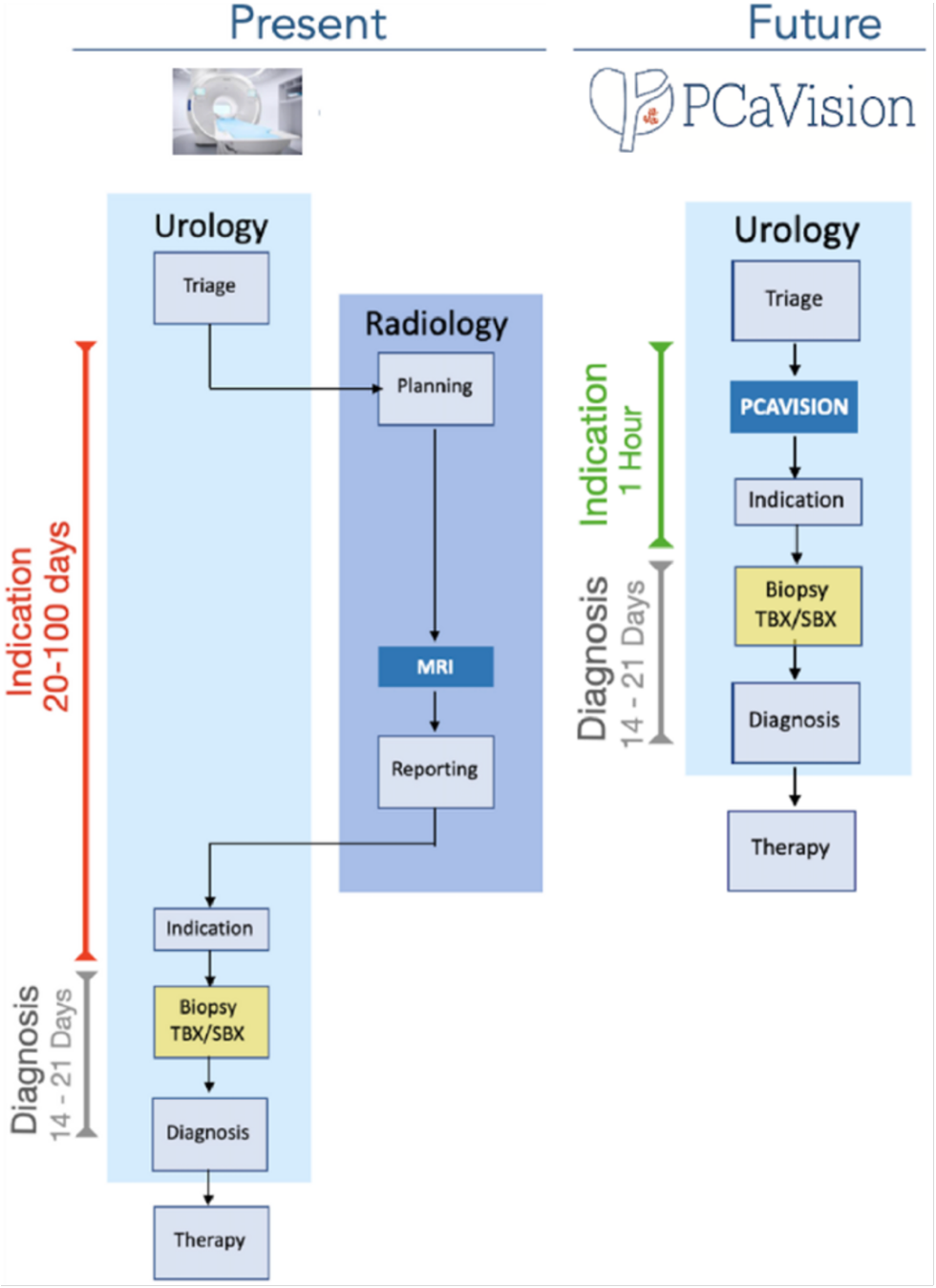


Fig. 1.4.: Present and future PCa diagnosis pathways.

Technical background

2

This chapter discusses multiple imaging modalities for prostate cancer diagnosis, including multiparametric MRI and its role in prostate biopsy. The potential benefits of multiparametric ultrasound and the importance of conducting usability studies for medical devices are discussed.

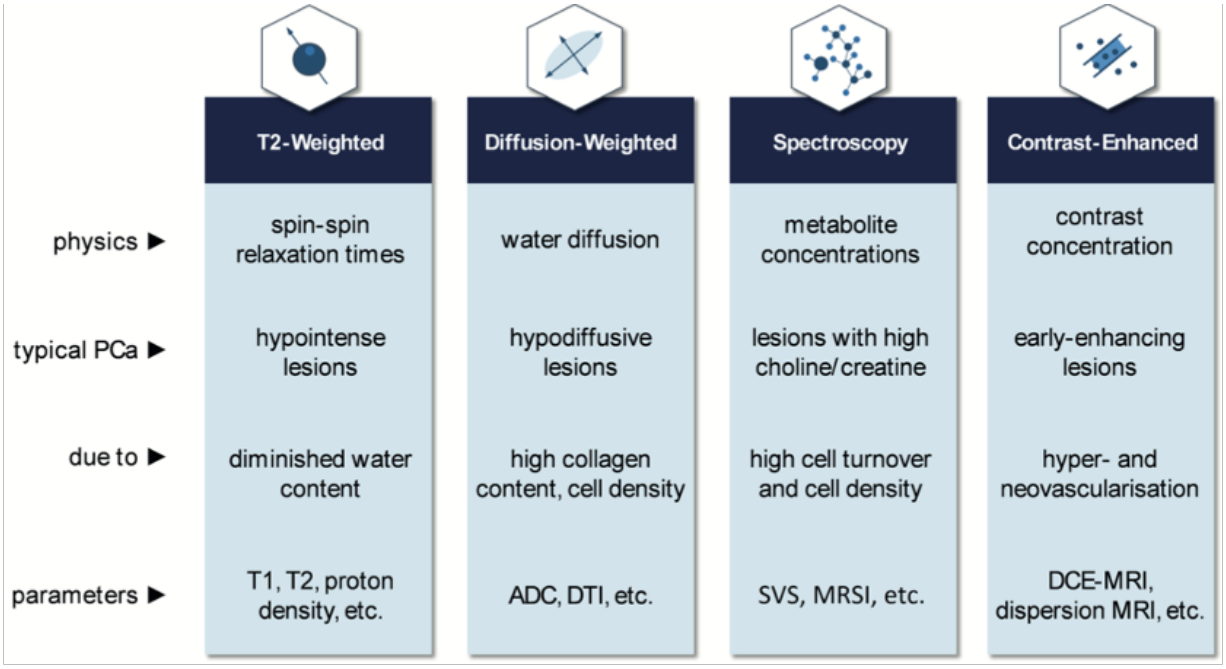
2.1 Multiparametric imaging

2.1.1 Multiparametric MRI

Since the 1980s, non-invasive MRI has been utilized to evaluate the prostate gland and its surrounding tissues. T1-weighted (T1W) and T2-weighted (T2W) pulse sequences were initially used in prostate MRI to determine morphology [38]. Technological advancements have led to the development of mpMRI, which combines anatomic T2W with functional and physiological assessment, such as diffusion-weighted imaging (DWI) and its derivative apparent-diffusion coefficient (ADC) maps, as well as dynamic contrast-enhanced imaging (DCE-MRI) [39]. DWI detects the random movement of water molecules [40]. The majority of csPCa displays impeded diffusion, resulting in DWI brightness at high b-values and decreased ADC-values, resulting in hypointense PCa lesions on ADC maps [41]. DCE-MRI requires the fast acquisition of T1W gradient echo images before, during, and after injecting a gadolinium-based contrast agent (CA) [39]. Like other cancers, PCa frequently shows early enhancement when compared to healthy tissue. Radiologists evaluate the likelihood that the combination of mpMRI results is associated with clinically significant PCa on a scale from 1 to 5, also called the Prostate Imaging-Reporting and Data System (PI-RADS) scoring system [39]. The most recent PI-RADS version-2.1 depends less on DCE-MRI because of the high variability and heterogeneity of PCa enhancement kinetics [42]. Figure 2.1 presents an overview of the MRI modalities in PCa imaging.

2.1.2 Cognitive and fusion targeted prostate biopsy

Prostate biopsy (PB) is widely regarded as the gold standard for PCa diagnosis, and it is one of the most common urological procedures [43]. Transrectal ultrasound (TRUS) was formerly used to guide systematic biopsy (SBx), although this is no longer the standard. The current standard for PCa diagnosis has evolved from SBx to MRI, followed by SBx with or without targeted biopsy, known as TRUS-guided MRI targeted biopsy (MRI-TBx). Targeted biopsy using mpMRI has shown improved detection rates of csPCa both in biopsy naïve patients and in patients with prior negative PB [10–12, 44]. MRI-TBx can be carried out using either a cognitive or an image-fusion strategy. A cognitive targeted biopsy involves combining cognitive information with real-time TRUS imaging to guide the placement of biopsy needles. Image-fusion targeted biopsy employs computer software to fuse pre-biopsy MRI images with real-time ultrasound using a digital overlay, creating a 3D model of the prostate gland with previously annotated regions of interest. Both strategies yield comparable detection rates, but fusion targeting appears to modestly improve the detection rate of csPCa in experienced hands [45, 46].



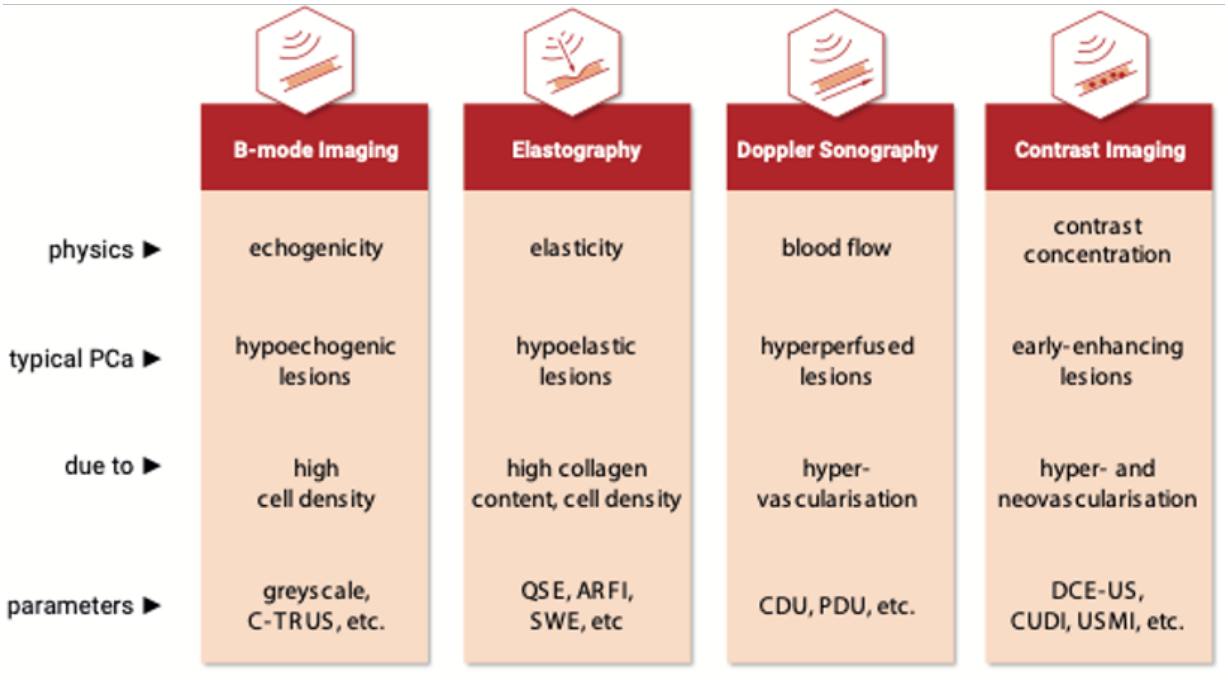


Fig. 2.1.: Overview of the MRI and US modalities in prostate cancer diagnosis. *Adapted from: Wildeboer R.R. (2019). Multiparametric and multidimensional: a three-dimensional and multiparametric approach to ultrasound imaging of prostate cancer [47].*

2.1.3 Multiparametric ultrasound

Grayscale TRUS has been considered insufficiently accurate for reliable PCa detection due to its inability to distinguish between PCa and healthy prostate tissue. Various improved US modalities have been developed to target specific tissue characteristics that distinguish between healthy and malignant tissue. Ultrasonic elastography techniques such as strain elastography and SWE are used to evaluate tissue stiffness, whilst Doppler ultrasonography and CEUS are used to detect changed vascularity in prostate cancers [26]. The combination of several US-based modalities, known as mpUS, could enhance diagnostic performance, much like the development of mpMRI [48, 49]. Because various methods assess diverse physical features of PCa, integrating them successfully has the potential to increase diagnostic performance. However, not a lot of studies utilize a system to combine US modalities similar to the PI-RADS system used for mpMRI. Figure 2.1 presents an overview of the US modalities in PCa imaging. The CADMUS trial includes a reporting system that generates a Likert score, similar to MRI, to score different ultrasound modalities independently [35]. The reporter determined the overall lesion score subjectively, based on the number of positive ultrasound modalities and their degree of positivity [37, 50]. This scoring system is intended to be comparable to the PI-RADS scoring system used in mpMRI reporting.

The advantages of reliable US-based imaging are the wide availability and experience in the urological community, relatively low cost and time consumption, real-time nature and high resolution, portability, and no nephrotoxic contrast agents used. Lastly, real-time imaging of tumors by the US minimizes targeting inaccuracies caused by registration errors in MRI-US fusion during biopsy procedures [48].

2.2 Usability study

Usability is crucial for the successful adoption of medical devices in clinical practice. Poor usability may cause healthcare practitioners to cease the use of a device. Conducting usability testing in simulated or real-world environments can identify areas of concern and improve the device's usability. Usability studies evaluate how users interact with a medical device, with the aim of ensuring that it is easy and safe to use for its intended users.

To achieve this, the first step is to conduct research on the intended use, users, use environments, and scenarios. Then, potential hazards and harms resulting from foreseeable misuse are identified. The design measures are then specified, and a prototype is evaluated in a formative study, with user feedback used to improve the device design. This process is repeated during development, and a validation study with at least 15 users is conducted to demonstrate the device's safety.

For PCaVision, a new Class 2A medical device, usability studies are critical due to the new working method and outcomes that depend on its execution. Standardization is necessary for reliable and consistent imaging results, and a usability study can help identify areas where the technology may fall short of standardization requirements. Two usability studies will be conducted using human-centered design to analyze user engagement with the technology (Figure 2.2) [51].

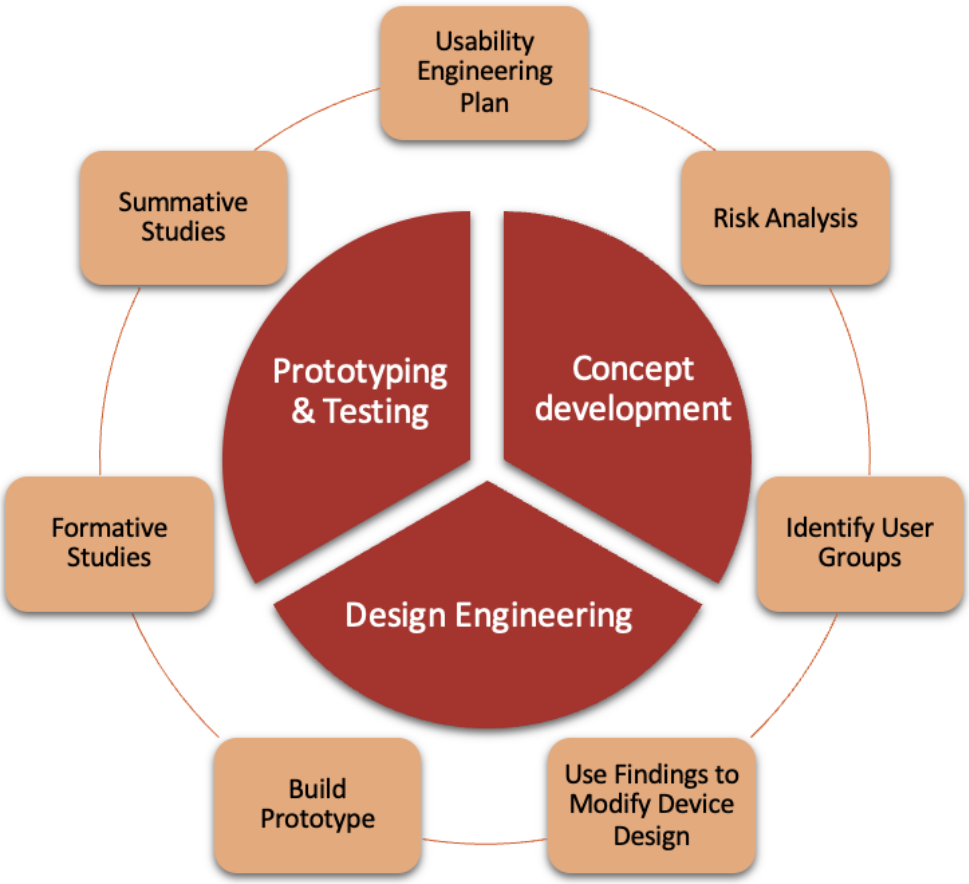


Fig. 2.2.: Human-centered design cycle with the several steps for conducting a usability study.

3 Objectives

This chapter provides an overview of the study's objectives to assist the reader in understanding the research's purpose and scope. The chapter sets the stage for subsequent chapters that will provide more detailed information about the research methodology and findings.

This thesis is divided into two studies:

1. **Usability of the PCaVision 3D mpUS recording procedure**
    - *Primary objective*: To evaluate the operator dependency of the standardized 3D mpUS recording procedure.
    - *Secondary objectives*:
        a) To evaluate the compliance rate of the recorded images with the quality standards among trained operators performing the standardized 3D mpUS recording procedure.
        b) To evaluate the feasibility of training healthcare professionals to accurately perform the 3D mpUS recording in a single day.
2. **Design study of the PCaVision diagnostic workflow and usability test of graphical user interface (GUI).**
    - *Primary objective*: To design a prototype of the PCaVision diagnostic workflow supporting cognitive targeted biopsy procedures (*henceforth*: primary workflow).
    - *Secondary objectives*:
        a) To design a prototype of the PCaVision diagnostic workflow supporting fusion targeted biopsy procedures (*henceforth*: secondary workflow).
        b) To evaluate the user satisfaction and ease of use of the PCaVision diagnostic workflow and GUI using the System Usability Score (SUS).

4 Standardized 3D mpUS recording procedure

This chapter reports on the usability study of the standardized 3D mpUS recording procedure for prostate cancer diagnosis using PCaVision. The study was conducted in collaboration with Angiogenesis Analytics, 's Hertogenbosch, at the Netherlands Cancer Institute and Amsterdam University Medical Centers, Amsterdam.

Abstract

Aim: Ultrasound (US) imaging plays a crucial role in evaluating the physical characteristics of prostate cancer (PCa), and 3-dimensional multiparametric ultrasound (3D mpUS) combines multiple imaging modalities. However, the accuracy and reliability of ultrasound scans heavily rely on operator skills and the quality of the procedure. This study aims to assess the operator dependency of the standardized 3D mpUS recording procedure for PCa diagnostics, focusing on training new users and evaluating image compliance with quality standards among trained operators.

Methods: Usability testing evaluated the operator dependency by training new users, which included a 15-minute explanation of the essential steps and a demonstration scan by an expert. Following that, users performed a supervised and autonomous scan, completing 23 tasks and resolving four errors. Task interviews evaluated the task difficulty, the device's ease of use, and the identification of any use errors, close calls, or operational difficulties. In addition, the level of operator confidence and adherence to image quality standards were recorded.

Results: Six new users participated in the formative test, and thirteen new users carried out the standardized 3D mpUS recording procedure in the summative test. Only two use errors were observed during the procedures, and none of them were considered potentially serious. The training program demonstrated its efficiency by being completed in half a day. Eleven of the thirteen operators expressed confidence in executing the recording procedure independently. Eleven out of thirteen scans met the image quality standards.

Discussion: The evaluation of operator dependency in the 3D mpUS recording procedure emphasizes the importance of standardized protocols and proper training for reliable and accurate scans in prostate cancer diagnostics. The study validated the efficacy of the training program, as seen by the low frequency of use errors. Integrating general knowledge into the training program and enabling seamless integration with the ultrasound machine can improve user-friendliness.

Keywords: Prostate cancer (PCa) diagnosis; PCaVision; 3-dimensional multiparametric ultrasound (3D mpUS); Standardized recording procedure; Automation; Risk mitigation; Operator dependency; Training; Usability evaluation; Human-factor engineering.

4.1 Introduction

Ultrasound (US) imaging can evaluate a variety of physical characteristics of prostate cancer (PCa). B-mode, Doppler, Shear wave elastography (SWE), and contrast-enhanced ultrasound (CEUS) are all combined into one imaging modality by 3-dimensional multiparametric ultrasound (3D mpUS) [52]. The accuracy and reliability of ultrasound scans are highly dependent on the operator's skills and the quality of the scan procedure. To achieve optimal image quality, it is essential to choose the right scan parameters, such as the transducer frequency, depth, and focus of the scan. These settings are often pre-configured in US machines, although errors might arise during operation, resulting in inferior scan quality.

To solve this issue, thorough ultrasound operator training is essential to ensure high-quality scans. Training programs typically involve both theoretical and practical training sessions. The theoretical lectures introduce the fundamental of US [53]. Participants learn to appropriately utilize US equipment in the practical sessions and how to differentiate between normal and pathological structures. US training aims to provide participants with the knowledge and abilities required to perform US imaging effectively and competently. However, the effectiveness of these training programs can be influenced by several factors that may impact the quality of the scan procedure, such as the operator's experience and the complexity of the procedure's equipment.

Understanding the effect of mitigating actions on scan quality is crucial for optimizing training programs for mpUS operators. Identifying these factors can aid in developing effective ways to improve the training process and generate high-quality scan findings. Studies have shown that the quality of the scan can be significantly impacted by the operator's skill in using the equipment, probe positioning, and ideal scanner settings [54–56]. Because of this, training programs ought to include these variables.

In summary, identifying factors that impact scan quality is critical for developing effective training programs for US operators. Training programs can increase the reliability as well as the accuracy of ultrasound scans for PCa diagnosis by adapting education to operator needs and addressing mitigating actions. This can ultimately improve the adoption of PCaVision as a trustworthy medical device in clinical settings, which will aid in the early detection of PCa in the long term.

The aim of this study is to conduct a thorough usability study in a real-world environment to evaluate the usability, adaptability, and user satisfaction of the novel medical device PCaVision. The primary objective is to evaluate operator dependency of the standardized 3D mpUS recording procedure. This study follows the procedure according to Jager *et al.* [52]. It is expected that with proper training and guidance, new users will be able to accomplish the procedure's essential steps. The secondary objectives are to evaluate the compliance rate of the recorded images with the quality standards among trained operators and evaluate the feasibility of training healthcare professionals to accurately perform the 3D mpUS recording in a single day. In order to optimize clinical workflow, improve PCaVision system usability, and aid in the early detection of clinically significant prostate cancer (csPCa), the study will evaluate how healthcare professionals use the PCaVision recording system and identify any usability difficulties or areas for improvement.

4.2 Methods

Risk assessment

A comprehensive usability test was conducted to evaluate the operator dependency of the 3D mpUS recording procedure. The study structure is described in Chapter 2.2. A multidisciplinary team (involving clinical-, technical-, and quality/regulatory staff) performed risk management, addressing the investigational device (PCaVision) and related risks in the clinical trial [57]. The risk management file included task scenarios for the recording procedure that aligned with Medical Device Regulations (MDR) guidance for usability testing. Test protocols were approved by THINC Healthcare [58]. The tasks were defined using risks that were specifically categorized as 'medium' hazards, meaning that the combination of severity and probability is acceptable. Participants from various backgrounds were chosen to evaluate real-world user interactions with the product.

Participants

This study included two groups: the formative group (six urologists/sonographers (henceforth: user) and seventeen patients) and the summative group (thirteen users and 36 patients). Users from varied backgrounds were recruited to depict real-world interactions with the product. All users had prior experience with transrectal ultrasound (TRUS) examinations and were trained in the standardized 3D mpUS recording procedure, including probe fixture handling, operation of the LOGIQ E10 US machine (GE Healthcare, Chicago, USA), and administration of the contrast agent (CA) SonoVue® (Bracco S.p.A., Milan, Italy). Patients were enrolled in the 3D mpUS trial at the Amsterdam University Medical Centers and Netherlands Cancer Institute in Amsterdam.

Data acquisition Part I - Formative test

The 3D mpUS recording procedure was standardized for an effective formative test. This guaranteed consistency and allowed for procedure improvements. Following the instructions, six users performed two to four scan procedures. The recorded events comprised:

- *Task completion* - a case in which the user completes a task successfully,
- *Use error* - a case in which the user commits an error during task completion, resulting in unintended outcomes or negative consequences,
- *Close calls* - a case in which the user almost commits an error, but 'catches' himself or herself in time to avoid making the error,
- *Operational difficulties* - a case in which the user appears to struggle to perform a task,
- *Post-test questions* - interview questions regarding the confidence of the user, inconveniences in the procedure, and user feedback.

The use of a macro script automated the acquisition of various US modalities, ensuring standardization of the procedure and reducing the risk of use errors. Training materials and a troubleshooting guide were developed to guide operators with essential user-related steps, including probe fixture use, US machine operation, and CA administration. Based on feedback from the formative test, the design of the training and troubleshooting guide was improved. The refined design was then used as the standardized procedure for the summative test, including training, evaluation, troubleshooting, and post-task interviews (Figure 4.1).

Data acquisition Part II - Summative test

Thirteen users followed a standardized protocol in a summative test, performing two scan procedures each. On-site training included a 15-minute explanation and a demonstration scan by an expert. The first scan was supervised, whereas the second scan was reviewed as a summative scan. A troubleshooting session addressed frequent errors. Users were graded on 23 tasks and the resolution of four errors and were asked about task difficulty, device usability, and feedback. The study aimed at an 85% compliance rate with image quality standards. Figure 4.1 provides a summary of the training and evaluation process. The tasks for the usability tests, as well as frequent errors, can be found in Appendix A.

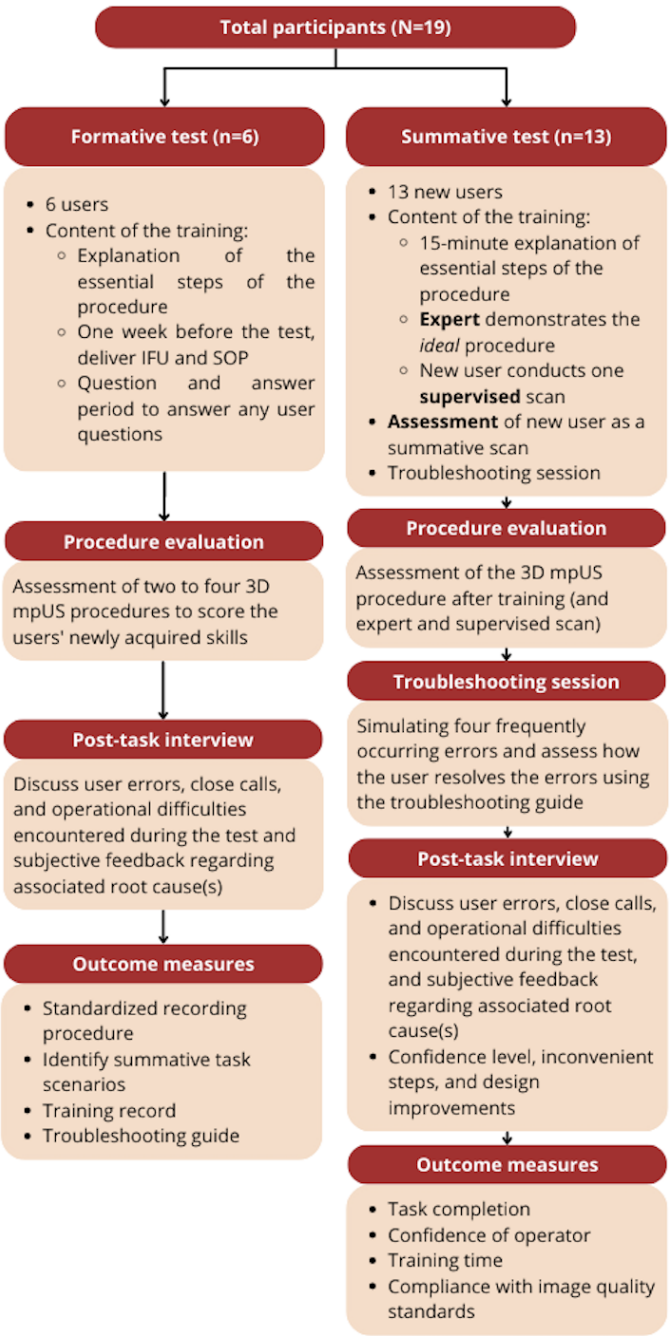


Fig. 4.1.: Training and usability evaluation. The training was provided by an experienced user.

Assessment
An experienced user who provided the 15-minute training documented use errors, close calls, and operational difficulties using a checklist. Users were not informed of any use error during the tests to stimulate independent execution of the procedure. As the patients were part of the 3D mpUS trial, the intervention was only performed when a critical step failed, establishing the procedure's acceptability.

Use errors, close calls, and operational difficulties
A *use error* was defined as an incorrect step leading to an undesired outcome. They can be classified as (1) handling-only use errors with no clinical implications, (2) non-serious use errors with no potential serious consequences, and (3) potentially serious use errors with the potential to cause serious consequences. *Close calls* are incidents in which users nearly made a mistake but caught themselves in time, or made a mistake but rapidly recovered before any consequences occurred. *Operational difficulty* refers to users having difficulties completing a task, which can be shown by several attempts, comments about difficulty, and displays of displeasure or confusion, potentially leading to prolonged task completion times.

Scan quality
After the ultrasound recording, scans were assessed for parameters such as field of view, depth, and transducer frequency. Scans not meeting the criteria were carefully reviewed (see Appendix B for the complete list of criteria).

Data analysis
THINC Healthcare and MD Squared reviewed formative and summative test protocols in compliance with Conformite Europeenne (CE) regulations. No statistical analyses were performed. Operator dependency is evaluated using task-specific pass criteria, with higher criteria for critical tasks and lower criteria for less critical ones. For critical tasks, only one operator is allowed to commit a use error, while multiple operators are allowed for less crucial tasks. The procedure is considered operator-independent if all task scenarios meet the pass criteria. The pass criteria can be found in Table 4.2. Descriptive data were collected from both tests, and proportions of use errors, close calls, and operational difficulties were calculated as percentages of total events per category and participant group.

4.3 Results

Participant characteristics

Participant characteristics are shown in Table 4.1. The formative usability test included six users and the summative thirteen users. Although all participants had previous TRUS experience, 69.2% had previously performed more than 200, and only 15.4% had more than 500 scan procedures.

	Formative test (n=6)	Summative test (n=13)	Total (N=19)
Experience level (scans)			
Beginner (<200)	-	4	4
Intermediate ($\geq$ 200, $\leq$ 500)	-	7	7
Expert ($\geq$ 500)	-	2	2
Expertise			
Specialized nurse	1	0	1
Medical doctor	3	5	8
Resident urologist	0	6	6
Urologist	2	2	4
Expert scan			
In a patient	-	10	10
In a phantom	-	3	3
Assessment on same day as training			
Yes	-	11	11
No	-	2	2
Confident after training			
Yes	-	11	11
Yes, with 1 or 2 extra supervised scans	-	2	2
No	-	0	0

Tab. 4.1.: Participant characteristics of the formative and summative usability test.

Part I - Formative test

Initially, five operators participated in the formative test, but an additional trained operator joined to address any initial issues with the troubleshooting guide. The training and troubleshooting guide was then refined based on operator feedback. Appendix C provides a detailed analysis of use errors, close calls, and operator feedback. The operators' feedback and action points were incorporated into a standardized procedure for the summative test, which included training, procedure evaluation, troubleshooting, and post-task interviews. The standardized 3D mpUS recording procedure is shown in Figure 4.2 and Appendix D.

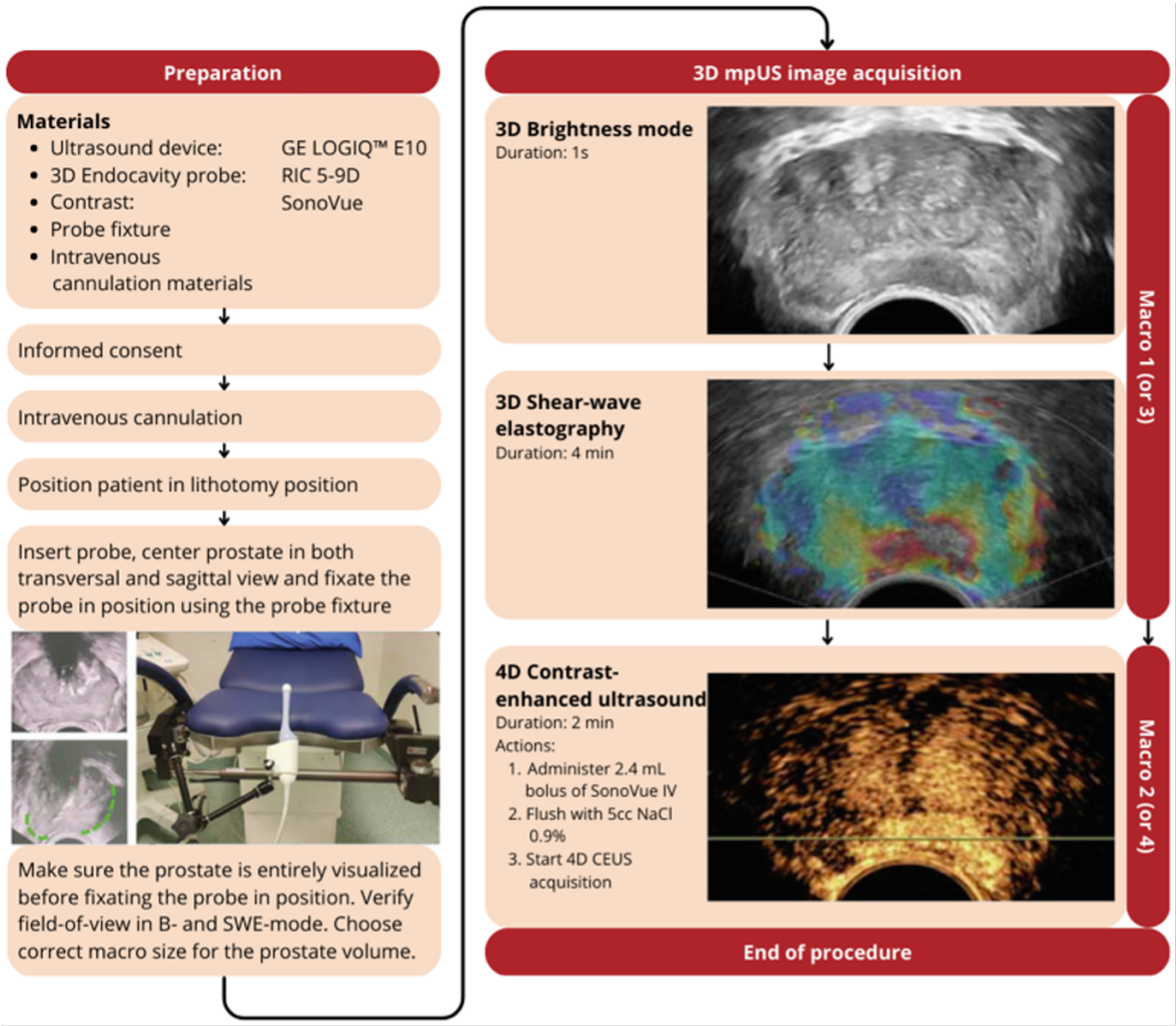


Fig. 4.2.: Standardized 3D mpUS recording procedure, using two sets of actions (i.e., a macro) for image acquisition. 3D = three-dimensional; 4D = four dimensional; B-mode = brightness mode; CEUS = contrast-enhanced ultrasound; IV = intravenous; mpUS = multiparametric ultrasound; SWE = shear wave elastography. *Adapted from Jager, A. (2023). Clinical Trial Protocol: Developing an image classification algorithm for prostate cancer diagnosis on three-dimensional multiparametric transrectal ultrasound [52].*

Part II - Summative test

Table 4.2 displays the outcomes of the summative test conducted on thirteen operators. The training was completed within half a day, and each procedure took a maximum of 30 minutes. In cases where only two patients were available, the expert scan was performed on a phantom (n=3). For two operators, the evaluation was conducted on a different day than the training due to the unavailability of the patient. All pass criteria for procedural steps and troubleshooting were met. Use errors during the procedure were limited to incorrect CA administration volume and aberrant exam termination. One operator deviated from the troubleshooting guide, resulting in two errors. Most operators demonstrated confidence in independently performing the recording procedure, whereas two operators expressed a desire for additional supervised scan procedures to further enhance their confidence.

Phase	Test parameter	Pass criteria	Result
Preparation	Proper use of probe fixture	*85%*	**100%**
	New patient ID	*92%*	**100%**
	US gel in rectum	*85%*	**100%**
Recording - B/DP/SWE	Probe fixated in correct orientation	*92%*	**100%**
	Safe probe insertion	*92%*	**100%**
	Verifies FOV (B-mode)	*92%*	**100%**
	3D B-mode visualization (apex/base visible)	*92%*	**100%**
	Verifies FOV (Elasto-mode)	*92%*	**100%**
	Correct macro (size) initialization	*85%*	**100%**
	Does not press any key during macro execution	*92%*	**100%**
Recording - CEUS	Preparation of CA	*92%*	**100%**
	Correct macro (size) initialization	*85%*	**100%**
	CA and NaCl attachment to 3-way valve	*85%*	**100%**
	3-way valve open for CA administration	*77%*	**100%**
	Reactivation CA just before administration	*85%*	**100%**
	Timing CA administration	*92%*	**100%**
	Volume CA administration	*92%*	**92%**
	3-way valve open for NaCl administration	*77%*	**100%**
	Volume NaCl administration	*92%*	**100%**
	Does not press any key during macro execution	*92%*	**100%**
End of procedure	Ends exam	*77%*	**92%**
	Data transfer	*77%*	**100%**
	Correct procedure (all scan modalities executed, non-operator errors in the session)	*92%*	**100%**
Troubleshooting	Error 1: patient ID missing	*78%*	**100%**
	Error 2: wrong FOV	*78%*	**83%**
	Error 3: wrong macro initialization	*78%*	**100%**
	Error 4: initialization with mode turned on	*78%*	**100%**
	Error 5: macro stalling	*75%*	**100%**
	Error 6.1: excessive movement during 1st macro	*50%*	**100%**
	Error 6.2: excessive movement after 1st macro	*50%*	**100%**
	Error 7.1: incorrect CA administration	*50%*	**100%**
	Error 7.2: excessive movement during 2nd macro	*50%*	**67%**

Tab. 4.2.: Results of the summative test. B = brightness mode; DP = Doppler; SWE = shear wave elastography; CEUS = contrast-enhanced ultrasound; CA = contrast agent; US = ultrasound; NaCl = sodium chloride; FOV = field of view; ID = identification.

Use errors

Participants committed 30 out of the potential 751 use errors in the usability test. The number of actual use errors versus potential use errors committed in the formative test, summative test, and troubleshooting session was 26/400, 2/299, and 2/52, respectively (Figure 4.3). Most of the use errors were committed because the supervisor performed the task instead of the new user. Of all use errors in the formative test, 76.9% were related to handling with no clinical impact, compared to 23.1%, which were non-serious use errors. In the summative test, only one handling and one non-serious use error were committed. In both the formative and summative, no potentially serious use errors were committed (Figure 4.4, Figure 4.5).

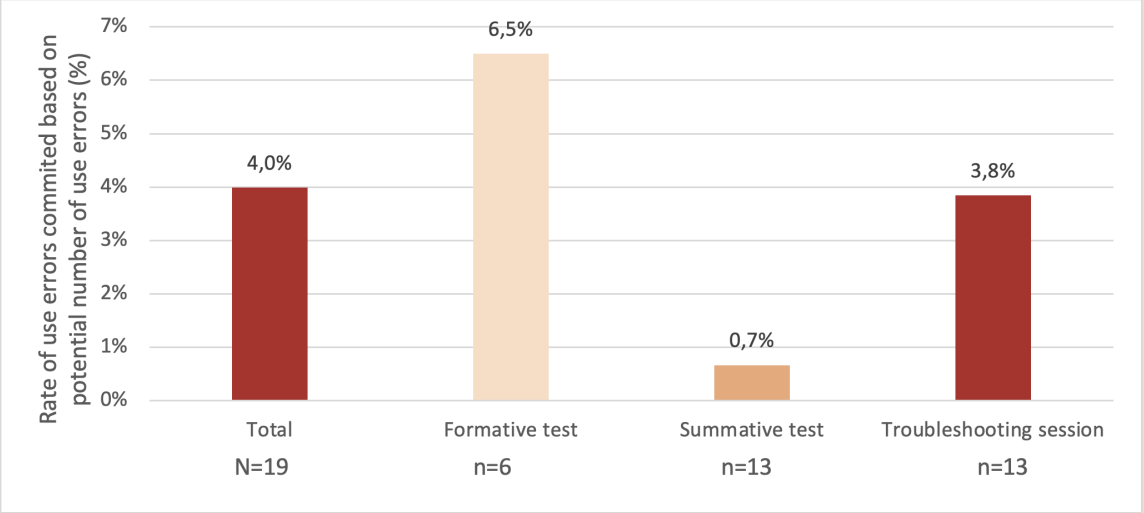


Fig. 4.3.: Use errors committed as a rate of the number of use errors possible for each usability test task for pooled formative, summative, and troubleshooting tests. N and n represent the total number of participants for each study group. The total errors committed were 30 of a potential 751. Possible use errors that could be committed during the formative test, summative test, and troubleshooting session were 400, 299, and 52, respectively.

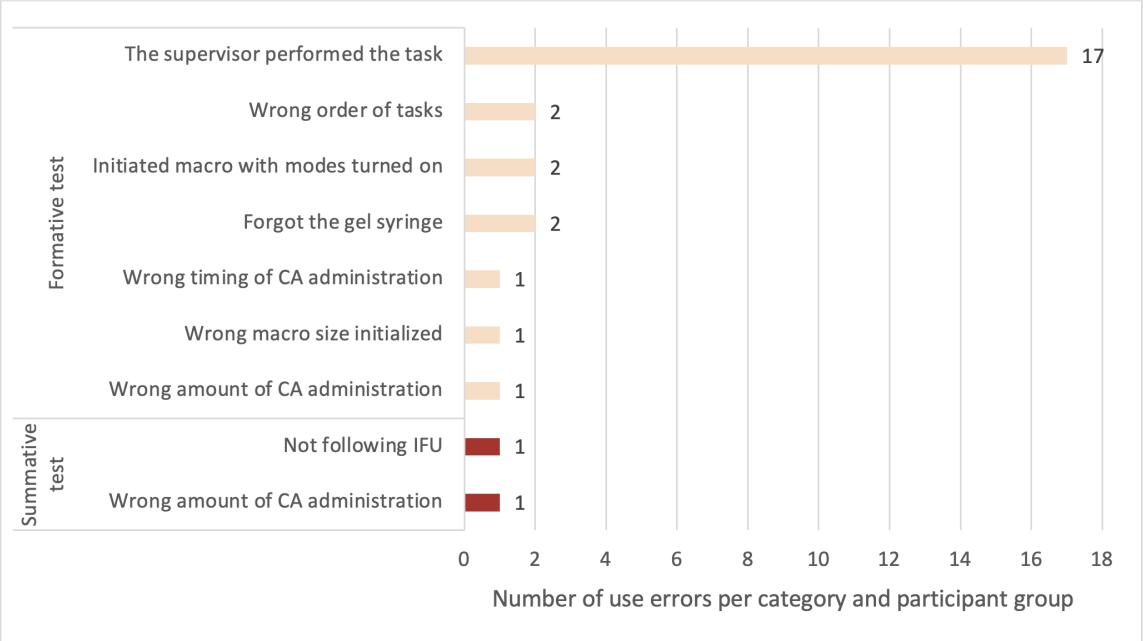


Fig. 4.4.: Incidence of use errors reported during task evaluation in the formative and summative test participant group. The total number of use errors was 28 (26 formatives, 2 summative).

Operational difficulties, close calls, and better than expected

Eight operational difficulties were observed during the summative test, with seven requiring the probe's repositioning for either patient comfort or improved visualization. Three close calls were noted during the test. However, it was surprising to see that two of the operators exceeded expectations and successfully resolved errors on their own without the supervisor's intervention.

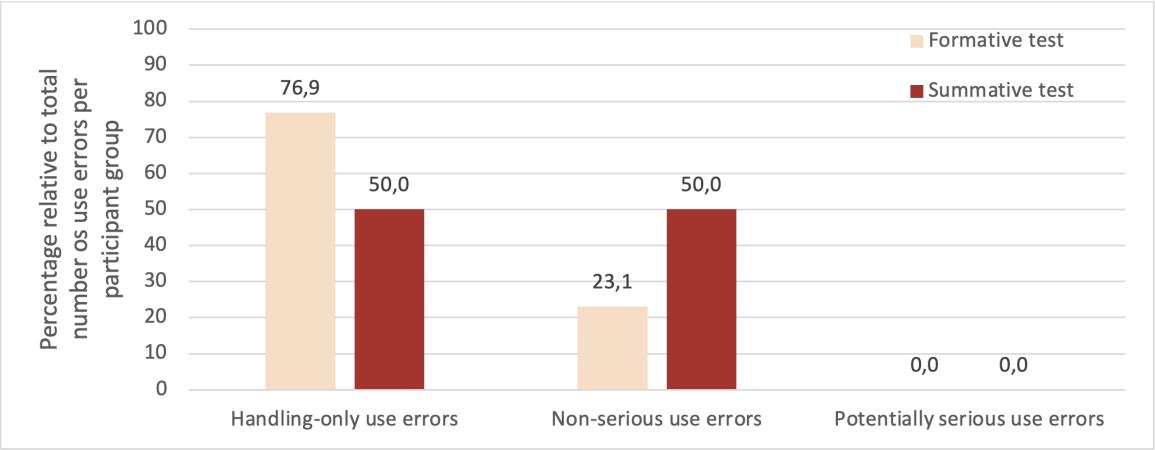


Fig. 4.5.: Type of use errors committed during task evaluation in pooled participant groups. The total number of use errors was 28 (26 in the formative and 2 in the summative test).

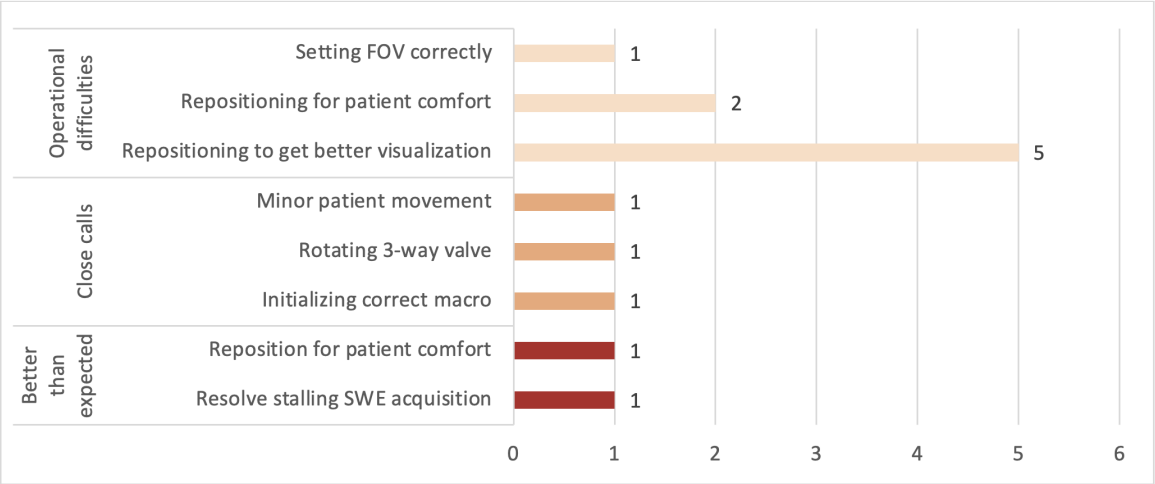


Fig. 4.6.: Operational difficulties, close calls, and better than expected during the summative procedures. The total number was 8, 3, and 2, respectively.

Quality standards

Quality standards were reached in eleven of thirteen scans, and the PCaVision algorithm was able to process them effectively. For the two which did not meet the quality standards, the FOV was adjusted in SWE mode, resulting in a scan that exceeded the azimuth mean step size. Both results were slightly above the quality standard range of 0.7 and 0.77 degrees at 0.778 and 0.781 degrees, respectively.

4.4 Discussion

Reflections on results

This study aimed to gain insight into the operator dependency of the standardized 3D mpUS recording procedure for prostate cancer diagnosis. To explore if the recording procedure can be trained with minimal effort, the completion of essential tasks, the ability to resolve errors, and the confidence after training were examined. The study found that the training was adequate to teach new users and give them the confidence to perform the procedure independently. Only two users expressed the desire to perform two additional scan procedures with supervision to gain a little more confidence, although they already felt confident performing them individually. Users reported that the system and its operations were very intuitive. The training only took half a day, implying a short learning curve.

The incorporation of the probe fixture into the standardized 3D mpUS recording procedure was found to be highly beneficial. Feedback obtained from users revealed that the fixture enhances user-friendliness, streamlines the process, and reduces the burden on users. The fixture relieves the clinical user from holding the probe throughout the scan. It enables them to use both hands for concurrent activities, such as controlling the US machine and preparation of the CA. After positioning the probe, stability during the scan can be ensured by locking the mechanical arm with the central knob. Figure 4.7 is a representation of the probe fixture.

Fig. 4.7.: PCaVision probe fixture.

The summative usability test demonstrated the safety-related aspects of the device. No potentially serious errors were observed, even for operators with little TRUS experience. Only one potentially non-serious use error occurred; the user administered too much contrast agent. In the case of the first users, the entire vial was aspirated (4.8 mL) during the preparation of the CA, while only 2.4 mL had to be injected during the CEUS acquisition. The use error occurred with the 7th user. As a mitigation action, the training instruction was subsequently changed by only aspirating the effective volume of 2.4 mL when preparing the CA. After that, the use error did not occur again. This means that the mitigation action is expected to be successful. When another user disobeyed instructions to end the exam, it resulted in a handling-only use error. The user discovered an alternative method for archiving the images. Because the essence of the step has been achieved in this manner, this is not weighted too heavily.

The 3D mpUS procedure was improved by incorporating macro scripts, which increased the automation of the procedure and allowed for faster and more efficient acquisition of imaging modalities. Four distinct macro scripts were developed, of which two have been configured to operate at a depth of 5 cm, providing coverage of 80-90% of all prostates. Macro 1 is designed to acquire B-mode, Doppler, and SWE, while macro 2 is intended for capturing 4D CEUS. In addition, two other macros (3 and 4) were created to accommodate larger prostates that exceed the field-of-view of the initial macros and capture images at a depth of 8 cm. Prior to initializing the first macro script, the operator verifies the visibility of the entire prostate and adjusts the depth and field-of-view in both B-mode and SWE-mode, if necessary, to achieve optimal settings. The macro script has the potential to produce high-quality scans when all settings are configured

correctly. During the initial macro acquisition, the operator can simultaneously prepare the CA, keeping in mind how to handle the 3-way valve and when to administer the CA. Once the first macro is finished, the operator can attach the CA and NaCl to the 3-way valve. Upon initiating the second macro, a sound notification is triggered to indicate the appropriate time for administering the CA, followed by flushing with NaCl. To summarize, the incorporation of macro scripts has considerably enhanced the automation of the 3D mpUS recording procedure, enabling quicker and more efficient acquisition of imaging modalities. Nevertheless, human interpretation and attentiveness are still essential to ensure smooth and optimal execution, resulting in the generation of high-quality scans. Despite this requirement, the procedure is extensively automated, with minimal human intervention before initiating the macro scripts.

Our findings highlight the significance of operator expertise and attention to detail in achieving trustworthy and reliable mpUS imaging results. The majority of scans met the quality standards, although the study emphasizes that wrong FOV adjustment can lead to quality issues, potentially impacting the accuracy of the PCaVision algorithm.

In conclusion, this study evaluated the operator dependency of the 3D mpUS recording procedure and its training. The results demonstrated that the training effectively taught new users and boosted their confidence to independently perform the procedure. The incorporation of the probe fixture and macro scripts considerably enhanced the automation and user-friendliness of the procedure, with no serious errors observed. Ultimately, this standardized 3D mpUS recording protocol has the potential to facilitate data comparison among institutions and clinicians while providing a more efficient and streamlined process for prostate cancer diagnosis.

Limitations of the study

It is important to understand that this study only focuses on the usability of the 3D mpUS recording procedure. It provides a thorough evaluation of the image acquisition process. However, the study does not address the image interpretation. Therefore, there is a substantial need for additional study in image interpretation and the workflow for analyzing the images.

The training and assessment procedures were not uniform for all operators, as two operators observed the expert scan in a phantom, and three operators were assessed on a different day than their training. However, despite this variation in the process, the results were still positive, indicating the flexibility of the training program. Furthermore, the study population mostly comprised MDs and (resident) urologists, which only partially reflected the intended end-user population. To make the benefits of the procedure available to a broader range of healthcare professionals, it is necessary to investigate the feasibility and effectiveness of training (specialized) nurses to perform the 3D mpUS procedure.

During the troubleshooting session, the distribution of errors that were tested was uneven, and the pass criteria for each error were not uniform. However, the primary goal of the troubleshooting session was to determine whether the operators could successfully address errors by utilizing the troubleshooting guide. It was not intended to test their capacity to resolve all errors, but rather to evaluate their comprehension and utilization of the guide.

While the LOGIQ E10 can accommodate all imaging modalities, including 3D B-mode, 3D Doppler, 3D Shear wave, and 4D CEUS, only a few ultrasound machines can offer comparable capabilities. This paper's 3D mpUS recording procedure automation is currently limited to the LOGIQ E10 device. This method must be incorporated into other ultrasound devices to be more broadly accessible.

This study evaluated the usability of the 3D mpUS recording procedure but did not address image interpretation, highlighting the need for further research in this area. The training program was found to be flexible despite variations in procedures. Expanding the training to other healthcare professionals and integrating the automated procedure into other ultrasound machines would improve the procedure's accessibility.

Recommendations

A comprehensive and effective training program is crucial for the adoption of new techniques into clinical practice. This study showed that the training program effectively taught new users the essential steps of the 3D mpUS recording procedure in a short period of time. Nevertheless, to enhance the training program, it is recommended to include theoretical knowledge of prostate anatomy, the physics of image acquisition with 3D probes, and how to interpret different imaging modalities. This would facilitate the operator's understanding of the procedure and subsequently refine their ability to generate high-quality scans. A comprehensive training program that comprises both theoretical and practical knowledge could considerably accelerate the adoption of this new procedure into clinical practice.

Integrating user feedback with the LOGIQ E10 US machine can improve the usability of the automated recording procedure. The following recommendations are made:

- Provide the operator feedback on proper prostate positioning and symmetry in the transversal view, possibly indicating the central position of the urethra;
- Alert the operator when the image has excessive shading or calcification. This would enable early determination of whether to continue the scan or suggest a mpMRI;
- Indicate whether the prostate is within the FOV or needs depth adjustment by using automatic segmentation of the prostate boundary. This feature would assist the operator in automatically selecting the right macro to initialize;
- Explore the feasibility of automating the process of properly setting the FOV in SWE mode. This eliminates the need for manual modification and reduces the likelihood of user error, making the procedure more reliable;
- Automated measurement of prostate volume would aid the operator in determining the patient's risk of csPCa;
- Combining the previous two features could allow the machine to automatically select the correct macro to initialize for normal or large prostates while blocking the other macro from being initialized.

These improvements would make the recording procedure more user-friendly, efficient, and less likely for user errors.

While the current 3D mpUS recording procedure is highly standardized with the use of macro scripts, the operator still needs to ensure the correct prostate visualization and FOV settings before initiating the macro. To address this, the FOV setting for SWE acquisition should be automated

to reduce the need for user interaction. In addition, given the smaller FOV of SWE compared to B-mode, further investigation is needed to determine whether the SWE FOV can be enlarged to capture the entire prostate, even for larger prostates. Therefore, it is recommended to explore methods to increase the SWE FOV and improve the overall usability of the procedure.

4.5 Conclusion

This study is the first to evaluate the operator dependency and usability of the standardized 3D mpUS recording procedure for prostate cancer diagnosis using PCaVision. Our findings demonstrate that new users can be trained in just half a day, with only a few minor errors reported during the procedure's execution. Incorporating mitigating actions, such as the probe fixture and macro scripts, improved the automation and standardization of the process. As a result, the procedure is easy to follow and can be performed within 30 minutes. Although the training program currently covers only the essential steps, it can be expanded to include theoretical explanations for a more comprehensive understanding of the application. Further research is required to address the image interpretation and analysis. Overall, this study demonstrated that the 3D mpUS recording procedure is a promising tool for prostate cancer diagnosis, and with further refinements, it has the potential to improve patient care and outcomes.

5 The design of a PCaVision-based prostate cancer diagnosis workflow

The following chapter reports on the design and usability study of the PCaVision-based prostate cancer diagnosis workflow. The study was conducted in collaboration with Angiogenesis Analytics, ‘s Hertogenbosch, and Amsterdam University Medical Centers, Amsterdam.

Abstract

Aim: This design study aimed to develop a user-friendly PCaVision-based prostate cancer diagnostic workflow prototype supporting cognitive and fusion-targeted biopsy procedures. The secondary objective was to evaluate the user satisfaction and ease of use of the graphical user interface (GUI).

Methods: Design requirements for the diagnostic workflow were developed with urologists and PCaVision product owners. Two workflows were developed using MIM Symphony Dx: a primary workflow for cognitive targeted biopsy and a secondary workflow for fusion-guided targeted biopsy procedures. A usability study evaluated urologists’ ability to operate the PCaVision-based diagnostic workflow. The GUI was assessed using the System Usability Score (SUS).

Results: The developed prototype only partially fulfilled three of the given design requirements. First, the primary workflow allowed urologists to independently execute cognitive targeted biopsy procedures. The usability study showed a SUS score of 60 in the formative evaluation.

Discussion: The primary PCaVision-based diagnostic workflow was designed entirely, allowing urologists to perform cognitive targeted biopsy procedures. Although the secondary workflow partially complied with the requirements, it still needs further clinical validation. The obtained SUS score indicates the potential to improve the GUI’s usability.

Keywords: Prostate cancer diagnosis, PCaVision, Targeted biopsy, Usability study, Clinical intervention planning.

5.1 Introduction

Current prostate cancer (PCa) diagnosis approaches, such as multiparametric magnetic resonance imaging (mpMRI), face challenges such as variable sensitivity and specificity, limited accessibility, high cost, and the need for specialized expertise. 3-dimensional multiparametric ultrasound (3D mpUS), a potential alternative or complementary tool, has promise for PCa detection but is not widely used due to the lack of an established clinical workflow.

This design study aims to develop a user-friendly PCaVision-based diagnostic workflow using 3D mpUS images. PCaVision is a medical diagnosis decision support system that detects, localizes, and characterizes PCa lesions. The objective is to create an efficient workflow that aids urologists (henceforth: users) in making accurate diagnoses, improves clinical intervention planning, and facilitates targeted biopsy procedures.

The study emphasizes usability and user experience, combining user feedback and taking human factors into account in order to develop an intuitive and seamless integration solution. The future diagnostic pathway envisioned using PCaVision is described in more detail in Chapter 1.3.2.

5.2 Design requirements

In consultation with four (resident) urologists and PCaVision product owners, several PCaVision-based diagnostic workflow design requirements were established, listed in Table 5.1. A preliminary prototype was created, two potential end-users evaluated it, and their wishes and demands were added to the design requirements. Two overarching product requirements were considered when drawing up the design requirements:

> **Product requirement 1**: PCaVision aims to assist in identifying suspected PCa lesions and supports the urologist in determining the need for additional diagnostic evaluation through prostate biopsy.
>
> **Product requirement 2**: PCaVision aims to support the urologist in executing targeted biopsy procedures[1]. This support shall be delivered in the following manners:
>
> 1. **Cognitive targeted biopsy**: providing optimal 3D and synthesized 2D images provides the urologist with optimal guidance for performing the cognitive biopsy procedure.
> 2. **Fusion-guided targeted biopsy**: by providing 3D DICOM images in formats compatible with a fusion-guided biopsy system

[1] *In both cases, the quality of the resulting biopsy is identical to the quality which would have been achieved using the MRI imaging alternative. The key aspect is providing identical positional accuracy of the cancer tissue, which needs to be 'hit' by the biopsy needle.*

Category	Number	Requirement	Importance	Requirement fulfilled?
File export	1.1	DICOM images compatible with MIM software	High	**Fulfilled**
	1.2	Spherical voxel data conversion to Cartesian domain	High	**Fulfilled**
	1.3	Scaling factor in DICOM information	High	**Fulfilled**
	1.4	Automatically export recordings and results in a format compatible with the MIM viewing software and store in a per-patient session subdirectory locally accessible by locally installed MIM software	High	**Fulfilled**
	1.5	Study number as *Patient Name* for all series	Moderate	**Fulfilled**
	1.6	Create 3D CEUS Mean Intensity (MI) projection	Low	**Fulfilled**
	1.7	Resample 3D B-mode to voxel size of 0.75 mm for fusion biopsy planning	Moderate	**Fulfilled**
Contours	2.1	Create AI-generated prostate contour	High	**Fulfilled**
	2.2	Create AI-generated peripheral and transitional (PZ/TZ) zonal contour	High	**Fulfilled**
	2.3	Create *area of interest and urethra* contour options	High	**Fulfilled**
	2.4	Lock the prostate and PZ/TZ zonal contour	Moderate	**Fulfilled**
Visualization	3.1	Registration of 3D B-mode, 3D SWE, 3D CEUS MI to the target 4D CEUS coordinate system for synchronized scrolling	High	**Fulfilled**
	3.2	3D SWE, 3D CEUS MI, 4D CEUS in axial, and 3D B-mode in axial and sagittal orientation	High	**Fulfilled**
	3.3	3D B-mode, 3D SWE, 3D CEUS MI, and 4D CEUS with a voxel size of 0.25 mm	High	**Fulfilled**
	3.4	3D classifier confidence map and 3D classifier output map with a voxel size of 0.75 mm	High	**Fulfilled**
	3.5	3D classifier output map as overlay on 3D B-mode, with a Blue-Red contrast and threshold of 8%	High	**Fulfilled**
	3.6	4D CEUS movie in a recurring loop of 30 frames, with an Amber-White contrast	High	**Fulfilled**
	3.7	3D SWE as overlay on 3D B-mode, with a Blue-Red contrast	High	**Fulfilled**
	3.8	3D classifier confidence map as overlay on 3D B-mode, with a White-Fresh Green contrast	High	**Fulfilled**
	3.9	Contours with a thickness of 2 pixels	Moderate	**Fulfilled**
	3.10	PZ/TZ zonal contour only visible inside prostate boundary	High	**Fulfilled**
	3.11	Contours in different colors	High	**Fulfilled**

Category	Number	Requirement	Importance	Requirement fulfilled?
Workflows	4.1	Provide a primary workflow for cognitive targeted biopsy	High	**Fulfilled**
	4.2	Generate PDF report snapshot of all modalities with annotations	High	**Fulfilled**
	4.3	Provide a secondary workflow for fusion-targeted biopsy	High	**Fulfilled**
	4.4	Provide an export compatible with the BkFusion biopsy system	High	**Fulfilled**
Results	5.1	Present urologist with heatmap(s) and original recordings facilitating the diagnosis of csPCa in the whole prostate using MIM software	High	**Fulfilled**
	5.2	Present urologist with heatmap(s) and original recordings in MIM software to indicate the 3D position for a targeted biopsy related to their suspicion of csPCa presence	High	**Fulfilled**
	5.3	Allow urologist to make a TBx plan in the MIM software, similar to an MRI TBx plan	High	**Fulfilled**
	5.4	Results and graphs should enable urologist to diagnose after 3 hours of training	High	**Partially fulfilled**

Tab. 5.1.: The design requirements of the new PCaVision-based prostate cancer workflow. The importance is scored as low, moderate, or high. It is scored whether the requirement is fulfilled with red (not fulfilled), orange (partially fulfilled), or green (totally fulfilled).

5.3 Design of the prototype

The MIM Symphony Dx was chosen as the visualization software for the prototype. All DICOM files had to be converted to Cartesian coordinates to be compatible with the software. The PCaVision-based MIM workflow provides step-by-step guidance from data import to contouring areas of interest to reporting. The recorded images and generated results are stored in a per-patient session subdirectory that is locally accessible through the locally installed MIM software. The workflow provides a deep learning-based contour of the prostate and peripheral and transitional (PZ/TZ) zone, which are locked, preventing adjustments by the user. Additionally, it offers contour templates for areas of interest (AOI) and the urethra. The prototype includes a graphical user interface with clear instructions and minimal steps, designed to be easily navigable even for users with little experience in ultrasound imaging.

The hanging protocol[2] is based on brightness-mode (B-mode), shear wave elastography (SWE), and contrast-enhanced ultrasound (CEUS) modalities that are registered to the 4-dimensional (4D) CEUS coordinate system for synchronized scrolling. The resolution and contrast of all modalities are comparable to the LOGIQ E10 US machine (GE Healthcare, Chicago, USA). The

[2] *A hanging protocol is the collection of rules that govern the layout of medical images presented on a diagnostic monitor. It details the images' quantity, dimensions, locations, and orientations. A hanging protocol aims to guarantee that the images are consistently presented in a standardized format to facilitate effective interpretation by the clinician. Hanging protocols can automate the layout of medical images and decrease the duration of image interpretation [59].*

classifier output visualizes predictions of regions suspicious for csPCa with a threshold of 8%. The confidence map indicates the reliability of the prediction output from 0 (no confidence) to 1 (maximum confidence). The classifier output, confidence map, and SWE are superimposed on the B-mode image. The operator can alter the opacity of the superimposition to view suspicious areas on the B-mode image. The 4D CEUS movie covers the entire inflow of contrast agent (CA), allowing the identification of early enhancement.

The primary PCaVision-based MIM workflow enables cognitive targeted biopsy, importing images, annotating suspicious areas, and automatically generating a report. A secondary workflow for fusion-targeted biopsies is also available, with an export compatible with the BkFusion biopsy system. All the choices and the design requirements of Table 5.1 have been translated into a design, as shown in Figure 5.1.

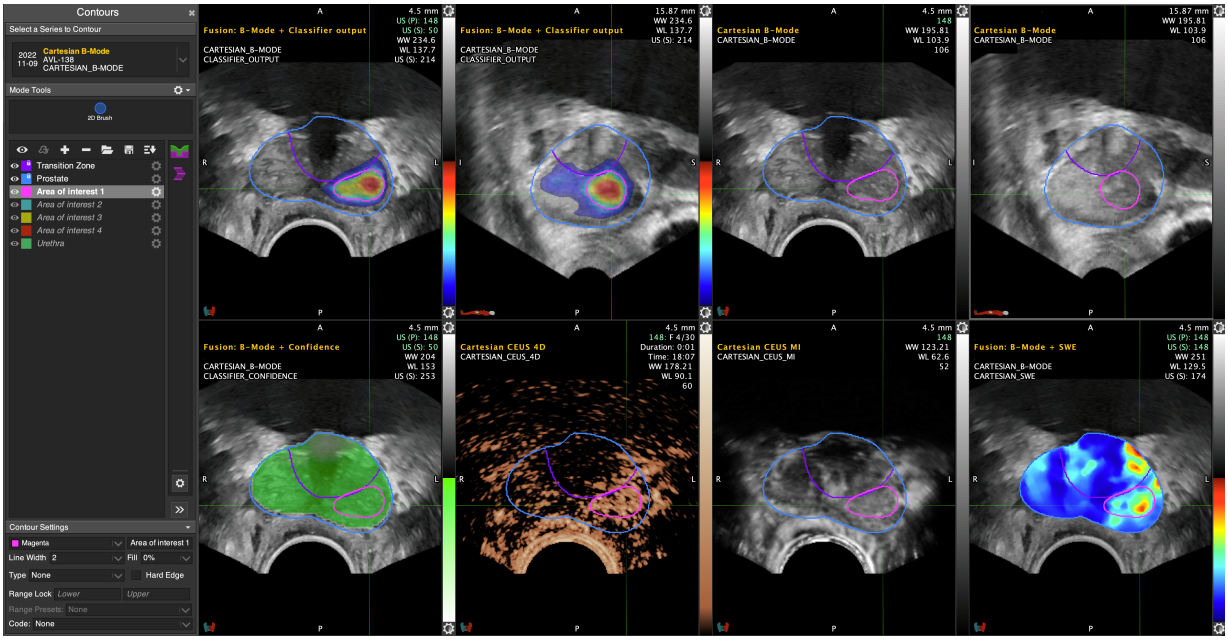


Fig. 5.1.: PCaVision GUI. HP1: axial B-mode overlaid with classifier output. HP2: sagittal B-mode overlaid with classifier output. HP3: axial B-mode. HP4: transversal B-mode. HP5: axial B-mode overlaid with confidence map. HP6: axial 4D CEUS movie. HP7: axial CEUS MI. HP8: axial B-mode overlaid with SWE. The prostate and PZ/TZ zone contour are visible in all series. In the left tab, the contours can be seen. Delineation of the AOI in one series will automatically be projected in the other series. GUI = graphical user interface; HP = hanging position; B-mode = brightness-mode; SWE = shear wave elastography; 4D = 4-dimensional; CEUS = contrast-enhanced ultrasound; MI = mean intensity; PZ = peripheral zone; TZ = transition zone; AOI = area of interest.

5.4 Evaluation of the prototype

The prototype of the PCaVision-based diagnostic workflow was evaluated for its design requirements (Table 5.1). This is indicated with red (not fulfilled), orange (partially fulfilled), and green (totally fulfilled).

A formative usability study was conducted to assess the ability of two urologists to use the PCaVision-based workflow. The users received extensive training to ensure they were prepared to evaluate images independently and perform the necessary tasks within the workflow. Following

the training, the users were given two interpretation instances to evaluate their ability to effectively execute the workflow. The completion of these tasks was recorded to evaluate task performance and efficiency. Data collection included getting user feedback and providing post-test questions to gain insights into the users' experience with the workflow. The System Usability Scale (SUS) was used to quantitatively assess the overall usability of the PCaVision-based workflow (Appendix E) [60]. The SUS is a tool that evaluates a given system's ease of use and learnability. It consists of ten questions and provides a SUS score. This score is then converted to a grading system where scores between 90–100 are categorized as A-class, 80–89 as B, 70–79 as C, 60–69 as D, and 0–59 as F [61]. The relation between the grading scale and the SUS score is depicted in Figure 5.2.

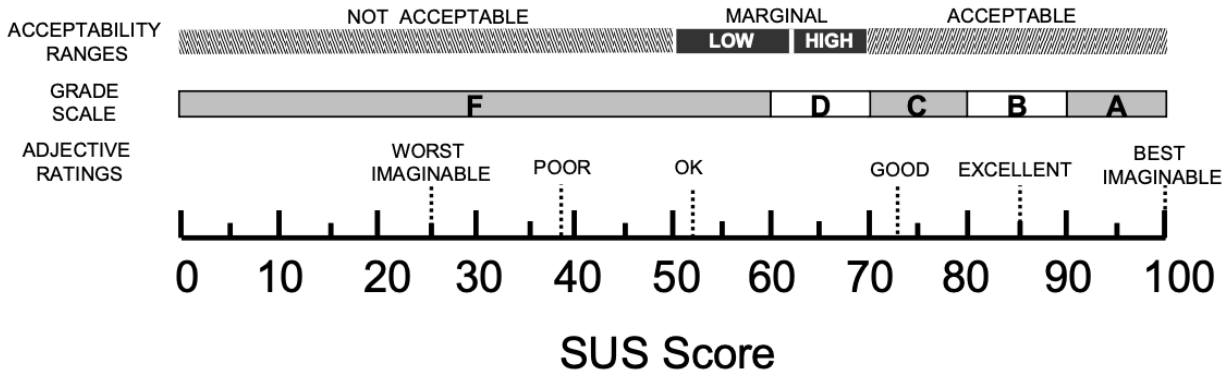


Fig. 5.2.: A comparison of the adjective ratings, acceptability scores, and school grading scales in relation to the average SUS score. *Adapted from: Bangor, A. (2009). Determining what individual SUS scores mean: adding an adjective rating scale [62].*

5.5 Results of evaluation

The prototype demonstrated high compliance with the requirements, except for requirement 5.4, which remains partially fulfilled due to ongoing formative testing and incomplete training saturation. Two urologists took part in the formative test, successfully adhering to and performing the steps required for annotating an area of interest. However, when they first opened and used the MIM software, they felt some initial discomfort and awkwardness. The derived SUS score was 60, which is marginally acceptable.

5.6 Discussion

Reflection on the results

The PCaVision prototype demonstrated promise in meeting design requirements and enabling urologists to independently execute a diagnosis using its primary workflow. Two requirements (4.3 and 4.4) were related to the secondary workflow for leveraging integration with a fusion biopsy system. Although the workflow has been successfully established and the export is compatible with the fusion system, clinical testing is required to validate its functionality. It is important to mention that this functionality is not required for PCaVision to operate properly, as not all hospitals have a fusion system. The SUS score of 60, which is marginally acceptable, suggests that further system usability improvements can be made.

A two-hour training session was provided for the initial operators. It consisted of demonstrating example annotations followed by independent execution by the new user. It is evident that the

training record still needs improvement. However, the users were able to properly register an area of interest (AOI) and felt confident in performing a diagnosis independently. The deep learning-based contours of the prostate and PZ/TZ zone were found to be accurate for the presented use cases. Adjustments for these contours were only necessary when a fusion-guided workflow was used.

Limitations of the study

To ensure the reliability of the prototype, it is important to acknowledge that this study was limited by its evaluation, with only two actual users during the formative test. Additional formative testing with a bigger sample size (n=5) should be conducted to obtain more user feedback for enhancing the prototype. To assess the reliability of the training time (requirement 5.4), a summative evaluation with multiple operators (n=15) should be carried out.

Recommendations

Based on the study findings, several recommendations can be made to improve the usability and reliability of PCaVision. Firstly, the training should include image interpretation to enable a urologist to interpret the images confidently. Secondly, clinical testing will be needed to evaluate the secondary workflow and confirm export compatibility with the fusion biopsy system, hence improving PCaVision integration and efficiency. Additionally, an optimal classification output threshold can be determined by combining the ROC value of the deep learning model with its diagnostic accuracy during the clinical inspection. Lastly, to provide a more versatile clinical report that can be used for multiple purposes, the current generated report should be improved by including more clinical information such as prostate gland volume, PSA value, PSA density, and volume of AOIs. By implementing these recommendations, the usability and reliability of PCaVision can be further enhanced. Overall, the PCaVision prototype shows potential for improving the detection and diagnosis of csPCa. By implementing these recommendations, the usability and reliability of PCaVision can be further enhanced. Therefore, PCaVision has the potential to become an important tool for urologists in their clinical practice.

5.7 Conclusion

The PCaVision-based diagnostic workflow prototype, evaluated for design requirements and usability, demonstrated promising results. The primary workflow enables cognitive targeted biopsy and generates an automatic report, while a secondary workflow for fusion targeted biopsies is also available. The prototype was evaluated through a usability study and demonstrated almost complete fulfillment of requirements, with only three partially fulfilled. Further improvements can be made to the system's usability, as suggested by the marginally acceptable SUS score.

General discussion

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The diagnosis and clinical intervention planning of PCa can be considerably improved by a standardized 3D mpUS recording procedure and an intuitive diagnostic workflow. This study developed a standardized recording procedure through a formative and summative usability study with 6 and 13 new users. It demonstrated that the training was adequate in educating new users, providing them the confidence to perform the procedure independently and ensuring reliable image acquisition. In addition, this study designed a promising prototype for a PCaVision-based diagnostic workflow with cognitive targeted biopsy and automatic report generation. However, the prototype developed around fusion-targeted biopsy requires further development and validation. Challenges remain in making these workflows applicable in a clinical context, but this study is an important advancement toward a more accurate and efficient 3D mpUS prostate cancer diagnosis.

First and foremost, one of the challenges for PCaVision is to demonstrate its clinical utility and establish its role in the diagnostic workflow of prostate cancer. To address this challenge, a head-to-head clinical trial will be conducted to compare the diagnostic accuracy of PCaVision with MRI. The results of this study will provide insight into the potential of PCaVision as a diagnostic tool and its ability to accurately detect prostate cancer. Furthermore, the summative usability study will test the PCaVision-based diagnostic workflow with new users, providing a more comprehensive evaluation of the feasibility of using PCaVision in clinical practice.

Following that, the establishment of a consistent system for image interpretation is a significant challenge facing the clinical adoption of PCaVision. An easy-to-understand and comprehensive image interpretation system should be included in training new PCaVision users. Despite multiple attempts to develop a mpUS image grading system, there is currently no agreement on image interpretation [35, 36, 63]. Therefore, further research is needed to establish a consistent and standardized method for mpUS image interpretation in the context of PCaVision-based diagnosis.

To conclude, integrating a new medical device into clinical practice can be difficult. Users need time to become familiar with the system, and introducing a new diagnostic workflow may require adjustments to existing clinical processes and workflows. However, the development of PCaVision has addressed these obstacles, making it simple to incorporate into conventional clinical workflows. Nevertheless, the cost of implementing a new system might be a significant barrier for smaller clinics or hospitals. Collaboration and support from healthcare professionals, administrators, and vendors will be crucial to achieve successful implementation. Avoiding the prospect of being carried away by the enthusiasm of a single clinician or patient champion is crucial. Instead, it is essential to have a broad view and consider the perspectives of a larger group. This is important because product developers frequently build devices that meet the champion's need, only to discover that it is not shared by the broader clinical or patient community. This approach is particularly important as it has been observed that crucial design aspects are frequently missed during the developmental stage [64].

Usability of PCaVision

The usability evaluations on the 3D mpUS recording procedure and PCaVision-based diagnostic workflow have yielded promising results. The training for the mpUS recording procedure was shown to be adequate and simple for new users to follow, with few errors during execution. The diagnostic workflow prototype also demonstrated encouraging results, but more validation through a summative test involving multiple users is required. While the SUS score was marginally acceptable, it suggests that there is still space for improvement. Overall, these usability studies show how PCaVision has the potential to improve the accuracy and efficiency of prostate cancer diagnosis, as well as the importance of ongoing development and testing to ensure optimal performance.

Recommendations

Comprehensive image interpretation training is recommended to ensure that the 3D mpUS recording procedure and PCaVision-based diagnostic workflow are employed effectively in clinical practice. While the existing training for the 3D mpUS procedure covers the user tasks, training users to interpret the images is also important. This would facilitate the operator's understanding of the procedure and, subsequently, their ability to generate high-quality scans. Furthermore, it is recommended for the diagnostic workflow to establish a uniform procedure for mpUS image interpretation; a preliminary system is suggested for this purpose (Appendix F). This will guarantee consistency in image interpretation and increase the accuracy of diagnosis outcomes. A robust training program that provides users with both theoretical and practical expertise will accelerate the adoption of these novel processes in clinical practice.

As a future step, the 3D mpUS and diagnostic workflow should be compatible with other ultrasound machines, visualization software, and fusion systems. This will allow healthcare providers and hospitals to extensively embrace the technology. In addition, compatibility with existing systems would reduce interruptions to established clinical processes and workflows, making integration of the technology into clinical practice easier.

The automated recording procedure can be further enhanced by incorporating user feedback with the LE10 US device. It is suggested to automate prostate volume measurement, alert on excessive darkening or calcification, and provide feedback on prostate location, symmetry, and correct probe positioning. These enhancements would make the recording procedure more user-friendly, efficient, and less error-prone.

Enhancements to the PCaVision's automatically generated report could significantly improve its versatility for multiple clinical purposes. Including the report's clinical data, such as prostate gland volume, PSA value, PSA density, and AOI volume, can help provide a more comprehensive and accurate diagnosis. This will allow the report to be used for cognitive targeted biopsy procedures and recorded as part of the clinical diagnosis in the electronic patient dossier.

Conclusion

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The results presented in this thesis show encouraging outcomes for the potential application of a standardized 3D mpUS recording procedure for prostate cancer assessment. Further validation through a head-to-head clinical trial is required to prove its diagnostic powers. The training program successfully taught new users and boosted their confidence to independently perform the procedure in a single day. Although the training program could be enhanced to provide a more comprehensive understanding of the 3D mpUS recording procedure, the results of this study indicate that it has great potential as a diagnostic tool for prostate cancer.

This study introduced and evaluated a PCaVision-based diagnostic workflow prototype, which can potentially improve prostate cancer diagnostics' efficiency. The developed prototype fulfilled most of the design requirements and provided promising results. The usability of the diagnostic workflow was evaluated using the Systematic Usability Score, which identified areas for improvement in the GUI design. The primary workflow enables cognitive targeted biopsy and generates an automatic report, while the secondary workflow supports fusion-targeted biopsies.

The key message remains that standardization of the 3D mpUS diagnostic procedure for prostate cancer is important. The study provides valuable insights into the usability and feasibility of a 3D mpUS recording procedure and a PCaVision-based diagnostic workflow. The establishment of these standardized procedures and workflows has the potential to simplify the diagnostic process for prostate cancer, resulting in a more efficient pathway.

> *The best designs are those that seamlessly integrate into our lives, simplifying and enhancing our interactions with technology.*
>
> **— Tim Cook**

Bibliography

[1] M. B. B. Culp and I. Soerjomataram, "Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates," *European urology*, vol. 77, no. 1, pp. 38–52, 2020.

[2] J. Ferlay, M. Colombet, I. Soerjomataram, and F. Bray, "Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods," *International journal of cancer*, vol. 144, no. 8, pp. 1941–1953, apr 2019.

[3] E. A. Platz and E. Giovannucci, "Prostate Cancer," *Cancer Epidemiology and Prevention*, oct 2006.

[4] R. B. Hayes, R. G. Ziegler, and G. Gridley, "Dietary factors and risks for prostate cancer among blacks and whites in the United States," *Cancer Epidemiology Biomarkers and Prevention*, vol. 8, no. 1, pp. 25–34, jan 1999.

[5] J. Ferlay, M. Colombet, and F. Bray, "Cancer statistics for the year 2020: An overview." *International Journal of Cancer*, vol. 149, no. 4, pp. 778–789, apr 2021.

[6] A. Matoso and J. I. Epstein, "Defining clinically significant prostate cancer on the basis of pathological findings," *Histopathology*, vol. 74, no. 1, pp. 135–145, jan 2019.

[7] J. R. Srigley, B. Delahunt, and H. Samaratunga, "One is the new six: The International Society of Urological Pathology (ISUP) patient-focused approach to Gleason grading," *Canadian Urological Association Journal*, vol. 10, no. 9-10, pp. 339–41, oct 2016.

[8] R. C. Chen and R. Bryan Rumble, "Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline)," *Journal of the American Society of Clinical Oncology*, vol. 34, no. 18, pp. 2182–2190, jun 2016.

[9] B. Hanna, W. Ranasinghe, and N. Lawrentschuk, "Risk stratification and avoiding overtreatment in localized prostate cancer," *Current opinion in urology*, vol. 29, no. 6, pp. 612–619, nov 2019.

[10] V. Kasivisvanathan, A. S. Rannikko, and A. Briganti, "MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis," *The New England Journal of Medicine*, vol. 378, no. 19, mar 2018.

[11] M. van der Leest, E. Cornel, and J. O. Barentsz, "Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study," *European Urology*, vol. 75, no. 4, pp. 570–578, apr 2019.

[12] O. Rouvière, P. Puech, and J. Walz, "Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study," *The Lancet. Oncology*, vol. 20, no. 1, pp. 100–109, jan 2019.

[13] F. J. H. Drost, D. Osses, D. Nieboer, and I. G. Schoots, "Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis," *European Urology*, vol. 77, no. 1, pp. 78–94, jan 2020.

[14] H. U. Ahmed, A. El-Shater Bosaily, and M. Emberton, "Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study," *Lancet (London, England)*, vol. 389, no. 10071, pp. 815–822, feb 2017.

[15] E. Hauth, H. Hohmuth, C. Cozub-Poetica, and H. Jaeger, "Multiparametric MRI of the prostate with three functional techniques in patients with PSA elevation before initial TRUS-guided biopsy," *British Journal of Radiology*, vol. 88, no. 1054, oct 2015.

[16] A. Stabile, F. Giganti, A. B. Rosenkrantz, and V. Kasivisvanathan, "Multiparametric MRI for prostate cancer diagnosis: current status and future directions," *Nature Reviews Urology 2019 17:1*, no. 1, pp. 41–61, jul.

[17] S. Woo, C. H. Suh, and S. H. Kim, "Diagnostic Performance of Prostate Imaging Reporting and Data System Version 2 for Detection of Prostate Cancer: A Systematic Review and Diagnostic Meta-analysis," *European Urology*, vol. 72, no. 2, pp. 177–188, aug 2017.

[18] N. L. Hansen, B. C. Koo, F. A. Gallagher, and T. Barrett, "Comparison of initial and tertiary centre second opinion reads of multiparametric magnetic resonance imaging of the prostate prior to repeat biopsy," *European Radiology*, no. 6, pp. 2259–2266, jun.

[19] B. G. Muller, J. H. Shih, and B. Turkbey, "Prostate Cancer: Interobserver Agreement and Accuracy with the Revised Prostate Imaging Reporting and Data System at Multiparametric MR Imaging," *Radiological Society of North America*, vol. 277, no. 3, pp. 741–750, jun 2015.

[20] A. B. Rosenkrantz, L. A. Ginocchio, and D. J. Margolis, "Interobserver Reproducibility of the PI-RADS Version 2 Lexicon: A Multicenter Study of Six Experienced Prostate Radiologists," *Radiological Society of North America*, vol. 280, no. 3, pp. 793–804, apr 2016.

[21] H. Van Poppel, M. J. Roobol, C. R. Chapple, and M. Wirth, "Prostate-specific Antigen Testing as Part of a Risk-Adapted Early Detection Strategy for Prostate Cancer: European Association of Urology Position and Recommendations for 2021," *European Urology*, vol. 80, no. 6, pp. 703–711, 2021.

[22] M. de Rooij, H. van Poppel, and J. O. Barentsz, "Risk Stratification and Artificial Intelligence in Early Magnetic Resonance Imaging–based Detection of Prostate Cancer," *European Urology Focus*, dec 2021.

[23] A. W. Postema, P. J. Frinking, M. Smeenge, T. M. De Reijke, and H. Wijkstra, "Dynamic contrast-enhanced ultrasound parametric imaging for the detection of prostate cancer," *BJU International*, vol. 117, no. 4, pp. 598–603, apr 2016.

[24] K. Boehm, G. Salomon, B. Beyer, and L. Budaeus, "Shear wave elastography for localization of prostate cancer lesions and assessment of elasticity thresholds: implications for targeted biopsies and active surveillance protocols," *The Journal of Urology*, vol. 193, no. 3, pp. 794–800, mar 2015.

[25] C. F. Dietrich, M. Averkiou, M. B. Nielsen, and S. Westerway, "How to perform Contrast-Enhanced Ultrasound (CEUS)," *Ultrasound International Open*, vol. 4, no. 1, pp. E2–E15, 2018.

[26] G. Russo, M. Mischi, and H. Wijkstra, "Angiogenesis in prostate cancer: onset, progression and imaging," *BJU International*, vol. 110, no. 11c, pp. E794–E808, dec 2012.

[27] R. J. Van Moorselaar and E. E. Voest, "Angiogenesis in prostate cancer: Its role in disease progression and possible therapeutic approaches," *Molecular and Cellular Endocrinology*, vol. 197, no. 1-2, pp. 239–250, nov 2002.

[28] Z. Melegh and S. Oltean, "Targeting Angiogenesis in Prostate Cancer," *International Journal of Molecular Sciences 2019, Vol. 20, Page 2676*, vol. 20, no. 11, p. 2676, may 2019.

[29] N. Nishida, H. Yano, T. Nishida, T. Kamura, and M. Kojiro, "Angiogenesis in cancer," *Vascular health and risk management*, vol. 2, no. 3, pp. 213–219, 2006.

[30] M. P. Kuenen, M. Mischi, and H. Wijkstra, "Contrast-ultrasound diffusion imaging for localization of prostate cancer," *IEEE Transactions on Medical Imaging*, vol. 30, no. 8, pp. 1493–1502, 2011.

[31] R. J. van Sloun, L. Demi, A. W. Postema, H. Wijkstra, and M. Mischi, "Ultrasound-contrast-agent dispersion and velocity imaging for prostate cancer localization," *Medical image analysis*, vol. 35, pp. 610–619, jan 2017.

[32] M. P. Kuenen, T. A. Saidov, H. Wijkstra, J. J. De La Rosette, and M. Mischi, "Spatiotemporal correlation of ultrasound contrast agent dilution curves for angiogenesis localization by dispersion imaging," *IEEE transactions on ultrasonics, ferroelectrics, and frequency control*, vol. 60, no. 12, pp. 2665–2669, dec 2013.

[33] C. K. Mannaerts, R. R. Wildeboer, M. Mischi, H. Wijkstra, and G. Salomon, "Multiparametric Ultrasound for Prostate Cancer Detection and Localization: Correlation of B-mode, Shear Wave Elastography and Contrast Enhanced Ultrasound with Radical Prostatectomy Specimens," *The Journal of Urology*, vol. 202, no. 6, pp. 1166–1173, jun 2019.

[34] van Kollenburg and van Sloun, "Detection of clinically significant prostate cancer in biopsy-naïve men," *BJU International*, vol. 126, no. 4, pp. 481–493.

[35] A. D. Grey, R. Scott, and H. U. Ahmed, "Multiparametric ultrasound versus multiparametric MRI to diagnose prostate cancer (CADMUS): a prospective, multicentre, paired-cohort, confirmatory study," *The Lancet Oncology*, vol. 23, no. 3, pp. 428–438, 2022.

[36] A. Maxeiner, C. Stephan, and T. Fischer, "Added Value of Multiparametric Ultrasonography in Magnetic Resonance Imaging and Ultrasonography Fusion-guided Biopsy of the Prostate in Patients with Suspicion for Prostate Cancer," *Urology*, vol. 86, no. 1, pp. 108–114, 2015.

[37] M. Brock, T. Eggert, R. J. Palisaar, and C. Von Bodman, "Multiparametric Ultrasound of the Prostate: Adding Contrast Enhanced Ultrasound to Real-Time Elastography to Detect Histopathologically Confirmed Cancer," *The Journal of Urology*, vol. 189, no. 1, pp. 93–98, jan 2013.

[38] M. R. Engelbrecht, G. J. Jager, R. J. Laheij, and J. O. Barentsz, "Local staging of prostate cancer using magnetic resonance imaging: A meta-analysis," *European Radiology*, vol. 12, no. 9, pp. 2294–2302, sep 2002.

[39] J. O. Barentsz, J. Richenberg, R. Clements, and J. J. Fütterer, "ESUR prostate MR guidelines 2012," *European radiology*, no. 4, pp. 746–757.

[40] J. Le Nobin, C. Orczyk, F. M. Deng, and A. B. Rosenkrantz, "Prostate tumour volumes: evaluation of the agreement between magnetic resonance imaging and histology using novel co-registration software," *BJU International*, vol. 114, no. 6b, pp. E105–E112, dec 2014.

[41] R. R. Engels, B. Israël, A. R. Padhani, and J. O. Barentsz, "Multiparametric Magnetic Resonance Imaging for the Detection of Clinically Significant Prostate Cancer: What Urologists Need to Know. Part 1: Acquisition," *European Urology*, vol. 77, no. 4, pp. 457–468, apr 2020.

[42] B. Turkbey, A. B. Rosenkrantz, M. A. Haider, J. Barentsz, and J. C. Weinreb, "Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2," *European Urology*, vol. 76, no. 3, pp. 340–351, sep 2019.

[43] G. Ortner, E. Tzanaki, B. P. Rai, U. Nagele, and T. Tokas, "Transperineal prostate biopsy: The modern gold standard to prostate cancer diagnosis," *Turkish Journal of Urology*, vol. 47, no. 1, pp. S19–S26, 2021.

[44] F.-J. H. Drost, D. F. Osses, and I. G. Schoots, "Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer," *Cochrane Database of Systematic Reviews*, no. 4, apr 2019.

[45] K. L. Watts, L. Frechette, B. Muller, and A. Aboumohamed, "Systematic review and meta-analysis comparing cognitive vs. image-guided fusion prostate biopsy for the detection of prostate cancer," *Urologic Oncology: Seminars and Original Investigations*, vol. 38, no. 9, pp. 734.e19–734.e25, sep 2020.

[46] C. C. Khoo, D. Eldred-Evans, M. Peters, and H. U. Ahmed, "A Comparison of Prostate Cancer Detection between Visual Estimation (Cognitive Registration) and Image Fusion (Software Registration) Targeted Transperineal Prostate Biopsy," *The Journal of Urology*, vol. 205, no. 4, pp. 1075–1081, apr 2021.

[47] R. R. Wildeboer, *Multiparametric and multidimensional: three-dimensional and multiparametric approach to ultrasound imaging of prostate cancer.*

[48] A. Postema, M. Mischi, J. de la Rosette, and H. Wijkstra, "Multiparametric ultrasound in the detection of prostate cancer: a systematic review," *World Journal of Urology*, vol. 33, no. 11, pp. 1651–1659, nov 2015.

[49] A. Grey and H. U. Ahmed, "Multiparametric ultrasound in the diagnosis of prostate cancer," *Current Opinion in Urology*, vol. 26, no. 1, pp. 114–119, jan 2016.

[50] E. J. Halpern, J. R. Ramey, and L. O. Gomella, “Detection of prostate carcinoma with contrast-enhanced sonography using intermittent harmonic imaging,” *Cancer*, vol. 104, no. 11, pp. 2373–2383, dec 2005.

[51] M. B. Weinger, M. E. Wiklund, and D. J. Gardner-Bonneau, “Handbook of Human Factors in Medical Device Design,” *Handbook of Human Factors in Medical Device Design*, pp. 1–822, jan 2010.

[52] A. Jager, A. W. Postema, M. Mischi, and J. R. Oddens, “Clinical Trial Protocol: Developing an Image Classification Algorithm for Prostate Cancer Diagnosis on Three-dimensional Multiparametric Transrectal Ultrasound,” *European Urology Open Science*, vol. 49, pp. 32–43, mar 2023.

[53] SonoSim Inc., “SonoSim® Ultrasound Learning Teaching Ecosystem.”

[54] A. Grimwood, K. Thomas, and H. A. Kember, Sallyand McNair, “Factors affecting accuracy and precision in ultrasound guided radiotherapy,” *Physics and Imaging in Radiation Oncology*, vol. 18, pp. 68–77, apr 2021.

[55] N. Tole and World Health Organisation, *Basic physics of ultrasonographic imaging WHO*, 2005.

[56] T. R. Nelson and D. H. Pretorius, “Three-dimensional ultrasound imaging,” *Ultrasound in Medicine Biology*, vol. 24, no. 9, pp. 1243–1270, dec 1998.

[57] Angiogenesis Analytics, “P10-RMP-001 Risk Management Plan - METC Documentation,” pp. 2–5.

[58] J. Trappenburg, “THINC. Healthcare.”

[59] E. Pepin, “Assessment of Hanging Protocol Impact on Turn Around Time.”

[60] J. Brooke, “SUS: A ’Quick and Dirty’ Usability Scale,” *Usability Evaluation In Industry*, no. January 1996, pp. 207–212, 2020.

[61] ——, “SUS : A Retrospective,” *Journal of Usability Studies*, vol. 8, no. January 2013, pp. 29–40, 2020.

[62] A. Bangor, P. Kortum, and J. Miller, “Determining what individual SUS scores mean; adding an adjective rating,” *Journal of usability studies*, vol. 4, no. 3, pp. 114–23, 2009.

[63] Y. Liu, S. Zeng, and R. Xu, “Application of Multiple Ultrasonic Techniques in the Diagnosis of Prostate Cancer,” *Frontiers in Oncology*, vol. 12, jun 2022.

[64] D. Clark, G. Dean, S. Bolton, and B. Beeson, “Bench to bedside: The technology adoption pathway in healthcare,” *Health and Technology*, vol. 10, no. 2, pp. 537–545, mar 2020.

Appendices

Task descriptions

A

Phase	Task	Task description
Preparation	Proper use of probe fixture	Use the fixture properly (know how to move the different articulations and understand how to fixate/unblock the fixture without help).
	New patient ID	Adds new *Patient ID* to the US machine correctly.
	US gel in rectum	Adds ultrasound gel to the rectum.
Recording - B, DP, SWE	Probe fixated in correct orientation	Fixates the probe in the correct orientation (the indentation in the probe pointing to the right side of the patient).
	Safe probe insertion	Inserts the probe safely (without generating extra pain and/or discomfort to the patient)
	Verifies FOV (B-mode)	Verifies the field-of-view in B-mode.
	3D B-mode visualization (apex/base visible)	Uses a 3D B-mode sequence to verify that the apex and base are visible.
	Verifies FOV (Elasto-mode)	Verifies the field-of-view in Elasto-mode
	Correct macro (size) initialization	Uses a correct macro depending on the size of the prostate
	Does not press any key during macro execution	Does not press any key or uses tracker ball during macro execution, except when an error occurs. If it is not applicable, the score will be 1.
Recording - CEUS	Preparation of CA Correct macro (size) initialization	Prepares the SonoVue contrast correctly. Uses the correct macro depending on the size of the prostate
	CA and NaCl attachment to 3-way valve	Attaches the CA and NaCl correctly to the 3-way valve (CA parallel and NaCl perpendicular to flow direction).
	3-way valve open for CA administration	Positions the 3-way valve so that only the contrast is administered.
	Reactivation CA just before administration	Reactivates the CA just before administering it.
	Timing CA administration	Administers the CA at the right time (after the sound signal).
	Volume CA administration	Administers the right amount of CA (2.4 mL of SonoVue).
	3-way valve open for NaCl administration	Positions the 3-way valve so that only NaCl is administered.
	Volume NaCl administration	Administers the right amount of NaCl to flush all the CA from the cannula.
	Does not press any key	Does not press any key or uses tracker ball during macro execution, except when an error occurs. If it is not applicable, the score will be 1.

Phase	Task	Task description
End scan	Ends exam	Ends the scan recording successfully on the LE10.
	Data transfer	Transfers the data of the scanned patients on a hard disk (can be done after completing all the patients of the day).
	Correct procedure (all scans modalities) executed, non-operator errors in the session).	Performs the procedure correctly (all scan modalities executed, non-operator errors in the session).
Troubleshooting	Error 1: patient ID missing	Resolves the error - abort macro, delete images, add patient ID, re-initialize macro.
	Error 2: wrong FOV	Resolves the error - abort macro, delete images, adjust FOV, re-initialize macro.
	Error 3: wrong macro initialization	Resolves the error - abort macro, delete images, (adjust FOV), re-initialize macro.
	Error 4: initialization with mode turned on	Resolves the error - abort macro, delete images, turn all modes off, re-initialize macro.
	Error 5: macro stalling	Resolves the error - abort macro, delete images, re-initialize macro
	Error 6.1: excessive movement during 1^{st} macro	Resolves the error - abort macro, delete images, reposition probe, verify prostate visualization 3D B-mode, turn all modes off, re-initialize macro.
	Error 6.2: excessive movement after 1^{st} macro	Resolves the error - reposition probe, verify prostate visualization 3D B-mode, turn all modes off, proceed to initialize 2^{nd} macro.
	Error 7.1: incorrect CA administration	Resolves the error - abort macro, delete CEUS, wait 5 min. before administering new bolus of CA, turn all modes off, re-initialize 2^{nd} macro.
	Error 7.2: excessive movement during 2^{nd} macro	Resolves the error - abort macro, delete CEUS, wait 5 min. before administering new bolus of CA, turn all modes off, re-initialize 2^{nd} macro.

Tab. A.1.: A task description per evaluated task in the summative test.

Quality standards

B

All GE LOGIQ E10 machines used in this research are configured prior to scanning patients according to the following modality settings:

Modality	Name	Value
B-mode	Axial voxel size	0.08-0.13 mm
	Dynamic range	69.0 dB
	Gain	55.0 dB
	Field of view	120.0 degrees
	Depth start	0 mm
	Depth end	49.9-50.1 mm
	Power level	100 pct
	Transducer frequency	9,000 kHz
	Depth of focus	25.0 mm
	Depth of scan field	48.0 mm
	Mechanical index	1.29-1.31
	Bone thermal index	0.39-0.41
	Soft tissue thermal index	0.39-0.41
	Radius start	0.0-14.0 mm
	Radius mean step size	0.08-0.13 mm
	Radius min step size	> 0.0 mm
	Azimuth range	120.0-150.0 degrees
	Azimuth mean step size	0.31-0.33 degrees
	Azimuth min step size	> 0.0 mm
	Elevation range	118.0-122.0 degrees
	Elevation mean step size	0.7-0.8 degrees
	Elevation min step size	> 0.0 degrees
4D CEUS	Dynamic range	42.0 dB
	Gain	55.0 dB
	Field of view	120.0 degrees
	Power level	10.0 pct
	Mechanical index	0.09-0.13
	Radius start	0.0-14.0 mm
	Radius mean step size	0.14-0.16 mm
	Radius min step size	> 0.0 mm
	Azimuth range	120.0-150.0 degrees
	Azimuth mean step size	0.79-0.81 degrees
	Azimuth min step size	> 0.0 degrees
	Elevation range	118.0-122.0 degrees
	Elevation mean step size	2.3-2.4 degrees
	Elevation min step size	> 0.0 degrees

Modality	Name	Value
SWE	Axial voxel size	0.09-0.11 mm
	Dynamic range	20.0 dB
	Gain	14.0 dB
	Field of view	120.0 degrees
	Depth start	0.0 degrees
	Depth end	49.9-50.1 mm
	Power level	100.0 pct
	Transducer frequency	9,000 kHz
	Mechanical index	1.39-1.41
	Radius start	0.0-14.0 mm
	Radius mean step size	0.09-0.11 mm
	Radius min step size	> 0.0 mm
	Azimuth range	110.0-130.0 degrees
	Azimuth mean step size	0.7-0.77 degrees
	Azimuth min step size	> 0.0 degrees
	Elevation range	118.0-122.0 degrees
	Elevation mean step size	4.9-5.1 degrees
	Elevation min step size	> 0.0 degrees
Doppler		Not applicable

Tab. B.1.: Quality standards of PCaVision.

Root-cause analysis use errors, close calls, and user-feedback

C

Use errors	Root-cause analysis	Action point
1 operator did not know how to articulate the probe fixture properly.	Operators were not trained on how to articulate the probe fixture.	Explaining operators how to articulate the probe fixture before starting a procedure.
1 operator administered the contrast agent in more than 5 seconds.	The operator was not familiar with the handling of the 3-way valve yet.	This step does not seem to be critical to get a high quality scan. Operators will be trained on handling of the 3-way valve.
1 operator had a painful insertion of the probe in 2 procedures.	The operator seemed to apply too much force to the probe during insertion. The reaction of the patient made him stressed, and he did not have the confidence to successfully complete the insertion of the probe.	Operators will be trained to insert the probe safely under image-guidance.
1 operator initialized a macro with still ultrasound modes turned on.	Turning all modes off was not included in the IFU.	Include 'turn all modes off' in the IFU and SOP.
2 operators forgot to inject gel into the rectum.	Operator felt confident enough about the procedure to not follow the SOP step-by-step.	This step does not seem to be critical to get a high quality scan. However, we instruct users to prepare the syringe with gel and place it on top of the ultrasound machine to have it within reach.

Tab. C.1.: Use errors and their root-cause analysis.

Close calls	Root-cause analysis	Action point
1 operator forgot to apply gel on the tip of the probe in 2 procedures.	Operators were not explicitly trained to apply on top of the probe.	This step does not seem to be critical since there is already ultrasound gel in the rectum.
1 operator did not use one of the components of the SonoVue kit.	The operator did not use one component of the kit, until the supervisor highlighted it. The preparation of the contrast was successful after that.	Instruct operator to follow instructions for use of SonoVue during training.
1 operator reactivated the contrast agent too much in advance prior to administration.	Not clear instruction about when to reactivate the CA.	Adapted training record: instruct operator to reactivate just before attaching to the 3-way valve.
1 operator took more time to rotate the 3-way valve correctly.	The operator was not familiar with the handling of the 3-way valve yet.	Explaining operators how to rotate the 3-way valve. Although this step is not time-sensitive.

Tab. C.2.: Close calls and their root-cause analysis.

User feedback	Action point
1 operator noticed that the steps for exporting the data were inverted.	Adjusted the steps in IFU and SOP.
1 operator realized that after fixating the probe it moved slightly because the patient puts force on it.	No further action needed.
1 operator suggested removing the IV after completion of the CEUS recording to prevent patient movement.	Added to the training record.
1 operator advised making a visual document with the essential SOP steps.	Designed a poster (Appendix D).

Tab. C.3.: User-feedback and their action points.

Standardized procedure

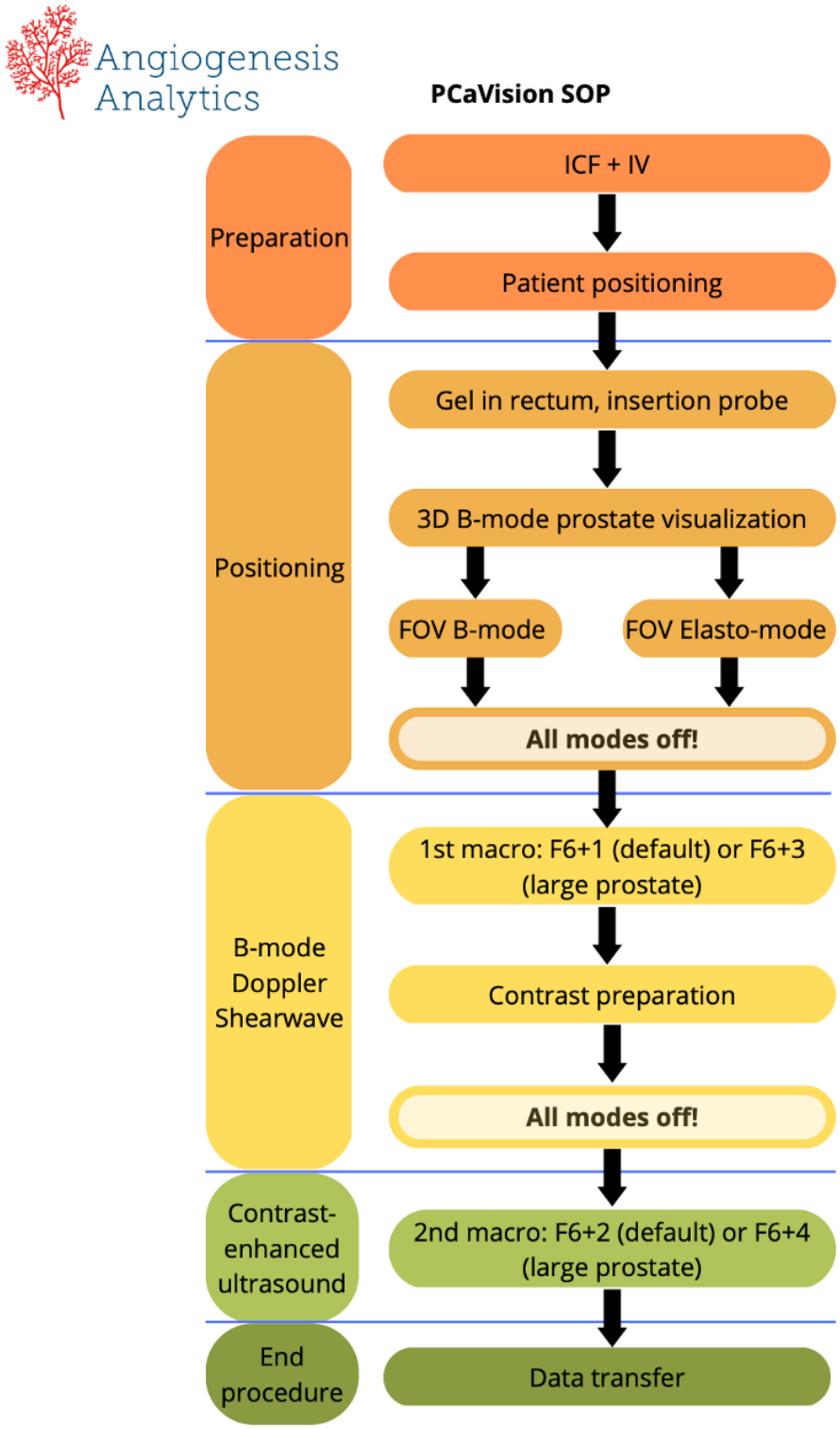

Fig. D.1.: PCaVision standardized 3D mpUS recording procedure.

System Usability Scale

E

Criteria	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I think that I would use this system frequently					
I found the system unnecessarily complex					
I thought the system was easy to use					
I think that I would need the support of a technical person to be able to use this system					
I found the various functions in the system were well integrated					
I thought there was too much inconsistency in this system					
I would imagine that most people would learn to use this system very quickly					
I found the system very cumbersome to use					
I felt very confident using the system					
I needed to learn a lot of things before I could get going with this system					

Tab. E.1.: The System Usability Scale (SUS) used in the evaluation of the PCaVision-based diagnostic workflow. *Adapted from: Brook, J. (1996) [60].*

Preliminary PCaVision interpretation system

F

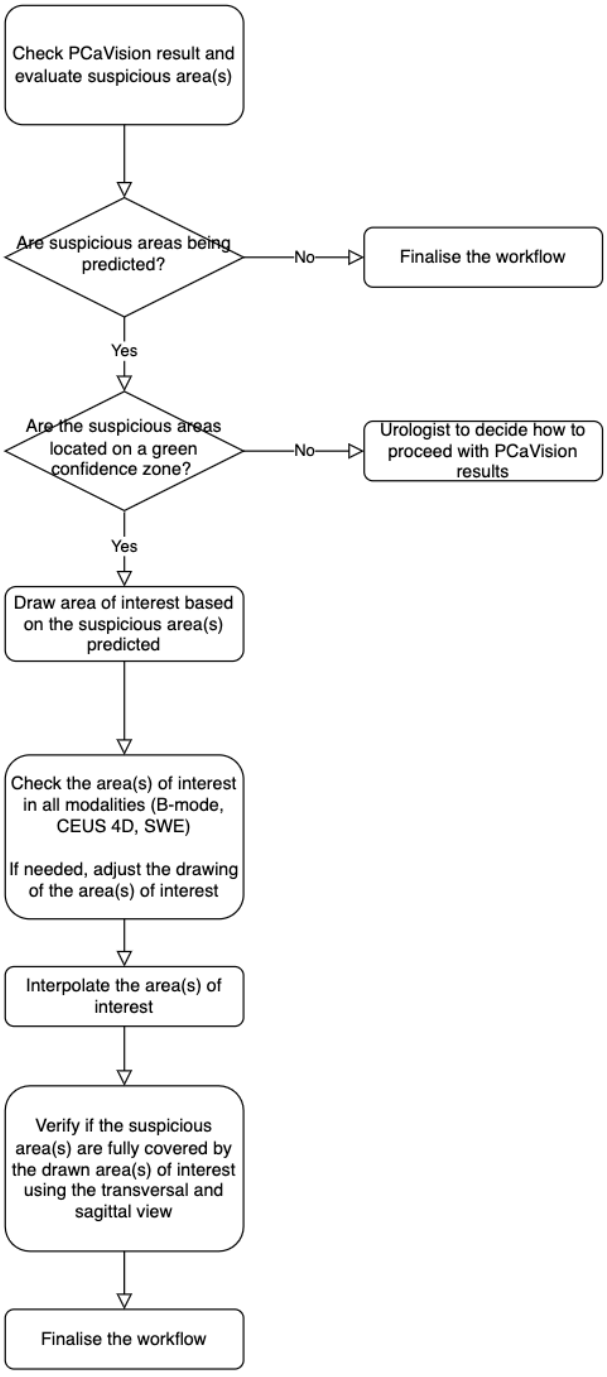

Fig. F.1.: Preliminary PCaVision interpretation system.