10 TRUS of the Prostate: State of the Art

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Background

Historically, most prostate cancers were initially detected by systematic random biopsy, either through elevated PSA or abnormal DRE. This diagnostic process used in prostate cancer was unlikely for most cancers in other organs, which are initially detected by an imaging technique. In most other cancers, detailed imaging information such as localization, contour and volume of the cancer, and its staging plays a critical role in the choice of treatment which includes organ preservation therapy. On the other hand, since the whole grand prostate has conventionally been the therapeutic target, clinicians demanded only knowledge of the presence of cancer anywhere in the prostate, and detailed visualization of the prostate cancer was not required.

However, the role of real-time transrectal ultrasonography (TRUS) has already changed. Its role is not simple guidance to sample biopsy tissue from the rough sextant portion of the prostate to determine whether cancer exists or not in the prostate. Today, the location and characteristics of the cancer are required. According to the increasing interest in avoiding treatment-related side effects with conventional radical whole grand treatment, future options in the management of clinically localized prostate cancer likely require more detailed anatomical and functional imaging to determine the most adequate management from the various options, including functional preservation whole grand therapy, active surveillance, or focal therapy to potentially control or cure the cancer while preserving function. What patients and clinicians need would be imaging to accurately visualize and stage the cancer and also to adequately guide the targeted sampling in order to distinguish aggressive from indolent cancer.

Ideal imaging may provide a detailed three-dimensional (3D) model of clinically significant cancer in the 3D space of the prostate, to provide detailed tissue characteristics (aggressiveness), and spatial location in relation to the important functional anatomy such as the prostate capsule, neurovascular bundle, or external sphincter in order to assist reliable surgical intervention. Nowadays, intraoperative image guidance is becoming an essential part of the surgical techniques for reliable image-guided surgery. Recently, TRUS guidance during radical prostatectomy has been increasingly reported [1–3].

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Among potential alternatives of focal therapy, cryoablation, HIFU, photodynamic therapy, and brachytherapy are all guided by real-time TRUS. Again, the role of real-time TRUS has already changed from being a simple diagnostic tool to becoming a comprehensive image guidance system, including the entire process of the management of prostate cancer from diagnosis to therapeutics and then the follow-up. This chapter focuses on the contemporary role of TRUS for image-guided urological surgery.

Evolving Technology to Enhance Real-Time TRUS Guidance

In principle, the prostate is a mobile and deformable organ. The prostate can move due to movement in the bowel, bladder filling, or postural change [4, 5], and also it can swell by multiple needle insertions or ablative energy [6]. While external radiation therapy (EBRT) is an image-guided standard therapy for localized prostate cancer, a study demonstrated that in over half of the patients undergoing EBRT, 5 mm or greater realignment errors in the required daily realignment of the beams had occurred, to cause potential missing cancer cells and serious damage to adjacent healthy tissues [7, 8]. Also, during a 20-min EBRT session, the prostate was found to move as much as 3 mm [9]. For image-guided surgery, the real-time feedback of the real spatial location of the target organ or cancer lesion is essential. Real-time TRUS has several advantages for intraoperative use, especially to visualize the reality of the target or any intraoperative change and motion of the organ.

Recent evolving digitalized technology has significantly improved the TRUS system (Table 10.1). Firstly, a 3D image can be constructed for preoperative planning and intraoperative monitoring, and importantly, real-time 3D TRUS is now routinely available in the urological field. Secondly, not only improvement toward a higher resolutional grayscale image but also multi-parametric ultrasound functions are now available. Multi-parametric TRUS includes Doppler, elastography, contrast-enhanced imaging, and image fusion technology with other imaging modalities such as MRI (magnetic resonance imaging). Thirdly, robotic manipulation of the TRUS probe enhances accuracy in

Table 10.1 Key points in the use of TRUS

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Key point 2: evolving technology for TRUS guidance
1st, a 3D image can be constructed for preoperative planning and intraoperative monitoring, and importantly, real-time 3D TRUS probe and real-time biplane TRUS probe is now routinely available
2nd, multi-parametric ultrasound functions are now available, including image fusion techniques and contrast enhancement
3rd, robotic manipulation of the TRUS probe enhances accuracy with minimizing operator dependency
4th, computer-assisted automated interpretation of an image potentially enhances the accuracy of tissue characterization
Key point 3: essential image guidance for focal therapy
TRUS is the most popular image guidance for urologist
Intraoperative feedback or navigation using real-time TRUS monitoring is the key for safety and efficacy for focal therapy of prostate cancer
Image fusion, contrast enhancement, and multi- parametric TRUS is a promising technology to support focal therapy strategy

visualization, targeting, revisiting, and reconstruction of 3D images by a 2D image, resulting in the potential decrease on operator dependency. Fourthly, computer-assisted automated interpretation of an image (tissue characterization) potentially enhances the accuracy of the visualization of prostate cancer, again resulting in a potential decrease on operator dependency.

A 3D image of the prostate could be reconstructed from continuous scanning of 2D TRUS images to visualize the entire prostate by use of a magnetic tracker or mechanical robotic arm attached to the 2D (end-fire or side-fire) TRUS probe. The magnetic sensor or mechanical sensor can digitally track the spatial motion of the manipulated 2D TRUS probe. A 3D ultrasound image is more accurate, with lower variability and higher reliability, than using 2D imagery in the measurement of the prostate volume and increased sensitivity in the detection of prostate cancer [10, 11]. Biopsy and surgical planning can be enhanced by an understanding of the 3D anatomy of the prostate (including the median lobe or protrusion to the bladder) as well as the suspicious or biopsy-proven lesion, in relation to the adjacent vital anatomies such as the sphincter muscle and neurovascular bundle. A 3D image enables us to interpret the prostate anatomy in every desired direction and to confirm it using multi-planar display of the sagittal, transverse, and coronal planes simultaneously. However, the prostate motion and deformations may also be induced by the use of endorectal instruments such as the TRUS probe itself. As such, the intraoperative image of the prostate can be already different from the previously acquired reconstructed 3D image of the prostate. It should be noted that continuous intraoperative feedback using real-time imagery to recognize the reality in the therapeutic target is essential in order to improve accuracy.

A real-time 3D TRUS image can be obtained using a specific end-fire 3D TRUS probe to scan the entire prostate automatically in only 3 s by freehand without any tracking system. This unique real-time 3D TRUS probe can enhance the accuracy of 3D registration of the biopsy trajectories in the digitalized volume data of the prostate [12]. The real-time 3D TRUS imaging to acquire a hyperechoic image of the metallic biopsy needle indwelling in the real 3D prostate could precisely register the spatial location of each biopsy in the prostate as a reality. Such information would be critical to develop reliable revisiting confirmatory biopsy in the active surveillance protocol, as well as to establish a clinically successful focal therapy protocol by precise 3D localization of the biopsy-proven cancer [13].

Recently, updated utility of Doppler and elastography have been increasingly reported. An important shortcoming of current systematic prostate biopsies is that they are most often image-blind procedures; in other words, they are unlikely to target any TRUS-visible lesions. However, when comparing TRUS-visible with image-invisible index lesions, the cancer-involved core lengths were 6.1 versus 1.5 mm ($P < 0.001$), respectively. Image visibility of prostate cancer allows the precise targeting of cancer and leads to a better characterization of tumor extent. Furthermore, targeted biopsies may enhance the appropriate selection of patients for active surveillance as well as focal therapy, augment the precision of targeted treatment, and provide an image-integrated monitoring protocol [14].

Contrast TRUS has shown promising results in cancer detection with improved accuracy of targeted biopsy. It may be useful for monitoring therapeutic effect for tissue preservation therapy as well as surveillance of local recurrence after treatment. This technology is based on the development of contrast enhancers and the computerized analysis of the pharmacokinetics of the contrast enhancement pattern. A major limitation of the widespread use of contrast TRUS was the difficulty in scanning and analyzing the entire prostate at the best timing of contrast enhancement, if using 2D TRUS; however, the introduction of a real-time 3D TRUS probe would provide a novel opportunity for simultaneous analysis of the entire prostate at the best timing of contrast enhancement. Nowadays, multi-sectional documentation of the early, middle, and late phase of contrast enhancement as well as pharmacokinetic analysis is available for contrast TRUS techniques, making them similar to contrast CT or MRI [15].

Image fusion technology has proved to enhance the image-targeted biopsy and potentially improve intraoperative targeting [13]. Multimodal MRI is emerging as a more reliable modality to detect clinically significant prostate cancer [16]. TRUS/MRI fusion image guidance could potentially increase the spatial accuracy of targeted biopsy or targeted focal intervention. However, this requires multiple steps including image acquisition, segmentation, image fusion, biopsy, and confirmation of biopsy trajectory. There are potential errors in each of these steps. It should be noted that since the MR-fused lesion is only a virtual image, the fundamental question is whether the virtual lesion biopsied was even in fact the real MR lesion. A recent study showed that when an MR lesion is TRUS visible, MR/US-targeted biopsy enhances the detection of clinically significant cancer [16]. This suggests that TRUS is important because the TRUS image is real, not virtual. When using TRUS/MR fusion for real-time guidance, it is important for the operator not to look at the virtual MR image but to look at the real-time TRUS image which is likely to have an ultrasound sign (such as hypoechoic lesion) corresponding with the MR suspicious lesion. The fused MR image should be used as a reference, not the real target. The reality of the target is always shown in the real-time image of TRUS.

Image fusion techniques also open the new opportunity to use augmented reality navigation for surgical guidance [17]. The surgical planning generally starts with the surgeon's consideration of the preoperative image together with the pathology of the biopsy. For intraoperative guidance, a 3D surgical model can be developed from the preoperative image as well as intraoperatively acquired images. In the operating room, this information is registered and overlaid onto the real-time endoscopic surgical view, to display the superimposed images of the 3D model on the display of the surgical view, using an intraoperative position sensor system which typically consists of ultrasound, CT, MRI, and 3D localization (laser, magnetic, or optical) system [17]. If necessary when the target organ moves or deforms, the surgical plan can be updated using the intraoperative real-time image.

Robotic control of the TRUS probe enhances the digitalized documentation of the trajectory of the positive biopsy, to achieve precise revisiting therapeutic delivery toward the biopsy-proven cancer [18]. Once the spatial location of the biopsy-proven cancer has been determined as a digitalized product of coordinates from (x1, y1, z1) to (x2, y2, z2), targets and needle paths are defined based on both real-time image and coordinates according to planning algorithms, and the robot can align the angle and depth and can direct the needle toward the specific point. The determination of the specific point with coordinates of (x1, y1, z1) in the 3D space needs to be determined using at least two crossing planes of real-time TRUS images. Therefore, a simultaneous biplane TRUS probe is also promising. As such, intraoperative guidance using real-time 3D or biplane TRUS probe would enhance the precision of the TRUS intervention.

The shortcoming of conventional grayscale ultrasound imagery for diagnosis of prostate cancer is the interobserver variability or operator dependency. Although a highly experienced expert can detect the majority of clinically significant cancers, a novice using conventional grayscale TRUS may have difficulty in discriminating between benign versus malignant nodules. A computerized analysis of tissue characterization can automate the contouring process of suspicious lesions according to algorithms based on the classification system of the signals. Since the computerized tissue characterization can include the invisible signs such as radiofrequency signals in addition to visible ultrasound signals, it may also be helpful to the expert.

Role of Real-Time TRUS Guidance for Ablative Intervention of the Prostate

TRUS-guided brachytherapy is an established procedure, with further recent advancements from evolved technologies (Table 10.1). In recent years, many advances have been made in

3D-reconstructed TRUS imagery [19]. They include boundary segmentation [20], pubic arch detection [21], needle segmentation, and seed segmentation [22]. These advances in brachytherapy have greatly enhanced the role of TRUS in image-guided surgery. In the same time period, initial robot-assisted TRUS intervention has been developed [23]. Since a robot can achieve precise position, orientation, and manipulation of surgical tools along the various trajectories in the 3D space, the medical robotic system is increasingly gaining interest in image-guided intervention. Such precision of the robotic delivery is supported digitally, dynamically programmed by computer workstation, and effectively integrated with the real-time TRUS navigation system to allow reconstruction of the 3D prostate.

Photodynamic therapy is another promising transperineal surgical approach that could be suitable for TRUS image-guided surgery of organ-confined prostate cancer [24–26]. A recent study in 85 patients using TOOKAD® soluble vascular targeted photodynamic therapy demonstrated it was a well-tolerated and effective therapy and followed by a phase III multicenter study in the form of hemi-ablation [26].

The initial medical use of ultrasonic waves was investigated in the 1950s [27], and the use of HIFU in the treatment of prostate cancer began in the 1990s with a pulsed ultrasound beam to generate heat sufficient to cause necrosis [28]. The ultrasound waves penetrate through the rectal wall with only minimum absorption of energy and reflection of the beam in it, but are centered on the focus point in the prostate. Current commercially available endorectal HIFU machines provide simultaneous TRUS imaging and therapeutics. The step-sectional transverse TRUS images are used to plan a treatment, including identifying the prostate boundary, neurovascular bundle, sphincter, urethra, bladder neck, and rectal wall for maximizing safety and efficacy. HIFU treatment automatically follows the predetermined computerized program which fits the individual anatomy of the prostate. During the procedure, according to potential movement in the bowels or positional change, it may be required to adjust the thickness of the water-filled balloon of the TRUS probe or readjustment of the location of the TRUS probe itself. The HIFU procedures can all be documented with each treated focus registered and overlaid on each step-sectional TRUS image, which can be reviewed for future reference in order to determine the potential requirement of additional therapeutics in addition to the initial plan. Since the prostate swells intraoperatively due to edema or inflammation, the shift of the prostate or targeted lesion needs to be taken into account to enhance efficacy [6]. Again, intraoperative feedback or navigation using real-time TRUS monitoring as well as following a specifically programmed safety system is the key for safety and efficacy.

Real-time biplane TRUS guidance is essential for performing modern cryosurgery for prostate cancer. Accurate TRUS measurement of the dimension of the prostate and identification of the anatomical relation to the adjacent organs are important initial steps for surgical planning of where and how big to create the ice ball. Real-time image guidance using both transverse and sagittal views is needed for precise cryoprobe and thermocouple placement and also essential for monitoring the freezing extension to achieve efficient ablation as well as prevent complications such as rectal injury. For reliable tissue destruction of cancers, freezing temperatures must reach certain critical limits (such as −40 °C or lower), which are monitored in real time by the thermocouples placed in the critical points, such as in the targeted tumor, sphincter, neurovascular bundle, and Denonvilliers space.

With the recent advent of the focal therapy of prostate cancer, TRUS image guidance for localizing biopsy-proven cancer and precise therapeutic targeting have become extremely important in patient care [24, 29]. Since the inadequate limited space between the prostate and the rectal wall involves the risk of rectal injury, the surgeon may hesitate to achieve adequate extension of freezing beyond the posterior margin of the prostate to result in inadequate cancer control if the cancer is located close to the posterior margin of the prostate.

The search to establish a reliable technique to protect the rectal wall from any thermal energy continues in order to establish safety in ablative therapy for prostate cancer in contact with the posterior prostatic surface. Using hydrogel (polyethylene glycol, named a "spacer") was investigated for developing a technique of expansion of the Denonvilliers space during focal cryoablation and also temperature mapping to secure protection of the rectal wall [30–32]. The application seems promising, when delivered precisely in the Denonvilliers space by TRUS guidance.

Role of TRUS in the Era of Endoscopic Surgery and Robotic Surgery

Intraoperative TRUS guidance during open radical prostatectomy (RP) was first reported by Zisman et al. in 1997. Since RP is associated with difficulty in determining the division site of the urethra adjacent to the apical region of the prostate, Zisman et al. demonstrated the utility of intraoperative TRUS guidance that assisted to identify the apex contour and a detailed view of the urethral stump and also to identify the residual apical tissue to perform complete excision of the prostate [33]. During minilaparotomy RP, Okihara et al. reported that application of TRUS resulted in a lower rate of positive margins and a longer postoperative membranous urethral length to be associated with an earlier return to urinary continence [2].

Intraoperative TRUS guidance during laparoscopic RP has been increasingly reported since 2004 [1, 3, 34–37]. The eventual goal of TRUS image guidance is to enhance the oncological and functional outcome of the laparoscopic approach even under limited tactile feedback in comparison to the open approach. TRUS guidance during laparoscopic RP appeared to be helpful for various technical aspects including (a) defining prostate apex contour, (b) identifying the bladder neck which was blind in the surgical view, (c) evaluating location and extent of the hypoechoic biopsy-proven cancer nodule, (d) identifying the neurovascular bundles in relation to the posterior laterally located cancer nodule. When identifying the higher risks of microscopic extra-prostate extension of the cancer, it may offer the surgeon the possibility of performing calibrated wider dissection at the site of the extra-prostate extension of the cancer nodule in order to achieve a negative margin, while maximizing preservation of the neurovascular bundle during lateral pedicle transection. According to the individual contour of the apex in relation to the sphincter, TRUS guidance may offer tailored apical dissection, to maximize the preservation of the membranous urethra and sphincter muscle. Comparing without versus with TRUS guidance, positive surgical margins significantly decreased in patients with pT3 disease (57 % versus 18 %, $p = 0.002$) [1].

Since robotic-assisted laparoscopic RP has a complete loss of tactile feedback, a more image-guided approach would be beneficial [38]. There is increasing interest in applying image guidance including the use of TRUS, the laparoscopic ultrasound probe, and the miniature drop-type ultrasound probe.

In the da Vinci S System (intuitive Surgical, Sunnyvale, CA), tile-pro system enables the display of two extra images referenced simultaneously with the 3D surgical endoscopic view. In 2008 van der Poel et al. reported real-time TRUS image-guided bladder neck dissection for facilitating the learning of robotic-assisted RP during its initial experience, to result in improved oncological outcomes [38]. The basal surgical margins (bladder neck and basal areas of both prostate lobes) were positive for cancer in 9.1 % versus 2.3 % of patients treated without versus with real-time TRUS guidance ($p = 0.001$).

Furthermore, recent researchers have developed various new robotic arms for automated manipulation of the TRUS probe to enable robotic control of TRUS image navigation during robotic-assisted RP [39–41]. The previous approach required an assistant to manipulate or reposition the TRUS probe inserted in the rectum, and also there is only limited space between the patient's legs in the lithotomy position for the assistant to access for manipulating the TRUS probe after the robot has been docked. However, the novel robotic arm for holding the TRUS probe provides a new opportunity to allow self-control image guidance by the console surgeon himself. When applying robotic control of the

TRUS probe, automatic registration of the kinematic frames of the da Vinci surgical system and the robotic TRUS probe manipulator is critical in order to register real-time TRUS images to the da Vinci system. Mohareri et al. recently reported an automatic registration technique based on automatic 3D TRUS localization of the robot instrument tips pressed against the air–tissue boundary anterior to the prostate [42].

Instead of using a TRUS probe, another approach for intraoperative ultrasound monitoring during robotic-assisted RP uses a laparoscopic ultrasound probe [43] or dropped mini US probe [44]. Using a laparoscopic ultrasound probe, elastography guidance may have higher accuracy and specificity in tumor detection, localization, and measuring of diameters and depths of the tumor [43]. A drop-type mini US probe is available for the surgeon to manipulate the US probe directly by a robotic arm [44]. The console surgeon's direct manipulation of the drop-type US probe may facilitate the recognition of the bladder neck as well as localization of the biopsy-proven hypoechoic cancer.

These new approaches for real-time ultrasound guidance could enhance the precision of image-guided robotic-assisted surgery by providing an understanding of the blinded anatomy or pathology beyond the endoscopic surgical view.

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