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Role of transrectal ultrasonography (TRUS) in focal therapy of prostate cancer: report from a Consensus Panel

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• To establish a consensus on the utility of ultrasonography (US) to select patients for focal therapy. Topics were the current status of US to determine focality of prostate cancer, to monitor and assess outcome of focal therapy and the diagnostic advantages of new US methods. In addition, the biopsy techniques required to identify focal lesions were discussed.
• Urological surgeons, radiation oncologists, radiologists, and basic researchers from Europe and North America participated in a consensus meeting on the use of transrectal US (TRUS) in focal therapy of prostate cancer. The consensus process was face-to-face and specific clinical issues were raised and discussed with agreement sought when possible.
• TRUS is commonly used and essential for diagnosing men with prostate cancer. It is particularly useful for targeting specific anatomical regions or visible lesions. However, it has several limitations and there is a need for improvement. Newer visualisation techniques, e.g. colour Doppler US, contrast-enhanced US and elastography, are being developed but currently there is no US technique that can accurately characterise a cancer suitable for focal therapy. Systematic biopsy is the only known procedure that allows the identification of prostate cancers suitable for focal therapy. Scarce data exist about the role of US for monitoring patients during or after ablative therapy.
• Consensus was reached on all key aspects of the meeting.
• US cannot reliably identify focal prostate cancer. New US methods show promising results in identifying prostate cancer focality.
• Currently selecting appropriate candidates for focal therapy should be performed using dedicated protocols and biopsy schemes.

What's known on the subject? and What does the study add?
Focal therapy techniques are emerging in prostate cancer treatment. However, several key questions about patient selection, treatment and monitoring still have to be addressed. The concept of focal therapy is barely discussed in current urological guidelines.

In the present manuscript, we report the results of a consensus meeting focused on ultrasonography, the most common used urological imaging method, in relation to focal therapy of prostate cancer.

KEYWORDS

prostate cancer, focal therapy, consensus, transrectal ultrasonography, contrast-enhanced ultrasonography, prostate biopsies

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TABLE 1 Attributes and affiliations of the contributors

Name	Speciality	Affiliation	Expertise	Country
M. Marberger	Urology		Uro-oncology	Austria
D. Cosgrove	Radiology		GU imaging (US)	UK
T. de Reijke	Urology	EORTC-GU	Uro-oncology	The Netherlands
S. Matin	Urology	SUO	Uro-oncology	USA
J. Barentsz	Radiology		GU imaging (MRI)	The Netherlands
J. Walz	Urology	ESUI	Uro-oncology	France
M. Mischi	Researcher		Imaging (US)	The Netherlands
S. Eggener	Urology		Uro-oncology	USA
P. Pinto	Urology	SUO	Uro-oncology	USA
A. Rastinehad	Urology	SUO	Uro-oncology	USA
H. Wijkstra	Researcher	ESUI	Imaging (US)	The Netherlands
T. Polascik	Urology	ES, SUO	Uro-oncology	USA
F. Frauscher	Radiology	ESUI	GU imaging (US)	Austria
G. Kovacs	Radiotherapy	ESTRO	Brachytherapy	Germany
G. Salomon	Urology	ESUI	Uro-oncology	Germany
O. Rouviere	Radiology		GU imaging (US/MRI)	France
J de la Rosette	Urology	ESUT	Uro-oncology	The Netherlands
M. Smeenge	Urology		Uro-oncology	The Netherlands

GU, gastrourology.

TABLE 2 Items selected for discussion

Item number	Discussion question
1	What is the minimal/optimal US imaging requirement for staging and electing therapy? What are the diagnostic advantages of new US techniques?
2	What is the minimum required/optimal technique to perform biopsies and how should biopsies be performed?
3	What are the minimal/optimal diagnostic requirements for focal therapy and can this be achieved by US guidance alone?
4	Is it possible to monitor therapy by US, and what is the minimal/optimal required technique?

INTRODUCTION

The established treatments for localised prostate cancer include surgical removal of the whole gland using radical prostatectomy, eradication of the tumour with radiotherapy, or ablative methods, e.g. cryotherapy or high intensity-focused ultrasound (HIFU). In recent years, with earlier identification of the disease when tumour volume is low (<1.0 mL), there has been a realisation that treatment could be targeted to specific sites in the prostate gland, i.e. the concept of focal therapy [1]. However, there remain several key issues to be addressed for focal therapy to succeed. Can cancers of clinical significance be reliably identified? Can such lesions be accurately localised? Can these lesions be targeted and ablated with lower morbidity? Finally, can complete ablation be monitored in order to determine treatment success? This concept of focal therapy is barely discussed in current urological guidelines. Therefore the issues of how to identify accurately which areas of the gland are affected by cancer and how to monitor the outcome of focal therapy were issues addressed at a recent consensus meeting of urologists, radiologists, radiation oncologists, and basic researchers. As ultrasonography (US) is one of the main imaging methods in urology, a consensus meeting was held to address the position of US in the diagnosis, treatment and monitoring of focal therapy. This is the second report made by the group on focal therapy, the previous findings being published in 2010 [2].

METHODS

The consensus meeting was held on 25 May, 2011, at the start of the 4th International Workshop on Focal Therapy and Imaging in Prostate and Kidney Cancer (Amsterdam, the Netherlands: http://www.focaltherapy.org). The meeting focused on different US imaging techniques. The group is aware of other imaging methods that can play an important role and these will be the topic of future meetings. There was a multidisciplinary board of international contributors to the meeting, who were selected based on their expertise in the topics to be discussed. There were representations and/or endorsement from the European Society of Therapeutic Radiology and Oncology (ESTRO), The European Organization for Research and Treatment of Cancer-Genito-Urinary Group (EORTC-GU), the European Association of Urology Section of Urotechnology (ESUT), the European Association of Urology Section of Urological Imaging (ESUI), the Society of Urological Oncology (SUO), and the Endourological Society (ES). The attributes and affiliations of the contributors are described in Table 1 and do not specifically represent the formal opinions of the aforementioned organisations. The meeting was chaired by Professor Michael Marberger (Vienna, Austria).

The conduct of the meeting conformed to an informal consensus process, in that no formal scoring system was used to measure the level of agreement that existed before or after the meeting [3]. However, the process did conform to the three generally accepted stages of a consensus process [4]. Items for discussion were preselected and discussed by four individual groups of members before the meeting and allocated a specific time for general discussion during the meeting. During the meeting, a brief presentation was made by one representative of each group. A moderated discussion then took place using the presentation as the basis (Level 1). Any issues were resolved within this section of the meeting (Level 2). A consensus was established by noting any individuals who did not agree to the general view on specific items (Level 3).

Contributors who were not invited to be present at the meeting were aware of the items for discussion in advance of the meeting and therefore also had the opportunity to prepare. Items selected for discussion are shown in Table 2. All contributors to the consensus process have seen and approved the present manuscript

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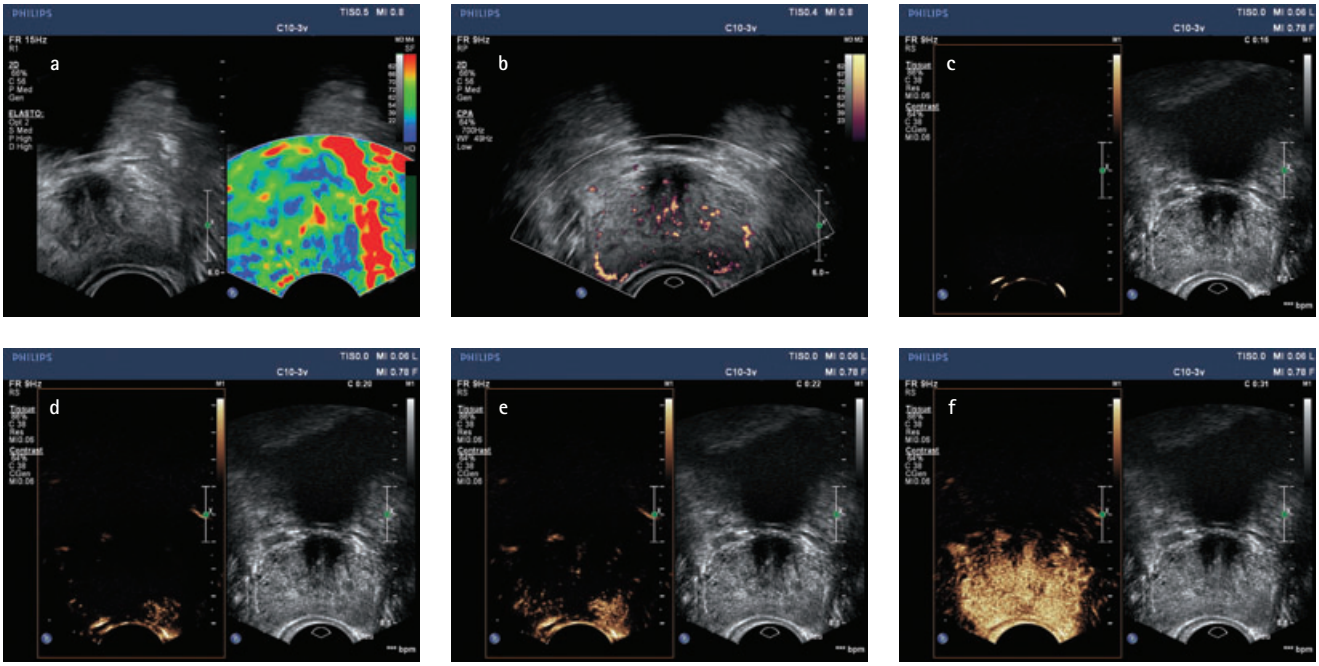
FIG. 1. Different TRUS methods in a patient with confirmed Gleason 3+4 prostate cancer on the left side of the prostate (on the images visible on the right). ***a****, Greyscale on the left side, note there is difficulty to exactly locate the tumour. Elastography on the right side, blue represents hard tissue, green intermediate and red soft.* ***b****, Doppler image shows slight different flow pattern on the left side.* ***c–f****, CEUS image on the left side, greyscale on the right.* ***c****, 16 s after injection, no microbubbles are present yet.* ***d****, 20 s after injection, early enhancement of the tumour on the left side.* ***e****, 22 s after injection, microbubbles arrive in the rest of the prostate.* ***f****, 31 s after injection, complete enhancement of the prostate.*



and, by agreeing to authorship, concur with the essential contents of this article.

RESULTS

WHAT IS THE MINIMAL/OPTIMAL US IMAGING REQUIREMENT FOR STAGING AND ELECTING THERAPY? WHAT ARE THE DIAGNOSTIC ADVANTAGES OF NEW US TECHNIQUES?

TRUS was introduced in the early 1970s and has become the 'gold standard' imaging platform for the diagnosis of prostate cancer made by needle biopsy [5]. However, conventional B-mode US cannot reliably detect lesions that prove positive on biopsy and is therefore always used in conjunction with biopsy. Prostate cancer can occasionally appear as a hypoechoic lesion on grayscale TRUS, although the absence of such lesions does not exclude it, see Fig. 1a. In addition, biopsy sampling of hypoechoic lesions does not necessarily increase the detection of prostate cancer compared with sampling of isoechoic lesions. A landmark study of 3912 patients conducted between 1993 and 1999 on prostate biopsy outcome showed that cancer was detected in 25.5% and 25.4% with and without hypoechoic lesions, respectively [6]. The per core cancer detection was fairly uniform and averaged between 9.3% and 10.4% for hypoechoic and isoechoic areas, respectively.

Thus, given the poor sensitivity and specificity of TRUS, the consensus meeting considered that conventional US without biopsy was not suitable for diagnosing and staging of prostate cancer. Although it is an inexpensive and simple procedure, it should be used solely for identifying the location of the prostate, directing biopsies and assessing gland volume, as well as anatomical variations (such as a large median lobe). The minimal US imaging requirement is considered to be sagittal and axial imaging of the entire gland, with notations of anatomical variations, hypoechoic lesions, and gland and transition zone volume. The optimal future US imaging requirement was considered to be three-dimensional (3D) or 4D (3D in real time) depending on the new imaging method used.

Colour Doppler US is an imaging technique that measures the Doppler shift resulting from flowing blood. The direction of blood flow in relation to the transducer receiving the signal is assigned a colour. The detection of prostate cancer relies on increased and asymmetric regional blood flow caused by an increase tumour vasculature (Fig. 1b). Results are variable with this technique; however, when it is combined with grayscale US, sensitivity and negative predictive values are improved over grayscale US alone [7]. The use of colour Doppler US-directed biopsies has been studied in men with suspected focal lesions treated with cryotherapy [8].

Another variation of US that has been developed is contrast-enhanced US (CEUS). The contrast agents used are microbubbles encased in a lipid shell and are smaller than red blood cells [9]. These agents allow for the imaging of organ and lesion perfusion using US in real time. The process of CEUS involves i.v. injection of the contrast agent, which perfuses the entire circulation, including the prostate microvasculature thus allowing visualisation using different

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TABLE 3 Detection of prostate cancer using sextant or extended biopsy strategies [25]

	% (range):				
	Accuracy	Sensitivity	Specificity	PPV	NPV
Sextant	45 (42–49)	84.1 (77–90)	37.1 (33–41)	21.9 (18–26)	91.8 (88–95)
Extended	59 (52–67)	88.0 (72–97)	53.9 (45–62)	27.2 (18–37)	95.8 (89–99)
Gain	14	3.9	16.8	5.3	4

PPV, positive predictive value; NPV, negative predictive value.

microbubble-specific imaging techniques [9,10]. CEUS improves the detection of tumours compared with grayscale US-guided biopsies [11] (Fig. 1c–f). Wink *et al.* [12] analysed CEUS in prostate cancer detection and outcome determination after therapy. Results showed that prostate cancer could be identified and localised in up to 78% of cases and that the imaging technique could visualise the effects of HIFU, hormonal therapy and radiotherapy. Available data on CEUS is relatively sparse; therefore, further evaluation is warranted.

Elastography imaging is based on the premise that significant differences exist between the elastic properties (stiffness) of normal and cancerous prostate tissue [13]. Most commonly, transrectal pressure is manually applied to the prostate and the change in reflection of sound waves is monitored by TRUS (Fig. 1a). An alternative system uses acoustic radiation force impulse (ARFI) to set up a shear wave whose speed can be measured and is related to Young's modulus. This method has the advantages of not requiring the operator to apply pressure and of giving numerical values. The elastography image is able to distinguish soft and hard tissue regions, the latter being suggestive of prostate cancer. Sensitivities for the detection of prostate cancer range between 74% and 90% in small studies [14–17]. Other imaging techniques under development in prostate cancer are histoscanning, a novel experimental US-based technology that uses computer-aided analysis to quantify tissue disorganisation induced by malignant processes [18], and sonohistology, which is based on analysis of the spectral content of radiofrequency ultrasonic echo data combined with evaluations of textural, contextual, morphological and clinical features in a multiparameter approach [19].

The consensus reached was that new technologies are developing rapidly but, at present, evidence comes from single centres and larger scale data from multicenter studies are needed. These new techniques should be compared with radical prostatectomy specimens. Preferably comparison should be done with whole mount specimens. New techniques should be quantifiable and this may be more difficult than with well-established methods.

It was considered that at the moment there is no US-based imaging technique available on which to base the decision to conduct focal therapy and that the current imaging techniques cannot replace TRUS-guided biopsy as the basis for making treatment decisions.

WHAT IS THE MINIMUM REQUIRED/OPTIMAL TECHNIQUE TO PERFORM BIOPSIES AND HOW SHOULD THESE BE TAKEN?

There was a consensus that current US-imaging techniques cannot reliably identify small prostate cancer lesions and tissue histology remains the 'gold standard' for a definitive diagnosis. The goal of early detection of prostate cancer and selection of patients for focal therapy should be to identify patients with clinically significant localised prostate cancer. There should be a strict selection of patients with unifocal and unilateral clinically significant disease that is amenable to focal therapy. The overall incidence of unifocal cancer is 20–30% and that of multifocal prostate cancer is 65–85% [20–22], most prostate cancers are bilateral (65%) [23]. At present, candidates for focal therapy should have unifocal or unilateral disease and a key question is how to select such patients. Several biopsy schedules are available, including sextant (6 cores), extended (8–12 cores), saturation (15–45 cores) and multicore (45–120 cores) [24]. There is an increased likelihood of identifying cancers with extended biopsies compared with sextant biopsies, which are no longer considered as an acceptable standard for focal therapy planning (Table 3) [25]. The group thus recommends performing extended biopsies in the initial biopsy setting as a minimum standard.

It was considered that conventional imaging techniques do not have the capability of distinguishing the Gleason score of the different prostate cancer foci. Mapping biopsies using appropriate imaging guidance including 3D-TRUS, contrast-enhanced TRUS, elastography and multiparametric MRI will have the potential to improve tumour characterisation, which is key to the use of focal therapy.

It was concluded that routine office-based prostate biopsy is not accurate in detecting unilateral disease but can be used as an initial 'screening' test to exclude patients with bilateral disease. The initial evaluation with 10–14 biopsy cores aimed at the peripheral zone only is optimal. If the patient has a unilateral tumour on routine diagnostic biopsy then prostate mapping involving systematic template biopsies should be strongly considered. It was emphasised that selecting appropriate candidates for focal therapy should be performed using dedicated protocols and biopsy schemes. The current European Association of Urology guidelines on prostate cancer state that the current standard for characterising men considering focal therapy is transperineal prostate biopsy using a template-guided approach [5]. If a 5 mm-sampling frame is used then prostate cancer foci measuring 0.2–0.5 cm can be identified with a 90% certainty [26].

In the case of an initial negative biopsy, repeat biopsies should include the transition zone, the anterior apex and the anterior lateral horn in the peripheral zone. The optimal number of biopsies is dependent on the size of the prostate with the minimum number being 20. Biopsy data generated should then be interpreted together with clinical indices (e.g. PSA level).

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WHAT ARE THE MINIMAL/OPTIMAL DIAGNOSTIC REQUIREMENTS FOR FOCAL THERAPY AND CAN THIS BE ACHIEVED BY US GUIDANCE ALONE?

Minimal diagnostic requirements for focal therapy should permit the identification of patients with low-risk prostate cancer. This allows zonal or sector ablation of tumour foci. The objective would be to exclude cancer in other areas of the prostate using template saturation biopsy or improved imaging methods, such as multiplanar MRI or US-MRI fusion technology. The consensus was that at present, US alone cannot do this.

Optimal diagnostic requirements theoretically would provide 3D mapping and visualisation together with biological characteristics of all cancer foci in the prostate, regardless of size or grade. 3D-mapping biopsy studies have shown that a significant proportion of men who were initially diagnosed with apparently low-risk disease actually had clinically significant cancers [27]. The consensus was that at the present time US alone cannot do this. It was also noted that high-grade disease can be present in small cancer foci and that there is a reported incidence of 8% extracapsular disease from non-index tumours [28].

A new promising development in CEUS imaging is analysis of haemodynamic parameters. A study comparing Gleason score, the arrival time of the contrast agent, time to peak and peak intensity showed that high-grade tumours had a significantly shorter arrival time of the contrast agent and time to peak intensity than low-grade tumours [29].

A slightly different approach is calculating the diffusion or dispersion of contrast agent in the tissue. A preliminary study in four patients compared with radical prostatectomy specimens showed a strong correlation between the diffusion parameter and the histology [30]. The area under the receiver operating characteristic curve was 0.909, which is better than any other measured perfusion-related parameter as proposed in literature until now.

The final consensus on this topic was that US is currently not helpful for visualising focal lesions but new promising techniques are in development. At the moment US does aid in performing sector biopsies.

IS IT POSSIBLE TO MONITOR THERAPY BY US, AND WHAT IS THE MINIMAL/OPTIMAL REQUIRED TECHNIQUE?

A consensus was reached that TRUS could be used to monitor focal ablation of the prostate. The advantages are that unlike MRI, the results are available in real time, although newer MRI units are under development to provide real-time feedback. Successful monitoring of tissue ablation after HIFU has already been achieved in real time with spectral analysis of backscattered B-mode US [31]. The same technique could be used for any thermal ablation technique.

Several studies have used grayscale TRUS to insert cryoprobes into the prostate via the transperineal route with subsequent monitoring of ice-ball formation [8,32,33]. Monitoring the adequacy of freezing within the ice-ball is hampered as up to 99% of acoustic waves are reflected from the surface of the ice-ball closest to the TRUS probe. However, the leading edge of the ice-ball is clearly visible by TRUS and allows the physician to monitor proximity to critical structures, e.g. rectal wall and the prostatic apex/urinary sphincter. At the moment, TRUS itself gives no indication of the temperatures being reached and thus cannot indicate completely treated target zones. The view of the consensus panel was that TRUS is extremely useful in focal cryoablation for needle placement and visualising the ice-ball. However, it should be noted there is a difference of 8–10 mm between the tumour margin and the edge of the ice-ball, which needs to be considered to avoid damage to surrounding tissue. The fact that the ice-ball itself is also echogenic does not allow visualisation of the whole tumour. It was considered that 3D-imaging US might be helpful in cryoablation.

CEUS has been used to evaluate the size of focal lesions after ablation therapy and was considered a potentially useful imaging method. One study involved radiofrequency ablation (RFA) of canine prostates and showed that the RFA lesions could not be imaged with conventional grayscale or power Doppler US, whereas CEUS imaging revealed a clear lesion at the site of each RFA application [34]. CEUS imaging has also been reported in a case study involving interstitial thermal laser focal therapy and associated with treatment outcome [35]. CEUS can also show the volume of the gland destroyed by HIFU and can be used in the operating theatre [36]. An excellent correlation was shown between post-HIFU CEUS and biopsy findings, where all devascularised areas corresponded to coagulation necrosis and all enhancing areas corresponded to viable tissue.

THE OVERALL CONSENSUS FINDINGS ARE SUMMARISED AS

TRUS is commonly used in prostate cancer and is one of the essential tools in diagnosing prostate cancer in patients. It is particularly needed to define biopsy targets. However, it has several limitations in defining the exact suspected areas and there is a need for improved US techniques.

Newer visualisation techniques are being developed but currently there is no US-imaging technique that can accurately define a prostate cancer suitable for focal therapy.

Multicore systematic biopsy under US guidance is the only procedure at this present time that allows the identification of prostate cancers suitable for focal therapy.

There are some imaging techniques, e.g. CEUS, that can be used with ablative therapies but there is a need for significant improvement.

CONCLUSIONS

Focal therapy in prostate cancer is a new and developing field of research, at the moment existing US methods are not reliably able to predict the target area for therapy. New promising US techniques for localisation and identification of prostate cancer are in development. However, more research and comparative studies are needed before we can use them for focal therapy selection.

Routine office-based prostate biopsy is not accurate in detecting unilateral disease but may be used as the initial test to exclude patients with bilateral disease. Selecting appropriate candidates for focal therapy should be performed using dedicated protocols and biopsy schemes.

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CONFLICT OF INTEREST

David Cosgrove received support from Bracco SpA attending scientific meetings. Jean de la Rosette received support from Galil and Bracco SpA for conducting studies. Scott Eggener received funding from Visualase, Inc. for conducting studies. Ferdinand Frauscher received support from Bracco SpA attending scientific meetings and training.

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Abbreviations: **US**, ultrasound/ultrasonography; **HIFU**, high-intensity focused ultrasound; **ESTRO**, European Society of Therapeutic Radiology and Oncology; **EORTC–GU**, European Organization for Research and Treatment of Cancer-Genito-Urinary Group; **ESUT**, European Association of Urology Section of Urotechnology; **ESUI**, European Association of Urology Section of Urological Imaging; **SUO**, Society of Urological Oncology; **ES**, Endourological Society; **3D**, three-dimensional; **CEUS**, contrast-enhanced US; **RFA**, radiofrequency ablation.

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