Introduction

- HistoScanning™ is a new non-invasive tissue characterisation technology based on ultrasonography. It consists of a computer-aided analysis of native ultrasound radiofrequency volume data to identify patterns in glandular tissue in order to detect differentiated tissue.
- Prostate HistoScanning™ is the commercially available transrectal ultrasound-based product of HistoScanning™, specifically conceived to detect suspicious areas in the prostate. Because of its unique ability to accurately identify, locate and assess the size of differentiated prostate tissue, Prostate HistoScanning™ may guide clinical decisions throughout entire prostate cancer care: detection and diagnosis, treatment planning, treatment guidance and post-treatment monitoring (Figure 1).
- To date over 1,500 patients have been enrolled in clinical studies on Prostate HistoScanning™ and more than 16,000 patients have benefited already from it in clinical practice.
**Determining biopsy need and predicting biopsy outcome**

- Prostate HistoScanning™ is often used in clinical practice to determine the need for prostate biopsy and aid in biopsy planning.
- The ability of Prostate HistoScanning™ to predict biopsy outcome has been evaluated in several clinical studies.1,4
- In 2 single-centre pilot studies, 42–50 men with an elevated prostate-specific antigen (PSA) level and/or suspicious digital rectal examination (DRE) underwent Prostate HistoScanning™ and thereafter had a first or repeat biopsy.1,2
- Men with a positive first or repeat biopsy had a statistically significantly larger median total cancer volume as determined by Prostate HistoScanning™ (Total HistoScanning Volume [THV]) compared to men with a negative biopsy (Figure 2).

- A higher median THV corresponded with a higher percentage of men having a positive biopsy (Figure 3).1,2
- In case of a median THV < 0.20 mL, no positive biopsies were observed.

**Targeting biopsies**

- Prostate HistoScanning™ may not only predict biopsy outcome but also aid in targeting biopsies by indicating suspicious areas in the prostate.7,8
- A study was performed in 80 men who underwent a systematic 14-core transrectal biopsy which was supplemented with a cognitive targeted transperineal biopsy (maximum 9 cores) in suspicious areas based on Prostate HistoScanning™.7
- Prostate cancer was detected in 28 of 80 men (35%).
- A total of 79% of all cancers were detected via the 14-core transrectal biopsy (Figure 4). Despite using a maximum of only 9 cores, the transperineal Prostate HistoScanning™-targeted biopsy detected 82% of all cancers.

- The cognitive targeted biopsy using Prostate HistoScanning™ by the transperineal approach thus resulted in similar prostate cancer detection rates as the 14-core systematic transrectal biopsy while reducing the number of cores needed.7
- By reducing the number of cores needed, Prostate HistoScanning™ may aid in decreasing local tissue trauma and complications, patients’ pain and discomfort and the surgical effort.
Clinical results of Prostate HistoScanning™

To provide direct instead of cognitive guidance in transrectal ultrasound-based biopsy, the Prostate HistoScanning™ TT system has been developed with the ability to aid in biopsy needle orientation and continuously monitor and document the planned prostate biopsy. Prostate HistoScanning™ TT complements Tissue Characterisation with True Targeting functionality.

For the definition and functionality of Prostate HistoScanning™ TT and True Targeting, refer to product documentation MK2U00146D-EN.

Detecting significant cancer

- Prostate HistoScanning™ has also been evaluated for its use to discriminate between clinically insignificant and significant prostate cancer.5-12
- A study in 32 men demonstrated that Prostate HistoScanning™ outcomes were statistically significantly different between pT2 and pT3 and between Gleason sum ≤ 6, 7 and ≥ 7 cancers.9
- Another single-centre study in a smaller population comparing Prostate HistoScanning™ results with radical prostatectomy specimens showed that the likelihood (calculated as relative risk) of Prostate HistoScanning™ to accurately grade tumours as Gleason grade 4/5 vs. 3 was 3.2 (P<0.0001).10
- Furthermore, a study in 85 men undergoing radical prostatectomy demonstrated that the sensitivity of Prostate HistoScanning™ in detecting prostate cancer increases with tumour stage, grade and volume (Table 1).11

<table>
<thead>
<tr>
<th>TABLE 1. Sensitivity of Prostate HistoScanning™ increases with higher pathological stage, grade and volume of prostate cancer.11</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2 (N=44)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Gleason sum 6 (N=9)</td>
</tr>
<tr>
<td>6%</td>
</tr>
<tr>
<td>Gleason sum 7 (N=50)</td>
</tr>
<tr>
<td>55%</td>
</tr>
<tr>
<td>Tumour volume &lt; 1 mL (N=10)</td>
</tr>
<tr>
<td>50%</td>
</tr>
<tr>
<td>Tumour volume 1-5 mL (N=40)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Tumour volume &gt; 5 mL (N=35)</td>
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</table>

- In another study in 25 men (50 prostate lobes) scheduled for nerve-sparing radical prostatectomy, the use of Prostate HistoScanning™ in addition to standard pre-operative clinical assessment and 3 T diffusion-weighted (DW) magnetic resonance imaging (MRI) changed the nerve-sparing approach in 32% of lobes.13 A trend for reduced use of intra-fascial and extra-fascial nerve-sparing, and increased use of side excision was apparent after refined staging with Prostate HistoScanning™. This was reflected in reduced positive margin rates.

- These studies suggest that Prostate HistoScanning™ may refine and optimise pre-operative staging resulting in an oncologically safer nerve-sparing radical prostatectomy and reduced positive margin rates.

Treatment planning

- Knowledge of the location and size of tumours may be useful for treatment planning of a nerve-sparing radical prostatectomy.
- A retrospective study in 80 patients who had undergone Prostate HistoScanning™ and radical prostatectomy assessed whether Prostate HistoScanning™ could predict a negative surgical margin.12
- It was shown that when no Prostate HistoScanning™ volume or a volume < 0.20 mL was found at the left or right side of the prostate, the probability of a negative surgical margin at that side was 91%.
- On multivariate analysis, the presence of a Prostate HistoScanning™ focus volume ≥ 0.20 mL was associated with a 3.7-fold increased risk of a positive surgical margin (P=0.027; Figure 5).

FIGURE 5. The risk of a positive surgical margin increases almost 4-fold in case of a Prostate HistoScanning™-detected focus ≥ 0.20 mL.12
Treatment guidance

- Because of its ability to characterise prostate tissue, Prostate HistoScanning™ may aid in guiding local prostate cancer therapy, such as brachytherapy.
- A prospective, single-centre, phase II study has explored the feasibility of selectively escalating the dose in tumour areas inside the prostate by image-guided interstitial pulse-dosed rate (PDR)/high-dose rate (HDR) brachytherapy, i.e. fine-tuned dose-painting that allows the creation of microboost volumes.\textsuperscript{14} Prostate HistoScanning™ was performed to detect high-risk areas.
- Table 2 presents the interim results of 19 patients.

Post-treatment monitoring

- The ability of Prostate HistoScanning™ to accurately localise cancer foci enables its use for monitoring patients for recurrent disease after prior prostate cancer therapy.\textsuperscript{15,16}
- A study in 90 patients who had been previously treated with high-intensity focused ultrasound (HIFU) for localised prostate cancer used Prostate HistoScanning™ to identify suspicious areas after 1-7 years. All patients underwent biopsy for histological verification.\textsuperscript{15}
- Prostate HistoScanning™ demonstrated a high diagnostic performance in detecting recurrent cancer foci of > 0.20 mL after prior HIFU therapy (Table 3).

Table 2. Feasibility of Prostate HistoScanning™ in determining brachytherapy areas.\textsuperscript{14}

<table>
<thead>
<tr>
<th>Dosimetric quantifier (N=19)</th>
<th>Prostate</th>
<th>Prostate HistoScanning™ defined high-risk areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median V100</td>
<td>99%</td>
<td>124%</td>
</tr>
<tr>
<td>Median D90</td>
<td>112%</td>
<td></td>
</tr>
<tr>
<td>Median V120</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Median V130</td>
<td>85%</td>
<td></td>
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</tbody>
</table>

Dx: dose that covers x% of the prostate volume; Vx: fractional volume of the prostate that received x% of the prescription dose.

- A good tolerability without significant acute side effects (no grade ≥ 3 toxicities) was shown during 3-months follow-up.
- This suggests that Prostate HistoScanning™ cognitive guidance for brachytherapy allows significant dose escalations as microboost to prostate tumour regions while meeting stringent dose constraints for the adjacent organs at risk.

Conclusions

Prostate HistoScanning™ can provide support to clinicians to make informed decisions throughout prostate cancer treatment to provide optimal patient care:
- determining the need for biopsy
- prediction of biopsy outcome and improved targeting of biopsies
- guidance in treatment planning and execution
- aid in monitoring of patients after treatment
The technology

- Prostate HistoScanning™ is a tissue characterisation technology using native radiofrequency data from transrectal ultrasound (TRUS) volume scans of the prostate. The native radiofrequency data are analysed by a set of validated, multiparametric mathematical algorithms to detect specific changes in tissue characteristics. This results in a 3-dimensional prostate image in which suspicious areas in the prostate are labelled in colour, superimposed on top of the simultaneously processed grey-scale TRUS image (Figure 6). A special volumetric tool enables measurement of total prostate volume and volume of suspicious areas.

- Prostate HistoScanning™ can be easily integrated in the existing clinical pathway and has a short acquisition and analysis procedure. Inter-observer agreement for presence or absence of cancer foci ≥ 0.50 mL in prostate sextants has been reported to be high (75%-90%).

Clinical validation

- Several studies have validated the ability of Prostate HistoScanning™ to identify and characterise cancer foci with histology results from radical prostatectomy specimens as reference test.

- The exploratory, open-label, proof-of-concept study PHS-01 demonstrated that the concordance in diameter of index tumour was high between Prostate HistoScanning™ and histology results (r=0.95, P<0.001). Moreover, there was a 100% concordance in attribution of multifocality and laterality. Prostate HistoScanning™ performed well in detecting cancer foci ≥ 0.50 mL on histology (Table 4). There was a strong correlation in lesion volumes (r=0.99, P<0.001) and total cancer volume (r=0.98, P<0.001) between Prostate HistoScanning™ and radical prostatectomy histology.

TABLE 4. Diagnostic performance* of Prostate HistoScanning™ in predicting lesions ≥ 0.50 mL in 13 patients with 28 lesions (12 lesions ≥ 0.50 mL).

<table>
<thead>
<tr>
<th>Volume threshold</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foci ≥ 0.50 mL</td>
<td>100%</td>
<td>81%</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>(12/12)</td>
<td>(13/16)</td>
<td>(12/15)</td>
<td>(13/13)</td>
</tr>
</tbody>
</table>

* Reference test radical prostatectomy

- The multi-centre, European, prospective cohort study PHS-02 in patients with organ-confined prostate cancer scheduled for radical prostatectomy examined the diagnostic accuracy of Prostate HistoScanning™ to locate a cancer focus of at least 0.20 mL or 0.50 mL in a sextant. Prostate HistoScanning™ showed 90% sensitivity and 70%-72% specificity for the correct localisation and identification of lesions ≥ 0.20 mL and ≥ 0.50 mL within a sextant compared with radical prostatectomy histology (Table 5).

TABLE 5. Diagnostic performance* of Prostate HistoScanning™ to correctly identify prostate cancer in 23 patients (138 sextants) with an index foci ≥ 0.50 mL and 27 patients (162 sextants) with an index foci ≥ 0.20 mL.

<table>
<thead>
<tr>
<th>Volume threshold</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foci ≥ 0.50 mL</td>
<td>90%</td>
<td>70%</td>
<td>84%</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>(79/88)</td>
<td>(35/50)</td>
<td>(79/94)</td>
<td>(80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(35/44)</td>
</tr>
<tr>
<td>Foci ≥ 0.20 mL</td>
<td>90%</td>
<td>72%</td>
<td>83%</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td>(87/97)</td>
<td>(47/65)</td>
<td>(87/105)</td>
<td>(47/57)</td>
</tr>
</tbody>
</table>

* Reference test radical prostatectomy

PPV: positive predictive value; NPV: negative predictive value

FIGURE 6.

a. Example slice of a surgical specimen case CLI-001
b. View of grid analysis of the example slice case CLI-001
c. View in Prostate HistoScanning™ of the example slice case CLI-001

Image courtesy of Prof. Dr. František Záťura, Univerzita Palackého v Olomouci (UPOL) - Urologická klinika - Fakultní nemocnice, Czech Republic.