Prostate HistoScanning™ Clinical Studies Summary

Introduction

HistoScanning™ has been the subject of a number of clinical studies. The studies themselves are available in the form of journal publications, poster presentations at scientific congresses, and, where the data has not yet been accepted for publication, from Advanced Medical Diagnostics (AMD). To date more than 600 patients have been enrolled in clinical studies on Prostate HistoScanning™.

This document summarises the main findings from these independent and AMD sponsored studies[i] but is not intended to replace the original publications which have the full details of the methodology and the results; and can be accessed at http://www.histoscanning.com/physician-support/publications.

Radical prostatectomy (RP) studies

Six studies[ii,iii,iv,v,vi,vii,viii] including a total of 259 patients have compared Prostate HistoScanning™ results and histopathological analysis of prostate glands removed during radical prostatectomy. Table 1 below gives the range for the reported sensitivity; that is the ability of Prostate HistoScanning™ to predict the presence of cancer foci ≥0.20 cc or ≥0.50 cc.

Table 1: Ability of Prostate HistoScanning™ to detect a prostate cancer.

Volume threshold → / Performance indicator ↓	Prostate HistoScanning™	
	≥0.20cc	≥0.50cc
Sensitivity to detect an index lesion	90 to 99%	90 to 99%
Sensitivity to locate an index lesion in left/right part of the gland	90 to 96%	90 to 96%

The PHS-02 study[iv] has specifically examined the ability of Prostate HistoScanning™ to locate a cancerous focus of at least 0.20 cc in a sextant, i.e. in the upper part of the gland, right or left, in the middle part, right or left and in the base, right or left. The histology was carried out by Bostwick Laboratories in London (GB), a centre highly experienced in the processing and analysis of whole mounted prostate glands. Table 2 shows the main results from this study and compares them with DCE-MRI[ix].

Comparison of the results of Prostate HistoScanning™ and of DCE-MRI in Table 2 shows a greater sensitivity for Prostate HistoScanning™.

Table 2: Performance[x] of Prostate HistoScanning™ for the location of cancerous lesions ≥0.2 cc or ≥0.5 cc in sextants of the prostate gland compared with DCE-MRI.

Volume threshold on the image for deciding that a lesion is present in a sextant → / Performance indicator ↓	Prostate HistoScanning™ [iv]		Prostate DCE-MRI [ix]	
	≥0.20cc	≥0.50cc	≥0.20cc	≥0.50cc
Sensitivity	90%	90%	77%	90%
Specificity	72%	70%	91%	88%
Positive predictive value (PPV)	83%	84%	86%	77%
Negative predictive value (NPV)	82%	80%	85%	95%

Comparison with DCE-MRI

The performance of Prostate HistoScanning™ in the PHS-02 study[iv] can be compared to the performance of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) as reported by studies that used a similar research method[ix,xi,xii]. Comparison of the results of Prostate HistoScanning™ and of DCE-MRI in Table 2 shows a greater sensitivity for Prostate HistoScanning™.

One study in the USA[v] on patients with biochemical recurrence after radical prostatectomy showed that the HistoScanning™ image processing correlated highly with DCE-MRI abnormalities and locally recurrent cancer detected by TRUS-guided biopsies.

Some studies suggest that the specificity would be higher for DCE-MRI[ix]. However, studies comparing Prostate HistoScanning™ analysis or MRI analysis with results of radical prostatectomy histology include few men with "truly negative" prostate areas at histology. Therefore, these studies are not ideal for estimating specificity. Most studies on MRI do not report volumes of cancerous lesions (see for example [xi] and [xii]), and thus, an advantage of Prostate HistoScanning™ compared to MRI is to provide information on the likely size of suspicious lesions in the prostate.

Negative predictive value (NPV)

The negative predictive value (NPV) for Prostate HistoScanning™ foci ≥0.20cc and ≥0.50cc was found to be 91% and 85% respectively as measured in a radical prostatectomy study[iv].

Biopsy studies

An analysis of data collected in two biopsy series[xiii,xiv] comprising a total of 92 patients has looked at the performance of Prostate HistoScanning™ in patients undergoing random biopsy. These patients all had a raised serum PSA-level. Some of the patients had had a previous negative biopsy. The results are summarised in Table 3 below. As the biopsies are taken randomly there is no actual reference as to whether cancer is present in the prostate or not.

Table 3: Summary of two biopsy studies[xiii, xiv]

		At least one biopsy core positive for cancer			
		Number of patients		% of patients	
Number of patients	Volume of suspicious lesion at Prostate HistoScanning™ ↓	No ↓	Yes ↓	No ↓	Yes ↓
31	<0.20 cc	31	0	100%	0%
21	0.20 to 0.49 cc	10	11	48%	52%
40	≥0.50 cc	10	30	25%	75%

The results in Table 3 show that if the suspicious lesions have a volume less than 0.20cc, no biopsy was positive. When volumes of suspicious lesions increase, more men will have a positive biopsy session. Twenty men had a negative biopsy session when Prostate HistoScanning™ suggests the presence of suspicious lesions ≥0.20cc. These data could mean false positive results from HistoScanning™, but also a false negative biopsy result.

Prostate HistoScanning™ has also been used to stratify men into two groups those at risk of significant disease and those with low risk disease. In a study of 94 men every cancer value of one millilitre estimated by Prostate HistoScanning™ was associated with a nearly three fold increase in the probability of having a positive biopsy[xv].

A further study of 43 patients has looked at the performance of Prostate HistoScanning™ guided transperineal biopsy compared to transrectal schematic 14 core biopsy and found a higher detection of cancer with a smaller number of cores using the HistoScanning™ guided approach[xvi].

The role of HistoScanning™ in treatment planning

In 80 patients undergoing radical prostatectomy the results of Prostate HistoScanning™ were compared to frozen sections to predict the ability to undertake a nerve sparing procedure and maintain a cancer-free margin[xvii]. When the volume of a suspicious lesion measured by HistoScanning™ on one side of the gland was less than 0.20cc, there was a 91% likelihood that a nerve sparing procedure could be performed on that side.

A second study[xviii] of 25 patients (50 lobes) compared the use of Prostate HistoScanning™ with standard pre-operative assessment and 3T DW-MRI. The information provided by Prostate HistoScanning™ reduced the positive margin rate. For pT2 (n=15) and pT3 (n=10) tumours positive resection margin rate was 6.6% and 30%, respectively for the Prostate HistoScanning™ cohort in contrast to 23% and 56%, respectively for a matched historical cohort.

Active surveillance studies

A study in 53 men of whom 35 have completed a year on the active surveillance programme show a good correlation between the increase over time in the Prostate HistoScanning™ volume, increase in PSA and the numbers of positive biopsy cores at TRUS biopsy[xv].

Inter observer agreement studies

Two independent observers processed and analysed scans from 53 patients in an active surveillance study. The concordance in Prostate HistoScanning™ between the two observers for prostate volume, predicted cancer volume and predicted cancer location was very high. Observers agreed on the presence or absence of a cancer focus in 87% of sextants[xix].

HistoScanning™ signal and cancer aggressiveness

One study[xx] has specifically examined the relationship between Prostate HistoScanning™ results and Gleason score determined by histology of the prostate gland. It was found that Prostate HistoScanning™ had the potential to distinguish lesions of Gleason score 6 and of Gleason score 7 or more. These results need confirmation in larger studies.

---

[i] The PHS-02 study is sponsored by AMD.

[ii] BRAECKMAN (J.G.), AUTIER (P.), GARBAR (C.), PIPELEERS-MARICHAL (M.), SOVIANY (C.), NIR (R.), NIR (D.), MICHIELSEN (D.), BLEIBERG (H.), EGEVAD (L.), EMBERTON (M.). 2007. Computer-aided ultrasonography (HistoScanning): a novel technology for locating and characterising prostate cancer. Published in British Journal of Urology International (BJUI). Vol. 101, Issue 3 (July), PP. 293-298, doi:10.1111/j.1464-410X.2007.07232.x.

[iii] BRAECKMAN (J.G.), AUTIER (P.), SOVIANY (C.), NIR (R.), NIR (D.), MICHIELSEN (D.), TRUERNICHT (K.), JARMULOWICZ (M.), BLEIBERG (H.), GOVINDARAJU (S.), EMBERTON (M.). 2008. The accuracy of transrectal ultrasonography supplemented with computer-aided ultrasonometry for detecting small prostate cancers. Published in British Journal of Urology International (BJUI). Vol. 102, Issue 11 (May), PP.1560-1565, doi:10.1111/j.1464-410X.2008.07878.x.

[iv] SIMMONS (L.A.M.), AUTIER (P.), ZÁT'URA (F.), BRAECKMAN (J.G.), PELTIER (A.), ROMÍCS (I.), STENZL (A.), TREURNICHT (K.), WALKER (T.), NIR (D.), MOORE (C.), EMBERTON (M.). 2011. Detection, localisation and characterisation of prostate cancer by Prostate HistoScanning™**.** e-Published 17/11/2011 in British Journal of Urology International (BJUI).

[v] SHIMKO (M.S.), KNOEDLER (J.J.), UMBREIT (E.C.), MYNDERSE (L.A.). 2010. Correlation of 3-dimensional ultrasound computer-aided interpretation with dynamic contrast enhanced pelvic MRI in the detection of post radical prostatectomy local recurrence of prostate cancer. Published and presented at the annual meeting of the American Urological Association (AUA). P.1002782, 29-03/05/2010, San Francisco (CA, USA).

[vi] EPPLEN (R.), van ESSEN (J.), van ERPS (T.), THÜER (D.), KNÜCHEL-CLARKE (R.), HEIDENREICH (A.). 2011. Detection of prostate cancer by HistoScanning. Published and presented at the annual meeting of the Société Internationale d'Urologie (SIU). Session "Podium Session 2: Prostate cancer, detection and screening", P.1432.00, POD-02.01, 17/10/2011, Berlin (D).

[vii] LABANARIS (A.P.), ECK (A.), ADDALI (M.), AFRAM (S.), WITT (J.), ZUGOR (V.). 2011. The value of computer-aided ultrasonography in the detection and evaluation of prostate cancer. Published and presented at the annual meeting of the Société Internationale d'Urologie (SIU). Session: "Moderated poster session 3: Prostate cancer, detection and staging", MP-03.12, 17/10/2011, Berlin (D).

[viii] SIMMONS (L.A.M.), LEMINSKI (A.), RASHID (T.), HAZELL (S.), MONZON (L.), WINKLER (M.). 2011. Blinded assessment of Prostate HistoScanning™ accuracy compared to elective radical prostatectomy step sectioned histopathology. Published at the International Symposium on Focal Therapy and Imaging in Prostate & Kidney Cancer (FTI-PKc). Poster #28, 25-27/05/2011, Noordwijk-aan-Zee (NL).

[ix] VILLERS (A.), PUECH (P.), MOUTON (D.), LEROY (X.), BALLEREAU (C.), LEMAÎTRE (L.). 2006. Dynamic contrast-enhanced, pelvic phased array magnetic resonance imaging of localized prostate cancer for predicting tumor volume: Correlation with radical prostatectomy findings. Published in the Journal of Urology (JUROL). Vol. 176, Issue 6 Pt1 (December), PP.2432-2437.

[x] Definitions of clinical performance indicators; applicable to the entire prostate gland or to parts of the gland according to the research question.

- Sensitivity: Test's ability to detect a cancer in a prostate gland (or in a part of the prostate gland) in which a cancer is truly present;
- Specificity: Test's ability to conclude that there is no cancer in a prostate gland (or in a part of the prostate gland) truly free of cancer;
- Positive predictive value (PPV): proportion of prostate glands (or in a part of prostate glands) with cancer among all prostate glands for which the test is positive;
- Negative predictive value (NPV): proportion of prostate glands (or in a part of prostate glands) without cancer for which the test is negative.

[xi] CHABANOVA (E.), BALSLEV (I.), LOGAGER (V.), HANSEN (A.), JAKOBSEN (H.), KROMANN-ANDERSEN (B.), NØRGAARD (N.), HORN (T.), THOMSEN (H.S.). 2010. Prostate cancer: 1.5T endo-coil dynamic contrast-enhanced MRI and MR spectroscopy-correlation with prostate biopsy and prostatectomy histopathological data. Published in European Journal of Radiology. Vol. 80, Issue 2 (November), PP. 292-296. doi:10.1016/j.ejrad.2010.07.004.

[xii] DELONGCHAMPS (N.B.), ROUANNE (M.), FLAM (T.), BEUVON (F.), LIBERATORE (M.), ZERIB (M.), CORNUD (F.). 2011. Multiparametric magnetic resonance imaging for the detection and localization of prostate cancer: combination of T2-weighted, dynamic contrast-enhanced and diffusion weighted imaging. Published in British Journal of Urology International (BJUI). Vol. 107, Issue 9 (May), PP. 1411-1418, doi:10.1111/j.1464-410X.2010.09808.x.

[xiii] NØRGAARD (N.), AUTIER (P.). 2010. Can HistoScanning™ help in the assessment of patients with raised serum PSA level: a pilot study. Published and presented at the annual meeting of the European Association of Urology (EAU). P.147, 16-20/04/2010, Barcelona (E).

[xiv] ZÁT'URA (F.), KLÉZL (P.), BÁRTA (J.), AUTIER (P.). 2010. Prostate HistoScanning™ examination in patients with past negative biopsy sessions: a pilot study. Published and presented at the annual meeting of the British Association of Urological Surgeons (BAUS). P.007, 21-24/06/2010, Manchester (GB).

[xv] de CONINCK (V.). 2011. The value of Prostate HistoScanning in men at risk of prostate cancer. Published thesis at the Dept. of Medicine and Pharmacy to the Vrije Universiteit Brussel (VUB), Jette (B). Promotor Dr. J.G. Braeckman. 24/06/2011, Jette (B). PP.1-48.

de CONINCK (V.), BRAECKMAN (J.G.). 2012. The value of Prostate HistoScanning™. Presented as candidature at the bi-annual joint ELAUT-prijs/prix-ELAUT meeting of the Belgische Vereniging voor Urologie (BVU) and Société Belge d'Urologie (SBU). 21/01/2012, Neerpelt (B).

[xvi] HAMANN (C.), SCHENK (E.J.), HAMANN (M.F.), NAUMANN (C.M.), JÜNEMANN (K.-P.). HistoScanning-guided prostate biopsy in comparison to a systemic 14-fold transrectal prostate biopsy. Published at the annual meeting of the Société internationale d'urologie (SIU). Session "Unmoderated poster session 2: BPO/LUTS, Minimally invasive surgery, Prostate cancer", P.2357.00, UP-02.116, 18/10/2011, Berlin (D).

[xvii] SPETHMANN (J.), LINSE (C.), HÄSE (A.), STEUBER (T.), SCHLOMM (T.), HEINZER (H.), GRÄFEN (M.), SALOMON (G.). 2010. Accuracy of computer-aided transrectal ultrasonography detection (HistoScanning™) of prostate cancer in the prediction of a negative margin in radical prostatectomy patients. Published and presented at the annual meeting of the European Association of Urology (EAU). P.103, 16-20/04/2010, Barcelona (E).

[xviii] LEMINSKI (A.), SIMMONS (L.A.M.), RASHID (T.), HAZELL (S.), MONZON (L.), WINKLER (M.). 2011. Pre-operative staging of prostate cancer with HistoScanning™ facilitates nerve sparing prostatectomy and may increase complete excision of prostate cancers. Published at the International Symposium on Focal Therapy and Imaging in Prostate & Kidney Cancer (FTI-PKc). Poster #29, 25-27/05/2011, Noordwijk-aan-Zee (NL).

[xix] van den HEUVEL (S.), SIMMONS (L.A.M.), AUTIER (P.), VERHAGEN (P.), MOORE (C.), EMBERTON (M.), BANGMA (C.). 2011. Inter-observer variability in the interpretation of HistoScanning™ characterisation of prostate cancer. Published and presented at the annual meeting of the Société Internationale d'Urologie (SIU). Session "Podium Session 7: Prostate Cancer, Localized", P.1260.00, POD-07.07, Berlin (D).

[xx] SIMMONS (L.A.M.), AUTIER (P.), MOORE (C.M.), EMBERTON (M.). 2011. Ultrasound spectral interrogation of histological grade in prostate cancer using Prostate HistoScanning™. Published and presented at the annual meeting of the Association of Urology (EAU). Poster Session #80 "Prostate cancer: Prognostics and treatment", P.967, 21/03/2011, Wien (A).