# Instrument towards Faster Diagnosis and Treatment of Prostate Cancer – Resonance Sensor Stiffness Measurements on Human Prostate Tissue *in vitro*

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*Abstract*— **Prostate cancer is the most common cancer among men and the methods used to detect and diagnose prostate cancer are not sufficiently accurate. Radical prostatectomy is a surgical treatment of prostate cancer where the whole prostate is removed from the patient. Prostate tissue stiffness can be measured with a stiffness sensitive resonance sensor. The aim of this study was to measure the stiffness on the anterior and posterior side of fresh human prostate tissue in vitro and compare these two groups with each other and relate the findings with the prostate tissue histology. In a prostate tissue slice with mostly normal healthy tissue, the anterior side was significantly harder (*p*-value < 0.05) as expected. In a prostate tissue slice with areas of cancer tumors, no difference was found between the anterior and posterior sides. However, large stiffness variations were found within groups with measurements points on cancer tissue (coefficient of variation, CV = 42 and 85%), as opposed to groups without cancer tissue (CV = 27 and 28%). The large stiffness variations could be used as a sign for the presence of cancer. The results are promising for the development of an instrument and method for faster diagnosis on radical prostatectomy samples.**

*Keywords*— **Prostate, cancer, diagnosis, resonance sensor.**

## I. Introduction

Prostate cancer is the most common type of cancer among men in Europe [1] and the United States [2]. Methods used today for detecting prostate cancer include the blood test for prostate specific antigen (PSA) and digital rectal examination (DRE), where harder lumpy areas can be sensed by palpation. If the presence of cancer is indicated, a follow-up ultrasound guided biopsy is taken to diagnose the tissue. However, as PSA and DRE are not cancer specific and traditional ultrasound is not sensitive enough to detect cancer, biopsies are taken at random and a cancer tumor might easily be missed as the biopsy volume is 1/1000 of the prostate volume. The needle biopsies are examined by optical microscopy and the cancer tissue is graded and scored.

Radical prostatectomy, where the whole prostate is removed, is a surgical treatment of prostate cancer in the gland. From this surgery, microscopic examinations of the resected prostate specimen are done to localize the presence of cancer and determine if it has spread through the prostate capsule.

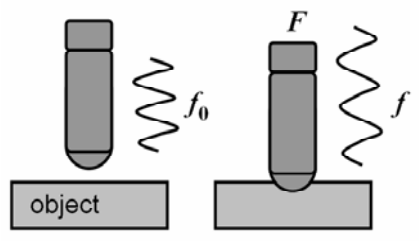


Fig. 1 The resonance sensor principle. At the non-contact state the resonance frequency is $f_0$, while at contact with an object the frequency changes to $f$ and thus a frequency change is observed $\Delta f = f_0 - f$. A force $F$ is measured with a force sensor.

Resonance sensor [3] technology is based on a piezoelectric transducer operating in resonance state through a feedback circuit. Upon contact with an object, the resonance frequency of the sensor changes due to the applied load (Figure 1). This frequency change is related to the mechanical properties of the object.

A resonance based sensor system can measure the stiffness variations in fresh prostate tissue slices from radical prostatectomy [4] and the measured stiffness is related to tissue histology [5]. Thus, objectively measured prostate tissue stiffness can be a clinical marker for prostate cancer.

One goal is to develop an instrument based on the resonance sensor technology that can be used in conjunction with the radical prostatectomy surgery in order to determine if the cancer has spread through the prostate capsule. Stiffness measurements could be done on the periphery of the prostate gland. This way, areas suspicious of cancer could be localized and the microscopic examinations could be done on the suspicious areas. In addition it would be possible to avoid re-surgery if it is found that more cancer tissue has to be removed. This would enable a faster diagnosis and treatment of prostate cancer and save patient bedtime and hospital resources.

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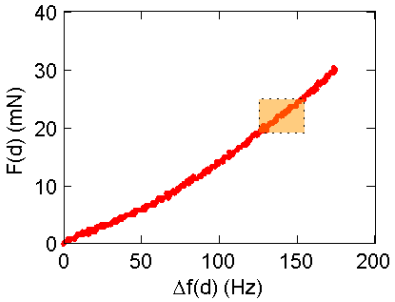


Fig. 2 Illustration of the measured $F$ and $\Delta f$ and the interval (the color shaded rectangle) used for calculating the derivatives of the stiffness parameter. The shaded rectangle shows $F$ and $\Delta f$ in the impression depth interval of 1.0 ± 0.1 mm. Note that both $F$ and $\Delta f$ depend on the impression depth $d$.

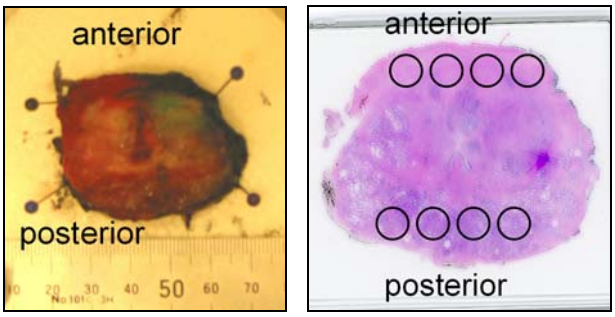


Fig. 3 (LEFT) Radical prostatectomy sample slice of 1 cm thickness seen from above the measured surface. Scale is in millimeters. (RIGHT) The topmost 5 µm prostate tissue section with haematoxylin and eosin staining shown with approximate locations of measurement points (circles). Orientation of the prostate is shown with anterior and posterior markings.

The aim of this study was to measure the stiffness of peripheral tissue on the posterior and anterior side of prostate tissue slices from radical prostatectomy surgery. Especially, it is of interest to compare the stiffness of the posterior and anterior side and to relate the stiffness to the tissue histological composition. Measurement of prostate tissue stiffness in an objective manner could enable a faster diagnosis and treatment of prostate cancer.

## II. Material and Methods

### A. Resonance sensor instrumentation

A piezoelectric rod element composed of a transducer and a pick-up part, driven by a feedback circuit, is the basis for the resonance sensor [3]. This set-up enables the sensor-circuit system to oscillate at the resonance frequency. When the sensor contacts an object (Figure 1), the resonance condition is changed and a frequency change $\Delta f$, is obtained [3]. This frequency change is related to the mechanical properties of the object.

A resonance sensor system, Venustron® (Axiom Co., Ltd., Koriyama Fukushima, Japan) was used in the measurements as described earlier [4, 5]. It is composed of a resonance sensor, a force sensor and a position sensor; all arranged in a motorized mounting and attached to a stable stand, thus enabling the simultaneous measurement of $\Delta f$, force ($F$), and impression depth ($d$) during the impression into the object. From the point of contact $\Delta f$, $F$, and $d$, are sampled with 200 Hz down to an impression depth of 2 mm with an impression speed of 1 mm $s^{-1}$. The hemispherical sensor tip radius was 2.5 mm.

Recently [6], a model relating $\Delta f$ and $F$ to the mechanical properties of the measured object, was shown as

$$\Delta f \propto \rho E^{-1} F \tag{1}$$

Here $\rho$ is the density and $E$ is the elastic modulus of the measured object. The validity of equation (1) was shown to hold mostly for small impression depths. For soft human tissue, mostly composed of water, the density variations are small and statistically non-significant in the resonance sensor measurements [6]. On the contrary, the elastic-related variations are statistically significant measureable. Thus, an elastic stiffness sensitive parameter is

$$\frac{\partial F}{\partial \Delta f} \propto \frac{E}{\rho} \tag{2}$$

The stiffness sensitive parameter of equation (2) was calculated from the derivatives of $F$ and $\Delta f$ with respect to $d$ [4, 5]. Both derivatives were estimated with linear regression in an interval of ± 0.1 mm around a specific $d$. Figure 2 illustrates an example measurement with the interval of $F$ and $\Delta f$ used for obtaining the stiffness parameter at $d$ = 1.0 mm.

### B. Measurement procedure on prostate tissue specimens

Resonance sensor measurements were performed at room temperature on two 1 cm thick fresh prostate tissue slices from radical prostatectomy of two patients (age 56 and 67). Each tissue slice was pinned down onto a Styrofoam plate (Figure 3) and kept moist with regular application of physiological saline solution with a brush [4, 5]. Measurements were done across the tissue surface on the anterior and posterior sides (Figure 3). The location of each measurement was registered with coordinates relative to the sensor tip by using a precision positioning stage (Parker Hannifin Co., Daedal Division, Irwin, PA, USA).

After the measurements, the prostate tissue slice was fixed in formalin and embedded in paraffin.

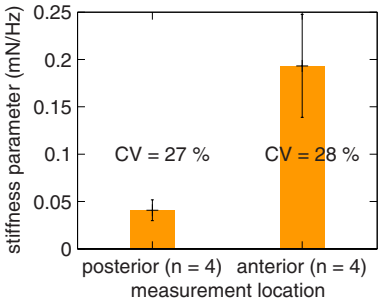


Fig. 4 Mean ± SD and CV of the stiffness parameter of the stiffness measurements on the anterior and posterior side of the prostate tissue slice labeled as PID1. The stiffness parameter was obtained at an impression depth of $d$ = 1.0 mm. The number of measurements ($n$) in each group is given in the parenthesis. A statistically significant difference was found between the groups, $p$-value < 0.05.

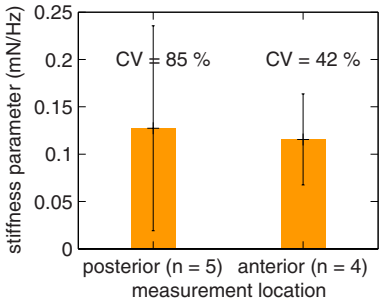


Fig. 5 Mean ± SD and CV of the stiffness parameter of the stiffness measurements on the anterior and posterior side of the prostate tissue slice labeled as PID2. The stiffness parameter was obtained at an impression depth of $d$ = 1.0 mm. The number of measurements ($n$) in each group is given in the parenthesis. No statistically significant difference was found between the groups, $p$-value > 0.05.

The participating patients gave an informed written consent and the study was approved by the Ethics Committee of Umeå University.

### C. *Histological data acquisition*

From the paraffin-embedded tissue samples a detailed histological analysis was done [5]. Four 5 µm thin slices were cut at intervals of 1 mm from the surface and prepared with haematoxylin and eosin staining onto glass slides according to routine histopathological procedure.

By the use of marked reference points and their coordinates, it was possible to extract the location of the measurements on a photograph with the correct scale and to transfer these onto the glass slides (Figure 3). In a circular area with a diameter of 5 mm, the tissue content was determined by the use of an optical microscope equipped with a digital camera [5]. Digital photos were taken and by the use of a grid, the tissue types were determined at the grid points. At each measurement point the proportion of glandular tissue, prostatic stroma, prostate stones (corpora amylacea), and cancer was calculated [5]. An average tissue proportion was calculated for the four sections from the four depths in the tissue.

### D. *Stiffness parameter analysis and statistics*

The stiffness parameter of equation (2) was presented with the mean and the standard deviation (SD), and with the coefficient of variation (CV (%) or SD relative to the mean). CV was used as a parameter to describe the variation within the anterior and posterior groups.

A Wilcoxon rank-sum test was made to compare stiffness measurements on the posterior and anterior side. A $p$-value < 0.05 was considered statistically significant.

Table 1 The range of tissue type proportions of the measurement points on the two prostate tissue slices PID1 and PID2. Mean values are shown in the parenthesis.

| Prostate slice | Tissue type | Posterior side (%) | Anterior side (%) |
|---|---|---|---|
| PID1 | Gland | 30 – 49 (41) | 0 – 1.4 (0.5) |
| | Stone | 0.1 – 0.3 (0.2) | 0 – 0.03 (0.01) |
| | Stroma | 51 – 70 (59) | 99 – 100 (99.5) |
| | Cancer | 0 – 0.03 (0.01) | 0 (0) |
| PID2 | Gland | 19 – 50 (37) | 8 – 40 (26) |
| | Stone | 0.09 – 0.7 (0.4) | 0.03 – 0.2 (0.1) |
| | Stroma | 41 – 62 (50) | 22 – 70 (53) |
| | Cancer | 0.1 – 34 (12) | 3 – 70 (21) |

## III. RESULTS

Results from the resonance sensor measurements on the two prostate specimens (PID1 and PID2) are shown in Figure 4 and Figure 5 respectively. Table 1 shows the histological composition of the measurement points on the anterior and posterior side for both PID1 and PID2.

On PID1, one anterior and one posterior point were subjected to repeated measurements totaling $n$ = 6 measurements on each point. Both of these measurement points had a CV = 10%. For PID2, two anterior and one posterior measurement point were subjected for repeated measurements with total $n$ = 6 for each point. The CV was 12% and 16% for the anterior points and 9 % for the posterior point.

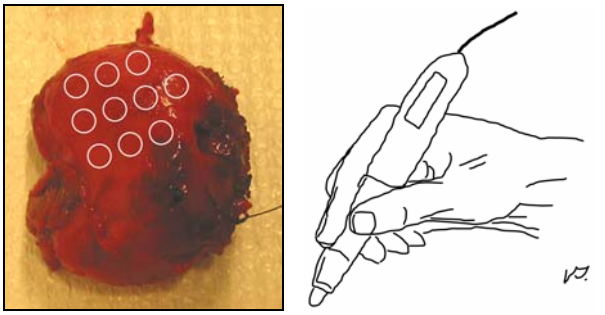

Fig. 6 (LEFT) A whole prostate specimen from radical prostatectomy, shown with possible locations of measurement points (circles). Note that the whole prostate surface becomes measureable, thus allowing a large area of tissue surface to be covered with many measurement points. (RIGHT) An illustration of a future pen-like resonance sensor based clinical instrument for faster diagnosis of prostate cancer.

## IV. Discussion

In this study we have shown that in a fresh prostate tissue slice composed mostly of healthy normal tissue (PID1) (Table 1), the posterior side, is of lower stiffness (i.e. softer) compared to the anterior side (Figure 4). This could be expected since the posterior side has a significantly high content of glandular tissue, while the anterior side is predominantly composed of prostatic stroma (Table 1). This coincides with the results of an earlier study [5], where the stiffness variations of prostate tissue were related to the histological composition. However, in that study no analysis was done concerning directed measurements on the posterior and anterior side exclusively.

In the other prostate tissue slice (PID2), which contained large areas of cancer tumors (Table 1), no significant difference was found between the anterior and posterior sides. Glandular tissue and tumors were found in the anterior side, but this was because the measurements were closer to the central part and thus these measurements would not be representative for the anterior side. The regions consisting predominantly of stroma were not accessible due to practical reasons.

The CV indicates if large stiffness variations relative to the mean are found. According to Figures 4 and 5, and Table 1 this would indicate on the presence of cancer, especially among normal healthy glandular tissue. The CV of the repeated measurements being smaller than the CV of the anterior or posterior group was expected.

The long-term aim is to develop a method that involves the measurement of stiffness of a whole prostate specimen surface in conjunction with a radical prostatectomy surgery to detect and diagnose prostate cancer (Figure 6). With this method the tissue surface, especially the posterior and anterior parts could be compared with each other. This comparison would aim to see if the anterior side is normally stiffer than the posterior side. It is especially interesting to know if stiff areas in the posterior side can be related to cancer and if large stiffness variations in the posterior side are the sign for the presence of cancer tumors. These surface stiffness measurements could locate suspiciously stiff areas on the surface and thereby guide more detailed microscopic examinations towards these areas. The presence of cancer on the surface would indicate that more tissue needs to be removed.

## V. Conclusions

The results of this study on slices of human prostate tissue in vitro are promising for the development of an instrument and method for surface stiffness measurements of a whole prostate specimen for a faster diagnosis and treatment of prostate cancer.

## Acknowledgment

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