Haptic assessment of tissue stiffness in locating and identifying gynaecological cancer in human tissue

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Haptic assessment of tissue stiffness in locating and identifying gynaecological cancer in human tissue

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This thesis is dedicated to my beloved parents,

my caring wife, my lovely son and Guruji

Abstract

Gynaecological surgeons are not able to gather adequate tissue feedback during minimal access surgery for cancer treatment. This can result in failure to locate tumour boundaries and to ensure these are completely resected within tumour-free resection margins. Surgeons achieve significantly better surgical and oncological outcomes if they can identify the precise location of a gynaecological tumour. Indeed, the true nature of tumour, whether benign or cancerous, is often not known prior to surgery. If more details were available in relation to the characteristics that differentiate gynaecological cancer in tumours, this would enable more accurate diagnosis and help in the planning of surgery.

HYPOTHESIS: Haptic technology has the potential to enhance the surgeon's degree of perception during minimal access surgery. Alteration in tissue stiffness in gynaecological tumours, thought to be associated with the accelerated multiplication of cancer cells, should allow their location to be identified and help in determining the likelihood of malignancy.

METHOD: Setting: (i) Guy's & St Thomas' Hospital (ii) Dept of Informatics (King's College London).

Permission from the National Research Ethics Committee and Research & Development (R&D) approval were sought from the National Health Service.

The Phantom Omni, capable of 3D motion tracking, attached to a nano-17 force sensor, was used to capture real-time position data and force data. Uniaxial indentation palpation behaviour was used. The indentation depth was calculated using the displacement of the

probe from the surface to the deepest point for each contact. The tissue stiffness (TS) was then calculated.

The haptic probe was tested first on silicone models with embedded nodules mimicking tumour(s). This was followed by assessing TS *ex-vivo* using a haptic probe on fresh human gynaecological organs that had been removed in surgery. Tissue stiffness maps were generated in real time using the haptic device by converting stiffness values into RGB values. Surgeons also manually palpated and recorded the site of the tumour.

Histology was used as the gold standard for location and cancer diagnosis. Manual palpation and haptic data were compared for accuracy on tumour location. The tissue stiffness calculated by the haptic probe was compared in cancer and control specimens. Several data analysis techniques were applied to derive results.

CONTRIBUTIONS: Haptic indentation probe was tested for the first time on fresh human gynaecological organs to locate cancer in a clinical setting.

We are the first one to evaluate the accuracy of cancer diagnosis in human gynaecological organs with a force sensing haptic indentation probe measuring tissue stiffness.

Acknowledgements

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List of Acronyms

CORE	Centre of Robotic Research
CT	Computerised Tomography
ECF	Extracellular Matrix
GSTT	Guy's & St Thomas' NHS Foundation Trust
HRA	Health Research Authority
LUS	Laparoscopic ultrasound image guidance system
MAS	Minimal access surgery
MDT	Multidisciplinary Team
MEMS	Microelectromechanical systems
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NRES	National Research Ethics Service
R&D	Research & Development
REC	Research Ethics Committees
RQ	Research Question
TS	Tissue Stiffness

Glossary of Terms

Cervix	Gynaecological reproductive organ which attaches to the lower part of the womb
Histology	The study of microscopic structures of tissues
Histopathologist	Doctor specialising in histology
Hyperplasia	Increased proliferation of cells causing enlargement of organ or tissue
Leiomyoma	Benign tumours of smooth muscle in the womb (also called fibroids)
Lymph nodes	Small round glands which are part of the immune system
Metastases	Spread of cancer to distant site
Neoadjuvant	Administration of therapeutic agent before a main treatment
Oncology	Study and treatment of cancer
Ovary	Gynaecological organ (gonad) producing eggs and female hormones
Parametrium	Tissue adjacent to the cervix and uterus (womb)
Sarcoma	A type of rare cancer arising in the womb
Tissue	Any distinct type of material consisting of specialised cells and their products
Uterus	Womb

Chapter 1

Introduction

Chapter 1. Introduction

Gynaecological cancers are the 4th most common malignancies in women in the United Kingdom (Cancer Research UK) .Over the last decade there has been an impressionable change in the surgical treatments offered to women diagnosed with gynaecological cancers. The uptake of minimally invasive surgery (both laparoscopic and robotic surgery) by gynaecologists has significantly increased. Such a trend is seen in the treatment of both benign and malignant tumours (Mabrouk et al., 2009).

Minimal access surgery (MAS) has been shown to have several advantages over traditional open surgery, including faster recovery, shorter hospital stays, less blood loss and being aesthetically more appealing (Boggess et al., 2008; Juhasz-Boss et al., 2012; Yu et al., 2013). However, MAS is known to offer low tactile sensation as compared to open abdominal surgery in which a surgeon can manually palpate the tissue or organ.

Currently in medical robotics, there are a few surgical devices, such as the *Intuitive Surgical Xi Robot*, that are considered leaders in the field. There is however still room for the development of instruments and technology that could improve feedback from the tissue or organ(s) during surgery. There have been a few developments in haptics, especially in relation to newly emerging tactile sensors, that help users in industry and other fields improve the quality of feedback information. There is scope in the application of these tactile sensor technologies in relation to locating and diagnosing cancer during surgery.

While this technology has been successfully applied in the past to identify tumours in tissue such as lung, liver, breast and prostate (Beccani et al., 2014; Li et al., 2012a; McCreery et al., 2008; Perri et al., 2010b; Trejos et al., 2008), there is no research to date with haptics conducted on gynaecological tissue or organs with cancer.

Each organ and tissue types are different, and the application of tactile sensing and haptic feedback therefore needs to be assessed in gynaecological organs to assess its usability. Haptic feedback from gynaecological organs should enable us to locate the exact site of cancer in the reproductive organs and perhaps to even identify the nature of the abnormal tissue when needed, so as to differentiate between cancer and benign tumours.

Malignant (cancer) cells are invasive and gynaecological tumours often feels hard on palpation. Solid tumours become increasingly rigid as normal tissue is replaced by malignant cells and there is compression from surrounding tissue. By using technology to measure tissue stiffness in gynaecological organs or tissue, it might also be possible to locate the exact site of such tumour and its boundaries.

If successful, the future application of this kind of haptic technology in minimal access surgery could be invaluable in improving diagnostic capabilities, helping with operative planning, and achieving tumour-free margins during surgical resection in gynaecological cancer. It could further be adapted by intervention radiologists or surgeons for use during biopsies to improve diagnostic accuracy.

1.1. Female Reproductive Organs

This section illustrates the anatomy of the female reproductive organs to five an overview of the tissue examined in this research. Gynaecological reproductive organs and the female pelvis are shown in Figure 1.1.

The specimens which were tested included the uterus, cervix, ovary, and lymph nodes.

(i) Uterus (womb): The uterus has three layers of cells (Figure 1.2). Its innermost lining is the *endometrium*, outside of which is the muscle layer known as the *myometrium* while the outermost layer is called the *serosa*. Uterine cancer tends to arise in the endometrium and then invades outwards into the muscle and then toward the surface of the organ.

Certain uterine tumours arise from the muscle and can become cancerous (uterine *leiomyosarcoma*) while others remain benign (*leiomyoma or fibroid*).

(ii) Cervix: This is attached to the lower part of the womb and its own lower part protrudes into the vagina. It is usually 2-3cm long and cylindrical in shape. It has a narrow central canal which runs along its entire length, connecting the uterine cavity to the vagina. The canal is lined by two different types of epithelial cell. The inner part (endocervix) is lined with columnar cells and outer part (ectocervix) is lined with squamous cells. There is an overlap area known as the *transformation zone*, and it is here that cervical cancer most commonly arises (Figure 1.3). Figure 1.4 shows a specimen following a radical hysterectomy for cervical cancer, in which the cervical tumour, complete with tumour-free margins, has been removed. To achieve this, the tissue around the cervix and uterus, known as the parametrium, along with part of the vagina, has been excised along with the uterus and cervix.

Underlying the epithelial layer is the *stroma*, which is composed of fibrous and elastic tissue formed by *collagen* and a protein called *elastin* along with smooth muscle. The surface epithelial layer infolds into the stroma and forms gland like appearances which secrete mucus. Cancer of the cervix can invade locally into the stroma and sometimes replace the cervix or spread locally into the surrounding parametrium, vagina and uterus.

(iii) Ovary: Normal ovaries are small almond shaped structures, covered by a connective tissue capsule- *tunica albuginea* (Figure 1.5).

An ovary affected with tumours can have cysts; fluid-filled pockets of varying size. Cancerous cysts tend to be more solid than their fluid-filled benign counterparts (Figure 1.6). Cancer of the ovary arises inside the organ and spreads outwards towards the surface.

(iv) Lymph Nodes: These are glands in the body which are part of the lymphatic system (Figure 1.7). Organs connect through lymphatic channels directly to the lymph nodes in their specific area of the body. The lymph nodes are connected to each other through a network of lymphatic channels in which lymphatic fluid circulates (Figure 1.8). Cancer can spread through the lymphatic channels and reach the lymph glands.

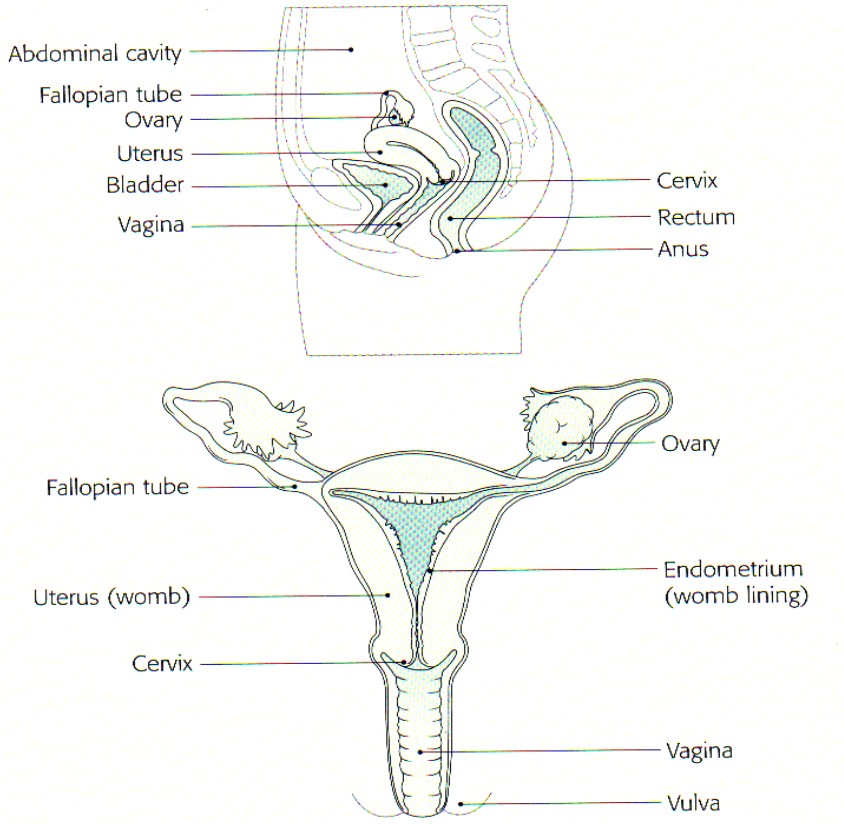


Figure 1.1 Anatomy of female genital tract

From Guy's and St Thomas' NHS Foundation Trust (2013)

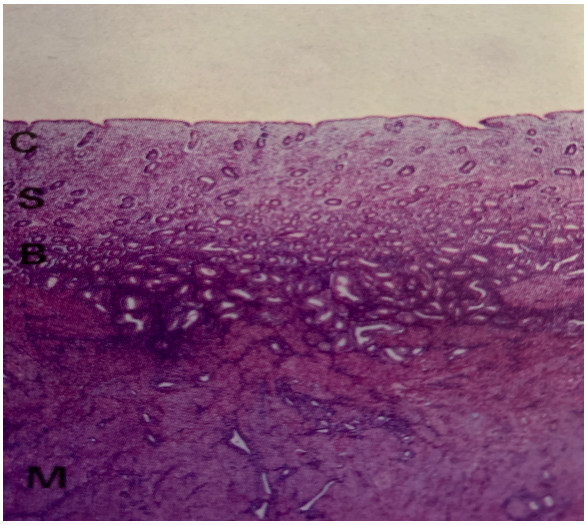


Figure 1.2 Histological section of uterus

M: Myometrium. **B:** Deeper layer of endometrium

C: Superficial layer of endometrium lining the inside of the uterine cavity

From Young et al. (2014)

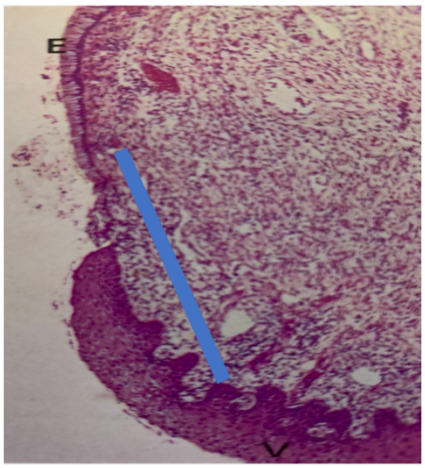


Figure 1.3 Histological section of cervix

V: Ectocervix lining with Squamous Cells (vaginal part).

E: Endocervical Canal lining with Columnar Cells (entrance into the uterine cavity).

Blue Indicator showing the Transformation Zone which is the commonest site of cervical cancer

From Young et al. (2014)

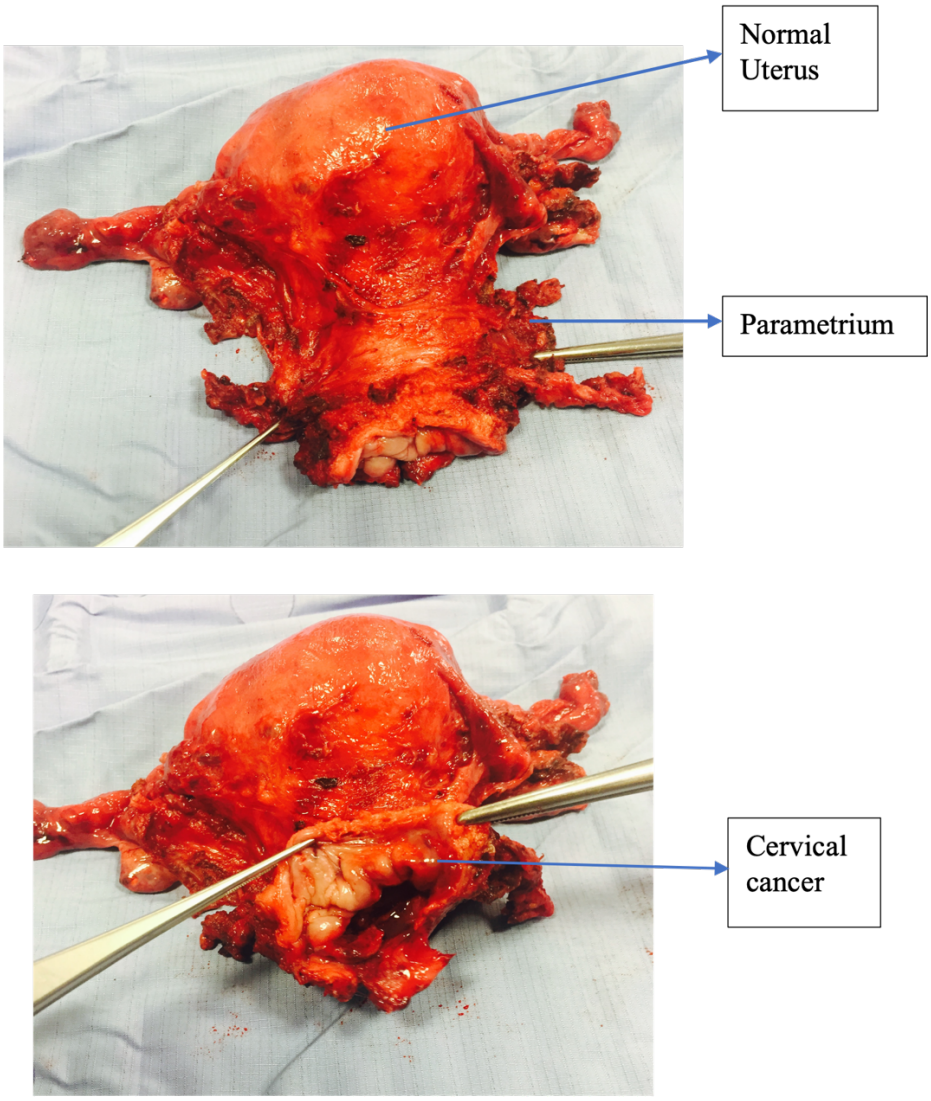


Figure 1.4 Gross specimen of cervical cancer

Specimen of uterus and cervix with parametrium following laparoscopic radical hysterectomy in a patient operated for early cervical cancer at Guy's & St Thomas' Hospital, London (all patient identifiable data removed for anonymity)

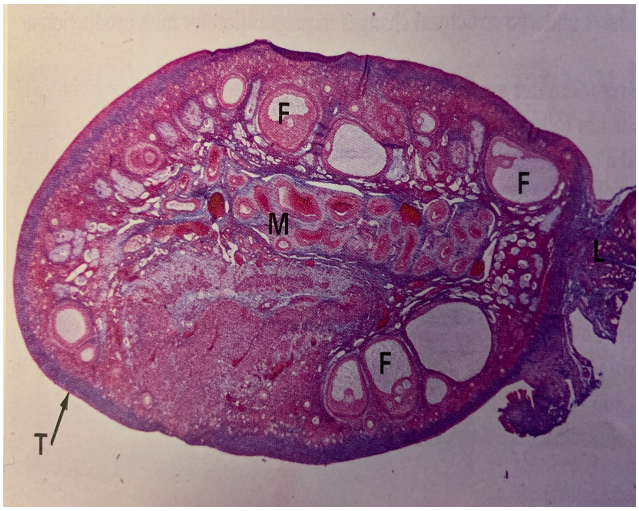


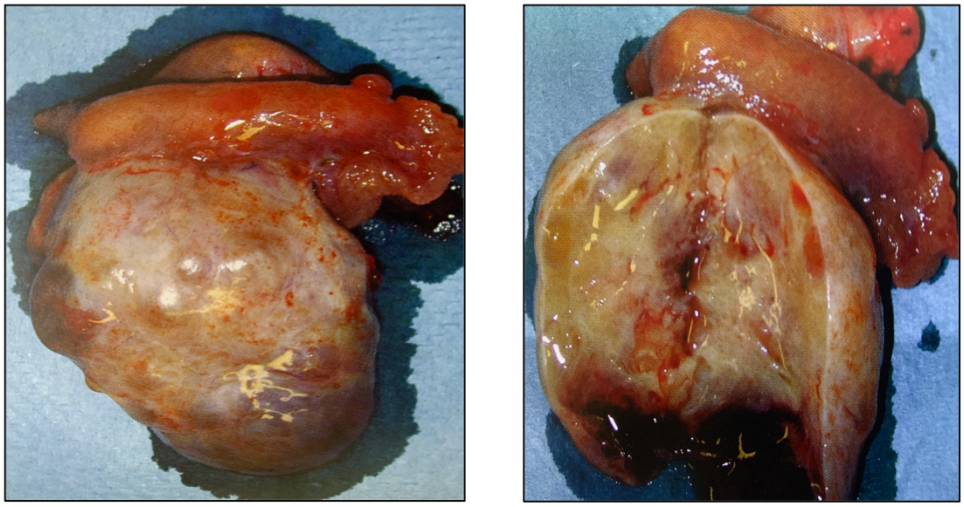
Figure 1.5 Normal Ovary

T. Body of the ovary consists of spindle shaped cells, reticular fibres and ground substance constituting the ovarian stroma. In the peripheral zone of the stroma is the cortex with numerous follicles **F** which contain the female gametes which produce eggs (ova)

M. Medulla - a deeper layer with blood vessels

L. Hilum - the part of the ovary where blood vessels and nerves enter

From Young et al. (2014)



(i) Intact ovary with cancer (ii) Cut section of ovary

Figure 1.6 Ovary with cancer

Specimen of ovary and tube excised surgically in a woman who was suspected to have ovarian cancer at Guys & St Thomas' Hospital, London. (all patient identifiable data removed for anonymity)

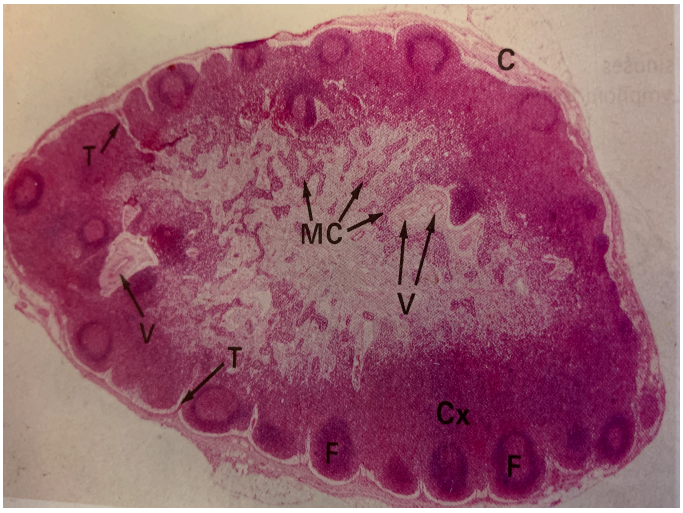


Figure 1.7 Histological section of Lymph Node

C: Capsule. **T:** Trabeculae. **Cx**: Cortex. **F**: Lymphoid follicles. **MC**: Medullary Cords. **V**: Blood vessel.

From Young et al. (2014)

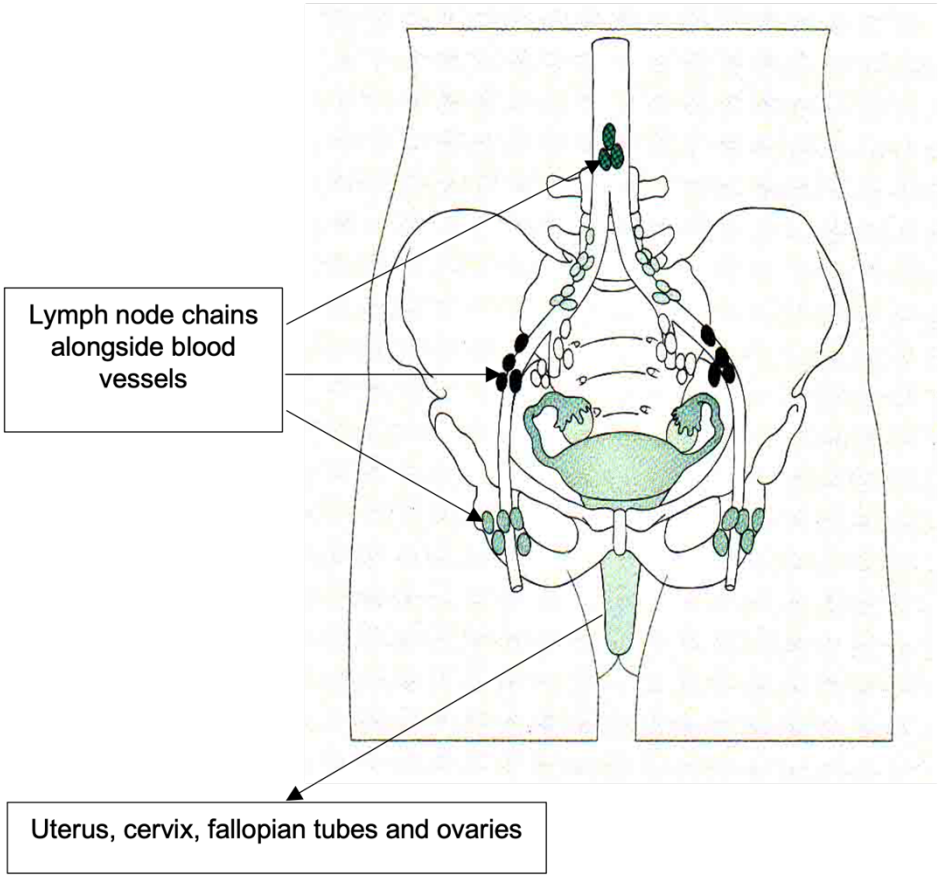


Figure 1.8 Anatomy of female genital tract & Lymph nodes draining reproductive organs

From Guy's and St Thomas' NHS Foundation Trust (2013)

1.2. Motivation of Thesis

1.2.1. Tissue feedback in minimal access surgery (MAS)

Both robotic and laparoscopic surgery (MAS) have been criticised on account of the minimal amount of tactile sensation and tissue feedback they offer the surgeon. The ability to palpate tissue is vital in the identification of the site and nature of the disease being treated. A surgeon relies on a combination of tactile and visual abilities to differentiate normal from abnormal tissue. In traditional (abdominal) surgery, the surgeon has direct contact with the organ and can readily palpate the tissue to identify the site of abnormality such as a tumour located within the organ; the disease causing the changes within the tissue that are evident to the surgeon. Unfortunately, in minimally invasive surgery (especially with robot-assisted surgical systems) the surgeon is not in direct contact with the patient and cannot obtain the requisite feedback.

Haptics has the potential to augment tissue feedback in gynaecological minimal access surgery. It has the potential to identify tissue characteristics, providing the surgeon with better quality feedback.

1.2.2. Locating tumours in gynaecological organs

During cancer surgery, the surgeon aims to excise tumours en bloc with surgical margins free of tumour. To accomplish this, the surgeon needs to fully appreciate the properties and characteristics of the tumour, as well as those of the organ or tissue surrounding it. Owing to inherent issues relating to tactile feedback with minimal access surgery, it is difficult to ascertain this during laparoscopic and robotic surgery when precise information of the location and extent of the tumour is unavailable.

Women often present with gynaecological conditions that, despite pre-operative imaging and blood tests, cannot be categorically diagnosed. They require tissue biopsies to confirm the diagnosis histologically before treatment can be started. Often these are carried out using laparoscopic or robotic surgery, if not by radiological guidance. Knowing the exact location of tumours in gynaecological organs can help target biopsies to improve the accuracy of tissue harnessing and diagnosis.

1.2.3. Differentiating benign tumours from cancer

Gynaecological tumours can present a diagnostic dilemma, as prior to surgery the diagnosis of malignancy is often not certain. If tissue characteristics changed because of high activity in cancer cells, one could use this to identify the likelihood of malignancy at the time of surgery. This would benefit the patient by allowing the surgeon to tailor the radicality of surgery in full knowledge of the accurate diagnosis.

1.3. Research Questions

RQ-1: Can the location of gynaecological cancer in human organs be accurately identified by feeding back information on tissue stiffness using haptic technology?

RQ-2: Can we reliably determine the likelihood of cancer in human gynaecological organs by determining tissue stiffness using haptic feedback?

1.4. Contributions

1) Novel research to demonstrate the use of haptics to detect location of cancer in gynaecological reproductive organs.

2) Novel approach to assess tissue stiffness of actual female human specimens (ovary, cervix and lymph nodes) using haptics.

3) Novel approach to test the performance of haptic measurement of tissue stiffness in diagnosing gynaecological cancer.

1.5. Structure of Thesis

Chapter 1 - Introduction

The first chapter provides an overview of the research in relation to current issues and identifies the aims and objectives of the work. It also provides information necessary to understand the research in relation to the human specimens studied.

Chapter 2 - Literature Review

This chapter presents an overview of the current literature on tissue feedback using haptics. It examines current knowledge on tissue stiffness in gynaecological cancer and other human organs/tissues. It explains the basis of tissue stiffness measurement and reviews the current literature on haptics in locating tumours in humans.

Chapter 3 - Approach & Methodology

This chapter details the work done to set up the research in the clinical setting.

It explains how the research was carried out on fresh human specimens explaining the methodology and how the data was recorded. It explains the techniques of haptic and manual palpation and the histology used.

It details the process used to manufacture silicone models used to validate the haptic set up.

Chapter 4 - Results & Analysis

This section is sub-divided as follows:

Results and experiments of silicone testing

Experiments with haptic probes and manual palpation

Statistical Analysis

Comparison of manual palpation and haptic detection for tumour location

Chapter 5 - Discussion

The discussion centres around the results and their significance in terms of practical applications within the context of current clinical needs.

Chapter 6 Conclusion

In conclusion, research findings are reiterated, while contributions are outlined and a scope for future research suggested.

Chapter 2

Background & Literature review

Chapter 2. Background and Literature Review

2.1. Haptics

'Haptics' refers to a technology that can provide information and feedback on touch (tactile sensation) to the user (in our case, the surgeon). The origin of the word 'haptics' derives from the Greek word '*haptikos'*, meaning the ability to grasp or perceive.

There are various types of feedback available to a surgeon during surgery. *Visual feedback* provides the surgeon with the most comprehensive information on tissue characteristics as it communicates not only shape and colour, but also the tissue's position in relation to the surgeon's hands and other objects (Reiner, 2008). *Kinaesthetic feedback* provides information about position, velocity and force and this type of perception relies on receptors within the muscle, skin, tendon, and joints (Craig & Rollman, 1999). *Tactile feedback* offers more detailed information on superficial tissue properties such as temperature, pressure distribution and texture (Kálmán & Csillag, 2005). '*Haptic' feedback* combines both kinaesthetic and tactile feedback (Loomis & Lederman, 1986). Although advanced vision systems in robotic surgery do indeed provide good visual feedback (Frank et al., 1997; van Bergen et al., 2000), the addition of haptic feedback, offering the surgeon kinaesthetic and tactile information, is clearly a significant additional benefit.

Tactile sensors help gather information when touching a surface or an organ, providing additional feedback to the user, and thereby aiding palpation. Sensing mechanisms convert energy from one form to another, such as when mechanoreceptors in humans receive stimuli and transduce physical energy into nervous signals. Tactile sensors, of

which many have been developed in the last four decades (Chi et al., 2018; Lee, 2016; Tiwana et al., 2012), can measure hardness, temperature, vibration, wetness, pressure or shape. The transduction method varies between sensors, with capacitive, piezoresistive, piezoelectric, magnetic and optical methods available.

For more than a decade, haptic devices have developed with increasing applications in the field of medicine and industry (Laycock & Day, 2003). Haptics has been applied in medical training where simulators have been developed to train doctors and students (Talhan & Jeon, 2018; Tse et al., 2010)

2.2. Tactile Sensing

2.2.1. Classification of Sensors

Sensor types can be classified by their transduction method and are set out in Table 2.1.

Capacitive sensors transform applied force into capacitive variation (Chu et al., 1996; Leineweber et al., 2000; Morimura et al., 2000), the changes in capacitance detected by the sensor. Typically, these sensors have three layers, with a middle layer made from dielectric materials sandwiched between two parallel-plate capacitors. Increase in capacitance is detected when force is applied and the two plates shift towards each other, compressing the middle layer of silicone or air (Kolesar & Dyson, 1995; Webster, 1988). Although these sensors are small, they do have issues with hysteresis (Dargahi & Najarian, 2004).

Piezoelectric sensors rely on detecting changes in strain polarisation on application of force. Electricity must be applied such that the dipoles in the piezoelectric material align

themselves along the direction of the applied electric field. On application of pressure, the dipoles shift, and the generated voltage gives a measure of the force applied. As with capacitive sensors, piezoelectric sensors have problems with hysteresis and are also sensitive to temperature.

Piezoresistive sensors measure the change in resistance at a single touch point, resistance being at its maximum when no force is applied. Conduction is through a carbon layer. Although relatively low cost, they offer limited tactile spatial resolution.

Table 2.1 Methods of transduction used in tactile sensation

Types of Sensors	Method of sensing	Features	Deficiencies	Example(s) of Application
Capacitive	Detects change in Capacitance	- Highly sensitive - Insensitive to temperature variation - High density due to small size	Issues with hysteresis	Medical use (Salo et al., 2006) Robotic hand (Shashank et al., 2009)
Piezoelectric	Detects changes in strain polarisation	- Highly sensitive & accuracy	Leakage of charge - Poor spatial resolution	Tele-manipulator for minimally invasive surgery (Qasaimeh et al., 2009)
Piezoresistive	Detects changes in resistance	- High spatial resolution - Simple structure and low cost	- High power consumption - Issues with hysteresis	Detection of hardness in above-knee prosthesis (Hsieh et al., 2001)
Magnetic	Detects changes in magnetic coupling	- High sensitivity - High power output	- Bulky - Low special resolution	Artificial Mechanoreceptors (Futai et al., 2004)
Optical	Detects changes in light intensity	- High reliability - High spatial resolution - Immune to electromagnetic noise	- Bulky - Susceptible to temperature variation - Non-conformable	Medical (Lee et al., 2013; Oleksyuk et al., 2018)

Optical sensors take advantage of the phenomenon of photoelasticity. On applying pressure to the photoelastic probe in the optical sensor there is change in the intensity of the light which can be measured. The advantages of optical sensors are their high resolution, flexibility and inertness to any electromagnetic interference (Chi et al., 2018; Lee & Won, 2011; Oleksyuk et al., 2018).

Magnetic-based sensors are tactile sensors that use magnetoelastic materials that deform when pressure is applied, and that then calculate the change in their magnetic characteristics. These sensors cannot be used with any metallic materials (Chi et al., 2018).

2.2.2. Tactile Sensing Systems

Tactile sensing systems have been developed to measure one or more touch sensations, effectively making tactile sensing more like the human sense of touch which can discern a wide range of material characteristics. In medical applications, a surgeon manually palpating an organ or tissue, in a bid to identify the site of pathology, will glean much information about the area under examination. This might include substance characteristics such as whether it is stiff or soft, hot or cold, rough or smooth. The better the information available to the surgeon, the higher the likely accuracy of identification. Tactile sensing systems involve complex mechanisms requiring multiple sensors and processors and are categorised into mechanical imaging systems (Egorov et al., 2009; Egorov & Sarvazyan, 2008), elasticity imaging systems (Dargahi & Najarian, 2004; Eltaib & Hewit, 2003) and tactile sensation imaging systems (Lee et al., 2013). In biomedical applications, such as tumour localisation, tactile sensing systems can also measure tumour properties such as size, depth and elastic modulus (Won et al., 2021).

Qualitative measurement of elasticity is determined by the degree of resistance of any tissue to deformation. Importantly, it is a property that is altered by the presence of any pathological tumour - particularly in soft tissue and human organs - and as such, elastography, the measurement of elasticity, has been used in both the classification and localisation of tumours (Ophir et al., 1991; Sarvazyan et al., 2011).

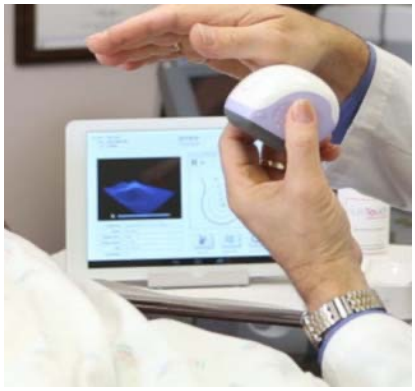


Figure 2.1 Sure Touch Visual Mapping System (Medical Tactile Inc).

From Egorov & Sarvazyan (2008)

The *Sure Touch Visual Mapping System* is a medical device that calculates elasticity using capacitive sensors (Figure 2.1) (Egorov & Sarvazyan, 2008). The probe has an array of capacitive pressure sensors that transmit electronic data to the computer, the information determining the stress distribution on the object surface. Although small, portable and able to function without any need of radiation or magnetic fields, it has limitations in tactile spatial resolution. Using it to generate tissue stiffness maps is therefore difficult and indeed also expensive.

Elasticity has also been determined using piezoelectric and piezoresistive sensors. Yegingil et al. (2010) developed a piezoelectric finger using a piezoelectric sensor (Figure 2.2). The sensor comprises a top layer of Piezoelectric Zirconate Titanate (PZT) that

drives the finger. Its bottom layer, also PZT, is used for sensing. An electric field induced in the top layer creates bend in the finger. Any bend in the lower sensing layer induces a change in voltage that can be correlated to elasticity. This apparatus is low cost but has limited spatial resolution, is difficult to calibrate and sensitive to temperature variation.

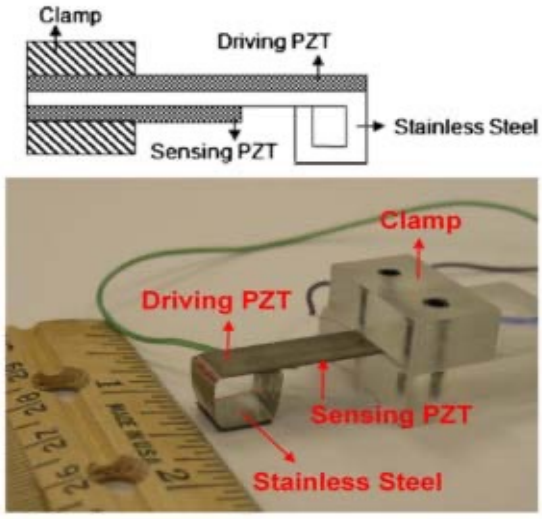


Figure 2.2 Piezoelectric finger

From Yegingil et al. (2010) and Nover et al. (2009)

Ultrasound elastography has also been used for this purpose (Vinckier & Semenza, 1998). There are three types of elastography: (i) transient (ii) compressive and (iii) sonographic. Transient elastography uses a transient vibration produced by a probe that causes tissue deformation. A shear wave is generated by a vibrating piston and this traverses through the tissue. The transducer probe at the end of the vibrating piston detects the extent of deformation using pulse-echo ultrasound. Compressive elastography compares the signals before and after compression using controlled compression of transducer probe and tissue stiffness calculated on a distribution map (Rivaz et al., 2008). Sonoelastography uses a real-time ultrasound doppler, recording the pattern of propagation through the tissue by low frequency (6 to 14 MHz) shear waves. Among the disadvantages of elastography techniques are the high cost of the requisite apparatus and

the requirement of ultrasound training for the user carrying out the procedure. The ultrasound machine itself is a large piece of equipment, not easy to accommodate in a surgical environment.

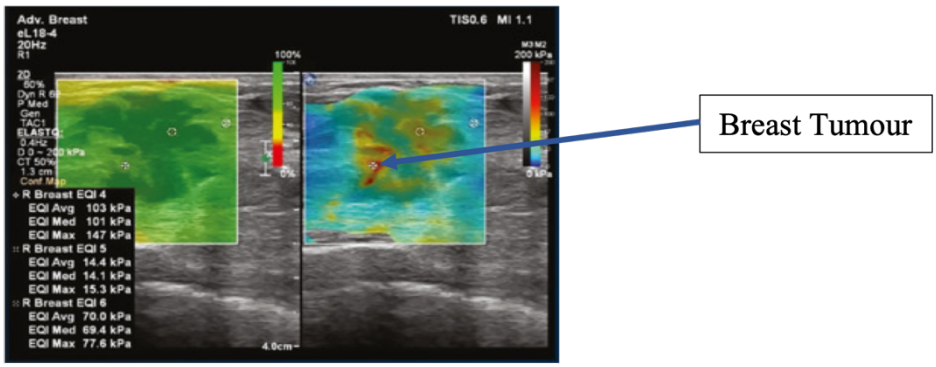


Figure 2.3 Ultrasonic elastography identifying breast tumour

From Shamdasani (2018)

Optical sensors have been used successfully in relation to tactile sensation. They work in one of two ways. The more popular method is based on light diffusion (Oleksyuk et al., 2018), in which the elastomer layer is lit up by passing light through a diffusion filter generating multi-layered intensity levels in the elastomer. When the contour of the elastomer layer is altered, the light is scattered, and this is captured by a camera. In the other, indeed older method, light is injected into an elastomer at a certain angle such that it is totally traverses the elastomer. Any extrinsic pressure will change the contour of the elastomer causing light to escape. This escaped light is then captured by a camera (Lee & Won, 2011).

2.3. Basic Principles for Tissue Stiffness Assessment

Better acquisition of tissue properties such as stiffness, ought to improve the likelihood of a surgeon being able to detect and locate a tumour within an organ or tissue. This can be achieved by measuring indenter displacement along with forces applied to the tissue.

Stiffness is a measure of the extent to which an object resists deformation in response to an applied force (Baumgart, 2000). The stiffness, k, of a body, is a measure of its resistance to deformation. For an elastic body with a single degree of freedom (DOF), such as stretching or compression of a rod, the stiffness is defined as:

$$k = F/\delta$$

where F is the force on the body and δ is the displacement produced by that force along the same degree of freedom (much like the change in length of a stretched spring).

Elastic Modulus E, also called the Young's modulus, is commonly referred to in the description of soft tissue behaviours (Miller et al., 2007). If the indentation force and tissue deformation are known, then, by using a hemispherical indenter and applying a small indentation, the elastic modulus of the tissue can be estimated as:

$$E = (3f(1+v))/(8d\_in\sqrt{(rd\_in)})$$

where E is the elastic or Young's modulus, f is the tissue reaction force, r is the radius of the indenter, d_in is the indentation depth and ν is the Poisson ratio (Lee & Radok, 1960). Many soft tissues are virtually incompressible and for such materials, ν is 0.5.

This is the principle we followed in identifying the tissue stiffness in all our experiments.

The techniques to elicit tissue feedback via force sensing methods either use the uniaxial indentation method (Doria et al., 2021; Samur et al., 2007) or the rolling and sliding indentation approach (Kumar et al., 2011; Li et al., 2012a; Liu et al., 2011; Noonan et al., 2007).

2.3.1. Indentation Technique

In the uniaxial indentation technique, a Force (F) / Torque (T) sensor is used. The deformation and the corresponding interaction forces are recorded. The tip of the instrument or the sensor is moved in an up and down motion. Yamamoto et al. (2009) demonstrated that this method could provide reliable estimations of tissue stiffness. This was further developed by Yamamoto et al. (2012) with the addition of augmented visual feedback using 3D graphical material property overlays and virtual fixtures.

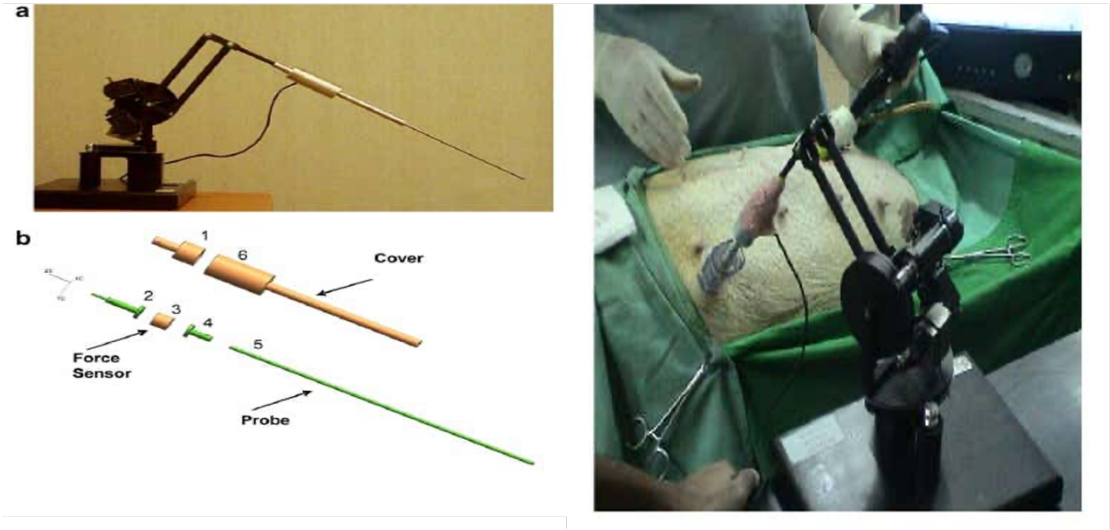


Figure 2.4 Indentation robotic probe

(a) Indenter probe (b) Components of the indenter probe (c) Animal experiment on pig liver.

From Samur et al. (2007)

Samur et al. (2007) successfully used the indentation technique to assess the tissue properties of porcine liver (Figure 2.4). They developed a probe for their animal experiments which had been adapted to reach the organ via minimal access surgical ports. A graphic user interface was used to record the displacement and force data. The position value was obtained from the encoders of the robotic arm holding the probe.

Using the indentation technique, Doria *et al* were able to generate feedback from silicone uterine models with artificial lumps resembling benign fibroids [Doria D 2021] (Figure 2.5). They later extended this technique to measure tissue stiffness of fibroids in the human uterus (Figure 2.5), successfully mapping the fibroids based on their stiffness.

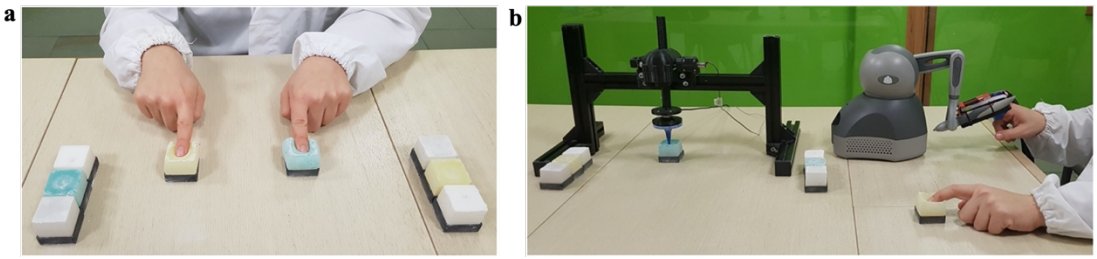


Figure 2.5 Indentation method for tissue stiffness acquisition from silicone samples with embedded lumps resembling fibroids

From Doria et al. (2021)

2.3.2. Rolling and Sliding Techniques

The rolling indentation technique to locate tumours has been successfully applied, its principal advantage being the speed of acquisition of stiffness data (Li et al., 2017; Liu et al., 2010; Liu et al., 2011; Noonan et al., 2007). The technique uses a rigid wheeled hemispherical indenter probe that needs to be rotated when changing direction. Maintaining a constant indentation depth is difficult, although this can be improved by

pre-registration of the surface, but this takes time, the deformability of soft tissue making surface pre-registration particularly challenging and is therefore not ideal in a clinical setting. The sliding indentation technique can generate more friction - using a round end effector fixed to the tip of the probe - than the wheel configuration in the rolling method but requires lubrication of the surface of the tissue being tested.

To overcome some of these problems, another developed probe incorporated an air-float mechanism (Wanninayake et al., 2012). When rolling over tissue while maintaining a constant air pressure, the displacement of a sphere at the end of the probe is measured by optical fibre displacement sensors (Fig 2.4).

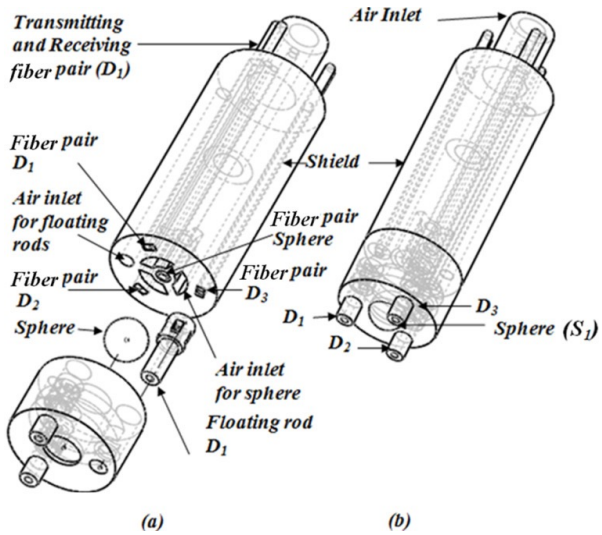


Figure 2.6 Stiffness probe

(a) The stiffness probe consisting of four fibre optic displacement sensors, *S1, D1, D2, D3*,

(b) exploded view of the probe showing internal detail.

From Wanninayake et al. (2012)

A miniaturised version of this probe was later proposed (Wanninayake, 2019)

In our experiments we adopted the uniaxial indentation technique, performed manually, to test the specimens. With human specimens, care must be taken not to damage the tissue during testing and only manual measurements were possible in the clinical theatre setting. Although gynaecological specimens are of various shapes and sizes and contoured differently, the indentation technique, although laborious, did allow controlled data acquisition by indenting several points on the surface of the organ.

2.4. Overview of Haptics in Medicine

It is generally accepted that the interposition of surgical instruments significantly reduces haptic feedback in minimally invasive procedures (Bholat et al., 1999; den Boer et al., 1999; Picod et al., 2005; Schostek et al., 2006; Westebring-van der Putten et al., 2008). Minimal access surgeons use laparoscopic or robotic instruments to palpate tissue and in doing so, acquire some level of haptic feedback. However, this is often insufficient to enable the detection of abnormal tissue, which would tend to be stiffer than healthy tissue – a consequence of a pathological condition. Even tele-robotic systems such as the da Vinci surgical robot, which are commonly used in clinical settings, offer little in the way of significant haptic feedback solutions to compensate for this deficiency. The situation is particularly noticeable in robotic assisted surgery, in which neither the clinician (referred to as the 'master) nor the robot (referred to as the 'slave') are able to discern any material properties of the soft tissue (Tavakoli et al., 2008).

Attempts to address this lack of haptic feedback tend to focus on improving the mechanical construction of the instruments or to improving the quality of other alternative feedback information (sensory substitution) which is transmitted electromechanically (Heijnsdijk et al., 2004a; Heijnsdijk et al., 2004b)

Mechanical instruments are not always beneficial; especially when palpation requires repeated motion and high mechanical efficiency (Westebring-van der Putten et al., 2008). The electromechanical approach uses sensors to measure the force applied to the tissue. They extract tactile tissue information and reflect this back to the surgeon using a haptic, auditory, or visual display. To optimise palpation, one therefore requires a reliable and

efficient system of sensors that can extract tissue related data, such as tissue stiffness, and relay that back to the surgeon in a meaningful way. In other words, rather than the 'direct force feedback' offered by surgical instruments, this route provides a form of 'indirect force feedback', say visual, an example being colour-coded maps indicating tissue stiffness and highlighting abnormal areas in the tissue or organ in question. This provides further information to the surgeon in relation to identifying the location of these abnormal areas (Hamed et al., 2012).

A few researchers have developed sensor probes and have even tested their prototypes in creating stiffness distribution maps that could be used during palpation in minimal invasive surgery (Beccani et al., 2014; Gwilliam et al., 2010; Li et al., 2012a; Liu et al., 2010; Liu et al., 2011; McCreery et al., 2008; Perri et al., 2010a; Perri et al., 2010b; Talasaz & Patel, 2013). Using pseudo-haptic feedback, Li et al. (2012b) introduced low-cost tissue stiffness mapping for stiffness simulation and abnormality localisation. However, most experiments of this type have been conducted ex-vivo in the laboratory or using porcine models. There is a paucity of translational research on the performance of these haptic devices in locating actual tumours or assessing the tissue stiffness distribution in human tissue, especially in relation to gynaecological organs.

One of the problems faced during measurement of tissue stiffness is that one needs to obtain accurate data on the force applied to the tissue as well as the indentation depth (the degree of tissue compression on application of the force) – in other words the displacement of the tip of the indenter. The problem with most probes or their prototypes is that when assessing stiffness in real time, it is difficult to keep the indentation depth constant when forces are applied. In addressing this problem, researchers have used

cameras to estimate the indentation depth, but this has its own limitations, especially on curved surfaces (Keller & Ackerman, 2000). Indeed, most organ surfaces are not flat but have contours. Others have developed different designs using fibre-optic displacement sensors on the indenter tip (Liu et al., 2010). More recently, wireless sensors have been used to detect the indentation depth, providing real-time data while experimenting on porcine liver (Beccani et al., 2014).

Various haptic systems have used force feedback for tissue diagnosis during minimally invasive surgery. Tholey et al. (2004) designed a laboratory prototype laparoscopic grasper to estimate the grasping force as a function of the current supplied to the joint motor. Unfortunately, because of the friction in joints, the inertia of all linkages including changes in motor brush conductivity and winding resistance, the device was not able to offer high accuracy in force estimation.

Strain gauges have been attached to graspers in minimally invasive surgery to deliver feedback in relation to force and tissue properties (Bicchi et al., 1996; Brown et al., 2003; Fischer et al., 2006; Hannaford et al., 1998). A 2-DOF force sensing sleeve was developed by Prasad et al. (2003) and integrated with a laparoscopic device. Microelectromechanical systems (MEMS) technology has also been used to develop force sensing instruments for MIS (Buess et al., 2000; Rebello, 2004). Lee & Wise (1982) developed a capacitive silicone pressure sensor with low temperature sensitivity.

Optical-based sensors have also been developed and as their sensing elements do not use electricity probes using this technology tend to be more practical for medical applications

as they can even be sterilised (Althoefer et al., 2010; Hirose & Yoneda, 1990; Polygerinos et al., 2010; Puangmali et al., 2018; Zbyszewski et al., 2008). Researchers are also working on biomimetic sensors - a new concept that has become very attractive in recent years (Lepora et al., 2018). The basis of this approach stems from mechanisms found in biological systems. As an example, by studying whisker movements in rodents, researchers have identified a mechanism through which rodents acquire tactile information through their whiskers, in turn affecting their behaviour.

Tactile array sensors have been developed to detect tumour and arteries within soft tissue (Sokhanvar et al., 2007; Suzuki et al., 1990), while vibrotactile sensors have been used to measure the dynamic response of soft tissue and to differentiate between healthy and unhealthy tissue (Baumann et al., 2001).

Zheng & Mak (1996) have used portable ultrasound indentation to measure initial tissue thickness as well as stiffness.

2.5. Location of Malignant tumours Using Haptics

Li et al. (2017) carried out a clinical study to identify the location of prostate cancer using a rolling indenter device (Figure 2.7). They examined 21 human prostates following prostatectomy in male patients and concluded that the method used to identify the location of tumour, based on tissue stiffness, was indeed accurate.

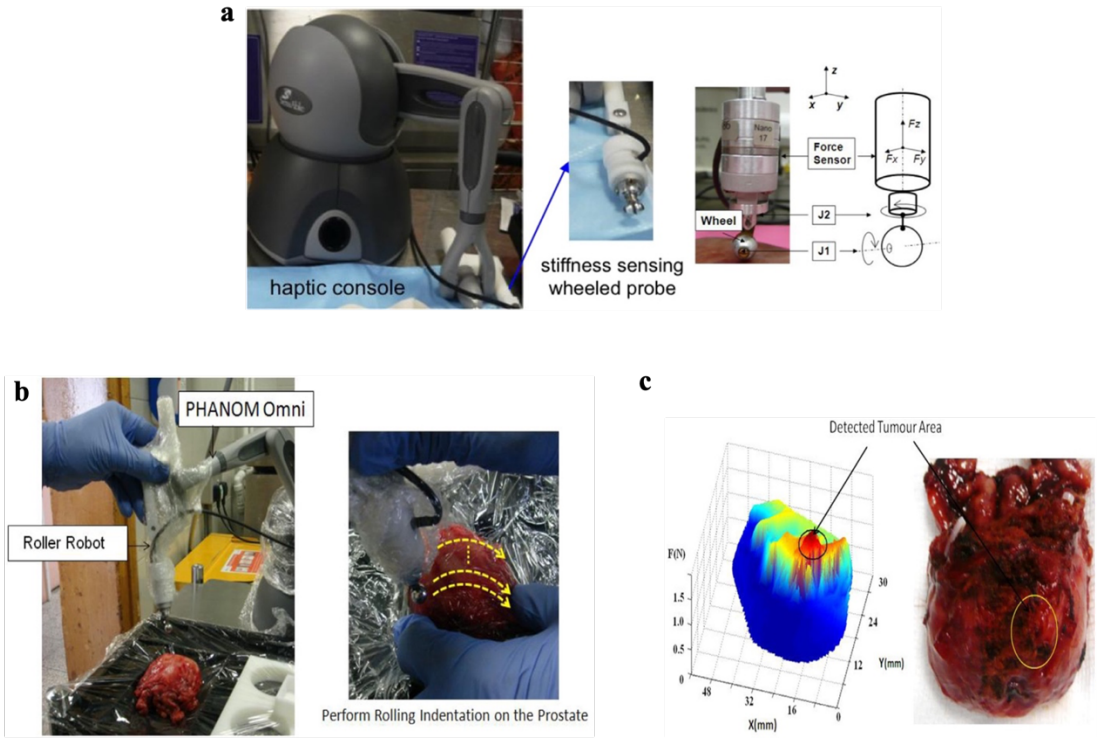


Figure 2.7 Rolling mechanical imaging device

(a) Rolling mechanical imaging device used by Li et al. (2017) on prostate to locate cancer

(b) Rolling technique used

(c) Tissue map generated in laboratory depicting stiff areas

In order to confirm that the location of cancerous or benign growth in the organ has been identified accurately by a haptic probe, the location has to be confirmed at histology by the histopathologist. Histology is considered the gold standard in finding the actual site and nature of tumour. At histology the organ is cut open and inspected. This is followed by more detailed analysis under the microscope to confirm the pathology. The use of

pictorial diagrams, which represents the organ, are often used to record tumour location to corelate and compare.

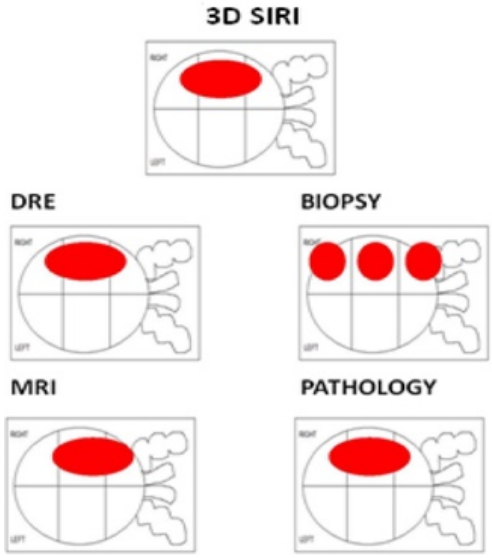


Figure 2.8 Pictorial diagram of prostate to record location of prostate cancer detected by haptic device (3D SIRI), direct rectal examination (DRE), preoperative ultrasound guided biopsy (biopsy), magnetic resonance imaging (MRI) and pathology

From Li et al. (2017)

Li et al. (2017) used pictorial diagram of human prostate to record and compare the site of prostatic cancer (Figure 2.8). Using these diagrams, they calculated the accuracy of 3D stiffness map generated by their haptic device. The performance of their haptic device was compared to histology as the gold standard. This technique had a 44.4% sensitivity and 71.4% specificity for the detection of prostate tumours. The negative and positive predictive value were 56.3% and 60.9% respectively while it had an overall accuracy of 57.9%.

The use of robotic technology in brain surgery has been demonstrated in the treatment of glioma tumours using the NeuroArm surgical System (Maddahi et al., 2016). This technique used MRI compatible robotic manipulators to identify and resect tumours in

seven cases using microsurgery and stereotactic surgery. The NeuroArm was equipped with force sensors at the end-effector allowing the quantification of tool-tissue interaction forces and the transmission of the force of dissection to a surgeon sited at a remote workstation with a haptic interface. The researchers measured the peak forces but could not find a relationship between forces exerted on the pathological tissue and its size, type or location. Brain tissue however differs in its composition from gynaecological tumours, the organ itself fundamentally softer.

Yu et al. (2015) used a non-invasive electrical probe that recorded impedance to locate tumours in human kidney specimens *ex-vivo*. They proved that there was a linear relationship between the surgical margin width of tumour and the recorded conductance.

Song et al. (2015) proposed a laparoscopic ultrasound image guidance system (LUS) for tumour resection in liver. They experimented on porcine models in which a vessel centre-line model that had been extracted from preoperative CT scan was registered to the ultrasound data during surgery. They concluded that you could use a locally rigid registration of a CT-derived model on vascular structures with LUS and that the accuracy of tumour location was commensurate with surgical requirements.

In gynaecology, haptic devices have not been used to locate malignant (cancerous) tumour. Recently, Doria et al. (2021) successfully identified benign fibroid in silicone and uterine specimens by characterising stiff areas using a wearable fabric yielding (W-FYD) haptic device, worn by a surgeon and fixed to a teleoperating console. The teleoperating system was composed of a console (teleoperating part) and the indenting

system (teleoperated part). W-FYD conveys feedback on stiffness information to the user's finger pad, allowing both active and passive haptic exploration by regulating the stretching state of a fabric band through two DC motors. The device is placed over the user's finger and fixed to it with an elastic clip that prevents rotation and ensures stability.

Giannini et al. (2019) proposed that the wearable haptic interface could be used iin a simulator to train doctors to do a myomectomy i.e. surgical removal of fibroid with uterine conservation.

2.6. Cancer Diagnosis

2.6.1. Tumour Assessment by Manual Palpation

Organs are types of soft tissue. Soft tissue is defined as tissue that connects, supports, or surrounds other structures and organs of the body, other than bone. It includes tendons, ligaments, fascia, skin, fibrous tissues, fat, and synovial membranes (which are all types of connective tissue), and muscles, nerves and blood vessels (which are not).

When trying to palpate for tumours in soft tissue or in a soft tissue organ, one needs to be aware of the changes that a tumour may have on that tissue. Malignant (cancerous) tumours are generally space-occupying lesions which invade into the surrounding tissue, and which could therefore potentially cause changes in the tissue stiffness.

Cancerous growths are usually hard in consistency to palpate. Figure 2.11 shows how a gynaecologist would undertake a bimanual examination for routine pelvic assessment, while feeling for any hard tumours.

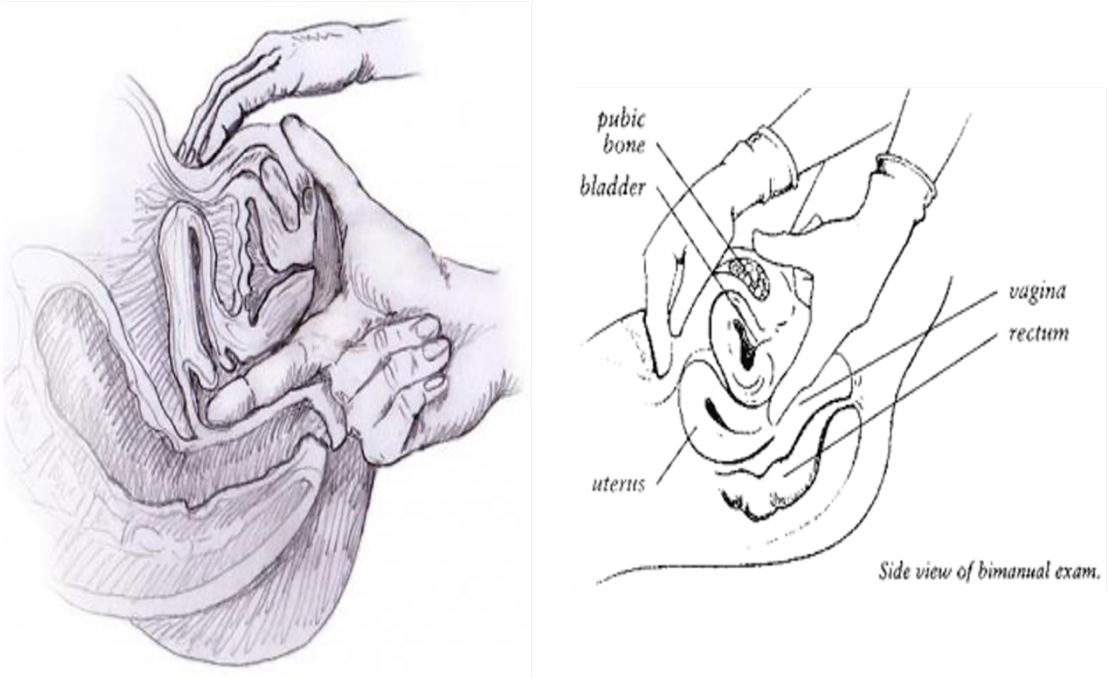


Figure 2.9 Bimanual vaginal examination using manual palpation to determine the pathology of gynaecological organs

From Miranda & Vasquez de Bracamonte (2018)

2.6.2. Tissue Stiffness Changes

2.6.2.1 Gynaecological Tumours

This research examines tissue stiffness in four types of gynaecological tumours, as discussed below:

(i) Uterine Tumour: Uterine cancer most commonly spreads from within the uterus (endometrium) outwards into the muscle and then to the surface. Histologically, this is known as the endometrioid type and is the most common type of uterine cancer. Such invasion can cause changes in the cells and alteration in tissue properties – notably stiffness. Uterine sarcomas (rare malignant tumours) arise from the smooth muscle (myometrium) and connective tissue of the uterus, are hard and hence cause alterations in the tissue stiffness. Fibroids (leiomyomas), which are the benign counterpart of leiomyosarcomas (a type of sarcoma) and quite common, also arise from the uterine

smooth muscle and despite often being buried within it, can cause changes in stiffness. Fibroids are often surgically removed, but during minimal access surgery the exact location can be difficult to determine if the tumour is buried deep within the muscle. Both uterine fibroids (unless they have undergone degeneration) and sarcomas are usually stiff to palpate, the extracellular matrix in leiomyomas increased in comparison to uterine myometrium (Norian et al., 2012; Wolanska et al., 1998). Fibroids display an increased stiffness by unconfined compression *in vitro* (Rogers et al., 2008). Other benign conditions such as adenomyosis (in which the inner lining encroaches the muscle but does not invade as in cancer) could also lead to stiffness changes and cause global enlargement of the uterus.

It is expected that areas invaded with cancer (such as tumour invasion into the myometrium) will show abnormal tissue characteristics – notably hardening. Che et al. (2019) used transvaginal sonographic elastography to distinguish endometrial cancer from benign masses and found cancerous tissue to be harder than benign.

Table 2.2 Performance of transvaginal sonographic elastography.

Derived from Che et al. (2019)

Transvaginal ultrasound elastography in endometrial cancer diagnosis	
Sensitivity	81%
Specificity	85%
Positive predictive value	83%
Negative predictive value	83.5%

Performing ultrasound or MRI elastography, a developing technique, needs specialist training that most gynaecologists do not have – thus limiting its practicality. It has however been used to generate stiffness maps in breast, liver, prostate, and musculoskeletal assessment (Mendelson et al., 2009; Ziol et al., 2005), although its adaptation, into miniaturised form, for MIS, is still in its infancy.

(ii) Cervical Tumour: The cervix is comprised of glands and stroma. Apparent lesions of the cervix are often felt as hard tumours. Clinical staging – a pre-requisite for surgical planning – is carried out by the surgeon by vaginal examination, under anaesthesia. The surgeon feels for tumour spread beyond the cervix by palpating, to assess for thickening in the cervical and parametrial tissue. Occasionally, in early-stage invasive tumours, there is no visible lesion apparent on the cervix. However, the invasive nature of cancer ought to change the cellular structure and hence alter the stiffness of the organ.

The same concept was adapted in relation to cervical elastography (Figure 2.10). Sun et al. (2012) used transvaginal elastography (TVES) to detect stiffness changes in the cervix in 110 women. The aim was to diagnose cervical cancer using the hypothesis that malignant cervical cells produced a measurable increased the stiffness of the tissue. They also estimated the infiltration region around the cervix. They compared the strain ratio between benign and malignant lesions and measured the depth of invasion into the stroma by cancer cells and correlated their findings with the final histology. They concluded that the strain ratio of malignant cells was much higher than that of benign lesions (8.19 +/- 5.66 versus 2.81 +/- 2.24, $p<0.01$), indicating that cancer cells were indeed stiffer than normal cells. They demonstrated a specificity and sensitivity for the best cut-off point as

0.788 and 0.897 respectively. Thomas (2006); Thomas et al. (2007) also used TVES to differentiate between benign and malignant cervical lesions.

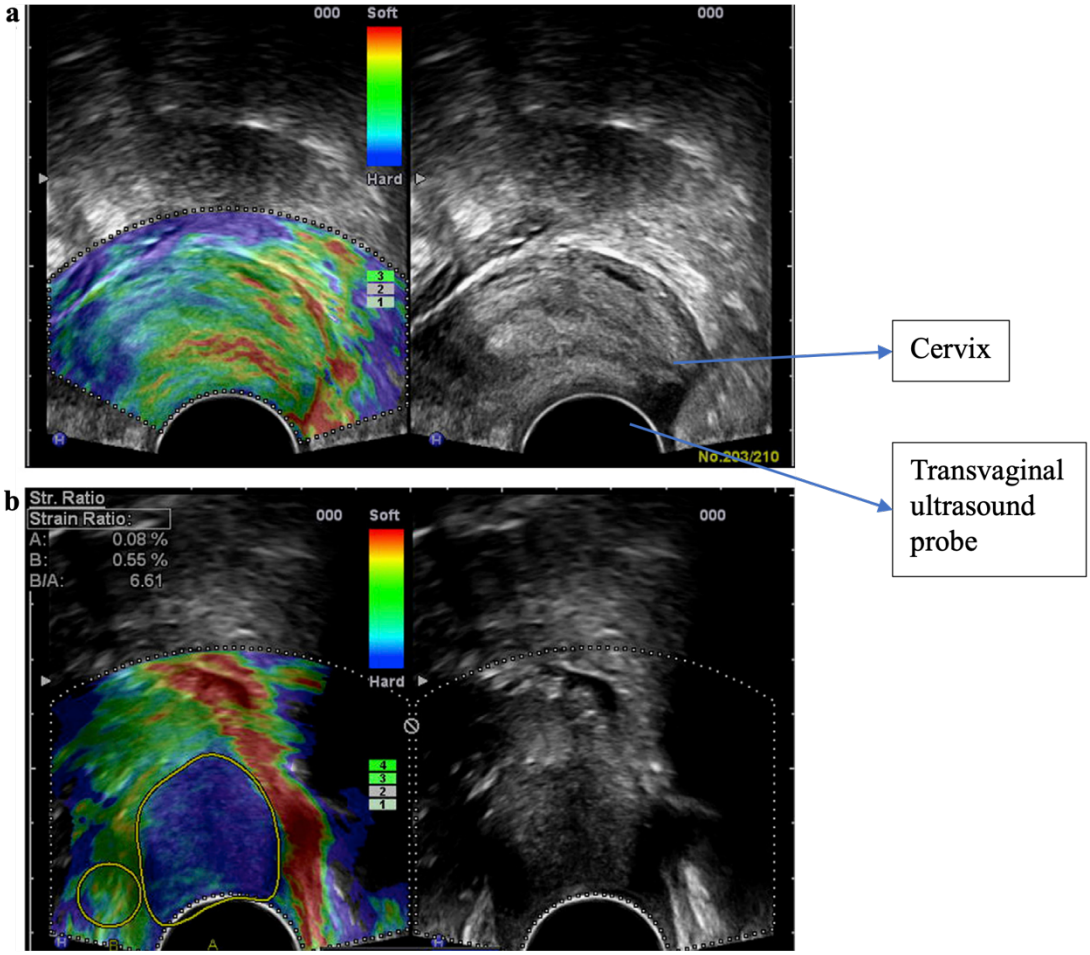


Figure 2.10 Transvaginal elastography (TVES) of cervix

Two examples of TVES of uterine cervix From Sun et al. (2012)

A: An elastogram from a 41-year-old woman who came in for a routine examination and had a normal cervix. The uterine cervix was coloured in homogeneous green with a red ribbon around the cervical capsule and the cervical canal.

B: An elastogram of a 48-year-old patient who had presented with vaginal bleeding. Dark blue was shown in the stroma of the uterine cervix. The red ribbon surrounding the capsule of the cervix was still continuous. MRI examination certificated that the invasion depth was 2.4 cm, not as far as the cervical capsule. Pathological investigations revealed it to be an invasive cervical squamous carcinoma.

(iii) Ovarian Tumour: Ovarian tumours enlarge by forming a cystic (simple), solid or cystic-solid lesion. This cyst usually has solid components when malignant. Simple cysts

with fluid are likely to be benign. Some benign ovarian tumours such as fibromas are of solid consistency while dermoid cysts may have solid elements within the cyst. **There is scarce data on using tissue stiffness as a method to locate tumours or cysts within the ovary.** However, the current utilisation of ultrasound and MRI/CT scans in the diagnosis of ovarian cancer rely to some extent on the characteristic features of the lesion which may help to determine the risk of malignancy (Dodge et al., 2012; Kaijser et al., 2013). They visualise solid (abnormal) tumours within the ovary and other complex features like thick septations within cysts, while also being able to determine abnormal blood supply to the tissue, a further factor in calculating the likelihood of cancer.

Although the consensus as regards palpation of an ovary is that cancer would increase areas of tissue stiffness, cellular stiffness assessment using atomic force microscopy (AFM) has suggested the opposite – that stiffness could be lower and that lower stiffness could potentially even be a marker for cells with a higher pre-disposition to metastasise (Xu et al., 2012). Azzalini et al. (2021) recently correlated cell stiffness and morphological architectural patterns using AFM in high grade serous ovarian cancers. They showed that some types of cancer with poorer prognosis, such as those with micropapillary pattern, had lower cell stiffness. Also, the more advanced stages of cancer were significantly softer than the earlier stages. Tissue stiffness can be hence a marker for prognosis.

(iv) Lymph Node Tumours: Pelvic and para-aortic lymph nodes are proximal glands to which the female reproductive organs connect through lymphatic channels. Cancer cells can metastasise to the lymph nodes, and in doing so, have a significant impact on treatment, type of surgical intervention required, and prognosis (Lecuru et al., 2011).

Radiological techniques are used to determine the status of lymph nodes and these include ultrasound, CT, MRI and PET scans (Choi et al., 2010). Cancer in the lymph nodes tends to alter the structure of the node and usually, but not always, increase its size – key indications sought for in radiological investigations to identify metastatic spread of cancer to the lymph nodes. Typically, lymph nodes tend to be hard, limiting palpation as a reliable indicator, given that enlargement alone can also occur following inflammation and infection which are more common. It appears therefore that to improve the detection accuracy of metastatic disease in the lymph nodes, analysing their tissue properties could be the solution – and indeed this is evident from studies in elastography.

A meta-analysis of real-time elastography on lymph nodes in different parts of the body demonstrated its usefulness in relation to the detection of cancer with an 80% disease probability following a positive measurement. Both elasticity and strain ratio were used in the interpretation, which explained that changes in tissue stiffness occurred with metastatic disease (Ying et al., 2012).

2.6.2.2 Non-Gynaecological Cancers

(i) Breast Cancer: Tourasse et al. (2012) measured stiffness in 103 sentinel axillary lymph nodes with ShearWave^{TM} elastography and found that the stiffness measurements (mean and maximal values) were significantly different between healthy and metastatic lymph nodes ($P<0.05$). They concluded that there was a correlation between the metastatic risk of lymph nodes and their increased mean stiffness in breast cancer patients. Tissue stiffness within lymph nodes has also been found to be a useful marker in the identification of metastatic disease by other researchers using elastography (Alam et al., 2008; Choi et al., 2011; Giovannini et al., 2009).

It is known that tumour derived extracellular matrices (ECM) are biochemically distinct in their composition when compared to normal ECMs, the tumour stroma being stiffer than normal stroma (~400 Pa compared with 150 Pa, respectively). Breast cancer has been shown to be up to ten times stiffer than normal breast tissue (Butcher et al., 2009; Kass et al., 2007; Levental et al., 2009)

Wellman et al. (1999) carried out experiments on breast tissue samples using punch indentation tests on specimens excised during surgery to measure tissue stiffness. They concluded that there was a significant difference in the tissue stiffness between cancerous and benign breast tissue. Infiltrating ductal carcinoma of the breast was 2.5 times stiffer than normal breast tissue.

Quantitative micro-elastography, which is an optical coherence tomography based elastography, allowed Kennedy et al. (2020) to detect any cancer within 1mm of surgical margin of the tumour resected.

(ii) Prostate cancer: Similar qualitative sonoelastographic results on prostates have shown that there is also a significant difference in stiffness between normal and cancerous prostate tissue ($p<0.01$) (Hoyt et al., 2008; Kumar et al., 2011).

These studies demonstrate that tumours seem to alter tissue stiffness and therefore that stiffness can be assessed to locate tumours. There are various methods available to measure tissue stiffness, among them ultrasound elastography and magnetic resonance elastography are the most popular. Unfortunately, these are not readily available and

cannot be used during minimal access surgery. The use of haptic technology to measure tissue stiffness and locate tumours does have the potential to be adapted for minimal access surgery.

2.7. Cancer Diagnosis in Gynaecology

Appreciating the precise nature of a disease is of vital importance, though often not apparent prior to the commencement of surgery. Gynaecologists occasionally face diagnostic challenges prior to surgery when it is difficult to differentiate benign from malignant tissue. Both CT & MRI scans have their shortcomings in the diagnosis of cancer and the identification of metastatic disease such as in the lymph nodes (Bipat et al., 2003; Dodge et al., 2012). Histology is considered the 'gold standard' in diagnosing the nature of disease, but this is not always available prior to surgery.

When using ultrasound and cross-sectional imaging, complex ovarian masses can occasionally be difficult to diagnose with any certainty as to whether they are benign, borderline or malignant tumours. Surgical treatment is different for each type, radical excision being reserved for cancerous growths. Similar difficulties arise in the surgical planning of uterine pathology such as when having to differentiate between a uterine sarcoma and a uterine fibroid, identify malignancy in uterine atypical hyperplasia or ascertain the degree of myometrial invasion of early-stage uterine tumours.

It is known that in women undergoing hysterectomy for complex atypical hyperplasia, up to 40% of uterine specimens will reveal occult cancer during final post-operative histology. Therefore, the provision of detailed information on tissue characteristics during

surgery could improve accuracy in the prediction of malignancy and prove invaluable in optimising surgical decision-making.

Furthermore, women with advanced ovarian cancer often receive neoadjuvant chemotherapy prior to any surgical intervention. Oncologists require a biopsy from the tumour to confirm the diagnosis before they can plan the appropriate treatment and proceed with chemotherapy – indeed, pelvic tumours can occasionally be a secondary from the breast or gastrointestinal tract. Interventional radiologists obtain biopsies under CT or MRI scans when ultrasound guided biopsies are not feasible. They need to locate the exact site of the tumour to mitigate the risk of generating a false negative biopsy. It is however difficult to obtain clear real-time images as pelvic structures are not static. Scans are also expensive, and the likelihood of obtaining false negative biopsies would be significantly reduced if the tumour could be more accurately located prior to biopsy.

In summary, given recent progress in haptic technology and various developments in tactile sensation, it is likely that minimally invasive surgery will see a shift toward strategies that incorporate these new technologies to improve cancer diagnosis and treatment. Haptic technology undoubtedly has the potential to enhance the surgeon's degree of perception during minimal access surgery. This research on tissue stiffness and the detection of cancer in gynaecological organs is needed to understand precisely what role haptics can play in gynaecological cancer location and diagnosis.

Chapter 3

Approach & Methodology

Chapter 3. Approach & Methodology

3.1. Ethical Approval

The National Research Ethics Service (NRES) is a part of the Health Research Authority (HRA) that provides help and leadership for National Health Service (NHS) Research Ethics Committees (RECs). Among its key roles, it reviews research proposals to protect the rights and safety of research participants and promotes research which is potentially beneficial to science and society.

This study involved the use of human tissue for experimental purposes, as well as interaction with research participants within the clinical environment. Ethical approval was therefore mandatory, and this was sought from the NRES committee for London and Dulwich (REC reference 13/LO/1658). The research proposal was further reviewed for final approval by the Research & Development (R&D) department at Guy's & St Thomas' NHS Foundation Trust (GSTT) in London (UK).

The patient information sheet and consent form, the process of recruitment and the research methodology were all scrutinised in detail by the REC before they sanctioned the study. As a part of the process, statements from specialists were obtained, that supported the research, highlighting its potential benefit to the medical profession, and corroborating the belief that it could go ahead without compromising best practise care principles for patients.

3.2. Clinical & Research Setting

3.2.1. Site of Research

This research project was carried out in collaboration with the Department of Informatics (Centre of Robotic Research; CORE) at King's College London (KCL) and the Department of Gynaecological Oncology at Guy's & St Thomas' NHS Foundation Trust (GSTT) in London. GSTT is a tertiary referral centre leading the cancer network in the Southwest London region. The Gynaecological Oncology department gets approximately 300 new cancer cases referred each year and is one of the leading cancer centres in the United Kingdom.

3.2.2. Recruitment of Research Participants

The experiments were carried out at GSTT. All patients were given detailed information sheets explaining the aims of the project and how the research would be carried out. Participation was voluntary. Written consent from all patients recruited to the study was obtained prior to their surgery date and they could withdraw from the research project at any time.

All the patients were referred to the gynaecological cancer centre and their cases were discussed in detail at the Gynaecological Oncology Multidisciplinary Team (MDT) meeting during which surgical treatments were planned. The diagnosis or suspicion of gynaecological cancer was based on different preoperative investigations including biopsies in some women, while all had had MRI or CT scans.

The patients who were recruited were having surgery for gynaecological cancers (uterine, ovarian or cervical), Some of them underwent lymph node sampling as a sole procedure.

Each participant was assigned a research trial number to maintain confidentiality such that no personal data was stored within the research data.

3.3. Manufacturing Silicone Models

Three kinds of silicon models were made in the laboratory. One was a curved silicone model with a 10mm tumour nodule embedded within it. The other was a block of silicone, with three tumour nodules of different diameter (8mm, 10mm and 15mm size) embedded within the silicone. The third was a similar silicone block but resembling a uterus shape with a single tumour nodule.

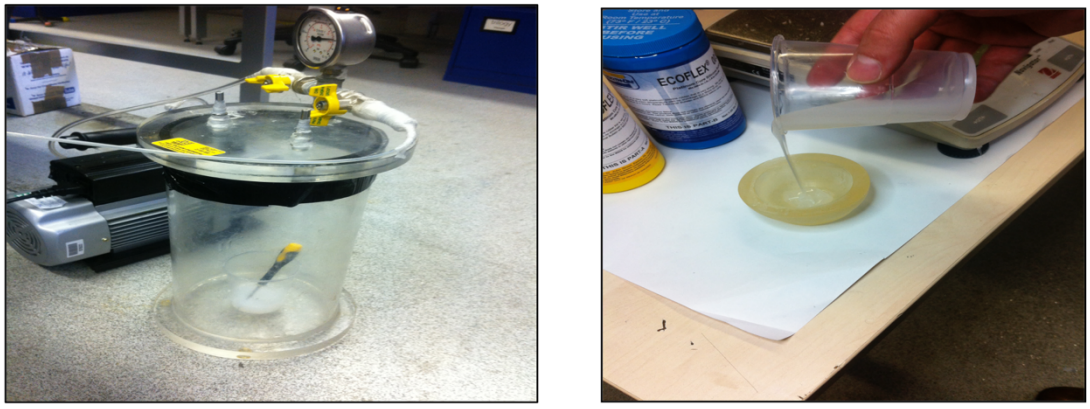
Method:

Two casts, one curved and the other a block, were first designed on the computer using the *Solid Works* programme and then printed using a 3-D printer.

Ecoflex 00-50 Platinum Cure Silicone was used to make the silicone models. Equal parts of part-A & part-B were mixed thoroughly for 3 minutes by stirring and scraping the sides and bottom of the container (Figure 3.1).

Figure 3.1 Preparation of Silicone Models - Materials Used

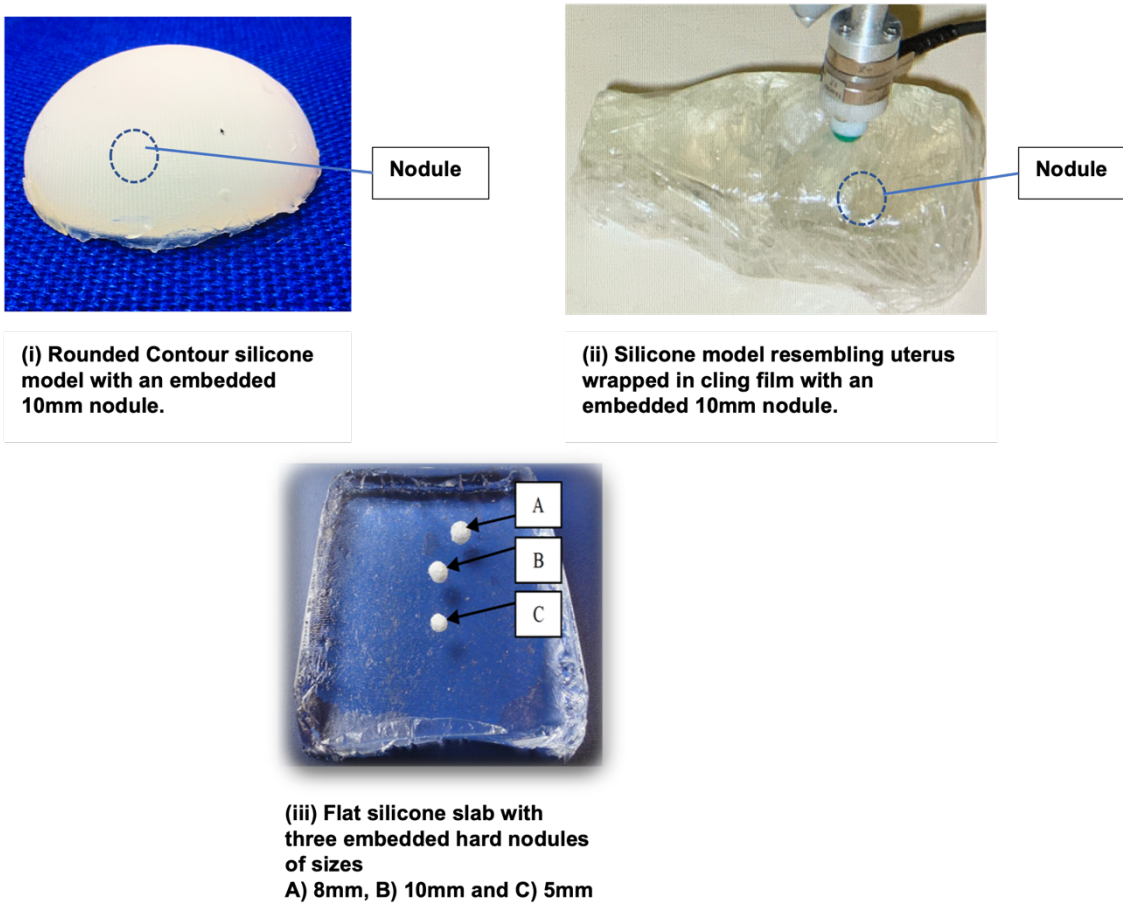
The mixture was then placed in a vacuum to remove any entrapped air (vacuum gassing) for 3 minutes (at 29 inches of mercury). The mixture was then poured uniformly into the cast avoiding any bubble entrapment. The tumour mimicking nodule was a hard pellet of 1cm diameter which was inserted into the middle of the mould being prepared Figure 3.2.



Mixture placed in vacuum

Figure 3.2 Preparation of Silicone Models - Method

This was cured at room temperature (23°C) in the cast and then baked in a preheated oven for 60 minutes at 55°C. The mould was allowed to cool down to room temperature before removing.



(i) Rounded Contour silicone model with an embedded 10mm nodule.

(ii) Silicone model resembling uterus wrapped in cling film with an embedded 10mm nodule.

(iii) Flat silicone slab with three embedded hard nodules of sizes
A) 8mm, B) 10mm and C) 5mm

Figure 3.3 Silicone samples with embedded nodules mimicking tumours used for tests

3.4. Experiments on Silicone models

Before proceeding with human specimen testing, the haptic probe was initially validated by carrying out tests on three silicon blocks with the embedded nodules.

3.4.1. Types of Silicone Models

Three different shaped silicone models were used - considering the human organs to be tested next would be of different contour. The silicone models included a flat rectangular slab measuring 120mm (length) x 80mm (width) x 40mm (depth) with three embedded nodules of different sizes The second silicone models was semi curved to resemble the contour of an ovary and the third one had the shape of the uterus (Figure 3.3)

3.4.2. Haptic Device

The prototype device used for conducting experiments was developed using the Phantom Omni, which is capable of three-dimensional motion tracking. A Nano-17 (ATI, Industrial Automation) force sensor with a circular 0.5cm diameter indenter was fixed to its tip (Fig 3.4).

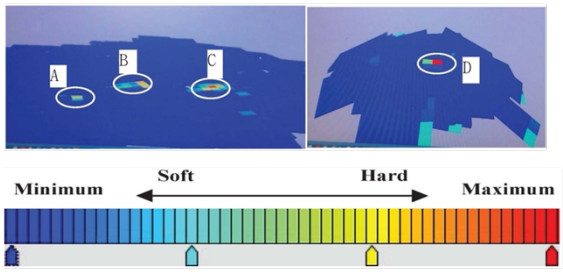
This enabled the capture of real-time positional data of the probe along with force data. A data acquisition card in the computer received data from the haptic device, while the computer software (developed using a C++ program) converted tissue stiffness data into a stiffness map that was generated live on the computer screen (Figure 3.4).

Figure 3.4 Experimental setup for the haptic test

(i) Schematic diagram of apparatus

(ii) Indentation haptic device made of Phantom Omni with nano-17 force sensor and indenter at the tip.

Uniaxial indentation technique was used with the probe to capture data. The visual display shown in giving real time display of tissue stiffness described by Li et al. (2016) was adapted by changing the display to red facets or dots (Figure 3.5). The RGB system focused on the capabilities of visual haptic stiffness feedback - consisting of position and tactile sensing modules with live representation of the tissue stiffness on the screen using RGB colour coded square planar facets or circular dots. Red facets or dots would represent high stiffness while green represented low and blue represented moderate stiffness (Figure 3.6).



Blue	Cyan	Yellow	Red
R:0	R: 0	R: 255	R: 255
G:0	G: 255	G: 255	G: 0
B:255	B: 255	B: 0	B: 0

Figure 3.5 Real time visual display of tissue stiffness on silicone tissue

From Li et al. (2016)

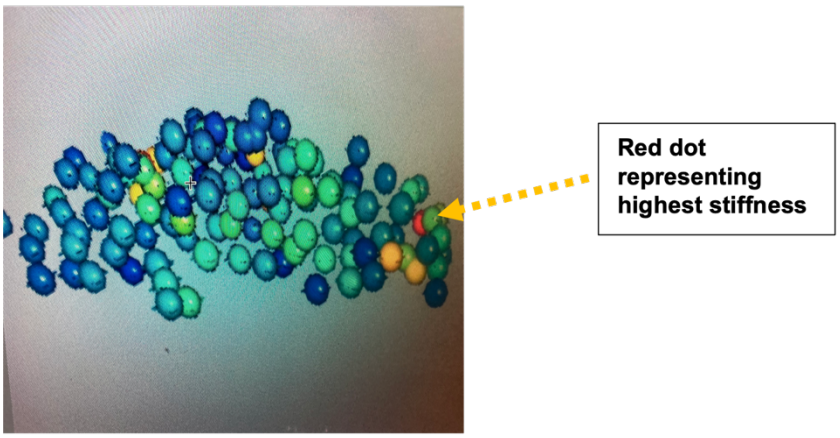


Figure 3.6 Stiffness mapped on computer screen using RGB colour coded dots

The tip of haptic probe had a hemi-spherical sensor tip with the nano-17 force sensor attached. The force sensor was secured to the Phantom Omni device, and this allowed the analysis of the position of the haptic probe in *X, Y & Z* axis (Figure 3.4).

3.4.3. Indenting Technique

The test was carried out manually. When testing, the haptic probe was first placed without indenting on the surface of the sample. This position was recorded by the software. The probe was then pressed to the deepest point, and its new position (*X2, Y2 and Z2* axis) and the force exerted (*F)*2 were recorded.

When the deepest indented point was reached, the coloured square planar facet or dot would persist on the screen at the contact point with its representation of the stiffness in colour. At each indentation point, the probe recorded two positional readings - one at the surface and the other where the probe came to rest – so as to determine the exact indentation depth. The position and orientation of the probe was obtained by the Phantom Omni stylus tip and care was taken to be perpendicular to the surface whilst indenting. This action was repeated at multiple sites, 2 cm apart, in a systematic manner spanning the whole surface from the left to the right side.

All three samples were tested this way and the stiffest area recorded on a pictorial diagram of the silicone sample. A copy of a blank pictorial diagram was kept for recording results from manual palpation by a surgeon.

A surgeon was asked to locate the site of the stiff nodule(s) in the silicone samples by manually palpating the surface of the silicone sample kept stable on a flat surface. The findings of the site of location were recorded in the pictorial diagram.

Figure 3.7 illustrates the method of the haptic test used and the record of the location of nodule on the pictorial diagram.

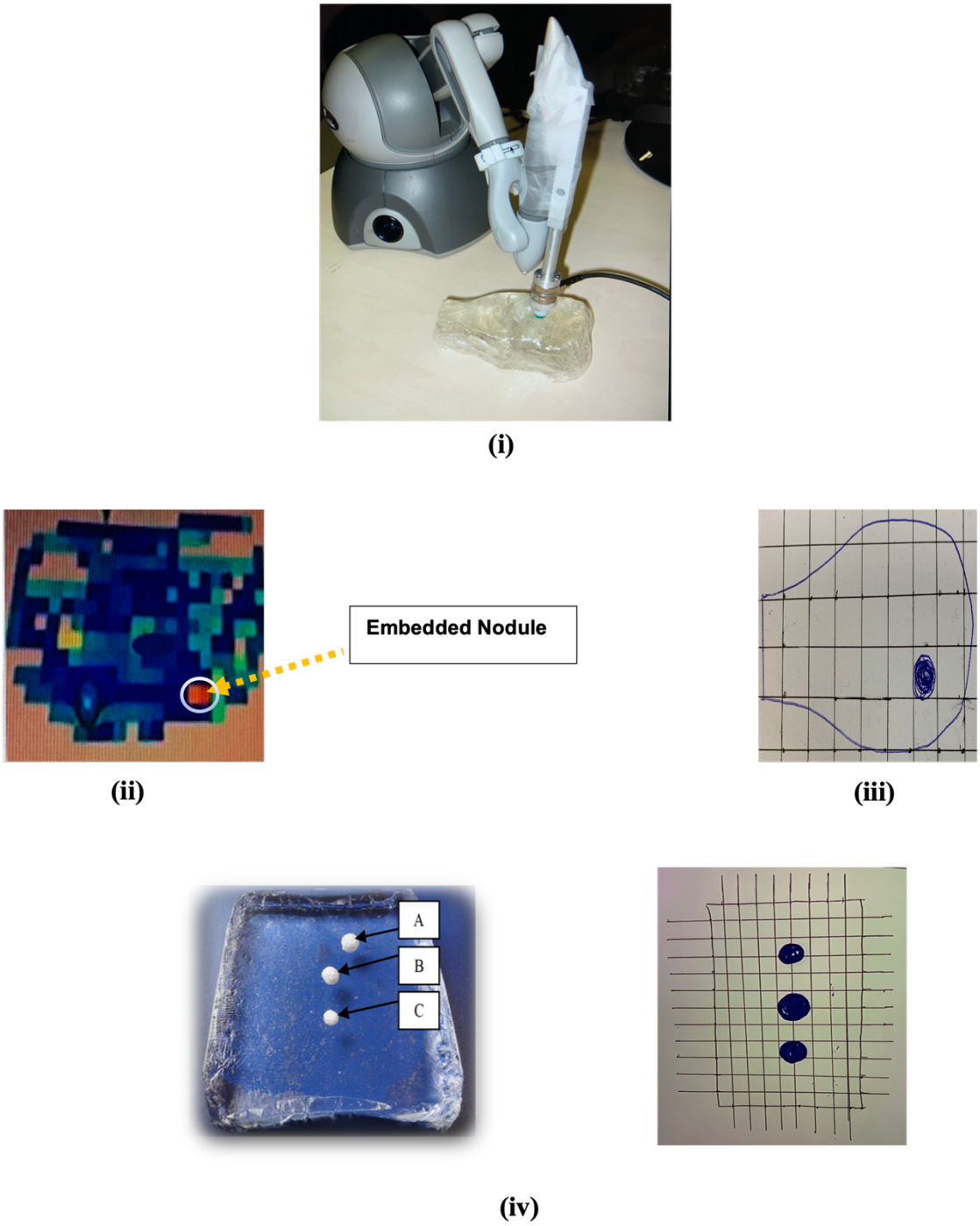


Figure 3.7 Test on silicone model with embedded nodule(s)

(i) Haptic probe and silicone model resembling uterus

(ii) Tissue stiffness identified on screen with RGB colour coded square planar facet

(iii) Pictorial diagram of uterine model

(iv) Silicone slab & pictorial diagram mapping test result

3.5. Tests on Human Samples

3.5.1. Gynaecological Specimen Retrieval & Preparation

The routine surgery for uterine, ovarian, and cervical cancer involves the removal of the uterus with fallopian tubes and cervix (total hysterectomy), removal of both ovaries and lymph nodes in the pelvis and para-aortic areas.

Fresh specimens were retrieved immediately following surgery in the operating theatre. Tests were conducted in the theatre, where the atmosphere was temperature controlled. The specimens were transported to the histopathology laboratory within 30 minutes of retrieval, immediately after performing tests involving haptic probes and manual palpation.

Whilst carrying out tests on the specimens, the tissue was kept moist using normal saline and the organ was wrapped in cling film to maintain its integrity. The specimen was oriented and then fixed to a pin board by inserting pins at the borders of the cling film, thereby attaching it to the board. Care was taken to ensure that neither tissue nor organ were damaged whilst securing them (Figure 3.8).

Pictorial diagram resembling the shape of the organ was sketched and three copies made for recording the data, one each for manual palpation, the second for the haptic probe test and the third for histopathology.

3.5.2. Manual Palpation

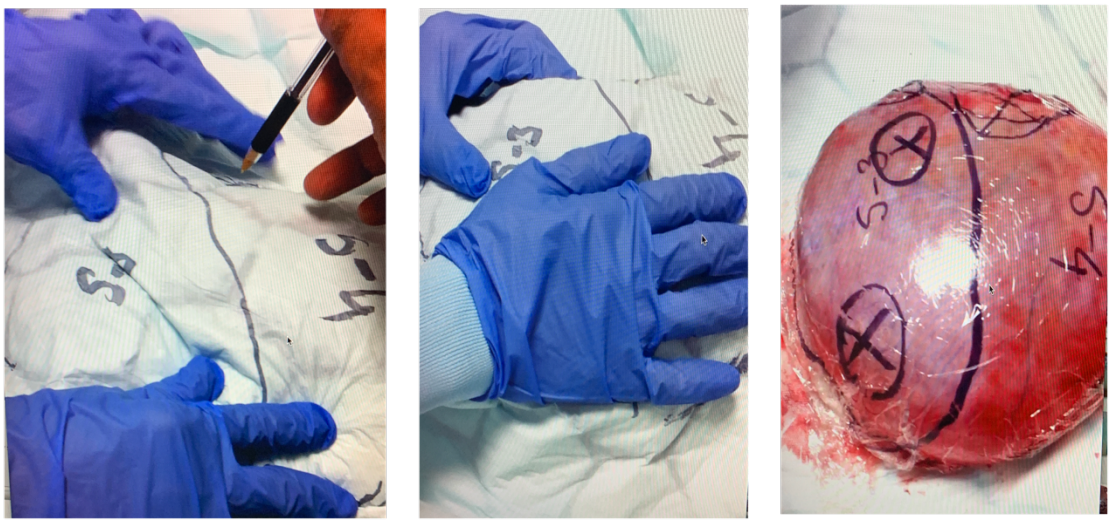


Figure 3.8 Surgeon palpating an ovarian cyst and recording stiff areas

Manual palpation was performed by an experienced surgeon *ex-vivo*. The specimen was palpated once it was prepared and oriented and areas of stiffness were recorded on the pictorial diagram.

To decrease observer bias, the specimen was covered by a thin sterile sheet and the surgeon asked to mark the stiff areas and location of the tumour(s). The observations were transcribed onto the pictorial diagram.

3.5.3. Haptic Test

The same haptic probe and technique used to study silicone models was used for gynaecological organs (see Section 3.4)

The readings were again obtained in a predetermined pattern, starting from the left-hand corner and moving towards the right in horizontal rows. Each point of assessment was 2 cm apart. The entire surface of the organ was probed in this way.

The red coloured square planar facets or circular dots generated on the screen were recorded on the pictorial diagram for each organ, thereby recording the location of the stiffest areas of the organ (Figure 3.9). The areas were marked with a suture and/or ink to correlate with the histopathologists (Figure 3.10).

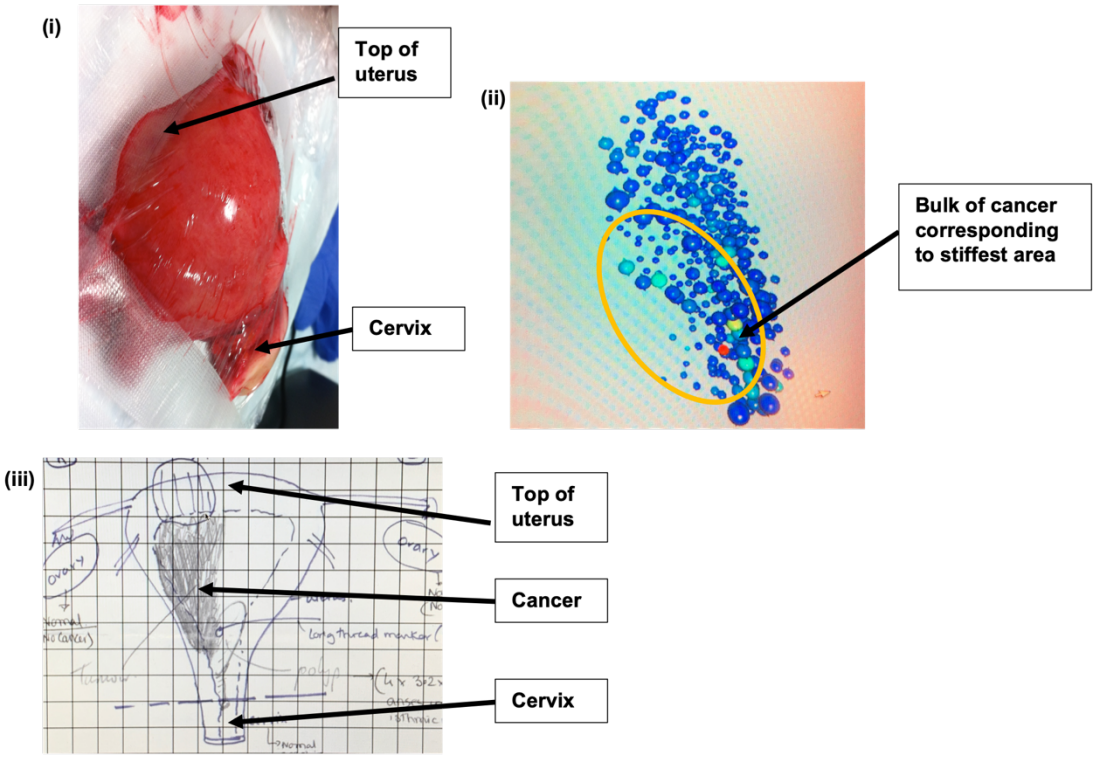


Figure 3.9 Determining tissue stiffness in a uterine specimen

(i) Uterus received after surgery and prepared for testing

(ii) Location of stiff area by the haptic test

(iii) Recording tissue stiffness on pictorial diagram.

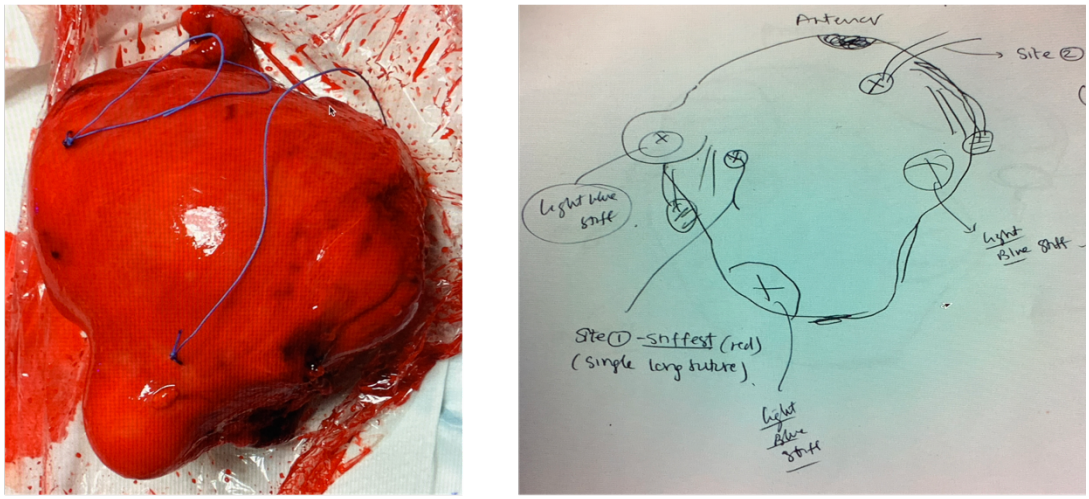


Figure 3.10 Location of uterine tumour recorded on specimen to aid orientation by the histopathologist when recording the data on pictorial diagram.

3.6. Histopathological Examination

Histological testing provides the gold standard for cancer diagnosis. Tissue is analysed by cutting specimens, fixing and staining them on slides, whereupon they can be studied under the microscope by histopathologist. In this way, abnormalities such as cancer can be identified, and definitive diagnoses made.

For this study, the histopathology was performed by experts in the diagnostics of gynaecological cancers. Each specimen was correctly oriented, cut, and gross appearance and all abnormalities recorded. The tissue was stained with haematoxylin and eosin and studied under the microscope by the histopathologist. When required, an immunohistochemistry study was carried out on the specimen to confirm the primary diagnosis and origin of cancer. The diagnosis and the exact location of cancer in the organ was recorded on the copy of the pictorial diagram provided to the histopathologist and the site of tumour was mapped out.

Chapter 4

Results & Analysis

Chapter 4. Results and Analysis

There were two data sets collected:

1. The manually derived data via palpation and histology, from the drawings.
2. The electronic data from the haptics probe.

The first data set was used to determine the location of cancer, addressing research question RQ1. The second data set was used to determine the likelihood of cancer based on tissue stiffness measures obtained by haptic sensing, addressing research question RQ2.

This chapter presents the results and analysis of these data sets in relation to the research questions. Section 4.1 analyses Cancer Location and Section 4.2 analyses Cancer Detection.

Section -I explains how data was compared on tumour location from pictorial diagrams

Section-II gives details on statistical analysis and results of tumour location in silicone and human organs

Section-III further analyses the data for cancer diagnosis

Section - I

4.1. Analysis of data on cancer location

The dataset was generated from the drawing of the organs generated from (i) haptic probing, (ii) manual palpation by a surgeon and (iii) cancer identification by a histopathologist as detailed in Chapter 3.

To compare the haptic and palpation tests, a grid was placed on each of the drawings and for each square of approximately 2 cm by 2 cm, it was noted whether a tumour was identified by these tests, histopathology providing the gold standard as comparison. This is shown in Figure 4.1, Figure 4.2, Figure 4.3, and Figure 4.4 for tests performed on cervix, ovary, uterus and lymph nodes respectively.

The red coloured numbers are the locations where a possible tumour was identified. Using this, true positives, false positives, true negatives, and false negatives for each test can be assessed against histology. For example, in the case of the cervix, palpation identified a tumour at locations 5 and 6 (Figure 4.1) As histology did not corroborate this, it was deemed a false positive. The other locations of the palpation test were true negatives. When testing by haptic probe, a false positive is found in location 6. Again, the other locations are true negatives. This manual process is repeated for every sample.

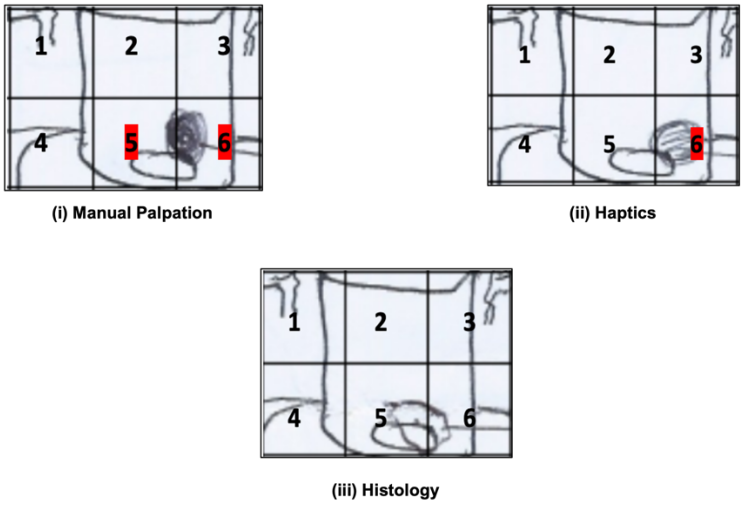


Figure 4.1 Comparing performance of haptic probe and manual palpation methods in detecting cancer location in the cervix – as compared to histology – the 'gold standard'.

Figure 4.2 shows an analysis of test results from an ovary. The cancer is in locations 16, 17 and 18 (histology). Manual palpation identified locations 16 and 17 but failed to identify 18. However, the haptic probe in this test identified all three areas.

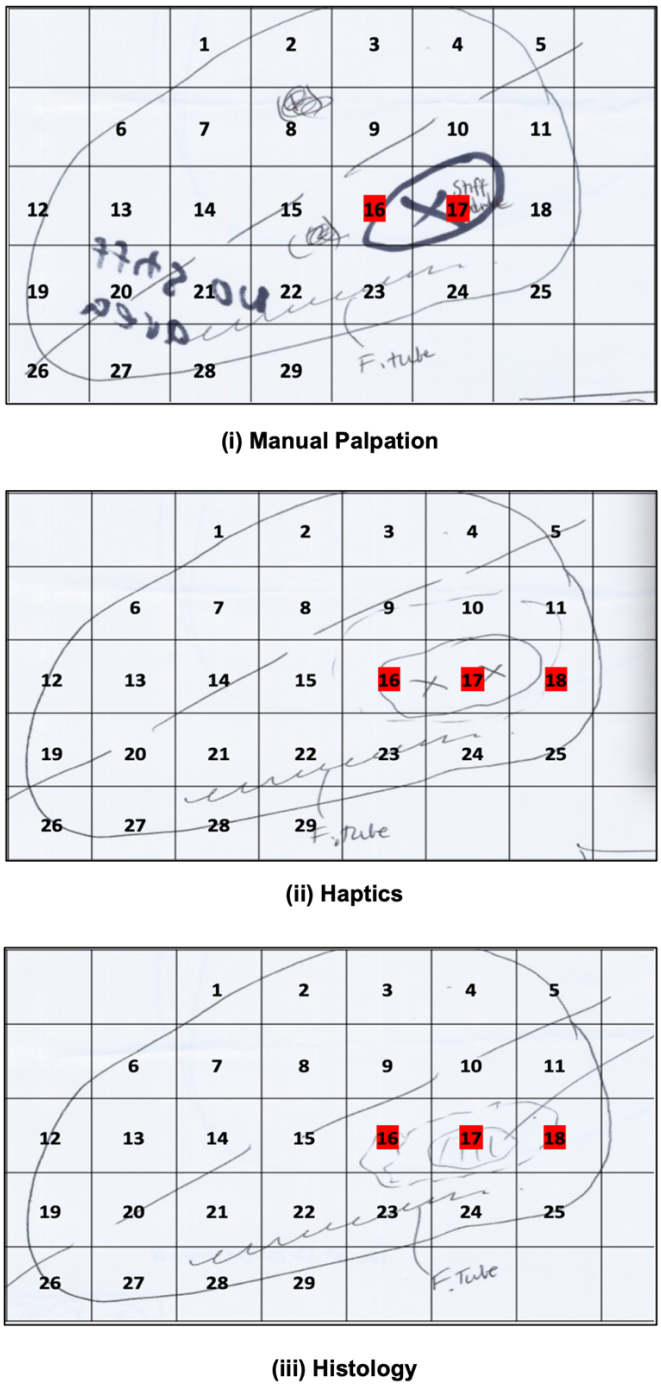


Figure 4.2 Comparing performance of haptic probe and manual palpation methods in detecting cancer location in the ovary – as compared to histology – the 'gold standard'.

Figure 4.3 shows a test performed on a uterus with cancer. The areas shaded red indicate the site where cancer was detected. The manual palpation identified four areas (squares 9, 10, 16 & 17) while haptics identified six areas correctly (10, 15, 16, 21 & 26).

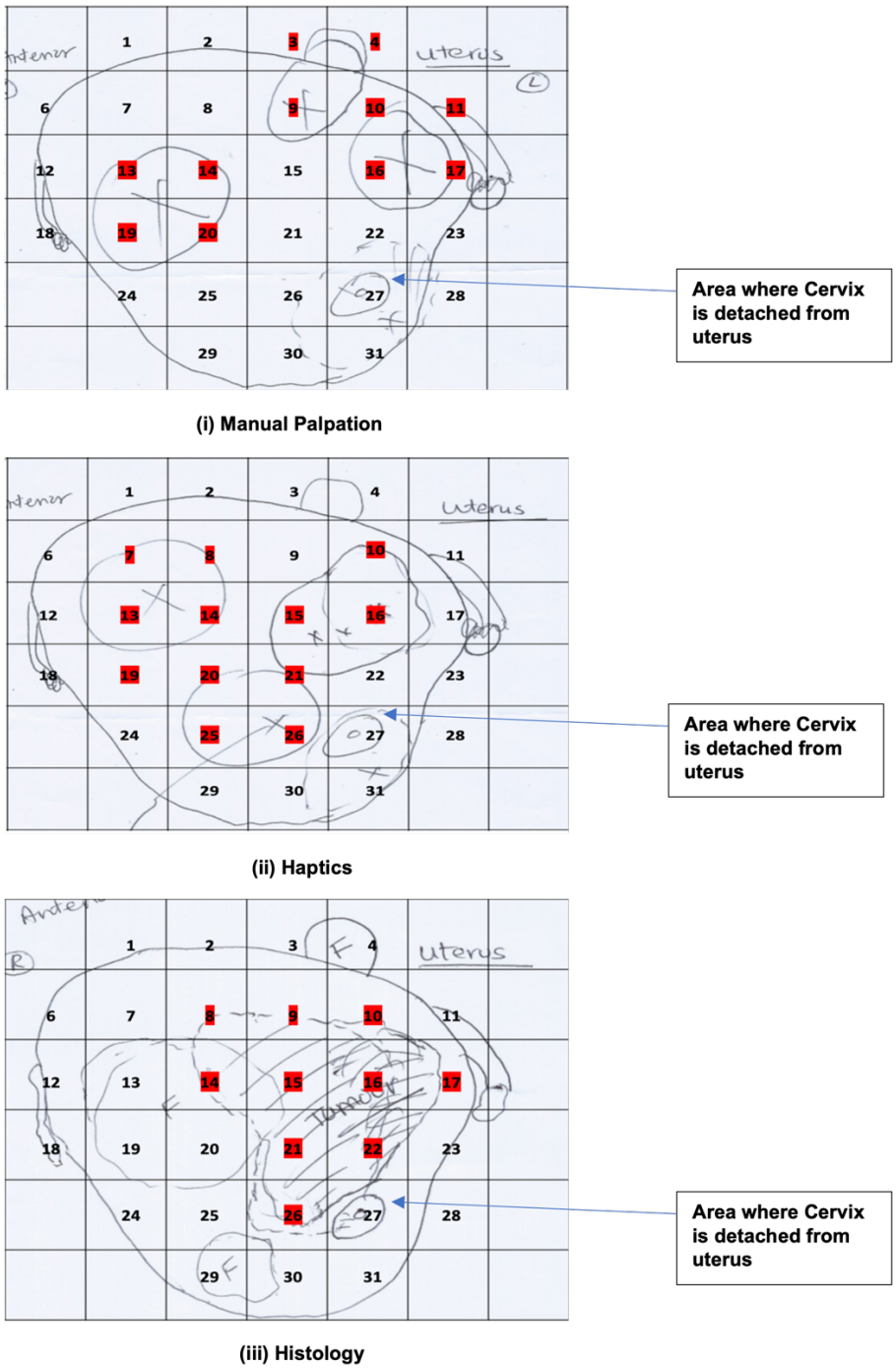


Figure 4.3 Comparing performance of haptic probe and manual palpation methods in detecting cancer location in the uterus – as compared to histology – the 'gold standard'.

Figure 4.4 shows the record of data from a bundle of lymph nodes (four). In this case manual palpation did not identify any areas which had cancer while haptic testing identified one area in the nodal tissue (No 3).

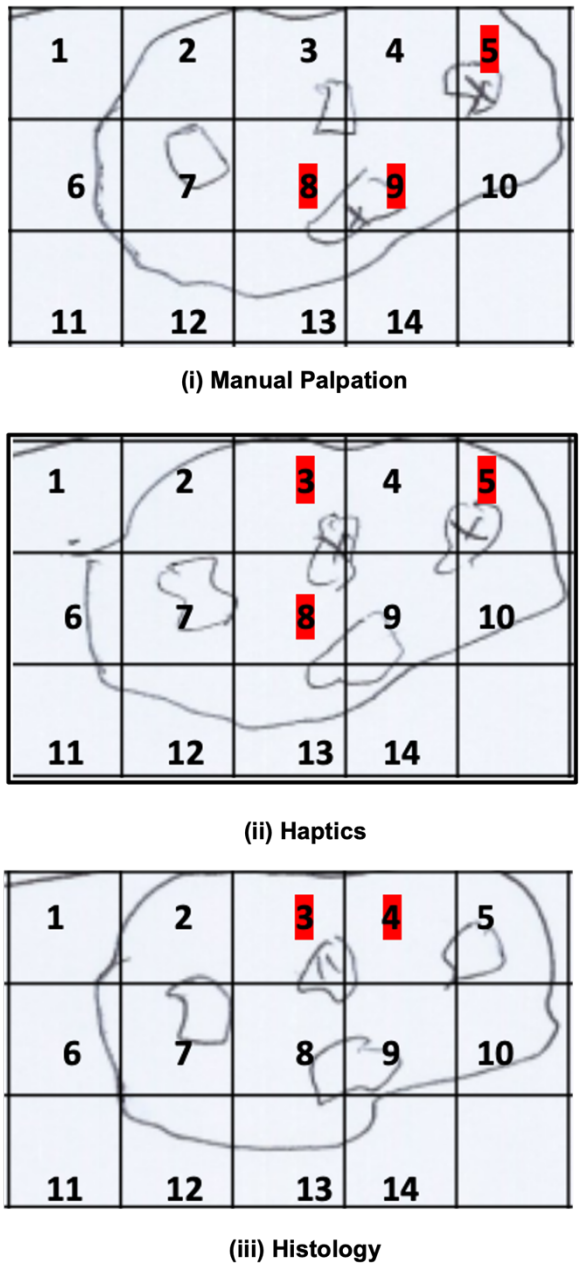


Figure 4.4 Comparing performance of haptic probe and manual palpation methods in detecting cancer location in the lymph nodes – as compared to histology – the 'gold standard'.

Section-II

4.2. Statistical Analysis

Analysis of this data involved comparing the haptic probe prediction to palpation results as well as to histopathology results. For each organ, the accuracy of the predictions are presented in a confusion matrix (Table 4.1), showing the number of correctly predicted positive values ("true positives" or "TP", i.e., cases in which the haptic probe predicted cancer, which was then corroborated by the histopathology) and correctly predicted negative values ("true negatives" or "TN", i.e., cases in which the haptic probe predicted no cancer, which was then corroborated by the histopathology and the), compared to the number of incorrectly predicted positive values ("false positives" or "FP", i.e., cases in which the haptic probe (incorrectly) predicted cancer, which was then not corroborated by the histopathology) and incorrectly predicted negative values ("false negatives" or "FN", i.e., cases in which the haptic probe (incorrectly) predicted no cancer, but histopathology suggested there was.

Table 4.1 Confusion matrix ('actual' is determined by histological results)

	Test Predicted: Tumour Present	**Test Predicted: No Tumour**
Actual: Tumour Present	True Positive	False Negative
Actual: No Tumour	False Positive	True Negative

Several standard metrics derived from the confusion matrix are also included as derived from Parikh et al. (2008):

- *sensitivity,* which measures the proportion of true positives that are correctly identified, computed as:

  $= TP/(TP + FN)$

- *specificity,* which measures the proportion of true negatives that are correctly identified, computed as:

  $= TN/(TN + FP)$

- *accuracy,* which measures the overall rate of correctly identified samples, computed as:

  $= (TP + TN)/(TP + TN + FP + FN)$

- *positive predictive value (ppv)*, which measures the percentage of patients with positive test results who have the disease, computed as:

  $= TP/(TP + FP)$

- *negative predictive value (npv)*, which measures the percentage of patients with negative test results who do not have the disease, computed as:

  $= TN/(TN + FN)$

- *f-measure*, also called "F1" score, which computes a weighted average of *precision* and *recall*, where 1.0 is the maximum (best) value and 0.0 is the minimum (worst) value, computed as:

  $= 2 \times (RECALL \times PRECISION))/(RECALL + PRECISION)$

  $= (2 \times TP)/((2 \times TP) + FP + FN)$

  where *precision* is a measure of accuracy, computed as $TP/(TP + FP)$ and *recall* is a measure of completeness, computed as $TP/(TP + FN)$.

4.3. Performance of Tests on Silicone Models

In all three silicone models, the exact location of the nodule(s) was correctly identified using both the haptic probe and manual palpation. The site of the nodule(s) corresponded to the red planar square facets or dots on the screen and were recorded on pictorial diagrams (Figure 3.7). The accuracy with haptic detection was 100%. There were no false negatives or false positives, suggesting high sensitivity and specificity.

4.4. Performance of Tests on Gynaecological Organs

Twenty-nine women undergoing gynaecological cancer surgery were recruited for research. Of these, specimens from four women could not be tested. This was because they either had surgery that was different from what had been anticipated, or the removal of the specimen rendered it unsuitable for analysis. Tests reported here were therefore conducted on fresh gynaecological specimens obtained from 25 women. Details of the specimens tested are shown in Table 4.2. Each square on the grid represented a test sample.

Table 4.2 Details of gynaecological organs tested, and the number of tests performed

Gynaecological organ	Number of organs	Number of test samples
Cervix	16	167
Lymph Nodes (LN)	13	47
Ovaries	14	375
Uterus	17	544

4.4.1. Cancer Location: Cervix

There were 16 cervixes examined. 167 points on these were assessed for tissue stiffness and data was collected. Taking tissue stiffness as the marker, the overall accuracy of haptic probe to locate cancer was 77%. This was lower than the manual palpation (88%).

Table 4.3 Statistical Analysis - Cervix

Cervix		Haptics		
		Cancer	**No Cancer**	**Total**
Histology	**Cancer**	1	3	4
	No Cancer	36	127	163
		37	**130**	**167**

Accuracy	0.77	F-1 Score	0.05
Sensitivity	0.250	(95% CI; 0.00 - 0.67)	
Specificity	0.779	(95% CI; 0.72 - 0.84)	
PPV	0.027	(95% CI; 0.00 - 0.08)	
NPV	0.977	(95% CI; 0.951 - 1.00)	

Cervix		Palpation		
		Cancer	**No Cancer**	**Total**
Histology	**Cancer**	1	3	4
	No Cancer	17	167	163
		18	**149**	**167**

Accuracy	0.88	F-1 Score	0.09
Sensitivity	0.25	(95% CI; 0.00 - 0.67)	
Specificity	0.90	(95% CI; 0.85 - 0.94)	
PPV	0.06	(95% CI; 0.00 - 0.16)	
NPV	0.98	(95% CI; 0.96 - 1.00)	

4.4.2. Cancer Location: Lymph Nodes

There were 13 lymph nodes examined. 47 different points were assessed for tissue stiffness and data was collected. Taking tissue stiffness as the marker, the overall accuracy of haptic probe to locate cancer was 75%. This was lower than the manual palpation (87%).

Table 4.4 Statistical Analysis – Lymph nodes

Lymph nodes		Haptics		
		Cancer	**No Cancer**	**Total**
Histology	**Cancer**	2	0	2
	No Cancer	12	33	45
		14	**33**	**47**

Accuracy	0.75	F-1 Score	0.25
Sensitivity	1.00	(95% CI; 1.00 – 1.00)	
Specificity	0.73	(95% CI; 0.60 – 0.86)	
PPV	0.14	(95% CI; 0.00 – 0.33)	
NPV	1.00	(95% CI; 1.00 – 1.00)	

Lymph nodes		Palpation		
		Cancer	**No Cancer**	**Total**
Histology	**Cancer**	2	0	2
	No Cancer	6	39	45
		8	**39**	**47**

Accuracy	0.87	F-1 Score	0.40
Sensitivity	1.00	(95% CI; 1.00 – 1.00)	
Specificity	0.87	(95% CI; 0.77 – 0.97)	
PPV	0.25	(95% CI; 0.00 - 0.55)	
NPV	1.00	(95% CI; 1.00 - 1.00)	

4.4.3. Cancer Location: Ovary

There were 14 ovaries examined. 375 points on these were assessed and tissue stiffness data was collected. Taking tissue stiffness as the marker, the overall accuracy of Haptic probe to locate cancer was 82%. This was higher than the manual palpation (72%).

The positive predictive value (PPV) was significantly higher with haptic probe when compared to manual palpation. (74% versus 95%). This implied that there was higher likelihood of the tumour being cancer in the stiff area located by the probe.

The negative predictive values were similar with both haptic feedback and manual palpation. Haptic probe had a high specificity, similar to palpation, implying that there was high probability that it could truly identify area(s) in the ovary which do not have cancer (true negatives).

Table 4.5 Statistical Analysis – Ovary

Ovary		Haptics		
		Cancer	**No Cancer**	**Total**
Histology	**Cancer**	48	50	98
	No Cancer	17	260	277
		65	**310**	**375**

Accuracy	0.821	F-1 Score	0.589
Sensitivity	0.490	(95% CI; 0.39 - 0.59)	
Specificity	0.939	(95% CI; 0.91 – 0.97)	
PPV	0.738	(95% CI; 0.63 – 0.85)	
NPV	0.839	(95% CI; 0.90 – 0.88)	

Ovary		Palpation		
		Cancer	**No Cancer**	**Total**
Histology	**Cancer**	33	65	98
	No Cancer	19	258	277
		52	**323**	**375**

Accuracy	0.78	F-1 Score	0.44
Sensitivity	0.34	(95% CI; 0.24 – 0.43)	
Specificity	0.93	(95% CI; 0.90 – 0.96)	
PPV	0.63	(95% CI; 0.50 – 0.77)	
NPV	0.80	(95% CI; 0.76 – 0.84)	

4.4.4. Cancer Location: Uterus

There were 17 uteruses examined. 544 sampling points were assessed, and data was collected. Taking tissue stiffness as the marker, the overall accuracy of haptic probe to locate cancer was 76%. This was higher than the manual palpation (70%). The haptic probe had a high negative predictive value (NPV) and specificity indicating that areas with lower tissue stiffness were highly likely be benign.

Compared to the cervix and lymph node group, the uterine and ovarian groups had higher number of sites analysed which actually had cancer as indicated by histology.

Table 4.6 Statistical Analysis - Uterus

Uterus		Haptics		
		Cancer	**No Cancer**	**Total**
Histology	**Cancer**	42	37	79
	No Cancer	95	370	465
		137	**407**	**544**

Accuracy	0.76	F-1 Score	0.39
Sensitivity	0.53	(95% CI; 0.42 – 0.64)	
Specificity	0.80	(95% CI; 0.76 – 0.83)	
PPV	0.31	(95% CI; 0.23 – 0.38)	
NPV	0.91	(95% CI; 0.88 – 0.94)	

Uterus		Palpation		
		Cancer	**No Cancer**	**Total**
Histology	**Cancer**	35	44	79
	No Cancer	122	343	465
		35	**14**	**544**

Accuracy	0.70	F-1 Score	0.61
Sensitivity	0.44	(95% CI; 0.33 – 0.55)	
Specificity	0.74	(95% CI; 0.70 – 0.78)	
PPV	0.63	(95% CI; 0.16 – 0.29)	
NPV	0.80	(95% CI; 0.85 – 0.92)	

Section-III

4.5. Cancer Diagnosis by Quantifying Tissue Stiffness Distribution

To study the hypothesis that the overall stiffness of the cancerous organ would be different, the distribution of tissue stiffness was analysed across the whole organ mapped by the haptic probe rather than at a selected point.

We classified the data using the gold standard histopathology results in to the “cancer” and “non-cancer” tissue. We further analysed the tissue stiffness and tested the distribution for normality using the Shapiro-Wilk test (Shapiro & Wilk, 1965)

We then analysed the differences between the two distributions for each organ, to determine if there is a statistically significant difference between the “cancer” sample values and “not cancer” sample values for tissue stiffness. If the distribution was determined to be normally distributed by the Shapiro-Wilk test, then a standard Student’s *t*-test of independent samples was used to compute statistical significance. If the distribution was determined to be not normally distributed, i.e., non-parametric, then the Kruskal-Wallis H-test of independent samples was used to compute statistical significance (Kruskal & Wallis, 1952). In all cases, a *p* value of 0.01 was used to determine if the test passed, indicating 99% confidence level of statistical significance.

Table 4.7 Electronic data gathered by haptic probe

Gynaecological organ	Number of organs	Number of readings
Cervix	17	2101
Lymph Nodes (LN)	16	1312
Ovaries	16	3390
Uterus	17	3963

4.5.1. Tissue Stiffness (TS)

Test for Normality. Firstly, we checked the distribution of the data, which was aggregated across all patients for each organ. We ran the Shapiro-Wilk test for normality (Shapiro & Wilk, 1965). The results are shown in the table below:

Table 4.8 First Statistical Analysis for Tissue Stiffness

	W	*p*	N	Median TS	Distribution
Cervix					
Not Cancer	0.59	0.0000	1620	0.2428	NORMAL
Cancer	0.27	0.0000	481	0.1674	NON-PARAMETRIC
Lymph Nodes (LN)					
Not Cancer	0.25	0.0000	1259	0.1687	NON-PARAMETRIC
Cancer	0.24	0.0000	53	0.2987	NON-PARAMETRIC
Ovary					
Not Cancer	0.44	0.0000	574	0.1351	NON-PARAMETRIC
Cancer	0.18	0.0000	2816	0.0612	NON-PARAMETRIC
Uterus					
Not Cancer	0.05	0.0000	1289	0.1973	NON-PARAMETRIC
Cancer	0.05	0.0000	2674	0.1602	NON-PARAMETRIC

Statistical Test of Sample Differences. Secondly, because the tissue stiffness data was not normally distributed, we ran the Kruskal-Wallis H-test for independent samples to test the null hypothesis that the population median of each sample is equal (Kruskal & Wallis, 1952).

The results, for each organ, are listed in the table 4.9. A p-value <0.05 is considered significant. The results show statistically significant differences in TS values between the “Cancer” and “Not Cancer” classes, for all organ except lymph nodes, with a 99% confidence or 0.01 level of significance.

Table 4.9 Second Statistical Analysis for Tissue Stiffness (TS)

	H	*p*	Result
Cervix	43.44	0.000000	SIGNIFICANT
Lymph Nodes (LN)	1.63	0.201734	NOT SIGNIFICANT
Ovary	25.36	0.000000	SIGNIFICANT
Uterus	44.38	0.000000	SIGNIFICANT

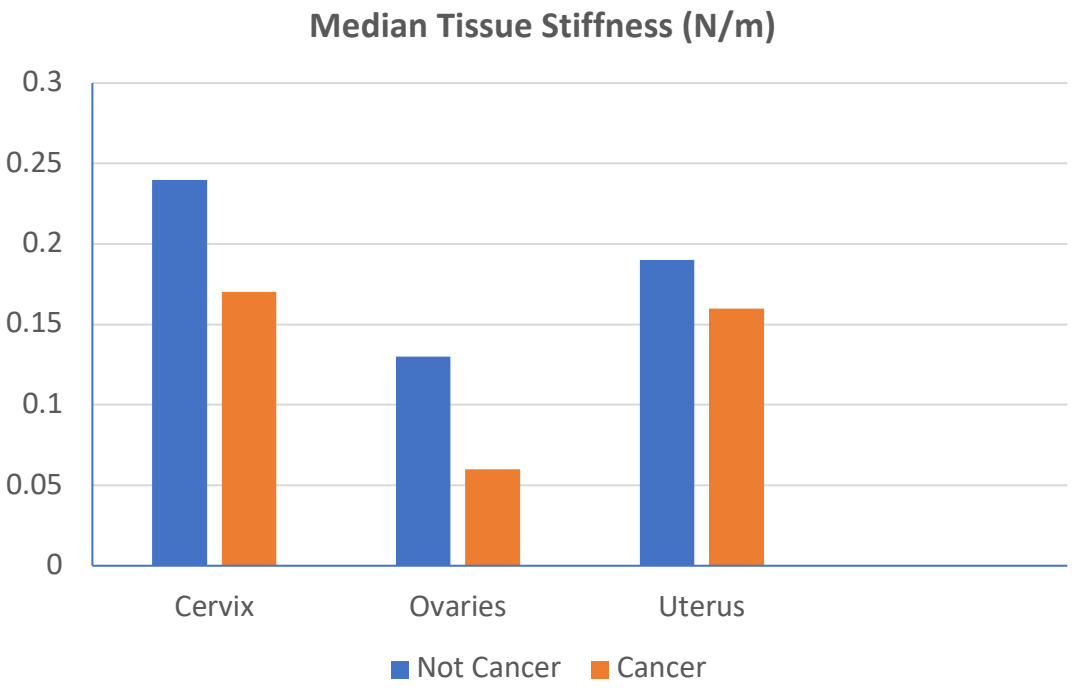


Figure 4.5 Tissue Stiffness

Median values are shown because the data is not normally distributed.

To quantify the tissue stiffness in the groups where there was significant difference i.e. cervix, ovary and uterus, we compared the median tissue stiffness between the "Cancer" and "Not Cancer" groups (Figure 4.5).

Median values were chosen because the data was not normally distributed.

We found that in cervix, ovary and the uterus, the median tissue stiffness of the whole organ in the “Cancer” specimen was lower than the “Not Cancer” specimen.

Chapter 5

Discussion

Chapter 5. Discussion

Using our technique on fresh human specimens, we have shown that by measuring the force and the indentation depth with the probe, we are able to quantify tissue stiffness (TS) in human gynaecological organs using haptics. We can identify the areas of maximal and minimal stiffness in real time, which has practical applications for gynaecologists performing surgery.

Our findings demonstrate that the haptic probe can locate the cancer in the ovary and the uterus with high accuracy, by measuring the TS. It even outperforms manual palpation by an experienced surgeon.

In both these organs, its overall accuracy for detecting the site of cancer is significantly higher than by manual palpation (82% vs 78% in ovary and 76% vs 70% in uterus). Also noteworthy is that it has a higher positive predictive value than does manual palpation for locating the tumour site in ovarian cancer. As a result, surgeons will potentially be better equipped to correctly predict where the cancer is in the organ, which is especially useful when a biopsy is required to make a definitive diagnosis or determine the correct management plan.

Currently, there are not many modalities for intraoperative characterisation of ovarian tumours in gynaecological oncology (Grewal et al., 2021). Yang et al. (1998) assessed laparoscopic ultrasound (LUS) to characterise ovarian tumours into cancer or benign. They had an accuracy of 83.8% which is similar to our haptic probe. Ultrasound is expensive and needs special training while the haptic technology we propose is easy to

use. We have used this in the real clinical setting in the operating room to allow its translation to clinical practise. It has potential to be used both in open abdominal surgery, given that it outperforms manual palpation, and also in minimal access surgery, which otherwise provides only very marginal tactile sensation for tumour site identification.

Yang et al. (1998) reported the performance of preoperative transvaginal ultrasound in ovarian mass characterisation and they had an accuracy of 73.5%, which is lower than the accuracy of our haptic probe.

Our study to locate cancer using tissue stiffness in uterus, cervix, ovary and lymph nodes is novel. This concept has never been studied on cancer tissue using haptic feedback on tissue stiffness in gynaecology. Doria et al. (2021) is the only group who assessed stiffness in gynaecological tissue using tissue feedback, but they studied benign uterine fibroids in two human uteri. Both cancer and benign tumours have different properties and tests results of benign tissue cannot be extrapolated for assumptions on cancer tissue.

Our technique used the indentation method to assess tissue stiffness. We appreciate that our technique involved manual indentation, but the probe was positioned perpendicular to the surface at each point and the subsequent displacement was accurately recorded using the Phantom Omni. Another option would be to mount the probe on a teleoperated system, similar to the method used by Doria et al. (2021). However, the tests we conducted were in the operating theatre - mimicking true clinical setting. This avoids any potential tissue degradation which may occur during transfer of specimen elsewhere for testing.

The indentation technique we followed allowed us to map areas systematically on the human organs which vary in shape and size. Although more laborious than the rolling method described by Li et al. (2017), with this technique we controlled the areas to trace and map on pictorial diagrams to allow comparison with histology.

One of the intra-operative assessments that is currently widely used to diagnose cancer and indeed to tailor on-going surgery is known as “frozen section” (Naik et al., 2006). It is performed by a histopathologist who takes a small biopsy from the most abnormal looking part of the organ. The tissue is frozen, sliced and then stained on a slide for viewing under a microscope. The histopathologist can then provide the surgeon with an immediate preliminary diagnosis of cancer or benign pathology. This is commonly performed during surgery for ovarian and uterine cancers in which diagnosis is in doubt. Depending on results, the surgeon can then elect to proceed with surgery as planned, revise the nature of the surgical intervention, or terminate the procedure. A Cochrane review of the intra-operative frozen section analysis for the diagnosis of early ovarian cancer in suspicious pelvic masses showed that the average sensitivity was 90% (95% CI 87.6% - 92.0%; range 64% to 100%) (Ratnavelu et al., 2016). In cases where there was discordance between frozen and paraffin sections, most studies attributed this to tissue sampling error (where the sampled portions of the mass failed to give the paraffin section diagnosis). The haptic technique described in this thesis, which has now been tested successfully on fresh specimens, has the potential to decrease this sampling error in ovarian and uterine cancer by allowing haptic directed biopsy of the areas with the highest tissue stiffness for the purpose of frozen section.

We reported that the detection of cancer in lymph nodes and cervix was more successful when manual palpation was used. However, in both the cervical cancer and lymph node groups, the sample size for cancer were small, and potentially not representative of haptic probe performance more generally. In the lymph node group, out of a total of 47 sampling sites, only 2 had actual cancer on histology. In the cervix only 1/167 sampled sites had cancer. Both metastatic disease in lymph nodes and cervical cancer are rare and the sample size was small. Hence, we cannot draw valid conclusions in these two groups.

Our results on cancer diagnosis demonstrate that, contrary to our original hypothesis, quantification of the whole organ tissue stiffness measurements is not a reliable means to determine cancer diagnosis. Even though the comparative samples ("cancer" versus "not cancer") for each organ show statistically significant differences in the median tissue stiffness values for cervix, ovary and uterus, the fact that the tissue stiffness measures are lower for the "cancer" sample (versus the "not cancer" sample) is incongruous. The possible explanation for this would be that cancer cells, unlike benign cells, multiply exponentially. It is not uncommon for the cancerous tissue to therefore become partially necrotic. This is owing to the devascularisation of the tissue when the organ is unable to cope with the increased demand for blood supply. Atomic force microscopy studies on ovarian cancer show that when the cancer is advanced, then the softness is more (Azzalini et al., 2021; Vinckier & Semenza, 1998). Hence when we are quantifying the whole organ stiffness, the areas of necrosis which are soft, will decrease the total stiffness of an organ. This does not mean that the whole cancerous growth is soft but there will still be stiff areas some parts of the tumour that we can reliably detect with the haptic probe.

Chapter 6

Conclusion

Chapter 6. Conclusion

This research has evaluated the performance of haptic tissue stiffness assessment in gynaecological organs. It has validated accurate detection of gynaecological cancer in uterus and ovaries using the indentation technique with a haptic probe calculating the tissue stiffness.

6.1. Contributions

1) This thesis has provided a novel contribution to research by testing haptic technology as a means of detecting the location of cancer in gynaecological human organs.

This is the first study on locating gynaecological cancer in fresh human specimens using tissue stiffness as a guide. It has demonstrated that the location of cancer can be determined with accuracy in the uterus and the ovary.

2) This research has shown the feasibility of measuring real time tissue stiffness in female human reproductive organs using haptics in clinical setting.

It tests a simple basic method of capturing and quantifying tissue stiffness in female reproductive organs which surgeons can then use for real time mapping. It demonstrates the feasibility of measuring real time stiffness in gynaecological organs in the operating room.

3) We have evaluated the role of quantifying the overall distribution of stiffness in gynaecological organs to diagnose cancer.

It has shown that quantifying the overall tissue stiffness of the whole organ calculated by the indentation method does not represent an accurate way to diagnose gynaecological cancer.

6.2. Directions for Future Work

We established that haptic assessment of tissue stiffness accurately detects the location of cancer in the uterus and ovary. There is scope to further develop our prototype sensing probe into a medical device which will be used in surgery to locate cancer in the uterus and ovary. Measuring tissue stiffness, it could be used in both open and minimally invasive gynaecological surgery.

Although the haptic probe in our experiment was operated manually, there is scope in future research to develop current platforms such as the d*a Vinci* and other surgical robots to incorporate tissue stiffness data acquisition at the time of robotic surgery. Indeed, the focus of the current INSTINCT project, for example, is to develop ways in which new devices could enhance current surgical cancer treatments.

More research is required for using tissue stiffness as a marker for cancer diagnosis. Techniques like elastography could might show more promising results.

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APPENDICES

Appendix A1 – Patient Consent Form

Guy's and St Thomas' NHS
NHS Foundation Trust

Guy's Hospital
St Thomas Street
London SE1 9RT
Tel: 020 7188 7188

R&D Study Number:
Ethics Committee approval number:
Patient Identification Number for this trial:

CONSENT FORM

Title of Project: EXAMINING THE ACCURACY AND EFFICACY OF LOCATING GYNAECOLOGICAL TUMOURS BY MEASURING TISSUE STIFFNESS USING A HAPTIC INDENTATION PROBE

Name of Researchers: G. Mehra, G. Lane, F. Lawton, R. Nath, H. Liu, L. Seneviratne, K. Althoefer, P. Dasgupta

Please initial box

1. I confirm that I have read and understand the information sheet (version 1:) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from this research team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Signature	Date
_____	_____	_____
Name of Person taking consent (if different from researcher)	Signature	Date
_____	_____	_____
Researcher		

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix A2 – Patient Information Sheet

LOCATING GYNAECOLOGICAL TUMOURS USING HAPTIC INDENTATION DEVICE

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. This information sheet and consent form contains important information to help you decide if you want to take part in this study.

Thank you for reading this.

If you agree to take part please retain this information sheet for future reference

What are we testing?

We are working with the biomedical engineers at Kings College London (KCL) to develop a probe that can detect the site of abnormality or tumour in Gynaecological organ(s) or tissue such as the uterus (womb), cervix, ovary and lymph nodes. This probe called the "haptic probe", when touches the surface of the tissue, it provides information on the stiffness of the tissue. Knowledge of this might help identification of abnormal areas in the tissue or organ. This is a project that we hope in the future will lead to development of a useful medical tool for surgeons to use during surgery to identify diseased areas in the organ.

We would anticipate that this tool can bring benefits to patient care. The use of this probe could help differentiate cancer from benign lesions, determine the extent of invasion by tumour and identify the exact site of a localised tumour in an organ. All this vital information is difficult for the surgeon to obtain during surgery and such detail can aid the surgeon to decide the extent of surgery he needs to carry out.

At this stage in the probes development, this project aims to demonstrate that the probe is at least able to detect normal from abnormal tissue in Gynaecological samples removed during surgery.

The surgical procedure will proceed as planned before surgery by the your surgical team. Once the specimen is removed from the body, we will examine the surface of the specimen by touching it at several points with the haptic probe. The tip of the haptic probe can measure the force when it touches the surface of the specimen and readings obtained are then analysed by a computer to measure the tissue stiffness. The whole process should take no more than 20 minutes in all.

The tissue sample will then be dispatched to the hospital histopathology laboratory in the usual fashion.

The tissue removed will be examined by a specialist pathologist in the usual way. We will obtain a copy of the final results to correlate with the findings of the probe.

Giving us permission to test the probe on your donated tissue will not impact in any way on the length of time the report takes to return or on the quality of the tissue the pathologists have to examine.

Your choice

We are inviting patients who are scheduled for Gynaecological surgery involving removal of their uterus (womb), cervix (neck of the womb), ovaries or lymph nodes to participate in this research. It is up to you to decide whether or not you allow us to use the tissue sample for research. We would also like to access your clinical / hospital records or obtain information about your disease in the future from other sources like your GP or NHS Cancer Registry. If you decide that we may do this, then you will be given this information sheet to keep and you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. We will then destroy any data gained so it cannot be used. We will also delete any information we have about you from the research database. A decision to withdraw at any time will not affect the standard of care you receive.

What happens to me if I take part?

Participation in this research has no effect on your current or future treatment or lifestyle. You will only be asked to permit the Gynaecological tissue (uterus, cervix, ovary or lymph nodes) removed at your routine surgery to be examined by the haptic probe prior to being dispatched on to the laboratory.

What are the possible benefits and purpose of the study?

This research is long term and you may not receive any personal benefit from it, although we hope that it will assist in the further development of the haptic probe for possible surgical use in the future. This research study is being undertaken for educational purposes and it will form part of higher research degree for the research student.

Confidentiality

All information we collect about you during our research is strictly confidential. Researchers who may wish to use your probe data will only ever receive anonymous data about you. In other words it is impossible for them to be able to identify you personally. Only a very few biomedical engineering staff along with associated Clinical staff directly involved with your treatment will have access to your details and medical records. It is also possible that Kings College London (KCL) and Guys and St Thomas NHS Foundation Trust (GSTFT) in their role as overseer of this research will ask to inspect records belonging to the patient and those of the biomedical engineering staff. As the information collected on you is anonymous, there is no mechanism of providing personal feedback on the results of any research.

How researchers can use your tissue?

Researchers will use the data obtained by the haptic probe on the tissue sample to compare with that found by the histopathologists at their detailed examination. The data will hopefully demonstrate that the haptic probe is very accurate in detecting the location of abnormality in the organs or tissue tested. Further testing will go on to

develop the haptic probe, based on these findings. At no stage will these researchers be able to identify you nor will their results be linked back to you.

What happens to the results of research?

When anything of importance is found during development of this haptic probe, it will be published in a well-recognised scientific journal and presented to colleagues at conferences where appropriate to do so.

Organisation and Funding of Research

The probe project is funded and organised by the Mechanical Engineering Department at Kings College London, in collaboration with the Department of Gynaecological Oncology (Womens Services) at St Thomas' Hospital and the Department of Urology at Guy's Hospital. The management and conduct of the study will be overseen jointly by the R&D departments of both Kings College and Guys & St Thomas NHS Trust.

What if there is a problem?

If you still have any questions after reading this information sheet and consent form, please ask the study doctor or one of his research study staff. If you have a study related injury or if you would like extra information, you can contact: the Patient Advisory Liaison office via the hospital switchboard. Alternatively, the office is available on Floor 2 at the footbridge entrance to the hospital if you wish to speak to someone in person.

Please contact our research team if anything is not clear or if you would like any further

-Mr G. Lane (Principal Investigator)
Consultant Gynaecological Oncologist
-Mr G. Mehra (Research Student)
Senior Academic Fellow in GynaeOncology
-Mr F.Lawton (Research Team Member)
Consultant Gynaecological Oncologist
-Mr R. Nath (Research Team Member)
Consultant Gynaecological Oncologist

Contact Details:
12th Floor, North Wing, St Thomas' Hospital
Gynaecological Oncology Unit
Department of Obstetrics & Gynaecology
Womens Services, London SE1 7EH
Ph: 02071882703

Professor P. Dasgupta (Chief Investigator)
Consultant Urological Surgeon
Guy's Hospital; Great Maze Pond
London SE1 9RT.
Tel: +44(0)20 7188 6796
Fax: +44(0)20 7188 6787

Ms. J. Watkins
Clinical Trials Nurse;
Department of Renal & Urology
Telephone 0207 188 0549

Whether or not you consent to allow us to use your tissues, thank you for taking the time to read this information sheet.

Appendix A3 – General Practitioner Letter

To

.....

..... **Date:**

Ref: Name of patient: ..... DOB: .....

Dear Doctor,

This is to inform you that ..... has enrolled in the following research project being conducted at Guy's & St Thomas' Hospital and King' College London:

"LOCATING GYNAECOLOGICAL TUMOURS USING HAPTIC INDENTATION DEVICE"

Her participation in this research will not alter her clinical care in any way.

Yours Sincerely

.....

Research Team

Department of Gynaecological Oncology

12th Floor, North Wing, St Thomas' Hospital

London, SW1 7EH

Ph: 02071882695

Appendix A4 - Health Research Authority Ethical Approval

08 January 2014

Professor Prokar Dasgupta
Professor of robotic surgery and urological innovation King's College London
The Urological Centre
Floor 1, Southwark Wing
Guy's Hospital
London SE1 9RT

Dear Professor Dasgupta

Study title:

REC reference: IRAS project ID:

EXAMINING THE ACCURACY AND EFFICACY OF LOCATING GYNAECOLOGICAL TUMOURS BY MEASURING TISSUE STIFFNESS USING A HAPTIC INDENTATION PROBE

13/LO/1658 131255

Thank you for your letter of 22 December 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Stephanie Hill, nrescommittee.london-dulwich@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

A Research Ethics Committee established by the Health Research Authority

NRES Committee London - Dulwich

Health Research Authority Skipton House 80 London Road London SE1 6LH

Telephone: 020 7972 2582

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential

participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter	Letter from Mehra	04 October 2013
GP/Consultant Information Sheets	2	15 December 2013
Investigator CV		
Other: Student CV (G Mehra)		22 October 2013
Other: Supervisor Cv (Prof Althoefer)		04 October 2013
Participant Consent Form	2	15 December 2013
Participant Information Sheet	2	15 December 2013
Protocol		04 October 2013
REC application		14 October 2013
Referees or other scientific critique report		12 October 2013
Response to Request for Further Information		22 December 2013

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

A Research Ethics Committee established by the Health Research Authority

13/LO/1658 Please quote this number on all correspondence

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project. Yours sincerely

Dr Michael Philpot Chair

Email:nrescommittee.london-dulwich@nhs.net *Enclosures:* "After ethical review – guidance for

researchers" *[SL-AR2]*
Copy to: Ms Karen Ignatian, Guy's & St Thomas' Foundation Trust

A Research Ethics Committee established by the Health Research Authority