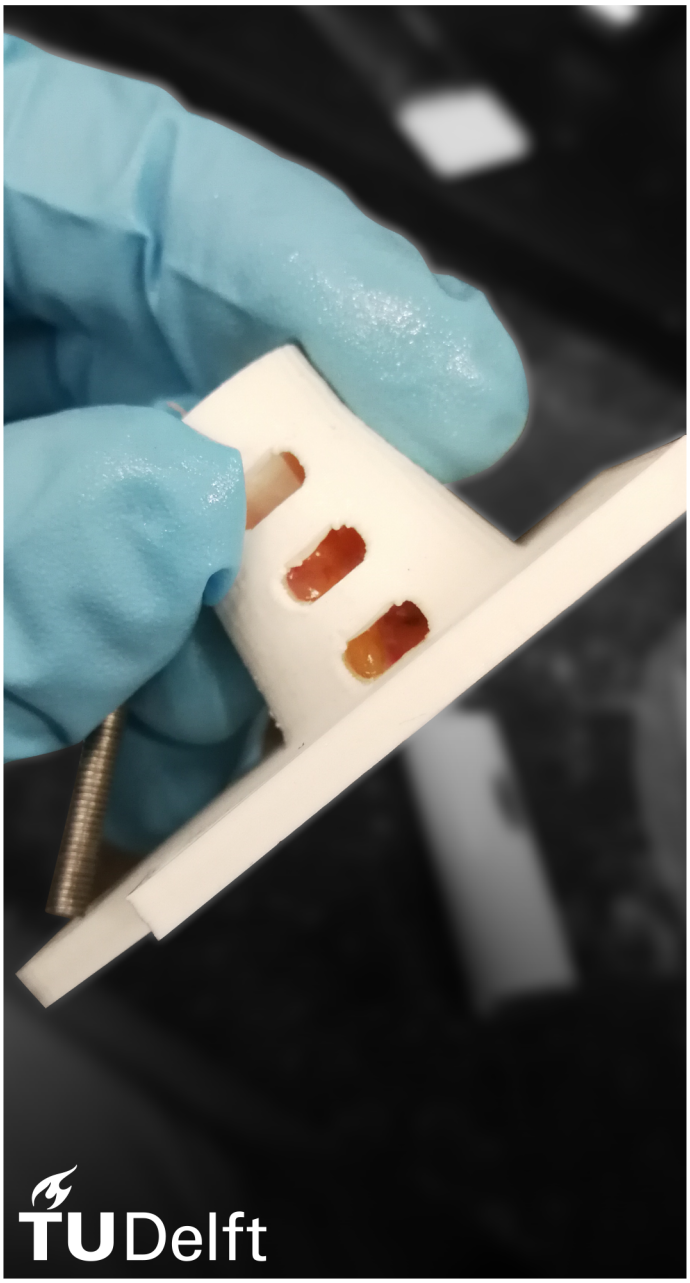
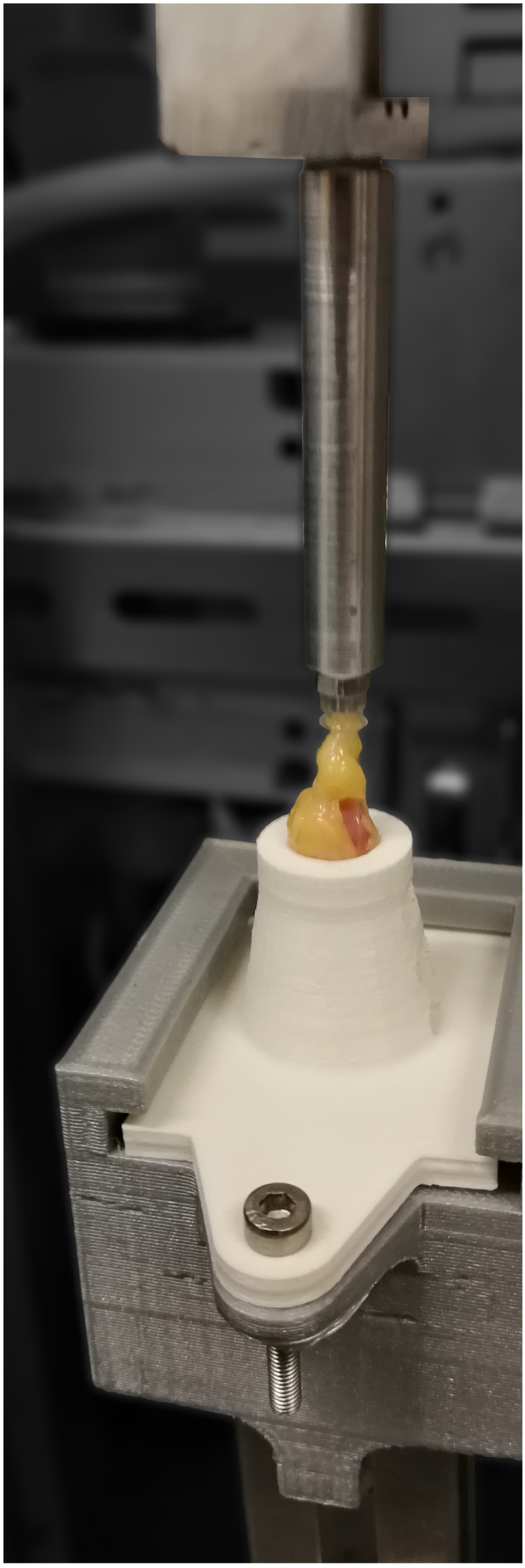
# MINIMALLY INVASIVE SENTINEL LYMPH NODE BIOPSY

|M.Sc thesis by M. I. Joosen | 21-01-2021 |





TU Delft

# Minimally Invasive Sentinel Lymph Node Biopsy

## Finding a less invasive alternative to an existing procedure

by

M.I. Joosen

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at the Delft University of Technology,
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# Abstract

Sentinel lymph node biopsy (SLNB) is a procedure that is used to determine the stage of disease of melanoma patients and determine further treatment. However, the morbidities accompanied with this procedure are not negligible (e.g., wound infection, lymphoedema and seroma). With the goal reduce the incidence of morbidities, this thesis investigated the possibility of minimally invasive sentinel lymph node biopsy (MISLNB).

Preceding this thesis, a literature study was written by the writer of this thesis to examine whether there was already a possible solution for this problem. This literature study showed that there are no off the shelf available solutions for MISLNB. Therefore, three solution with the reduction of comorbidities and the importance of en bloc excision at their core were proposed. These solutions were found through literature, patents, and some ingenuity. The solution with the highest probability was selected to develop further. This concept was then subjected to different experiments to determine whether it was viable option for MISLNB. This study also aimed to fill some of the missing data on the material behaviour of lymph nodes (LN), specifically stress-strain behaviour under compression.

By using a set of requirements one solution was selected to be the most viable given the available information. This solution was called the Pull-and-Harvest method. This concept uses a vacuum to grip the sentinel lymph node (SLN) and stash it in a tube, hereafter a snare would cut the lymph ducts and blood vessels. This concept scored well mainly due to the low risk of damaging SLN and its simplicity. The next step was to determine whether this concept was a feasible solution to MISLNB. The problem was divided into three subproblems to estimate this feasibility. The first being the force required to separate the SLN from its surrounding tissue. Since no data on this subject was available a simplified model was created to estimate this value based on the stretch of lymph ducts. The second part of this problem was, determining the force required to stash the SLN inside the tubular volume. Finally, the maximal force of two silicon suction cups was determined. From these experiments several conclusions could be drawn: the conical silicon suction cups used in this study are very inefficient ((10%) efficiency) for gripping LNs, these suction cups will stash the LNs but probably not with the additional estimated adherence force and the risk of damaging the LN using a vacuum seems to be low. Based on these observations during these experiments possible ways of were suggested and could make the Pull-and-Harvest a viable procedure. Lastly stress-strain behaviour of LNs could be described using an exponential relationship.

This thesis outlines the problem of MISLNB and highlights the areas of interest for further research. However, there is more research and development needed to find a definitive solution for MISLNB.

# Contents

# 1 Introduction

In 2019, 700 Dutch citizens were diagnosed with melanoma, a malignant form of skin cancer that originates in pigment producing cells known as melanocytes[1]. The life expectancy of this form of cancer is determined by disease stage: ten-year overall survival rates range from 98% (stage I, melanoma confined to the skin) to 32% (stage IV, metastasized melanoma). These overall survival rates have been improved since the introduction of effective systemic treatment [2].

A very important step prior to treatment is thorough and accurate diagnosis. The first step to determine disease stage, after diagnostic excision of the skin lesion, is performing sentinel lymph node biopsy (SLNB). SLNB is a procedure to detect early signs of the cancer spreading. However, SLNB procedure is accompanied with not negligible morbidity and there is reason to think that this procedure could benefit greatly from a minimally invasive solution.

Therefore, the goal and aim of this research project is:

> ***"Explore the concept of minimally invasive sentinel lymph node biopsy and propose a solution for it"***

In the following sections of this chapter, the SLNB current procedure will be explained in greater detail. As this will help understand what is expected from the new procedure and help identify the main requirements for the new method. Thereafter the reasoning for why the current procedure has significant room for improvement will be explained. Then the last chapter will highlight in short what is already known in the literature for this problem.

## 1.1. Sentinel lymph node biopsy

The sentinel lymph node (SLN) is the first node that is receiving lymphatic drainage from a tumour (here: melanoma) in the axillar, inguinal, or head and neck region. By removing the SLNs and looking for metastases the stage of the disease can be determined, and a prognosis can be made for a patient. Using lymph nodes(LN) in this manner is called nodal staging. In addition, it can also give the treating physician (surgeon and/or medical oncologist) an indication of what treatment path to continue[3]. For example, patients who are diagnosed with high risk (for disease recurrence/metastasis) (stage III) melanoma using SLNB, adjuvant therapy has improved their chance of two-year-recurrence-free survival significantly[4, 5]. This is a clear advocate for the importance of SLNB in melanoma patients as this includes half of the aforementioned $7000$ patients.

The current standard for SLNB in breast cancer[6], as well as melanoma[7][8] is described by the following steps. A blue dye and technetium-99m are injected into the (scar of) the primary melanoma. These substances will drain from the affected area through lymph ducts to collect downstream in the SLNs[7][9]. Once these tracers have had time to settle the site of high nuclear activity (due to the technetium-99m) is identified and marked on the patient by a nuclear medicine physician. Subsequently, the patient is subjected to open surgery to excise the SLNs. The skin is opened with a $+/-5cm$ incision depending on various factors, including the BMI of the patient and how easy it is to find the SLN[10]. During the procedure, the surgeon will look for what in literature is called a hot'(high level of Technetium-99m is detected with a gamma probe) and/or (methylene) blue lymph node(s, usually 1 -

4 lymph nodes are removed[7]). Often a combination of these techniques is used as this increases the likelihood of the identified LN being SLN. Hereafter the node is excised. The European Organisation for Research and Treatment of Cancer put forth a protocol for nodal staging[11]. This protocol highlights the importance of examining the SLN slice per slice(as small as $50\mu m$) to increase the likelihood that a metastasis is detected. In addition, the location, shape, size, and number of the metastases have value for the diagnosis and prognosis of a patient[11]. Therefore, it is of importance that the SLN is not damaged as this could significantly impact the subsequent examination by the pathologist.

## 1.2. Why there is need for a new form of SLNB procedure

The importance of SLNB is evident. However, a SLNB procedure is accompanied with a relatively high occurrence of comorbidities. A pooled systematic review by Moody et al. reported a high occurrence of adverse events of 11.3[12]. The most common complications are wound infection, seroma, and lymphoedema[8, 12, 13]. Espinosa-Pereiro et al.[9] reported 11% significant scar formation. These complications weigh heavily on the decision of whether performing SLNB is warranted, as a majority($70 - 85\%$) of the patients that undergo SLNB do not have nodal metastases[2]. On top of that, one should consider that in some cases SLNB can only serve as a prognostic tool to determine survival rates, therefore the damage caused to someone's quality of life by performing SLNB should be taken in careful account. It is therefore not unusual for writers to call for critical patient selection and informing of patients of co-morbidities to prevent unnecessary harm[8, 12–14]. A minimally invasive solution could help reduce the occurrence of these co-morbidities.

## 1.3. Background information on MISLNB

In a preceding literature study conducted by the writer of this report it was discovered that there are only two devices were used in minimally invasive sentinel lymph node biopsy(MISLNB)(this report is available in appendix A.11). These two devices were used in two separate studies and no further instances of using MISLNB can be found in literature. The first study by Evans et al. used a vacuum-assisted core needle device to excise the SLN[6]. Using this device for MISLNB was not ideal as it caused significant bleeding and would cut the SLN up in several pieces. The second recorded instance of MISLNB is using the Intact Breast lesion Excision System(BLES™, Medtronic plc, Dublin, Ireland). In the study by Sever et al., they were quite successful in removing LNs from pigs and was a good indicator for what could be possible in MISLNB[15]. Both studies show that performing SLNB in a minimally invasive manner is feasible and that the procedure times could be low($3 - 23$ minutes)[6, 15]. Moreover, in their intended procedure(removing breast lesions) both devices can be operated under local anaesthetic. If this feature can be translated to MISLNB, this would reduce the overall risk of the procedure. Sadly, there is very little additional information that can be deduced from these articles. The actual mechanics, challenges, and intricacies of performing MISLNB at the point of writing this thesis are still unknown. Further research is required to quantify these values and learn more about the intricacies of MISLNB.

## 1.4. Shape and material properties of lymph nodes

A lymph node is a small spheroid organ, approximately $0.6cm^3$ in size with malignant(meaning with metastases) LNs being slightly larger on average[16]. In these LNs act as fluid collection and dispersion points, but also provide space for white blood and tumour cells to multiply[17, 18]. The lymph fluid(containing: proteins, fluids, and cells) flows to the node through $6 - 12$ afferent lymph ducts and exit through 1 efferent lymph duct[17, 18].

The available literature on the mechanical properties of LN is limited. No studies that tested stiffness of human LNs mechanically(through compression, elongation of indentation) could be found. However, the stiffness of human LNs has been recorded using shear wave modulation [19]. Research does indicate that this modulus is comparable to the Young's modulus [20, 21]. Therefore, the assumption can be made that the results shown in table 1.1 give a rough indication of the stiffness of LNs.

Table 1.1: Material properties of lymph nodes, $n$ is the number of samples, Stiffness is determined through shear wave modulation and STD is standard deviation.
** Only the largest extracted lymph node of each SLNB procedure was measured*
*** This is the only study that investigated stiffness modulus through indentation, however the tested values are for pig lymph nodes*

| **Study** | $n$ | **Stiffnessmodulu Benign**$[kPa]$ | **Stiffnessmodulu Malignant**$[kPa]$ | **Volume Benign**$[cm^3]$ | **Volume Malignant**$[cm^3]$ |
|---|---|---|---|---|---|
| [22] | 141 | mean:14.0 ± STD:6.6 | mean:30.6 ± STD:14.9 | mean:0.6 ± STD:0.6 | mean:1.0 ± STD:0.7 |
| [23] | 77 | mean:11.9 ± STD:4.4 | mean:105.9 ± STD:5.2 | N/A | N/A |
| [24] | 55 | median:21.4 (range 8.9–30.2) | median:25.0 (range 6.9–278.9) | N/A | N/A |
| [25] | 67 | mean:14.22 ± STD:4.19 | mean:41.06 ± STD:36.34 | N/A | N/A |
| [16]* | 826 | N/A | N/A | median:0.6 (range 0.3-1.3) | median:0.8 (range 0.4-1.5) |
| [20]** | 22 | mean:26.06 ± STD:6.03 | N/A | mean:4.7 ± STD:2.4 | N/A |

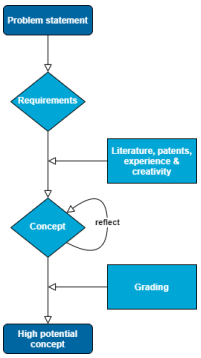
# I

# Instrument conceptualization for minimally invasive SLNB

# 2

# Method part I

Figure 2.1: Design strategy for MISLNB conceptualization




This part of the report elaborates on the method that was used to find a medical instrument that could deliver upon the desire to improve the current SLNB procedure. To guide the design process a design strategy was set up. A substantial part of the gathering of information used in design process resulted from a literature research by the writer that precedes the writing of this report(see appendix A.11). This literature research concluded that there are no current in-use devices for MISLNB, but there are some instruments that have potential in solving the problem. To guide these findings into a possible MISLNB solution a design strategy was set up(symbolically depicted in figure 2.1). The process started with a clear description of the problem followed by a set of design requirements. Then aided by research and creativity, three concepts were proposed. These concepts can be adaptations/implementations of existing ideas, as the aim is not to find an original solution but a working solution. The proposed solutions were then scrutinized to see whether some early issues with each of them can be exposed. Judging was the last step which led to the selection of the solution which had the most potential based on the requirements, available data, assumptions, and estimations. The next few sections will elaborate further on these steps in the design process.

## 2.1. Problem Statement

The problem statement and design requirements form the backbone of the overarching design process. The problem statement for the first part of this thesis was:

> ***Conceptualize/Find a medical instrument that could significantly reduce co-morbidities of sentinel lymph node biopsy, without compromising the intact retrieval of the sentinel lymph node***

This problem statement highlights the two most important design requirements of a MISLNB instrument. Thereby it is the main focus during the solution finding phase.

## 2.2. Criteria and Requirements for Solutions

The problem statement, however, does no not cover the details and nuance that was required from this solution. Therefore, a list of criteria and requirements was set up to further help guide the design process and allow for more elaborate comparison between concepts. This list will aid the focus of this project and help determine the adequate distribution of resources.

The requirements and criteria listed combine what is essential in successful SLNB(discussed in section 1.1) with the main driving force for change(discussed in section 1.2) and requirements in mechanical design. A draft version was set-up it that was deliberated and scrutinized by various members

of the project team. That consists of members at the Erasmus Medical Center and the TU Delft. This allowed for attaining a consensus regarding what was expected of the device. During these discussions, a weighting factor was determined for each of the requirements. This weighting factor acts as an indicator for the priority at which each requirement should be fulfilled.

The following factors influenced decisions on how to weigh each of the requirements.

- **Lack of literature and previous experience:** There is almost no experience with minimal invasive removal of lymph nodes. A considerable amount of information that was of importance in setting up boundary requirements is unknown and undefined. Since this knowledge was still missing there are assumptions are made on little to no information.
- **Extend of project:** There are requirement of designing an instrument which are of importance for the implementation of the final product but are of less importance in the exploratory part of a study. An example of such a requirement is Durability. Durability is important in designing a final product but less important in the initial part of the process where the feasibility testing of a solution has priority.
- **Improvement over current procedure:** This is not explicitly stated in the requirements themselves but is an important driving factor in this project. Currently, there is a procedure that works in successfully removing lymph nodes(section 1.1). However, as stated in section 1.2 of the report there is reason to believe that this current method can be improved upon. This improvement is the main stimulus for the success of this endeavour.

Table 2.1 shows the final version of the requirements table that was agreed upon before entering the solution design phase of this project. Priority of each of the requirements is ranked one up to five. With five being the requirement of the highest priority for this research project and one being the lowest. From this table we can discern that the highest priority lies in the en bloc(meaning: as a whole) excision of the LN and the safe retrieval of said node. This is followed by minimal disturbance of healthy tissue which is in the interest of improving upon the current SLNB procedure.

Some of the requirements with a lower priority play a small role in the concept selection and design phase of this process. However, they are something that should be kept in mind for the final rendition of a minimally invasive SLNB instrument once the core functionality of the instrument is validated. For instance, safe failure, this is a core principle in mechanical engineering which should always be in the back of one's mind during design. However, will need extensive testing and development which would only be worthwhile once a concept is truly viable for its intended role.

Table 2.1: Complete set of requirements for an instrument that performs minimally invasive SLNB

| Requirement | Definition | Why of importance | Priority | How measured | Comments |
|---|---|---|---|---|---|
| Single pass en bloc excision of lymph node | The lymph node should be excised as a whole, and not be cut up in multiple excisions | Breaking up the lymph node in several pathological samples could [11, 26] | 5 | En bloc excision of spherical objects ranging from 0.5 cm in diameter to 2.2 cm [16, 22] | Sentinel lymph node sizes vary and an excisional path should accommodate the various sizes of lymph nodes plus the thickness of the excisional artifact. |
| Retrieval with minimal damage to lymph node | Minimizing damage to the internal structure of the lymph node that is caused by pressure, or other mechanisms of the device | The lymph node is needed for pathological analysis, therefore reliable retrieval is essential. The method of retrieval should also have minimal impact on pathology | 5 | Pathologist can still perform an accurate nodal staging analysis | Careful handling of the lymph tissue is required. In an ideal case there is no damage to the sentinel lymph node itself. |
| Minimal healthy tissue disturbance | An incision smaller than the current required incision of +/- $5cm$[10], and minimal disruption by the device to the tissue | A large incision results in longer hospital stay, increased incidence of infection and larger scar formation | 4 | The amount of adjusting and cutting needed before the lymph node is reached | Smaller is better, the aim would be incision comparable to laparoscopic instruments. Action of the device should preferably be located only at the tip, and only affect the SN. Precision plays an important factor, this could be realized with high control over the device, using good ultrasonic visualisation or a clever technical safety feature. The use of the device around nerves and blood vessels around the lymph node should be controlled and safe. |
| Biocompatible | Materials components should be safe for surgical use | To reduce comorbidities caused by the materials/shape of the device | 4 | Based on literature | Non-toxic materials that strike a balance minimize corrosion and wear and durability should be the default |
| Sealing lymph ducts and capillaries | Managing the internal bleeding and swelling caused by the lymph node removal | To reduce incidence of seroma, haematoma and lymphoedema | 3 | Based on existing literature | Use of RF energy helps coagulate tissue and reduce haematoma formation. Several studies also indicate that coagulation, staples, ligatures or sutures could reduces seroma formation[13, 27, 28]. |
| Simplicity | Simple design and function | Directly positively impacts requirements: safe failure, durability and sterilization. | 3 | Complexity, number of parts and are they moving or stationary | The goal is to limit part count and the complexity of each part. Incorporate little to no moving delicate and moving parts. |
| Ease of Use | Straightforward surgical use, control and grip | Increase surgical accuracy and reduce learning curve, procedure time and incidence of accidents | 2 | Length of procedure in comparison to current SLNB procedures | Use Input from medical professionals, minimize steps to complete procedure and facilitate the positioning of the device relative to the Sentinel lymph node(e.g. through ultrasound visualisation) |
| Universal use of Device | Ability to use the device for removal of lymph nodes at different locations and orientations | Broad field of application increases the value of developing this device further for clinical use. | 2 | Excision and translation capabilities across phantoms with different material properties | One should consider that certain features could increase the universal-use of the device but could come at the cost of simplicity which affects other requirements for the device. Also of consideration is that movement of the tip inside the tissue could increase the disturbance and morbidity due to the procedure. TBD: variety of excision depths across basins, orientation of the lymph nodes(in which direction lies the longest diameter and how does this vary), tissue differences across the inguinal and axillar tissue(e.g./ fat content) |
| Sentinel node detection | Distinguish the sentinel lymph node from its surroundings | Ensure that the surgeon is excising the right lymph node pre-excision to increase the chance of excising the right lymph node | 2 | Based on existing literature and previous experience | In open surgery the sentinel lymph node is detected using blue dye and technetium-99, a way to facilitate this kind of detection without requiring open surgery would be ideal. |
| Safe failure | If the device fails, damage to the surrounding tissue should be minimal | To reduce harm to the surrounding tissue in case a failure occurs | 2 | Based on existing literature and previous experience | When an element of the instrument fails, energy should be dissipated safely and fragmentation should be prevented. Preferably the device should be able to be retracted without leaving behind pieces. |
| Building upon CE devices | Adapting existing concepts to accomplish goals | Certified and proven devices are easier to pass through certification as the are already validated in a clinical setting | 2 | Based on existing literature and patents | This limits the possibility of new creative solutions that could be a better fit for the task at hand. However, it also facilitates a shorter road to a true solution. |
| Sterilization | The ability to re-use the device and keep it clean. (It is assumed is that before first insertion the device is always clean) | Reduce procedure costs and risk of infection | 1 | Based on existing literature and experience | Design features take into account factors that, make it easier to keep the instrument clean and allow for multiple uses. There are no areas where build-up can happen and that shield pathogens during sterilization. Such a design would allow for easy disassembly and good access to all surfaces of the device. Surface of the device has to prevent pathogens from adhering to it(e.g./ smooth surface). |
| Durability | The device should be able to withstand forces and environmental factors that affect it | To ensure that the device can last through the surgery and perform its task without fail | 1 | Design choices based on existing literature and experience | Materials and design decisions that minimize corrosion and wear, and allow for easy replacement of broken parts. |

## 2.3. Conceptualization of each Solution

The next step involved gathering available knowledge to find solutions for the given problem. This where the research conducted in the preceding literature study was of importance [19]. That study explored literature (PubMed, web of science and Scopus) and patents (Espacenet) to find inspiration for a device that could fit the set requirements.

Using this knowledge/inspiration in combination with some ingenuity, three solutions for MISLNB were established. These solutions were defined by their working principles with the focus on the excision of the SLN. Working principles that originated from existing ideas, will be accredited in the results section of the report The basic definition of each solution was enough for side-by-side comparison and thereby enable grading of each one.

## 2.4. Reflection

Once three solutions were described and defined, they were subjugated to critique. However, it should be noted these are partly to non-existing concepts that will have to operate in conditions which are largely unknown and not described in literature. Therefore, in this part of the process critique is based mostly on assumed interactions between tissue and instrument and known issues and challenges within mechanical design. Thereby already laying bare some issues with a certain design and highlight the areas of each solution which are important to focus on when developing the instrument further.

## 2.5. Judging Contenders

The purpose of grading and reflecting on each solution was to ensure that the selected solution has the most chance of succeeding among the proposed options given the available information. The requirements from table 2.1 are used to judge the solutions. Each requirement can be scored one to five, with five being the highest score for a requirement and one being lowest. As with the reflection step of this process, the grading of each solution was also based mostly on assumptions as a lot of factors in this problem are still unknown. A range from one to five was used since some of the requirements are hard to determine at this stage of the research. Therefore a neutral option was required to grade them(which was three in this case). When no clear distinction in performance could be made all three solutions would receive a score of three. The final score was determined by multiplying the priority of the requirement with the achieved score for that particular requirement. The outcomes are summed to determine a final winning concept/solution. The main reasoning for scoring a certain solution higher or lower than its counterparts were provided as a comment.

# 3

# Results part I

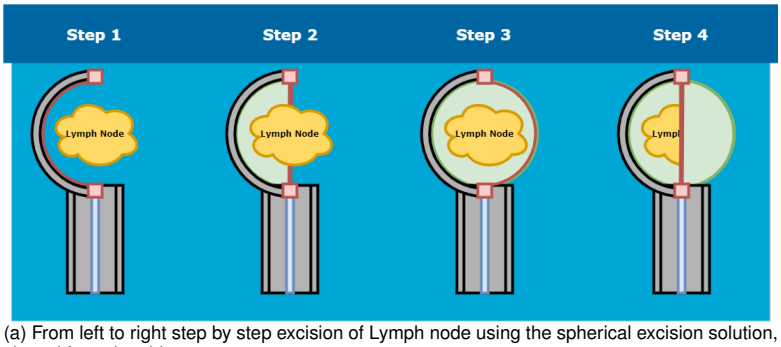
Results of concept design This chapter of the report presents the three designs that were proposed as a solution for MISLNB that were the result of the design/research process described in chapter 2.1. The chapter ends with a decision on which of these subjects has the most chance of succeeding in a MISLNB context.

## 3.1. Instrument Description

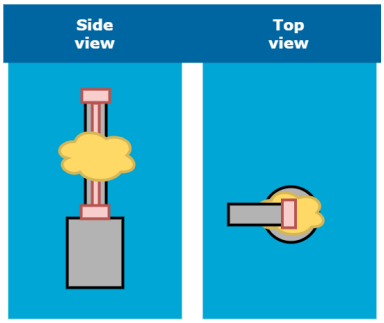
The following paragraphs will describe each of the proposed designs, discuss sources for inspiration and explain their working principles.

### 3.1.1. Spherical Excision

Figure 3.1: Description of spherical excision solution, the illustrations in the figure show the distal end of the instrument




(a) From left to right step by step excision of Lymph node using the spherical excision solution, viewed from the side




(b) Views from different sides of the design

The spherical excision solution is based on patents found in the Espacenet database. The writer of this report does not claim to own the rights to the solution proposed in this section of the report. The patents describe two different ways in which a spherical body is excised[29, 30]. The patent described by Racenet et al. explores a concept which functions much like an ice scoop[30]. A half sphere cup is moved as close as possible to the tissue that needs to be excised. Thereafter, a vacuum is applied, and a circular blade is used to separate a circular volume from its surrounding tissue. The patent by Albrecht et al. has no cup like the patent of Racenet et al.[29]. The spherical volume is excised using C-shaped cauterizing knife which drags a 'net' behind it enveloping the spherical volume. Both instrument designs have not yet been implemented in medical procedures, therefore there is also no literature available on the performance of these devices. Using these principles, the device shown in figure 3.1 was proposed for MISLNB.

**Working principle Spherical Excision solution:** First the device is inserted through a small incision in the skin. Then under ultrasonic guidance, the LN is positioned in a manner that it is in the centre of the arc to get to the situation depicted in step 1 in figure 3.1a. Once the device is in the

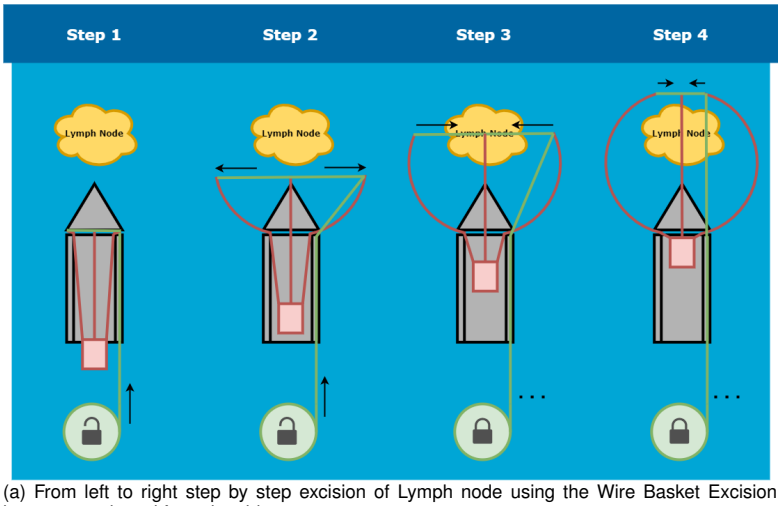
correct position relative to the LN a C-shaped cauterizing knife is spun using an axle(highlighted in blue). The knife makes a full rotation to completely excise the LN from its surrounding tissue. Dragging behind the knife is a catch bag(highlighted in green) that will envelop the LN. This catch bag is in place to allow for safe retrieval and minimizes the chance of spilling tumour cells to the surrounding tissue. The whole instrumented is retracted and the catch bag can be unfolded to reveal the LN, which then can be processed by pathology.

### 3.1.2. Wire Basket Excision

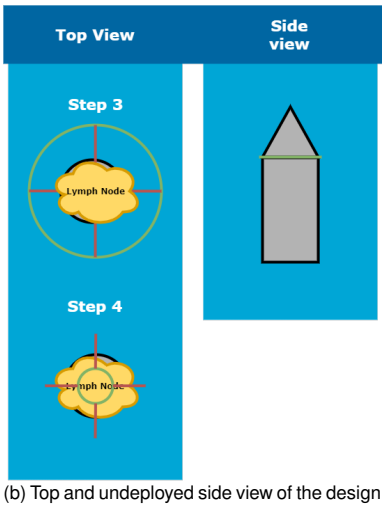
This solution is inspired by wire basket biopsy devices. The two main inspirations are The Intact Breast Lesion Excision System(BLES™, Medtronic plc, Dublin, Ireland) and the Ovitron( Ovitron, Rubicor Medical, California, Redwood City). Therefore, the writer of this report does not claim to own the rights to the solution proposed in this section. From the conducted literature study it was concluded that the BLES™ could be the best off-the-shelf solution for the MISLNB[19]. Currently it used and marketed as a biopsy device. Therefore, its reported intact excision rates are low[31]. The device was not available for extensive to this study. Therefore, an own rendition of this instrument has to be designed and built to further explore this solution and improve it to better fit MISLNB. This resulted in the solution presented in figure 3.2.

**Working principle Wire Basket Excision solution:** First it is inserted through a small skin incision. A pointed tip allows it to travel through the tissue with reduced resistance. Once positioned in front of the SLN the core(marked in red in figure 3.2a) is pushed towards the distal tip. The core exists of a block with metal wires attached to it. As the core moves up the metal wires are pushed out at an angle. All the wires are connected with a coagulation wire(marked green in figure 3.2). This coagulation wire is attached to a winch which controls the length of the coagulation wire. In step one the coagulation wire is allowed to lengthen without resistance from the winch. This resistance is slowly increased and eventually halted to create the circular trajectory seen in figure 3.2a. The top view shown in figure 3.2b gives further insight in how this device will excise the spherical volume. Once the cut has been completed the whole device is retracted taking with it the LN that is encased in the wires.

Figure 3.2: Description of Wire Basket Excision solution, the illustrations in the figure show the distal end of the instrument




(a) From left to right step by step excision of Lymph node using the Wire Basket Excision instrument, viewed from the side

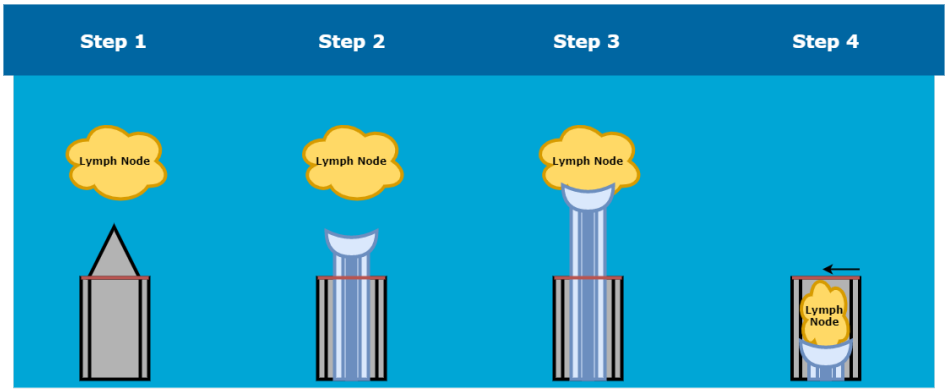



(b) Top and undeployed side view of the design

### 3.1.3. Pull-and-Harvest Excision

The Pull-and-Harvest is loosely based on principles used in polypectomy snares and the Full Thickness Resection Device(FTRD®, Ovesco Endoscopy, Tübingen Germany). These devices are used to remove polyps from the intestinal wall. Although these are meant to be used for use through a natural orifice, they could offer a solution for MISLNB. Testing will have to determine whether this principle can be translated to SLNB.

Figure 3.3: Description of Pull-and-Harvest Excision solution, the illustrations in the figure show the distal end of the instrument




(a) From left to right step one through four Lymph node excision using the Pull-and-Harvest Solution


(b) Top view of step four and five

**Working principle Pull-and-Harvest solution:** First it is inserted through a small incision in the skin. Similar to the previous solution a pointed tip allows it to travel through the tissue with reduced resistance. Once it has reached its destination the point is retracted, and empty tube remains in place inside of the tissue. A vacuum gripper(highlighted in light blue in figure 3.3a) is moved through this tube and brought into contact with the LN. Once in contact, a vacuum pump will be engaged to grip the LN. This LN is then retracted into the lumen of the device. Once completely enveloped a snare(highlighted in red in figure 5.1) will close to resect any of the lymph ducts and vessels connecting the LN to the surrounding tissue. This is most clearly shown in step four and five depicted in figure 3.3b. RF energy can be applied to the snare to coagulate the vessels and ducts. After this process has been completed the whole device is retracted from the tissue. With the LN safely stowed away in the tip of the outer tube.

## 3.2. Critical Reflection of each Proposed Solution

The following sections are the result of critical investigation of each of the aforementioned designs. Including a prediction on potential challenges that would lie ahead for further development of that solution.

### 3.2.1. Critique on Spherical excision instrument

One of the main requirements for this thesis is to lower the impact to a patient's health caused by SLNB. In this design it is anticipated that the dimension of the arc may play a large role in this. This dimension directly influences the required skin incision length and could also affect disturbance of surrounding healthy tissue. Because the tip of this design is not optimal for tissue penetration. As a minimal dimension the arc must be able to excise a wide range of LNs in its entirety the radius has to be at least $15mm$. From a health perspective, it is preferred to have a small diameter just large enough to excise almost all sizes of LNs. However, from a usability perspective this is less desirable. It is going to be challenging to get the LN in the position shown in 3.1a. Decreasing the radius of the arc is going to make this even harder and more time-consuming. It is hard to make any assumptions what and how the dimensions are exactly going to affect behaviour and usability, and where this solution selected a major part of the research resources would be spent learning more about this.

Secondly, this solution is not straightforward to produce, it has rotating parts and parts that have to conduct electric energy. The complexity of the design makes it more challenging to develop into a working prototype. A major part of the resources will be spent in developing this prototype before anything can be said if it could work or not.

Table 3.1: Important advantages and disadvantages of the Spherical Excision Solution

| Main Advantages | Main Disadvantages |
|---|---|
| Large and sturdy profile, this design is stiff and non-pliant, making it easier to predict its movement throughout the body | Large diameter of instrument, the arc will have to be at least 15mm in diameter to ensure that it can excise larger lymph nodes |
| Reliable retraction, since the excised tissue is completely enveloped and encased it can reliably be extracted from the body | Resistance during insertion, due to its shape manoeuvring it around inside tissue to reach the intended target might be challenging |
| Cauterization, this will reduce some of the seroma and hematoma formation caused by the procedure[13, 27, 28] | |

### 3.2.2. Critique on Wire Basket Excision Solution

Several challenges will arise when developing this particular solution. First and foremost, this is a very intricate and complex design as mentioned in table 3.2. Building a prototype will require knowledge of and experience with niche not readily available manufacturing techniques. Therefore, A lot of resources will be spent on developing and designing this prototype.

Additionally, in the available literature on the BLES™ it is stated that the basket can turn up empty after the presumed excision process has been completed. This is something we cannot afford in the MISLNB. There is a different hypothesis on why this happens. Namely, the stiffness of the tissue[32], melting fat tissue allows the sample to escape[33] and the quenching of the coagulation wire by surrounding fluids which interferes with cutting[34]. Resources will have to be spent to get an accurate representation of these situations to be able to solve for them. Recreating this specific test setup will be challenging as not all phantom materials are compatible with artificial tissue phantoms.

Table 3.2: Important advantages and disadvantages of Wire Basket Solution

| Main Advantages | Main Disadvantages |
|---|---|
| The device diameter can be relatively small, as the wires reach out from the initial diameter | Complex design, this design has a lot of fragile and intricate moving parts |
| Flexible excision volume, the resistance of the winch determines the excision path and can therefore be adapted to the size of a specific node | Unreliable extraction, the BLES™ which uses the same principles as this solution, is known to have so reliability issues with retracting samples[31, 33, 34] |
| Cauterization, this will reduce some of the seroma and hematoma formation caused by the procedure[13, 27, 28] | |

### 3.2.3. Critique on Pull-and-Harvest Solution

The first major challenge for this Solution is ensuring that the LN can enter the lumen of the device. The forces play a role in this are currently unknown. Additionally, the lymph ducts and blood vessels might get stuck on the edges of the device, making it difficult for the LNs to get deep enough into the device for the snare to be closed. Different solutions might be required for each of these problems and resources need to be allocated to ensure that these mechanisms are identified.

Furthermore getting a good grip on the LN might be challenging. The force that a vacuum sucker can exert on material depends a lot on the seal between the material and the sucker. Once a leak occurs the force that the sucker can exert rapidly decreases and the two will be separated. Getting a good seal between the sucker and the LN is essential and should therefore be well researched.

## 3.3. High potential Instrument

The last step in the concept development process is selecting the solution which has the most chance of succeeding. Table 3.4 shows the grading of each of the solutions for each of the requirements.

Table 3.3: Important advantages and disadvantages of the Pull-and-Harvest Solution

| Main Advantages | Main Disadvantages |
|---|---|
| Minimal damage to lymph node, a vacuum suckers a known to cause little to no damage to tissue[35] | Multiple instruments required, the assembly requires multiple instruments and would probably be more time intensive than the other Solutions |
| Simple Solution, little to no moving parts | Large diameter, this is dependent on the compress-ability of the lymph node and strength of the gripper which are currently unknown |

The scores of each solution are displayed at the bottom row of the table. The last column of this table contains comments, explaining why the requirements were graded in this manner. Using this scoring mechanism, the Pull-and-Harvest solution came out as the favourite to continue developing for MISLNB.

This decision was based also based on discussion and debate with all members of the project team. In this discussion, all project team members were presented with the three solutions with the critique on each of these solutions alongside it. Based on the available information and the ensuing debate the Pull-and-Harvest method was agreed to be the best solution to pursue. With the main pros for this solution being the low risk of damaging the SLN using a vacuum and its simplicity.

Table 3.4: Scoring table of each solution based on the requirements for MISLNB

| Requirement | Priority | Spherical Excision Concept | Wire Basket Excision Concept | Pull-and-Harvest Excision Concept | Comments |
|---|---|---|---|---|---|
| Single pass en bloc excision of lymph node | 5 | 5 | 5 | 3 | Pull and harvest scores lowest because it might be challenging to grip the lymph node and get it in the required position to be resected. |
| Retrieval with minimal damage to lymph node | 5 | 3 | 3 | 5 | Pull-and-Harvest scores highest because RF energy is only applied(if applied at all) when the lymph node is safely stored away. For the other two misalignment can have a significant impact on the thermal damage to the node. |
| Minimal healthy tissue disturbance | 4 | 3 | 4 | 5 | Pull-and-Harvest scores highest because almost no thermal energy is used during the excision process. Spherical excision scores lowest since the profile of the device can damage the tissue during both insertion and extraction. Additionally it will require the largest insertion diameter. |
| Biocompatible | 4 | 3 | 3 | 3 | All instruments will be designed to be bio-compatible, so all are scored the same. |
| Sealing lymph ducts and capillaries | 3 | 4 | 4 | 3 | The use of RF energy throughout the excision process places the Spherical and Wire Basket Excision concepts makes them more likely to perform better in this task. |
| Simplicity | 3 | 3 | 2 | 5 | The components of the Pull-and-Harvest concept are simple and straightforward to manufacture. The wire Basket Excision concept scores lowest since this will require expert knowledge to construct. |
| Ease of Use | 2 | 3 | 3 | 3 | Can´t be determined at this point as no physical test have been conducted, so all are scored the same. |
| Universal use of Device | 2 | 3 | 3 | 3 | Can´t be determined at this point as no physical test have been conducted, so all are scored the same. |
| Sentinel node detection | 2 | 1 | 1 | 2 | All concepts score low since none of them have an integrated solution for detection yet. The Pull-and-Harvest solution scores the best since the lumen of the device allows for the introduction of an endoscope or gamma probe to help with detection of SN. |
| Safe failure | 2 | 2 | 2 | 3 | Can´t be accurately determined as no physical test have been conducted. However Pull-and-Harvest scores slightly higher because it uses no motorized parts of parts under stress at the distal tip of the device. |
| Building upon CE devices | 2 | 2 | 4 | 3 | The Wire Basket Excision Concept scores highest since a very similar device exists and is used in an similar setting as MISLNB. |
| Sterilization | 1 | 3 | 3 | 3 | Can´t be determined at this point as no physical test have been conducted, so all are scored the same. |
| Durability | 1 | 3 | 2 | 3 | Can´t be accurately determined as no physical test have been conducted. However the Wire Basket concept is scored slightly lower since it contains small delicate parts. |
| | | **113** | **117** | **130** | |

# 4

# Discussion part I

In this part of the report an assessment was made of the possible solution for minimally invasive sentinel LN biopsy. Inspiration and ideas were gathered to find possible solutions for the given problem. With this information in hand and some creativity, three solutions were proposed. From these solutions the Pull-and-Harvest method came out to be the best one. This concept uses a vacuum to grip the sentinel lymph node (SLN) and stash it in a tube, hereafter a snare would cut the lymph ducts and blood vessels. This concept scored well mainly due to the low risk of damaging SLN and its simplicity. Since there is little literature available on this particular subject, this decision was made based mostly on predictions on how this instrument might behave in this setting. Therefore, there is no definitive answer whether this is truly the best option for the given problem. Further research is needed to determine whether this concept is truly viable and can deliver upon the basic requirements set by the problem statement. Nonetheless, this design is a good starting point in solving this problem, as all information regarding this subject will add to a better understanding of MISLNB.

## 4.1. Connotation of simplicity

The Pull-and-Harvest method was selected in large part due to its simplicity. In some context simple sounds insulting or lazy, but in the context of instrument design simplicity can be a huge feat. This is because simple design often brings other benefits. For instance, less complexity makes it easier to take apart for sterilizing or the replacement of parts which positively impacts durability and longevity of a device. Additionally, there are no rotating or moving parts at the distal part of this device. This means there are little to no stresses in the part of the instrument that is inside the body reducing the chance that major damage occurs when the device fails.

## 4.2. Sentinel lymph node detection

One of the weaknesses of this report is that it ignores a large part of the SLNB procedure namely SLN detection. This is one of the hardest parts of the procedure and improving on this could also have a significant positive impact on the overall procedure. The chosen Pull-and-Harvest solution as described in the results section of the report does not address this challenge. This decision was made in agreement with the stakeholders. Nonetheless, there are some ways that this feature can be introduced into the instrument.

The first being ultrasonic imaging. Ultrasonic imaging is a widespread visualisation tool used to show how tissue is related to one another. It is already used to guide devices in breast lesion excision to excise breast lesions[31, 36–38]. This procedure is in many ways very similar to what MISLNB would be. Important for this to work is that the SLN is visible on the ultrasound. Yamashita et al. have shown that it is feasible to determine what LNs are sentinel nodes using ultrasound[39]. It would require a trained radiologist and good visibility of the device on ultrasound to enable this option. The addition of a radiograph and gamma probe could help further confirm the location of the sentinel node. Another way of detecting the SLN could come in the form of visual confirmation. This could be realized by introducing an endoscope through the lumen of the Pull-and-Harvest device. Which would send an image back to a screen on which the surgeon can try and discern any of the blue dye that would be

present in the SLN similar to an open procedure. SLN detection using Indocyanine green Fluoresce could also be a valid option as this technique works better in a dark laparoscopic setting than in open surgery[40]. The SLN detection could also be performed using an imaging program that analyses the image from the endoscope or photo-sensor to detect the presence of the green fluorescence. Lastly, a specially adapted Gamma probe could be designed to fit down the hollow tube of the Pull-and-harvest instrument. So, there are multiple ways in which the Pull-and-Harvest method could facilitate SLN detection and thereby ensure that the correct LN is resected. It is however important to note that the success in SLN detection lies in using multiple different detection methods has the greatest chance of success as SLNs are hard to find[41].

# II

# Is MISLNB using the Pull-and-Harvest approach a viable option

# 5

# Methods part II

In the previous part of this thesis, the Pull-and-Harvest concept was selected as the concept that had the most potential to be developed into a working instrument. In this part of the thesis, the goal was to prove or disprove whether this concept could work as minimally invasive sentinel lymph node procedure(MISLNB). To determine this a new problem statement was set up to guide this process:

> ***Can lymph nodes be harvested minimally invasive utilizing a vacuum sucker without hindering nodal staging?***

This main question was subdivided in several sub-questions to gain more insight in the different processes that take place. Splitting this up into several sub-problems allows for a better understanding of what could work and what does not. Thereby also providing a foundation for further research into this subject.

The following sub-questions are set which this thesis will attempt to answer:

- **Sub question 1:** What forces are required to separate the lymph node from the surrounding tissues?
- **Sub question 2:** Is vacuum suction an effective gripper for lymph node manipulation?
- **Sub question 3:** Can a Lymph node be stashed inside a cylindrical volume without impairing nodal staging, to prevent spillage and enable safe extraction?

Three tests were designed to find answers to these questions. The first test was a mechanical test(section 5.1). Since there was limited data available on mechanical behaviour of LNs, expanding this base of knowledge is of interest. Furthermore, it will help compare the artificial LNs to the real ones. The second test was a vacuum suction maximal force test(section 5.2). In this test two different vacuum suction cups were used to determine how efficient they are at gripping LNs. This test setup also offered a chance to observe the interaction between LN and the suction cup. The third experiment was a LN stashing experiment(section 5.3.1). In this experiment the concept of stashing the node inside of a tubular volume using a vacuum was tested. Afterwards, a measurement of the forces that keep the LN in place was required to determine whether this solution suitable. This report tried to estimate this value on a basic theoretical model described in section 5.3.2 of the report. Finally, all results were combined to estimate whether this concept is feasible(section 5.3.3).

Before any of the test setups were used for testing human tissue, all tests were performed using grapes and olives. This would reveal issues with the test setup which could then be addressed. This allowed for reliable testing once human LNs became available. Furthermore, the test setup required experiments to calibrate the setup(appendix A.3). In the case that no real human LNs would become available artificial LNs were created more on this in appendix A.2.

For most experiments, more repetitions equals a larger dataset which in turn allows for a better approximation of the sampled value. However, there is an upper boundary to how many tests can be conducted when using real tissue. This is due to tissue dehydration and rigor mortis which can significantly impact material properties of the tissue that is tested[42, 43]. To limit the impact of these

effects on the recorded data, each LN was only tested five times per experiment. Tests were carried out as close to the moment of LN excision as possible. In-between tests LNs would be stored in a Natrium Chloride solution to reduce dehydration. Thereby hopefully minimizing the effect elapsed time has on the outcome of these experiments.

## 5.1. Deriving material properties of Lymph Nodes

This experiment was set up to learn more about the deformation behaviour of LNs, specifically under compression conditions. Compression was of interest since reducing the volume of the LN before extraction could reduce the size of the instrument and thereby the length of the incision.

As for testing compression parameters, the most common way of quantifying this material property is through the Young´s modulus(denoted by an $(E)$). This modulus describes the stress as a function of strain. Wherein the strain is the pressure exerted on the surface of the specimen, and strain is the deformation normalized by the initial shape of the specimen. The Young's modulus can be calculated using equation 5.1. In this equation $F$ is the magnitude of compressing force (in Newton), $H$ is the initial height of the object(in meter), $A$ is the cross-sectional area (in square meter) and $\Delta D$ is the difference in length due to the compression(in meter). The higher the Young's modulus the stiffer a material behaves. It should be noted that this modulus applies only to isotropic materials which have a linear stress-strain relationship. Using the Young's modulus to describe the material of properties of tissues was a simplification of the true stress-strain behaviour of LNs. Nonetheless, for this thesis this modulus was chosen to enable comparison between the results of the compression experiment and the literature that is available(a further in-depth explanation on why this choice was made is given in section 8.1).

$$E = \frac{F * H}{A * \Delta D} \tag{5.1}$$

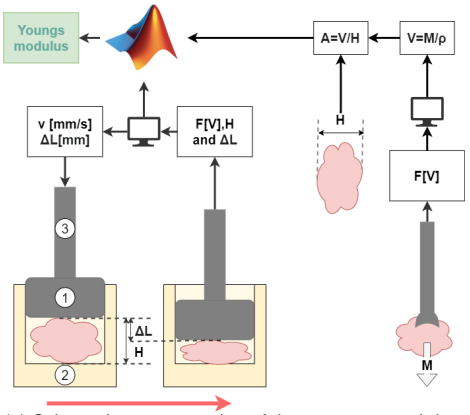
### 5.1.1. Stress-strain test setup

This section will focus on the test setup that was designed to quantify the stress-strain relationship of LNs. Figure 5.1a schematically depicts how the relationship was determined showing how the data flows and how it is processed. Figure 5.1b is a picture of the actualized setup. Marked with a one is the stamp that was connected to the adapter and force sensor with a cylindrical connector(marked with a three). The stamp itself was 3d printed and bolted to the aluminium connector. The stamp was shaped to cover the whole tray to apply a uniform force to the LN. It covers the whole LN since this study was aimed at learning more about the compression behaviour of the LN as a whole. The tray(marked with a two) was 3D printed in Polylactic acid(PLA)and mounted on an aluminium profile to provide a stable platform to line up with the stamp. The printed assets where custom design using Solidworks(Dassault Systèmes, Vélizy-Villacoublay, France) modelling software.

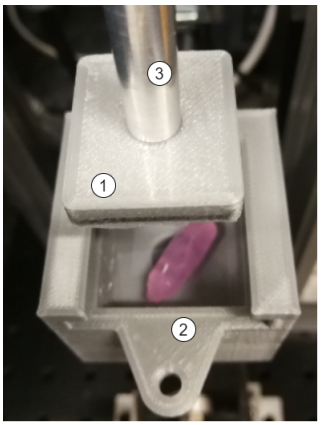
During the experiment, the stamp was moved downwards at $1mm/s$ for $25mm$ using a linear stage. Due to the small size of the LNs, only small indentations could be achieved. Important in this step was to determine the deepest point the stamp could go. This would be used later on in data processing to determine the initial height of the LN. After each test, the test specimen would be picked up and re-positioned in the centre. This was done to standardize the initial conditions at the start of each experiment and help restore some of the deformation that has occurred during the test. The second experiment required for determining the material properties of the LN was weighing it. Weighing the LN was also achieved using the linear stage and the $6mm$ vacuum nozzle. A measurement would be commenced and after 5 seconds the LN will be attached to the vacuum sucker. Thereby the first 5 seconds could be used as a baseline measurement to get an accurate approximation of the weight. This weight would later be used to calculate the square area.

Once a test was completed a MATLAB(Mathworks, Natick Massachusetts, United States) script stores position and force data in a capture file which could thereafter be used to further process the data. Voltage output could be tracked in real-time. By paying close attention to this voltage behaviour, faulty measurements could be removed and re-tested. Once all necessary tests were completed all

Figure 5.1: Experimental setup for stress-strain relationship testing




(a) Schematic representation of the test setup and data flows within the stress-strain relationship experiment




(b) Picture of physical setup for Young's modulus testing, with a pink artificial lymph node inside the tray

parts of the test setup were disinfected using ethanol to ensure they are clean and safe for subsequent use.

A comprehensive overview of the dependant and independent variables that were of interest in this experimental setup is provided in appendix A.8.

### 5.1.2. Stress-strain data processing

To estimate the Youngs' modulus of each specimen the stress and strain values need to be extracted from the data. In this section, a description will be given on how these values were attained using the data from the aforementioned experiment.

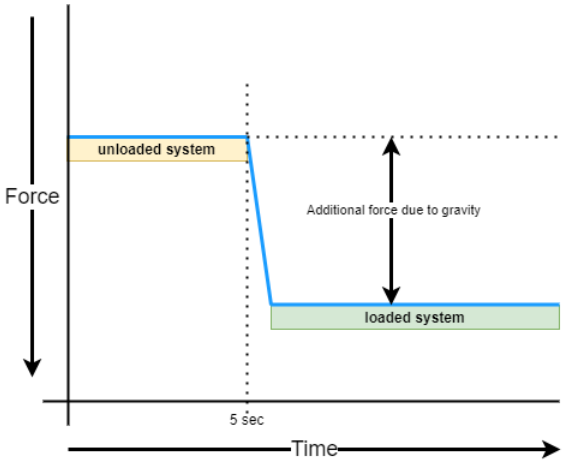
$$\sigma = \frac{F}{A} \tag{5.2}$$

Starting with the stress($\sigma$) described by equation 5.2. ($A[mm^2]$) is the cross-sectional area of the sample. This was one of the harder parameters to attain. The shape of the specimens was simplified and modelled to be cubic in shape. The area of this cubic volume was assumed to be approximately the same size as the average cross-sectional area of the sample. To determine the volume of these cubic shapes equation 5.3 was used. Wherein $\rho$ is the density of the specimen and value $m$ was the weight of the node. The density of LNs is approximately $1.030Kg/m^3$[44]. The LNs also came with a considerable amount adipose tissue attached which has a density between $0.925 - 0.970Kg/m^3$. Therefore, the combined density was estimated to be around $1Kg/m^3$.

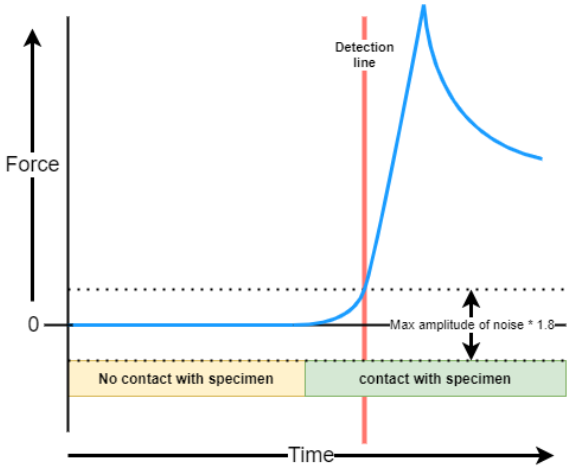
$$Volume = m/\rho \tag{5.3}$$

The weight($m$) of the LN was determined using the weighing experiment. The experiments would produce a graph which would look like figure 5.2a. Subsequently, a custom script was used to determine the difference between the unloaded and loaded state of the system. This difference in negative force(negative due to the downwards direction of gravity) could then be translated to a weight. Thereafter this weight would be converted to a volume estimation using equation 5.3. The volume was also calculated manually using measurements taken with a calliper and treating the LN as an elliptical object. Generally, the estimated volume was larger than the manually measured volume. This was in part explained by the adipose tissue that was still attached during the weighing experiment but did not contribute to the manual measurement. The mean estimated volume was multiplied by two and added to the measured volume, the sum was divided by three. This gave the mean estimated volume more weight to reflect the volume of adipose tissue that was present during the experiment. The aim of including two different methods of measuring the volume was to get a more accurate estimation of the true value.

Figure 5.2: Graphs illustrating the how the custom MATLAB(Mathworks, Natick Massachusetts, United States) scripts process the data taken from the force measurements




(a) This graph shows the theoretical force output throughout the weighting experiment. Time = 5 seconds indicates the time when the specimen was attached to the setup




(b) Force time curve, illustrating how the detection line works which was used to determine the start of an experiment and subsequently the strain

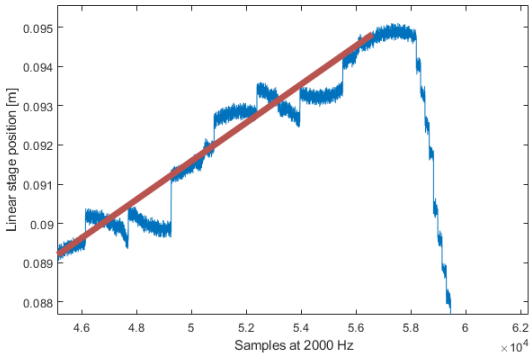
From there the average area was calculated using the height of each sample. Since the height differs in between experiments(due to the low stiffness of the LNs), custom code was written to calculate the initial height for each experiment. The script detects whenever there is a significant deviation from the mean force in the initial part of the experiment. This deviation then indicates the start of the experiment. This process is illustrated by figure 5.2b. Thereafter it was manually confirmed whether the code has found the correct starting point of the experiment by inspecting the graphs. Measurements were made to determine the deepest point of the tray. By subtracting this measurement from the position at the start of the experiment an estimation of the initial height $H$ could be made. This was used to calculate the initial cross-sectional area. Since the experimental setup does not restrict deformations of the specimen in lateral directions one has to account for this in the data processing. As the stamp moves down and compresses the specimens it will lead to an increase in surface area of the specimen. The translation from longitudinal deformation to lateral deformation was described using the Poisson's ratio. Using this Poisson ratio, the cross-sectional area can be derived as a function of $\Delta H$. The Poisson ratio of tissues is high and approaches $0.5$ for tissues [45]. For the data processing of the experimental data a constant isometric Poisson ratio of $0.45$ was used to calculate the incremental increase in cross-sectional area($A$) of the specimen. It should be noted that using an isometric Poisson ratio to calculate this increase in area was a simplification of the true complex tissue mechanics.

The last part that needs to be solved to determine the stress is the force. This force was calculated by converting the voltage force data from the experiments to force data using the calibration constants(more information on this process in appendix A.3).

$$\varepsilon = \frac{\Delta D}{H} \tag{5.4}$$

The second part that needed to be calculated was the strain($\varepsilon$ in equation 5.4). The previous paragraph explained how the initial height $H$ was approximated. The other part of the equation is the compression depth or $\Delta D$. This was where inaccuracies of the linear stage position data became apparent. Besides the expected noise which can be filtered out, the recorded position would also move in the direction opposite to linear stage movement(as can be seen in figure 5.3). Using this position data in data processing would result in unwanted negative strain ratio. The force data of the experiments was smooth, only the steps made by the linear stage are noticeable, but no other movements could be observed in the behaviour of this data. This suggests that the linear stage movement was relatively fluid. Therefore, it was safe to process the data using a theoretical position which was linear and contains no noise. The $\Delta H$ can then be discerned by subtracting the starting position from the theoretical position at each timestamp.

Figure 5.3: Position measurements(blue) is inaccurate and at times moves in the opposite direction of theoretical linear stage position(red)




With the stress and strain calculated it was now possible to approximate a Young's modulus. The stress was plotted versus the strain to visualize how these parameters relate to one another. If there is a linear part in this plot the slope of this section is the Young's modulus.

## 5.2. Determining peak force for vacuum suction cups

The goal of this experiment was to determine what force the selected vacuum sucker can exert on the and form a better understanding of tissue sucker interaction. To test this, two experimental setups were designed. One using weights and one setup where the tissue was clamped in. After doing some preliminary testing using olives, grapes, and non-LN tissue the decision was made to use the weight test to test the peak force. This test allowed for better observation of the vacuum sucker behaviour as the trajectory of the test was longer and a more gradual increase in force application. There was one significant downside to this test due to the longer travel distance the effect of the vacuum tubes pushing and pulling on the force sensor was more pronounced. To counter the effect of this force and get a more accurate approximation of the peak fore, some dry tests were done to predict the behaviour of the test setup without a load(more on this in section 5.2.2).

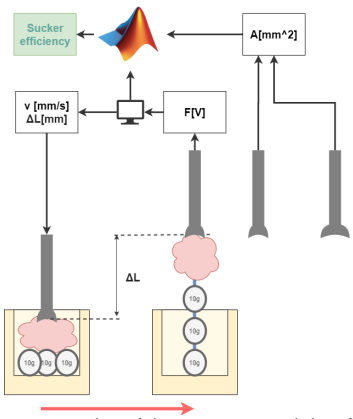
### 5.2.1. Peak force test setup

For these tests three different silicon suction cups were selected(SUF 2 SI-55 M3-AG, SUF 4 SI-55 M3-AG and SUF 6 SI-55 M5-AG from J. Schmalz GmbH(Nürensdorf, Zurich, Switzerland)). These are conical shaped suction cups of three different diameters namely two, four and six millimetre in across. These suction cups are commercially available and not rated for medical use. Silicon suction cups were chosen as this is a safe material to work within contact with tissue as it is actively used for implants and lenses. After initial testing using grapes and olives, the two-millimetre suction cup was withdrawn from future tests. The forces that this suction cup could produce were small and accuracy of measurements would be debatable given the resolution of the force sensor available to this research project.

To ensure that testing parameters are consistent throughout tests a glass slid was attached to the suction cup to see the level the negative pressure vacuum would climb to. This was part of the testing process because the experimental setup had to be disassembled and reassembled when changing tests. During this process air leaks would occur. If the vacuum of the $4mm$ and $6mm$ test setup would reach a negative pressure of $85KPa$ and $90KPa$ respectively, testing could begin. If the vacuum did not reach this point the setup was disassembled and new teflon tape would be applied until the desired value was reached. Once the vacuum setup was ready the specimens were prepared for testing.

The weights were attached to the LN using a stitching wire that was pulled through end-to-end as shown in figure 5.4b. Subsequently, this wire was tied to a loop to which a different wire with the weights would attach. Weights($10$ grams per weight) were approximately $15mm$ spaced from one another. The specimen with the string of weights attached to it would be placed in a container. The linear stage would then be put at its lowest point and the vacuum would be engaged. The specimen was attached to the suction cup and the negative pressure would build-up to the aforementioned level.

Figure 5.4: Test setup that determines peak force($F_{actual}$)




(a) Schematic representation of the test setup and data flows within the experiment

(b) Picture of weight attachment to the specimen in this case an artificial lymph node

Once this pressure level was achieved the experiment was commenced the linear stage was moved up at $5mm/s$ which would slowly increase the weight pulling on the . An experiment was deemed successful once the specimen and the weights had detached from the nozzle before they had reached the highest point. During the experiment, air was continuously pumped out of the system using a vacuum pump. Variable and data flow are schematically depicted in figure 5.4a.

A comprehensive overview of the dependant and independent variables that were of interest in this experimental setup is provided in appendix A.6.

### 5.2.2. Peak force data processing

Calculating the Peak force from the data was possible by using the calibration parameters(see sectionA.3). These calibration parameters translate the force in voltage to a force in Newton.

During initial testing it was observed that an unloaded setup would produce a significant force on its own. There are two suspected causes for this, the first being the weight of the adapter setup. This could be accounted for by testing at a slow speed and acceleration, so the disturbance would be almost constant. The harder component to account for was the tension in the air tubes that are connected to the vacuum suction cups. This effect was countered by keeping the test conditions in between experiments similar. Ensuring that no external forces were applied to the tubes and that they were free to move. Once a standardized layout was in place a series of unloaded experiments were conducted, for both the small $4mm$ and larger $6mm$ suction cups. This gave a force profile for an unloaded setup that can be subtracted from the force that was recorded during the maximal force experiments. Thereby giving a better approximation of the true peak force. This subject is discussed further in section 8.2.

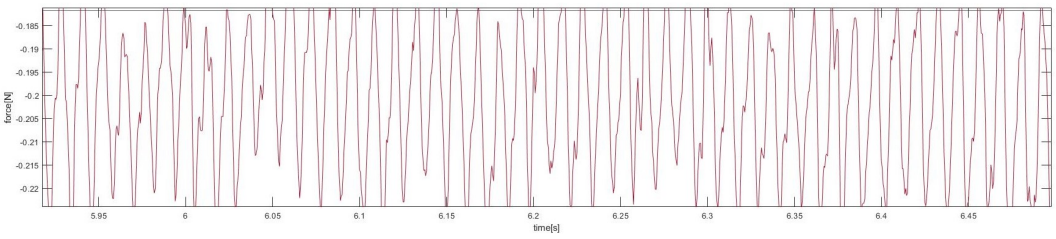
Furthermore, due to the noisy nature of the force recordings some adjustment needs to be made to get a better approximation of the true peak force(see equation 5.5). Close inspection of the data revealed that it was sinusoidal in shape, with an amplitude of about $0.02[N]$ at a period of about $85Hz$(as can be recognised in figure 5.5). To account for this a script was employed. This script takes the average of the 5 periods before $F_{peak}$ was detected. At a sampling rate of $2000Hz$ this equates to approximately $115$ samples before the peak. By doing this approximation some of the impact noise has on the outcome was reduced. This force will be referred to as the attenuated maximal force.

$$F_{max} = F_{peak} + Noise_{peak} \tag{5.5}$$

Finally, the effectiveness of vacuum sucker was calculated. The theoretical vacuum force depends on its surface area and the ability to prevent air leakage. The maximal force that a vacuum sucker is theoretically able to exert on the follows the following function:

$$F_{theorethical} = \Delta P * A \tag{5.6}$$

Figure 5.5: Sinusoidal behaviour of force data, in this case of the fourth peak force experiment conducted with the 4mm suction cup on Lymph Node 1




Wherein $\Delta P$ is the pressure differential between the negative pressure within the system and the atmospheric pressure surrounding the . $A$ is the area over which the negative pressure is applied onto the specimen. By combining equation A.4 and 5.6 into equation 5.7, the efficiency of the vacuum suction cup could be determined.

$$\eta = \frac{F_{actual}}{\Delta P * A} \tag{5.7}$$

## 5.3. Proof of concept experiment and analysis

The proof of concept was based around whether equation 5.8 can be proven. In this equation $F_{stash}$ will be determined using the stashing force experiment(5.3.1), $F_{actual}$ was proven in the peak force experiment(section 5.2 and $F_{adherence}$ was estimated roughly and will be discussed further in section5.3.2 of the report. Together they provide an estimation on whether this procedure could be successful.

$$F_{stash} + F_{adherence} < F_{actual} \tag{5.8}$$

In addition, it was also of importance to gather more knowledge on the functioning of the concept through observation. How far does the specimen go up into the tube and does that allow for it to be safely stowed into the lumen of the device?

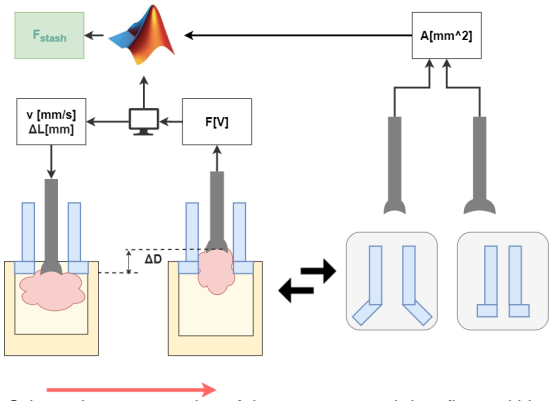
### 5.3.1. Test setup stashing force

The proposed Pull-and-Harvest concept uses a tube to safely store the LN before extraction. This is to prevent spillage, allow the snare to cut any vessels or lymph ducts and decreases the chance that the node is lost on the way out. The last test was set up to determine the force required to achieve the LN to be safely stowed away. This force was referred to as $F_{stash}$. For this test, two different tubes were designed. One straight tube which has a constant diameter and a tapered tube that tapers from a large diameter to a smaller diameter. Detailed drawings are available in Appendix A.10. The dimensions are based on discussions in-between project members and determined on what was deemed a significant decrease in wound size. It was decided that up to $20mm$ was an improvement on the current SLNB procedure. Based on this the inner diameter of the straight tube was set at $10mm$ and the inner diameter of the tapered tube starts at $14mm$ and reduces to $8.5mm$. The side of each of the tubes was lined with holes to observe the progress of the specimen through the tube(as seen in figure 5.6b). The tubes are designed to fit on top of the tray shown in figure 5.6b, both elements are connected through one another with an M2 bolt. The tubes were designed in Solidworks(Dassault Systèmes, Vélizy-Villacoublay, France) and printed in PLA.

For this test setup, the same two silicon suction cups were used as in the peak force experiment. The SUF 4 SI-55 M3-AG and SUF 6 SI-55 M5-AG from the J. Schmalz GmbH(Nürensdorf, Zurich, Switzerland) catalogue. Like the previous experiment the seal of the vacuum setup was tested using a glass slid. Once the seal was adequate( $85KPa$ for $4mm$ setup and $90KPa$ for the $6mm$ setup) the experiments could commence. The specimen was placed inside the tray before the tube plate was connected to the tray. The suction cup would be positioned over the tube to minimize contact between the sides of the tube and the cylinder that connects the vacuum suction cup to the adapter during movement. Once in position the linear stage would move the suction cup down $50mm$ where it would come in contact with the specimen. The continuous vacuum suction would create a seal between the

specimen and suction cup. The linear stage stays at this lowest point for two seconds to allow the vacuum to build up before moving up. Afterwards the specimen would be moved up at $1mm/s$ till the setup had travelled up $50mm$. An experiment was deemed successful once a good seal was created between specimen and suction cup at the linear stages' lowest point. In between experiments, the sample would be re-positioned to minimize effects caused by possible reshaping of the sample. The SUF 6 SI-55 M5-AG it could not be tested with the tapered tube as it was slightly too large to fit through the lumen of this tube. During the experiment voltage data would be captured that will be used to get force data from this experiment. Lastly, observation data was gathered of how far the sample made it through the tube.

Figure 5.6: Test setup that determines the force required to stash the lymph node($F_{stash}$)




(a) Schematic representation of the test setup and data flows within the experiment

(b) Picture of artificial lymph node moving through the tapered tunnel plate

To evaluate the damage to the LN caused by the system a specimen would be tested and evaluated by a pathologist. This test was conducted by subjecting a specimen to this experiment once using the $6mm$ suction cup as this would exert the most force on a specimen. The following question was relayed to the pathologist "is there visible damage to the LN, if so, would it impact the nodal staging process?". Once the necessary experiments were conducted all parts of the setup where cleaned using ethanol.

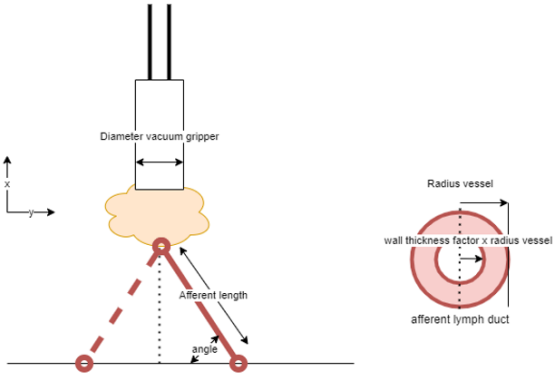
A comprehensive overview of the dependant and independent variables that were of interest in this experimental setup is provided in appendix A.8.

### 5.3.2. Determining adherence force

There was no literature available that details the mechanics and forces at work during SLNB. For this study it was important to quantify these forces to estimate whether the vacuum forces the system could deliver were sufficient. To approximate these forces a model was created that predicts the force($F_{adherence}$) that performing SLNB using the Pull-and-harvest method would require.

For the pull-and-harvest method to function the LN has to move into the lumen of the device in its entirety. This would allow the snare to safely cut all lymph ducts and vessels. The model assumes that the lymphatic vessels are the main anchors that keep the LN in its place. Therefore, the model uses the force required to stretch these lymph ducts to determine the force required to displace the LN. For resection to be successful the LN will have to be displaced for approximately $3cm$ as this allows for the larger LNs to be completely inside the lumen of the device. The force required to stretch these lymph ducts was determined using the Young's modulus(equation 5.1). Like the LNs, the Youngs modulus of lymph ducts is non-linear[46]. To account for this in the prediction of $F_{adherence}$ the highest Youngs modulus at a significant strain was used. The next variable was the initial length of each duct. This is defined by the position where the lymph ducts are clamped in by its surroundings and is an adaptable variable in the model. The area of the lymphatic vessel was modelled as a tubular object which can range between $0.5-1mm$ in radius[18, 47]. Lastly, the model allows the number of ducts to be defined and the angle at which they are positioned with respect to the applied force. With this information in hand, a worst-case scenario was set up to determine a constant for $F_{adherence}$.

Figure 5.7: Overview of the inputs that determine the force estimation of $F_{adherence}$ using the afferent model




### 5.3.3. Proof of concept data processing

To proof the pull-and-harvest method in its current state could theoretically work as a minimally invasive means of performing SLNB equation 5.8 has to be solved. To quantify this as a result the probability that this statement is true was approximated. Using the model described in the previous scenario a worst case $F_{adherence}$ was determined. The $F_{actual}$ distribution was determined in the peak force experiment(section 5.2). $F_{stash}$ distribution was determined using the data gathered using the setup described in section 5.3.1.

Determining $F_{stash}$ was quite similar to the Peak Force data processing. Similar scripts were used to determine what the peak force was during the experiment. To isolate the forces that act upon the vacuum suction cups from the total force unloaded measurements were recorded and analysed. The unloaded state was subtracted from the total force measurement to give a better approximation of the forces that act upon the suction cup. To determine $F_{stash}$ the script orders the force measurements by magnitude order and takes the average of the 1000 largest samples (at $2000$ Hz sampling rate). This was done because this test does not have a linear increase in force applied(unlike the max force experiment) to the suction cup and multiple peaks were present during each experiment.

To determine whether a procedure could be successful only the data wherein the specimen travelled through the complete length of the tube was considered. This was done since the $F_{stash}$ value for the times a specimen did not make it through is unknown because the suction cup failed before this value was achieved. Therefore, the value and distribution $F_{stash}$ is skewed towards the smaller LNs that did make it through. To partially account for this the $F_{stash}$ distribution will be scaled with a factor $c$. This factor was determined using equation 5.9. In this equation $TST$ is total number of successful trials, $ST_{ln}$ is the number of successful trials using a specific LN and $V_{ln}$ is the volume of that LN. This equation compares the mean volume of the LNs that made it through to the results of the study by Merkow et al.[16]. Merkow et al. found a median of $0.6cc$ for the $677$ benign LNs they measured and $0.8cc$ for the $149$ metastatic LNs. It should be noted that Merkow et al. selected the largest LNs from each batch to find the aforementioned values. However, since in SLNB metastatic LNs are usually the target which are in general larger than benign LNs(as discussed in section 1.3). It can be assumed that the device will have to be able to handle LNs that are larger in volume. Using this data from Merkow et al. the average LN volume for SLNB was set at $0.64cc$[16].

$$c = \frac{\sum_{ln=1}^{5} ST_{ln} * V_{ln}}{TST * 0.64} \tag{5.9}$$

All these results can be combined into equation 6.1. Probability density functions are fitted to the data of $F_{required}$ and $F_{actual}$. These functions reflect the chance the chance that these two variables are a certain value(A.6 and A.7. Where $F_{actual}$ and $F_{stash}$ are distributed variables and $F_{adherence}$ was a constant. These functions are used to calculate the probability of equation 6.1 being true. The probability of the MISLNB being successful, is the area underneath the curve right of $0$. Thereby putting a value on the chance of a successful procedure.

$$0 < F_{actual} - (c * F_{stash} + F_{adherence}) \tag{5.10}$$

# 6

# Results part II

The results are based on experiments conducted on six human LNs. One of them was put aside for pathological examination. This LN was only put through one proof of principle test to evaluate any damage that might occur during this new SLNB procedure. The remaining LNs were used for all experiments.

## 6.1. Peak force measurement

A total of $50$ peak force experiments were conducted. All these experiments provided useful data for data processing. Of these experiments half were conducted using the $6mm$ suction cup and the other half using the $4mm$ suction cup. The mean attenuated maximal force for the $6mm$ suction cup was $0.253N$ with a $95\%$ confidence interval that lies between $0.240N$ and $0.265N$. The peak force that was recorded during these experiments was on average $0.059N$ higher than the attenuated max force. For the $4mm$ suction cup the attenuated max force has a mean of $0.116N$ and a $95\%$ confidence interval that ranges from $0.105N$ till $0.127N$. The average difference between the attenuated max force and the peak recorded forces is $0.030N$. Through one-way ANOVA testing it could be determined that there is no significant difference between outcomes of individual LNs for the attenuated max force using either one of the suction cups. Using the earlier stated equation A.4 the efficiency of each of the suction cups can be determined. The average of efficiency of $6mm$ and $4mm$ suction cups was $9.9\%$ and $11.4\%$ respectively. During these experiments it became also apparent that the suction cup would wander over the surface of the LN, rather than holding in one place.

Figure 6.1: Distribution of the attenuated maxforce experiment for each of the used suction cups

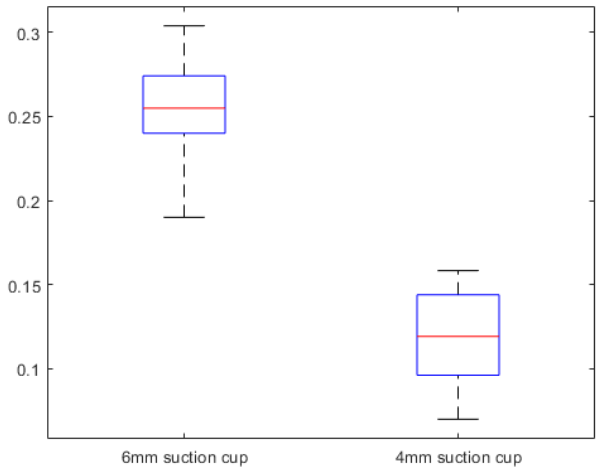
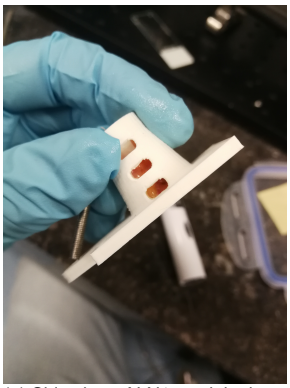
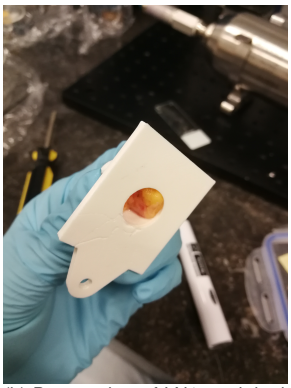


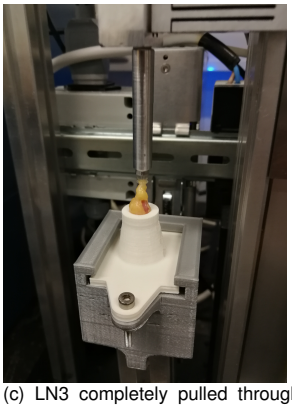
Figure 6.2: Pictures of the lymph node stashing experiments



(a) Side view of LN1 stuck in the tapered tube following an experiment



(b) Bottom view of LN1 stuck in the tapered tube following an experiment



(c) LN3 completely pulled through the tapered tube

## 6.2. Proof of principle

A total of $50$ experiments were completed using the straight tube(appendix figure A.10). Of which $24$ experiments for both the $6mm$ and $4mm$ suction cups provided valuable data. For the $6mm$ suction cup the attenuated maximal force that was detected during its traversal of the tube averaged at $0.107N$. However, the distribution of the data(red histogram figure A.6 has more samples left of the mean ) and the median($0.051N$) indicate that the true mean may lie more to the left of the curve. Additionally, it can be observed that the size of the LN has a significant impact on the force required. Four of the six times the attenuated maximal force peaked above $0.107N$ it concerned one of the two largest LNs(LN1 and LN2). Of the $24$ conducted experiments the LN would travel down the complete length of the tube in $20$. The four times a LN did not make it through the complete length all concerned LN1. LN1 would travel an average of $58\%$ of the complete length of the tube. For the $4mm$ suction cup the average attenuated maximal force was $0.069N$. Of the $24$ experiments the LN would make it through the complete length of the tube in $16$ cases. The eight cases it did not make it through all concerned LN1 or LN2. LN1 did once pass through the complete length of the tube, the other four attempts made it on average $60\%$ through the tube. LN2 which is slightly smaller than LN1 would travel an average of $79\%$ per cent through the tube. Of the $11$ times the maximal attenuated force would surpass the $0.069N$ mark eight times it is either LN1 or LN2.

For the tapered tube, a total of $25$ experiments were done using the $4mm$ suction cup. Of these experiments $24$ provided valuable data. The mean attenuated max force of these experiments was $0.240N$ with a standard sample deviation of $0.094N$. What is noteworthy from this outcome is that this max force exceeds the estimated max force determined in the previous experiment. Even though the mean force was higher LNs made it through the complete length of the tube in $14$ out of the $24$ experiments. LN2 made it through once and on other occasions would make it through on average $82\%$ of the way. LN1 never made it through the complete length of the tube and would get stuck on average at $68\%$ of the complete trajectory. When a LN got stuck inside the tube it did always clear the bottom of the tube, as can be seen in figure 6.2b. Meaning that if a resection snare were present it could still have safely resected all ducts and vessels without damaging the specimen.

Using the results of these experiments a distribution for $F_{stash}$ can be determined as described in section 5.3.3. The mean $F_{stash}$ value for the tapered tube is $0.066N$ with a $95\%$ confidence interval that lies between $0.045N$ and $0.088N$. The resulting distribution is multiplied with $c = 1.126$ to account for the volume fraction not represented in this sample. The same process is repeated for the $14$ experiments with the tapered tube which produces a mean value of $0.269N$ with a confidence interval that lies between $0.238N$ and $0.300N$. This distribution is multiplied with a factor $c = 1.296$ to account for the volume fraction not represented.

The peak force that the suctions cups can deliver were determined in the previous experiment. Therefore, the $6mm$ suction cup $F_{actual}$ is a normally distributed value around $0.253N$ with a standard deviation of $0.031N$. For the $4mm$ suction cup $F_{actual}$ is a normally distributed value around $0.116N$ with a standard deviation $0.028N$.

To determine $F_{adherence}$ the model described in section 5.3.2 was used to produce a worst-case scenario. In this scenario, nine ducts are at an angle of $90$ degrees. This will put the entire required stretching force directly opposite the pulling direction of the suction cup. Each vessel is defined to be $2mm$ in diameter and have a wall thickness factor of $0.5$. A value for afferent length could not be found in literature. Therefore, it was estimated that the afferent would be clamped in at approximately $5cm$ from their attachment point to the lymph node. Athanasiou et al. found out that to elongate a lymph duct by $30\%$ a force of $0.006N$ was required[46]. Since the lymph duct has to be stretched from $50mm$ to $80mm$ a $60\%$ elongation is required. By looking at the results of [46] an estimation can be made for the Youngs modulus of $60\%$ elongation which is $17KPa$. Therefore, to estimate the worst-case scenario a Young's modulus of$17KPa$ was used. The highest value at $32mm$ stretched length is $0.141N$ this will be the $F_{adherence}$ value for the proof of concept. A more extensive results table is included in appendix section A.4 table A.3. $F_{required}$ is then attained by adding the $F_{adherence}$ to the $F_{stash}$ distribution.

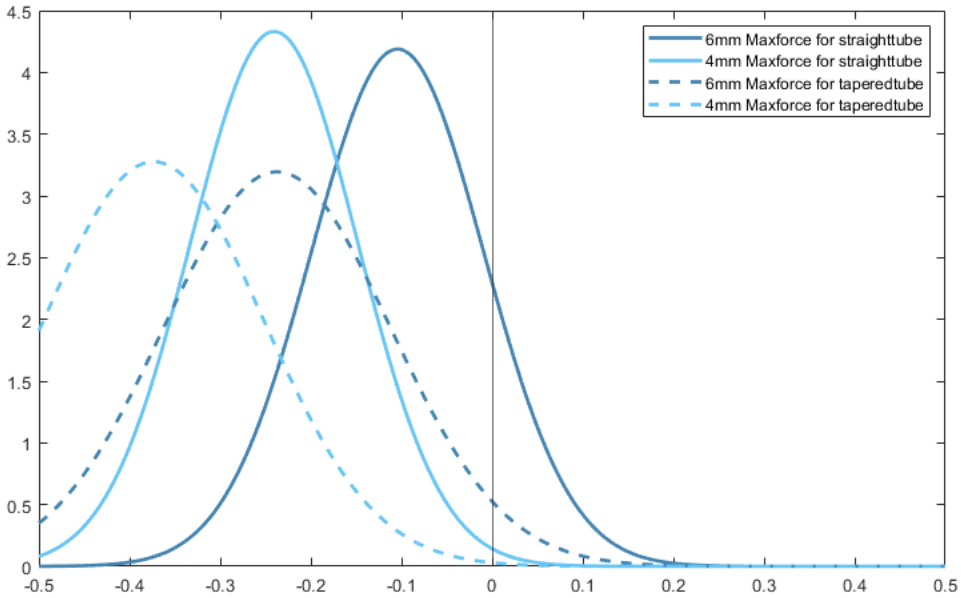
$$0 < F_{actual} - F_{required} \tag{6.1}$$

The probability density distributions of $F_{required}$ is subtracted from the probability density distribution of $F_{actual}$ and combined into one distribution to produce the distributions depicted in figure 6.3(in appendix A.7 the graphs of the separate probability density functions are available). The area of these combined probability curves that is larger than $0$ gives an estimation of the likelihood that the procedure is successful given the available data(based on equation 6.1). The probabilities of this analysis are summarized in table 6.1.

Table 6.1: Chance that a Pull-and-Harvest procedure is successful based on the available data

| | Straighttube | Taperedttube |
|---|---|---|
| **6 mm cup** | 8.2 % | 2.8 % |
| **4 mm cup** | 0.3 % | 0.1 % |

Figure 6.3: Four combined probability density functions each for a different configuration, where the area of the probability density function larger than 0 represents the probability of a successful procedure(straigttube is drawing in appendix A.10, taperedtube is drawing in appendix A.11)



## 6.3. Deriving material properties of tissue

To attain the stress-strain relationship of LNs under compression a total of $25$ weighing tests were completed using human LNs of which $23$ produced usable data. Using this data set, estimations could be made of the volume of each of the LNs. These findings are presented in table 6.2. Wherein the mean estimated volume is the standard mean of the volume approximation script. The standard deviation is calculated using the sample standard deviation formula. The manually measured volume is the result of measuring the LNs using a calliper. Lastly the Volume used for further analysis was derived by combining these two measurements using the method described in section 5.1.2.

Table 6.2: Lymph node volume approximation results

| | LN1 | LN2 | LN3 | LN4 | LN5 |
|---|---|---|---|---|---|
| **Mean Estimated volume [mL]** | 1.110 | 1.216 | 0.645 | 0.387 | 0.502 |
| **Standard deviation [mL]** | 0.180 | 0.210 | 0.070 | 0.096 | 0.040 |
| **Manually measured volume[mL]** | 0.898 | 1.123 | 0.314 | 0.346 | 0.285 |
| **Volume used for further analysis[mL]** | 1.104 | 1.118 | 0.535 | 0.374 | 0.430 |

In total $25$ material property tests were conducted on the five available LNs. Of these experiments, the data of one trial was not usable for further analysis. The sixth of the available LNs was exempted from this test. This was done to exclude the effect this experiment might have on the pathological examination needed for the proof on concept experiment. During these experiments, a mean strain rate of $0.38$ was achieved. Only eight experiments surpassed a max strain rate of $0.40$. This led to a mean indentation depth of $1.44mm$. The stress-strain curves of these experiments are presented in appendix A.1. Closer inspection of these curves reveals that in a majority of the curves no linear part can be identified. Therefore, determining Young's modulus based on these results is not possible. However, the stress-strain curves could be fitted using exponential curves. These fits are described by equation 6.2 wherein $a$ and $b$ are constants specific to each experimental result, and $\sigma$ and $\varepsilon$ are stress and strain. These results are summarized in table 6.3. to predict LN stress-strain behaviour, this prediction is presented in figure A.4. By using one-way ANOVA analysis, it was determined that there is no significant difference between the constants of each LN given the available data set. The complete dataset is available in appendix A.4.

$$\sigma = a * e^{b*\varepsilon} \tag{6.2}$$

Figure 6.4: The estimated fit for stress strain behaviour of Lymph nodes

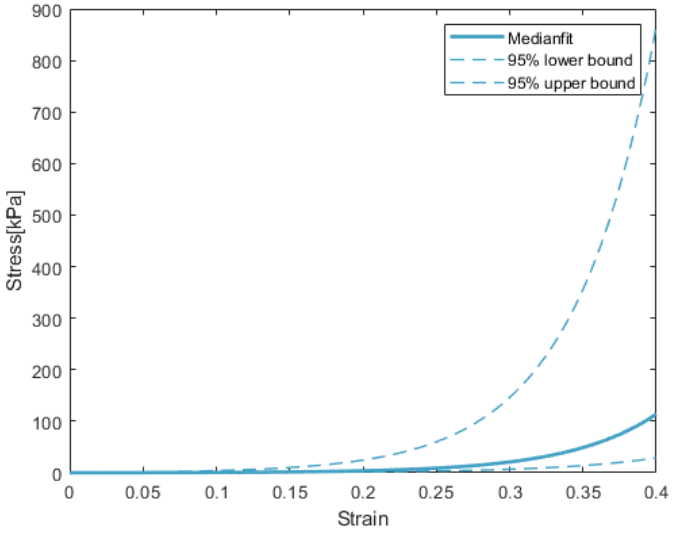


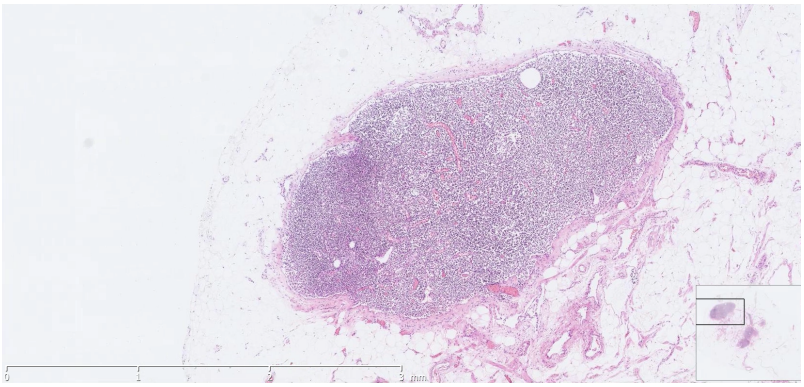

Table 6.3: Table summarizing the constants of the exponential fit of the stress-strain relationship

| All LN | a | b |
|---|---|---|
| **Mean** | 394.3 | 16.2 |
| **Median** | 132.0 | 16.9 |
| **Std** | 782.8 | 4.3 |
| **High CI 95%** | 701.1 | 17.8 |
| **Low CI 95%** | 87.4 | 14.5 |

## 6.4. Pathological results

From the six LNs that were available to this study one was used for pathological examination to determine whether the pull-and-harvest method would interfere with nodal staging analysis. This LN was subjected once to a straight tube experiment with a negative pressure of $90KPa$ acting upon its surface. Following this experiment, the node was handed over to the pathologist. After investigating the node for possible damage, the pathologist came back with the following result: the histological architecture has not been disturbed by the vacuum tests.

Figure 6.5: Cross section of the examined haematoxylin and eosin stained (H&E) lymph node with an intact lymph node capsule and dense accumulations of lymphocytes



# 7

# Conclusion

This study has opened the topic of minimally invasive sentinel lymph node biopsy and found some interesting results but was not able to give a conclusive solution for this problem. In part I of this report a design study was performed to find a solution for this problem. Out of three potential options, the Pull-and-Harvest solution came out at the favourite for further development. The Pull-and-Harvest technique uses a vacuum suction cup to pull the sentinel node inside of a tube, hereafter it uses a snare to separate the node from it is surrounding tissue.

In the second part of this thesis, the goal was to investigate Pull-and-Harvest method and determine the feasibility of performing sentinel lymph node biopsy in this manner. Since it was not attainable to test a conceptual instrument in vivo in this study, three sub-questions were set up to test this ex vivo.

Sub question one focuses on the force that keeps the SLN in its place. Since there was no literature available on the specific interaction of displacing a lymph node from its embedded position a simplified model was created to quantify this force. This model assumes that the main part of the required force comes from elongating the lymph ducts and vessels. With this model, a worst-case scenario for this force was determined. This worst-case scenario set the adherence force of the lymph node at $0.141N$.

Sub question two focused on the efficiency and interactions between vacuum suction cup and LN. Through experimental testing, the peak force of both suction cups could be determined with relatively high accuracy. The average peak force these suctions cups could provide was $0.116N$ for the $4mm$ cup and $0.253N$ for the $6mm$ cup. These results also revealed that the efficiency of the $4mm$ and $6mm$ silicon suction cups was very low($9.9\%$ and $11.4\%$ respectively) so there is room for significant improvement. A hypothesis as to why the efficiency of these type of suction cups is this low is provided in the discussion of this thesis.

The third and last sub-question combined the two sub-question to predict whether the set-up as is could perform MISLNB. The result of the first question and the results of an experiment that determined the force needed to pull the lymph node inside of two differently shaped tubes where summed to construct a required force. This required force was compared with the result of the second sub-question to determine whether this set up could perform its intended task. The results of this analysis indicate that the setup can stash the LN but has little chance of performing a successful procedure with the additional adherence force. One lymph node was put through a MISLNB pull-and-harvest procedure to determine whether it could have an impact on the nodal staging procedure. A pathologist examined this node and could not find any significant damage to the node.

Furthermore, the study attempts to fill a gap in the available knowledge of stress-strain behaviour of human lymph nodes. An attempt was made to define a Young's modulus to enable comparison of the results to the limited available literature, but the results of these tests did not show any linear behaviour. By observing the stress-strain behaviour of the lymph nodes an exponential fit could be found. The data set and spread of the data was too large to discern differences in material properties of individual lymph nodes.

To conclude, this thesis has not yet found a definitive solution. However, it does fulfil the goal set at the start of this project to outline the problem of MISLNB and highlights the areas of interest for further research.

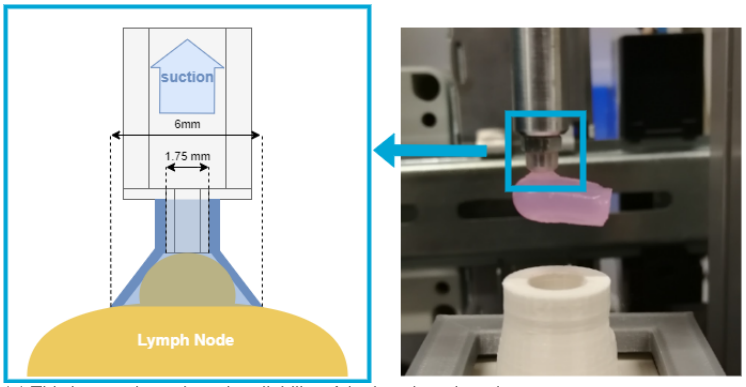
# 8

# Discussion

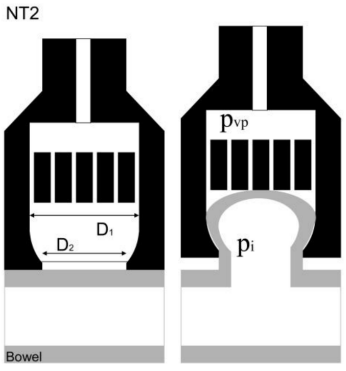
Is the Pull-and-Harvest method a suitable option for minimally invasive sentinel lymph node biopsy? From the results of this thesis, the conclusion would be that it is unfit for this task. Since the force that the two suction cups could handle does not out-scale the required force. However, the peak force experiments revealed that the efficiency of the silicon cone-shaped suction cups used for these experiments was very low. One hypothesis is that this is related to the shape and flexibility of the suction cup. The suction cups that were used are meant for picking up flat objects. The pliancy and low stiffness of the lymph nodes may harm the efficiency of the suction cup because they reduce the effective area over which the negative pressure is applied. This can be observed in figure 5.7, where the artificial lymph node is sucked up into the volume of the suction cup. While the outer diameter of the suction cup is $6mm$ as shown in figure 8.1a, it only moves straight in at $1.75mm$). This could in a worst-case scenario result in the situation depicted in figure 8.1a reducing the theoretical force from $2.547N$ down to $0.217N$. This of course is a huge drop in force and should be prevented. Further evidence that this effect could be happening comes from the experiments done with grapes. Grapes are stiffer(as long as their outer skin is intact) and have a surface that is less pliant than that of lymph nodes. The average efficiency that the $6mm$ and $4mm$ suction cups were able to produce under the same testing conditions was on average $47.3\%$ and $63.9\%$ respectively. Compare this to the efficiency results using lymph nodes of $9.9\%$ for the $6mm$ cup and $11.4\%$ for the $4mm$ cup, and one can conclude that the impact of this behaviour is substantial.

If it is possible to increase the efficiency of both suction cups to $40\%$ the feasibility of this concept will increase significantly. The $6mm$ will be able to provide $1.02N$ of force which is approximately four times higher than the force that is required to perform a pull and harvest procedure. For the $4mm$

Figure 8.1: Illustrations of cause and possible solution of low efficiency of suction cups




(a) This image shows how the pliability of the lymph node reduces the effective surface area of the suction cup, a possible reason for efficiency loss of the conical silicon suction cups used in this thesis




(b) Illustration from the research study by Durandus Vonck[35], illustrating a vacuum suction cup that could perhaps prevent the issue shown in figure 8.1a

suction cup an increase to $40\%$ efficiency will boost its force $0.428N$ which is also more than suitable to deliver the required force. So how could this jump in efficiency be made? In the previous paragraph it was mentioned that the shape of the suction cups used in these experiments was not ideal. A solution to this problem would be a suction cup wherein the pliancy of the lymph node does not decrease the effective area. A solution to this problem could be the suction cup designed by D. Vonck[35], the diameter of the suction is constant, and a filter prevents the tissue from reducing the area of the suction cup. Small restriction like the one shown in figure 8.1b would help limit leakage from occurring. This design by Vonck reported a mechanical efficiency of $70\%$, such an increase would make the Pull-and-Harvest a feasible solution. It should be noted that the device was used to grip bowels which are in many ways different from lymph nodes. Further research and experimentation will be required to adapt these principles for use in SLNB. However, It is the writer's opinion that this design could help combat the aforementioned effects and make vacuum suction a viable tool for MISLNB.

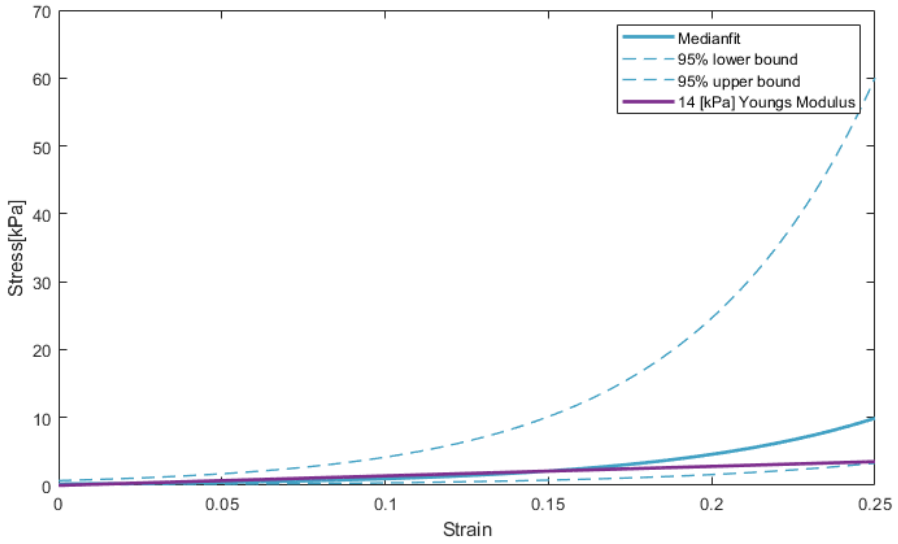
## 8.1. Annotations on material property experiements and results

Material behaviour of tissues is often described as viscoelastic. For viscoelastic materials, Hooke's law does not accurately portray actual material behaviour. A more accurate to describe material properties is through the loss and storage moduli which describe the dynamic modulus. The dynamic modulus is a time-dependant property which takes into account lost energy and the effects of time. This complexion in material properties is not modelled by Hooke's law. The reason that it was attempted to measure Young's modulus instead of the dynamic modulus has to do with availability of measuring instruments and the results that were needed. For this study only an approximate description of material properties was required. Unfortunately, the tools to measure the dynamic modulus were not available for use on-site and the human tissue could not be transported and tested off location.

The expected non-linear behaviour of LNs was consistent with what was found in the experiments and can observed by looking at the stress-strain graphs. In these curves no clear linear part could be observed. Therefore, the results were fitted exponentially. Since there is a lack of data available regarding compression testing of lymph nodes it is difficult to confirm these results. However, comparing the data available for other tissue structures to the results found in this study reveals that these lie within the expected range for tissue[48]. Furthermore, the initial part of the found exponential relationship is in the same order of magnitude as the values found through shear wave modulation[22, 23, 45]. In figure 8.2 it can be observed that lines start off close to one another and diverge at strain rates larger than $0.2$.

Since every lymph node could only be used five times to estimate the stress-strain relationship the

Figure 8.2: The stress-strain relationship that resulted from the material tests in comparison with a $14kPa$ stress-strain relationship that is found through shear wave modulation[22, 23, 45]



available data set is very small. Increasing the number of repetitions may have implications on material properties by both exposure to stress and dehydration[42, 43]. Since the main focus of this study lies on proving the pull-and-harvest concept, it was of importance that the lymph nodes were in good condition going into the other experiments. Therefore, a larger sample size in finding the stress-strain relationship was given up for a higher accuracy result in the following tests.

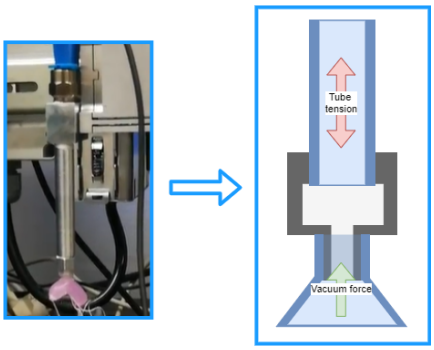
There were also physical limitations of the linear stage. Since the relatively high minimal velocity of $1mm/s$, the limited reliability of the positional data and the small size of lymph nodes(initial height ranging $2-5mm$) made it challenging to achieve a constant strain rate as the indentations are in the order $1-3mm$. This results in a small data capture window($1-3$ seconds). Thereby, making it difficult to capture full stress strain behaviour and keep conditions the same across every experiment.

Another inconsistency with the material testing is reflected in the stress-strain curves(appendix A.1) and the estimates for the $a$ and $b$ constants. From these results its apparent that the first measurement of an experimental series deviates significantly from the following experiments. This could be related to the stamp altering the shape of the lymph node. This is reflected in the dataset(see appendix A.4) as the initial height for the first measurement was significantly larger than the follow-up experiments for each lymph node. The assumption was that re-positioning the lymph node in between experiments would solve this issue but this seems not to be the case. Compressing a small part of the lymph node instead the whole lymph node might make the outcome for the first measurement more coherent with the rest.

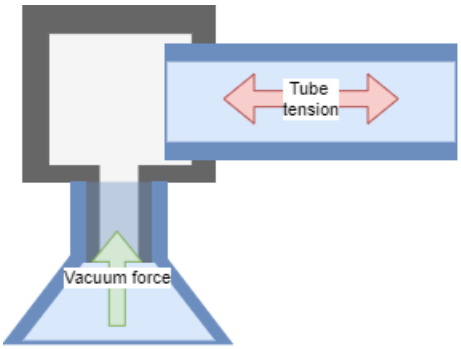
## 8.2. Improvements for the current test-setup

Besides the expected noise of the force measurement there was also a more serious form of systemic error in this data. This error was created by the way in which the test setup was constructed. In the setup the vacuum suction tube directly in line with the force measurements as illustrated in figure 8.3a. By creating a standard layout for the setup and recording the forces of an unloaded system the goal was to filter these effects from force measurement of interest. However, this was proven to be more challenging than anticipated. A solution for this could be orientating the tubes perpendicular to the vacuum force as depicted in figure 8.3b. This would limit effect of tension on the force measurement. However, this is no impeccable solution as the tube will still impose a moment force put on the assembly might and it would require a larger adapter block. The better option would be to build a setup that ensures that the tension is the same each subsequent experiment.

Figure 8.3: Vacuum tube interfering with force measurements




(a) Tension in the vacuum that is in line with force measurement by the sensor




(b) Possible solution for the problem illustrated in figure 8.3a

## 8.3. The effect of low sample size on the outcome of this study

Due to the limited availability of human lymph nodes only a few tests could be carried out using the vacuum suction cups. Therefore, the strength of the claim that this vacuum setup is unfit to complete a MISLNB is somewhat weakened. However, even with a low sample size the peak force the suction cups can bear is well defined with little variance. Further testing using these two suction cups given their low efficiency has a low likelihood of changing the outcome of this thesis. Investing in the next step in the research and development of this new procedure would be the logical next step. Wherein

the design and testing of a better suction cup could further proof whether this a suitable method for MISLNB.

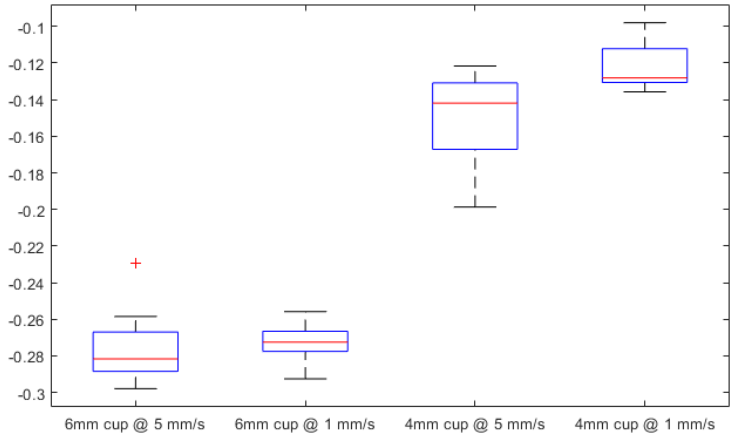
As mentioned is section 6.2, $F_{stash}$ has high likelihood to be dependent on lymph node size. Since only a small sample of the various sizes of lymph nodes were tested the found distribution of $F_{stash}$ does not completely reflect the actual distribution. To account for this a $c$ factor was introduced in equation 6.1. However, a larger sample is needed to truly estimate the distribution.

Due to the low availability of tissue samples, only one lymph node could be used for pathological analysis. The result of this analysis was positive for the pull-and-harvest method, however, due to the low sample size not completely conclusive. In the study by Vonck bowels were held using a vacuum for $15$ minutes and no clinically relevant damage was found[49]. Vonck does report that fluids gather at the site where the negative pressure is applied, but this balance restores once the pressure is relieved. Presumably, the time the vacuum will be engaged during a Pull-and-Harvest procedure is shorter due to the simplicity of the solution. This furthers the probability that this procedure is asfe for MISLNB, and does not impact further diagnosis of said node. However, the available data in this study is not enough to substantiate a definite claim, therefore further research should be conducted on this subject.

## 8.4. The effect of velocity on peak force measurements

Velocity is listed as one of the independent variables for the max force and proof of principle experiments (see tables A.6 and A.8). The effect of this variable on the test outcomes could not be tested due to the limited availability of lymph nodes. However, a small set of tests could be performed using the artificial lymph nodes(more info on artificial LNs in appendix A.2). The hypothesis was that reducing the velocity at which the linear stage moves up increases the max force a suction cup would produce. As velocity could perhaps influence the chance of leakage occurring. Two different velocities were used to test this hypothesis, $5mm/s$ which is similar to the conditions of the real LN experiments and $1mm/s$. Comparing the outcomes of the $40$ tests using one-way ANOVA analysis(significance level $\alpha = 0.05$) resulted in a p-value of $0.63$ for the $6mm$ suction cup and $0.009$ for the $4mm$ suction cup. These results indicate that there is no evidence found for velocity impacting the outcome of the $6mm$ max force results, but there is evidence that it has an impact on the $4mm$ results. The mean sampled max force of the $4mm$ experiments at $5mm/s$ is slightly higher at $0.149N$ than the slower $1mm/s$ experiments which average around $0.121N$. This implies that slowing down might have a slightly negative effect on the efficiency of the $4mm$ suction cup. This could have to do with the air having more time to escape before a peak force is achieved, but more research is needed to definitively prove this. The distribution of these additional tests is shown in figure 8.4.

Figure 8.4: Distributions of peak force measurements at two different velocities using the artificial lymph nodes



## 8.5. Clamped experiment vs. weighted experiment, the effect on peak force measurements

Another factor that may have impacted the max force experiments is how the downward force was applied to the specimen. During the max force test weights(as described in section 5.2.1) were attached to the lymph node using stitching wire. While observing the experiments suspicion arose on whether the attachment points increased the chance a leak would occur and therefore would inhibit the chance of the suction cup to reach its true potential. While it could be argued that this is somewhat like the in vivo situation where afferent lymph ducts and blood vessels might apply force to the lymph node in a similar fashion. Some additional testing was done to see whether these effects were present and could be quantified. To perform these experiments two different artificial lymph nodes and two grapes were used.

The control experiment was set up similar to the setup described in section 5.2.1 of the report. While in the test case each specimen would be clamped in along all sides to ensure that the force that pulled the specimen downwards was equally distributed along the clamped surface of the specimen. This would ensure that the specimen would peel away from each side equally instead of two concentrated spots.

The results from the experiments 80 experiments are presented in the box plot graphs in appendix A.6. What could be observed is that the experiment using weights have a larger variance than the clamped experiments in each setting. The median max force for the weighted experiments is higher than its counterpart in five out of the eight different settings. Translating this to result to lymph nodes however is difficult as there could be many factors that play a part in this happening. What can be said about this data is that there is no clear evidence that puts one test setup is superior over another, based on their median results.

## 8.6. Further Research

To solve the problem of MISLNB one of the more important factors to focus on the adherence force of the lymph node. As Literature offers little to no insight into the mechanisms and forces that are at play during such a procedure. Delineating and quantifying the problem at hand will make it easier to design and determine an effective design for MISLNB. In addition, there is an inherent value in finding a way in which such measurements can be done and standardized, just to help to get this information out in the scientific community to it help develop medical instruments for many other implementations.

The Pull-and-Harvest method could not be definitively proven in this thesis, but maybe one of the other two proposed solutions could. Or perhaps the vacuum assisted core needle device as Evans et al. tried to use for MISLNB [6]. It would need significant modification to limit the bleeding and require less cuts to extract the SLN intact, but it could be a viable solution. So further research should explore these concepts and others that are perhaps even better.

It is the writer's opinion that using a vacuum gripper is a good solution for this problem. The low risk of damaging the tissue, simplicity, ease of use, its ability to approach the target from any direction and the untapped potential increase in efficiency of the suction cup substantiate that opinion. Thereby the observations made and discussed in this report could be of aid. An increase in efficiency could perhaps mean that an outer tube is not even needed to stash the LN and it can be pulled all the way out. Therefore, further research and development into a suction cup that optimizes the footprint could be fruitful to solve the problem of minimally invasive sentinel lymph node biopsy.

# 9

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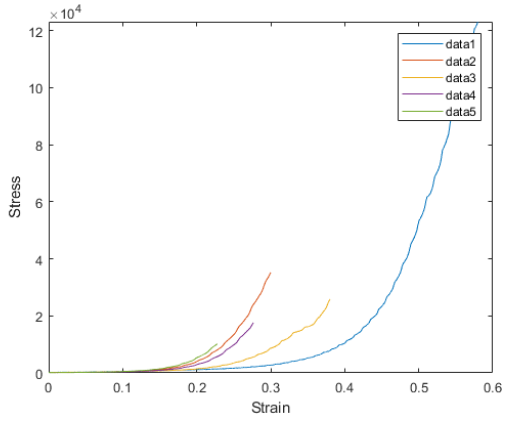
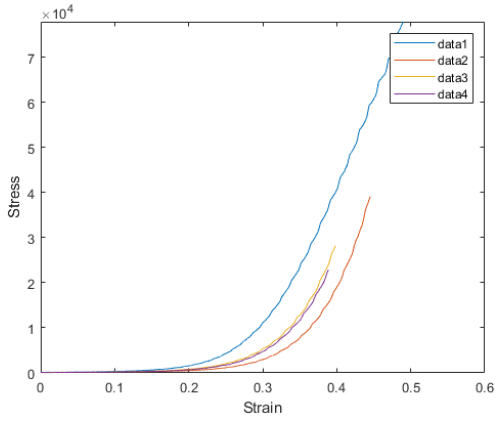
# A

# Appendix

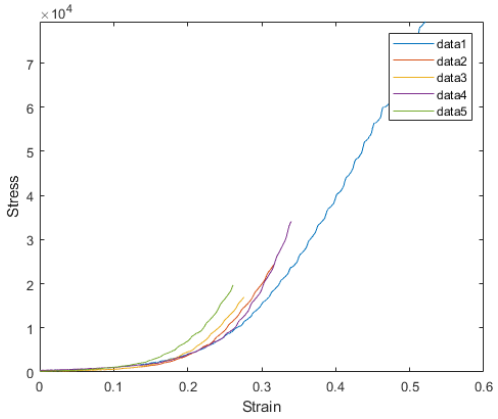
## A.1. Stress-strain graphs



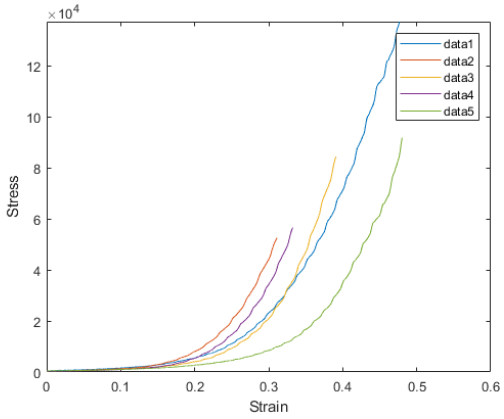

(a) Results of material tests of LN1



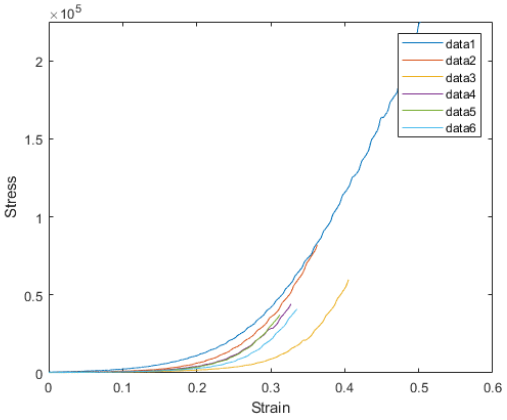

(b) Results of material tests of LN2



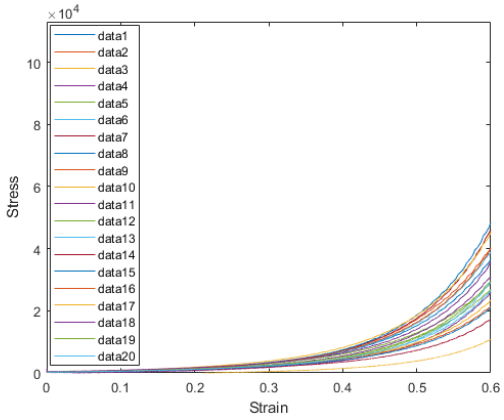

(c) Results of material tests of LN3




(d) Results of material tests of LN4




(e) Results of material tests of LN5




(f) Results of material tests of Artificial node

## A.2. Creating artificial lymph nodes

The goal was to use real human LNs supplied by the Erasmus Medical Center for all the tests. In the case that these human LNs were unavailable Artificial LNs were produced to take their place.

### A.2.1. Phantom creation method

Artificial LNs are created to mimic the biomechanical properties of real LNs. In this study the phantoms were made using PVA hydrogel. As mentioned in section 1.3 of the report the stiffness of LNs can range from $2-80KPa$. The non-malignant nodes are less stiff than metastatic nodes. With the creation of the phantoms the aim was to create at least one type of artificial node in the low category$(10-20Kpa)$ and one type in the high category $(40-80Kpa)$.

The material properties of PVA-H can be altered by varying concentrations of each of the ingredients and the number of freeze-thaw cycles. For this study five different batches of artificial nodes were created using PVA-H. To mimic the shape of the LNs, the PVA-h was cast in the distal end of paint pipettes as shown in figure A.2a. Once cured they could be carefully removed from the mould.

The first three batches were not fit for the experiments. From discussions with fellow students and experience from the MISIT lab the following solutions for the problems that are described in section A.2.2 were given: a lower Number of freeze-thaw cycles and the addition of cooling fluid or Dimethyl Sulfoxide increase the homogeneity of the material making it less likely to crumble[50, 51]. With these findings in mind batch four and five were created. The recipe for each batch is given in table A.1. Ultimately human LNs became available and the urgency of creating an accurate LN phantom decreased.

Table A.1: Table of recipes of created phantom lymph nodes

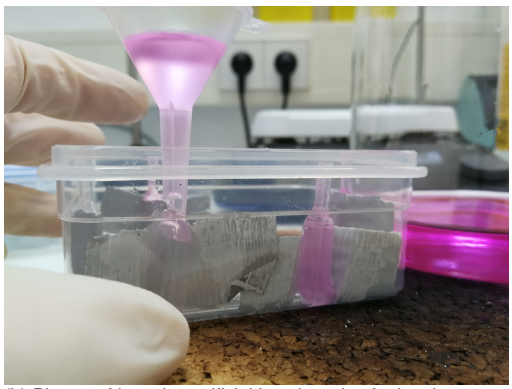
| Phantoms | Batch 1 | Batch 2 | Batch 3 | Batch 4 | Batch 5 |
|---|---|---|---|---|---|
| Grams of water | 94.0 | 150.0 | 92.0 | 47.5 | 45.5 |
| Grams of PVA | 6.0 | 15.0 | 8.0 | 5.0 | 10.0 |
| Grams of cooling fluid | 0.0 | 0.0 | 0.0 | 47.5 | 45.3 |
| Total start weight | 100.0 | 165 | 100 | 100 | 100.8 |
| Initial WT% PVA | 6.0 | 9.1 | 8.0 | 5.0 | 9.9 |
| Total end weight | 63.9 | 135.8 | 80.9 | 90.2 | 88.8 |
| End WT% PVA | 9.4 | 11.0 | 9.9 | 5.5 | 11.3 |
| No. of freeze cycles | 2 | 2 | 3 | 1 | 1 |

### A.2.2. Results of artificial lymph node creation

The first few batches of artificial LNs were unsuccessful in providing a good alternative for human LNs in these specific test settings. The cohesion between grains of the samples was insufficient to keep the material together once vacuum suction was applied. This resulted in grains of the artificial node

Figure A.2: Photographs of the phantom node creation process

(a) Picture of how the artificial lymph nodes for batch one, two and three looked once removed from the mould



(b) Picture of how the artificial lymph nodes for batch one and five were casted

Table A.2: Table summarizing the constants of the exponential fit of the stress-strain relationship

| ALL AN | a | b |
|---|---|---|
| Mean | 138.0 | 9.3 |
| Median | 137.5 | 8.9 |
| Std | 59.8 | 1.0 |
| High 95% | 164.2 | 9.7 |
| Low 95% | 111.8 | 8.8 |

Figure A.3: Photo of the damage the 6mm suction cup inflicted on an Artificial node from batch 1

to be sucked into the suction cups. This damaged the artificial nodes significantly as can be seen in figure A.3, a secondary effect of this phenomena is that at times it would clog the test setup.

Therefore, two new batches were made to try and prevent this from happening. Batch four was too soft and would not separate from the mould. Batch five however was successful and could be used for the tests. Batch five produced artificial nodes that were usable for testing. These could then be used to test some additional questions described in section 8.4.

The stress-strain behaviour of the samples of batch five were tested using the compression test described in section 5.1. In total $20$ compression tests were performed on two artificial LNs from batch five. The results of these experiments were fitted using equation 6.2. By investigating these results, it can be observed that the spread of data is much smaller than the results of the experiment conducted on LNs. The mean indentation depth of these experiments was $3.4mm$. Strain rates ranging from $0.6$ to $0.7$ were consistently reached using the artificial LN.

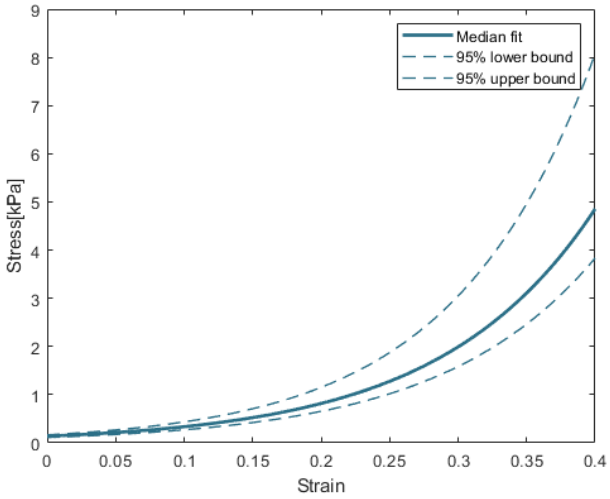



Figure A.4: The estimated fit for stress strain behaviour of Lymph nodes

## A.3. Force calibration process

The force sensor(LSB200 series, FUTEK Advanced Sensor Technology, Inc., California, USA) provides force data in the form of a voltage readout. This had to be translated to Newtons to enable further data processing. Therefore, calibration experiments were conducted to find the parameters that translate the voltage data to newton data.

### A.3.1. Force calibration Method

The experiments were set up so that the force that was exerted on the force sensor was known. Weights were used to apply a constant force to the sensor. For each weight($50, 100, 150, 200, 250 and 300 grams$) ten tests were conducted to have an accurate estimation of the force they applied on the sensor. During the experiment, the platform was not moved up or down so that the force could be purely described as gravity and no other forces such as inertia would be involved. The force could then be calculated using equation A.1, wherein $m$ is the mass in kilograms and $g$ is the gravity acceleration constant($9.8 m/s^2$ on earth).

$$F = m * g \tag{A.1}$$

By plotting the mean voltage output for each of the weights versus the Newton's force of the weights a fit could be made to determine the voltage to newton relation. This fit was then used to translate the voltage output of the sensor to a force output for the other experiments.

### A.3.2. Force calibration results

Plotting the mean voltage outputs for the force calibration experiments resulted in the graph shown in figure A.5. In this graph it could be observed that there was a linear relation between Voltage and Newtons. Since the relation that couple's voltage to newton does not cross the (0,0) point, the two variables can be fitted using equation A.2.

$$Force[N] = a * Force[V] + b \tag{A.2}$$

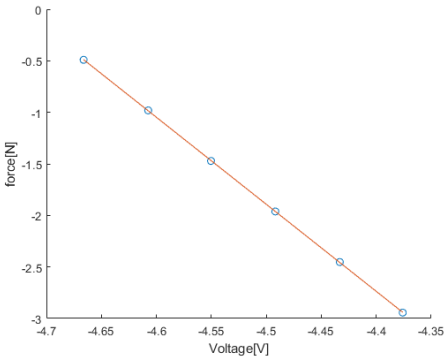



Figure A.5: Linear relation between force in newton versus force in voltage. Blue dots represent mean voltage of experiment vs their supposed weight, the red line is a plot of the calibration function A.3

Using linear regression, the two calibration constants were found which resulted in the translation formula A.3. These calibration constants were used to process the force data for the other experiments.

$$Force[N] = -8.4456 * Force[V] - 39.8978 \tag{A.3}$$

Additionally, it was observed during the calibration experiments that the provided force sensor did not provide the same base voltage at the start of each experiment. This happened even though experimental setup was kept constant throughout testing. As the effects of this offset were significant, each force dataset was normalized around the force on a known unloaded time frame in the experiment.

## A.4. Probability density distributions of the MISLNB required force and the peak force of each suction cup

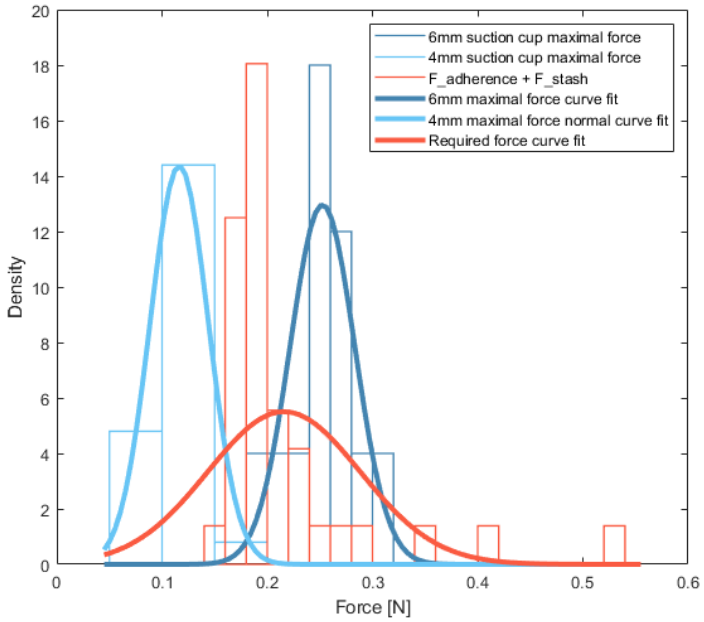



Figure A.6: Probability density function fitted to the data(histograms) of the maximal attainable forces of the suction cups and the Required Force to perform a procedure using a straight tube(drawing in appendix A.10)

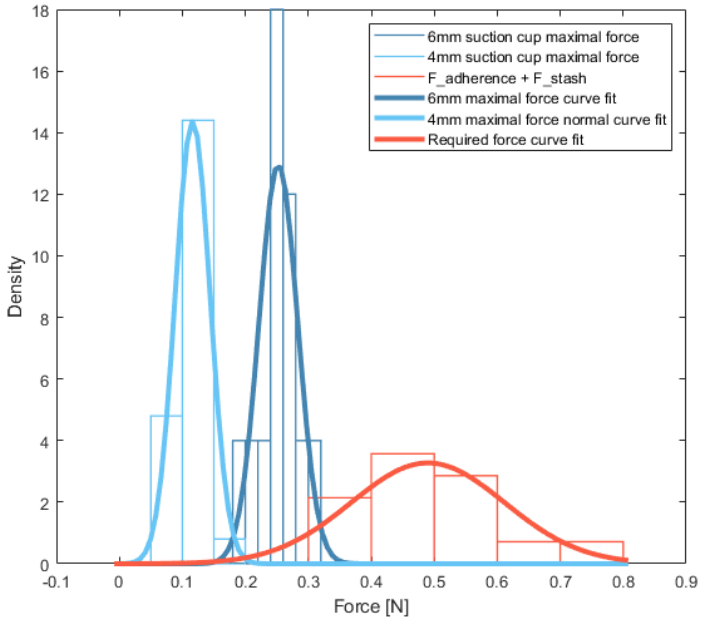



Figure A.7: Probability density function fitted to the data(histograms) of the maximal attainable forces of the suction cups and the Required Force to perform a procedure using a tapered tube(drawing in appendix A.11)

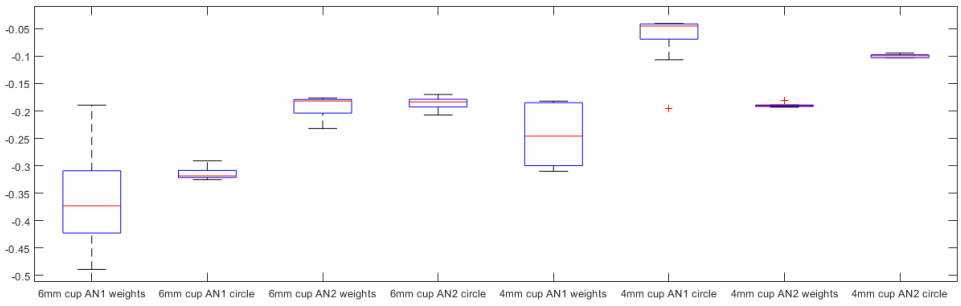
## A.5. Results of adherence force model

Table A.3: Estimated required force to elongate nine $5cm$ long lymph ducts of $2mm$ in diameter a wall thickness factor of 0.5 with a Young's modulus of $7.5KPa$ and $17KPa$ at various afferent angles

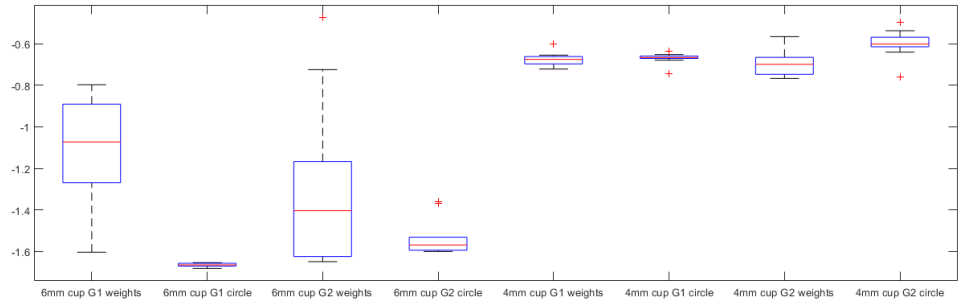
| Node displacement[mm] | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 |
|---|---|---|---|---|---|---|---|---|---|---|
| Force[N], 90 Deg, 17Kpa | 0.000 | 0.027 | 0.050 | 0.070 | 0.087 | 0.103 | 0.117 | 0.129 | 0.141 | 0.151 |
| Force[N], 90 Deg, 7.5Kpa | 0.000 | 0.012 | 0.022 | 0.031 | 0.039 | 0.045 | 0.052 | 0.057 | 0.062 | 0.067 |
| Force[N], 60 Deg, 17Kpa | 0.000 | 0.024 | 0.045 | 0.063 | 0.080 | 0.096 | 0.109 | 0.122 | 0.133 | 0.144 |
| Force[N], 60 Deg, 7.5Kpa | 0.000 | 0.010 | 0.020 | 0.028 | 0.035 | 0.042 | 0.048 | 0.054 | 0.059 | 0.063 |
| Force[N], 30 Deg, 17Kpa | 0.000 | 0.015 | 0.029 | 0.044 | 0.058 | 0.072 | 0.085 | 0.097 | 0.109 | 0.120 |
| Force[N], 30 Deg, 7.5Kpa | 0.000 | 0.006 | 0.013 | 0.019 | 0.026 | 0.032 | 0.037 | 0.043 | 0.048 | 0.053 |

## A.6. Weighing max force using weights versus clamped in at all sides

Figure A.8: Testing the effect on Maxforce measurement using two different measurement methods




(a) Distribution of experimental results to determine the effect of different maxforce testing methods using artificial nodes




(b) Distribution of experimental results to determine the effect of different maxforce testing methods using grapes

## A.7. Complete database of stress-strain relationship tests

Table A.4: Table with the results of the stress-strain relationship testing

| Specimen Name | Estimated Volume$[m^3]$ | Used Volume$[m^3]$ | Exponential fit constant $a$ | Exponential fit constant $b$ | initial height$[mm]$ | Indentation $[mm]$ |
|---|---|---|---|---|---|---|
| LN1 | 1.35E-06 | 1.04E-06 | 81.30 | 12.78 | 5.59 | 3.24 |
| LN1 | 1.07E-06 | 1.04E-06 | 67.55 | 21.05 | 3.32 | 1.00 |
| LN1 | 9.54E-07 | 1.04E-06 | 109.50 | 14.31 | 3.76 | 1.43 |
| LN1 | 9.39E-07 | 1.04E-06 | 28.29 | 23.34 | 3.21 | 0.89 |
| LN1 | 1.24E-06 | 1.04E-06 | 33.87 | 25.10 | 3.04 | 0.69 |
| LN2 | 1.42E-06 | 1.18E-06 | 694.10 | 9.88 | 4.58 | 2.25 |
| LN2 | 1.22E-06 | 1.18E-06 | 19.04 | 17.20 | 4.17 | 1.86 |
| LN2 | 1.00E-06 | 1.18E-06 | 30.12 | 17.23 | 3.83 | 1.52 |
| LN2 | | 1.18E-06 | 23.21 | 17.75 | 3.76 | 1.46 |
| LN2 | | 1.18E-06 | | | | |
| LN3 | 5.34E-07 | 5.35E-07 | 1660.00 | 7.63 | 4.81 | 2.50 |
| LN3 | 6.56E-07 | 5.35E-07 | 172.90 | 15.85 | 3.41 | 1.08 |
| LN3 | 7.20E-07 | 5.35E-07 | 124.70 | 18.00 | 3.16 | 0.87 |
| LN3 | 6.34E-07 | 5.35E-07 | 177.40 | 15.51 | 3.54 | 1.20 |
| LN3 | 6.82E-07 | 5.35E-07 | 206.70 | 17.53 | 3.15 | 0.82 |
| LN4 | 5.02E-07 | 3.74E-07 | 1153.00 | 10.18 | 4.46 | 2.13 |
| LN4 | 2.98E-07 | 3.74E-07 | 285.20 | 16.89 | 3.31 | 1.03 |
| LN4 | 3.46E-07 | 3.74E-07 | 208.50 | 15.44 | 3.76 | 1.47 |
| LN4 | 4.78E-07 | 3.74E-07 | 213.70 | 16.84 | 3.50 | 1.16 |
| LN4 | 3.13E-07 | 3.74E-07 | 218.20 | 12.56 | 4.52 | 2.17 |
| LN5 | 5.22E-07 | 4.30E-07 | 3673.00 | 8.34 | 4.67 | 2.35 |
| LN5 | 4.94E-07 | 4.30E-07 | 376.50 | 14.98 | 3.60 | 1.31 |
| LN5 | 4.72E-07 | 4.30E-07 | 43.76 | 17.85 | 3.85 | 1.56 |
| LN5 | 5.60E-07 | 4.30E-07 | 132.00 | 17.83 | 3.49 | 1.14 |
| LN5 | 4.62E-07 | 4.30E-07 | 68.20 | 20.25 | 3.37 | 1.05 |
| LN5 | | 4.30E-07 | 55.96 | 19.77 | 3.54 | 1.19 |
| AN1 | 8.95E-07 | 8.95E-07 | 192.60 | 8.77 | 5.01 | 3.37 |
| AN1 | 8.95E-07 | 8.95E-07 | 211.20 | 8.78 | 5.50 | 3.87 |
| AN1 | 8.95E-07 | 8.95E-07 | 4.39 | 12.95 | 5.31 | 3.68 |
| AN1 | 8.95E-07 | 8.95E-07 | 57.27 | 10.21 | 5.08 | 3.43 |
| AN1 | 8.95E-07 | 8.95E-07 | 206.10 | 8.29 | 5.18 | 3.54 |
| AN1 | 8.95E-07 | 8.95E-07 | 192.20 | 8.87 | 5.10 | 3.45 |
| AN1 | 8.95E-07 | 8.95E-07 | 129.30 | 9.83 | 5.28 | 3.64 |
| AN1 | 8.95E-07 | 8.95E-07 | 173.70 | 9.38 | 5.28 | 3.61 |
| AN1 | 8.95E-07 | 8.95E-07 | 180.20 | 9.02 | 5.12 | 3.51 |
| AN1 | 8.95E-07 | 8.95E-07 | 232.40 | 8.79 | 4.94 | 3.28 |
| AN1 | 8.95E-07 | 8.95E-07 | 139.30 | 9.04 | 4.85 | 3.22 |
| AN2 | 8.95E-07 | 8.95E-07 | 165.50 | 8.48 | 5.13 | 3.48 |
| AN2 | 8.95E-07 | 8.95E-07 | 63.87 | 10.25 | 5.23 | 3.58 |
| AN2 | 8.95E-07 | 8.95E-07 | 91.41 | 8.80 | 4.97 | 3.32 |
| AN2 | 8.95E-07 | 8.95E-07 | 103.90 | 8.90 | 5.03 | 3.38 |
| AN2 | 8.95E-07 | 8.95E-07 | 131.30 | 8.55 | 4.82 | 3.21 |
| AN2 | 8.95E-07 | 8.95E-07 | 135.70 | 8.62 | 4.76 | 3.14 |
| AN2 | 8.95E-07 | 8.95E-07 | 168.40 | 8.93 | 4.52 | 2.89 |
| AN2 | 8.95E-07 | 8.95E-07 | 107.00 | 9.42 | 4.75 | 3.11 |
| AN2 | 8.95E-07 | 8.95E-07 | 74.36 | 9.88 | 4.80 | 3.19 |

## A.8. Dependant and Independant variables of experimental setups

Table A.5: Dependent and independant variables of Material Property Testing

| Kind of variable | Variable | How recorded | Notes |
|---|---|---|---|
| Dependant | $E$, Young's modulus[MPa] | The Futek force sensor that is connected to the linear stage allows us to record force as a function of voltage. By calibrating the system using weights(and load of the system) the voltage output of the sensor can be translated to a force that is acting on the lymph node. Which in turn can be used to find Young's modulus. | The current calibration sequence does not account for the weight of the adapter block. |
| Independent | $A_{lymph}$, Lymph node size$[mm^2]$ | The average area of the lymph node can be measured by measuring the volume(Mass / Density) of the lymph node and dividing this by the dimension that is in line with the pressure that is applied by the device. | The density of lymph nodes is generalized and set at $1$ |
| Independent | $v$, Linear stage speed $[mm/s]$ | Constant set by the linear stage at $1mm/s$ | The speed at which the linear stage moves has an effect on the Young's modulus. Tissues often give more resistance to fast deformation than they do to slow. |
| Independent | $\Delta D$ , Linear stage position $[mm]$ | Recorded by the linear stage | the aim is to decrease the size of the lymph node to allow for smaller instrument dimensions. Therefore the displacements we are interested in are in the range of $5 - 10mm$. |

Table A.6: Dependent and independant variables of Vacuum sucker efficiency testing

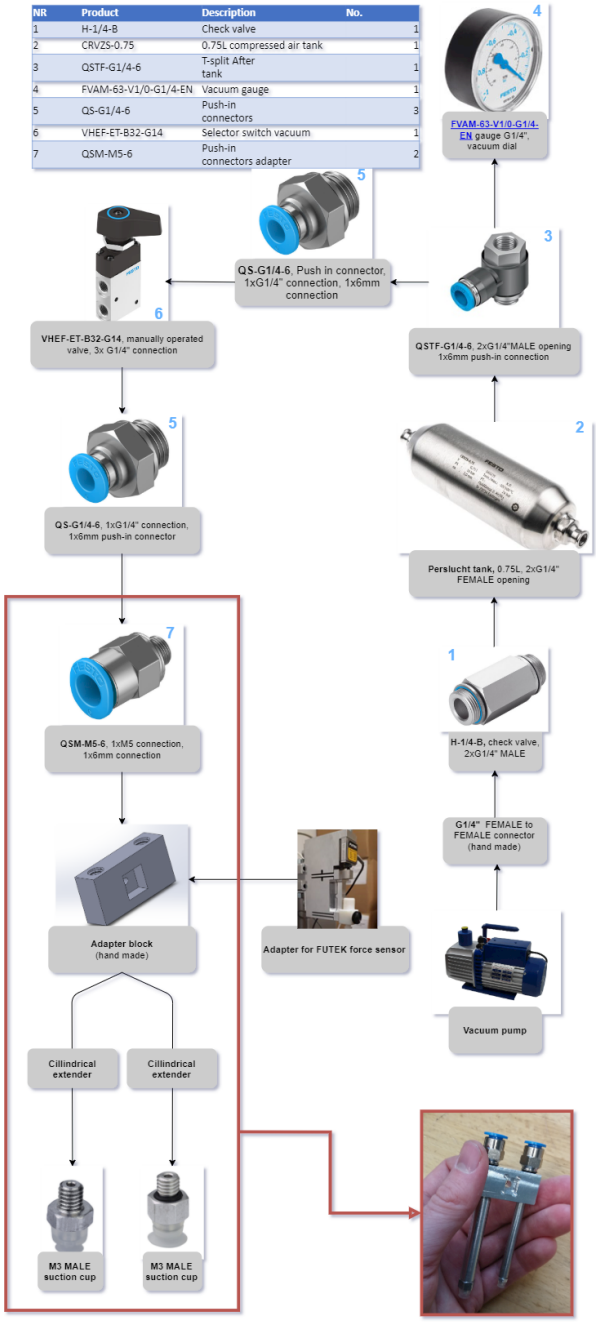
| Kind of variable | Variable | How recorded | Notes |
|---|---|---|---|
| Dependant | $F_{actual}[N]$ | The Futek force sensor that is connected to the linear stage allows us to record force as a function of voltage. By calibrating the system using weights(and load of the system) the voltage output of the sensor can be translated to a force | Efficiency of each sucker can be determined by the following formula $$\eta = \frac{F_{actual}}{F_{theorethical}} \quad \text{(A.4)}$$ |
| Dependant | Leakage | Observation and data analysis(Efficiency of sucker) | Which behaviours can be observed and could have an impact sucker efficiency and grip |
| Independant | Cup size($D[mm]$) and shape | Set by experiment design | Two different sizes of silicon cups will be used |
| Independant | Sentinel lymph node shape | Predefined gripping place | Always attempt to grip a smooth surface for the gripper to attach to, and confirm a good seal before starting the experiment |
| Independant | $v$, Linear stage speed $[mm/s]$ | Constant set by the linear stage | The speed at which the linear stage moves may have an effect on the Leakage that might occur. For tests will be set at$5mm/s$ |
| Independent | Linear stage position/ displacement$[mm]$ | Recorded by the linear stage | Increased displacement of sucker is increased chance of leakage. |

Table A.7: Dependent and independant variables of proof of concept testing

| Kind of variable | Variable | How recorded | Notes |
|---|---|---|---|
| Dependant | $\Delta D$, Displacement distance | Recorded by the linear stage | Ideally the complete specimen travels through tube |
| Dependant | Damage to lymph node | Examination by pathologist | Are structures still intact, and would nodal staging still be possible |
| Dependant | $F_{stash}[N]$ | The Futek force sensor that is connected to the linear stage allows us to record force as a function of voltage. By calibrating the system using weights(and load of the system) the voltage output of the sensor can be translated to a force | Goal is to prove that the following equation is true: $$F_{stash} + F_{adherence} < F_{actual} \quad \text{(A.5)}$$ |
| Independant | $v$, Linear stage speed$[mm/s]$ | Constant set by the linear stage | The speed at which the linear stage moves could have an effect on the |
| Independant | Cup size(diameter) and shape | Set by experiment design | In this case the most efficient of the suckers will be used |

## A.9. Part-by-part test setup

Figure A.9: Description of the vacuum setup that was used for the performance testing of the suction cups



# A.10. Drawings tunnel plates for proof of concept experiment

Figure A.10: Drawing created in Solidworks(Dassault Systèmes, Vélizy-Villacoublay, France) of the straight tube used in the proof of concept experiments(dimensions are in $mm$)

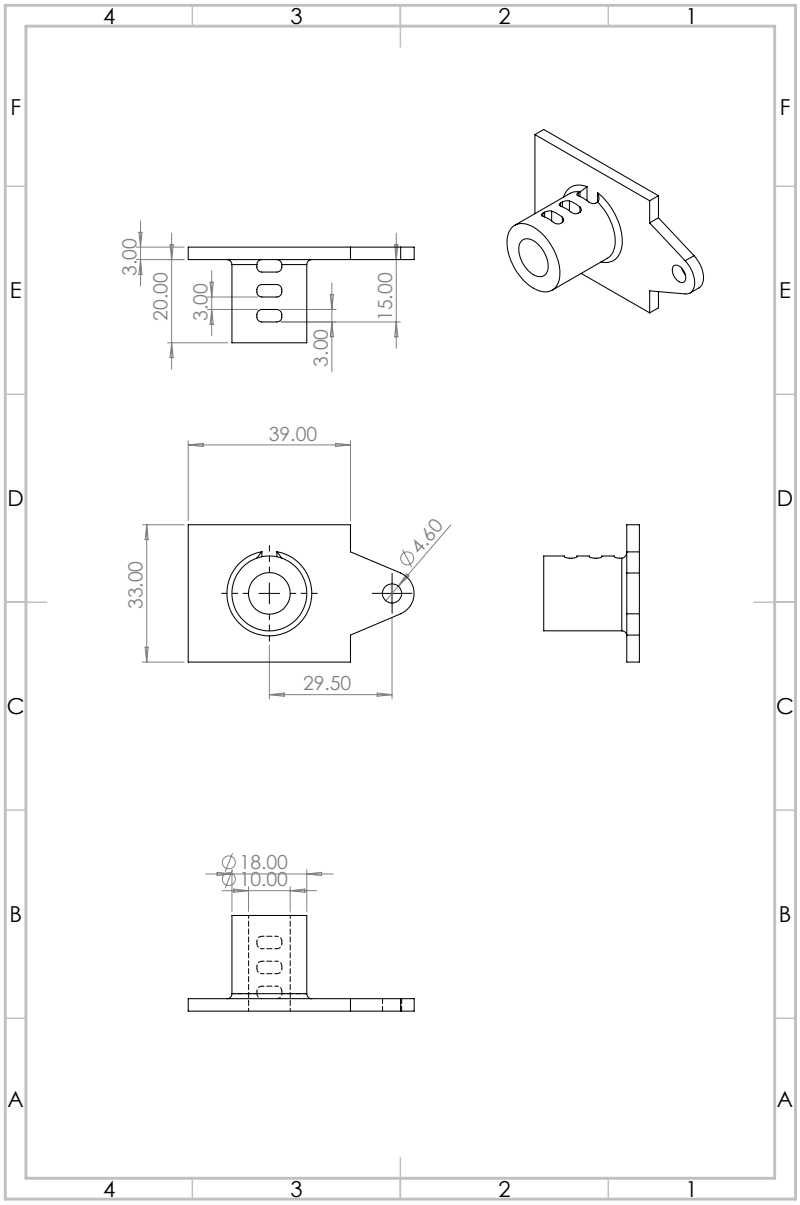
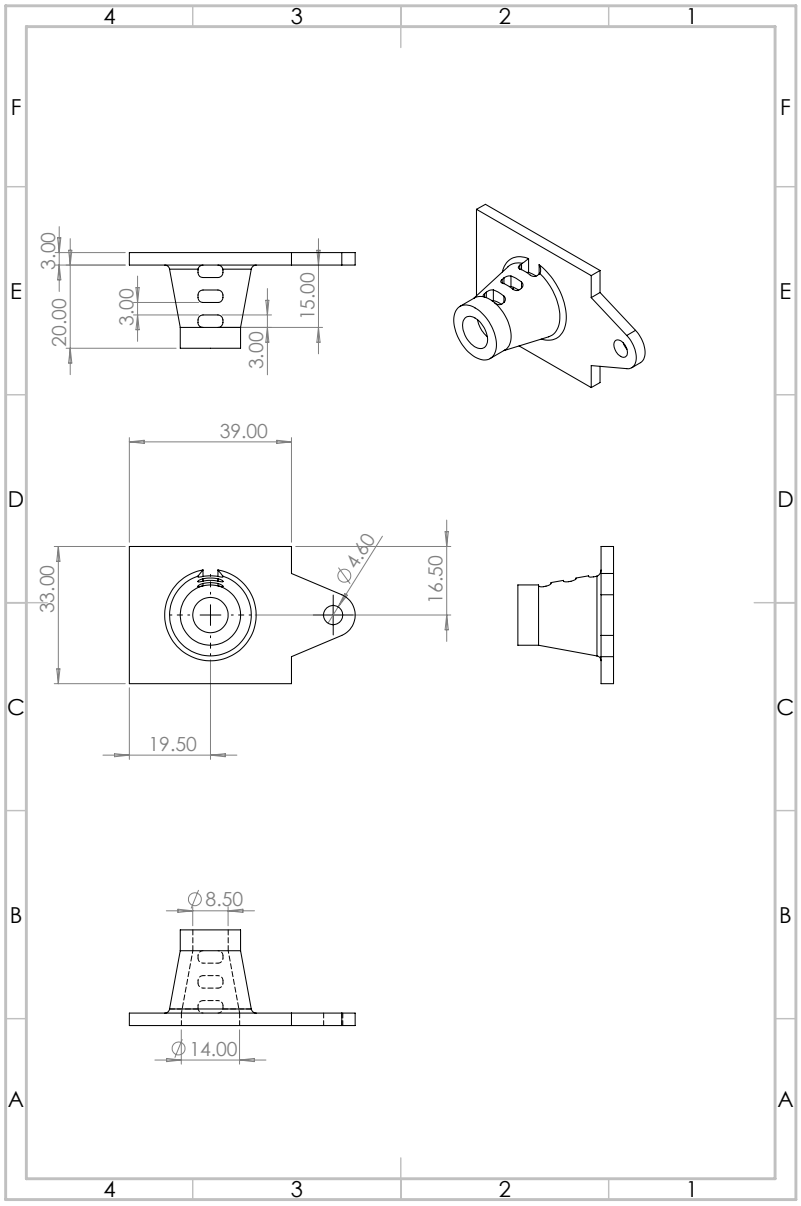


Figure A.11: Drawing created in Solidworks(Dassault Systèmes, Vélizy-Villacoublay, France) of the tapered tube tube used in the proof of concept experiments(dimensions are in $mm$)



## A.11. Literature research

The following pages contain the literature research conducted by the writer before the start of this thesis. This research is relevant to this thesis as it delved into the state-of-the art and possibilities for minimally invasive sentinel lymph node biopsy.

# Potential solutions for en bloc minimally invasive sentinel lymph node excision for nodal staging purposes.

M.I. Joosen - 4314336, 06-05-2020

*Abstract*— **Sentinel lymph node biopsy is an essential procedure used to determine whether cancer cells have spread to the sentinel nodes. This procedure helps diagnose the stage of the disease, gives a prognosis and in some cases determine further treatment. In its current form sentinel lymph node biopsy leads to serious comorbidities which have a significant negative impact on the body. To combat this there is a need for a device that can perform this procedure and reduce the impact on the body. This minimal invasive device should be able to perform en bloc excision of the sentinel lymph node to preserve tissue structures and allow for accurate pathological analysis. This literature review explored in use surgical devices that could offer a solution for reducing the impact of this procedure. There are no current percutaneous minimal invasive devices for the excision lymph nodes through a single incision that could across all lymph basins. However, what did arise from this literature study are some interesting concepts currently in use for other procedures. The first being an expandable endoluminal tissue retractor, that allows for a stable precise insert-able surgical platform. The device is intricate but would allow for full control over the excision. Secondly, polypectomy snares are an easy to use solution that in combination with a manner to lift lymph nodes up into the loops can ensure en bloc excision. Thirdly, the full-thickness resection device is an already existing solution that combines a polypectomy snare with a pull and grab method to lift and excise tissue in one simple to use device. Fourthly, from the field of biopsy, vacuum-assisted core needle devices could offer a solution. These devices are currently widely used for excising breast lesions. A larger needle in combination with a means to cauterize the tissue could make this device a viable solution. Lastly two types of wire basket devices were found in this study, these excise a circular sample in one pass using radiofrequency cutting. One has been recalled due to sterilization issues and the other is currently still in use. Overall there is a lot of further research and testing required to validate whether these devices offer a less invasive alternative for regular sentinel lymph node biopsy. Some will need some rigorous adaptation to be fit for the task.**

## I. Introduction

Sentinel lymph node biopsy(SLNB) has become an important procedure used in patients with breast cancer[1] or melanoma[2]. SLNB has presented itself as a less invasive alternative to complete lymphadenectomy and is associated with reduced morbidity[3]. In the SLNB procedure only a small number of the lymph nodes(usually 1 - 4 nodes[4]) in the node basin(in the Axillar, Ingiunal, and head/neck regions)are excised, these are the nodes are directly fed by the melanoma or tumour drainage. By harvesting the sentinel lymph nodes and looking for metastases the stage of the disease can be determined and a prognosis can be made for a patient. Using lymph nodes in this manner is called nodal staging. More importantly, besides a prognosis it could also give the oncologist an indication of what treatment path to continue[5], overall survival rates for patients who underwent SLND are higher[2]. For patients who are diagnosed with high risk(stage III) melanoma using SLNB, adjuvant therapy improves their chance of two-year-recurrence-free survival significantly[6]. This is a clear advocate for why performing SLNB in melanoma patients is an important procedure.

The current standard for SLNB in breast cancer[7], as well as melanoma[4][8] is described by the following steps. A blue dye and technetium-99 are injected into the affected tumour area. These substances will collect somewhere downstream in the sentinel lymph nodes[4][9] either in the axilla, groin, or neck region. Thereafter the patient is subjected to open surgery and the surgeon will look for a blue or hot sentinel node. He does so by either looking for the blue dye or the presence of technetium-99 with a gamma probe. Often a combination of these techniques is used to confirm whether a lymph node is a sentinel node. Hereafter the node is excised, and sent to a pathology lab to perform nodal staging and find any node metastases.

Even though SLNB is an improvement in comparison to other lymph node dissection protocols[3] and its advantages are apparent, there is still demand for change in this procedure as the comorbidity is relatively high. A pooled systematic review by Moody et al. reported a high occurrence of adverse events of $11.30\,\%$[10]. The most common complications are wound infection, seroma, and lymphodema[8][10][11]. Espinosa-Pereiro et al.[9] reported $11\,\%$ significant scar formation. These complications weigh heavily on the decision of whether performing SLNB is warranted, as a majority($70\%$) of the patients that undergo SLNB are free of metastases[12]. On top of that one should consider that in some cases SLNB can only serve as a prognostic tool to determine survival rates, therefore the damage caused to someone's quality of life by performing SLNB should be taken in careful account. It is therefore not unusual for writers to call for critical patient selection and informing of patients of comorbidities to prevent unnecessary harm[2][8][10][11].

Consequently, this literature study inquires the following research question: What certified medical devices are currently used to excise sentinel lymph nodes across all lymph basins through a single incision and what current certified clinical devices can form a basis for the development of new solutions. The aim of this literature review is to discover solutions that can bring back the incidence of comorbidities to an acceptable level to ensure that the advantages of SLNB weigh up to the disadvantages. It does so by exploring mechanical concepts that tackle a similar problem and have

proven themselves in a clinical setting. Thereby providing a starting off point for a solution which could be applicable for SLNB in both the inguinal and axillary lymph basin.

## II. Methods

To explore existing solutions for the minimally invasive en bloc removal of sentinel lymph nodes a broad Boolean expression was constructed to create a search query(see Appendix A). The created expression doesn't limit itself to one field of surgery or solely the removal of lymph nodes. This is done by design, and allows for a wide variety of solutions to show up which might be of interest given the problem statement. Results were gathered from three different databases namely Pubmed, Scopus and Web of Science. The Boolean expression had to be altered slightly to accommodate each database(as seen in Appendix A), and get the required results. Scopus and Web of Science were selected because these are the largest academic databases, Pubmed was added to ensure no medical articles would be overlooked. The results of these search queries were bundled and duplicates were removed. From this pooled database articles were excluded, first by investigating their title and abstract, followed by a scan of the article content and finally a round of complete reading of the article. Their relevance for this study is judged by using the following criteria to which the article should adhere:

- **Pathological evaluation:** After the tissue has been removed from the body it should be able to be investigated for tissue pathology. e. g. Gettman et al. (2001) coagulated a spherical volume which thereafter would be removed[13], this complicates reliable pathology significantly.
- **Single incision percutaneous:** The procedure should be done completely minimally invasive by either single incision or natural orifice. Minimization of scar formation and chance of infection are a requirement for improvement of the procedure.
- **Article is device centred:** The article contains no in-depth information regarding the performance or the functioning of the device was provided in the article. Nor any of the technical challenges of performing this procedure.
- **Tissue excision:** The ultimate aim of this study is to excise a lymph node therefore the discussed technique in the article should be able to excise a spherical volume.
- **English:** The Journal should be available in English or a translation should be available.
- **Available:** The article must be available with the TU Delft licence.

Once all articles had been subjected to this evaluation a selection of final articles was made. The articles in this final selection were divided up into different device groups. The articles found in the literature review acted as a base for further investigation of each device/mechanism. Thereby exploring device working principles and performance in the results section of this paper.

The viability and possible hurdles for the use of the device in the context of SLNB will be debated in the discussion, using the following points of debate:

- The device has to be minimally invasive to reduce the scar formation, risk to develop wound infections and shorten hospital stay[14][15]. Therefore larger incisions are seen as a negative aspect for a device.
- The device should inhibit the incidence of comorbidities common in SLNB, to improve the prospects of using it. So for instance by means of electrocautery, clips or ligatures as suggested by Solari et al.[11]. This coincides with the findings in other papers that suggest that the use of electrocautery indeed reduces the incidence of seroma formation[16][17].
- The excision should preferably be en bloc, meaning that the lymph node should be excised in its entirety to increase the accuracy of pathological examination. As non-en-bloc excision such as with fine-needle aspiration were unable to detect metastases in a significant amount of the cases[18]. The largest dimension of the lymph nodes ranges from $1.2 - 2.2cm$ and the nodes have a volume ranging from $0.4 - 1.5cm^3$ [19], the excision capabilities of the device should encompass these dimensions.

## III. Results

Pubmed, Scopus and Web of science resulted in 38, 133 and 69 articles respectively. After removing duplicates 168 articles remained for evaluation. Eligibility was tested according to the aforementioned criteria in the methods sections, this resulted in a remaining 22 articles. This process is illustrated in Figure 1. None of the found articles presented a medical device currently in use for the excision of sentinel nodes through a single incision. There are surgeons that use laparoscopic and robotic surgery to excise sentinel lymph nodes such as a study by Brouwer et al.[20], but these use multiple access ports to perform a procedure and were therefore excluded from the study. Some reports discussed single site transvaginal, transanal or transumbilical lymphadenectomy such as the study by Vizza et al. [21], however, these techniques can not be translated to use in the axillar regions where these access points do not exist. So one can conclude that there is no single incision solution for SLNB in the axillar and inguinal region. There were only 2 small scale studies that investigated the feasibility of using one of the existing devices for the percutaneous en bloc removal of sentinel lymph nodes, Evans et al. investigated the use of vacuum-assisted core needle devices[7] and Sever et al. did so for the Intact Breast Lesion Excision System manufactured by Medtronic[22].

From the 22 papers two main device branches of interest arose. The first one being endoscopy, wherein three devices where identified, the endoluminal operating platform, polypectomy snares and the full-thickness resection dissection device. The second branch being biopsy devices, where vacuum-assisted core needle biopsy showed up most prominently followed by two different wire basket devices.

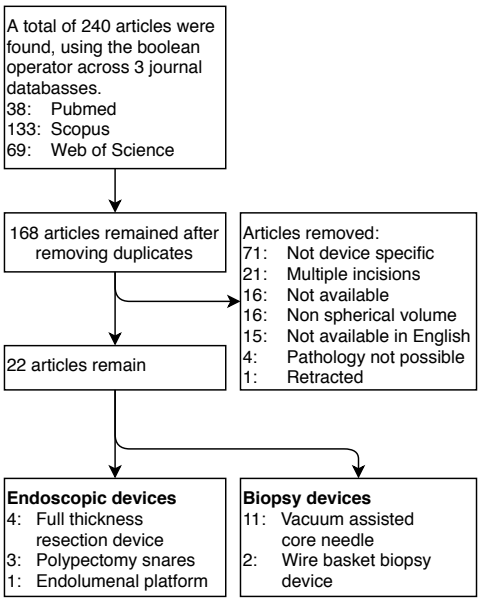



Fig. 1: Flow diagram illustrating article selection process

In the following paragraphs of the report a brief description of the working principles of each of the devices is given. This will be followed up by the discussion that focuses on testing the viability of using each device in the context of SLND.

### A. *Endoscopic devices*

Although not in direct association with SLND, endoscopic devices add an interesting perspective to the given problem.

*1) ORISE$^{TM}$ Endoluminal platform:* The tissue retractor system(ORISE$^{TM}$ Tissue retractor system, Boston Scientific, Massachusetts, United States) is an endoscopic device that can best be described as a small deploy-able surgical theatre. It's currently in use as a stable operating platform to remove lesions from inside the bowels of the patient. Figure 2 gives the reader an initial impression of the working principle of this device. It consists of an expanding capsule on the distal end of the endoscope that prevents the surrounding tissue from collapsing onto the surgery site[23]. In the working procedure described by Kantsevoy et al. the rat tooth forceps are used to pull up the edge of the tissue and a bipolar surgical knife is used to separate the simulated lesion from the underlying layer(See fig. 3). However, other approaches to excising a lesion are possible as a variety of different tools can be advanced through the scope. Once the lesion is separated from the surrounding tissue the device collapsed and the whole device including the specimen is retrieved.

*Performance of the ORISE$^{TM}$ endoluminal platform:* The procedure slightly more time-intensive than the others mentioned in this report, as the initial 11 procedures had a mean operating time of 99 minutes[23]. Kantsevoy et al. do report that after mastering low learning curves, mean operating times could be reduced to a respectable $29.1min$[23]. Reported advantages of the device are its improved stability and that it allows the instruments to move separate from the endoscopic view allowing for better instrument triangulation during the surgery[23][24][25]. Kantsevoy et al. report $100\%$ en bloc excision rate of the $19$ simulated lesions which reached upwards of $50mm$ in diameter[23], two case studies also reported complete excision of large lesions[24][25]. No reported disadvantages or complications with the use of this device could be found were found in the available literature.

Fig. 2: Picture of the ORISE$^{TM}$ tissue retractor system, figure provided by Boston Scientific, Massachusetts, United States.

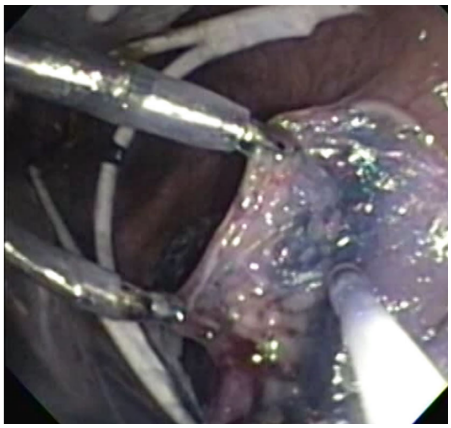


Fig. 3: Picture of the ORISE$^{TM}$ tissue retractor system performing excision of a simulated lesion by pulling it up a using two rat tooth forceps and separating it from the submucosa using bipolar knife, picture from the study by Kantsevoy et al.[23].

*2) Polypectomy snares:* Using snares to completely or partly re-sect polyps in the gastrointestinal tract is common practice in the world of endoscopy[26]. An endoscope with multiple working channels can be advanced to the operation site, the scope can then be used to visually inspect the resection space. Thereafter a snare is advanced through one of the working channels and the snare is slipped over the polyp and a small needle tip at the distal end of the snare is used to keep it stable[27]. Once in place either with or without electrocautery the tissue is excised. An important note is that to achieve en bloc excision it the whole lesion has to be lifted through the snare, before the snare is closed[28].

*Performance of polypectomy snares:* En bloc excision is more frequent in smaller polyps than larger, as en bloc excision of larger comes with higher risk of adverse advents[29]. Each lesion is judged and a careful consideration is made whether en bloc excision should be attempted, this depends on the size and shape of the lesion[27][30]. In practice this implies that for some of the lesions the surgeon deliberately chooses piecemeal excision[28], to avoid additional risks. Therefore the actual rate of success using snares for en bloc excision might be higher if it was attempted in all polypectomy cases. An indication can be derived by looking at the study of Tanaka et al., as they were able to en bloc excise $78\%$ of their $20-29mm$ lesions[29]. For these size lesions Tanaka et al. declare bleeding in $7.6\%$ of cases[29]. The other significant morbidity is perforation of the bowel which occurs in $1.1\%$ of cases[28]. Reports indicate low mean procedure times for hot snare polypectomy of $5.5$ minutes[31], which is slightly longer than cold snare polypectomy procedures[32].

*3) Full-thickness resection device:* The Full-Thickness Resection Device(FTRD®, Ovesco Endoscopy, Tübingen Germany) is a CE certified device that is currently used for full-thickness colon resections of polyps. It is a so-called over the scope attachment that allows the endoscopist to inspect, resect and close the defect by inserting only 1 instrument. The working principle of the device is illustrated by figure 4. The attachment is put onto an existing endoscope and advanced into the colon. Once the polyp is identified a grasping forceps is advanced through the lumen of the scope, and grabs a hold of the polyp and pulls it up into the cavity of the device. Once completely enveloped, the clip is deployed to pre-emptively close the defect. This action also helps push the tissue up into the cap for proper en bloc resection [33]. Thereafter a RF hot cautery snare located at the tip of the device is closed, which resects the polyp and helps prevent bleeding. Leaving the resected en bloc polyp inside the cap of the device.

*Performance of the full-thickness resection device:* The device is approved for removing lesions up to 25 mm in diameter[33], although the literature has shown that the removal of lesions of up to 40mm in diameter is feasible[34][35]. However, this is wholly dependant on the stiffness of the tissue that is retracted into the cap. Stiffer tissues are harder to retract than more flexible tissue. The maximal dissect-able volume lies $3cm^3$, this is limited by the $1.3cm$ diameter and $2.3cm$ height of the cap[36][37]. In polypectomy, the FTRD® has proven to be a very capable solution for removing lesions, as the meta-analysis by Li et al.[38] reported a high rate of nearly $90\,\%$ en bloc resection rate and low rates of adverse events with bleeding only occurring in $2.2\%$ of the cases. However, it should be noted that in doing a radical resection of a large lesions comes with increased risk to cause significant adverse events such as perforation[35]. The multicentre study by Schmidt et al. found a mean procedure time of $50$ minutes and a mean resection time of $5$ minutes [39].

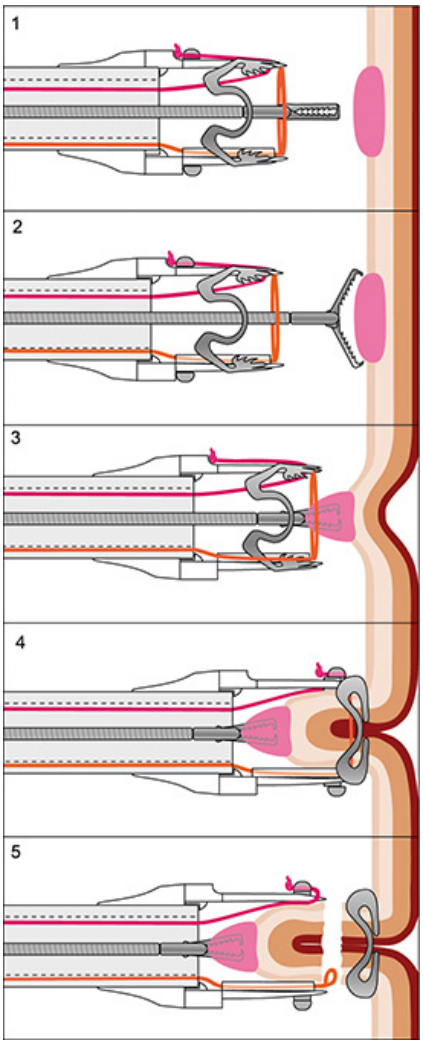



Fig. 4: Illustration of the working principles of the FTRD® device, figure provided by Ovesco Endoscopy, Tübingen, Germany.

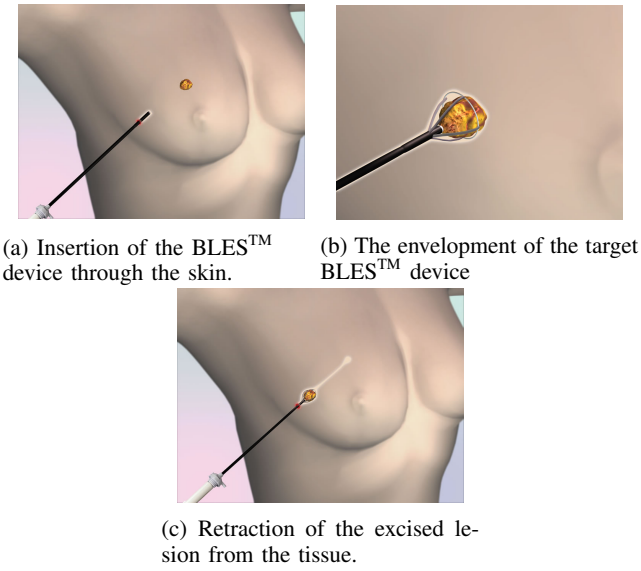
## B. Biopsy devices

Biopsy devices are the instinctive solution for the given problem. They allow access to tissue deep inside the body through a small incision. Thereby they are better designed to traverse through tissue than many other devices.

*1) Vacuum-assisted core needle device:* The vacuum-assisted core needle device(VACND) has become a household tool in breast lesion removal, since its proven superiority over the previously used biopty gun[40]. This device operates as follows: a hollow needle is inserted through a $3-5mm$ skin incision(depending on gauge size of the needle)[41][42][43]. Thereafter the needle is positioned underneath the lesion. The large hollow needle contains a window through which tissue can expand into the lumen of the needle, the vacuum sucks in the tissue to fill the lumen. Where-after a high-speed rotary knife comes in and cuts the tissue that has come through this window. An advantage of the vacuum-assisted core needle biopsy over its predecessor, is that the vacuum allows more tissue to be collected per cut. The parts of the instrument are simple and smooth which could aid in the sterilisation of the device. The operation can be performed using ultrasound or stereotactic guidance of an experienced radiologist[44].

*Performance of the vacuum-assisted core needle device:* Reports indicate that using this device to remove lesions from the breast result in high rates of complete excision ranging from $86\,\%$ to even $100\,\%$ [41][43][45][42][44][46]. However, a significant amount of the reports show a drop in complete excision rates for larger lesions who exceed lengths over $1.5cm$ or volumes larger than $2.5cm^3$ [41][44][45][47]. A VACND does not remove lesions en bloc. It can take as little as two samples to as much as forty to remove a lesion[44][48]. Typically the mean or average amount of removed cores range from nine to sixteen cores[42][44][47][49]. The most common complications in VACND use are bleeding and hematoma formation[44][42]. Jiang et al. reported $22.90\,\%$ cases of bleeding and $5.50\,\%$ of cases of severe hematoma formation for the VACND(total percentage of hematoma cases was $27.50\,\%$)[42]. Procedure times range from eight to a maximum of forty minutes[44][45].

*Vacuum-assisted core needle usage in SLNB:* So far a VACND has only once been used in a study for the complete excision of sentinel lymph nodes from the axilla, by Evans et al. in a small study of 20 patients[7]. They describe an additional advantage of using the VACND in SLNB, namely that once one core sample has been taken the presence of technetium-99 can immediately be checked by holding the probe next to the collection tray to confirm the excision of the right node. Operating times are reported by Evans et al. are quite short ranging from three to twenty-three minutes[7], which is similar to the previously mentioned operating times for a VACND. Evans et al. found four cases of metastatic disease by investigating the VACND harvested tissue, no further metastatic disease could be found in the follow up standard open axillary surgery[7]. This is promising when taking into account the concerns of splitting up the node mentioned in the last paragraph. However, it should be noted that the 20 patient sample size used by Evans et al. is too small to truly determine whether this has no impact on pathology.



(a) Insertion of the BLES$^{TM}$ device through the skin.

(b) The envelopment of the target BLES$^{TM}$ device

(c) Retraction of the excised lesion from the tissue.

Fig. 5: A visual representation of the working principles of the Intact BLES$^{TM}$, figures provided by Medtronic plc, Dublin, Ireland.

*2) BLES$^{TM}$ Wire basket biopsy:* The Intact Breast lesion Excision System(BLES$^{TM}$, Medtronic plc, Dublin, Ireland) is a unique device that allows for the whole intact excision and retrieval of lesions in breast tissue. Most often this is done under stereotactic or ultrasound guidance[50]. The device operates as follows: Its inserted into percutaneous through a $6-8mm$ incision[50], where the sharp point of the polymer tip can be pushed through the tissue towards the lesion(Fig. 5a). Once the lesion is positioned in front of the instrument, the basket is deployed as shown in Fig. 5b. The arms of the basket are connected with a radio frequency(RF) cutting wire, which excises an almond-shaped sample $7-30mm$ in length across its deployment trajectory[51]. This part of the procedure is the most painful and takes about ten seconds[51][52]. During the cutting phase a vacuum suction at the tip is used to keep the cavity clear from fluids[50][53]. Once fully extended the sample can be retrieved(Fig. 5c) and inspected for pathology.

*Performance of the BLES$^{TM}$ Wire basket:* In comparison to the aforementioned devices the reported complete excision rates of the BLES$^{TM}$ are low, the systematic review by Sanderink et al. reports a median of $50\,\%$ complete excision[50]. This low rate of complete excision might be skewed because some of the included studies do not aim for

complete en bloc excision[50]. Therefore this statistic might be a poor indicator for the device its ability to achieve en bloc excision. In procedures with Intact BLES$^{TM}$ bleeding is recorded to take place in a range $0 - 11.8\%$ of cases and hematoma formation in $0 - 11.8\%$ of cases[50]. The excision step takes about 8-10 second[51][52]. There was no further mention of the total procedural time of using the device in its intended context.

*BLES$^{TM}$ Wire basket usage in SLNB:* Currently the only clinical in vivo study of the prospects of removing lymph nodes using the BLES device was conducted by Sever et al. [22]. They tested the device in a small study using swine models. SLNB procedures in this swine model took about $5$ minutes[7], which is comparable to procedure lengths of a VACND. Based on their results Sever et al. are hopeful of the pathological prospect of harvesting the lymph node in this manner[22]. They do express concerns for the usage of the device in deeper layers of the axilla, closer to delicate structures. Evans et al. bring further nuance to this concern by stating that the usage of the device in the human axilla might be safer compared to their test setting, as the human axilla contains more protective adipose tissue[22].

*3) OVITRON Wire basket biopsy:* The other wire basket biopsy device comes from the Ovitron series by Rubicor Medical, California, Redwood City. This device functions as follows[54][55](excerpts of the patents are included in Appendix B for illustrative purposes): a sharp needle tip is inserted through a $6 - 7mm$ skin incision[43]. Once the tip is adjacent to the lesion, a band is expanded to form a sort of loop. RF energy is applied to this loop and the device is turned to collect the lesion, trailing behind the loop is a flexible bag that collects the excised tissue. Once the lesion has enveloped by the bag, the loop is closed and while retracting the device the sample moves to the tip of the device minimizing drag.

*Performance of the device:* Fine et al. report that the device was used to en bloc excise lesions ranging from $6 - 27mm$[55]. Of the 100 patient study, only two patients developed minor complications in the form of bleeding. This seems to be a promising statistic. However, besides the paper of Fine and Staren no further papers were found on this particular device[55]. Upon further research a recall report by the food and drug administration was found, indicating that this device was recalled due to inadequate sterilization capabilities[56]. In their paper Fine and Staren made no mention of the total procedure length.

## IV. Discussion

From this literature research it can be concluded that there is a gap in the available medical instruments for a device that can remove lymph nodes minimally invasive and en bloc. In this discussion the viability of using each of the found the devices in the context of SLNB is explored, to discover whether these devices or an adaptation of the device could work. This is achieved by highlighting the areas in which they could excel in the given context, and also highlight some areas for concern and further investigation.

### A. Lessons from the field of endoscopy

There are some general benefits to endoscopic devices that translate well to SLNB. They allow for visual confirmation of the blue dye, as well as a means to introduce a gamma probe through the working channel for the detection of technetium-99. A major disadvantage of these endoscopic devices is that they would have to be adapted and tested thoroughly to fit SLNB purposes. Further device-specific advantages and disadvantages will be discussed in the following paragraphs. The prospects of using an endoscopic device for inguinal lymph node dissection were explored by Tobias et al.[57]. They used two trocars to perform the procedure and concluded that performing a lymph node dissection(which in many ways is similar to SLNB), reduces morbidity and hospitals. Which is promising sign for trying to adapt these devices for SLNB use.

*1) ORISE$^{TM}$ Endulumal platform:* Theoretically the tissue retractor system(ORISE$^{TM}$ Tissue retractor system, Boston Scientific, Massachusetts, United States) could prove a viable solution for SLNB. It provides the surgeon with a clear picture of the lymph node(s)[23]. Its stability and multiple working channels allow the surgeon to work precise, be flexible in their approach to ensure en bloc excision and help avoid delicate structures in the lymph basin. This high level of control over the surgery could also help seal the lymph ducts to reduce the incidence of complications associated with SLNB[11]. As previously mentioned, the device is not associated with any complications in its current field of application. It should be noted that no large scale clinical studies were available during the writing of this report to confirm these findings. This is possibly because of its recent(2018) approval for clinical use by the United States Food and Drugs Administration.

*Technical considerations for ORISE$^{TM}$ platform:* Two foreseeable challenges in using this device in SLNB are its large diameter of $26mm$[58] and its ability to deploy the operating space. The relatively large diameter will require a larger skin incision to be inserted percutaneousnly. Other difficulties will arise trying to advance the device through tissue instead of a pre-existing lumen. The second hurdle could be its ability to deploy the platform inside the axilla or groin while the surrounding tissue is exerting pressure onto the device. Testing is needed to discover whether these issues are significant and if they can be resolved. Of course this should be re-evaluated in the context of the excision of lymph nodes, however, it is a promising sign. Overall the device in its current form does not seem well suited for SNLD, but with some adaptations a detractor of this current device might be an interesting solution.

*2) Polypectomy snares:* Polypectomy snares seem like a simple solution for en bloc resection which could transfer well to SLNB. The polypectomy snares are the only device in this list that does not suffer from an excision direction bias, as for the other devices the volume that is being excised is predetermined by the insertion path. As previously mentioned en bloc excision of polyps $20 - 29mm$ is feasible[29], which encompasses the size range of a sentinel lymph nodes[19]. For the excision of larger polyps$>$ $8mm$ it is advised to use electrocautery in combination with a slow cutting movement to prevent the occurrence of complications[26]. As mentioned in the introduction of this report the use of electrocautery would also beneficial in reducing seroma formation[16][17], so the previously mentioned advice would be the preferred method of implementing polypectomy snares in SLNB.

*Technical considerations for polypectomy snares:* The efficiency of a polypectomy snare depends for a large majority on the ability of the lesion to rise up into the loop[28], this could also prove a technical challenge when using snares in SLNB. To tackle this problem and ensure that the polyp does rise up into the loop, there have been several solutions found in endoscopy. For instance the injection of saline to push the tissue up into the loop[59]. Although this is not always a reliable solution in endoscopy as the 'roots' of some malignant polyps penetrate more deeply and prevent the lesion from lifting[28]. Its efficiency in the case of lifting lymph nodes where surrounding structures might pull the node down should be investigated further. Another proposed solution is submerging the surgery site in water, this allows the polyp to float up into the loop[30]. This technique only works for smaller superficial polyps and might not work for lymph nodes. As lymph in-plane physiology could probably be better compared to flat lesions(and not a protruding polyp structure) where this technique would most likely not make a difference. An added benefit of submerging the tissue during snare cutting would be that it does inhibit the amount of thermal damage[30] caused by electrocautery, to both the surrounding structures as to the sample. There has also been a brief mention of using vacuum suction to pull the tissue up into the polyp[59]. Finally there is mention of the grasp and pull technique where the polyp is pulled into the loops[60]. To translate polypectomy snare technology to SLNB it would have to be in combination with one of these aforementioned techniques to ensure 'en bloc' resection. The last crucial part for this device to be successful in SLNB that current endoscopic research can't answer, is whether it is possible to reliably position a snare around a lymph node. This could be explored by means of an animal study or an accurate phantom that mimics the lymph basin environment, this would reveal what effect the surrounding structures have on the positioning of the snare.

*3) Full thickness resection device:* The Full Thickness Resection Device(FTRD®, Ovesco Endoscopy, Tübingen Germany) can be seen as an instrument that combines the grasp and pull technique discussed by De Melo et al.[60] with a polypectomy snare into one device. Thereby making it an interesting device to study for SLNB use. In literature this instrument is praised for its simplicity[34][36][61], and the ability to perform in hard to reach places. The aforementioned size of lesions that can be excised using the device envelops the size of sentinel lymph nodes, so in theory en bloc resection is plausible. Whether the shape and the surrounding structures of the lymph node allow it to be pulled into the cap to perform en bloc resection, should be investigated further. Excising larger bowel lesions was ill-advised due to the increased risk of perforations[35]. This does not directly translate to excising lymph nodes but should be taken as a word of caution. Further research is therefore needed to estimate the morbidity that this device would cause in SLNB.

*Technical considerations for FTRD®:* Only one drawback of the design was mentioned across the studied literature, namely that the cap on top of the endoscope limits its flexibility and visibility of the operating site[38]. Some challenges can be predicted to arise when adapting this device for use in SLNB. The first being that the clip has to be removed after the defect has healed, when applied in the colon the clip detaches by itself or has to be removed using bipolar instruments[62]. In the case of SLNB the clip will not be able to leave the body by itself, and would require manual extraction. This increases the invasiveness of the overall procedure which in turn increases the chance of further complications. The second main hurdle is that the device is built to traverse through a pre-existing lumen. The outer diameter of the device at $2.1cm$[63] is quite large in comparison to standard laparoscopic instruments. This could prove to be an issue when using it in the context of removing lymph nodes from the axilla as it will have to cut through fatty tissue to reach its destination.

### *B. Lessons from the field of biopsy*

In comparison to endoscopes biopsy devices have a significant advantage in that they are designed to traverse through tissue. However, what is lacking for these biopsy devices is a manner of visual confirmation whether the lymph node that is being resected is a sentinel node. The surgeon would have to rely on the radiologist's ability to identify the right nodes through imaging and test the extracted nodes if they are indeed the sentinel nodes. This is a plausible solution that can work[64], but is less accurate than direct confirmation before excision by using the blue dye and technetium-99[64]. There would also be the risk of excising more nodes than necessary thereby increasing the morbidity of the procedure.

*1) Core needle biopsy:* While looking at the vacuum-assisted core needle devices(VACND) short procedure times, low incidence of comorbidities and rates of complete resection it seems to be promising for SLNB. However, problems

arose when excising larger, this could be a negative indication for the ability of a VACND to excise a sentinel lymph node. This problem seems not to be an issue related to the device being too small, but rather imaging and experience related issue[45][47]. To combat this in breast lesion removal protocols are in place to take additional samples, even after traces have disappeared from the imaging device[48]. What impact this might have on the ability to completely excise lymph nodes is yet to be determined.

Another serious disadvantage for VACND is that it does not remove lesions en bloc. Splitting the lymph node up into this many cores could have a significant effect on the pathological analysis of the samples, as was mentioned in the introduction that en bloc excision is preferred. Additional research is required to determine if pathology is hindered by splitting the node into several samples and what would be the maximum amount of cuts to still arrive at an accurate diagnosis and an acceptable percentage of false-negatives.

*Technical considerations for VACND:* Jiang et al. stated that one of the limiting factors of the ability to remove larger lesions using a VACND is bleeding[42], this statement translates to lymph nodes which can be interpreted as large lesions. To combat bleeding and hematoma formation, it is advised to minimize the amount of core samples[65]. Evans et al. therefore used a large 7-gauge needle to excise sentinel lymph nodes[7], this needle is $4.5mm$ in diameter. The larger needle allowed them to remove the node using only four core samples. To limit the forming of hematoma even further Evans et al. applied manual pressure to the surgery site. Even with these precautions Evans et al. concluded in their report that using VACND for SLNB resulted in relatively high cases of morbidity and hematoma formation[7]. This is in line with the aforementioned prediction of Jiang et al.[42]. But Evans et al. remain hopeful and report that using a VACND for SLNB could be a feasible future solution, but argued that to truly make this device a viable solution a means of coagulating the tissue should be devised. This in combination with an even larger needle to reduce the number of core samples needed, could offer a solution to the occurrence of hematoma and other complications. With the additional benefit that fewer core samples relate to less damage to the sentinel lymph node and possibly a more accurate diagnosis. This would be an interesting area for further research and development.

*2) BLES$^{TM}$ Wire basket biopsy:* When comparing the BLES$^{TM}$ to the VACND there are two main advantages. The first being that it theoretically allows for en bloc resection of the lymph node without dividing it into several samples(as no current VACND allows for complete excision). The reported complete excision rates of the BLES$^{TM}$ are low, but its $7-30mm$ excision length[51] indicates that en bloc SLNB should be feasible. Further research is needed to determine whether it can reliably excise lymph nodes. It might be the case that it runs into the same difficulties as VACND, where experience and imaging play an important limiting factor[45][47]. The second main advantage of this device is the RF cutting which improves haemostasis which is one of the main gripes with the VACND. When comparing the statistics of the two devices, the Intact BLES$^{TM}$ is a favourable candidate in terms of complication rates. But it's hard to do a true one to one comparison as no specific definition of hematoma formation may slightly differ.

However, one disadvantage that comes with using radiofrequency cutting is the presence of thermal artifacts in the sampled tissue. Reports suggest that cases of thermal damage while using the BLES$^{TM}$ are limited, Al-Harethee et al. reported an incidence of $5.13\,\%$[66]. This thermal damage is most prevalent at the poles and outer layer[50]. However, for these damaged samples with thermal artifacts pathology was not hindered[51][66]. Sanderink et al. advise surgeons to use a larger wand size for excision and ensure that the lesion is in the centre to further minimize this effect of thermal artifacts and it might also need some time for pathologists to become familiar with the kind of samples the BLES$^{TM}$ produces[50].

*Technical considerations for BLES$^{TM}$:* The most reported technical issues of the BLES$^{TM}$ include the basket turning up empty, the basket not opening and a broken RF cutting wire[50][53]. The basket not opening might be related to the hardness of the tissue that is excised[67]. The basket returning up empty after presumed excision has might be caused by different effects. One hypothesis points to the high-fat content in the tissue which causes the sample to melt rather than excise[66]. Another hypothesis talks about the possibility that the surrounding fluids(e.g. cystic fluids) quench the RF cutting which halts the cutting process[53]. The surrounding tissue in the lymph basin is mainly adipose and the lymph fluid might also cool down the cutting wire, so adequate testing is required to see how this device performs in a lymph basin. Overall using the BLES device in SLNB seems like a promising proposition, however large scale investigative studies to test the true prospects are lacking. Overall from this research one can conclude that the BLES$^{TM}$ intact device is at the current moment the best fit device for minimally invasive en bloc SLNB.

*3) OVITRON Wire basket biopsy:* As mentioned in the Results section of this paper Fine et al. reported that the OVITRON device could be used to excise lesions ranging from $0.6-2.7cm$[55]. The typical sentinel lymph node size lies within this range, so excision using this device is feasible[19]. Even though the OVITRON wire basket is no longer on the market the functioning principle might be of interest to investigate further for SLNB. However the severe lack of available literature makes investigating the feasibility of this device difficult at this moment in time.

It can be hypothesized that the difficulty with sterilizing the device is related to the intricate and delicate design of the instrument. The BLES$^{TM}$ device which functions similarly

is classified as a one-time use device[50], so the inability to adequately sterilise these wire basket devices could be an inherent design feature.

### C. Strengths and Limitations

The strength of this study is that it has looked across multiple disciplines in search of a solution for the given problem. Thereby uncovering some interesting concepts that would not have showed up by looking solely at what is currently used for SLNB. Using the initial literature as a foundation to snowball further into available information was a useful way to suggest design adaptations for SLNB use and point out areas that could be of interest for further research.

The main limitation of this literature review was that articles do not often tread into detail on the technical performance of their respective devices. In the articles both in the initial as in the expansive research there was little to no mention of technical challenges or possible design improvements. Complications were only in a handful of cases linked to a certain design features of a device. In the case of some of the devices there were only small scale studies available with little or no reported difficulties or complications, this resulted in a positive information bias. Some patents were inspected, and these reveal a bit more of the design philosophy, but could not give any insight into the actual functioning of the device. This resulted in that a lot of the aforementioned statements are based on assumptions and only limited data.

This study could have also been conducted in the patent databases to look for other inventions that could lead to functional solutions for the given problem. However, it has limited itself to published articles and in use devices, mainly to uncover the clinical advantages, disadvantages and experiences of each device.

## V. CONCLUSION

Sentinel lymph node biopsy is an important procedure that allows pathological examination of lymph nodes. It provides the oncologist with crucial information regarding the prognosis and treatment options of a patient. However, the impact of sentinel lymph node dissection is significant on the body and there is interest in a new less invasive procedure. An alternative that reduces wound infection, scar formation, hematoma and lymphodema occurrence is needed. Therefore this literature review looked into what currently used surgical devices could offer a solution for this issue. No device is currently in use to excise sentinel lymph nodes through a single incision that can perform in all lymph basins, so the niche is left empty. What did arise from this literature study were some interesting mechanisms currently used for other procedures than SLNB. These concepts could offer a solution, or form a foundation to develop a device that can perform SLNB minimally invasive.

Some interesting concepts came from the field of endoscopy. The advantages of using endoscopes are, visual confirmation of blue dye(an indicator that a lymph node is a sentinel lymph node), multiple working channels for using multiple instruments that also could facilitate a gamma probe(another way to detect a sentinel lymph node). The main drawback of endoscopes is that they would require a larger incision to insert the device percutaneously the skin. Mechanisms that were of interest were that of polypectomy snares, an expandable endoluminal platform and a full-thickness resection device. A major disadvantage of these endoscopic mechanisms is that they are meant to travel and operate in a lumen, not in tissue, further investigation is needed to determine if and how these devices need to be adapted to function in the context of SLNB.

Other concepts emerged from the field of biopsy. The main advantage of these devices is that they are used to operate in similar conditions as in which a SLNB is performed. The main hurdle that these biopsy devices face that they currently have no way to detect sentinel lymph nodes. The concepts of interest are the vacuum-assisted core needle device(VACND), the breast lesion Excision System(BLES$^{TM}$, Medtronic plc, Dublin, Ireland) and OVITRON(Rubicor Medical, California, Redwood City) and are all currently used for the excision of breast lesions. Increasing the size of the VACND in conjunction with manner to coagulate the tissue would both bring down limit morbidity as well as preserve lymph node architecture to aid pathology and could make this a viable solution. The BLES$^{TM}$ device seems fit for SLNB its the complication rates and ease of use 1 step excision are promising. However, the available literature on the device is limited and reported en bloc resection rates are low. Further tests should be performed to asses its ability to perform reliably, especially in fatty tissues as this might cause issues. There was very sparse information available on the OVITRON device as it was recalled due to unreliable sterilization. Nonetheless the underlying mechanism remains interesting for further research.

## VI. FUTURE RESEARCH

This report has brought forward some of the plausible solutions for the given problem of excising en bloc lymph nodes percutaneously through a single incision. However there is little to no evidence that these devices can work in the given context. Therefore in future research the viability of using these devices in SLNB should be explored further, either in animal models or accurate phantom models that reflect the physical properties of the lymph basin. Performance in these studies would indicate whether or not these devices are truly viable for SLNB, or what improvements could be made to achieve true viability. Some suggestions points for follow up research for each of the separate devices are defined in the discussion section of this paper, under the heading '*technical considerations*'.

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## APPENDIX A

Search query used for the systematic review used in *Scopus*:

```
TITLE-ABS-KEY (
(instrument* OR device* OR apparatus)
AND
(radical OR complete OR intact )
AND
(tumour* OR (tissue AND structure) OR
(lymph node*) OR polyp* OR lump* OR
malignanc* OR carcinoma OR fibroadenoma
OR (suspicious mass) OR biopsy OR biopt)
AND
(extract* OR remov* OR encapsulating)
AND
(resection OR excision OR harvest*)
AND
((minimally AND invasive) OR
percutaneous OR laparoscopic))
```

Search query used for the systematic review used in *Pubmed*:

```
((instrument*[Title/Abstract] OR
device*[Title/Abstract] OR
apparatus[Title/Abstract])
AND
(radical[Title/Abstract] OR
complete[Title/Abstract] OR
intact[Title/Abstract])
AND
(tumour*[Title/Abstract] OR
(tissue[Title/Abstract] AND
structure[Title/Abstract]) OR
(lymph[Title/Abstract] AND
node*[Title/Abstract]) OR
polyps[Title/Abstract] OR
lump[Title/Abstract] OR
malignancies[Title/Abstract] OR
carcinoma [Title/Abstract] OR
fibroadenoma[Title/Abstract] OR
(suspicious[Title/Abstract] AND
mass[Title/Abstract]) OR biopsy[Title/Abstract] OR
biopt[Title/Abstract])
AND
(extract*[Title/Abstract] OR
remov*[Title/Abstract] OR
encapsulating[Title/Abstract])
AND
(resection[Title/Abstract] OR
excision[Title/Abstract] OR
harvest*[Title/Abstract])
AND
((minimally[Title/Abstract] AND
invasive[Title/Abstract]) OR
percutanous[Title/Abstract] OR
laparoscopic[Title/Abstract]))
```

Search query used for the systematic review used in *Web of science*:

```
(TS=((instruments OR device* OR apparatus)
AND
(radical OR complete OR intact)
AND
(tumour* OR (tissue AND structure) OR
(lymph AND node*) OR polyp* OR lump* OR malignanc* OR
carcinoma OR fibroadenoma OR (suspicious AND mass) OR
biopsy OR biopt)
AND
(extract* OR remov* OR encapsulating)
AND
(resection OR excision OR harvest*)
AND
((minimally AND invasive) OR percutanous OR
laparoscopic))
AND
(LA=(English)))
```

## APPENDIX B

Illustrations from the patent of Vetter et al. [54], showing the working principle of the recalled Ovitron series by Rubicor

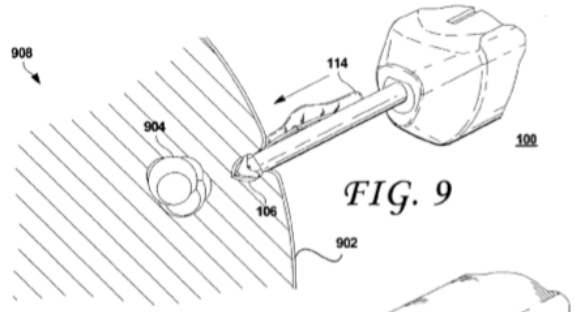


FIG. 9

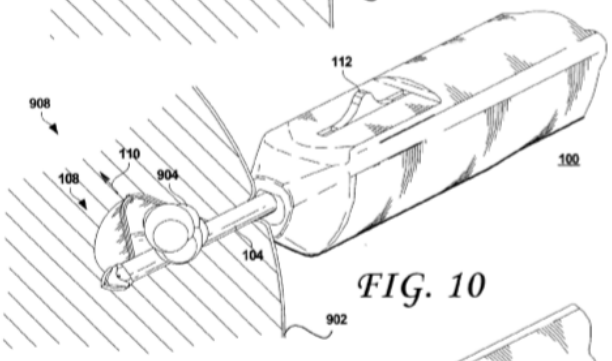


FIG. 10

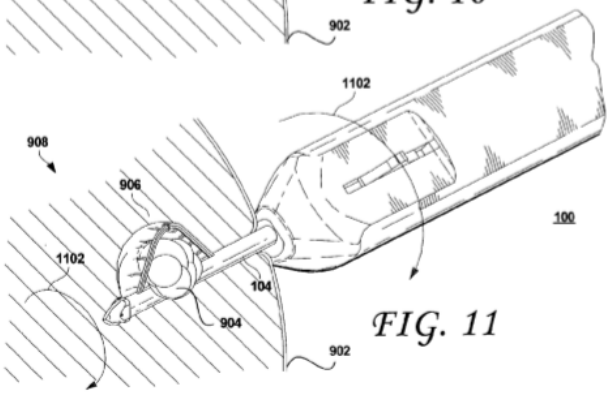


FIG. 11

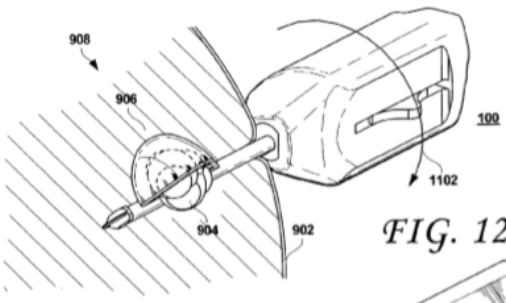


FIG. 12

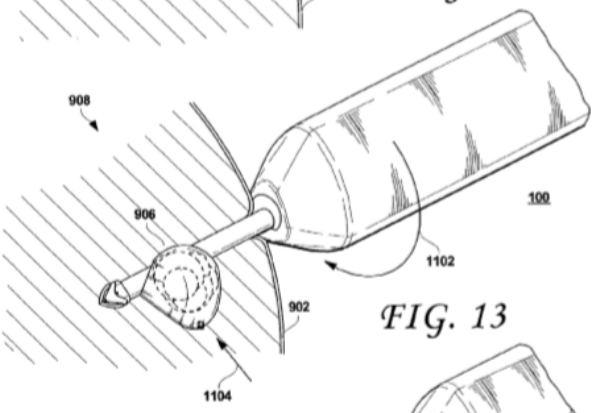


FIG. 13

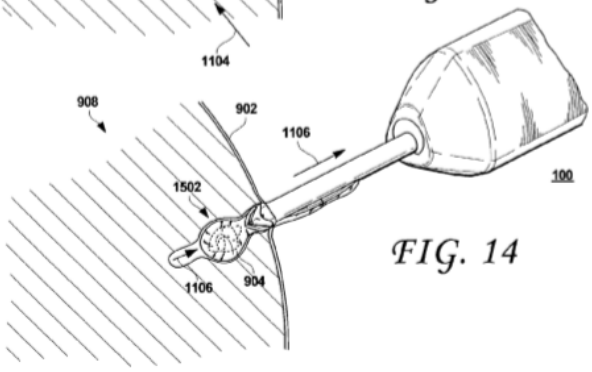


FIG. 14