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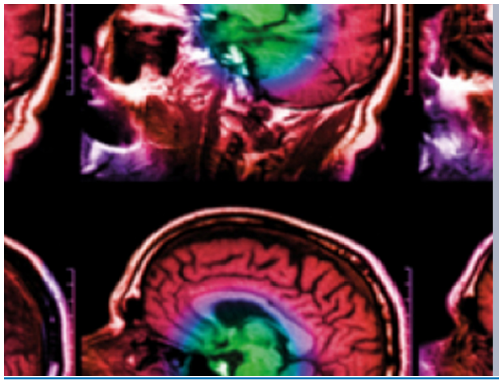

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Design of a novel miniature breast biopsy needle for ductoscopy

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Keywords: biomedical equipment, biopsy needle, ductoscopy, medical device design

Abstract

Background. The majority of the benign and malignant lesions in the breast arise from the ductal epithelium and terminal ductlobular unit. A minimally invasive procedure called ductoscopy is able to visualize these lesions as it inspects the ductal epithelium using a small micro-endoscope. Unfortunately, it is currently challenging to obtain a tissue sample during ductoscopy and reach the most distal duct. *Methods.* In this study we have, therefore, developed a novel miniature (Ø1.2 mm) biopsy needle that can be used during ductoscopy. This biopsy needle consists of two coaxial counter-rotating hollow blades with a distal cutout to resect lesions from the ductal wall. Three cutouts were manufactured resulting in a *beveled*, *straight*, and *reverse-beveled* blade. The blades were actuated using a novel mechanism containing two helical paths that allows for the counter-rotating motion of the blades at different velocities. In a proof-of-principle experiment, the performance of the biopsy needle was evaluated using a polymeric duct model and gelatin tissue phantom. *Results.* During the experiment, the straight and reverse-beveled blades were able to obtain a sufficiently large tissue sample for histopathological examination. Based on these promising results, a second experiment was performed in which the micro-endoscope was integrated in the needle and we were able to take a biopsy from a chicken breast. *Conclusions.* In a future clinical instrument, the biopsy needle will be miniaturized and optimized to allow for an efficient, safe, and effective intraductal biopsy procedure without the need for an invasive excisional biopsy procedure.

List of Abbreviations

CNC	Computer Numeric Control
TDLU	Terminal Ductal Lobular Unit

1. Background

1.1. Ductoscopy for early cancer detection

The majority of benign and malignant lesions (tumors) of the breast arise from the ductal epithelium (approximately 85%) and the Terminal DuctLobular Unit (TDLU, i.e. milk-producing gland) [1–3]. Current breast cancer diagnosis modalities play a vital role in primary screening for breast cancer, diagnosing lesions, treatment selection, progression monitoring, and in determining cancer recurrence. However, by the time a lesion is found by the patient herself or with the preferred population based method, namely mammography, the lesion has been growing for approximately 8 years [4]. The cancerous breast tissue is usually about 1 cm at the time it is palpable, and Ø5–10 mm when detected by mammography [4]. Early detection of breast cancer plays a vital role in increasing the survival rate of women [5].

A minimally invasive procedure called 'ductoscopy', 'mammary ductoscopy' or 'breast endoscopy' has revolutionized breast disease diagnosis, as it is able to visualize smaller lesions (Ø0.1 mm) compared to mammography, ultrasound, and MRI, and provides surgeons direct access to the ductal epithelium [2]. Ductoscopy can be performed as an in-office or outpatient diagnostic procedure using a local anesthetic [3]. In ductoscopy, the mammary ductal epithelium is inspected using a small Ø0.45–1.2 mm fiber-optic

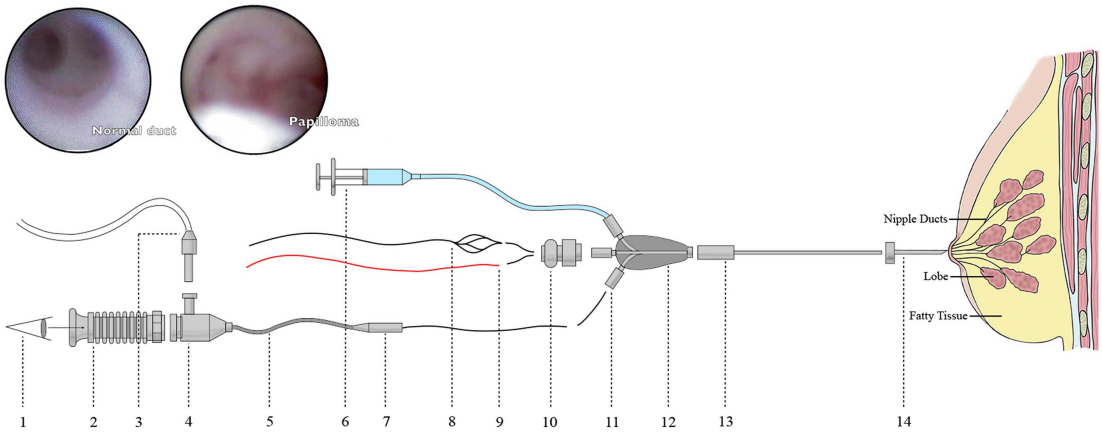

Figure 1. Overview of a Ductoscope. The ductoscope contains a cannula (Ø1.15–1.4 mm; stainless steel or Polyshaft tube (13)) connected to a hub/handle (12) to insert the micro-endoscope (7 inserted in 11), irrigation fluid (6), and other tools (such as a biopsy basket (8) and laser wire (9) via a connector (10)). During the first step of the surgery surgeon enlarges the milk duct using the lumen expander (14), followed by the insertion of the cannula (13) containing the micro-endoscope. To obtain the images, the micro-endoscope is coupled to an auto fluorescence endoscopic imaging system (3, 4, 5, and 7) via a custom-made eyepiece (2). When the milk duct is entered a salt solution (6) is used to enlarge the milk ducts diameter. During the procedure the surgeon can view the milk duct on a LCD monitor (1). After the entire breast is examined the instrument is extracted, finishing the procedure.

micro-endoscope that magnifies the duct up to 60 times normal size and provides high-quality images (10.000 pixels, see figure 1) [3, 6, 7]. The micro-endoscope is used in conjunction with a cannula containing 2 or 3 lumens; one for the endoscope, one irrigation lumen, and one for an additional tool, such as a (biopsy) forceps [3]. The cannula is inserted into the breast milk ducts via the nipple surface. Subsequently, the milk duct of interest is dilated using saline and the micro-endoscope is gently advanced into the duct under video guidance. After assessment of the main ducts, side ducts or branches are evaluated until further advancement is no longer possible due to the size of the cannula (Ø1.15–1.4 mm) [3].

1.2. Current challenges

Although current ductoscopy instruments are effective tools for early detection of breast lesions, some limitations still need to be overcome to allow for widespread application of this technology. Due to the micro-endoscope's diameter and relatively short length (~150 mm), the current ductoscope is unable to reach the peripheral small branches of the ducts and is thus also unable to visualize the TDLU [2, 3]. Although the main central milk ducts are examined, which drain approximately 75% of the breast volume, it is unknown if these ducts represent the most common site where breast lesions arise [7]. To overcome this limitation, smaller and longer micro-endoscopes are needed [3, 6, 7].

The second limitation that needs to be overcome during ductoscopy is related to histological verification of the findings. Unfortunately, it is not always possible to make a final diagnosis based on visual appearance of the lesion. Diagnostic accuracy based on visual appearances alone is in between 39 and 97% depending on the lesion type and visibility [2, 3]. Lesions identified during ductoscopy are most commonly assessed by ductoscopy-directed surgical removal (also known as excisional biopsy) for a definitive diagnosis of the suspicious lesion, which is a cumbersome and invasive procedure in which the entire lesion is surgically removed [3, 6]. In order to minimize the need for excisional biopsy, an intraductal biopsy instrument is needed [3]. Unfortunately, no reliable intraductal biopsy instruments is currently available capable of obtaining tissue sample suitable for histological diagnosis [3, 6]. The development of intraductal biopsy instruments has been limited by the small diameter of the working channel of the cannula, which severely limits the available space to integrate a biopsy instrument [7].

1.3. Goal of this study

This paper describes the development a novel intraductal biopsy instrument that can be inserted in the cannula of a ductoscope and allows for taking a biopsy under direct guidance of the micro-endoscope. The development of an intraductal biopsy instrument is a necessity to allow for early diagnosis of breast cancer precursors and enable a histologic diagnosis without the need for surgical excision [3]. To allow for future examination closer to the TDLUs, the biopsy instrument has been designed with further miniaturization in mind.

1.4. Layout of this study

In section 2, an overview of the current state of the art in biopsy devices used during ductoscopy and percutaneous biopsy is given. In section 3, the design requirements and the resulting designs of the tip and handle are discussed. Section 4 describes the validation of the prototype biopsy needle. The results of this experiment will be discussed in

section 5. As the results of these experiments were promising, an *ex-vivo* animal test was performed and described in section 6. Finally, the results of both experiments are discussed in section 7 and a conclusion will be drawn in section 8.

2. State of the art in biopsy devices

As of today, ductoscopy has been combined with ductal lavage cytology, in which a double-lumen catheter is used to inject saline into the milk duct, and subsequently retrieve this using suction, to obtain cells from the epithelium and as such increase the diagnostic sensitivity of the procedure. An advantage of ductal lavage is that cells can be obtained from the TDLU even if this part cannot be reached with the ductoscope [3]. However, this biopsy method has a relatively low cellular yield and is also unable to obtain a tissue sample for histological examination.

Additionally, a variety of devices has been developed to pass down the working channel of the cannula to obtain a histologic specimen. Examples of such devices are biopsy baskets, cytological brushes, and biopsy forcipes. Biopsy baskets (see figure 1) consist of flexible metallic coils, which are expanded in, or distal to, the lesion, and subsequently retracted to obtain the tissue sample, whereas a cytological brush contains radially orientated bristles. Two clinically available cytology brushes are the *Cellebirty Single-Use Cytology Brush* (Ø1.0–2.0 mm; Boston Scientific, Marlborough, MA, USA) [8] and the *Infinity ERCP Sampling Device* (Ø2.5–3.0 mm; USEndoscopy, Mentor, OH, USA) [9]. Biopsy forcipes resemble regular forcipes except that they are hollow to resect and, subsequently, enclose the tissue sample. Different tip jaws are available from smooth to toothed variants, such as the reusable *Oval Cup* (*with Needle*) and *Alligator Swing-Jaw* biopsy forceps (Ø1.2–2.8 mm; Olympus, Center Valley, PA, USA) [10]. Biopsy forcipes are available with a rigid and flexible shaft, making them suitable for both needle and catheter interventions. During the procedure, the forceps is placed over the target tissue, after which the tip jaws are closed to obtain the tissue sample.

The addition of these instruments during ductoscopy results in a greater cellular yield than with ductal lavage cytology alone [3]. However, biopsy baskets and brushes have been designed for collecting soft, mostly in-coherent, tissue types and not for high precision resection of high-density breast tumor tissue from the ductal wall. Biopsy forcipes, on the other hand, require the micro-endoscope to be retracted during the biopsy procedure and additional room for opening the device tip, which is not always possible as space is limited in the milk duct.

If a small lesion is detected during ductoscopy and no tissue sample could be obtained using the previously mentioned methods and devices, the patient is referred for excisional biopsy (in which the lesion is surgically removed) or, on some occasions, to ductoscopy-directed core biopsy. In core biopsy, a small tissue core is removed from the patient using a special core biopsy needle, which preserves the obtained tissue architecture; enabling histological analysis. Core biopsy needles can be distinguished based on the tip design, which can be subdivided into 'side cut', in which the biopsy is obtained along at the circumference of the biopsy needle or 'end cut', in which the biopsy is obtained at the distal end of the needle. Side cut (also known as 'Tru-cut') biopsy needles consist of an inner solid stylet with a rectangular cutout and an outer hollow cutting needle, such is seen in *SemiCut* (Ø0.9–2.1 mm; MDL, Tavani, Italy) [11]. These types of needles are introduced with the stylet slightly in front of the outer cutting needle. After the stylet is advanced into the lesion, the cutting needle is advanced over the stylet resulting in the containment of the tissue inside the rectangular cutout. The *BioPince* (Ø1.2–1.8; Argon medical devices, Plano, Texas) end cut design consists of three parts: a sharp inner stylet (i.e. a solid sharpened rod) surrounded by an inner hollow coring cannula and an outer cannula with a pincer [12]. During a biopsy the needle is advanced with the stylet slightly protruding from both cannulas. Near the lesion the inner coring cannula is advanced over the stylet; cutting the tissue, where after the outer cannula with pincer slides over the inner coring cannula and cuts off the core of tissue at the distal end of the needle.

As of today, (core) biopsy needles have not been combined with ductoscopy. The main reason is that they do not allow for integration with the micro-endoscope. The side cut needles are solid and thus do not contain a lumen for guiding the micro-endoscope. Furthermore, both the side cut and end cut biopsy needles are currently too long to fit the 180 mm long micro-endoscope.

3. Design process

3.1. Design requirements

To obtain a tissue sample during ductoscopy, the biopsy needle should meet the following requirements. The biopsy structure should be able to resect all types of breast lesions that can be encountered. The Young's moduli of these lesions are reported to have a value of in between 34.5–201.9 kPa [13]. To obtain a sample that is usable for the pathologist, the sample cells need to be intact and sufficiently large with a minimum number of 10 cells, which are in perfect condition. However, it is preferred to obtain a larger sample of at least 0.5 mm^3. Furthermore, during the removal of the instrument the tissue should be confined inside the cannula.

During insertion of the combined diagnostic and biopsy instrument into the nipple, several clinical situations can be encountered depending on the character development stage of the lesion. At the early stage of the development of the lesion, the cells are confined within the milk duct epithelium (figure 2(A)). At this

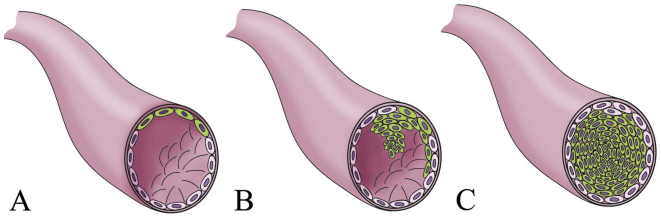

Figure 2. Diseased Milk duct at Different Developmental Stages. (A) Milk duct with cancerous cells in the epithelium (ductal wall). (B): Milk duct with cancerous cells protruding into the ductal lumen. (C): Milk duct completely filled with cancerous cells. The green cells represent the cancerous cells/lesion.

stage the lesion is not (easily) visible during ductoscopy. When the condition progresses, the cells can protrude into the milk duct itself; partly obstructing the duct (figure 2(B)). Finally, the entire duct can be filled with cells (figure 2(C)). The biopsy needle should be able to take a biopsy from all these different clinical situations. When the cells fill the complete duct, the instrument needs to be able to take an end cut, while in a partially filled duct a side-cut mechanism is preferred. Therefore, the biopsy instrument should combine an end-cut and side-cut mechanism.

To allow for easy integration of the biopsy needle into the ductoscopy procedure, the device should fit into an existing cannula, which has an inner diameter of 1.2 mm, and an outer diameter of 1.4 mm. For diagnosis and visualizing purposes, the Ø0.55 mm fiber-optic endoscope *LaDuScope T-flex* (Polydiagnost, Hallbergmoos, Germany) should be able to be guided through the biopsy needle and allow for an unobstructed view of the milk duct during the biopsy procedure. Additionally, for duct enlargement, an irrigation channel should be present. Finally, the biopsy needle should be able to be miniaturized towards a sub-millimeter scale to allow for inspecting the most distal milk ducts and TDLU.

3.2. Tip design

Based on the design requirements, a needle tip design was developed. The tip design consists of two axially counter-rotating coaxial tubular cutting blades surrounded by an optional cannula (see figure 3). The biopsy needle can be equipped with three types of cutting blades: *beveled blades, straight blades*, and *reverse-beveled blades.* The *beveled blade* design resembles a scissor and contains a triangular cutout ($L = 3$ mm, $w =$ radius of the blade r) with a blunt 95° angle between the horizontal and the cutting edge, resulting in a 10° angle between the blades (see figure 3). The *straight blade* design contains rectangular (90°) cutouts ($L = 3$ mm, $w = r$), resulting in axially directed cutting blades. The *reverse-beveled blade* design contains a sharp 85° angle between the horizontal and the cutting edge, resulting in a 10° angle between the blades (see figure 3).

Based on the encountered clinical situation (see figure 2), different modes of operation can be applied. In a semi-filled milk duct, a tangential force can be applied on the cancerous tissue by maneuvering the blades around the tissue and, subsequently, axially rotating the blades in opposite direction. In a completely filled milk duct, the blades are pushed forward into the tissue, during or after which a rotational motion can be applied.

3.3. Handle design

To allow for handheld operation and actuation of the blades of the biopsy needle, a handle was designed. The actuation mechanism was designed to counter-rotate the blades at equal (but opposite) velocity, controlled by one hand. Furthermore, the cannula should be able to move over the axial axis to shield the blades during the insertion and retraction process, and expose the blades during the resection process.

The final handle design is illustrated in figure 4. The handle consists of five main parts: (*A*) an outer shell, (*B*) a rotational bearing of the inner blade, (*C*) a helical tube containing two counter-rotating helical paths, (*D*) a rotational bearing of the outer blade, and (*E*) a cap connected to the cannula. The helical tube contains two helical slots; one rotating counter clockwise and the other rotating clockwise, allowing for the desired counter-rotating movement of the bearings *B* and *D* that run in these slots and that are connected to the inner and outer blade, respectively (see figure 5). The handle is operated by axially translating the helical tube (*C*). The cap *E* can be translated over the outer shell *A* to move the cannula backwards and forwards for shielding the blades during insertion and retraction.

3.4. Prototype design

The final design was translated into a prototype consisting of 24 parts (see figures 6 and 7). The cutouts of the blades were manufactured using electric discharge machining, resulting in a length of 3 mm, and width of 0.5 and 0.6 for the inner and outer blade, respectively (see figure 8). Subsequently the blades were sharpened using a small file. The overall length of the needle was set to 100 mm (measured from the cap *E*).

To minimize friction losses, low friction material combinations were used for the functional parts. The cannula and cutting blades were manufactured out of stainless steel. Parts (B_1), (B_2), (D_1), (D_2), (*G*) and (*H*)

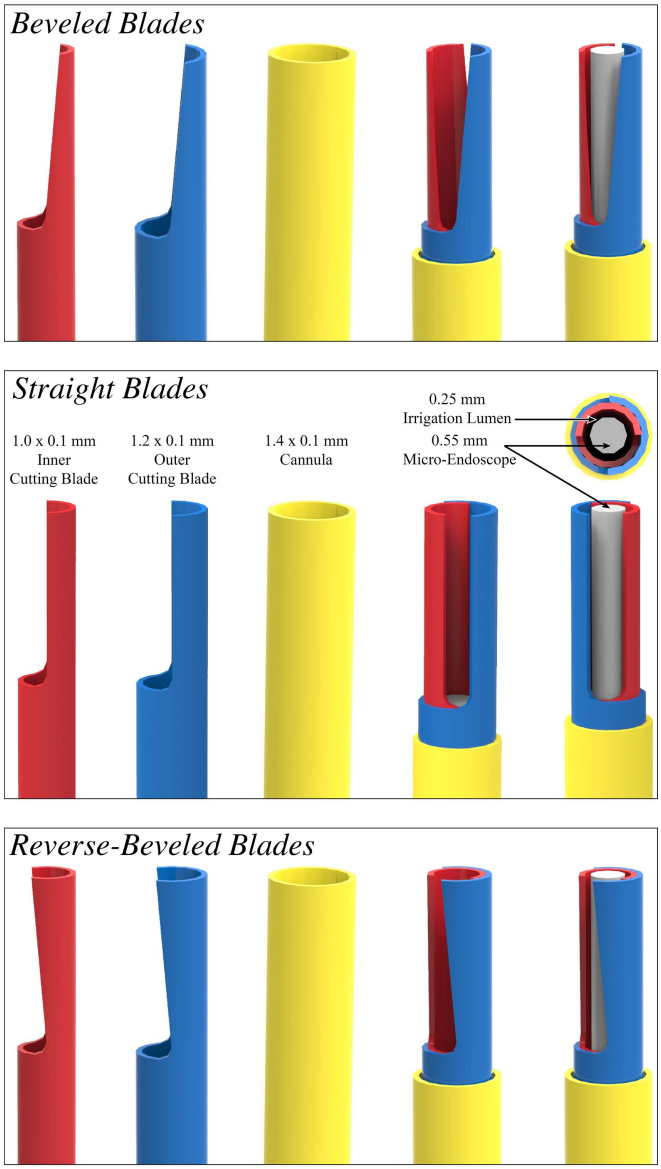

Figure 3. Biopsy Needle Tip Designs. The biopsy needle tip consists of three parts: an inner cutting blade (Ø1.0 × 0.1 mm, red), an outer cutting blade (Ø1.2 × 0.1 mm, blue), and an optional cannula (Ø1.4 × 0.1 mm, yellow). The Ø0.55 micro-endoscope can be placed in the Ø 0.8 mm lumen of the biopsy needle, leaving room for a concentric irrigation channel. Three different blade designs have been manufactured: Top—*beveled blade* design. Middle—*straight blade* design. Bottom—*reverse-beveled blade* design. For explanation see text.

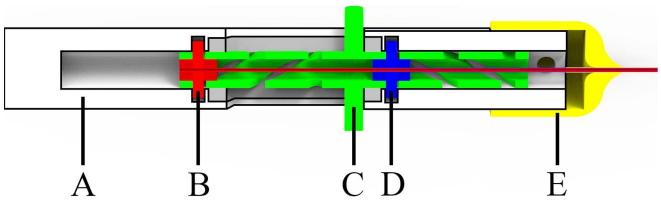

Figure 4. Handle Design of the Biopsy Needle. The handle of the biopsy needle consists of: (A): outer shell, (B): rotational bearing connected to the inner cutting blade, (C): helical tube, (D): rotational bearing connected to the outer cutting blade, and (E): cap connected to the cannula to shield the blades during insertion and retraction.

were made out of aluminum, whereas brass was used for part (C_1) and (C_2). Two nylon rings (F) were fitted around the bearings B_1 and D_1 to prevent axial translation of the inner- and outer bearing and allow for smooth rotational motion. Figure 9 shows the final assembled prototype.

The following steps have to be followed to obtain a biopsy with the prototype biopsy needle (see

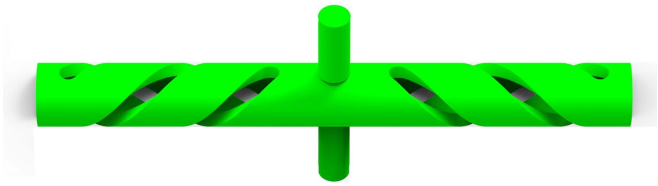

Figure 5. Detail of Helical Tube with Control Rods. The angle of the helical paths was set to 45° with the number of revolutions equal to one to allow for one complete rotation of the inner and outer cutting blade during a cycle.

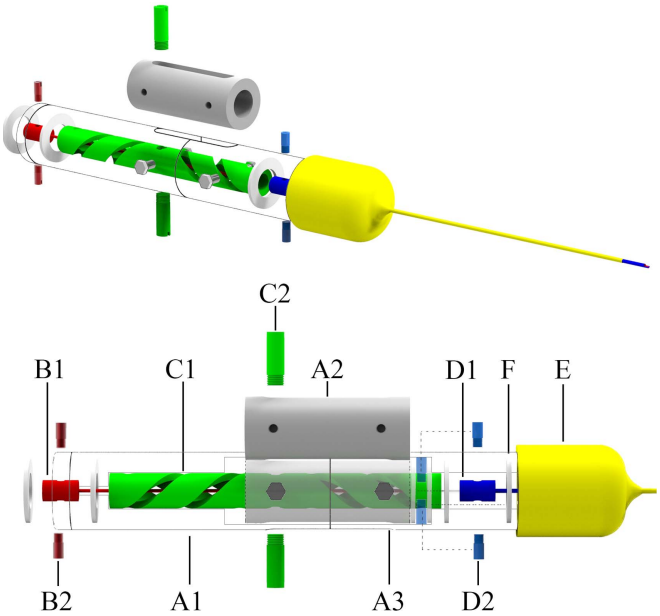

Figure 6. Biopsy Needle Handle Design—Exploded View. Top row: perspective view, Bottom row: side view. Letter indications: (A1): bottom tube, (A2): middle tube, (A3): top tube, (B1): inner bearing connected to the inner cutting blade, (B2): cylindrical protrusions, (C1): helical tube, (C2): control rods (2x), (D1): outer bearing connected to the outer cutting blade, (D2): cylindrical protrusions, (E): cap connected to the cannula, and (F): nylon rings (4x).

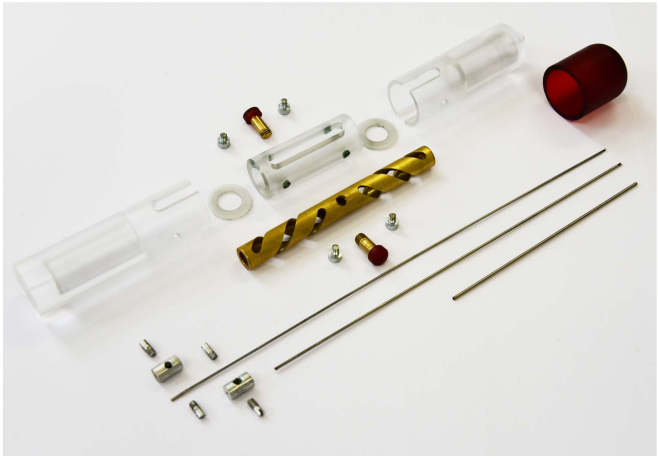

Figure 7. Prototype Biopsy Needle showing all the parts.

figure 10). First, the biopsy needle is inserted into the milk ducts with the cannula shielding the cutting blades to prevent damage to the milk ducts. The milk ducts are examined by the micro-endoscope inserted in the biopsy needle's lumen. Once a lesion is detected, the cannula is translated backwards to expose the cutting blades. Subsequently, the two control rods are pushed forwards or backwards to counter-rotate the blades at equal, but opposite, velocities, to obtain the biopsy. After a successful biopsy procedure, the blades

Figure 8. Prototype Biopsy Needle Tip Designs. Top—*beveled blade* design. Middle—*straight blade* design. Bottom— *reverse-beveled blade* design. The match is shown for scale purposes.

are covered by the cannula and retracted from the milk duct.

4. Proof-of-principle experiment

4.1. Experiment goal

In order to evaluate the prototype, a proof-of-principle experiment was set up. The main goal of the experiment was to determine whether the proposed prototype is able to obtain a biopsy from a ductal wall.

4.2. Experimental variables

The mechanical cutting performance of the prototype biopsy needle was evaluated based on its ability to obtain a tissue sample (Y/N) of a phantom. To give an indication about the effectiveness of the resection procedure the resection time t [s], gelatin compression until resection δ [mm], and sample size V [mm^3] were measured. Additionally, the operation force F [N] was measured to give an indication about the required forces to operate the prototype biopsy needle.

4.3. Experimental facility

4.3.1. Measurement facility

The prototype biopsy needle was fixed in a measurement facility (see figure 11). To move the blades, a U-profile was connected to the control rods (parts C_2 in figure 8), which in turn was connected to a linear motion stage (*Almotion LT*50-*TR*-*G*8; Almotion, Elst, the Netherlands) via a load cell (*LSB*200, Futek, Irvine, CA, USA) to measure the operation force. To initialize the linear stage and the load cell, a multifunctional data acquisition system was used (*NI USB*-6008, National Instruments, Austin, Texas, USA). The biopsy process was observed in detail using a high-speed video camera *Fastcam APX RS* (Photron, San Diego, California, USA) in combination with the *Questar QM*1 (magnification factor of 11/2; Company Seven, Montpelier, MD, USA) lens. The high-speed video camera was positioned in front of the needle tip.

4.3.2. Milk duct mimicking phantom

In order to determine the ability of the cutting blades to obtain a biopsy from the ductal wall, a transparent PMMA milk duct phantom (Ø1.7 mm) was created in which a gelatin lesion-mimicking phantom could be placed (see figure 12). To mimic the properties of ductal carcinoma and papilloma, a mixture of 25 wt% 250-bloom gelatin powder and water was used. When cooled down, this mixture has a similar Young's modulus as ductal carcinomas and papillomas of approximately 100–150 kPa [13].

The phantom was placed in the duct phantom just before the beginning of the experiment. The filling ratio of the duct phantom was set to 50% (see figure 12) to mimic semi-filled milk ducts illustrated in figure 2(B).

4.4. Experimental protocol

The linear motor stage was set to 0.4 mm s^{-1}, resulting in a rotational velocity of 16 rpm of the blades. All the variables were determined 3 times per phantom for each of the blade designs, resulting in a total of 9 tests. To prevent the effect of gelatin hardening over time, all the test were executed within one hour of manufacturing.

4.5. Data acquisition and analysis

Data acquisition and position control of the linear stage were achieved using a dedicated laptop equipped with Labview to initialize the data acquisition (National instruments, Austin, Texas, United States), Q-programmer feeding the linear motion stage (moons Industries, Shanghai, China), and Photron Fastcam Viewer to analyze the camera feed.

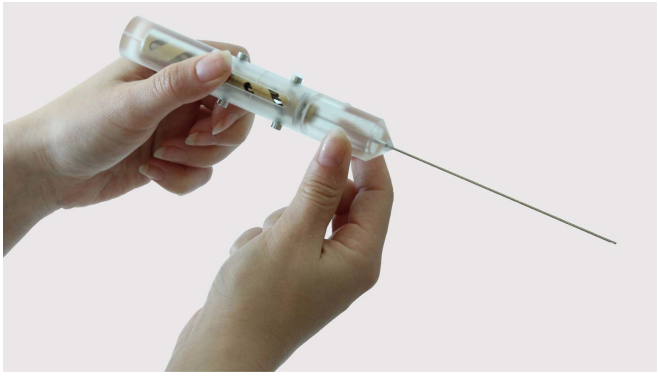

Figure 9. Prototype Biopsy Needle—Assembled.

5. Results

5.1. Tissue sample obtainment

In the experiments, it became clear that the *beveled blade* design was unable to obtain a tissue sample. The gelatin breast tissue phantom was pushed forward, resulting in an incomplete cut (see figure 13). The *straight* and *reverse-beveled blades* were able to fully resect all the gelatin phantoms (see figure 14). In each test, a sufficiently large tissue sample was obtained for histopathologic analysis of at least 0.5 mm^3, which was determined visually from the video images.

5.2. Effectiveness resection procedure

Slight differences between the *straight* and *reverse-beveled blades* were identified in terms of resection time t and gelatin compression δ (see table 1). Both the resection time t and gelatin compression δ were smaller for the *straight blade* design. However, in the *straight blade* design a more 'abrupt' resection procedure was seen, in which the entire tissue sample was obtained simultaneously, while in the *reverse-beveled blade* design the resection process was more constant.

5.3. Operating force

The mean operation force was on average 4 N ($n = 9$) with a maximum value of 4.4 N, which allows for easy single-handed control. No significant differences between the different blade designs were found.

6. *Ex-vivo* animal test

The biopsy needle has illustrated the ability to obtain a tissue sample in the proof-of-principle experiment. To illustrate the clinical feasibility of the biopsy needle, a second experiment was performed at the University Medical Center Utrecht (Utrecht, the Netherlands) that resembles the clinical situation more closely. In the clinical validation experiment, the Ø0.55 mm micro-endoscope (*LaDuScope T-flex*, Polydiagnost, Hallbergmoos, Germany) was inserted in the lumen of the biopsy needle (see figures 15 and 16). The biopsy needle was, subsequently, used to obtain a tissue sample from a piece of chicken breast, whichresembles breast tissue [14]. Two different needle placements were investigated to determine the needle's ability to obtain a biopsy from different clinical situations (see also figure 2). First, the biopsy needle was placed tangent to the outer surface of the chicken breast, resembling the situation of when a semi-filled milk duct is encountered. Secondly, to determine the ability of the needle to puncture and obtain a tissue sample from a completely filled milk duct, a small strip of 10 mm thick chicken breast was penetrated with the biopsy needle after which the blades were actuated. In both situations, the biopsy needle was able to obtain a biopsy as is illustrated in figure 17. Unfortunately, as of today no suitable animal model is available for ductoscopy that allows for travelling through milk duct-type structures. In future, the biopsy needle will, therefore, be tested on mastectomy samples.

7. Discussion

7.1. Summary of main findings

7.1.1. Mechanical validity

The biopsy needle has illustrated the ability to fully resect gelatin phantoms along the ductal wall. Three different tip geometries were tested. At the beginning of experiment, however, it became clear that one of the designs; the *beveled blade* design, was unable to fully resect the gelatin phantom, due to the forces exerted by this blade configuration, which are directed slightly forward (perpendicular to the cutting edge); pushing the tissue forward. Based on these results it was decided to abandon this tip geometry. The *straight* and *reverse-beveled blades* were able to fully resect all the phantoms from the ductal wall.

The *straight* or *reverse-beveled blades* both have their advantages and disadvantages and thus should be selected on based on the encountered clinical situation. The *reverse-beveled* blade provides a more

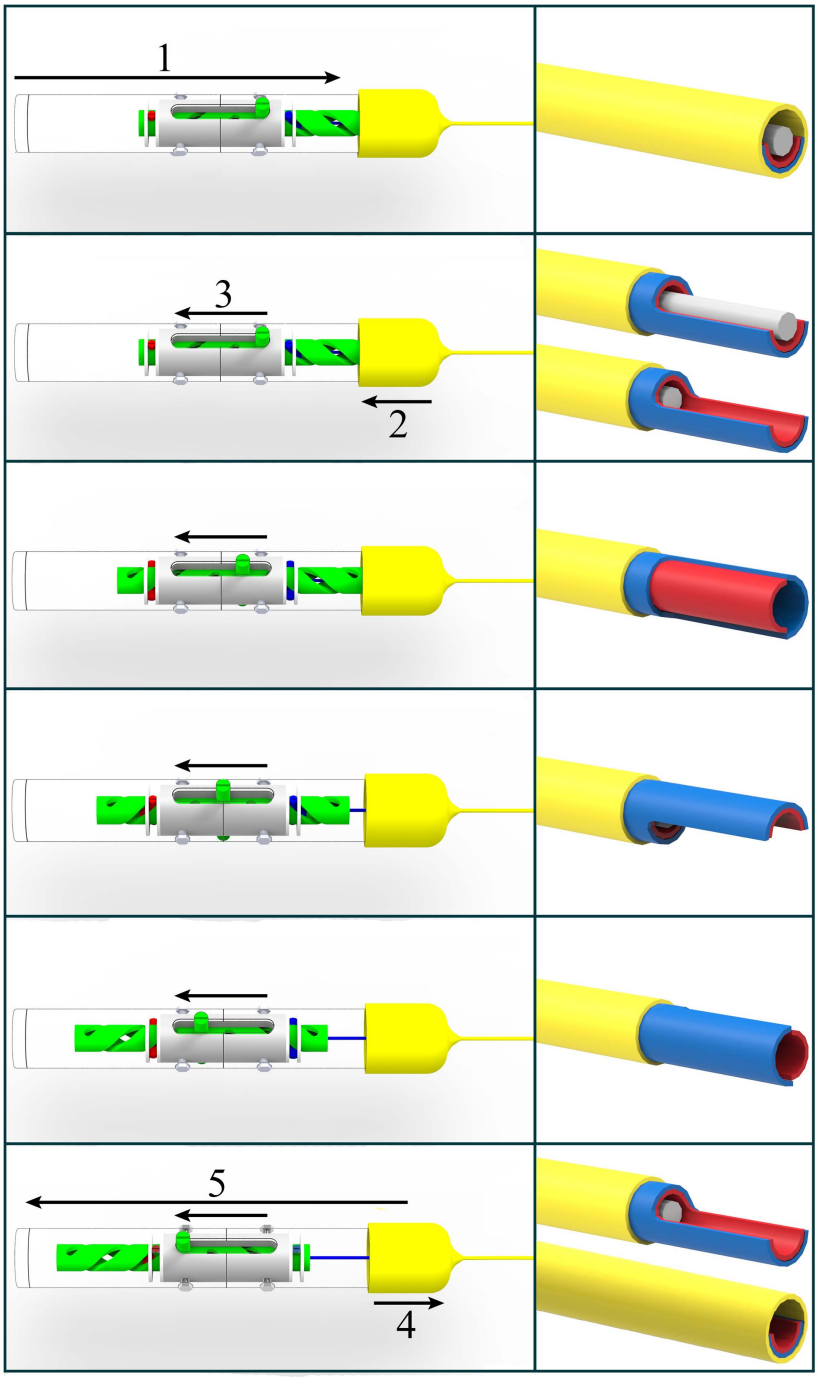

Figure 10. Biopsy Procedure with the Prototype Biopsy Needle. (1) Insertion of the biopsy needle in the milk duct with the cannula positioned over the cutting blades. (2) Cannula moved backwards to expose the blades. (3) Rotation of the blades to take the biopsy. (4) Repositioning of the cannula over the blades. (5) Removal of the biopsy needle from the milk duct.

'constant' resection procedure, as the angled blades provided high pressures, and thus relatively low forces, on the tissue during the entire process due to the sliding contact point between the blades, similar to a scissor. The *straight blade,* on the other hand, exerts a distributed line force onto the tissue for resection, resulting in a more 'abrupt' resection process in which the entire tissue is resected at once when sufficient pressure is delivered by the blades. Furthermore, the *reverse-beveled blade* design is able to grip the lesion and pull it inward due to the inward directed cutting surface. On the other hand, the *straight blade* design was able to obtain the tissue sample faster with less gelatin compression than the *reverse-beveled blade* design, which might be beneficial for preserving the tissue structure. Additionally, the *straight blade* design allows for grasping larger lesions due to the larger endpoint opening span of the blades than the *reverse-beveled blade* design and is less likely to cause unwanted damage the ductal wall during actuation.

The obtained tissue samples had a volume of approximately 0.5 mm^3, as determined visually from

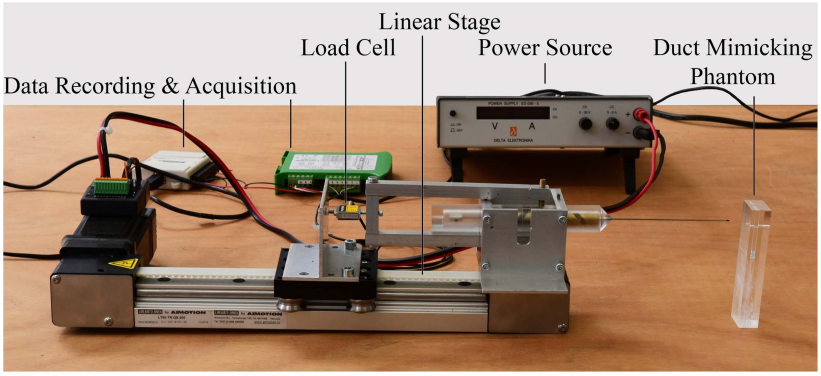

Figure 11. Measurement Facility. The measurement facility consisted of the prototype confined within an aluminum facility, the duct-mimicking phantom, a linear motion stage to actuate the cutting blades, a power source to power the motion stage, and data recording and acquisition boxes.

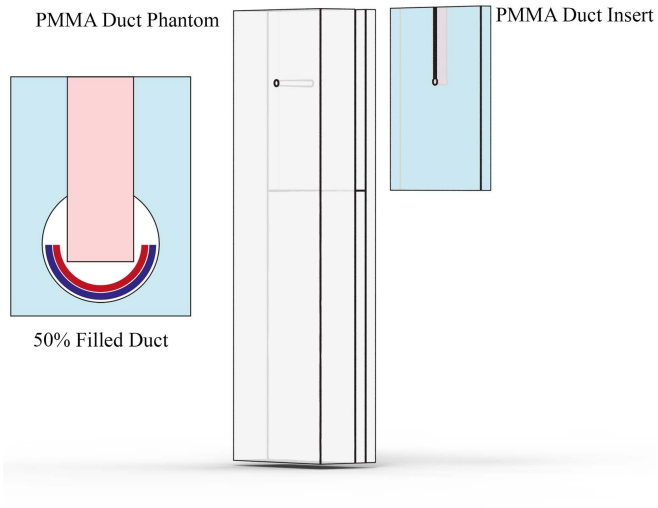

Figure 12. Milk Duct Mimicking Phantom. The breast-mimicking phantom consists of a PMMA laser-cut duct model through which a gelatin lesion phantom is inserted, which mimics a 50% filled duct. Color indications: Blue = Outer cutting blade, Light Blue = Rigid PMMA duct model insert, Light Grey = PMMA duct phantom, Pink = lesion-mimicking phantom, and Red = Inner cutting blade.

the video images. When it is assumed that the tissue sample of the lesion is homogeneous; containing only lesion cells, this is sufficient for histopathologic analysis.

7.1.2. Clinical validity

The developed biopsy needle allowed for easy integration of the micro-endoscope. A clear and unobstructed view of the text directly in front of the endoscope tip and blades was obtained. Furthermore, the biopsy needle was able to obtain tissue sample from the chicken breast, which closely resembles human breast tissue.

7.2. Limitations of this study

It is recommended that future tests will be performed on *ex-vivo* breast tissue removed during mastectomy procedures. Although the gelatin mimics the Young's modulus of the malignant cells, it is unsure how well the gelatin mimics the other tissue properties of these lesions. Furthermore, the ductal wall was mimicked using a stiff PMMA phantom, while the milk ducts are flexible. The chicken breast mimicked the clinical situation more closely than the gelatin phantom; however, it still differs significantly differs from a milk duct in human breast tissue.

7.3. Recommendations for future research

7.3.1. Optimization blade design

In a future clinical prototype, the blade design should be optimized. First, the blades should be sharpened using professional equipment, such as a wetstone or CNC drilling and milling machine. Secondly, to allow for obtaining larger biopsies in a single actuation cycle, the cutout length could be increased towards 10 mm, the maximal length of the lesions in 95% of the cases. Thirdly, different tip geometries could be researched, such as toothed blades. Finally, to prevent the obtained tissue sample from falling out of the needle during retraction it is preferred to create a slight under-pressure in the shaft.

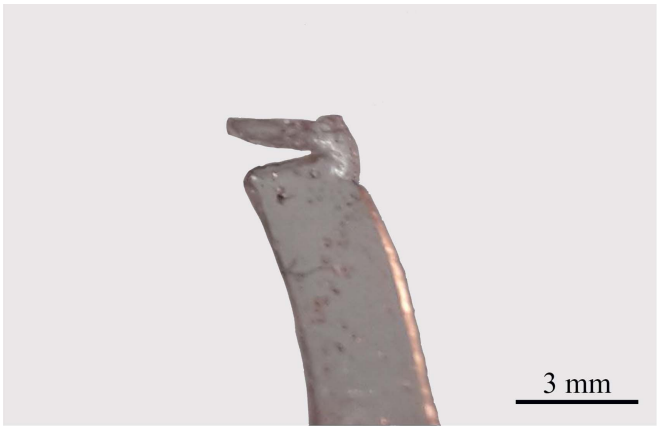

Figure 13. Incomplete resection of the gelatin phantom with the *beveled blade* design.

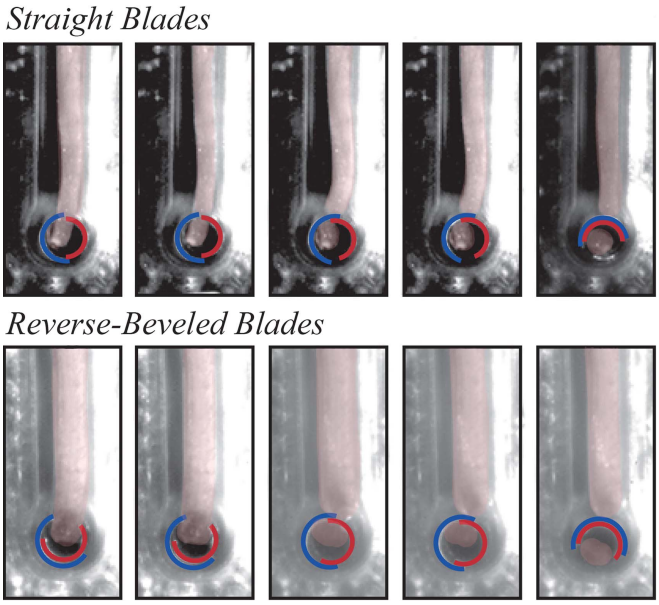

Figure 14. Tissue sample obtainment with the *straight* and *reverse-beveled blades*. Top—*Straight blade* design. Bottom—*Reverse-beveled blade* design.

Table 1. Measured resection time and gelatin compression for the *straight blade* and *reverse-beveled blade* designs ($n = 3$). The values are indicated as mean (minimum value–maximum value).

Blade design	Resection time t [s]	Gelatin compression δ [mm]
Straight blade design	4.3 (3.9–4.6)	0.04 (0.03–0.05)
Reverse-beveled blade design	6.5 (5.8–7.3)	0.09 (0.07–0.11)

7.3.2. Optimization handle design

In a future clinical biopsy needle, the handle should allow for easy integration of the micro-endoscope, irrigation system, and a work channel. For this purpose, it is a necessity to shorten the handle, which can be executed by minimizing the blade rotation from 360° to 100° (reduction of approximately 70%), minimizing the clearance between the helical paths, and minimizing the slot diameter of the helical paths (amongst others). Additionally, we will also investigate alternative mechanisms to counter-rotate the blades that allow for the development of an even shorter handle.

7.3.3. Miniaturization biopsy needle diameter

It is preferred to further miniaturize the outer dimensions of the needle towards a sub-millimeter scale to allow for inspecting the peripheral milk ducts. Due to the relative simplicity of the design this could be achieved by minimizing the diameters and wall-thickness of the cutting blades. However, miniaturization is restricted by

Figure 15. Clinical Experimental Facility at University Medical Center (Utrecht, the Netherland). The experimental facility consisted of the biopsy needle integrated with the micro-endoscope connected to the imaging equipment.

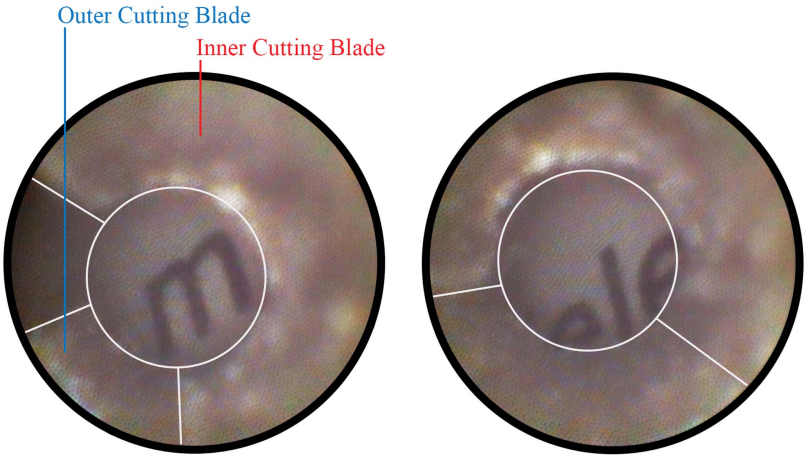

Figure 16. Micro-Endoscopic Images obtained from the Biopsy Needle. In the background a piece of text is illustrated which is imaged using the micro-endoscope.

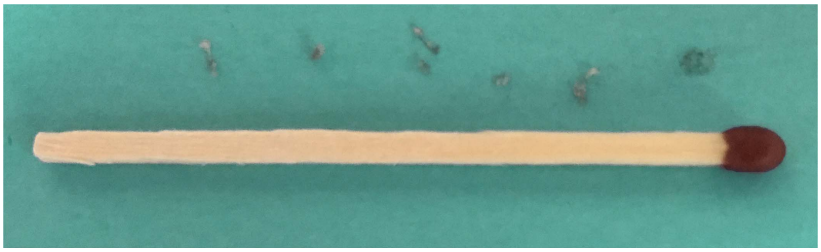

Figure 17. Tissue Sample Obtainment with the Biopsy Needle from the Chicken Breast. The match is illustrated for scale estimation.

the required inner lumen of at least 0.60 mm to allow for the insertion of the micro-endoscope and irrigation. Furthermore, miniaturization of the diameter should not impede the ability to obtain sufficiently large tissue samples. Therefore, we feel that the outer diameter of the biopsy needle should not be smaller than approximately Ø0.8 mm (with two 0.05 mm thick cutting blades), leaving sufficient room to insert the smallest Ø0.45 mm micro-endoscope, allow for irrigation, and take the biopsy.

7.3.4. Future clinical validation biopsy needle

In future, the biopsy needle will be tested on human mastectomy samples. During this experiment the biopsy needle will be used in combination with post-mastectomy ductoscopy for visualization of the insertion and biopsy procedure. If the mastectomy experiment has been completed successfully, we will work towards a clinical study on women with bloody nipple discharge. For this purposes, in the upcoming years the biopsy needle will be developed further into a clinical instrument, which can be easily sterilized and assembled.

8. Conclusions

In this study we have developed a novel Ø1.2 mm biopsy needle that consists of two counter-rotating blades that allows for taking an intraductal biopsy under direct visualization of the micro-endoscope, and thus prevents the need for a subsequent highly invasive excisional biopsy. The blades are actuated using two counter-rotating helical paths in the handle. A proof-of-principle experiment has illustrated the effectiveness of the biopsy needle in fully resecting gelatin tissue phantoms that mimic the Young's modulus of ductal carcinoma and papilloma from a stiff ductal wall model with high precision. Based on these promising results, an *ex-vivo* test on chicken breast was successfully performed by integrating the micro-endoscope in the biopsy needle. We will continue to develop this biopsy needle, which, in time, may improve the survival rate of breast cancer in women by early detection of suspicious lesions without the need of an invasive excisional biopsy procedure.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Design of the prototype: AS, KS, and PB. Wrote the paper: AS and KS. Proof-of-principle experiment design: AS and KS. *Ex-vivo* experiment: AS and AW. Advice on structure and content of paper: GS, AW, and PB.

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